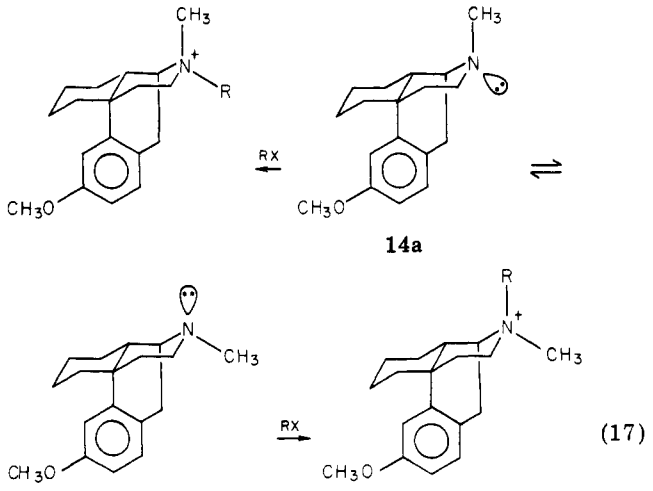
Table II. Stereoselectivity of the Quaternization of Dextromethorphan (14) by a Series of *n*-Alkyl Iodides (Eq 17)[a]

n-alkyl iodide	stereoselectivity, axial/equatorial attack	axial/equatorial ratio calcd from α (Table I)
methyl-d_3	0.14	2.6
ethyl	3.0	1.3
ethyl-d_5	4.0	1.3
propyl	3.5	
butyl	3.0	

[a] From ref 27.

the R and R′ groups, McKenna proposed that the stereoselectivities observed in pairs of eq 13 reactions would allow accurate assignment of nitrogen quaternization products. Thus, a very bulky R-substituted alkyl halide would tend to favor a decreased product ratio $[A_4]/[A_1]$ *relative* to the product ratio resulting from a smaller, more reactive RX. This follows directly from eq 4, in that a bulkier RX would influence the ratio k_{21}/k_{34} dramatically while not affecting K in Scheme I or eq 12–13.

These considerations throw into question the recent report of Wainer and Sheinin[27] on the quaternization of dextromethorphan (14) shown in eq 17 and Table II. If



(17)

we make the reasonable assumption that **14e** is more stable than **14a**, then for these alkylations to be consistent with pyrrolidine and piperidine quaternizations, the axial/equatorial product ratio should decrease with increasing bulkiness of the alkyl halide. This is not what is reported.[27] An estimation of the product ratio determined using α and eq 5 is shown in Table II. Thus, either some of the assignments are incorrect or there are special substituent effects occurring in the dextromethorphan chemistry which should be further elucidated.

Conclusions

We have herein demonstrated a conceptual extension of the Curtin–Hammett principle; namely, that under LFER conditions, the product composition $[A_4]/[A_1]$ of a chemical reaction described by Scheme I or III kinetics *is* directly related to the ground-state equilibrium distribution $[A_3]/[A_2]$ of the starting material. The relationship is of the form $[A_4]/[A_1] = K^{1-\alpha}$ (eq 5), where α is a reaction-dependent parameter which quantifies the effects of substituents on $\Delta G°$ relative to their effects on $\Delta G^{\ddagger}_{TS}$. We have derived eq 5 on the basis of LFERs. The utility of these concepts is demonstrated in terms of the reactivity of equilibrating reacting conformations and reacting tautomers, and a relationship between α and the Taft-type steric parameter $S°$ is shown. Equation 5 will find utility in qualitative comparisons, and analysis of a recent example from the literature indicates either incorrect structural assignments or the occurrence of unusual reaction stereochemistries.

Acknowledgment is made to the National Science Foundation (Grant #CHE 81-16800) and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research. One of us (J.I.S.) thanks Professor Jack E. Baldwin for affording the hospitality at the Dyson Perrins Laboratory during which some of this manuscript was written. We acknowledge Anne Donathan for invaluable secretarial assistance.

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Heteroadamantanes. 3. The Effect of Changing Electron Demand on O-3 Participation in the Solvolysis of 2-Oxaadamantanes[1]

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The tosylates of *anti*-2-oxaadamantan-4-ol, *anti*-4-methyl-2-oxaadamantan-4-ol, and *anti*-4-cyano-2-oxaadamantan-4-ol have been solvolyzed in buffered acetic acid. The solvolyses yield oxaadamantyl products of exclusively retained configuration and oxaprotoadamantyl products of exclusively inverted configuration. Comparison of the CH_3/H and CN/H rate ratios with the same ratios for 2-adamantyl suggests that O-3 participation in the oxaadamantyl compounds provides anchimeric assistance of the order of 10^4.

Of late, the chemistry of heteroadamantanes has drawn much attention.[2-9] In part, this attention has been devoted to the physical properties of the solid phases of these materials, which are indicative of considerable orientational disorder.[7] On the other hand, because the adamantane

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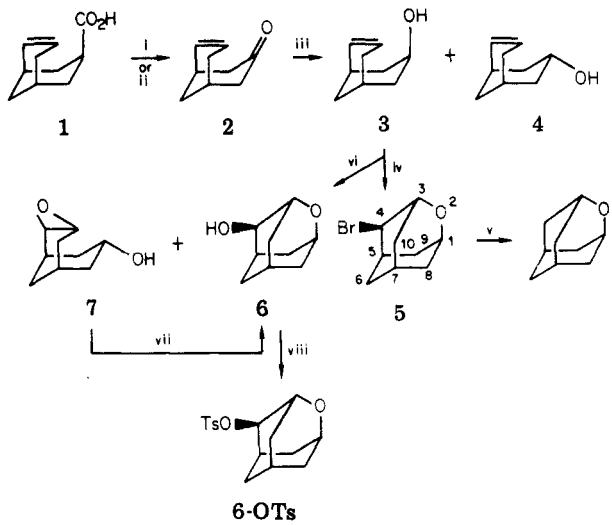
0022-3263/84/1949-2891$01.50/0

Scheme I[a]



[a] i, LDA, O_2; ii, LDA, O_2, $(MeO)_3P$, $Pb(OAc)_4$; iii, $LiAlH_4$, ether; iv, NBS, H_3O^+, dioxan; v, $LiAlH_4$, ether; vi, *m*-$ClPhCO_3H$, CH_2Cl_2; vii, 50% H_2SO_4; viii, *n*-BuLi, TsCl.

system strictly defines the stereochemical relationship between the heteroatom and substituent groups, and because it is anticipated that secondary heteroadamantanes, like 2-adamantyl itself,[10] will undergo limiting solvolysis, these molecules are of importance to the study of heteratom participation in S_N1 reactions.[3-6,8,9]

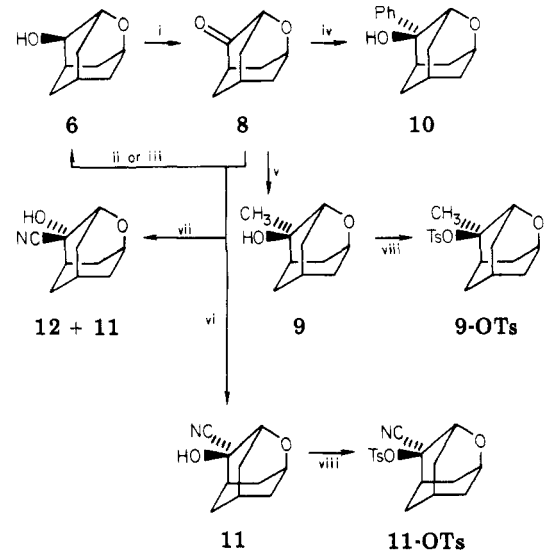
We report here an efficient new synthesis of 4-substituted-2-oxaadamantanes and the results of the solvolysis of several such compounds. We believe the data provide substantial evidence for significant anchimeric assistance by O-3 participation.

Syntheses

Scheme I presents our approach to 2-oxa-4-adamantanol, from which the solvolysis substrates were prepared. In part, we followed our previous synthesis of 3-heterodiamantanes.[8] The bicyclononene carboxylic acid **1**, obtained from adamantanone by an abnormal Schmidt reaction,[11] was decarboxylated by a modification of the procedure of Wasserman.[12] This reaction gives ketone **2** in virtually quantitative yield, albeit only 60% conversion. Conversion may be improved by adding trimethyl phosphite once the α-hydroperoxide has formed,[13] producing the α-hydroxy acid, which may be isolated and decarboxylated to **2** in quantitative yield by means of lead(IV) acetate in dry benzene. The overall conversion in this latter process is 75%. In either case, unreacted acid is the only other material recovered.

Reduction of **2** with lithium aluminum hydride in refluxing ether gives a mixture of the endo and exo alcohols

Scheme II[a]



[a] I, CrO_3, acetone; ii, $NaBH_4$, MeOH-H_2O; iii, $LiAlH_4$, ether; iv, PhMgBr; v, MeMgI; vi, Me_3SiCN, CH_2Cl_2, H_3O^+; vii, vi + ZnI_2; viii, *n*-BuLi, TsCl.

3 and **4** in 95% yield. The composition of the alcohol mixture was estimated by ^{13}C NMR to be $^2/_3$ **3** and $^1/_3$ **4**. The chemical shift difference (Experimental Section) between the alkene carbons in **3** is about 8 ppm, whereas in **4**, this difference is only about 3 ppm.[8] The large variation between the two compounds may be the result of intramolecular hydrogen bonding in the endo epimer **3**[14] or may reflect conformational differences. Changing the reducing agent produced no appreciable enrichment of the mixture in endo alcohol, nor could we achieve a useful chromatographic separation of the isomers.

In the event, separation proved unnecessary, for both **3** and **4** give the same products in subsequent reactions. Thus, treatment of the mixture of alcohols with *N*-bromosuccinimide in aqueous acid dioxane gives *anti*-4-bromo-2-oxaadamantane (**5**) in 89% yield. The structure of **5** rests upon its reduction to the known[15] oxaadamantane (lithium aluminum hydride in refluxing ether), and upon its ^{13}C NMR spectrum (Experimental Section), which, like the spectrum of the corresponding 5-bromo-3-oxadiamantane,[8] shows upfield shifts of 6.6 and 6.4 ppm (relative to oxaadamantane) for carbons 6 and 10, which are γ to the axial bromine.[16]

The formation of **5** from **3** is readily explicable as intramolecular interception of an intermediate bromonium ion by the endo hydroxyl. The generation of the identical product from **4** is less straightforward; we believe it to succeed by formation of a bromohydrin and subsequent acid-promoted ring closure.

Epoxidation of the mixture of alcohols **3** and **4** with *m*-chloroperbenzoic acid in methylene chloride gives a mixture of *anti*-2-oxaadamantane-4-ol (**6**) and the epoxide **7** of **4**, as judged by the ^{13}C NMR spectrum of the crude

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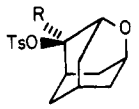
Table I. Data for Solvolysis in AcOH/NaOAc



R	T, °C	$k \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, c/m/C
H	121.5	2.88 ± 0.08	21.8 ± 0.7	−19.8 ± 1.8
	111.0	1.37 ± 0.02		
	101.0	0.59 ± 0.02		
	75[a]	0.062		
CH_3	75	1100	23.9 ± 0.3	5.5 ± 1.0
	30.0	6.00 ± 0.03		
	22.0	1.94 ± 0.03		
	15.0	0.72 ± 0.02		
CN	160.0	1.32 ± 0.2	26 ± 2	−16 ± 4
	151.0	0.61 ± 0.01		
	141.0	0.31 ± 0.02		
	75[a]	0.0006		

[a] Values extrapolated from rates at other temperatures.

product. This mixture, without separation or purification, was stirred with 50% sulfuric acid, to produce **6** in 89% overall yield from the alcohols.

The structure assignment of **6** rests upon its mode of formation, analogous to the formation of **5**, and upon its ^{13}C NMR spectrum (Experimental Section), which is closely similar to the spectrum of **5**, even to the upfield shift (6.5 ppm relative to oxaadamantane) of carbons 6 and 10 (the use of $Eu(fod)_3$ was necessary to resolve the spectrum completely). Furthermore, the infrared spectrum of **6** in dilute chloroform solution is missing the OH stretch for an intramolecular hydrogen bond, which might be expected in the syn isomer. Although we were unable to prepare a sample of *syn*-**6** for comparison, the subsequent chemical behavior of our **6** is consistent with our assignment.

Scheme II details the further synthetic transformations of **6**. Oxidation with the Jones reagent gives 2-oxaadamantan-4-one (**8**) in over 90% yield. Subsequent reactions of **8** occur stereospecifically from the syn face. Thus, reduction of **8** with either lithium aluminum hydride or sodium borohydride gives exclusively anti alcohol **6**. Addition of the methyl or phenyl Grignard reagents likewise is stereospecific,[17] producing the anti alcohols **9** and **10**. In each case, the ^{13}C spectra (Experimental Section) are in complete accord with the assigned structures and stereochemistry. The stereospecificity of these reactions likely results from complexation of the metal with the ether oxygen.

Stirring **8** with trimethylsilyl cyanide in methylene chloride, followed by hydrolysis of the cyanosilane, gives 85% of *anti*-4-cyano-2-oxaadamantan-4-ol (**11**). When a trace amount of anhydrous zinc iodide is employed to catalyze this reaction, a mixture of **11** and its epimer **12** is obtained, presumably through equilibration of first-formed **11**.

Alcohols **6**, **9**, and **11** all were converted to the corresponding tosylate esters with *n*-butyllithium and tosyl chloride in ether/hexane.

Solvolyses

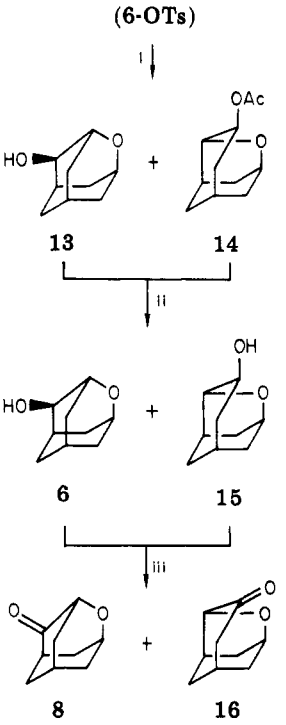
Tosylates **6-OTs**, **9-OTs**, and **11-OTs** were solvolyzed for three half-lives in deuterioacetic acid (CD_3COOD) buffered with 2 equiv of sodium deuterioacetate ($NaOOCCD_3$). The rates were measured by ^1H NMR spectroscopy, as described in the Experimental Section, and are collected in Table I.

Preparative solvolyses employed protioacetic acid and sodium protioacetate at reflux. The solvolysis of **6-OTs** led quantitatively to a mixture of two acetates, in the ratio 92:8, as judged by gas chromatography (Scheme III). We believe from control experiments that we could have detected as little as 0.5% of related materials; within this limit, only two products are found. The ^{13}C NMR spectrum of the major component was identical with the spectrum of an authentic sample of *anti*-4-acetoxy-2-oxaadamantane (**13**).

Identification of the minor product posed some problems, for we were unable to separate it cleanly from the mixture. Nor could we separate the minor alcohol from the mixture obtained by reducing the combined acetates with lithium aluminum hydride. Consequently, we oxidized the mixture of alcohols with the Jones reagent. Had the minor acetate/alcohol been the syn epimer of **13**/**6**, a single ketone (**8**) should have been obtained. Instead, oxidation gives a mixture of (**8**) and a second ketone, which must have a rearranged skeleton.

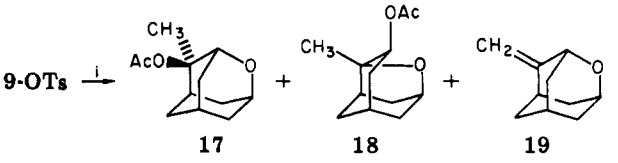
The ^{13}C NMR spectrum of this ketone, obtained by subtracting the spectrum of **8** from the spectrum of the mixture, is in accord with structure **16**. Spectra of the acetate and alcohol, similarly obtained, are likewise in accord with structures **14** and **15**. In particular, **14** and **15** both show the significant deshielding of the bridgehead

Scheme III[a]



[a] i, AcOH/NaOAc; ii, $LiAlH_4$, ether; iii, CrO_3, acetone.

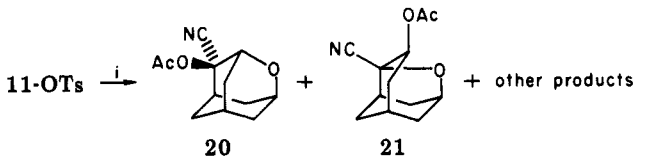
Scheme IV[a]



[a] i, AcOH/NaOAc.

(17) Some precedent for this stereoselectivity is found in the reaction of methyllithium with 9-thiabicyclo[3.3.1]nonan-2,6-dione: Vincent, J. A. J. M.; Vereyken, F. P. M.; Wauben, B. G. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 236.

Scheme V[a]



20 21

[a] i, AcOH/NaOAc.

carbons connected to oxygen that has been remarked in this system by other investigators.[18]

The assignment of anti (or exo) stereochemistry to **14** and **15** is less secure. We obtained the ^{13}C NMR spectra of the mixture of **13** and **14** in the presence of $Eu(fod)_3$ shift reagent and found that both the carbon bearing the acetate, and the carbons of the acetate group itself, experienced only minimal shifts. Since in the syn isomer the Eu might bind simultaneously to both the ether oxygen and the acetate carbonyl, and the acetate at the least would be quite close to the Eu, the absence of induced shifts was taken to imply anti stereochemistry. To confirm this point, an independent synthesis of **15** is underway.

Gas chromatographic analysis of the mixture obtained from solvolysis of **9-OTs** indicated the presence of one major (92%) and two minor (4%, 4%) components (Scheme IV). The major component was identified as **17** by comparison of its retention time and its ^{13}C NMR spectrum with those of an authentic sample.

Again, separation of the minor components in useful quantity proved impossible. Treatment of the mixtures as above and analysis of the ^{13}C NMR spectra led to the assignment of structures **18** and **19**.

Similar analysis of the mixture of products from solvolysis of **11-OTs** demonstrated the formation of **20** and **21** in a 9:1 ratio (Scheme V); these were accompanied by traces of several other substances that appear to arise by thermal decomposition of **20** and **21** at the elevated temperature of this solvolysis. These compounds, comprising together about 5% of the reaction mixture, could not be identified.

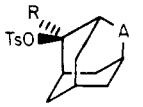
Discussion

Neighboring group participation typically announces itself in three ways: (1) the formation of rearranged products; (2) retention of stereochemical configuration in unrearranged products, inversion in rearranged ones; (3) an enhancement in the rate of reaction as compared to a closely related model compound in which participation is believed not to occur.

Our results clearly contain the first two indicators of neighboring group participation. The solvolysis products have both adamantyl and protoadamantyl skeletons. The adamantyl products (**13**, **17**, **20**) are of completely retained configuration; the protoadamantyl ones (**14**, **18**, **21**) are completely inverted.

Interpretation of the rate data is more complex. Heteroatom neighboring groups can affect the rate of reaction by inductive electron withdrawal and dipolar destabilization as well as by participation.[19] Various approaches have been tried to sort out the conflicting influences of these phenomena.[19,20] We have chosen to dodge the problem by selecting our substituents to allow variation in electron demand by the reaction center,[21] and also to allow direct comparison of the results of such variation with the behavior of the entirely carbocyclic adamantane system.

Table II. Relative Rates of Solvolysis



A	R	k_{rel}	k_R/k_H
CH_2	H	1.0	
	CH_3	1.5×10^8	1.5×10^8
	CN	2.0×10^{-3}	2.0×10^{-3}
O	H	0.6	
	CH_3	1.8×10^4	3.0×10^4
	CN	9.7×10^{-3}	1.6×10^{-2}

In Table II are presented the CH_3/H and CN/H rate ratios for 2-adamantyl and 2-oxa-4-adamantyl solvolyses, as well as oxaadamantyl/adamantyl rate comparisons. The latter reflect a distinct rate retardation by the inductive and dipolar effects of the ether oxygen. However, the relative substituent effects provide evidence of substantial anchimeric assistance in 2-oxa-4-adamantyl solvolyses.

We see that the introduction of a methyl group into 2-adamantyl produces a rate increase of more than eight powers of ten, arguably the result of converting a secondary carbocation intermediate into a tertiary one.[22] The introduction of a methyl into 2-oxa-4-adamantyl, on the other hand, facilitates solvolysis by a factor of only 3×10^4. We believe this reduction, of roughly 10^4, in the effect of methyl substitution corresponds directly to stabilization of the secondary 2-oxa-4-adamantyl carbocation by oxygen participation, thereby reducing the "demand" for methyl stabilization.[23]

Conversely, the introduction of a cyano group into 2-adamantyl produces a significant net *de*stabilization of the secondary carbocation and a corresponding rate decrease of about 2×10^{-3}. In the 2-oxa-4-adamantyl system, the cyano group produces about a 10-fold smaller rate diminution. This difference again reflects stabilization of the 2-oxa-4-adamantyl carbocation by oxygen participation. Since there appears to be significant σ-bond participation in the 2-adamantyl compound[24] however, the effect actually measured by this comparison is the relative participating ability of an ether oxygen and a carbon–carbon σ-bond. Unsurprisingly, the oxygen is more effective.

All three of the usual manifestations of neighboring group participation thus appear in the solvolyses of 2-oxa-4-adamantyl tosylates. Free of inductive and dipolar effects, *and measured in comparison to a model substrate undergoing k_c rather than k_s solvolysis*,[10] O-3 participation is shown to produce a rate enhancement of about 10^4, corresponding to nearly a 5 kcal/mol stabilization of the 2-adamantyl carbocation. Finally, the tool of varying electron demand is seen to be an especially useful way of sorting out the several influences of a neighboring heteroatom in solvolysis reactions.

Experimental Section

All NMR spectra were obtained with a Varian Associates FT-80

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(21) Brown, H. C.; Periaswamy, M. *J. Org. Chem.* **1982**, *47*, 4742.
(22) (a) Reference 2a, chapter 4. (b) Schadt, F. L.; Bentley, T. W.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.
(23) A similar use of the methyl substituent effect to measure the extent of anchimeric assistance has recently been reported: Gassman, P. G.; Doherty, M. *J. Am. Chem. Soc.* **1982**, *104*, 6408.
(24) Gassman, P. G.; Saito, K.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7613.

spectrometer, operating at 80 MHz for protons and 20 MHz for carbon-13. The solvent was $CDCl_3$ with Me_4Si as internal standard. Infrared spectra were obtained with a Perkin-Elmer 238 spectrophotometer; except for the attempts to observe intramolecular hydrogen bonding in dilute carbon tetrachloride solutions, solid compounds were run in Nujol mulls and liquids were run neat. Gas chromatographic analyses were obtained with a Shimadzu GC-Mini-2 equipped with a 1 m × 2.4 mm Apiezon L column. HPLC was run on an LDC ConstaMetric III equipped with a variable frequency ultraviolet detector, the Spectromonitor III. Melting points were obtained in sealed capillary tubes with a Hoover-Thomas melting point apparatus, and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc. Most commercial materials and reagents were obtained from Aldrich Chemical, except for the 90% butyllithium in hexane, which was supplied by Alfa Chemicals. *endo*-Bicyclo[3.3.1]non-6-ene-3-carboxylic acid was prepared according to the procedure of Spurlock.[25]

Rates of reaction in deuterioacetic acid containing 2 equiv of sodium deuterioacetate were measured according to Hanson,[27] by variable temperature ^1H NMR. The kinetics program for the FT-80 was supplied by Varian Associates. Rate constants were obtained by linear least-squares analysis of data from at least two runs. Activation parameters are based on rates at three temperatures.

Bicyclo[3.3.1]non-6-en-3-one (2). Method A. In a three-necked flask equipped with a magnetic stirring bar, a thermometer, and an addition funnel were placed dry tetrahydrofuran (THF) (100 mL) and dry diisopropylamine (36.4 g, 60.5 mL, 0.36 mol). The solution was cooled to −50 °C under dry argon, and *n*-butyllithium (90%) in hexane (35 mL, 23.2 g, 0.36 mol) was added dropwise, maintaining the temperature below 5 °C. The solution was stirred for an hour after addition was complete. To this cold solution was added 1 (20.0 g, 0.12 mol) in dry THF (100 mL) dropwise over several hours. The temperature was continued at 0–5 °C during addition and for 3 h thereafter. Using Dry Ice/acetone, the mixture was then cooled to −78 °C, the argon flow was interrupted, and dry oxygen was bubbled through the mixture for 2 h. Upon completion of the oxygen flow, the mixture was stirred overnight, and allowed to return to room temperature. After addition of 10 mL of water, stirring was continued for a further 3 h. Most of the THF was removed on the Rotovap, the residue was diluted with ether (100 mL), and the ether solution was poured into ice-cold 10% hydrochloric acid (500 mL). The ether layer was separated and combined with two additional ether extracts (100 mL each), and the combined extracts were washed successively with 10% KOH, water, and brine. Neutralization of the basic wash gave unreacted 1, which was recycled. The ether was dried over Na_2SO_4 and stripped to yield 2 (12.5 g, 92 mmol, 61% based on recovered 1).

Method B. The same procedure was followed through the oxygenation step. Then trimethyl phosphite (37.2 g, 300 mmol) was added to the mixture, which was stirred for an hour. Most of the THF was removed on the Rotovap and replaced with ether (200 mL). The ether solution was extracted thrice with 10% KOH, and these basic extracts were back extracted with ether to remove trimethyl phosphite. The KOH then was neutralized with 10% HCl, and the precipitated material was extracted into ether (3 × 100 mL). Drying and removal of the ether gave a mixture containing principally the hydroxy acid and a small amount of unreacted 1. This crude mixture was oxidized by stirring it with lead tetraacetate (88.7 g, 200 mmol) in dry benzene at room temperature for 1 h. The benzene was diluted with ether and filtered through Celite. The filtrate was washed successively with 10% KOH, water, and brine and dried over NaD_2SO_4. Removal of the solvent gave 2 (15.5 g, 113.8 mmol, 76%): mp 92–95 °C; ^{13}C NMR 210.9, 130.8, 125.6, 49.1, 46.1, 32.2, 31.2, 30.2, and 30.0; ^1H NMR 5.7 (m, 2 H), 2.69–1.78 (complex, 10 H); IR CO 1700 cm^{-1}.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.43; H, 8.95.

Bicyclo[3.3.1]non-6-en-3-ol (3 and 4). To a solution of 2 (5 g, 36.7 mmol) in anhydrous ether (100 mL) was added lithium aluminum hydride ($LiAlH_4$) (1.0 g, 26 mmol). The mixture was stirred at reflux for 8 h. Excess $LiAlH_4$ was destroyed by adding 10% NaOH dropwise, and the granular hydroxides were filtered off with suction. The filter cake was washed repeatedly with ether, and the combined ether filtrate was washed with 10% HCl and dried over Na_2SO_4. Evaporation of the solvent gave a mixture of 3 and 4 that was purified by sublimation at water pump pressure: yield, 4.8 g (34.7 mmol, 95%); mp 157–159 °C; ^{13}C NMR of 3, 135.9 (C-7), 128.6 (C-6), 67.3 (C-3), 40.0 (C-8), 38.5 (C-4), 32.8 (C-2), 31.3 (C-9), 27.7 (C-5), and 25.7 (C-1); of 4: 131.1 (C-7), 128.5 (C-6), 65.4 (C-3), 43.8 (C-8), 36.6 (C-4), 32.5 (C-2), 31.2 (C-9), 30.1 (C-5), 28.3 (C-1); ^1H NMR of the mixture 6.19–5.71 (complex, 2 H), 3.9 (m, 1 H), and 2.43–1.39 (complex, 11 H); IR OH′ 3525 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 11.58. Found: C, 78.16; H, 11.67.

***anti*-4-Bromo-2-oxaadamantane (5).** The mixture of 3 and 4 (2.5 g, 18 mmol) was dissolved in water (20 mL) and enough dioxan to give a true solution. To this solution was added freshly recrystallized *N*-bromosuccinimide (7.0 g, 39 mmol) and enough drops of concentrated H_2SO_4 to bring the pH to about 3. The mixture was stirred overnight, the pH being maintained at 3 by occasional addition of more acid. Three ether extracts (100 mL) of the solution were combined and washed with 10% $NaHSO_3$. After drying over Na_2SO_4, the ether was stripped, and the residue distilled: bp 137 °C (14 mm); yield, 3.5 g (16.1 mmol, 89%); ^{13}C NMR 67.2 (d, C-1), 71.2 (d, C-3), 56.0 (d, C-4), 34.6 (d, C-5), 29.4 (t, C-6), 25.7 (d, C-7), 36.0 (t, C-8), 38.6 (t, C-9), and 29.9 (t, C-10).

2-Oxaadamantane. To a stirred solution of 5 (2 g, 9.2 mmol) in anhydrous ether (20 mL) was added $LiAlH_4$ (1 g, 26 mmol), and the mixture was refluxed overnight. Excess $LiAlH_4$ was destroyed by dropwise addition of 10% NaOH, the granular hydroxides were filtered with suction, and the filter cake was washed with ether (3 × 50 mL). The combined ether filtrates were washed with dilute HCl and brine, dried over Na_2SO_4, and stripped. Sublimation of the residue on the steam bath at 2–5 mm gave pure 2-oxaadamantane (1.1 g, 8.0 mmol, 87%): mp 214–217 °C [lit.[26] mp 215–218 °C].

Epoxidation of Bicyclo[3.3.1]non-6-en-3-ol. To a mixture of 3 and 4 (4.0 g, 28.9 mmol) in methylene chloride (50 mL) was added a solution of *m*-chloroperbenzoic acid in methylene chloride (50 mL) dropwise with stirring, at such a rate that the temperature remained near 25 °C. Stirring was continued for 30 min after addition was complete. Excess peracid was destroyed by the addition of 10% $NaHSO_3$ (starch–iodide paper). The organic layer was separated and washed repeatedly with saturated $NaHCO_3$, with water, and with brine and dried over Na_2SO_4. Removal of the solvent gave a mixture of 6 and 7, which was not further purified (4.28 g, 27.8 mmol, 96%).

***anti*-2-Oxaadamantan-4-ol (6).** To a solution of 50% H_2SO_4 (100 mL) in an ice bath was added the mixture of 6 and 7 from the previous preparation. The solution was stirred at 0 °C for 1 h, poured into ice/water (100 mL), and extracted with ether (3 × 100 mL). The combined ether extracts were washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4, and stripped to give pure 6 (4.0 g, 25.9 mmol, 89% from 3 and 4): mp 268–273 °C; ^{13}C NMR 67.3 (d, C-1), 71.3 (d, C-3), 70.2 (d, C-4), 33.1 (d, C-5), 29.5 (t, C-6), 25.6 (d, C-7), 36.1 (t, C-8), 36.1 (t, C-9) (resolved with $Eu(fod)_3$) and 29.7 (t, C-10); ^1H NMR 4.0–3.84 (m, 3 H), 2.94 (s, 1 H), and 2.09–1.56 (complex, 10 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.15.

2-Oxaadamantan-4-one (8). An acetone (50 mL) solution of 2-oxaadamantan-4-ol (4.0 g, 25.9 mmol) was maintained at 25 °C with stirring, and 8 N chromic acid in aqueous sulfuric acid was added dropwise until the orange color persisted in the reaction mixture. After stirring for another 2 h, acetone was removed from the mixture under reduced pressure, and water (50 mL) was added. The aqueous solution was extracted with ether (2 × 75 mL), and the combined extracts were washed with saturated $NaHCO_3$ and brine, dried over $CaCl_2$, and stripped. The residue was purified by sublimation on a steam bath at 2–5 mm: yield, 3.8 g (25.4 mmol, 98%); mp 218–220 °C; ^{13}C NMR 67.3 (d, C-1), 78.0 (d, C-3), 212.6 (s, C-4), 45.8 (d, C-5), 37.8 (t, C-6), 25.8 (d, C-7), 34.7 (t,

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C-8), 39.1 (t, C-9), and 38.1 (t, C-10); ^{1}H NMR 4.10–3.99 (m, 2 H), 2.75–1.74 (complex, 10 H); IR ν_{CO} 1735 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.04; H, 8.03.

***anti*-4-Methyl-2-oxaadamantan-4-ol (9).** To a mixture of magnesium metal (2.0 g, 82 mmol) and dry ether (20 mL) was added dropwise with stirring a solution of methyl iodide (11.7 g, 82 mmol) in dry ether (10 mL). The rate of addition was chosen to maintain a gentle reflux, and the solution was refluxed for an additional 30 min after addition was complete. To this solution at room temperature was added dropwise a solution of 2-oxaadamantane-4-one (3.0 g, 19.7 mmol) in dry ether (20 mL) at such a rate that gentle reflux was maintained. After 2 additional h of reflux, the reaction mixture was poured into cold 10% H_2SO_4 (100 mL). The ether layer was separated and the aqueous layer extracted with ether (2 × 50 mL). The combined extracts were washed with 10% H_2SO_4 and brine, dried over Na_2SO_4, and stripped to give pure **9**: yield, 3.11 g (18.5 mmol, 94%); mp 108–110 °C; ^{13}C NMR 67.5 (d, C-1), 75.1 (d, C-3), 70.4 (s, C-4), 38.0 (d, C-5), 30.7 (t, C-6), 25.0 (d, C-7), 36.6 (t, C-8), 34.5 (t, C-9), 31.3 (t, C-10), and 27.0 (q, CH_3); ^{1}H NMR 3.85 (m, 1 H), 3.49 (m, 1 H), 2.85 (s, 1 H), 1.42 (s, 3 H), and 2.25–1.54 (complex, 10 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.59.

4-Cyano-2-oxaadamantan-4-ol (11 and 12). Method A. To a solution of 2-oxaadamantan-4-one (4.0 g, 26.3 mmol) in methylene chloride (20 mL) maintained under an argon atmosphere trimethylsilyl cyanide (4.0 g, 40.3 mmol) was added slowly with stirring, at room temperature. Stirring was continued for 2 days, the CH_2Cl_2 was removed under vacuum, 3 N HCl (100 mL) was added, and the mixture was stirred for another 3 h. The reaction mixture then was extracted with ether (3 × 75 mL), and the combined extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Removal of ether gave pure **11** (4.0 g, 22.3 mmol, 85%): mp 98–102 °C; ^{13}C NMR 67.3 (d, C-1), 70.8 (d, C-3), 72.0 (s, C-4), 35.6 (d, C-5), 29.1 (t, C-6), 24.4 (d, C-7), 35.4 (t, C-8), 34.6 (t, C-9), 29.3 (t, C-10), and 122.1 (s, CN); ^{1}H NMR 4.04 (m, 2 H), 3.54 (m, 1 H), 2.45–1.79 (complex, 11 H).

Anal. Calcd for $C_{10}H_{14}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.13; H, 7.28; N, 7.78.

Method B. Method A was followed, with the exception that anhydrous ZnI_2 (500 mg, 1.5 mmol) was added to the solution of **8** before addition of trimethylsilyl cyanide commenced. The product obtained in this way was a mixture of **11** and **12** (4.4 g, 24.6 mmol, 94%): ^{13}C NMR of **12** 67.6 (C-1), 70.7 (C-3), 72.6 (C-4), 35.9 (C-5), 29.1 (C-6), 24.3 (C-7), 35.4 (C-8), 29.3 (C-9), 33.0 (C-10), and 120.7 (CN).

Tosylate of 2-Oxaadamantan-4-ol (6-OTs). To a solution of **6** (2.0 g, 13.0 mmol) in dry ether (30 mL) at 0 °C under an argon atmosphere was added 1.7 M *n*-butyllithium in hexane (8.0 mL, 13.6 mmol). This mixture was stirred for 30 min and allowed to warm to 25 °C, whereupon a solution of *p*-toluenesulfonyl chloride (2.6 g, 13.6 mmol) (TsCl) in ether (10 mL) was added slowly. After stirring overnight, the LiCl precipitate was filtered with suction and the solvent was stripped. The crude tosylate was recrystallized from petroleum ether at 0 °C: yield, 3.6 g (11.7 mmol, 90%); mp 60–65 °C; ^{13}C NMR 66.9 (C-1), 68.3 (C-3), 80.0 (C-4), 31.5 (C-5), 29.6 (C-6), 25.0 (C-7), 35.5 (C-8), 36.2 (C-9), 29.9 (C-10), 21.5 (CH_3), and 130.0, 127.6, 130.4, 127.0 (Ar); ^{1}H NMR 7.86–7.32 (AA′BB′, 4 H), 3.92 (s, 2 H), 2.42 (s, 3 H), 2.69–1.71 (complex, 10 H).

Tosylate of 4-Methyl-2-oxaadamantan-4-ol (9-OTs). The procedure for **6-OTs** was followed employing 3.0 g (17.6 mmol) of **9**, 11.2 mL (19.0 mmol) of *n*-butyllithium solution, and 3.6 g (19.0 mmol) of TsCl: yield, 5.0 g (15.5 mmol, 88%); mp (from petroleum ether) 52–56 °C; ^{13}C NMR 67.4 (C-1), 72.7 (C-3), 92.7 (C-4), 36.2 (C-5), 30.8 (C-6), 24.6 (C-7), 36.9 (C-8), 34.6 (C-9), 31.5 (C-10), 22.9 (CH_3), 21.4 ($ArCH_3$), and 144.0, 137.2, 129.7, 127.0 (Ar); ^{1}H NMR (CD_3COOD) 7.84–7.30 (AA′BB′, 4 H), 3.92 (m, 2 H), 2.39 (s, 3 H), 1.76 (s, 3 H), 2.66–1.41 (complex, 10 H).

Tosylate of 4-Cyano-2-oxaadamantan-4-ol (11-OTs). The procedure of **6-OTs** was repeated with 4.0 g (22.3 mmol) of **11**, 14.2 mL (24.0 mmol) of *n*-butyllithium solution, and 4.8 g (24.0 mmol) of TsCl: yield, 6.0 g (18.0 mmol, 81%); mp (from petroleum ether) 77–80 °C; ^{13}C NMR 66.8 (C-1), 70.9 (C-3), 80.3 (C-4), 32.9 (C-5), 29.0 (C-6), 24.0 (C-7), 35.6 (C-8), 34.8 (C-9), 32.9 (C-10), 21.6 ($ArCH_3$), 116.7 (CN), and 145.4, 134.3, 29.9, 127.8 (Ar); ^{1}H NMR (CD_3COOD) 7.94–7.36 (AA′BB′, 4 H), 4.34 (s, 1 H), 3.99 (s, 1 H), 2.44 (s, 3 H), 2.75–1.59 (complex, 10 H).

Preparative solvolyses employed 6.5 mmol of the tosylate, and 13 mmol of anhydrous NaOAc in freshly distilled AcOH, heated with exclusion of moisture at a temperature appropriate to the rate of solvolysis for a period equivalent to 10 half-lives. The reaction mixture then was poured into ice–water, extracted with ether (3 × 50 mL), and the combined extracts washed with water and brine and dried over $NaDSO_4$. Solvent was stripped and the residue injected into the gas or liquid chromatograph. Material balances were >98%: ^{13}C NMR of **13** 67.1 (C-1), 70.0 (C-3), 72.6 (C-4), 36.0 (C-5), 29.8 (C-6), 25.6 (C-7), 36.0 (C-8), 33.8 (C-9), 30.8 (C-10), 21.0 (CH_3), and 169.0 (CO); ^{13}C NMR of **14** 76.1 (C-1), 33.7 (C-2), 29.8 (C-3), 40.5 (C-4), 68.1 (C-5), 76.7 (C-6), 27.6 (C-7), 39.9 (C-8), 25.6 (C-10), 20.0 (CH_3), 169.9 (CO); ^{13}C NMR of **17** 67.5 (C-1), 72.1 (C-3), 81.7 (C-4), 36.3 (C-5), 33.8 (C-6), 24.7 (C-7), 30.7 (C-8), 34.9 (C-9), 31.4 (C-10), 169.8 (CO), 22.1 (CH_3), 21.8 (CH_3CO); ^{13}C NMR of **18** 75.1 (C-1), 36.0 (C-2), 33.2 (C-3), 45.0 (C-4), 70.4 (C-5), 82.6 (C-6), 32.8 (C-7), 44.0 (C-8), 25.6 (C-10), 170.8 (CO), 22.1 (CH_3), 21.8 (CH_3CO); ^{13}C NMR of **20** 70.0 (C-1), 70.3 (C-3), 92.6 (C-4), 35.1 (C-5), 29.7 (C-6), 26.4 (C-7), 33.5 (C-8), 34.5 (C-9), 32.2 (C-10), 170.0 (CO), 121.8 (CN), 21.3 (CH_3); ^{13}C NMR of **21** 76.1 (C-1), 38.0 (C-2), 36.9 (C-3), 42.7 (C-4), 72.8 (C-5), 95.8 (C-6), 32.6 (C-7), 41.2 (C-8), 26.4 (C-10), 174.1 (CO), 121.8 (CN), 21.3 (CH_3).

Reduction of 13 and 14. Lithium aluminum hydride (250 mg, 6.6 mmol) was added to the mixture of acetates (500 mg, 2.6 mmol) from preparative solvolysis in dry ether (10 mL). The mixture was refluxed overnight, and excess $LiAlH_4$ was destroyed by dropwise addition of 10% NaOH solution. The salts were filtered with suction and the filtrate was washed with dilute H_2SO_4 and brine and dried over Na_2SO_4. The residue remaining when solvent was stripped was sublimed at water pump pressure: yield, 380 mg (96%) of a mixture of **6** and **15**; ^{13}C NMR of **15** 76.2 (C-1), 33.3 (C-2), 29.6 (C-3), 40.5 (C-4), 70.2 (C-5), 79.5 (C-6), 38.4 (C-7), 39.9 (C-8), and 30.3 (C-8), and 30.3 (C-10).

Oxidation of 6 and 15. To a stirred solution of the mixture of **6** and **15** (300 mg, 1.95 mmol) in acetone (10 mL) was added 8 N chromic acid dropwise until the orange color persisted. This solution was stirred at room temperature for a further 2 h, when most of the solvent was removed on the Rotovap. Water (20 mL) was added, and the aqueous solution was extracted with ether (2 × 25 mL). The combined ether extracts were washed with saturated $NaHCO_3$ and dried over $CaCl_2$. The solvent was stripped and the residue was sublimed at reduced pressure: yield, 290 mg (97%) of a mixture of **8** and **16**; ^{13}C NMR of **16** 78.3 (C-1), 32.3 (C-2), 29.7 (C-3), 44.7 (C-4), 211.8 (C-5), 83.1 (C-6), 38.8 (C-7), 39.8 (C-8), and 32.3 (C-10).

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