Properties of α-Keto Cations. Facile Generation under Solvolytic Conditions

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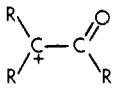
Abstract: α-Keto mesylates **2–10** have been prepared. In a variety of solvents, they undergo solvolysis under relatively mild conditions. Product and rate data implicate the intermediacy of tertiary α-keto cations in the solvolyses of **2–6** and secondary benzylic α-keto cations in the solvolyses of **7–10**. On acetolysis, mesylate **2** gave the Wagner–Meerwein rearrangement product **35** and the product of 1,3-hydride shift, **34**, along with the elimination product, **33**. A labeling study on **2**-d_2 showed proton loss from the α-keto cation, **36**, occurred largely before Wagner–Meerwein rearrangement. Mesylate **5** gave mainly the elimination product **57**, while mesylate **6** gave mainly the substitution product **61**. Mesylates **7–10** gave unrearranged substitution products under all conditions. Optically active **9** gave completely racemic products in trifluoroacetic acid and hexafluoroisopropyl alcohol and an 11% enantiomeric excess of inverted product in acetic acid. These products are inconsistent with neighboring group participation mechanisms and in line with the α-keto cation mechanism. Analysis of solvolysis rates of **2–10** led to the conclusion that the electron-withdrawing carbonyl group has a negligible rate-retarding effect relative to hydrogen. This has been interpreted in terms of stabilizing conjugative effect which offsets the inductive destabilizing effect of the carbonyl group.

Studies describing the generation and properties of carbocations substituted with potent electron-withdrawing groups have begun to appear in the recent literature. We have described studies on cations where the electron-withdrawing group, E, is the dimethyl ketal[1] (E = $C(OCH_3)_2R$). We have also initiated studies on carbonyl-substituted cations of type **1**[2,3] where E = COR.



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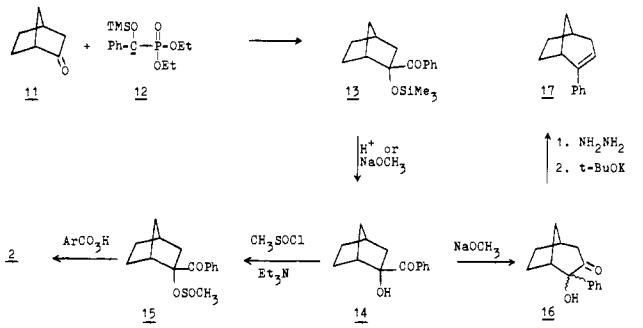
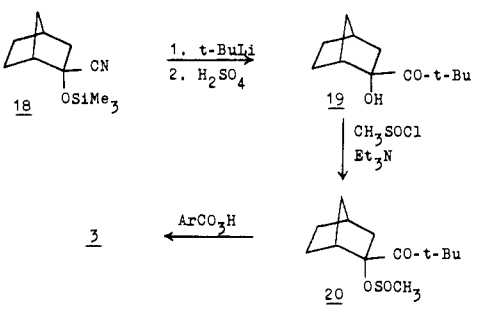
Charpentier-Morize[3] has also studied carbonyl-substituted carbocations and this work has recently been summarized. Gassman[4] and Olah[5] have described the chemistry of α-cyano cations (E = CN). Tidwell[6] and Liu[7] have investigated trifluoromethyl-substituted cations (E = CF_3). The studies have all firmly established the viability of electronegatively substituted carbocations.[8]

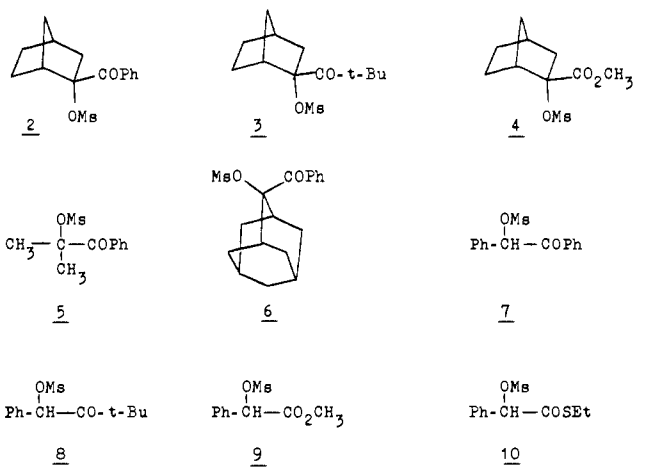
In a recent communication,[2b] we described the solvolytic chemistry of mesylate **2**. Solvolysis occurred more rapidly than expected. The possibility of stabilization of the cationic intermediate by carbonyl conjugation was considered. We now report details on the chemistry of **2** as well as the preparation and chemistry of mesylates **3–10**. These studies were designed to further demonstrate the viability of α-keto cations and to determine the properties of such cations under solvolytic conditions. A further evaluation of carbonyl conjugation as a cation-stabilizing feature is presented.

Scheme I



Scheme II





(1) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4231–4238.

(2) (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–3945. (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–2465.

(3) Bēguē, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207–212.

(4) (a) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214–1216. (b) Gassman, P. G.; Talley, J. J. *Ibid.* **1980**, *102*, 4138–4143. (c) Gassman, P. G.; Saito, K.; Talley, J. J. *Ibid.* **1980**, *102*, 7613–7615.

(5) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *J. Am. Chem. Soc.* **1980**, *102*, 6640–6641.

(6) (a) Koshy, K. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 1216–1218. (b) Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *Ibid.* **1981**, *103*, 3863–3867. (c) Allan, A. D.; Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 207–211.

(7) (a) Liu, K.-T.; Sheu, C.-F. *Tetrahedron Lett.* **1980**, 4091–4094. (b) Liu, K.-T.; Kuo, M.-Y.; Shu, C.-F. *J. Am. Chem. Soc.* **1982**, *104*, 211–215.

(8) Earlier studies by Lambert et al., where incipient cationic centers are substituted with the electron-withdrawing β-acetoxy and β-tosyloxy groups, have been summarized. See: Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979**, *12*, 317–324.

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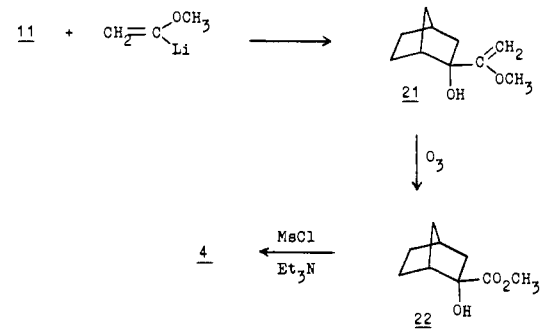
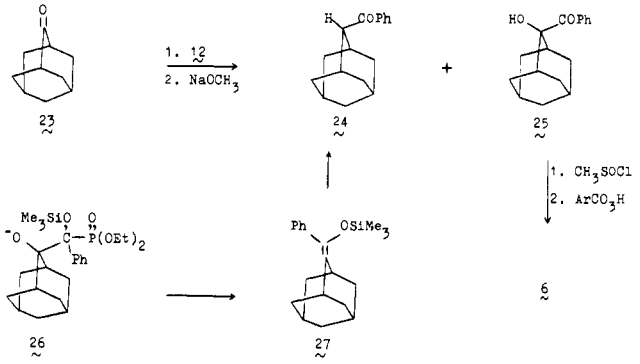
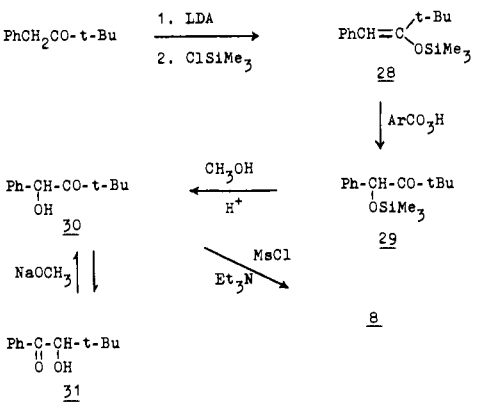
Scheme III



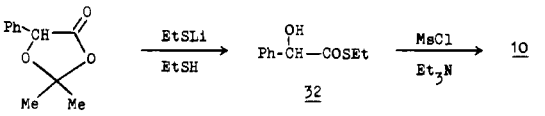
Scheme IV



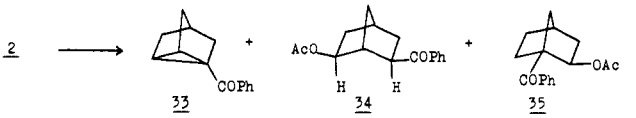
Scheme V



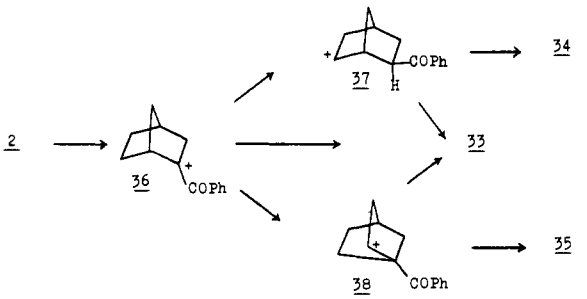
Scheme VI



Scheme VII



Scheme VIII



Results and Discussion

Synthetic Aspects. Mesylate **2** was prepared as shown in Scheme I. Treatment of norcamphor with **12**, an acyl anion equivalent recently introduced by Zimmer,[9] gave the protected hydroxy ketone **13**. Removal of the trimethylsilyl group to give **14** could be accomplished under either acidic or basic conditions. More vigorous treatment of **14** with base (reflux with sodium methoxide) led to rearrangement to **16** via the ketol rearrangement.[10] The structure of this ring-expanded product, **16**, was established by conversion to 2-phenylbicyclo[3.2.1]oct-2-ene, **17**, by treatment with hydrazine followed by potassium *tert*-butoxide in Me_2SO. This established the location of the phenyl group and indicated that only **16** and no 3-hydroxy-3-phenylbicyclo-[3.2.1]octan-2-one was produced by rearrangement of **14**.

Conversion of **14** to mesylate **2** with standard procedures (mesyl chloride in pyridine[11] or mesyl chloride–triethylamine[12] in methylene chloride) was unsuccessful. Alcohol **14** was recovered unchanged. Attempts to convert **14** to the *p*-toluenesulfinate ester for potential oxidation to the tosylate, according to the Coates procedure,[13] were also unsuccessful. The procedure which successfully converted **14** to the mesylate involved treatment of **14** with CH_3SOCl and triethylamine[14] to give the methanesulfinate ester **15**. Oxidation of **15** with *m*-chloroperbenzoic acid proceeds smoothly to give mesylate **2**.

Mesylate **3** was prepared as shown in Scheme II. The silated cyanohydrin **18** was treated with *tert*-butyllithium and the adduct hydrolyzed under acidic conditions. Again, it was necessary to convert alcohol **19** to the sulfinate ester **20**, followed by peracid oxidation, in order to convert the alcohol function to a suitable leaving group.

Mesylate **4** was prepared as shown in Scheme III. Addition of α-methoxyvinyllithium to norcamphor, according to Baldwin's procedure,[15] gave **21**. Ozonolysis of **21** gave the desired α-hydroxy ester **22**. The overall transformation represents addition of the acyl anion formally derived from methyl formate ($^-CO_2CH_3$) to a carbonyl group. This extension of Baldwin's methodology should compliment the present method for carrying out this conversion which involves cyanohydrin hydrolysis followed by esterification.[16]

The preparation of the alcohol precursor to mesylate **5** from acetone and **12**, followed by hydrolysis, was straightforward. The mesylate **5** was prepared by the methyl sulfinate–peracid oxidation method, as this procedure gave a cleaner product than the Servis procedure.

Addition of **12** to adamantanone (Scheme IV) was complicated by the formation of a side product, ketone **24**. This product presumably arises from hydrolysis of the silyl enol ether **27**, derived from a Wittig-type reaction of **12** with adamantanone. This Wittig-type reaction of **12** has not been observed previously.[9] Presumably intramolecular transfer of the trimethylsilyl group to oxygen is more rapid than attack at phosphorus under normal

(9) (a) Koenigkramer, R. E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994–3998. (b) Koenigkramer, R. E.; Zimmer, H. *Tetrahedron Lett.* **1980**, 1017–1020.

(10) For discussions of this general rearrangement, see: (a) Nickon, A.; Nishida, T.; Lin, Y. *J. Am. Chem. Soc.* **1969**, *91*, 6860–6861. (b) Eastham, J. F.; Huffaker, J. E.; Raaen, V. F.; Collings, C. J. *Ibid.* **1956**, *78*, 4323–4328. (c) Curtin, D. Y.; Leskowitz, S. *Ibid.* **1951**, *73*, 2633–2636. (d) Mazur, Y.; Nussin, M. *Tetrahedron Lett.* **1961**, 817–821. (e) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

(11) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235–241.

(12) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.

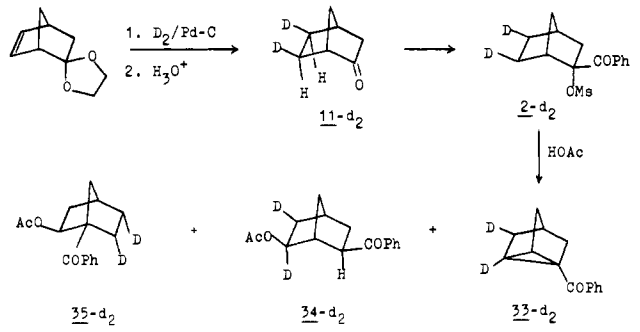
(13) Coates, R. M.; Chen, J. E. *Tetrahedron Lett.* **1969**, 2705–2707.

(14) Alcohol **14** does not react with CH_3SOCl until triethylamine is added. However, cyclohexanol-OD gave an undeuterated sulfinate ester. This is inconsistent with $CH_2{=}SO$ as an intermediate.

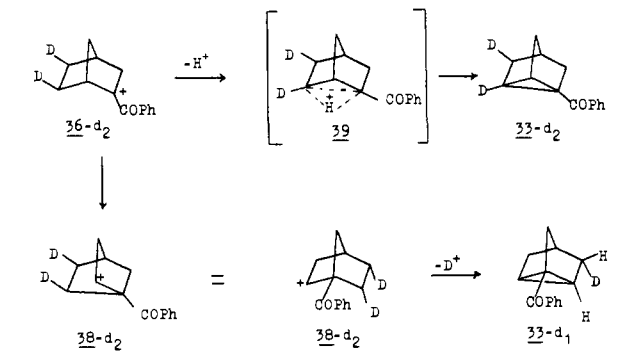
(15) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125–7127.

(16) For a representative example of the cyanohydrin hydrolysis method, see: Corson, B. B.; Dodge, R. A.; Harris, S. A.; Jeaw, J. S. "Organic Synthesis"; Wiley, New York, 1941; Collect. Vol. I, pp 336–340.

Scheme IX



Scheme X



circumstances and hence **12** can function as a benzoyl anion equivalent. However, silicon transfer to oxygen in **26** is apparently slowed due to the hindered nature of this intermediate. This allows the competing Wittig reaction to occur. The hydroxy ketone product **25** was separated from **24** and converted to the mesylate by the methyl sulfinate ester–peracid oxidation method.

Mesylates **7** and **9** were prepared by the respective reactions of benzoin and methyl mandelate, using the Servis procedure. The alcohol precursor to mesylate **8** was prepared as shown in Scheme V. Silation of benzyl *tert*-butyl ketone gave **28**. Peracid oxidation of **28**[17] gave **29** which was desilated under mild acid conditions. Under strongly basic conditions, desilation of **29** is complicated by equilibration of **30** with ketol **31**. Conversion of **30** to the mesylate **8** was straightforward.

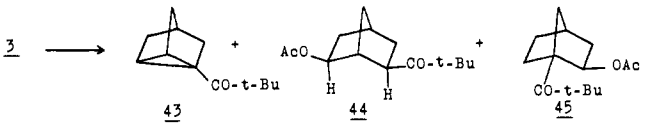
Mesylate **10** was prepared (Scheme VI) by cleavage of the acetonide of mandelic acid with ethenethiolate in THF followed by conversion of **32** to the mesylate, using the Servis procedure.

Solvolytic Studies. Solvolysis of mesylate **2** in acetic acid gave a 96% yield of a mixture of **33**, **34**, and **35** in a 64:12:24 ratio. These products are all stable under the reaction conditions. In trifluoroacetic acid and trifluoroethanol, products of the same general structure are seen. In terms of mechanism (Scheme VIII) these products imply the discrete intermediacy of the α-keto cation **36**. This cation lives long enough to undergo a 1,3-hydride shift to give **37**, the source of acetate **34**. Alternatively, **36** can undergo Wagner–Meerwein rearrangement to the secondary cation **38**, the source of acetate **35**. The endo stereochemistry of the mesylate leaving groups in **2** precludes concerted ionization, hydride shift or concerted ionization, and Wagner–Meerwein rearrangement. Hence **36** must have a finite lifetime in this solvolytic process.

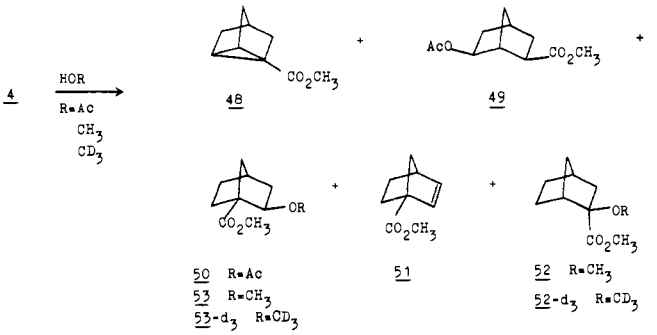
Tricyclic ketone **33** can potentially arise from proton loss from either **36**, **37**, or the rearranged ion **38**. Labeled mesylate, **2**-d_2, was prepared from labeled norcamphor, **11**-d_2, to shed light on the origin of this major product. Acetolysis of **2**-d_2 gave a tricyclic ketone product which contains 1.72 D/molecule. The tricyclic ketone had therefore retained most of the deuterium and was assigned structure **33**-d_2 on the basis of ^{1}H and ^{13}C NMR spectra.

(17) For examples of this general transformation, see: (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319–4322. (b) Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19–21. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427–3429.

Scheme XI

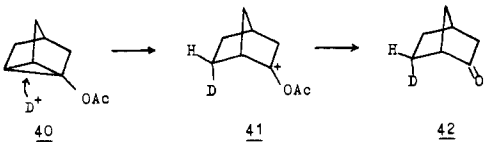


Scheme XII



The α-keto cation **36**-d_2, derived from **2**-d_2, can, in principle, lose either the exo D^+ or endo H^+. It is suggested that loss of endo H^+ is seen for the following reason. By microscopic reversibility, the formation of a cyclopropane from **36**-d_2 can proceed via only one edge-protonated cyclopropane, namely **39**. (Loss of exo D^+ is the microscopic reverse of deuteration of **33**-d_1 to give the β-keto cation **38**-d_2.) This requires that the endo H^+ be removed in cyclopropane formation from **36** or **36**-d_2. Similar arguments apply to proton loss from **37**.

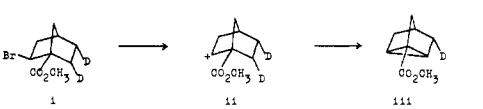
The idea behind this suggestion comes from the work of Nickon[18] which shows endo deuterium incorporation on reaction of tricyclic acetate **40** with D_3O^+. This is readily explained in terms of preferred interaction of the deuterium with the electron-rich edge of the bent cyclopropane bond. Microscopic reversibility therefore suggests that formation of a cyclopropane from a norbornyl cation such as **41** would involve only loss of the endo proton (deuterium).[19]



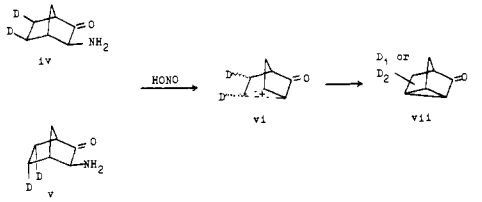
If the source of tricyclic ketone **33** were the rearranged cation **38**, then the endo D^+ would be lost from the labeled cation **38**-d_2.

(18) Nickon, A.; Lambert, J. L.; Williams, R. O.; Werstuik, N. H. *J. Am. Chem. Soc.* **1966**, *88*, 3354–3358.

(19) In support of this suggestion, Werstiuk has seen loss of *endo*-deuterium in solvolysis of i. See: Werstiuk, N. H. *Can. J. Chem.* **1975**, *53*,

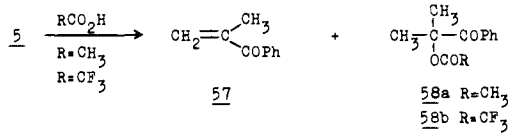


26–40. A related labeling study on iv and v has recently been reported by Edwards. It is suggested that the nortricyclanone, vii, arises from a nonclassical ion vi. See: Edwards, O. E.; Dixon, J.; Elder, J. W.; Kolt, R. J.;



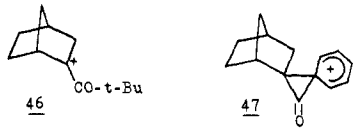
Lesage, M. *Can. J. Chem.* **1981**, *59*, 2096–2115. See also: Collins, C. J.; Glover, I. T.; Eckart, M. D.; Raaen, N. J.; Benjamin, B. M.; Benjaminov, B. S. *J. Am. Chem. Soc.* **1972**, *94*, 899–908 for a related labeling study.

Scheme XIII



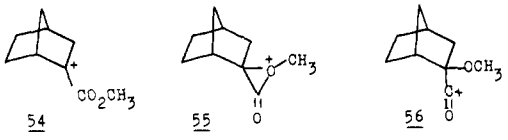
Little **33**-d_1 is seen. Therefore the tricyclic ketone must arise predominantly from proton loss from the α-keto cation **36** (or **36**-d_2) *before* Wagner–Meerwein rearrangement to **38** (or **38**-d_2).

Solvolysis of mesylate **3** in acetic acid (Scheme XI) gave 92% of **43**, **44**, and **45** in a 73:13:14 ratio. These products are analogous to those derived from **2**. They can all be ultimately derived from the α-keto cation **46** by processes similar to those suggested for **36**. The similar behavior of mesylates **2** and **3** suggests similar cationic intermediates and argues against involvement of a bridged ion such as **47** in the solvolysis of **2**. Such a bridged intermediate cannot be derived from **3**.



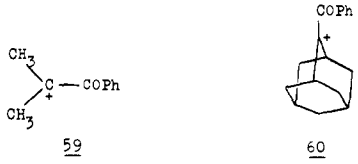
Acetolysis of mesylate **4** gave **48**–**51**, which can all be derived from the α-carbomethoxy cation **54**. A labeling study on *exo*-5,6-dideuterio-*exo*-2-carbomethoxy-*endo*-2-norbornyl mesylate (**4**-d_2) gave results completely analogous to those from the study on **2**-d_2. Acetolysis of **4**-d_2 gave a tricyclic ester which contained 1.76 D/molecule. Therefore the ester **48** arises predominantly from proton loss from **54** before Wagner–Meerwein rearrangement.

Further evidence for the discrete intermediacy of the α-keto cation **54** was obtained when the solvolysis of **4** was carried out in methanol. In this more nucleophilic solvent, 16% of the unrearranged product **52** is produced. When methanol-d_3 was used as solvent, deuterated methoxy esters **52**-d_3 and **53**-d_3 were isolated. These methanolysis products can all be ultimatley derived from ion **54**. They rule out neighboring methoxy participation leading to ions such as **55** and **56**. In methanol, which is more



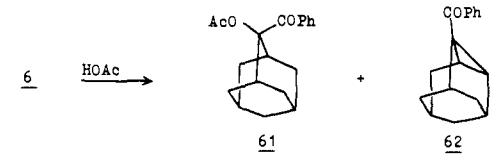
nucleophilic than acetic acid, some capture of **54** could occur before rearrangement and account for the unrearranged product **52**. It is also possible that **52** could be derived from a competing k_s process.

The propensity for rearrangement of the cations derived from mesylates **2**, **3**, and **4** is large. Information on the behavior of systems where Wagner–Meerwein rearrangement is less favorable was therefore desired. Mesylate **5** represents such a system. Solvolysis in acetic acid or trifluoroacetic acid gave mainly (90–93%) the elimination product **57** along with smaller amounts (6–7%) of the substitution product, **58**. The products are suggested to arise from the α-keto cation **59**. The propensity of this cation to suffer proton elimination is similar to that of the analogous α-cyano cation[4c] and α-trifluoromethyl cation[6b] which give exclusive elimination products.

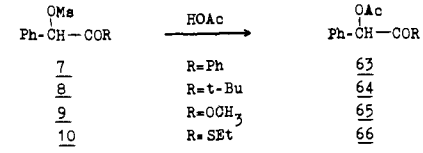


The behavior of mesylate **5** contrasts with that of mesylate **6**. Acetolysis of **6** gave mainly the substitution product **61** along with smaller amounts of **62**. Apparently the unstrained adamantyl

Scheme XIV



Scheme XV



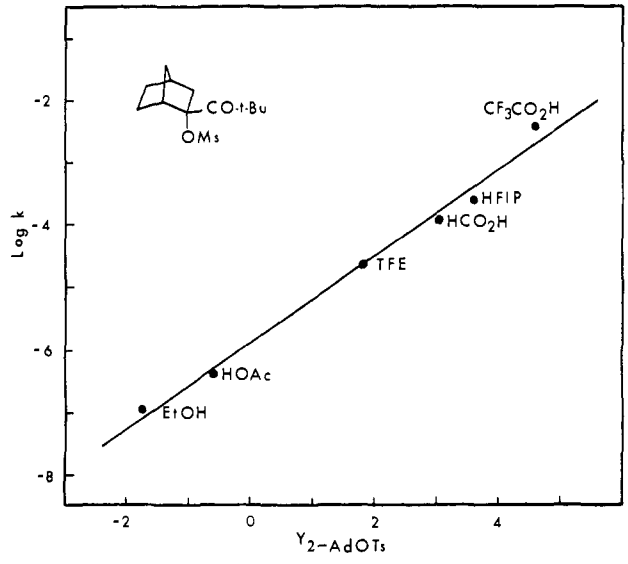
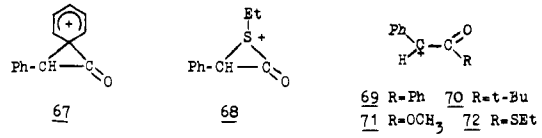


Figure 1. A plot of log k for the solvolysis of **3** in various solvents vs. log (k/k_0) for the solvolysis of 2-adamantyl tosylate ($Y_{2\text{-AdOTs}}$).

cationic intermediate **60**[20] shows little propensity to rearrange via a 1,2-alkyl shift (which would give a more strained system). 1,2 Elimination to give an adamantene is also prohibitive. However, 1,3 elimination, to give **62**, can occur.

Acetolysis of mesylates **7**–**10** gave exclusively the corresponding acetate product. In no case is any rearrangement seen. Even in nonnucleophilic highly ionizing solvents such as trifluoroethanol, formic acid, hexafluoroisopropyl alcohol, and trifluoroacetic acid mesylate **7** gave only unrearranged products. Mesylate **10**, which contains the thioethoxy group, an extremely good participating group,[21] gave no rearranged products, even in the nonnucleophilic trifluoroethanol solvent. These results are inconsistent with the involvement of bridged ions such as **67** and **68** and imply the involvement of discrete secondary benzylic cations of the type **69**–**72**.

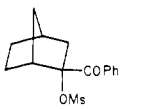
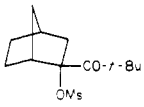
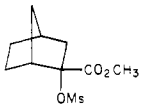
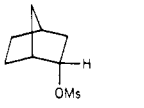
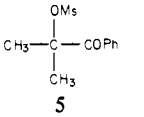
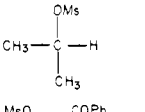
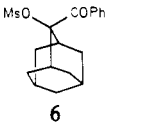
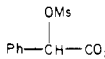


The Effect of Solvent on Solvolysis Rates. Solvolysis rate data for mesylates **2**–**10** in various solvents are given in Table I. Data for mesylates **3**, **7**, and **9** are presented graphically in Figures 1, 2, and 3. Rates of solvolysis of **3**, **7**, and **9** are correlated vs. rates of solvolysis of 2-adamantyl tosylate, a secondary substrate which

(20) This cation has been generated and arylated with benzene. See ref 4.

(21) For leading references, see: Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45–111.

Table I. Solvolysis Rates in Various Solvents

compound	solvent[b]	T, °C	k,[a] s^{-1}	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
 2	HOAc	100.0	2.14×10^{-4}		
		80.0	2.41×10^{-5}	27.8	−1.2
		25.0[c]	1.35×10^{-8}		
	CF_3CO_2H	25.0	1.3×10^{-4}		
 3	EtOH	90.0	3.08×10^{-4}		
		70.0	3.69×10^{-5}	25.6	−4.6
		25.0[c]	1.11×10^{-7}		
	HOAc	80.0	4.06×10^{-4}		
		60.0	4.27×10^{-5}	25.6	−1.8
		25.0[c]	4.05×10^{-7}		
	CF_3CH_2OH	25.0	2.26×10^{-5}		
	HCO_2H	25.0	1.16×10^{-4}		
	$(CF_3)_2CHOH$	25.0	2.50×10^{-4}		
	CF_3CO_2H	25.0	3.9×10^{-3}		
 4	HOAc	110.4	7.11×10^{-5}		
		90.0	8.50×10^{-6}	28.1	−4.9
		25.0[c]	1.45×10^{-9}		
	HOAc	95.0	4.37×10^{-4}		
		75.0	5.74×10^{-5}	25.2	−6.0
		25.0[c]	1.10×10^{-7}		
 5	HOAc	100.0	2.39×10^{-4}		
		75.0	1.44×10^{-5}	28.3	0.3
		25.0[c]	1.30×10^{-8}		
	CF_3CO_2H	25.0	3.8×10^{-5}		
	HOAc	25.0	(8×10^{-8})[e]		
	CF_3CO_2H	25.0	5.6×10^{-5}		
 6	HOAc	70.0	5.86×10^{-4}		
		50.0	4.62×10^{-5}	27.3	6.1
		25.0[c]	1.20×10^{-6}		
	HOAc	100.0	1.37×10^{-4}		
		80.0	1.49×10^{-5}	28.3	−0.7
		25.0[c]	7.32×10^{-9}		
 7	EtOH	90.0	2.43×10^{-4}		
		70.0	4.77×10^{-5}	19.4	−21.9
		25.0[c]	5.61×10^{-7}		
	HOAc	90.0	2.29×10^{-4}		
		70.0	2.45×10^{-5}	27.0	−1.3
		25.0[c]	5.41×10^{-8}		
	CF_3CH_2OH	25.0	1.82×10^{-5}		
	HCO_2H	25.0	1.15×10^{-4}		
	$(CF_3)_2CHOH$	25.0	4.45×10^{-4}		
	CF_3CO_2H	25.0	3.1×10^{-3}		
 8	HOAc	90.0	2.87×10^{-4}		
		70.0	3.27×10^{-5}	26.2	−3.0
		25.0	8.59×10^{-8}		
 9	HOAc	110.0	2.62×10^{-4}		
		90.0	3.66×10^{-5}	26.4	−6.4
		25.0	1.02×10^{-8}		
	HCO_2H	25.0	2.65×10^{-5}		
	$(CF_3)_2CHOH$	25.0	4.61×10^{-5}		
	CF_3CO_2H	25.0	2.1×10^{-4}		
	$(CF_3)_2CHOH$[d,f]	25.0	1.76×10^{-4}		
	CF_3CO_2H[d]	25.0	1.72×10^{-3}		
 10	HOAc	100.0	1.41×10^{-4}		
		80.0	2.20×10^{-5}	23.6	−13.3
		25.0	3.75×10^{-8}		
$PhCH_2OMs$	$(CF_3)_2CHOH$	25.0	9.23×10^{-3}		

[a] Standard deviations are ±2% for titrimetric rates, ±10% for rates in CF_3CO_2H (by NMR), and ±5% for polarimetric rates. [b] HOAc; 0.05 M NaOAc + 1% acetic anhydride in acetic acid. CF_3CO_2H; 0.2 M CF_3CO_2Na + 1% trifluoroacetic anhydride in CF_3CO_2H. EtOH; 0.025 M 2,6-lutidine in ethanol. CF_3CH_2OH; 0.025 M triethylamine in 100% trifluoroethanol. HCO_2H; 0.05 M HCO_2Na in formic acid. $(CF_3)_2$-CHOH; 0.05 M Et_3N in 97% hexafluoroisopropyl alcohol–3% water. [c] Extrapolated value. [d] Polarimetric rate constant. [e] Estimated from the tosylate rate. See ref 22c. [f] 0.12 M 2,6-lutidine in 100% hexafluoroisopropyl alcohol.

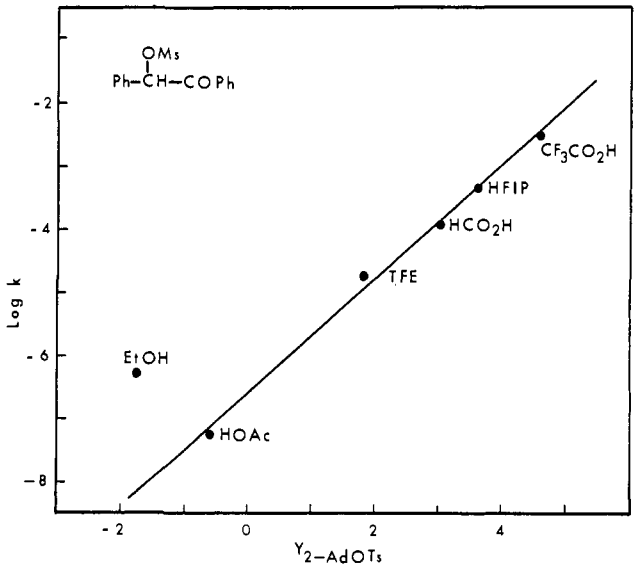


Figure 2. A plot of log k for the solvolysis of **7** in various solvents vs. $Y_{2\text{-AdOTs}}$.

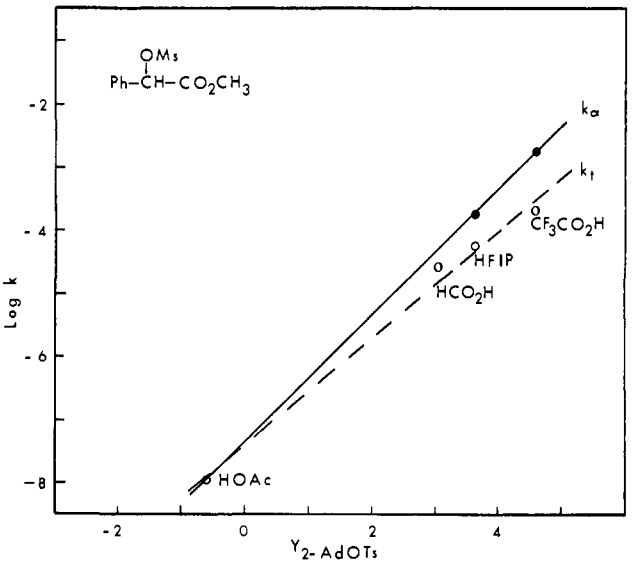
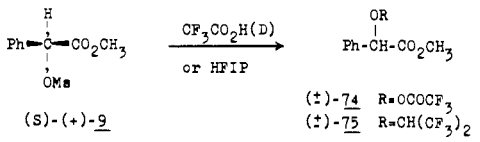


Figure 3. A plot of log k for the solvolysis of **9** in various solvents vs. $Y_{2\text{-AdOTs}}$.

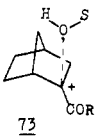
Schleyer[22] suggests undergoes solvolysis by a limiting (k_c) mechanism. Good correlations are seen despite the large structural differences between these mesylates and 2-adamantyl tosylate. The m_{OTs}[23] value for mesylate **3** is 0.69 (r = 0.994). m_{OTs} values

Scheme XVI



of 0.77 and 0.67 can be calculated for mesylates **2** and **5** with the limited data in acetic and trifluoroacetic acids. These data suggest that solvolyses of **2**, **3**, and **5** lead to transition states having a large amount of cationic character, but are not completely limiting. A small amount of nucleophilic solvent participation may be involved. However, the product studies indicate that *cationic intermediates are involved* which can subsequently rearrange.

The nature of the solvent involvement in solvolyses where m values are somewhat less than unity has been a topic of recent interest. Schleyer and Bentley[24] have recently suggested a mechanism, termed S_N2 (intermediate), in which there is evidence for cationic intermediates, but also evidence for nucleophilic solvent involvement. If one accepts the S_N2 (intermediate) concept advanced by Schleyer and Bentley, then solvolyses of **2** and **3** would fall into this mechanistic category. However, our studies show that nucleophilic solvent involvement in **2**, **3**, and **4** is not important enough to prevent Wagner–Meerwein rearrangement or 1,3-hydride shifts or to give unrearranged products. If one accepts that solvolyses of **2** and **3** involve an intermediate represented by **73** (as suggested by Schleyer and Bentley for substrates where m_{OTs} is somewhat less than unity), then the degree of bonding to solvent cannot be large.[25]



73

The solvolysis of mesylate **7** can be classified as virtually limiting (a k_c process involving the α-keto cation **69**) on the basis of the m_{OTs} value of 0.91 (r = 0.997). The deviation from the line exhibited in ethanol suggests that in this more nucleophilic solvent, nucleophilic solvent involvement becomes more important. The entropy of activation in ethanol (−21.9 eu) is also not in line with a k_c process. If one assumes that the solvolysis of mesylate **7** is completely limiting in the extremely nonnucleophilic but highly ionizing trifluoroacetic acid solvent, then Schleyer has developed a method for calculating minimum k_s/k_c values. The minimum k_s/k_c value for **7** in ethanol is 380. This compares to k_s/k_c values of close to unity for the other solvents where solvolyses are close to limiting.

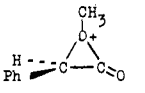
The solvolysis of mesylate **9** also appears to be limiting based on the solvent-effect study (Figure 3). The m_{OTs} value of 0.87 based on solvolysis rates (k_t) is actually larger if one considers racemization rates (k_α) of the optically active mesylate to be a truer measure of ionization rates. The m_{OTs} value based on k_α is 1.0 and suggests formation of the α-carbomethoxy cation **65** without nucleophilic solvent assistance.

Studies on Optically Active Mesylate (*S*)-(+)-9. Optically active mesylate (*S*)-(+)-**9** could be prepared from (*S*)-(+)-mandelic acid. Trifluoroacetolysis of this mesylate gave completely racemic trifluoroacetate **74**. Racemization is not a result of acid-(or base) catalyzed enolization of (+)-**9**. No deuterium is incorporated when mesylate **9** is solvolyzed in CF_3CO_2D. Additionally, optically active (+)-**74** could be prepared and was found to completely retain its activity under the reaction conditions. Solvolysis of optically active (+)-**9** in hexafluoroisopropyl alcohol also gave completely racemic product **75**. When the solvolysis of (+)-**9** was monitored polarimetrically, racemization rates (k_α) were found to exceed product formation rates (k_t) by factors of 8.2 and 3.8 in CF_3CO_2H and HFIP, respectively.

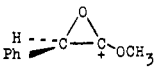
Acetolysis of (*S*)-(+)-**9** gave an 11% enantiomeric excess of the *inverted* acetate (*R*)-(−)-**65**. No deuterium incorporation was observed when solvolysis was carried out in CH_3CO_2D, arguing against an enolization mechanism accounting for the partially racemized product. As before, optically active acetate (+)-**65** was found to completely retain its activity under the solvolysis conditions.

These studies are completely consistent with the intermediacy of the α-keto cation **71** in the solvolyses of **9**. Internal return at an ion-pair stage results in racemization occurring at a faster rate than solvolysis in trifluoroacetic acid and HFIP. The slight excess of inverted (−)-**65** produced in acetic acid suggests a shorter cation lifetime in this more nucleophilic solvent. Solvent capture probably occurs at an earlier ion-pair stage and is slightly more probable from the side opposite the mesylate leaving group in the ion pair.

These studies on (+)-**9** completely rule out any participation in the solvolysis. Participation of neighboring methoxy to give an ion such as **76** would result in a product of retained configuration, not racemization (if solvent attack were to occur at the benzylic carbon). Participation of the carbonyl nonbonding



76



77

electrons to give **77** would also result in net retention of configuration in solvolysis products. Intermediates such as **76** and **77** are also inconsistent with the slight excess of inverted acetate, (*R*)-(−)-**65**, formed on acetolysis of (+)-**9**. The α-keto cation mechanism is in complete accord with the studies on optically active (+)-**9**.

The Effect of the Carbonyl Group on Solvolysis Rates. In view of the electron-withdrawing properties of the benzoyl, pivaloyl, and carbomethoxy groups relative to hydrogen, it was of interest to determine the solvolysis rate effect of substituting these groups for hydrogen directly on a cationic center. Examination of the rate data in Table I shows the effect of substituting these groups for hydrogen is relatively small. Mesylate **2**, at 25 °C in acetic acid, solvolyzes only 8 times more slowly than *endo*-2-norbornyl mesylate[26] while mesylate **4** solvolyzes only 76 times more slowly. The solvolysis rates of mesylate **5** and isopropyl mesylate are almost equal in trifluoroacetic acid, a highly ionizing nonnucleophilic solvent where solvolyzes of these two substrates should be limiting. Mesylate **3** actually solvolyzes 3.7 times *faster* than *endo*-2-norbornyl mesylate in acetic acid.

The small effect of the electron-withdrawing carbonyl group is also apparent in the solvolyses of mesylates **7**–**10**. For comparison purposes, benzyl mesylate was solvolyzed in HFIP, where nucleophilic solvent participation should be small. In this solvent, mesylate **7** solvolyzes only 21 times more slowly than benzyl mesylate. Mesylates **8**–**10** solvolyze at rates comparable to **7**, and it is therefore concluded that the rate-retarding effect of the carbonyl group in these systems is also small.

How would one expect the electron-withdrawing benzoyl, pivaloyl, and carbomethoxy groups to effect the rate of generation of cationic intermediates? To answer this question, consider first their effect on solvolysis rates of substituted 2-phenyl-2-propyl

(22) (a) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2538–2540. (b) Fry, J. L.; Harris, J. M.; Bingham, R. C.; Schleyer, P. v. R. *Ibid.* **1970**, *92*, 2540–2542. (c) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *Ibid.* **1970**, *92*, 2542–2544.

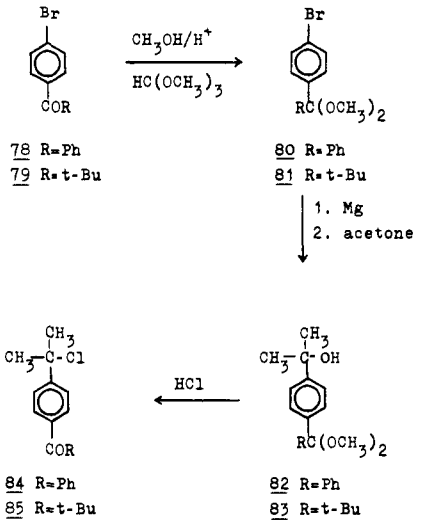
(23) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667–7674.

(24) (a) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658–7666. (b) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *Ibid.* **1981**, *103*, 5466–5475.

(25) An alternative explanation which could account for the less than limiting m value would be one involving reaction of solvent with the cation at an earlier ion-pair stage in the case of increasingly nucleophilic solvents.

(26) Our previous estimate[2] of the solvolysis rate of *endo*-2-norbornyl mesylate, based on a commonly used tosylate/mesylate rate ratio of 2, is incorrect. In acetic acid, *endo*-2-norbornyl mesylate actually solvolyzes slightly faster than the tosylate. This is also true for 2-adamantyl mesylate in acetic acid and isopropyl mesylate in CF_3CO_2H.

Scheme XVII



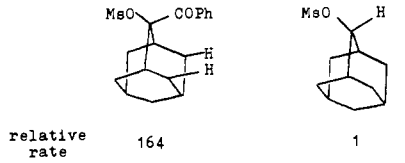
chlorides (cumyl chlorides). Brown's well-known studies on substituted cumyl chlorides give a σ_p^+ value of 0.466 for the carbomethoxy group.[27] This corresponds to a 151-fold rate decrease in solvolysis of *p*-(carbomethoxy)cumyl chloride relative to unsubstituted cumyl chloride. This is readily rationalized in terms of destabilization of the transition state by the electron-withdrawing carbomethoxy group. Data are not available on the benzoyl and pivaloyl groups. Therefore cumyl chlorides **84** and **85** were prepared (Scheme XVII) in order to quantitatively determine their effect on the solvolytic rate of the corresponding cumyl chloride. Rate data are summarized in Table II and indicate that the benzoyl and pivaloyl groups are also destabilizing to a cumyl cation.

What, then, should the effect of substituting a benzoyl, pivaloyl, or carbomethoxy group for hydrogen directly on a cationic center be? Normally the effect of the intervening aromatic ring in a substituted cumyl chloride is to insulate the developing cationic center from the effect of a substituent. The substituent effect is therefore attenuated relative to the effect when the substituent is attached directly to the cationic center. For example, a *p*-methyl substituent increases the solvolysis rate of cumyl chloride by a factor of 27,[28] while methyl substitution for hydrogen attached directly on a cationic center gives rate increases from 10^5 to 10^8.[22b] A *p*-cyclopropyl group increases the solvolysis rate of cumyl chloride by a factor of 154,[29] while the unattenuated cyclopropyl group, when substituted for hydrogen directly on a cationic center, increases the rate by greater than 10^9.[30] A *p*-trifluoromethyl substituent slows the solvolysis rate of cumyl chloride by a factor of 600,[27] while substitution for hydrogen directly on a cationic center[7a] gives an unattenuated rate decrease of 10^5 to 10^6. In light of these considerations one might expect the unattenuated carbonyl groups in mesylates **2–10** to slow solvolysis rates by large factors, perhaps as large as 10^5, relative to the model mesylates. Some other factor must therefore increase the solvolysis rates of mesylates **2–10** so that their rates are comparable to those of the "hydrogen-substituted" model compounds.

A variety of reasons could account for the unexpectedly rapid solvolysis of carbonyl-substituted mesylates **2–10**. Four such reasons have been considered and are described below:

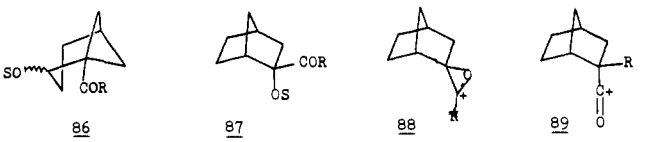
(A) A mechanism involving solvent addition to the carbonyl followed by solvolysis of this adduct has been considered. This mechanism is highly unlikely in the case of mesylates **3**, **4**, **6**, **8**, **9**, and **10** where steric and electronic factors should make solvent addition to the carbonyl group very unfavorable.[31] Also, solvent addition to mesylates **3** and **9** should result in transesterification and such a process is not observed. The solvent-effect studies are also not in accord with this carbonyl addition mechanism, i.e., rates are faster in less nucleophilic solvents.

(B) Steric rate accelerations[32] due to relief of ground-state strain have been considered. It is felt that this effect may contribute slightly to increased solvolysis rates of certain mesylates. For example, the hindered mesylate **6** undergoes acetolysis 164 times faster than 2-adamantyl mesylate. Part of this rate increase may



well be a steric effect where an additional 1,3-diaxial interaction is relieved on solvolysis of **6**. However, the strain relief argument cannot account for the enormous rate enhancement in **6** over the rate expected on the basis of the carbonyl inductive effect. In systems less congested than **6**, steric rate accelerations are probably not large. It should be kept in mind that the large *tert*-butyl and phenyl groups in the mesylates are two carbons removed from the ionization center and add little to congestion at that center.[33] Therefore it is felt that steric factors alone cannot account for the unexpectedly rapid solvolyses of **2–10**.

(C) The possibility of neighboring group participation as a rate-enhancing feature has been considered and ruled out. In the solvolyses of **2**, **3**, and **4**, the stereochemistry of the leaving groups would require that participation involve the C_1C_7 bond. However, products such as **86** and **87**, which would result from this k_Δ process, are not seen. No products derived from ions such as **88**



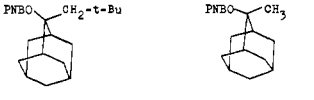
and **89** (or analogous bridged ions) are observed, which argues against neighboring carbonyl, phenyl, *tert*-butyl, or methoxy participation. Studies on optically active (+)-**9**, discussed previously, rule out k_Δ processes in **9** and indicate that such k_Δ processes are probably of no importance in solvolysis of the analogous mesylates **7**, **8**, and **10**.

(D) One possibility that could account for the unexpectedly facile solvolysis of mesylates **2–10** is stabilization of the developing α-keto cation by carbonyl conjugation as represented by **90b**.

Gassman[4] has suggested that α-cyano cations derive an analogous type of stabilization. Olah's recent study[5] on long-lived α-cyano

(27) Okamoto, Y.; Inukai, T.; Brown, H. C. *J. Am. Chem. Soc.* **1958**, *80*, 4972–4976.
(28) Brown, H. C.; Brady, J. D.; Grayson, M.; Bonner, H. W. *J. Am. Chem. Soc.* **1957**, *79*, 1897–1903.
(29) Brown, H. C.; Cleveland, J. D. *J. Org. Chem.* **1976**, *41*, 1792–1799.
(30) Brown, H. C. "The Nonclassical Ion Problem"; Plenum Press: New York, 1977.

(31) This mechanism has been ruled out in solvolyses involving tertiary benzylic α-keto cations by a combination of product studies and rate arguments. See ref 2.
(32) Peters, E. N.; Brown, H. C. *J. Am. Chem. Soc.* **1975**, *97*, 2892–2895 and references therein.
(33) In support of this suggestion, it has been shown that viii solvolyzes only 10 times faster than ix.

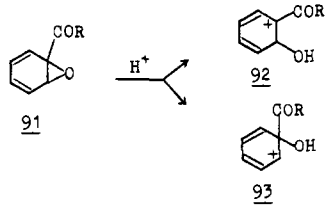


See: Fry, J. L.; Engler, E. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 4628–4634.

cations supports this contention. It is suggested that the potent electron-withdrawing effect of the carbonyl group in the α-keto cations derived from **2–10** is largely offset by a stabilizing conjugative effect as in **90b**. This effect is manifested in the α-keto cations derived from **2–10** since the demand for some sort of stabilization is quite large. It is not manifested in para-substituted cumyl cations since the demand for additional stabilization in these tertiary benzylic cations is quite small, i.e., the inductive effect is the most important effect.

The theoretical study of Houk and Paddon-Row[34] is in agreement with our suggestion based on our experimental findings. Their theoretical study indicates that a formyl group in a conjugating conformation can stabilize a cationic intermediate relative to a nonconjugating (perpendicular) formyl group.

The suggestion that substitution of a carbonyl-containing function for hydrogen on a cationic center is not destabilizing is also supported by the recent studies of Berchtold.[35] Arene oxides such as **91** have been found to aromatize by processes involving cations **92** and **93**. Reaction to give **92** occurs with a rate com-



91 92 93

parable to the rate of formation of **93**. These studies support our contention that α-keto cations can be formed with surprising ease.

Conclusions. Studies on mesylates **2–10** show that solvolytic processes involve tertiary and secondary benzylic α-keto cations as discrete intermediates. This has been verified by product studies and solvent-effect studies. These cations give products derived from 1,2- or 1,3-proton elimination and Wagner–Meerwein rearrangement followed by solvent capture, or solvent capture of the unrearranged cations. Optically active mesylate (+)-**9** gave racemized solvolysis products which rule out k_Δ processes in solvolysis. Solvent-effect studies also support the limiting (k_c) nature of these solvolyses. It is concluded that solvolysis rates of **2–10** are exceptionally rapid. This is attributed to stabilization of the α-keto cation by carbonyl conjugation which largely offsets the inductive destabilizing effect of the carbonyl group. α-Keto cations are therefore much more stable than one might naively expect.

Experimental Section

Gas-chromatographic analyses were carried out on a Hewlett-Packard 5750 chromatograph with flame ionization detector and a 5 ft 5% SE-30 on Chromosorb G column. A Varian 920 chromatograph was used for sample isolation. NMR spectra were recorded on Varian A-60A, EM 390, XL-100, or Nicolet NB 300 spectrometers. Infrared spectra were recorded on a Perkin-Elmer 727B spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 spectrometer or on a DuPont DP1 GC/MS system. Titrations were carried out on a Metrohm E576 automatic recording titrator.

Preparation of Alcohol 14. Lithium diisopropylamide (LDA) was prepared by the addition of 37.5 mL of 1.6 M butyllithium in hexane (Aldrich Chemical Co.) to a solution of 6.36 g of diisopropylamine in 120 mL of dry tetrahydrofuran (THF) at −40 °C. The solution was cooled to −78 °C and 18.09 g of diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate[9b] was added dropwise. The yellow solution was warmed to −60 °C for 5 min and then recooled to −100 °C in a frozen methanol–liquid N_2 slurry. A solution of 6.0 g of norcamphor in 6 mL of THF was added dropwise. The mixture was allowed to warm to room temperature and water was added. The mixture was transferred to a separatory funnel and washed with dilute HCl until the aqueous phase remained acidic. After the mixture was washed with saturated NaCl and dried over $MgSO_4$, the organic phase was filtered and the solvents were removed by rotary evaporator. (This is the standard aqueous workup that will be subsequently referred to.) Gas-chromatographic analysis at 170 °C showed the presence of a small amount of unreacted diethyl 1-(trimethylsiloxy)-1-phenylmethane-phosphonate along with the silated hydroxy ketone **13**. This crude product, **13**, was dissolved in 70 mL of 0.3 M $NaOCH_3$ in methanol. Periodic monitoring by gas chromatography showed no remaining **13** after 2.5 h. A standard aqueous workup with ether extraction followed. After solvent removal by rotary evaporator, the residue was distilled to give 8.23 g (70%) of alcohol **14**, bp 112–115 °C (0.03 mm). Gas-chromatographic analysis at 170 °C shows a trace (5%) of **16**. Pentane was added to the distilled product and after cooling at −20 °C 7.4 g of solid was collected. The entire product was recrystallized by dissolving it in 9 mL of cyclohexane and adding 25 mL of pentane. After the solution was cooled at −20 °C, 5.1 g of alcohol **14**, mp 59–62 °C, was collected. No **16** is present by gas chromatography. IR (CCl_4) 3610, 3490 (OH), 1686 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.6–7.1 (3 H, m), 2.8–1.8 (5 H, m), 1.7–1.1 (6 H, m). Anal. ($C_{14}H_{16}O_2$) C, H.

Preparation of Mesylate 2. A solution of 508 mg of alcohol **14** in 5 mL of CH_2Cl_2 was cooled to −78 °C and 0.32 g of CH_3SOCl[36] was added. After 5 min at −78 °C, 400 mg of triethylamine was added and the mixture was allowed to warm to 0 °C. A standard aqueous workup followed with ether extractions and a wash with dilute HCl to remove the excess Et_3N. After being dried over $MgSO_4$, the solvent was removed by rotary evaporator, leaving 684 mg (100%) of crude sulfinate ester **15** as an oil: IR 1685 cm^{-1} (C=O), 1140 cm^{-1} (S=O); NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.7–7.4 (3 H, m), 3.0 (1 H, m), 2.8–1.2 (12 H, m with sharp singlet at 2.38).

The crude sulfinate **15** was dissolved in 6 mL of CH_2Cl_2 and 606 mg of 85% *m*-chloroperbenzoic acid was added. The peracid dissolved and the temperature rose to about 30 °C after 5 min. Periodic cooling with a water bath kept the temperature below 30 °C. After 1.5 h, the mixture was taken up into ether and washed with 0.3 g of KOH in water followed by a solution of $Na_2S_2O_3$, NaI, and KOH in water. After being dried over $MgSO_4$, the solvent was removed by a rotary evaporator, leaving 679 mg (94%) of mesylate **3**: mp 122–124 °C; ^1H NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.7–7.3 (3 H, m), 3.07 (1 H, m), 2.79 (1 H, m), 2.51 (3 H, s), 2.6–1.1 (8 H, m); ^{13}C NMR ($CDCl_3$) δ 196.03, 134.65, 132.53, 129.66, 128.14, 97.55, 46.40, 40.61, 39.55, 36.81, 35.78, 28.35, 22.42. Anal. ($C_{15}H_{18}O_4S$) C, H.

Isomerization of 14 to 16. A solution of 0.30 g of alcohol **14** in 3 mL of 0.5 M $NaOCH_3$ in methanol was stirred at room temperature for 3 h. A significant amount of rearrangement to **16** was indicated by gas chromatography. Reflux for 15 min gave an equilibrium mixture containing about 80% of **16** and 20% of **14**. After a standard aqueous workup, the crude mixture was recrystallized from 3 mL of cyclohexane to give 0.19 g of **16**: mp 98–99 °C; IR (CCl_4) 3610, 3490 (OH), 1718 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.27 (5 H, bs), 3.1–2.1 (5 H, m with singlet at 2.70) 1.9–1.2 (6 H, m).

Wolff–Kishner Reduction of 16. A solution of 110 mg of the ketol formed on rearrangement of **14** in 2 mL of ethanol was refluxed with 400 mg of anhydrous hydrazine for 30 min. A standard aqueous workup was followed with $MgSO_4$ drying. After solvent removal by rotary evaporator, the solid residue was dissolved in 3 mL of dimethyl sulfoxide (Me_2SO) and added to 400 mg of *t*-BuOK in 2 mL of Me_2SO. After 3.5 h at room temperature, a standard aqueous workup followed. After solvent removal by a rotary evaporator, the residue was distilled to give 42 mg (44%) of **17**. The NMR of **17** was identical with a sample independently prepared by $KHSO_4$-catalyzed dehydration of 2-hydroxy-2-phenylbicyclo[3.2.1]octane. The NMR of **17** was distinctly different from that of an authentic sample of 3-phenylbicyclo[3.2.1]-oct-2-ene.[37a] NMR of **16** ($CDCl_3$): δ 7.6–7.1 (5 H, m), 5.73 (1 H, m), 2.86 (1 H, m), 2.7–1.3 (9 H, m).

Preparation of Alcohol 19. A solution of 12.46 g of the silated cyanohydrin **18** (prepared in 98% yield by following the procedure of Evans[37b]) in 100 mL of ether was cooled to −78 °C and 32.7 mL of 2.1 M *t*-butyllithium in pentane was added dropwise. The mixture was warmed to room temperature, then cooled in an ice bath as water was slowly added. A standard aqueous workup followed with solvent removal by a rotary evaporator. The residue was dissolved in 60 mL of THF and a solution of 6.2 g of H_2SO_4 in 65 mL of water was added. After 30 min of vigorous stirring, the mixture was neutralized with K_2CO_3 and an aqueous workup followed. GC analysis indicated incomplete hydrolysis and the residue, after solvent removal, was recycled with 62 mL of THF

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(37) (a) Jefford, C. W.; Yen, E. H. *Tetrahedron* **1967**, *23*, 4549–4555. (b) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917 and references therein.

Table II. Solvolysis Rates of 2-Aryl-2-chloropropanes (Cumyl Chlorides) in Ethanol at 25 °C

substituent	$k^{25\,°C}$, s^{-1}	k_H/k_X	σ^+
p-CO-*t*-Bu	1.68×10^{-5}	23.5	0.293
p-COPh	5.01×10^{-6}	78.7	0.406
p-CO_2CH_3	2.61×10^{-6}	151	0.466
p-H	3.94×10^{-4}	1.0	0.000

and 6 g of H_2SO_4 in 60 mL of water. After 1 h a standard aqueous workup followed with solvent removal by rotary evaporator. The crude residue was chromatographed on 70 g of silica gel. Initial elution was with 5% ether in Skelly F followed by increasing portions of ether. The alcohol **19** (4.61 g (40%), mp 104–106 °C) eluted with 9% ether. IR (CCl_4) 3615, 3520 (O–H) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.45 (1 H, m), 2.17 (1 H, m), 2.14 (1 H, s, exchanges with D_2O), 2.1–0.9 (8 H, m), 1.25 (9 H, s). Anal. ($C_{12}H_{20}O_2$) C, H.

Preparation of Mesylate 3. The preparation of **3** (87%) from alcohol **19** was analogous to the preparation of **2**. Details are given as supplementary material.

Preparation of Alcohol 21. In accordance with Baldwin's procedure,[15] a solution of 11 g of methyl vinyl ether in 50 mL of THF was cooled to −78 °C and 59 mL of 1.9 M *tert*-butyllithium was added dropwise. The mixture was allowed to warm to 0 °C, then recooled to −78 °C. A solution of 10.3 g of norcamphor, **11**, in 13 mL of THF was added and the mixture was warmed to 0 °C. Water was added and the organic phase was separated. After the mixture was washed with saturated NaCl solution and dried over $MgSO_4$, solvent was removed by rotary evaporator. The residue was distilled to give 12.4 g (79%) of **21**: bp 78–79 °C (2 mm); NMR (CCl_4) δ 4.13 (1 H, d, J = 3 Hz), 3.92 (1 H, d, J = 3 Hz), 3.57 (3 H, s), 2.4–1.0 (11 H, m with singlet at 2.10).

Preparation of Hydroxyester 22. A solution of 12.4 g of **21** in 140 mL of methanol and 1 drop of pyridine was cooled to −78 °C and exhaustively ozonized (until a faint blue color appeared). The mixture was warmed to room temperature and a solution of 5 g of sodium iodide and 18 g of sodium thiosulfate in 50 mL of water was added. After 30 min, a standard aqueous workup followed. The solution was dried over $MgSO_4$ and the solvent was removed by rotary evaporator. The residue was distilled through a Vigreux column to give 9.35 g (75%) of **22**: bp 78 °C (1.9 mm); IR 3500 (O–H), 1720 cm^{-1} (C=O); NMR (CCl_4) δ 3.75 (3 H, s), 2.80 (1 H, bs), 2.4–1.0 (10 H, m). Anal. ($C_9H_{14}O_3$) C, H.

Preparation of Mesylate 4. A solution of 1.16 g of hydroxy ester **22** and 1.38 g of Et_3N in 20 mL of CH_2Cl_2 was cooled to −78 °C. Methanesulfonyl chloride (0.93 g) was then added dropwise and the mixture was allowed to warm to 0 °C. A standard aqueous workup with ether extraction followed. Solvent removal by rotary evaporation gave 1.62 g (96%) of mesylate **4** as a viscous oil. IR 1743 cm^{-1} (C=O); NMR (CCl_4) δ 3.77 (3 H, s), 3.02 (3 H, s), 2.64 (1 H, m), 2.5–1.1 (9 H, m).

Preparation of 2-Benzoyl-2-hydroxypropane (α-Hydroxyisobutyrophenone). Lithio diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate, **12**, was prepared from 1.84 g of diisopropylamine, 10.3 mL of 1.6 M butyllithium, and 5.23 g of the phosphonate as described earlier. The mixture was cooled to −100 °C and 1.0 g of acetone in 4 mL of THF was slowly added. The mixture was warmed to 0 °C and an aqueous workup followed. The organic phase was washed with a solution of 2.6 g of $KHSO_4$ in water and dried in the usual fashion. GC analysis showed a small amount of unreacted phosphonate along with the product, α-(trimethylsiloxy)isobutyrophenone, at shorter retention time. Solvents were removed by a rotary evaporator and the residue was distilled through a Vigreux column to give 2.70 g (69%) of the silated hydroxy ketone: bp 74 °C (0.3 mm); IR 1685 (C=O); NMR ($CDCl_3$) δ 8.3–8.0 (2 H, m), 7.5–7.2 (3 H, m), 1.57 (3 H, s), 0.04 (9 H, s).

The siloxy ketone obtained above (2.70 g) was dissolved in 20 mL of 2×10^{-3} M trifluoroacetic acid in methanol. The desilation occurs with a half-life of about 7 min as determined by GC. After 2 h, a drop of Et_3N was added and the solvent was removed by rotary evaporator. Distillation of the residue gave 1.86 g (99%) of α-hydroxyisobutyrophenone: bp 95–97 °C (1.5 mm); NMR ($CDCl_3$) 8.2–8.0 (2 H, m), 7.7–7.3 (3 H, m), 4.10 (1 H, br s), 1.62 (6 H, s). This compound has previously been prepared by other methods.[38]

Preparation of Mesylate 5. The preparation of **5** (97%) from α-hydroxyisobutyrophenone was analogous to the preparation of **2**. Details are given as supplementary material.

Preparation of Hydroxy Ketone 25. Anion **12** was prepared from 1.82 g of diisopropylamine, 10.3 mL of 1.6 M butyllithium, and 5.23 g of diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate as earlier described. After the mixture was cooled to −100 °C, a solution of 2.44 g of adamantanone in 10 mL of THF was added dropwise. The mixture was warmed to room temperature and a standard aqueous workup followed. The organic phase was washed with a solution of 2.6 g of $KHSO_4$ and dried in the usual manner. After solvent removal by a rotary evaporator, the residue was dissolved in 30 mL of 2×10^{-3} M CF_3CO_2H in methanol. GC analysis after 15 min at 25 °C showed ketone **24** and the silated derivative of **25**. Reflux for 3 h gave no further reaction. After solvent removal under vacuum, 60 mL of 0.5 M $NaOCH_3$ in CH_3OH was added. After the solution was refluxed for 1 h a standard aqueous workup followed. GC analysis showed **24** and **25** in a 26:74 ratio. After solvent removal by a rotary evaporator, the residue was slurried with Skelly F and the solid was collected. Ketone **25** mostly remained dissolved in the Skelly F. A pure sample of **24**, mp 93–94 °C, was isolated by preparative gas chromatography from the Skelly F wash. IR (CCl_4) 1682 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.9–7.6 (2 H, m), 7.5–7.2 (3 H, m), 3.42 (1 H, m), 2.30 (2 H, m), 2.2–1.4 (12 H, m). Mass spectrum *m/e* 240, 135, 105.

The crude ketol **25** was recrystallized from 40 mL of cyclohexane to give 1.68 g (40%) of **25**: mp 161–162 °C; IR (CCl_4) 3610, 3490 (O–H), 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–8.0 (2 H, m), 7.6–7.2 (3 H, m), 2.5–2.1 (5 H, m, 1 H exchanges with D_2O), 2.1–1.3 (10 H, m). Anal. ($C_{17}H_{20}O_2$) C, H.

Preparation of Mesylate 6. The preparation of **6** from **25** was analogous to the preparation of **2**. Details are given as supplementary material.

Preparation of 28. LDA was prepared from 3.13 g of diisopropylamine in 10 mL of THF and 20.2 mL of 1.4 M methyllithium in ether. A solution of 4.54 g of benzyl *tert*-butyl ketone in 16 mL of THF was added dropwise at −78 °C. The mixture was warmed to 10 °C and 4.17 g of chlorotrimethylsilane was added. After the mixture was refluxed for 30 min, it was transferred to a separatory funnel with pentane. The mixture was washed with water and 2.18 g of $KHSO_4$ in cold water and dried over $MgSO_4$. After solvent removal by a rotary evaporator, the residue was distilled to give 6.24 g (97%) of **28**: bp 93–94 °C (1.8 mm); NMR (CCl_4) δ 7.4–7.1 (5 H, m), 5.60 (1 H, s), −0.07 (9 H, s).

Preparation of 29. A solution of 4.13 g of **28** in 15 mL of CH_2Cl_2 was cooled to −10 °C as a solution of 3.70 g of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was added dropwise. After 2 h at −10 °C, the mixture was transferred to a separatory funnel with ether and washed with a solution of 0.9 g of NaOH in water. After the mixture was washed with a sodium iodide, sodium thiosulfate, and NaOH mixture and dried in the usual manner, the solvent was removed by rotary evaporator. Distillation of the residue gave 4.23 g (96%) of **29**: bp 98–99 °C (2.1 mm). **29** solidifed when the mixture was left undisturbed: mp 44–46 °C; IR (CCl_4) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 7.28 (5 H, br s), 5.35 (1 H, s), 1.07 (9 H, s), 0.05 (9 H, s).

Preparation of 30. The α-siloxy ketone **29** (993 mg) was dissolved in 15 mL of 10^{-4} M CF_3CO_2H in methanol. After 4 h of reflux, GC showed no remaining **29**. Solvent was removed by a rotary evaporator, leaving 524 mg of **30**: mp 41–42.5 °C; IR (CCl_4) 3520 (O–H), 1710 cm^{-1} (C=O); NMR (CCl_4) δ 7.26 (5 H, br s), 5.25 (1 H, br s), 4.04 (1 H, br s, exchanges with D_2O), 1.02 (9 H, s). Anal. ($C_{12}H_{16}O_2$) C, H.

A 260-mg sample of **30** in 30 mL of 0.5 M $NaOCH_3$ in methanol was stirred at 25 °C for 40 min. About 5% of **31** is present as determined by NMR. After 8 h of reflux an equilibrated mixture of **30** and **31** is present (a 1:2 ratio) as determined by NMR.

Preparation of Mesylates 7, 8, 9, and 10. These mesylates were prepared by following the Servis procedure.[12] Details are given as supplementary material.

Preparation of 32. To a solution of 2.14 g of ethyl mercaptan in 9 mL of THF at −78 °C was added 10.8 mL of 1.6 M butyllithium in hexane. After the solution was warmed to 25 °C 2.20 g of the acetonide of mandelic acid[39] in 4 mL of THF was added. After 1 h at room temperature, a standard aqueous workup followed. After solvent removal by a rotary evaporator, distillation of the residue gave 1.62 g (72%) of **32**; bp 101 °C (0.12 mm); IR 3460 (O–H), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.33 (5 H, br s), 5.15 (1 H, d, J = 4 Hz), 3.64 (1 H, d, J = 4 Hz), 2.86 (2 H, q, J = 7 Hz) 1.21 (3 H, t, J = 7 Hz). Anal. ($C_{10}H_{12}O_2S$) C, H.

Preparation of *exo*-5,6-Dideuteronorcamphor (11-d_2). To a solution of 4.2 g of the ethylene glycol ketal of norbornenone[40] in 25 mL of ether

(38) (a) Stevens, C. L.; Blumbergs, P.; Munk, M. *J. Org. Chem.* **1963**, *28*, 331–336. (b) Hünig, S.; Wehner, G. *Synthesis* **1975**, 391–392. (c) House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067–3076.

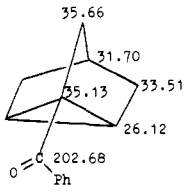
(39) Audrieth, L. F.; Sveda, M. "Organic Syntheses"; Wiley, New York, 1955; Collect. Vol. III, pp 536–538.

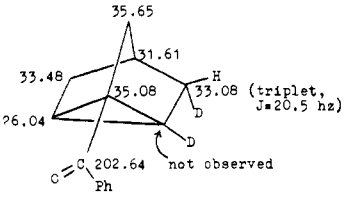
in a 100-mL three-necked flask was added 200 mg of 10% Pd on charcoal. The mixture was stirred under a positive pressure of deuterium for 18 h. The uptake of deuterium was monitored by periodic NMR which showed disappearance of the olefinic hydrogens. On completion of the reaction, the mixture was filtered through Celite and the ether was removed by a rotary evaporator. The residue was dissolved in 10 mL of THF and 30 mL of 2% H_2SO_4 in water was added. After the solution was stirred vigorously for 1 h $NaHCO_3$ was added followed by Na_2SO_4 until the solution was saturated. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$. The solvents were removed by distillation through a glass helice packed column. The crude product was distilled through a Vigreux column to give 2.74 g (88%) of **11**-d_2. The product will solidify in the condenser. A steam line therefore is used to aid the distillation. IR (CCl_4) 2200 (C–D) 1750 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 217.55, 49.71, 45.15, 37.62, 35.22, 26.76, (t, J = 20 Hz), 23.76 (t, J = 21 Hz).

Preparation of 2-d_2. The preparation of **2**-d_2, starting with **11**-d_2, was analogous to the preparation of **2** from **11**. Desilation of the intermediate α-siloxy ketone formed on reaction of **11**-d_2 with **12** was accomplished by refluxing the mixture for 3 h with 1.7×10^{-3} M CF_3CO_2H in methanol. Conversion to the mesylate **2**-d_2, via the sulfinate ester, was accomplished as described for **2**. ^{13}C NMR of **2**-d_2 ($CDCl_3$) δ 196.00, 134.59, 132.54, 129.63, 128.13, 97.48, 46.29, 40.55, 39.52, 36.76, 35.66, 27.87, (t, J = 20 Hz), 21.95 (t, J = 20 Hz).

Solvolysis Studies in Acetic Acid. General Procedure. A solution of the mesylate in acetic acid containing approximately 1.5 equiv of sodium acetate was heated for 10 half-lives in a sealed tube. The mixture was then taken up into ether and washed with two portions of water followed by Na_2CO_3 solution until the aqueous phase remained basic. After the solution was dried over $MgSO_4$, the ether solvent was removed by a rotary evaporator. Product mixtures were separated by preparative gas chromatography. Details on specific solvolyses are given below or as supplementary material.

Solvolysis of 2 in Acetic Acid. Solvolysis of 224 mg of **2** in 11 mL of 0.1 M NaOAc in HOAc for 10 h at 100 °C gave 96% of **33**, **34**, and **35** in a 64:12:24 ratio was determined by GC. Samples of each product were isolated by preparative GC at 165 °C. **33**: IR (CCl_4) 1652 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.8–7.6 (2 H, m), 7.5–7.2 (3 H, m), 2.17 (1 H, m), 2.12 (2 H, s), 1.71 (2 H, d, J = 1.5 Hz), 1.45 (4 H, AB quartet). **34**: IR 1738, 1688 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.7–7.3 (3 H, m), 4.87 (1 H, d of d, J = 2.5 Hz), 3.18 (1 H, d of d, J = 8.5, 5.5 Hz), 2.62 (1 H, br s), 2.43 (1 H, m), 2.02 (3 H, s), 2.2–1.2 (6 H, m). **35**: IR (CCl_4) 1740, 1672 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.9–7.7 (2 H, m), 7.6–7.2 (3 H, m), 5.27 (1 H, doublet of quartets, J = 7, 1.5 Hz), 2.31 (1 H, m), 2.2–1.2 (8 H, m), 1.75 (3 H, s). The ^{13}C NMR of **33** is shown below. Assignments are based on the off-resonance single-frequency-decoupled spectrum.





Solvolysis of 2-d_2 in Acetic Acid. Solvolysis of 246 mg of **2**-d_2 in 12 mL of 0.1 M NaOAc in HOAc for 10 h at 100 °C gave 97% of **33**-d_2, **34**-d_2, and **35**-d_2 in a 54:13:33 ratio as determined by GC. Samples of each product were isolated by preparative GC at 165 °C. **33**-d_2: NMR ($CDCl_3$) δ 7.8–7.6 (2 H, m), 7.5–7.2 (3 H, m), 2.17 (1 H, m), 2.12 (1.28 H, s), 1.71 (2 H, d, J = 1.5 Hz), 1.45 (3 H, AB quartet). The ^1H NMR spectrum of this product therefore indicates 72% of **33**-d_2 and 28% of **33**-d_1. The ^{13}C NMR spectrum of this product (mainly **33**-d_2) is shown above. **34**-d_2: NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.7–7.3 (3 H, m), 3.18 (1 H, d of d, J = 8.5, 5.5 Hz), 2.62 (1 H, br s), 2.43 (1 H, m), 2.02 (3 H, s), 2.2–1.2 (5 H, m). NMR of **35**-d_2 ($CDCl_3$) same as **35** except for δ 2.2–1.2 where the complex pattern has an area of 6 H.

Solvolysis of 2 in Trifluoroacetic Acid. Solvolysis of 178 mg of **2** in 6 mL of 0.2 M sodium trifluoroacetate in CF_3CO_2H at 36 °C for 6.5 h gave 95% of a mixture of **33**, 1-benzoyl-*exo*-2-(trifluoroacetoxy)norbornane, and *exo*-2-benzoyl-*exo*-6-(trifluoroacetoxy)norbornane in an 18:67:15 ratio as determined by GC. Samples of each product were isolated by preparative GC at 160 °C. 1-Benzoyl-*exo*-2-(trifluoroacetoxy)norbornane: NMR ($CDCl_3$) δ 7.8–7.2 (5 H, m), 5.42 (1 H, doublet of triplets, J = 7, 1.8 Hz), 2.44 (1 H, m), 1.37–1.20 (8 H, m). *exo*-2-Benzoyl-*exo*-6-(trifluoroacetoxy)norbornane: NMR ($CDCl_3$) δ 8.1–7.8 (2 H, m), 7.6–7.3 (3 H, m), 5.05 (1 H, br d, J = 7 Hz), 3.17 (1 H, d of d, J = 9, 5 Hz), 2.75 (1 H, br s), 2.49 (1 H, m), 2.3–1.3 (6 H, m).

Solvolysis of 2 in Trifluoroethanol. Reaction of 102 mg of **2** in 4.6 mL of TFE containing 46 mg of 2,6-lutidine at 70–73 °C for 6 h gave 97% of a mixture of **33**, 1-benzoyl-*exo*-2-(trifluoroethoxy)norbornane, and *exo*-2-benzoyl-*exo*-6-(trifluoroethoxy)norbornane in a 62:25:13 ratio as determined by GC. 1-Benzoyl-*exo*-2-(trifluoroethoxy)norbornane: NMR ($CDCl_3$) δ 7.8–7.6 (2 H, m), 7.5–7.2 (3 H, m), 4.03 (1 H, m), 3.50 (1 H, q, J = 8.5 Hz), 3.48 (1 H, q, J = 8.5 Hz), 2.34 (1 H, m), 2.2–1.2 (8 H, m). *exo*-2-Benzoyl-*exo*-6-(trifluoroacetoxy)norbornane: NMR ($CDCl_3$) δ 8.0–7.8 (2 H, m), 7.6–7.3 (3 H, m), 3.81 (1 H, q, J = 8.5 Hz), 3.79 (1 H, q, J = 8.5 Hz), 3.72 (1 H, m), 2.97 (1 H, d of d, J = 9, 6 Hz), 2.68 (1 H, br s), 2.40 (1 H, m), 2.0–1.1 (6 H, m).

Solvolysis of 4 in Acetic Acid. Reaction of 197 mg of mesylate **4** in 10 mL of 0.1 M NaOAc in HOAc (1% Ac_2O) for 8 h at 116 °C gave an 88% yield of a mixture of **48**,[41] **49**, **50**, and **51** in a 54:2:40:4 ratio as determined by GC. **48**: NMR ($CDCl_3$) δ 3.65 (3 H, s), 2.05 (1 H, m), 1.86 (2 H, br s), 1.48 (2 H, d, J = 1.5 Hz), 1.36 (4 H, br s). **50**: NMR ($CDCl_3$) δ 4.91 (1 H, m), 3.68 (3 H, s), 2.31 (1 H, m), 1.98 (3 H, s), 2.1–1.2 (8 H, m). **51**: NMR ($CDCl_3$) δ 6.17 (2 H, m), 3.75 (3 H, s), 2.97 (1 H, m), 2.2–1.0 (6 H, m).

Solvolysis of 4 in Methanol. Reaction of 217 mg of mesylate **4** in 23 mL of 0.05 M 2,6-lutidine in methanol for 48 h at 100 °C (sealed tube) gave 96% of a mixture of **48**, **51**, **52**, and **53** in a 30:1:16:53 ratio as determined by GC. The column used for the separation of this mixture was a 6 ft 10% XE 60 on Chromosorb P column. **52**: NMR ($CDCl_3$) δ 3.77 (3 H, s), 3.13 (3 H, s), 2.37 (2 H, m), 2.1–1.0 (8 H, m). **53**: NMR ($CDCl_3$) δ 3.71 (3 H, s), 3.49 (1 H, m), 3.22 (3 H, s), 2.26 (1 H, m), 2.0–1.0 (8 H, m).

Solvolysis of 4 in Methanol-d_4. Reaction of **43** mg of mesylate 4 in 3 mL of 0.075 M 2,6-lutidine in methanol-d_4 for 52 h at 100 °C gave 97% of **48**, **51**, **52**-d_3, and **53**-d_3 in a 26:1:16:57 ratio as determined by GC. **52**-d_3: NMR ($CDCl_3$) δ 3.77 (3 H, s), 2.37 (2 H, m), 2.1–1.0 (8 H, m). **53**-d_3 NMR ($CDCl_3$) δ 3.71 (3 H, s), 3.49 (1 H, m), 2.26 (1 H, m), 2.0–1.0 (8 H, m).

Solvolysis of 5, 6, 7, 8, 9, and 10. Details of these procedures are given as supplementary material.

Mesylate Solvolyses. Kinetics Procedures. Solvolyses of the mesylates in Table I in acetic acid, 0.05 M in NaOAc and containing 1% acetic anhydride, were carried out by using the sealed ampule technique previously described.[43] Reactions were monitored for approximately 2 half-lives. Titrimetric end points were determined potentiometrically by titration with 0.01 M $HClO_4$ in HOAc and infinity values were determined in duplicate. Correlation coefficients for rate constants were greater than 0.9999.

Solvolyses of **3**, **7**, and **84** in ethanol were carried out in absolute ethanol containing 0.025 M 2,6-lutidine. Solvolysis of **85** was carried out with 0.025 M triethylamine in ethanol. The sealed ampule technique was used and end points were determined by potentiometric titration of unreacted base with 0.01 M $HClO_4$ in ethanol.

Solvolyses in formic acid were carried out in anhydrous formic acid containing 0.05 M sodium formate by using the sealed ampule technique. At given times, 1-mL aliquots were quenched by dilution with 4 mL of acetic acid. End points were determined by potentiometric titration with 0.01 M $HClO_4$ in HOAc.

Solvolyses in trifluoroethanol were carried out in distilled trifluoroethanol containing 0.025 M triethylamine in sealed ampules. At given times, 2-mL aliquots were quenched by dilution with 4 mL of absolute ethanol. End points were determined by potentiometric titration with 0.01 M $HClO_4$ in ethanol.

Solvolyses in hexafluoroisopropyl alcohol were carried out in 97% HFIP–3% water containing 0.05 M triethylamine. At given times, 1-mL aliquots were quenched by dilution with 4 mL of absolute ethanol. End points were potentiometrically determined by titration with 0.01 M $HClO_4$ in ethanol.

Solvolyses in trifluoroacetic acid were carried out with 0.20 M sodium trifluoroacetate in CF_3CO_2H containing 1% trifluoroacetic anhydride. Reactions were monitored by NMR spectroscopy. Trifluoroacetolysis of **2** was followed by monitoring the decrease in intensity of the methyl singlet due to the mesylate group as a function of time. The product CH_3 singlet appears approximately δ 0.5 downfield from **2** in CF_3CO_2H. Mesylates **3** and **7** were also followed by monitoring the decrease in intensity of the methyl singlet intensity of the mesylate group. Mesylate

(40) Prepared by ketalization of dehydronorcamphor. See: Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211–2214.

(41) Wilt, J. W.; Wagner, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 6135–6141. Properties of **48** have also been described by Werstiuk. See ref 19.

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5 was followed by monitoring the decrease of the singlet due to the two equivalent aliphatic methyl groups. Mesylate **9** was followed by the decrease of the intensity of the benzylic proton with time. Correlation coefficients (greater than 0.998) were generally lower than in titrimetric runs. Standard deviations for duplicate (or multiple) runs are ±10%.

The solvolysis of benzyl mesylate in 97% hexafluoroisopropyl alcohol was followed spectrophotometrically by monitoring the absorbance decrease at 219 nm.

Polarimetric rates for mesylate **9** were followed by monitoring observed rotation as a function of time on an O.C. Rudolph and Son No. 574 polarimeter.

Preparation of (+)-9. Mesylate (+)-**9** was prepared from (+)-methyl mandelate, $[\alpha]^{25}_D$ 147.7° (*c* 2.5, CH_3OH) (lit.[44] $[\alpha]^{18}_D$ −143° for (−)-methyl mandelate), as described for racemic **9**. The yield of (+)-**9**, mp 113–114 °C, $[\alpha]^{25}_D$ 112.6° (*c* 2, CH_2Cl_2), was 98%. Spectra were identical with those of racemic **9**.

Preparation of (+)-74. A solution of 249 mg of (+)-methyl mandelate in 2.4 mL of pyridine was cooled to 0 °C as 0.63 g of trifluoroacetic anhydride was added dropwise. After the mixture was warmed to 25 °C for 20 min, it was taken up into ether and pentane (50:50) and water was added. The organic phase was washed with water and dilute HCl and dried in the usual manner. Solvents were removed by a rotary evaporator, leaving 374 mg (96%) of (+)-**74**, $[\alpha]^{25}_D$ 107° (*c* 1.5, CH_2Cl_2). **74**: IR 1795, 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.50 (5 H, s), 6.08 (1 H, s), 3.78 (3 H, s). A 188-mg sample of (+)-**74** in 5 mL of a 0.2 M sodium trifluoroacetate in CF_3CO_2H containing 1% $(CF_3CO)_2$ was heated at 35 °C for 4.5 h. A standard aqueous workup gave 96% of recovered (+)-**74** of the same specific rotation as before.

Preparation of (+)-65. A solution of 290 mg of (+)-methyl mandelate in 3 mL of pyridine at 25 °C was treated with 0.36 g of acetic anhydride. After 3 h, the mixture was taken up into ether and washed with water and dilute HCl and dried in the usual manner. Solvent removal by a rotary evaporator gave 340 mg (94%) of (+)-**65**, $[\alpha]^{25}_D$ 126.5° (*c* 2, CH_3OH) (lit.[44] $[\alpha]^{18}_D$ −124.7° for (−)-**65**). Spectra were identical with those of racemic **65**.

A 191-mg sample of (+)-**65** in 10 mL of 0.1 M NaOAc in HOAc (1% Ac_2O) was heated at 116 °C for 4 h. A standard aqueous workup gave 89% of recovered (+)-**65** with an identical specific rotation as before.

Solvolysis of (+)-9 in Trifluoroacetic Acid. A solution of 367 mg of (+)-**9** in 10 mL of 0.2 M sodium trifluoroacetate in CF_3CO_2H containing 1% trifluoroacetic anhydride was held at 35 °C for 5 h. The mixture was then taken up into ether and water and solid $NaHCO_3$ was added until CO_2 evolution ceased. A standard workup followed. After the mixture was dried over $MgSO_4$, solvent was removed by a rotary evaporator to give 320 mg (82%) of optically inactive **74**.

Solvolysis of 9 in CF_3CO_2D. Reaction of 133 mg of **9** in 4 mL of 0.2 M sodium trifluoroacetate in CF_3CO_2D (1% $(CF_3CO)_2O$) for 5 h at 35 °C gave 126 mg (88%) of **74**. The NMR and IR spectra were identical with the previously described spectra of **74**. NMR integration of the signal at 6.08 shows no deuterium incorporation.

Solvolysis of (+)-9 in Hexafluoroisopropyl Alcohol. A solution of 345 mg of (+)-**9** in 10.5 mL of HFIP containing 135 mg of 2,6-lutidine was held at room temperature for 4 days. After a standard aqueous workup and solvent removal by a rotary evaporator, distillation gave 387 mg (87%) of racemic **75**: bp 66 °C (0.02 mm); NMR ($CDCl_3$) δ 7.49 (5 H, s), 5.27 (1 H, s), 4.27 (1 H, heptet, J = 6 Hz), 3.73 (3 H, s).

Solvolysis of (+)-9 in Acetic Acid. A solution of 236 mg of (+)-**9** in 13 mL of 0.1 M NaOAc in HOAc was heated at 116 °C (sealed tube) for 4 h. After a standard aqueous workup, 182 mg (91%) of acetate **65** was obtained ($[\alpha]^{25}_D$ −14.8°). IR and NMR spectra were identical with previously described spectra of **65**.

Solvolysis of 9 in CH_3CO_2D. Reaction of 180 mg of **9** in 10 mL of 0.1 M NaOAc in CH_3CO_2D for 4 h at 116 °C gave 135 mg (88%) of **65**. NMR integration of the signal at δ 5.94 shows no deuterium incorporation.

Preparation of 80. *p*-Bromobenzophenone (3.68 g) was added to 20 mL of methanol followed by 1.8 g of trimethylorthoformate and 200 mg of toluenesulfonic acid. The mixture was refluxed for 8.5 h during which time the ketone dissolved. Sodium methoxide (100 mg) was added and most of the methanol was removed by a rotary evaporator. The residue was taken up into ether and CH_2Cl_2 and washed with a Na_2CO_3 solution. After the mixture was dried over $MgSO_4$, the solvent was removed by rotary evaporator. The solid residue was slurried with cold methanol and collected, giving 3.70 g (85%) of **80**: mp 59–60 °C; NMR ($CDCl_3$) δ 7.7–7.2 (9 H, m), 3.13 (6 H, s).

Preparation of 82. The bromo ketal **80** (1.00 g) was converted to the Grignard reagent with 200 mg of magnesium in 10 mL of ether. The reaction was initiated with ethylene dibromide and periodically small amounts were added to keep the reaction going. After 1 h of reflux, a solution of 300 mg of acetone in 2 mL of ether was added. A solution of NH_4Cl was added and a standard workup followed. The crude product, after solvent removal, was chromatographed on 40 g of silica gel and eluted with 10% ether in Skelly F. A small amount of benzophenone dimethyl ketal eluted along with a yellow impurity. The percentage of ether was gradually increased to 35%. Hydroxy ketal **82** (0.69 g (74%), mp 114–7 °C) eluted with 35% ether. NMR (CCl_4) δ 7.6–7.0 (9 H, m), 3.07 (6 H, s), 1.70 (1 H, s), 1.46 (6 H, s).

Preparation of 84. A solution of 0.55 g of **82** in 2 mL of CH_2Cl_2 was stirred at room temperature for 1.5 h with 10 mL of concentrated HCl. The mixture was taken up into ether and the organic phase was separated and washed with two portions of saturated NaCl. After the mixture was dried over $MgSO_4$, the solvent was removed by a rotary evaporator to give 0.43 g (86%) of **84**: mp 50–52 °C; NMR (CCl_4) δ 7.9–7.14 (6 H, m), 7.6–7.3 (3 H, m), 2.00 (6 H, s).

Preparation of 81. A solution of 1.93 g of bromo ketone **79**[45] (prepared by addition of *p*-bromophenyllithium[46] to trimethylacetaldehyde followed by Jones oxidation) in 15 mL of methanol was treated with 3.41 g of trimethylorthoformate followed by 500 mg of toluenesulfonic acid. After 2 h of reflux, the acid was neutralized with $NaOCH_3$ powder and an aqueous workup followed. After the mixture was dried over $MgSO_4$, the solvent was removed by a rotary evaporator, and the residue was distilled to give 2.43 g (88%) of ketal **81**: bp 79–80 °C (0.06 mm); NMR (CCl_4) δ 7.33 (4 H, AA'BB' quartet), 3.29 (6 H, s), 0.89 (9 H, s).

Preparation of 83. The bromo ketal **81** (2.43 g) was converted to the Grignard reagent with 300 mg of magnesium in 20 mL of ether. The reaction was initiated with ethylene dibromide. A solution of 0.98 g of acetone in 2 mL of ether was added. A solution of NH_4Cl was added and a standard aqueous workup followed. The crude product was chromatographed on 30 g of silica gel and eluted with 10% ether in Skelly F. The percentage of ether was gradually increased to 30% and 1.39 g (62%) of **83**, mp 83–4 °C, eluted followed by mixed fractions of **83** and the deketalized product. **83**: NMR ($CDCl_3$) δ 7.42 (5 H, br s), 3.33 (6 H, s), 1.78 (1 H, s), 1.58 (6 H, s), 0.93 (9 H, s).

Preparation of 85. A solution of 0.697 g of **83** in 3 mL of CH_2Cl_2 was stirred at room temperature with 10 mL of concentrated HCl for 2.5 h. Ether was added and the organic phase was separated and washed with two portions of saturated NaCl. After the mixture was dried over $MgSO_4$, the solvent was removed by a rotary evaporator, leaving 84% of **85** as an oil: NMR ($CDCl_3$) δ 7.70 (5 H, br s), 1.99 (6 H, s), 1.35 (9 H, s).

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Registry No. 2, 82027-11-0; **2-d_2**, 82043-82-1; **3**, 82027-12-1; **4**, 82027-13-2; **5**, 17231-17-3; **6**, 82027-14-3; **7**, 19255-01-7; **8**, 82044-29-9; **9**, 82027-15-4; (+)-**9**, 60633-83-2; **10**, 82044-30-2; **11**, 497-38-1; **11-d_2**, 28956-11-8; **12**, 82027-16-5; **13**, 82027-17-6; **14**, 34546-64-0; **15**, 82027-18-7; **16**, 82078-96-4; **17**, 82027-19-8; **18**, 82027-20-1; **19**, 82027-21-2; **20**, 82027-22-3; **21**, 82027-23-4; **22**, 82027-24-5; **23**, 700-58-3; **24**, 68157-27-7; **25**, 82027-25-6; **28**, 82027-26-7; **29**, 82027-27-8; **30**, 6050-53-9; **31**, 56346-02-2; **32**, 82027-28-9; **33**, 80325-62-8; **33-d_2**, 82027-29-0; **34**, 82027-30-3; **34-d_2**, 82064-36-6; **35**, 82027-31-4; **35-d_2**, 82043-83-2; **43**, 82027-32-5; **44**, 82027-33-6; **45**, 82027-34-7; **48**, 23235-44-1; **49**, 82027-35-8; **50**, 82027-36-9; **51**, 15023-46-8; **52**, 82027-37-0; **52-d_3**, 82027-38-1; **53**, 82027-39-2; **53-d_3**, 82065-79-0; **57**, 769-60-8; **58a**, 7476-41-7; **58b**, 82027-40-5; **61**, 82044-31-3; **62**, 82027-41-6; **63**, 574-06-1; **64**, 65786-58-5; **65**, 947-94-4; (+)-**65**, 79416-45-8; (−)-**65**, 82078-97-5; **66**, 82027-42-7; (±)-**74**, 82027-43-8; (+)-**74**, 82027-44-9; (±)-**75**, 82027-45-0; **78**, 90-90-4; **79**, 30314-45-5; **80**, 28225-70-9; **81**, 82027-46-1; **82**, 82027-47-2; **83**, 82044-32-4; **84**, 82027-48-3; **85**, 82027-49-4; *endo*-2-norbornanol mesylate, 28627-78-3; 2-adamantanol mesylate, 31616-68-9; isopropanol mesylate, 926-06-7; benzyl alcohol mesylate, 55791-06-5; 2-(*p*-carbomethoxyphenyl)-2-chloropropane, 82027-50-7; methyl vinyl ether, 107-25-5; diethyl 1-(trimethylsiloxy)-1-phenylmethanephosphonate, 31675-43-1; benzoin formate ester, 82027-51-8; benzoin trifluoroethyl ether, 82027-52-9; benzoin hexafluoroisopropyl ether, 82027-53-0; benzoin trifluoroacetate ester, 2247-65-6; methyl (+)-mandelate, 21210-43-5; trifluoroacetic acid,

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76-05-1; hexafluoroisopropyl alcohol, 920-66-1; acetone, 67-64-1; α-(trimethylsiloxy)isobutyrophenone, 55418-35-4; α-hydroxyisobutyrophenone, 7473-98-5; benzyl *tert*-butyl ketone, 6721-67-1; mandelic acid acetonide, 6337-34-4; norborneneone ethylene glycol ketal, 31444-18-5; 1-benzoyl-*exo*-2-(trifluoroacetoxy)norbornane, 82027-54-1; *exo*-2-benzoyl-*exo*-6-(trifluoroacetoxy)norbornane, 82027-55-2; 2-phenyl-2-chloropropane, 934-53-2; $PhCH(OCH_2CF_3)COSEt$, 82027-56-3; $PhCH(OCH_2CF_3)CO_2CH_2CF_3$, 82044-33-5; $PhCH(OCH_2CF_3)CO_2H$, 82027-57-4.

Supplementary Material Available: Experimental details for the preparation of mesylates **3** and **5–10** and various solvolyses procedures (6 pages). Ordering information is given on any current masthead page.

Photooxidation of Vitamin K Chromenol Derivatives[1]

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Contribution from the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221. *Received June 1, 1981*

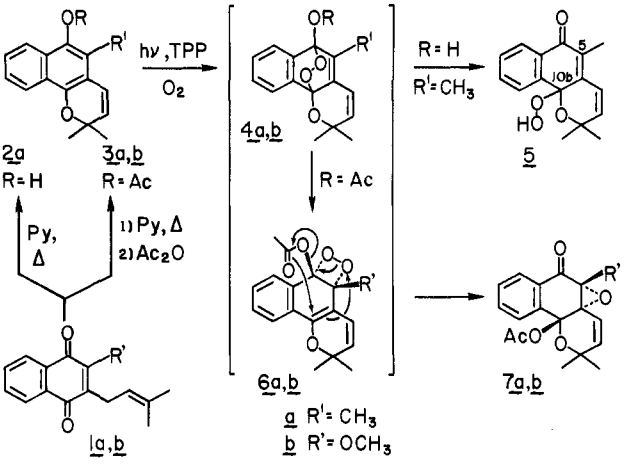
Abstract: The TPP-sensitized photooxidation of the chromenol of menaquinone 1 affords the stable peroxy-*p*-quinol. This oxidation route is blocked in the corresponding chromenol acetates of menaquinone 1 chromenol and *O*-methyllapachol. Photooxidation of these acetates leads to a unique stereoselective 1,4-acetoxy migration and the formation of novel epoxy quinone ketal derivatives. These unstable substances undergo facile hydrolysis reactions to form stable hemiketals in which the chromenol skeleton remains intact. The menaquinone 1 chromanol acetate undergoes the same type of 1,4-acetoxy migration. However, hydrolysis of this epoxy quinone ketal leads to an unstable hemiketal which undergoes pyran ring opening to form the epoxy quinone.

Vitamin K is involved in a wide variety of important biological processes such as oxidative phosphorylation,[2] blood clotting,[3] active transport of amino acids[4] and antibiotics, heme and uracil biosynthesis, and perhaps even bacterial genetic regulation.[5] Several of these processes either require molecular oxygen[2,3] or are disrupted by molecular oxygen upon exposure to ultraviolet light.[2] Consequently, it is surprising that so little information is available bearing on the reactions of vitamin K and its derivatives with oxygen. Recently, we[6] have extended the observations of Snyder and Rapoport[7] dealing with the photooxidative cleavage of vitamin K side chains. In this report, the chemistry associated with the photooxidation of vitamin K chromenol and its derivatives is described.

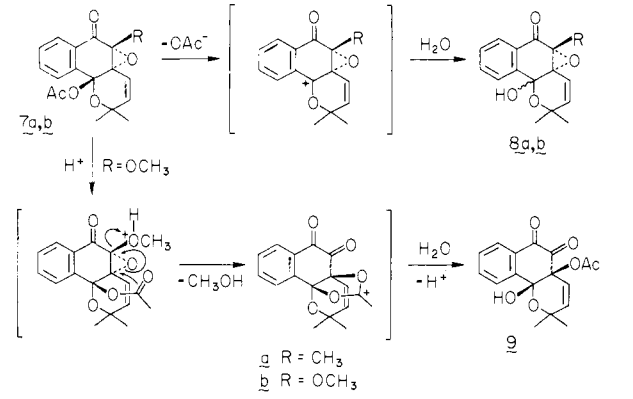
Results

Both menaquinone 1 (MK-1, **1a**) and *O*-methyllapachol (**1b**) undergo a facile base-catalyzed cyclization to chromenols **2a** and **2b**, respectively (Scheme I). These chromenol derivatives with gem-dimethyl groups at the 2-position have been selected for this study, since they do not give rise to the trivial product isomers associated with the long-chain analogues in which an asymmetric carbon atom exists at this position. Tetraphenylporphine- (TPP-) sensitized photooxidation of **2a** in acetone affords a single crystalline hydroperoxide, mp 140–141 °C, in 85% yield. That this substance is the 10b-hydroperoxide **5** rather than the isomeric 5-hydroperoxide (Scheme I) was confirmed by spectroscopic data: IR ($CHCl_3$) 1650 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6) $>C(CH_3)_2$ δ 1.42 and 1.70, $=CCH_3$ 2.10; $\lambda_{max}^{CH_3CN}$ 318 nm (ε 10 000).[8]

Scheme I



Scheme II



Under the same conditions, the acetates of these chromenols, **3a** and **b**, give rise to the epoxy ketones **7a** and **b**, respectively, in nearly quantitative yield (Scheme I). Both of these epoxy ketones are quite labile. Fortunately **7b** can be obtained in pure

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