Solvolytic Elimination Reactions. Stepwise or Concerted?

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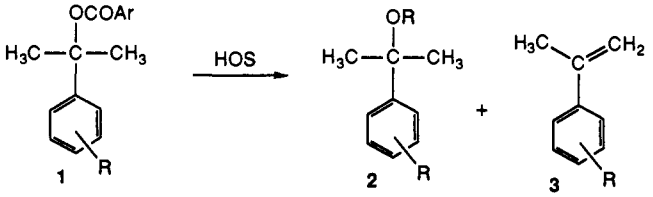
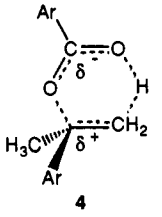
Abstract: 2-Aryl-*endo*-2-norbornyl trifluoroacetates **11** solvolyze to give a significant fraction of elimination product. A deuterium labeling study showed that the exo hydrogen is lost exclusively when the elimination product forms. A concerted ester pyrolysis type of mechanism is therefore ruled out. The tertiary benzylic trifluoroacetate $Ph(CH_3)C(CONMe_2)(OCOCF_3)$, **12**, solvolyzes to give exclusively an elimination product. The β-CD_3 isotope effect on rate was 1.15. There is, however, a larger isotope effect (2.5) in formation of the elimination product when $Ph(CH_2D)C(CONMe_2)(OCOCF_3)$ solvolyzes. The mechanism therefore has a minimum of two steps since the product-determining step and the rate-determining step have differing isotope effects. A concerted elimination mechanism is ruled out. The ortho-dimethyl-substituted cumyl trifluoroacetate **13** also solvolyzes to give an elimination product. The β-D_6 isotope effect of 1.61 is in the "normal" range for a secondary isotope effect in a carbocation-forming reaction. This argues against a concerted elimination mechanism. These results contrast with the recent suggestion that cumyl systems give elimination product via a concerted elimination mechanism. The analogous tertiary benzylic systems **11-13** all give solvolytic elimination products via discrete cationic intermediates.

Elimination reactions are among the most fundamental reaction types in organic chemistry. It is well established that solvolytic reactions often give competing elimination products as well as substitution products. For example, *tert*-butyl chloride gives up to 26% isobutylene along with substitution product when solvolyzed in methanol.[1] While it has often been assumed that the elimination product results from proton loss from the intermediate carbocation, Richard has recently challenged this general assumption.[2] Cumyl derivatives **1** have been observed to give



1 2 3

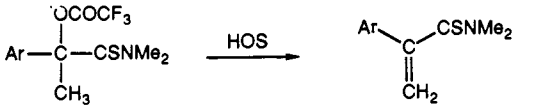
increasing amounts of the elimination product **3** as substituents on the aromatic ring become more electron-withdrawing. On the basis of kinetic isotope effects, ρ^+ values, and the Winstein-Grunwald m value for the elimination reaction, it has been suggested that the elimination product actually arises via a concerted unimolecular process as represented by transition state **4**. In this



4

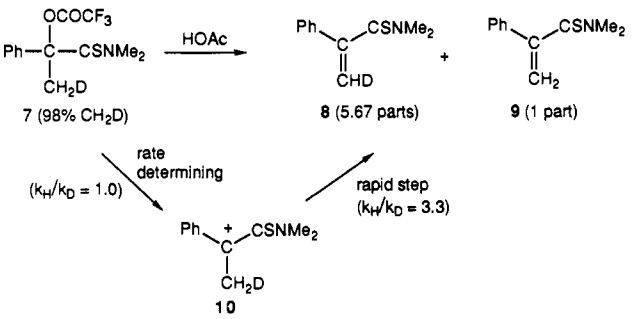
transition state there is some charge development on the benzylic carbon, but the extent of charge development is less than in the transition state leading to the substitution product **2**.

While this concerted mechanism is well accepted for pyrolytic elimination reactions[3] of esters, it is a novel concept for a solvolytic elimination reaction. In a related study, we have recently reported on the solvolytic reactivity of **5**, and this substrate gives exclusively elimination product **6** under all conditions.[4] There is a very small rate response to aryl group substituents. The response to solvent ionizing power is small, and the β-deuterium isotope effect is also small ($k_{CH3}/k_{CD3} = k_{CH3}/k_{CH2D} = 1.0$ for Ar = Ph). There are



5 6 (exclusive product)

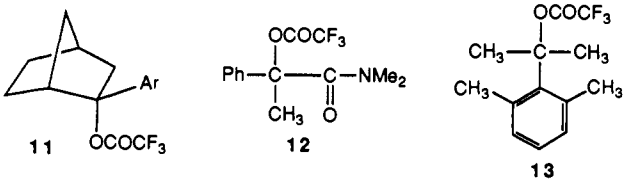
similar to the reasons for the recent proposal of a concerted elimination mechanism in the cumyl derivative **1**. Yet we have examined the isotope effect for the product-forming step by studying the monodeuterated substrate **7**. Hydrogen is lost 3.3 times faster than deuterium.[5] Therefore the rate-determining step and the product-determining step cannot be identical. Since the reaction therefore has a minimum of two discrete steps, an intermediate is necessarily involved. This intermediate was suggested to be the cation **10**.



7 (98% CH_2D) 8 (5.67 parts) 9 (1 part)

10

With these considerations in mind, we would now like to report our findings on the solvolytic elimination reactions of the substrates **11-13** (which are related to the cumyl system **1**). In light of recent questioning of the validity of a stepwise solvolytic elimination mechanism for cumyl derivatives,[2] the goal of these studies was to develop a better picture of how such eliminations occur.



11 12 13

Results and Discussion

Elimination Processes in 2-Aryl-*endo*-2-norbornyl Trifluoroacetates. In conjunction with carbocationic mechanistic studies,

(1) Bunnett, J. F.; Migdal, C. A. *J. Org. Chem.* **1989**, *54*, 3037. For data in CF_3CH_2OH-H_2O mixtures, see: Shiner, V. J., Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofsky, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838.

(2) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8960.

(3) For leading references, see: (a) Smith, G. G.; Kelly, F. W. *Prog. Phys. Org. Chem.* **1971**, *8*, 75. (b) Maccoll, A. *Adv. Phys. Org. Chem.* **1965**, *3*, 91.

(4) Creary, X.; Hatoum, H.; Barton, A.; Aldridge, T. *J. Org. Chem.* **1992**, *57*, 1887.

(5) Our previously reported isotope effect of 2.8 was calculated from the ratio of products **8**:**9**. In fact, since the trifluoroacetate **7** contained 2% of the unlabeled trifluoroacetate (which can only form **9**), the isotope effect must be corrected for the 2% of **9** that results from unlabeled starting trifluoroacetate. This gives a corrected isotope effect of 3.3 for the loss of hydrogen relative to deuterium when **7** undergoes elimination.

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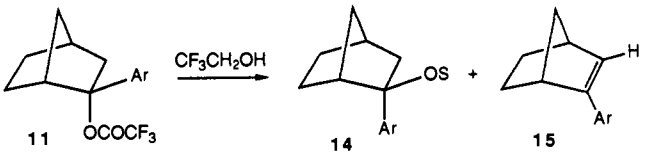
Table I. Solvolysis Rates of Substrates in Acetic Acid

substrate	temp, °C	k, s^{-1} [a]
12	80.0	3.07×10^{-4}
25	80.0	2.67×10^{-4}
13	25.0	3.42×10^{-2}
29	25.0	2.13×10^{-2}
32	25.0	2.77×10^{-2}
cumyl trifluoroacetate	25.0	3.98×10^{-4}
30	25.0	2.43×10^{-4}

[a] Determined by UV or ^{19}F NMR. Maximum standard deviations in duplicate runs were ±1%. See Experimental Section for the kinetic method.

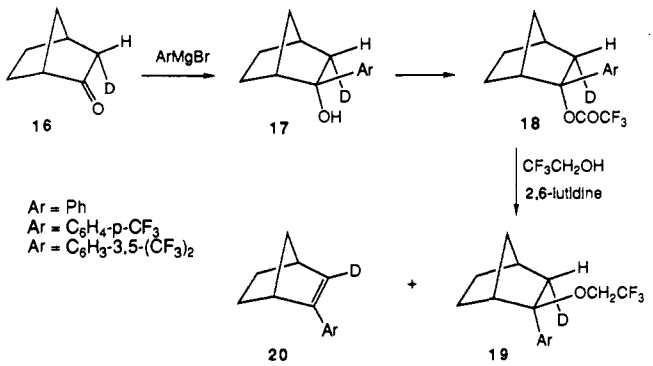
2-norbornyl derivatives have been among the most intensely investigated systems.[6] Over the years, in conjunction with other solvolytic studies, we have had occasion to prepare and solvolyze derivatives **11**.[7] We have also seen varying amounts of the elimination product **15** when these substrates are solvolyzed. In



11 14 15

this respect, these tertiary benzylic systems **11** are analogous to the cumyl system **1**. Unlike the cumyl system, the norbornyl system **11** can provide a stereochemical test for the idea of a concerted elimination mechanism. A concerted elimination mechanism via a transition state analogous to **4** would require loss of the hydrogen atom cis to the departing trifluoroacetate leaving group.

The stereospecifically deuterated analogs **18** have therefore been prepared from the labeled norcamphor **16**. These trifluoroacetates were solvolyzed in trifluoroethanol buffered with 2,6-lutidine. In addition to the substitution products **19**, the elimination products **20** were also formed (19% when Ar = Ph; 14% when Ar = C_6H_4-*p*-CF_3; 23% when Ar = C_6H_3-3,5-$(CF_3)_2$. These products are all stable to the reaction conditions and are therefore primary products. In all cases, the elimination products **20** contained no olefinic hydrogens within the limits of NMR detection. Therefore the exo hydrogens of **18** is lost during the step that leads to the elimination product. *These results rule out a concerted elimination process when these norbornyl analogs of the cumyl systems 1 suffer elimination under solvolytic conditions.* The probable mechanism for the formation of **20** involves carbocation formation followed by preferential proton loss from the exo side of this discrete tertiary benzylic norbornyl carbocation intermediate.[8]



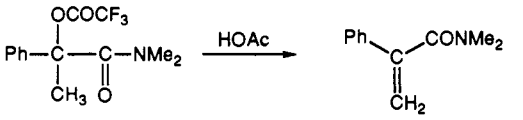
16 17 18 20 19

(6) For leading references, see: Brown, H. C. *The Nonclassical Ion Problem*: Plenum Press: New York, 1977.

(7) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938.

(8) Protonation of norbornenes occurs preferentially from the exo direction to give norbornyl cations. By microscopic reversibility, loss of the exo hydrogen from a norbonyl cation will therefore be faster than loss of the endo hydrogen. See: (a) Kropp, P. J. *J. Am. Chem. Soc.* **1973**, *95*, 4611. (b) Stille, J. K.; Hughes, R. D. *J. Org. Chem.* **1971**, *36*, 340. (c) Brown, H. C.; Liu, K.-T. *J. Am. Chem. Soc.* **1975**, *97*, 2469. (d) Brown, H. C.; Kawakami, J. H. *Ibid.* **1975**, *97*, 5521.

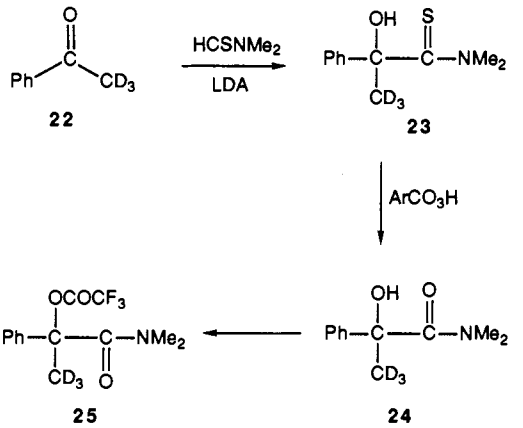
Elimination Processes in the α-CONMe$_2$ Derivative 12. In order to shed further light on the true mechanism of formation of elimination products under solvolytic conditions, we have now studied the trifluoroacetate **12**. In this analog of the cumyl system **1**, the formally electron-withdrawing $CONMe_2$ group replaces one of the methyl groups. This trifluoroacetate, **12**, gives the elimination product **21** under acetolysis conditions. Since elim-



12 21

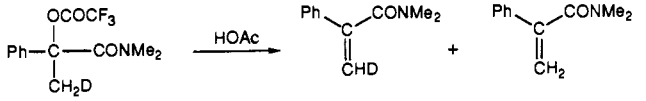
ination is the exclusive process (rather than a minor process as in cumyl systems **1** or the norbornyl systems **11**), it is therefore very appropriate to study this reaction as a model for solvolytic elimination mechanisms.

The approach to determination of the elimination mechanism involves the isotope effect test that we have previously applied to the thioamide derivative **5**.[4] The α-CD_3 analog **25** was prepared from deuterated acetophenone, **22**, and the isotope effect on the rate-determining step of the elimination was determined from the rate of acetolysis of **25** (Table I). The kinetic isotope effect was



22 23 25 24

1.15 ± 0.01 at 80 °C in acetic acid. The preference for loss of deuterium vs hydrogen in the product-determining step was next determined by solvolyzing the monodeuterated derivative **26**. The



26 27 (4.28 parts) 21 (1 part)

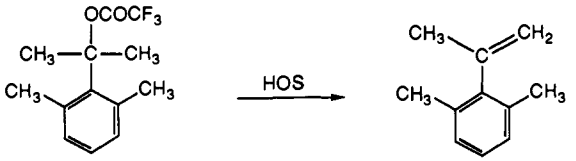
substrate was prepared from $PhCOCH_2D$ (using the same methodology as in the preparation of **25**) and contained 3% of the unlabeled trifluoroacetate **12**. As measured by 500-MHz ^1H NMR, the solvolysis products **27** and **21** are formed in a 4.28:1 ratio. When corrected for the 3% unlabeled **12** present in **26**, this corresponds to a loss of hydrogen 2.5 times faster than the loss of deuterium in the product-determining step. Therefore the product-determining step (isotope effect of 2.5) cannot be the same as the rate-determining step (isotope effect of 1.15).[9] The reaction mechanism has a minimum of two steps, and there must therefore be a reactive intermediate. *This rules out the concerted mechanism for formation of the elimination product 21 under solvolytic conditions.*

The reactive intermediate in the transformation of **12** (or **26**) to **21** is proposed to be an α-carbonyl cation.[10] Proton loss is

(9) A reviewer has pointed out that secondary deuterium isotope effects contribute to the isotope effect on rate and to the isotope effect on product formation and that these contributions are different. For example, formation of **27** vs **21** from **26** involves a secondary deuterium isotope effect as well as a primary effect. *Our analysis assumes that secondary isotope effects are not large.* Indeed, this reviewer has pointed out that (since isotope effects on the overall rate for **5** and **12** are quite small) unrealistically large inverse secondary isotope effects are required to be consistent with the single-step mechanism.

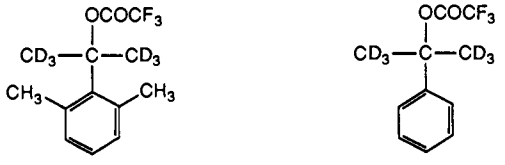
believed to occur at a relatively early ion-pair stage. These results suggest that α-CD_3 isotope effects[11] on the overall rate can be rather small (1.15) when elimination occurs at an early ion-pair stage. This conclusion is in line with our earlier finding for **5**.[4] In this system, the α-CD_3 isotope effect was negligible (1.0) despite the fact that there is a carbocation intermediate involved in this solvolytic elimination. Solvent effects on rates of solvolysis of **5** were also remarkably small for a reaction involving a cationic intermediate. For example, the rate of solvolysis of **5** in trifluoroethanol was only 2.3 times faster than that in acetic acid. This led to the conclusion that **5** yields a cationic intermediate that loses a proton at a very early, tight ion-pair stage. A similar pattern is seen for **12**, which reacts only 24 times faster in trifluoroethanol than in acetic acid. By way of contrast, the standard k_C substrate 2-adamantyl trifluoroacetate[12] reacts 123 times faster in trifluoroethanol than in acetic acid,[13] and cumyl trifluoroacetate reacts 207 times faster.[14] The trifluoroacetate **12** appears to be intermediate in its response to solvent. We believe that both solvent effects and α-CD_3 isotope effects are an indication that **12** is forming an ion-pair which undergoes proton loss at a more solvated stage than does **5**, but not at the highly solvated stage attaind by ions derived from the model substrate 2-adamantyl trifluoroacetate.

Elimination Processes in Trifluoroacetate 13. Attention was next turned to the 2,6-dimethyl-substituted analog of cumyl trifluoroacetate, **13**. This substance was selected for study in more detail since it gives exclusively the elimination product **28** when solvolyzed in acetic acid or trifluoroethanol.[15]



13 **28**

In order to evaluate the potential concerted elimination mechanism, the deuterated analog **29** was prepared. The measured β-D_6 kinetic isotope effect in acetic acid was 1.61 ± 0.03. This is quite similar to the value of 1.64 ± 0.02 measured for cumyl trifluoroacetate, **30** in acetic acid. The isotope effect of 1.61 for



29 **30**

1.61 β-D_6 isotope effect 1.64

this reaction is quite different from the calculated isotope effect of 4.3 for the elimination reaction of **1** (R = *m*-F)[2] and does not support a concerted elimination mechanism for **13**. It is completely consistent with rate-limiting ionization of **13** to give a tertiary benzylic cationic intermediate with a normal secondary deuterium isotope effect of 1.27 per CD_3.

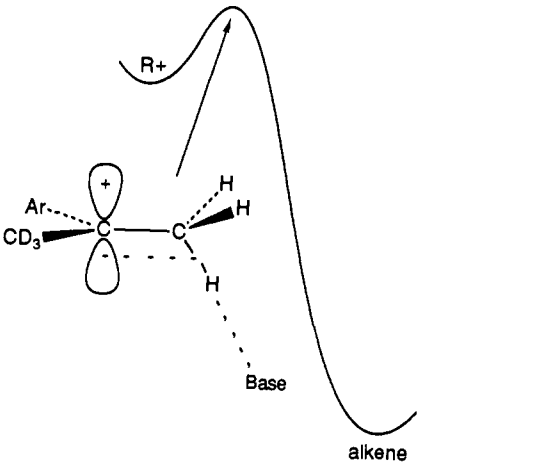
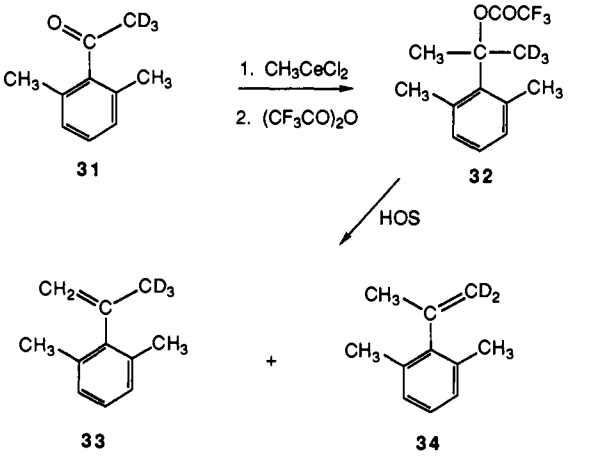


Figure 1. Early transition state for proton loss from a cationic intermediate.

The mono-CD_3 substrate **32** was of interest in order to determine the rate of deuterium vs hydrogen loss in the product-forming step. The requisite alcohol precursor was prepared by CH_3CeCl_2



31 **32**

33 **34**

addition[16] to the deuterated ketone **31**. The ratio of solvolysis products **33** to **34** was determined by ^1H NMR, and this ratio represents the isotope effect in the product-forming step. The ratio **33**:**34** was 1.46 in acetic acid (where these products are stable under the reaction conditions). This isotope effect in the product-forming step is somewhat different from the value of 1.61 observed in the rate-determining step. The difference in the rate-determining and product-forming isotope effects is not as large as in the case of **5** or **12**. Therefore attempting to rule out the concerted elimination mechanism on the basis of this difference is problematic since small secondary isotope effects can operate. Our probe for a multistep mechanism, which involves a comparison of the isotope effect on rate with the product-determining isotope effect, is therefore inconclusive when applied to solvolysis of **13**, **29**, and **32** in acetic acid.

The product ratio **33**:**34** appears to vary with solvent. The value is 2.09 in trifluoroethanol. The rapid solvolysis rates of these systems in trifluoroethanol do not permit determination of kinetic isotope effects in this solvent. However, if one assumes that the kinetic isotope effect in trifluoroethanol will be similar to the value in acetic acid (1.61), then the product-forming isotope effect of 2.09 in trifluoroethanol would require an unusually large secondary isotope effect to be consistent with the concerted elimination mechanism.

Our suggestion on the basis of the isotope effect on rate (β-D_6 isotope effect = 1.61) is that the classic E1 mechaniam operates in the elimination reactions of **13**. A comment regarding the isotope effect on product formation from a carbocation is ap-

(10) For a recent review of carbocations substituted with electronegative groups, see: Creary, X. *Chem. Rev.* **1991**, *91*, 1625.

(11) For a discussion of β-deuterium isotope effects on rates of solvolytic reactions, see: (a) Shiner, V. J., Jr. In *Isotope Effects in Chemical Reactions*; Collins, C. J.; Bowman, N. S., Eds.; ACS Monograph Series 167; Van Nostrand Reinhold Co.: New York, 1970. (b) Schepple, S. E. *Chem. Rev.* **1972**, *72*, 511. (c) Shiner, V. J., Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofsky, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838. (d) Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomic, M.; Sunko, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 2408.

(12) Bentley, T. W.; Roberts, K. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1055.

(13) Creary, X.; Wang, Y.-S. *J. Org. Chem.* **1992**, *57*, 4761.

(14) The first-order rate constant for solvolysis of cumyl trifluoroacetate in trifluoroethanol is 8.23×10^{-2} s^{-1}.

(15) For an analogous elimination reaction, see: Evilia, R. F.; Pan, D.; Timberlake, J. W.; Whittenburg, S. L. *Tetrahedron Lett.* **1991**, *32*, 871.

(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

propriate. While the effect of CD_3 substitution on the rate of carbocartion formation should be a secondary isotope effect, the effect on which product forms (**33** or **34**) is essentially a primary isotope effect (with a small secondary effect). While cleavage of C–H bonds can often lead to large primary isotope effects,[17] it should be kept in mind that proton loss from a carbocationic intermediate is a very exothermic process. Hence the transition state can occur quite early along the reaction coordinate (as illustrated in Figure 1). Hence primary isotope effects as small as 1.46 are not inconsistent with proton loss from a cationic intermediate. The variation of the product-forming isotope effect for **32** (from 1.46 to 2.09) with solvent may simply reflect a shift from an early to a later transition state with changing solvent.

Conclusions. 2-Aryl-*endo*-2-norbornyl trifluoroacetates **11** solvolyze to give a significant fraction of elimination product where the exo hydrogen is lost exclusively. This rules out a concerted elimination mechanism analogous to that recently proposed from cumyl derivatives. The tertiary benzylic α-$CONMe_2$-substituted trifluoroacetate **12** solvolyzes to give exclusively an elimination product with a kinetic isotope effect that differs from the isotope effect in the product-forming step. The mechanism therefore has a minimum of two steps, and a concerted elimination mechanism is ruled out. An α-$CONMe_2$-substituted cation is the proposed intermediate, which undergoes proton loss at an early ion-pair stage. The ortho-dimethyl-substituted cumyl trifluoroacetate **13** solvolyzes to give an elimination product. The β-deuterium isotope effect is in the "normal" range for a secondary isotope effect in a carbocation-forming reaction. This argues against a concerted elimination mechanism. Where do these studies fit in the overall scheme of mechanistic studies? Our results imply that, at a minimum, the recent challenge to the classic E1 mechanism in the cumyl system may not have generality. The analogous tertiary benzylic systems **11–13** all give solvolytic elimination products via discrete cationic intermediates.[18]

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a General Electric GN 300 spectrometer. ^{19}F NMR spectra were recorded on a Nicolet NT 300 spectrometer at 282.3 MHz. Mass spectra were recorded on a Finnigan MAT 8430 high-resolution spectrometer. All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were carried out using EM Science 230–400-mesh silica gel 60. The preparation of trifluoroacetate **12** has previously been described.[4]

Preparation of *exo*-2-Phenyl-*endo*-bicyclo[2.2.1]hept-2-yl Trifluoroacetate, 11 (Ar = Ph). The preparation of this trifluoroacetate has previously been described.[7] In the present study, this material was prepared via a modified procedure using ether as solvent. A solution of 370 mg of *exo*-2-phenyl-*endo*-bicyclo[2.2.1]heptan-2-ol and 306 mg of 2,6-lutidine in 8 mL of ether was cooled to 0 °C, and 537 mg of trifluoroacetate anhydride was added. After 10 min at 0 °C, water was added, and the aqueous phase was separated. The ether extract was washed with cold dilute HCl solution, $NaHCO_3$ solution, and saturated NaCl solution and dried over $MgSO_4$. The ether solution of the trifluoroacetate **11** was stored at −20 °C, and the ether solvent was removed from portions of this stock solution just prior to use. The trifluoroacetate **11** is stable for only short periods of time after solvent removal. After a few minutes, however, autocatalytic decomposition occurs. With care, ^1H NMR spectra of **11** can be obtained that contain no trace of alkene **15** as well as a small amount of ether. However, prolonged evacuation using a rotary evaporator to remove the last traces of ether results in formation of increasing amounts of **15**.

The preparation of trifluoroacetates **11** (Ar = C_6H_4-*p*-CF_3 and C_6H_3-3,5-$(CF_3)_2$) was completely analogous to the above procedure.

Preparation of *exo*-2-Phenyl-*endo*-3-deuterio-*endo*-bicyclo[2.2.1]heptan-2-ol, 17 (Ar = Ph). A Grignard reagent was prepared from 525 mg of bromobenzene and 130 mg of Mg in 15 mL of ether. The Grignard solution was cooled to 15 °C, and a solution of 310 mg of *endo*-3-deuterionorcamphor (>99% *endo*-D)[4,19] in 5 mL of ether was added dropwise. After 1 h, dilute NH_4Cl solution was added, and the ether phase was separated, washed with saturated NaCl solution, and dried over $MgSO_4$. After solvent removal using a rotary evaporator, the product was chromatographed on 15 g of silica gel and eluted with 10–15% ether in hexanes. The yield of **17** was 345 mg (65% yield) as a white solid, mp 42–44 °C. ^1H NMR ($CDCl_3$): δ 2.60 (m, 1 H), 2.30 (m, 2 H), 2.18 (m, 1 H), 1.77–1.40 (m, 5 H), 1.33 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 149.00, 128.21, 126.78, 125.87, 80.68, 47.18, 46.15 (t, J = 20.1 Hz), 38.70, 37.46, 29.07, 22.26.

The preparation of labeled alcohols **17** (Ar = C_6H_4-*p*-CF_3 and C_6H_3-3,5-$(CF_3)_2$) from *endo*-3-deuterionorcamphor was completely analogous to the above procedure.

The preparation of labeled trifluoroacetates **18** (by reaction of the corresponding alcohols **17** with trifluoroacetic anhydride and 2,6-lutidine in ether) was completely analogous to the preparation of **11**.

Preparation of α-Hydroxy Amide 24 and Trifluoroacetate 25. The deuterated α-hydroxy thioamide **23** was prepared (58% yield) by reaction of acetophenone-d_3, **22** (>99% D), with dimethylthioformamide and lithium diisopropylamide by the same procedure as that previously employed for unlabeled acetophenone.[4] Following the general method of Pinnick,[20] a solution of 2.242 g of **23** in 75 mL of methylene chloride was cooled to 0 °C, and 2.291 g of 90% *m*-chloroperbenzoic acid was added in small portions. The mixture was then stirred at room temperature for 12 h. Silica gel was then added to the reaction flask, and the CH_2Cl_2 was removed using a rotary evaporator. The residue was then chromatographed on 70 g of silica gel and eluted with increasing amounts of ether in hexanes. The product **24** (945 mg) eluted with 80% ether in hexane. This was recrystallized from 25 mL of hexanes to give 767 mg (34%) of **24**. The ^1H NMR of **24** was identical with that of unlabeled material[4] except for the absence of the singlet at δ 1.817.

The trifluoroacetate **25** was prepared from **24** using the same procedure as for the unlabeled trifluoroacetate **12**. The ^1H NMR of **25** was identical with that of **12**[4] except for the absence of the singlet at δ 1.955.

Preparation of Trifluoroacetate 26. A solution of 0.50 g of Ph-$(CH_2D)C(OH)(CSNMe_2)$[4] in 15 mL of CH_2Cl_2 was oxidized with 90% *m*-chloroperbenzoic acid using the same procedure as in the oxidation of **23**. The 500-MHz NMR spectrum of the product $Ph(CH_2D)C(OH)(CONMe_2)$ shows 3% undeuterated $Ph(CH_3)C(OH)(CONMe_2)$ (CH_3 at δ 1.828). ^{13}C NMR of $Ph(CH_2D)C(OH)(CONMe_2)$ ($CDCl_3$): δ 175.00, 142.94, 128.75, 127.76, 125.35, 74.69, 38.1 (br), 37.5 (br), 24.56 (t, J = 19.8 Hz).

The trifluoroacetate **26** was prepared from $Ph(CH_2D)C(OH)(CONMe_2)$, trifluoroacetic anhydride, and 2,6-lutidine in ether using the previously described procedure.[4] ^1H NMR ($CDCl_3$): δ 7.46–7.33 (m, 5 H), 2.980 (br s, 3 H), 2.630 (br s, 3 H), 1.937 (br, s 2 H). ^{13}C NMR ($CDCl_3$): δ 168.00, 155.03 (q, J_{C-F} = 43 Hz), 139.07, 129.20, 128.66, 123.49, 114.48 (q, J_{C-F} = 287 Hz), 88.34, 37.29 (br), 37.22 (br), 27.42 (t, J = 20 Hz).

Preparation of Trifluoroacetate 13. A solution of 1.508 g of 2-bromo-*m*-xylene in 15 mL of tetrahydrofuran was cooled to −78 °C, and 5.5 mL of 1.6 M *n*-butyllithium was added dropwise. The mixture was kept at −78 °C for 30 min, and then 0.59 g of acetone in 2 mL of THF was added dropwise. The mixture was warmed to room temperature, and water was added. The mixture was transferred to a separatory funnel with ether, and the organic extract was washed with saturated NaCl solution and dried over $MgSO_4$. After solvent removal using a rotary evaporator, the residue was chromatographed on 10 g of silica gel and eluted with increasing amounts of ether in hexanes. The product eluted with 10% ether in hexanes and was further purified by sublimation at 1.6 mm. The yield of 2-(2,6-dimethylphenyl)-2-propyl alcohol was 0.32 g (24 % yield), mp 57–59 °C. ^1H NMR ($CDCl_3$): δ 6.966 (s, 3 H), 2.510 (s, 6 H), 1.832 (br s, 1 H), 1.694 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 145.32, 135.86, 131.06, 126.02, 75.89, 31.57, 25.18. Exact mass calcd for $C_{11}H_{16}O$: 164.1201. Found: 164.1200.

A solution of 208 mg of 2-(2,6-dimethylphenyl)-2-propyl alcohol and 190 mg of 2,6-lutidine in 6 mL of ether was cooled to −10°C, and 336 mg of trifluoroacetic anhydride was added. After the mixture was stirred for 10 min at −10 °C, an aqueous workup followed, with the solution of **13** being immersed in an ice bath during the entire workup. Cold water was added with stirring, and the aqueous phase was removed. Dilute HCl solution was next added and decanted, followed by $NaHCO_3$ solution and saturated NaCl solution. The mixture was then dried over $MgSO_4$. This

(17) The magnitude of this primary isotope effect should be dependent on a number of factors, including temperature and position of the transition state. See: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 233–7, 786.

(18) A very recent study on the solvolysis of 1,1-diphenyl-1-chloroethane, which gives a large fraction of elimination product, has appeared. Kinetic isotope effect data indicate that both elimination and substitution products arise from a common intermediate (probably a contact ion-pair). See: Thibblin, A.; Sidhu, H. *J. Am. Chem. Soc.* **1992**, *114*, 7403.

(19) (a) Abad, G. A.; Jindal, S. P.; Tidwell, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 6326. (b) Boyer, B.; Lamaty, G.; Roque, J. P.; Geneste, P. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 260. (c) Jefford, C. W.; Boschung, A. F. *Helv. Chim. Acta* **1974**, *57*, 2242.

(20) Kochhar, K. S.; Cottrell, D. A.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 1323.

solution of **13** was used for kinetic studies.

The trifluoroacetate **13** is an unstable compound and cannot be isolated in the pure state. Removal of the ether solvent left only the alkene **28**. The ^{1}H NMR spectrum of **13** (free of the alkene **28**) could be obtained in ether solution. If 2,6-lutidine is added to the ether solution of **13** before solvent removal and the solvent is rapidly removed using a rotary evaporator, a spectrum of **13** can be obtained in $CDCl_3$. However, the spectrum shows a small amount of the alkene **28**, along with 2,6-lutidine and residual ether. Even under these conditions in $CDCl_3$, **13** slowly eliminates to form **28**. ^{1}H NMR of **13** (ether): δ 6.90 (s, 3 H), 2.38 (s, 6 H), 1.92 (s, 6 H). Solutions of **13** in ether were used immediately or stored at −20 °C. If the ether solution is left at room temperature, a signal at δ 2.16 due to the alkene **28** slowly begins to appear.

Preparation of Trifluoroacetate 29. The preparation of 2-(2,6-dimethylphenyl)-2-propyl alcohol-d_6 from reaction of 2-bromo-*m*-xylene and *n*-butyllithium followed by addition of acetone-d_6 was completely analogous to the preparation of the undeuterated alcohol. The yield was 62%. ^{1}H NMR ($CDCl_3$): δ 6.984 (s, 3 H), 2.524 (s, 6 H), 1.707 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 145.27, 135.86, 131.04, 126.02, 75.59, 30.63 (heptet, J = 19.3 Hz), 25.13.

The preparation of trifluoroacetate **29** from 2-(2,6-dimethylphenyl)-2-propyl alcohol-d_6 was completely analogous to the preparation of the undeuterated analog **13**.

Preparation of Trifluoroacetate 32. The general procedure of Imamoto[16] was used for preparation of the alcohol precursor. A flask containing 2.97 g of $CeCl_3 \cdot 7H_2O$ was evacuated at 0.05 mm and heated for 2 h at 125–130 °C. Dry tetrahydrofuran (15 mL) was then added to the salt under N_2, and the mixture was stirred at room temperature for 2 h. The mixture was cooled to −78 °C, and 5.3 mL of 1.5 M methyllithium in ether was then added. The mixture was stirred for another 1 h at −78 °C. A solution of 602 mg of 2,6-dimethylacetophenone-d_3 (prepared by NaOD-catalyzed exchange of 2,6-dimethylacetophenone with D_2O) in 2 mL of tetrahydrofuran was then added dropwise. The mixture was slowly warmed to room temperature, and NH_4Cl solution and ether were added. The organic extract was washed with water and saturated NaCl solution and dried over $MgSO_4$. The solvents were removed using a rotary evaporator, and the residue was chromatographed on 15 g of silica gel. The column was eluted with increasing amounts of ether in hexanes. About 45 mg of unreacted ketone eluted followed by 599 mg (90% yield) of 2-(2,6-dimethylphenyl)-2-propyl alcohol-d_3. This product was further purified by sublimation at 1.5 mm. ^{1}H NMR ($CDCl_3$): δ 6.991 (s, 3 H), 2.533 (s, 6 H), 1.70 (br s, 1 H), 1.720 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 145.30, 135.89, 131.08, 126.06, 75.82, 31.34, 25.17. The carbon signal from CD_3 was not visible under the spectral conditions.

The preparation of trifluoroacetate **32** from 2-(2,6-dimethylphenyl)-2-propyl alcohol-d_3 was completely analogous to the preparation of the undeuterated analog **13**.

Solvolysis of 11 (Ar = Ph) in Trifluoroethanol. A solution of trifluoroacetate **11** (Ar = Ph) was prepared in ether solution from 148 mg of *exo*-2-phenyl-*endo*-bicyclo[2.2.1]heptan-2-ol as described above. The ether solvent was rapidly removed using a rotary evaporator. Examination of a small portion by ^{1}H NMR showed only **11** (R = Ph) and some residual ether. No trace of alkene **15** was present. The trifluoroacetate **11** was immediately dissolved in 11 mL of trifluoroethanol that contained 152 mg of 2,6-lutidine. After 250 min at room temperature, the solvent was removed using a rotary evaporator. The residue was taken up into ether, and the ether solution was washed with dilute HCl solution, $NaHCO_3$ solution, and saturated NaCl solution. After the solution was dried over $MgSO_4$, the solvent was removed using a rotary evaporator, and the crude residue was analyzed by NMR. The products **14** and **15** (Ar = Ph) were present in a 100:24 ratio as determined from the area of the peaks of the bridgehead hydrogen of **14** at δ 2.60 and the bridgehead hydrogen of **15** at δ 2.99. The following controls were also carried out to ensure that **15** is a primary product and that it does not arise from **14** via a secondary acid catalyzed process.

In a separate run, portions of the trifluoroethanol solution were withdrawn from the solvolysis mixture and worked up after 3-, 8-, and 52-min reaction times. In these workup procedures, the HCl wash was omitted so that at no time did the mixture become acidic. All of the reactions had gone to completion and the ratio **14**:**15** was 100:24 in all cases.

In a separate run, excess 2,6-lutidine was added to 4 mL of a solution of **11** in ether, and the ether solution was added with stirring to 16 mL of trifluoroethanol. After 45 min, a standard workup followed. The ratio **14**:**15** was again 100:24.

Solvolysis of 18 (Ar = Ph) in Trifluoroethanol. The ether solvent was rapidly removed via a rotary evaporator from a solution of the trifluoroacetate **18** prepared in the usual fashion from 201 mg of **17**. A solution of 178 mg of 2,6-lutidine in 15 mL of trifluoroethanol was immediately added with stirring. After 35 min most of the trifluoroethanol was removed via a rotary evaporator, and the residue was taken up into ether. A standard aqueous workup followed, and the solvent was removed from the ether extract via a rotary evaporator. ^{1}H NMR analysis showed the presence of **19** and **20** in a 100:23 ratio as determined from the ratio of the peaks at δ 2.60 and 2.99. Examination of the olefinic region of the spectrum showed no trace of a signal at δ 6.29 that would arise from the presence of **15**.

Solvolysis of Trifluoroacetate 12 in Acetic Acid. A solution of 75 mg of trifluoroacetate **12** in 4 mL of acetic acid (0.1 M NaOAc) was heated at 80 °C for 7 h. The mixture was then taken up into ether and water. The acetic acid was carefully neutralized with solid Na_2CO_3. The ether extract was then washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was removed using a rotary evaporator, leaving 44 mg (97% yield) of olefin **21** as an oil. ^{1}H NMR of **21** ($CDCl_3$): δ 7.47–7.25 (m, 5 H), 5.742 (s, 1 H), 5.361 (s, 1 H), 3.067 (s, 3 H), 2.893 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.82, 145.34, 135.63, 128.79, 128.50, 125.66, 113.97, 38.50, 34.63. Exact mass calcd for $C_{11}H_{13}NO$: 175.0997. Found: 175.0998.

Solvolysis of Trifluoroacetate 26 in Acetic Acid. The acetolysis conditions and workup procedures were identical with those of the undeuterated analog **12**. The ratio of the products **27** and **21** was determined by 500-MHz ^{1}H NMR, where the olefinic hydrogens of **27** (mixture of isomers) appear at δ 5.727 and 5.342 (upfield from the corresponding hydrogens in **21**).

Solvolysis of Trifluoroacetate 13 in Acetic Acid. A solution of trifluoroacetate **13** in ether, prepared from 172 mg of alcohol in 6 mL of ether as described above, was immediately added to 13 mL of acetic acid (0.1 M in NaOAc). The mixture was placed on a rotary evaporator for 5 min to remove the ether. After 2 h at room temperature, the mixture was cooled in an ice bath, ether was added, and the acetic acid was neutralized by the addition of NaOH solution. The ether extract was dried over $MgSO_4$, and the solvent was removed by distillation through a Vigreux column. The residue was distilled using a short-path distillation head to give 135 mg (88% yield based on starting alcohol) of **28**, bp 85 °C (35 mm). ^{1}H NMR ($CDCl_3$): δ 5.253 (m, 1 H), 4.754 (m, 1 H), 2.254 (s, 6 H), 1.949 (d of d, J = 1.4, 1.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 144.67, 143.24, 134.63, 127.19, 126.33, 114.57, 23.50, 19.62. Exact mass calcd for $C_{11}H_{14}$: 146.1096. Found: 146.1095.

The following control was carried out in order to verify that **28** was the only primary product. A small amount of 2,6-lutidine was added to a solution of **13** in ether. NMR analysis of the ether solution showed >1 equiv of 2,6-lutidine and no alkene **28**. The ether solvent was quickly removed with a rotary evaporator, and CD_3CO_2H was immediately added. The reaction was monitored by NMR at 20 °C. Although the reaction is rapid, some unreacted **13** could be observed if NMR spectra were recorded immediately after mixing. The only product that was observed as **13** disappeared was the alkene **28**. No trace of substitution product was observed even at a short reaction time.

Solvolysis of Trifluoroacetate 32 in Acetic Acid. A solution of trifluoroacetate **32** in ether prepared from 152 mg of alcohol was reacted in acetic acid (0.1 M in NaOAc) using the same procedure as for **13**. After the workup, solvent removal with a rotary evaporator gave 84 mg of **33** and **34**. The ratio **33**:**34** was determined by ^{1}H NMR from the area of the peaks of the two olefinic hydrogens of **33** at δ 5.25 and 4.75 and the three methyl hydrogens of **34** at δ 1.95.

Solvolysis of Trifluoroacetate 32 in Trifluoroethanol. A solution of trifluoroacetate **32** in 3 mL of ether containing excess 2,6-lutidine (prepared from 60 mg of alcohol) was added to 14 mL of trifluoroethanol. After 17 h at room temperature most of the trifluoroethanol was removed with a rotary evaporator, and the residue was taken up into ether. The ether was then washed with water and dried over $MgSO_4$. The excess 2,6-lutidine was not removed by an acidic wash to ensure that the mixture at no time became acidic. Solvent removal showed **33** and **34** in a 100:48 ratio as determined by NMR.

Kinetics Procedures. Rates of solvolyses of trifluoroacetates **12** and **25** were determined by ^{19}F NMR as previously described.[13] Correlation coefficients were all greater than 0.9998. Maximum standard deviations in duplicate runs were ±1%. Rates of solvolyses of **13**, **29**, **30**, cumyl trifluoroacetate, and **32** were determined by UV spectroscopy as previously described.[4] Absorbance changes were all monitored in acetic acid at 270 nm.

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