Mechanistic Studies of Fluorodecarboxylation with Xenon Difluoride

Timothy B. Patrick,* Sadegh Khazaeli,* Sourena Nadji, Katy Hering-Smith, and Dirk Reif

Department of Chemistry, Southern Illinois University, Edwardsville, Illinois 62026

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The reaction of xenon difluoride with primary carboxylic acids involves a free-radical mechanism. Trifluoroacetic acid (1) decarboxylates in benzene to give (trifluoromethyl)benzene (2). 6-Hexenoic acid (3) produces a free radical in a radical clock reaction in which the k_{abs} (25 °C) for XeF_2 was determined as 1.1×10^6 M^{-1} s^{-1}. The primary radical from hexanoic acid was spin-trapped to give ESR signals diagnostic for the alkyl radical. Secondary acids were shown to proceed through a trivalent intermediate, but its exact nature was not proven. The acid 6 gave a rearranged product (7) characteristic of carbocations, whereas the diacid 8 gave difluoro compounds without stereoselectivity. The tertiary bicyclic acids 13 and 15 gave products only from solvent hydrogen abstraction strongly indicative of free radicals.

In previous papers we described a process, fluorodecarboxylation, in which alkyl fluorides are generated from the reaction of carboxylic acids with xenon difluoride (eq 1).[1]

$$RCOOH + XeF_2 \rightarrow RF + CO_2 + HF + Xe \quad (1)$$

Fluorodecarboxylation, the fluorine analog of the Hunsdiecker and Kochi reactions, proceeds through a xenon ester, involves trivalent intermediates, and incorporates $^{18}F^-$ into the products. Further details about the reaction mechanism especially with regard to the nature of the intermediates are the subject of this report.

Scheme I shows possible reaction paths of fluorodecarboxylation. The formation of the xenon ester A is

Scheme I

$$RCOOH + XeF_2 \rightarrow \underset{A}{RCOOXeF} + HF \quad (a)$$

$$RCOOXeF + {}^{18}F^- \rightarrow R\text{-}{}^{18}F + CO_2 + Xe + F^- \quad (b)$$

$$RCOOXeF \rightarrow RCO_2^{\bullet} + Xe + F^{\bullet} \quad (c)$$

$$RCO_2^{\bullet} \rightarrow R^{\bullet} + CO_2 \quad (d)$$

$$R^{\bullet} + XeF^{\bullet} \rightarrow R^+ + Xe + F^- \quad (e)$$

$$R^+ + F^- \rightarrow RF \quad (f)$$

$$R^{\bullet} + XeF_2 \rightarrow RF + {}^{\bullet}XeF \quad (g)$$

postulated because DesMarteau isolated a xenon ester from the reaction of trifluoroacetic acid and xenon difluoride at low temperature. The xenon ester, CF_3CO_2XeF, decomposed to XeF_2, CO_2, Xe, C_2F_6, and CF_4. Xenon esters have also been suggested in other studies of reactions of acids with xenon difluoride.[3] The ester is likely not formed when nucleophilic functions such as NH_2, OH, and SH are present in the substrate. Oxidation occurs with the thiol function to produce the disulfide quantitatively (eq 2).

$$HS\text{-}X \xrightarrow[25\ °C,\ 5\ min]{XeF_2,\ CH_2Cl_2} \underset{100\%}{\text{-}(S\text{-}X)_2} \quad (2)$$

$$X = CH_2COOH,\ CH_2CH_2COOH,\ C_6H_5$$

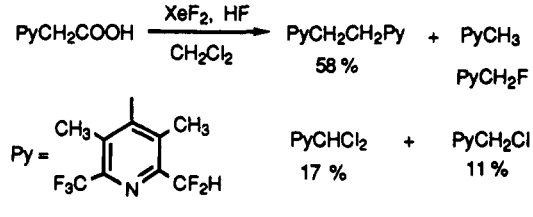
Reaction path b is postulated because $^{18}F^-$ incorporates into the final alkyl fluoride, and $^{18}F^-$ exchange with XeF_2 is not observed. A radiolabeled alkyl fluoride (RF^{18}) is also obtained from the processes given by paths b and g.

In our initial studies, primary acids reacted smoothly with xenon difluoride to produce alkyl fluorides. 3-Phenylpropanoic, 4-phenylbutanoic, and 3,3-diphenylpropanoic acids gave the corresponding fluorinated products without indication of free-radical rearrangement or cyclization (eq 3).

$$RCH_2COOH \xrightarrow[rt,\ 30\ min]{XeF_2,\ CHCl_3} \underset{63\text{-}76\%}{RCH_2F} \quad (3)$$

$$R = C_6H_5CH_2,\ C_6H_5CH_2CH_2,\ (C_6H_5)_2CH$$

Phenylacetic acid in the presence of benzene produced diphenylmethane, indicating the involvement of a trivalent species. Chupp recently observed that a pyridylacetic acid derivative reacted with xenon difluoride to produce several products characteristic of radical intermediates (eq 4).[4]



In further studies of primary acids we find that trifluoroacetic acid (1) reacts with benzene in the presence of xenon difluoride to give (trifluoromethyl)benzene (2). Tanabe et al. used this process as a general method for the

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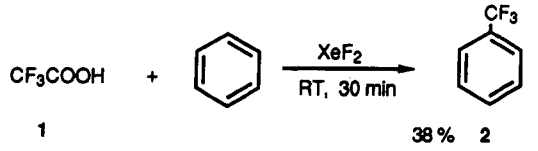
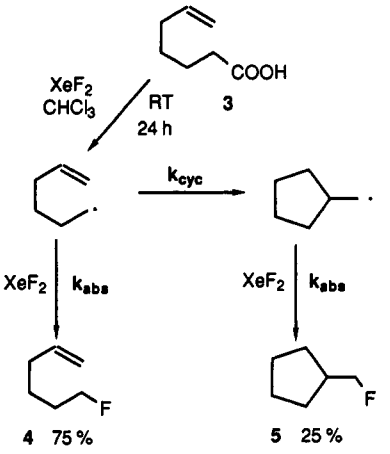
perfluoroalkylation of aromatics.[5] The highest yield of 2 (42%) is achieved with only 1 equiv of XeF_2, whereas the yield drops to 32% when 1.5 equiv are used. Alkyl fluoride production competes with perfluoroalkylation with higher amounts of XeF_2. Alkyl fluoride yields are optimized with 2 equiv of xenon difluoride.



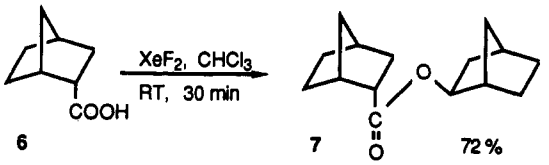
The primary acid, 6-heptenoic acid (3), was allowed to react with xenon difluoride in chloroform solution. The objective was to trap any primary free radical by internal cyclization, a reaction which is diagnostic for a free radical.[6]



(Fluoromethyl)cyclopentane (5) and 6-fluoro-1-hexene (4) were obtained in 25% and 75% yields, respectively. The observation of (fluoromethyl)cyclopentane (5) is considered proof for the free-radical intermediate.[7] The six-membered-ring fluoride, 1-fluorocyclohexane, was not observed as a product. All products and 1-fluorocyclohexane were subjected individually to the reaction conditions and were found not to undergo interconversion. By use of this radical clock technique and given the known rate constant for cyclization of the 6-hexenyl radical of 1×10^5 s^{-1}, the second-order rate constant for abstraction of fluorine from xenon difluoride was determined: k(abs, 25 °C) = 1.1×10^6 M^{-1} s^{-1}. In comparison with known rate constants for abstraction by alkyl radicals of chlorine from *tert*-butyl hypochlorite, 7.5×10^4 M^{-1} s^{-1} (30 °C), and of bromine from *tert*-butyl hypobromite, 1.3×10^6 M^{-1} s^{-1} (50 °C),[7] xenon difluoride shows very efficient fluorine transfer.

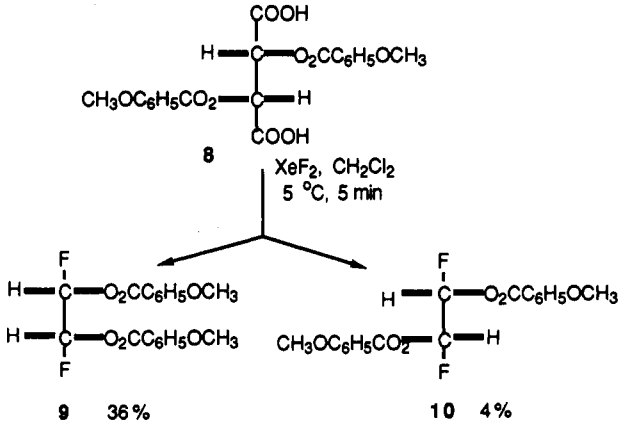
In attempts to observe primary radicals by ESR spectroscopy, we enlisted the spin-trapping technique of Janzen which utilizes α-phenyl-*N*-*tert*-butylnitrone (PBN).[8] PBN is known to react with free radicals to produce a triplet of doublets with coupling constants largely independent of alkyl radical structure, A_N = 13–14, A_β^H = 2–3. The reaction of hexanoic acid with xenon difluoride in the presence of PBN in $CDCl_3$ solution at room temperature gave an ESR spectrum of a strong triplet (A_N = 13.7) and poorly resolved doublets (A_β^H = 2.1, g = 2.022). The known rate constant for spin-trapping of 5-hexenyl radicals by PBN at 40 °C (1.3×10^5 M^{-1} s^{-1}) indicates that PBN can compete with XeF_2 for the free radical.

Secondary carboxylic acids were previously shown to be poor substrates for fluorodecarboxylation. Indeed *endo*-2-norbornanecarboxylic acid (6) gave no fluorinated product. A reinvestigation of this reaction confirms the absence of fluorinated material, but the ester, 2-*exo*-norbornyl 2-*endo*-norbornanecarboxylate (7), was obtained in 72% yield. The alcohol portion of this ester possesses



only the exo configuration even though the endo substrate was used. The formation of the 2-norbornyl cation which gives exclusively exo product best explains this observation but does not exclude a free radical.[11]

The chiral L-tartaric acid derivative 8 reacted with xenon difluoride to produce mainly the *meso*-difluoro product (9, 36%) and a small amount of the *dl*-difluoro isomer (10, 4%). The lack of any stereospecificity indicates the operation of a trivalent intermediate.



Attempts to detect a spin-trapped secondary radical in the presence of α-phenyl-*N*-*tert*-butylnitrone showed no evidence for the expected triplet of doublets. However a reaction between xenon difluoride and the nitrone was observed, and this process is still under investigation.

Tertiary acids are known to produce alkyl fluorides in good yield. Trivalent intermediates are indicated from the observation of loss of optical purity when chiral α-(trifluoromethyl)-α-methoxyphenylacetic acid is used as the substrate. Only the optically inactive alkyl fluoride is observed (eq 5).

Our report that 3-phenylbicyclo[1.1.1]pentanoic acid (11) gave a dimeric product was in error. Michl and coworkers found that only the reduced ring system 12 is

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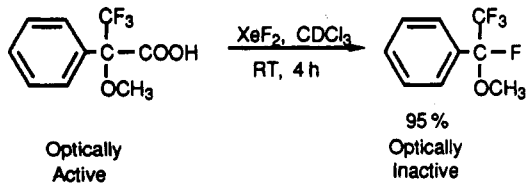
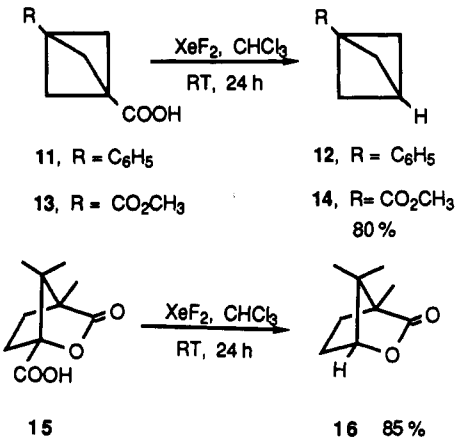


(5)

obtained.[12] Methyl 3-carboxybicyclo[1.1.1]pentane-1-carboxylate (13) reacts also with exclusive solvent hydrogen (or deuterium) abstraction to produce the bicyclo-[1.1.1]pentane system 14 in 95% yield. Further, camphoric acid (15) shows the same behavior with hydrogen abstraction to produce (16). These results coupled with the results of Della et al. who have studied 13 and several other bicyclic acids[13] give strong evidence for the intermediacy of free-radical intermediates. The bicyclo-[1.1.1]pent-1-yl radical is known to maintain the integrity of the ring system to produce 1-substituted bicyclo-[1.1.1]pentane products.[14,15] However, the bicyclo-[1.1.1]pent-1-yl cation loses the ring system to give products derived from methylene cyclobutane.[16] Thus, facts that rearrangement products are absent and that only the solvent hydrogen abstraction products, 12 and 14, are observed strongly indicate involvement of the bicyclo[1.1.1]pent-1-yl radical system. If bicyclo[1.1.1]-pent-1-yl cations were present, rearranged products would surely be observed. Hydrogen abstraction seems to occur best in systems which have stabilization by 1,3 bridging or by neighboring group assistance.[13,16,17]



Attempts to observe the radical from 13 by the ESR spin-trap with PNB gave ambiguous results. The major ESR signal observed came from the reaction of XeF_2 with PNB. Peaks from reaction of radical 13 with PNB were masked and small. Thus, without distinctive ESR signals the better evidence for radical intermediary comes from the products observed.

In conclusion, radical intermediates have been demonstrated from primary acid substrates through both product studies and ESR spin-trapping with PNB. Product studies with tertiary systems also strongly indicate the presence of free radicals, especially in the bicyclo-[1.1.1]pentyl systems. Secondary acids show evidence of a trivalent intermediate, but its nature is uncertain at this time.

Experimental Section

General. Xenon difluoride was purchased from PCR, Gainesville, FL, and used without further purification. All solvents were dried prior to use. NMR spectra were obtained on a JEOL FX 90Q. ESR spectra were obtained on a Bruker 200D instrument. Mass spectra were obtained from the Washington University School of Medicine, St. Louis, MO, Department of Psychiatry.

Reaction of Thiol with Xenon Difluoride. 3-Mercaptopropanoic acid (90 mg, 0.85 mmol) in dry methylene chloride was treated with xenon difluoride crystals (72 mg, 0.42 mmol) at 25 °C for 5 min. Crystals of 3,3-dithiopropanedioic acid (177 mg, 99%) were filtered from the mixture, mp 150–152 °C, identified by comparison with a authentic sample.

In a similar manner dithiodiacetic acid was prepared from mercaptoacetic acid in 99% yield, mp 99–101 °C, and 2,2'-dithiodibenzoic acid was prepared from 2-mercaptobenzoic acid in 99% yield, mp 284–286 °C.

Preparation of (Trifluoromethyl)benzene (2). Benzene (10 mL) and trifluoroacetic acid (87.0 mg, 0.77 mmol) were placed in a polypropylene vial, and crystals of xenon difluoride (134.5 mg, 0.79 mmol) were added. The capped vial was allowed to stand for 1 h, and the cap was loosened to permit CO_2 release. The cap was tightened, and the contents were allowed to stand for 24 h at 25 °C. The reaction mixture was washed with 5% sodium bicarbonate and dried over sodium sulfate. Flash chromatography (silica gel, hexane/ethyl acetate, 4:1) produced, after careful removal of the solvents, (trifluoromethyl)benzene (47 mg, 42%) which was identified by comparison with an authentic sample. ^{19}F NMR (TFA): δ −48.6 (m). Mass spectrum (CH_4): 147 (M + 1), 175 (M + C_2H_5), 187 (M + C_3H_5), 127 (M + 1 − HF).

Several experiments were conducted in which the molar ratio of trifluoroacetic acid (0.79 mmol) to xenon difluoride was varied in order to determine the optimum yield of (trifluoromethyl-)benzene. Yields were determined from ^{19}F NMR analysis with *p*-fluorophenol as an internal standard. Mole ratio XeF_2/TFA (% yield): 0.5:1 (22%); 1:1 (42%); 2:1 (17%); 3:1 (18%).

Reaction of 6-Heptenoic Acid (3) with Xenon Difluoride. 6-Heptenoic acid (15.3 mg, 0.12 mmol) was dissolved in 0.9 mL of $CDCl_3$ in a 5-mm NMR tube. Xenon difluoride (41.4 mg, 0.24 mmol) crystals were added to the tube, and the capped tube was kept at 25 °C overnight. ^{19}F NMR analysis (TFA standard) of the product mixture showed multiplets at δ −140.2 (dt) and −154.7 (m) which were identified by comparison with authentic samples as 6-fluoro-1-hexene (4, 75%) and (fluoromethyl)cyclopentane (5, 25%), respectively. The reaction yield of fluorinated products was 95%. Mass spectral analysis confirmed the masses of the products and also showed the presence of tetrachloroethene. 1-Fluorocyclohexane was not present as a reaction product.

Authentic samples of 6-fluoro-1-hexene and 1-fluorocyclohexane were prepared from reaction of the respective alcohol (0.33 mmol) with (diethylamino)sulfur trifluoride (0.73 mmol) in $CDCl_3$ at 25 °C overnight. ^{19}F NMR ($CDCl_3$, TFA): 6-fluoro-1-hexene δ −154.7 (m); 1-fluorocyclohexane δ −96.9.

Reaction of cyclohexanecarboxylic acid with xenon difluoride gave a mixture of fluorinated products, but none were observed as fluorocyclohexane. Authentic (fluoromethyl)cyclopentane was prepared from reaction of cyclopentylacetic acid (35.9 mg, 0.28 mmol) with xenon difluoride (97.7 mg, 0.58 mmol) in $CDCl_3$ overnight at room temperature. (Fluoromethyl)cyclopentane (4) ^1H NMR (90%) gave ^1H NMR ($CDCl_3$) δ 1.61 (m, 9 H), 4.06, 4.60 (dd, J_{HF} = 48.6, J_{HH} = 6.8, 2 H). ^{19}F NMR ($CDCl_3$, TFA): δ −140.3 (t, J_{CH_2-F} = 48.6 Hz, J_{CH-F} = 17.1 Hz).

Each of the authentic fluoro products was submitted to the xenon difluoride reaction conditions, and each was observed to be stable. Thus, none of the products is interconverted on reaction with xenon difluoride.

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(17) Wiberg, K. B.; Williams, V. Z. *J. Am. Chem. Soc.* **1967**, *89*, 3373.

The rate constant, k(abs), for abstraction of fluorine from xenon difluoride was determined from the equation (25 °C) k(abs) = (k(cyclization) × concentration of 6-fluoro-1-hexene)/(concentration of XeF_2 × concentration of (fluoromethyl)cyclopentane); k(cyclization) = 1.0×10^5 s^{-1}. Thus, k(abs) = 1.1×10^6 M^{-1} s^{-1}.

Reaction of *endo*-2-Norbornanecarboxylic Acid (6) with Xenon Difluoride. Xenon difluoride (1 mmol, 169 mg) was dissolved in 10 mL of dried methylene chloride at 0 °C. A solution of *endo*-2-norbornanecarboxylic acid (0.95 mmol, 133 mg) in 10 mL of methylene chloride was added by syringe at 0 °C. The mixture was allowed to warm to room temperature (2 h) and then allowed to stand under argon for 18 h. The methylene chloride was removed under reduced pressure, and the residue was dissolved in ethyl acetate which was washed with sodium bicarbonate solution followed by drying ($MgSO_4$). Flash chromatography (silica gel, ethyl acetate/hexane, 1:4) gave 155 mg (72%) of 2-*exo*-norbornyl 2-*endo*-norbornanecarboxylate (7) as a clear oil. The ^1H NMR spectrum ($CDCl_3$) showed peaks at δ 1–2 (m, 10 H), 2.28 (m, 3 H), 2.56 (m, 2 H) for the ring protons and a carbinol proton at 4.57, 4.63 (complex doublet). Chemical ionization mass spectrum: 235 (M + 1), calcd (235).

Samples of authentic 2-*exo*-norbornyl 2-*endo*-norbornanecarboxylate (4) and 2-*endo*-norbornyl 2-*endo*-norbornanecarboxylate were prepared in 74% and 65% yields, respectively, by coupling 1 mmol of authentic alcohol with 1 mmol of *endo*-norbornanecarboxylic acid with diclohexylcarbodiimide and 4-(dimethylamino)pyridine in methylene chloride solution overnight. The ^1H NMR spectrum obtained from coupling *exo*-2-norborneol with 2-*endo*-norbornanecarboxylic acid was identical with the product obtained from the xenon difluoride reaction. The ester from the *exo*-alcohol shows the complex carbinol proton doublet at δ 4.57, 4.67 whereas the carbinol proton from the *endo*-alcohol is observed as a multiplet at δ 4.91.

Tartaric Acid 8 Reaction with Xenon Difluoride. Xenon difluoride (2.05 mmol, 347 mg) was dissolved in 5 mL of dry methylene chloride at 0 °C under nitrogen atmosphere. A solution of 2,3-bis(*p*-methoxybenzoyl)-L-tartaric acid (8, 0.52 mmol, 202 mg) in dry methylene chloride was injected and the mixture was stirred at 5 °C for 14 h. The solution was washed with 5% sodium bicarbonate solution, and the dried methylene chloride mixture was evaporated. The residue was dissolved in ethyl acetate, dried with magnesium sulfate, and subjected to flash chromatography on silica gel with 20% methanol–80% ethyl acetate as the elution solvent. Two major fractions were obtained. The first fraction was rechromatographed (silica gel, 10% ethyl acetate–90% hexane) to give two components. The first component contained 1,2-difluoro-2,3-bis(*p*-methoxybenzoyl)-1,2-ethanediol (70 mg, 40%) as a mixture of diastereomers. The second minor component (3.5 mg) was unidentified.

The ^1H NMR spectrum ($CDCl_3$) showed methoxy peaks at δ 2.42 and 2.44, alphatic protons from 6.42 to 7.07 as a symmetrical six line pattern, and aromatic at δ 7.03 (m) and 8.03 (m). The ^{19}F NMR ($CDCl_3$) showed a meso component (~90%) at δ −58.6 (J_{HF}(geminal) = 59.5 Hz, J_{HF}(viscinal) = 5.9 Hz, J_{HH} = 0), and an entiomeric component (10%) at δ −62.3 (ddd, J_{FF} = 181.4 Hz, J_{HF}(geminal) = 59.1 Hz, J_{HF}(viscinal) = 5.7 Hz). The chemical ionization mass spectrum (CH_4) show a parent peak at 335 (8%, M + 1), 315 (17%, − HF), 199 (100%, M − $CH_3OC_6H_5CO_2H$).

The second major fraction obtained was further subjected to chromatography (silica gel, methanol/ethyl acetate, 1:4) and produced 5 mg of an unidentifiable two part mixture of high molecular weight components. When the reaction was conducted as above in the presence of lead tetraacetate (200 mg), a 65% yield of the difluoro mixture was obtained.

Methyl Bicyclo[1.1.1]pentane-1-carboxylate (14). A solution of methyl 3-carboxybicyclo[1.1.1]pentane-1-carboxylate (13, 20 mg, 0.12 mmol) in 2 mL of dry chloroform was treated with xenon difluoride crystals (50 mg, 0.30m mmol) and allowed to react overnight. The reaction evolved carbon dioxide and xenon. The mixture was treated with dilute sodium bicarbonate solution, dried with $MgSO_4$, and concentrated on a rotary evaporator. The product 14 was examined by ^1H NMR ($CDCl_3$) to give δ 2.07 (6 H, s, CH_2), 2.41 (1 H, s, CH), and 3.64 (s, 3 H, CH_3) in accordance with reported values.[13] The yield by NMR was 80%. When the reaction was conducted in $CDCl_3$ solution, the peak at δ 2.41 was gone. No fluorine resonance could be found.

(−)-Camphanic Acid (15) Reaction with Xenon Difluoride. (−)-Camphanic acid (151.6 mg, 0.76 mmol) was dissolved in 15 mL of chloroform at 25 °C. Xenon difluoride (256.7 mg, 1.52 mmol) was added as crystals, and the mixture was lightly capped. After 24 h the expulsion of carbon dioxide was complete. The mixture was washed with 5% sodium bicarbonate, dried over sodium sulfate, and concentrated to give 1,7,7-trimethyl-3-oxabicyclo[2.2.1]heptan-2-one (16, 100 mg, 85%). ^1H NMR ($CDCl_3$): δ 4.27 (bridgehead, 1 H), 1.80–1.97 (ring, 4 H), 0.85, 0.94, 1.01 (CH_3). Mass spectrum (CH_4) calcd for 155 (M + 1), observed 155. Anal. Calcd for $C_9H_{14}O_2$: C, 70.12; H, 9.09. Found: C, 70.17; H, 8.91.

When the reaction was conducted as above in 99.4% deuteriochloroform and the product was subjected to mass spectral analysis, the percentage of deuterium incorporation was found to be 83.3%.

ESR Experiments. A solution of the acid (10 mg) in $CDCl_3$ was treated with 2–3 crystals of XeF_2. After 3–4 min, the α-phenyl-*N*-*tert*-butylnitrone (5 mg) was added. The solution became bright yellow and was subjected to ESR analysis at room temperature; sweep widths of 100 gauss were used to determine coupling constants.

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