Fatty Acids Containing Photoactivable Carbene Precursors. Synthesis and Photochemical Properties of 3,3-Bis(1,1-difluorohexyl)diazirine and 3-(1,1-Difluorooctyl)-3*H*-diazirine

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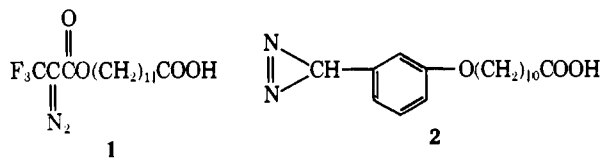
Abstract: Phospholipids containing photoactivable carbene precursors in fatty acyl chains are of interest for the study of phospholipid-protein interactions in biological membranes. In the present work, the aim was to prepare new photoreactive precursors, which would be small and would yield carbenes that do not undergo intramolecular rearrangements. Alkyl diazirines were prepared with α hydrogens replaced by fluorine. 3,3-Bis(1,1-difluorohexyl)diazirine was obtained from 6,6,8,8-tetrafluoro-7-tridecanone and 3-(1,1-difluorooctyl)-3*H*-diazirine from α-difluorononaldehyde. On irradiation in cyclohexane or methanol at 310 nm, neither of the two diazirines showed insertion into the C-H or O-H bonds. Both diazirines underwent photoisomerization to the stable, linear diazo compounds and photofragmentation to the carbenes. The carbenes reacted by intramolecular insertion into the β C-H bond to form cyclopropanes and by 1,2 alkyl shift to form *gem*-difluoro olefins. When irradiated at 410 nm, the fluorodiazo compounds underwent isomerization back to the diazirine and further photofragmentation. Irradiation of the diazo compounds at 260 nm produced only fragmentation and no isomerization.

Introduction

Studies on interactions between phospholipids and membrane-embedded proteins are important to the understanding of structure and function of biological membranes. An organochemical approach to this problem has been developed which involves preparation of phospholipids containing photoactivable groups in the fatty acyl chains and their use in reconstitution of defined membrane functions with appropriate proteins.[2-5] On subsequent photolysis, highly reactive carbenes are produced which react to form covalent cross-links with phospholipids and proteins.

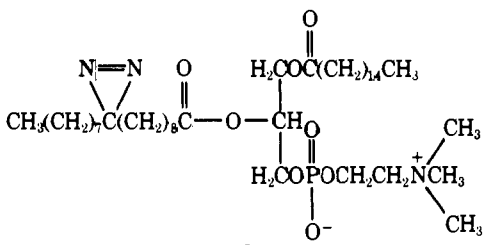
Two photoactivable carbene precursors have proved to be particularly satisfactory in intermolecular cross-linking reactions. These are α-diazo-β-trifluoropropionyloxy and diazirinophenoxy groups, and are shown as components of fatty acids in structures **1** and **2** (Figure 1), respectively. Phospholipids prepared from these fatty acids show extensive cross-linking on photolysis. However, the use of the photoactivable groups in **1** and **2** is restricted to the ω positions of fatty acid chains. It would be desirable to have a photoreactive group which can be incorporated in any position along the alkyl chain. Such a group should have the following additional properties: (1) it should be as small as possible so as to cause minimal perturbation of the normal phospholipid-protein contacts; (2) the photogenerated intermediate should be a carbene rather than a nitrene;[4] (3) the photoreactive group must be chemically stable during experimentation up to the point of photolysis; (4) its UV absorption properties should be such that photolysis should require wavelengths >300 nm where photodamage to proteins and nucleic acids is minimized.

The simplest possibility is the 3,3-dialkyldiazirine, with its carbon atom as a part of the alkyl chain of a fatty acid. However, carbenes of aliphatic diazirines react mainly by intramolecular rearrangement (hydride shift) and not by intermolecular insertion into C-H bonds.[6] Nevertheless, the possibility existed that the ordered packing of hydrocarbon chains in phospholipid bilayers would restrict the conformational mobility of the carbene and promote intermolecular insertion. Therefore, the phospholipid **3** was prepared containing 10-azistearic acid in position *sn*-2 and ^{14}C-labeled palmitic acid in *sn*-1. However, photolysis of multilamellar liposomes prepared from **3** showed the absence of any intermolecular insertion into C-H bonds of the radiolabeled palmitic acid.[7] Therefore, it was decided to prepare and test two diazirines corresponding to the structures **4** and **5**.



1 **2**

Figure 1.



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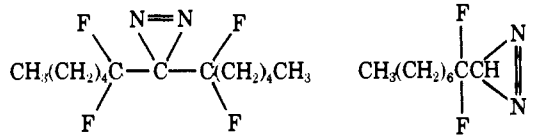

4 **5**

Substitutions of the hydrogens α to the diazirine carbon (**4**, **5**) by fluorines were suggested by the observations that carbenes photogenerated from the α-diazo-β-trifluoropropionyl group[3,5,8] and from perfluorinated diazo and diazirino compounds[9,10] insert into C-H bonds of solvent without intramolecular rearrangement by fluorine migration. Because the C-F bond length and van der Waals radius are close to those of the C-H bond,[11] these structures would remain acceptably small. Further, partially fluorinated fatty acids, present in the growth medium, are incorporated into phospholipids of bacteria[12] to produce functional membranes. Finally, the "tetrafluorodiazirine unit" in **4** could be placed anywhere along the fatty acid chain. While structure **5** would only be attached to the end of the fatty acid chain, similar to the α-diazo-β-trifluoropropionyl **1** and the diazirinophenoxy group **2**, it would have the advantages of being less polar and small.

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Table I. Fluorination with Diethylaminosulfur Trifluoride of 1,3-Diketones with Different Substituents at Carbon 2

$$RCH_2COCXYCOCH_2R \xrightarrow{Et_2NSF_3{}^a} RCH_2CF_2CXYCOCH_2R$$

educt no.	R	X	Y	product no. (yield, %)	$\delta(CDCl_3)$ of CH_2CO[b]	
					educt	product
6	C_5H_{11}	$S(CH_2)_3S$		dec	2.8	
7	C_2H_5	H	Br	dec	2.7	
8	C_2H_5	H	phthalimido	dec	2.2	
9	C_2H_5	=NOH		dec	2.7	
10	C_2H_5	$=NOCOCH_3$		13 (30)	2.95, 2.61	2.7
11	C_2H_5	$=NOCH_3$		14 (20)	2.80, 2.60	2.65
12	C_2H_5	$=CHC_6H_5$		15 (23)	2.75, 2.45	2.4

[a] The reaction conditions are given in the Experimental Section. [b] The chemical shifts are discussed in note 17.

Synthesis of 6,6,8,8-Tetrafluoro-7-tridecanone (23)

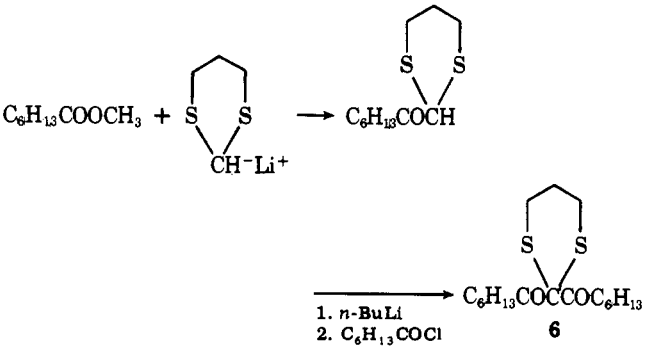
Hexafluoroacetone has been converted to the 3,3-bis(trifluoromethyl)diazirine.[10] Therefore, the first synthetic aim was preparation of the above $\alpha,\alpha,\alpha',\alpha'$-tetrafluoro ketone.

There are a number of reports[13] where chlorine and bromine have been exchanged with fluorine using, e.g., potassium fluoride[14] or antimony pentafluoride.[13] However, attempts to prepare the model $\alpha,\alpha,\alpha',\alpha'$-tetrabromo derivative of dipropyl ketone failed and, furthermore, in the bromo derivatives prepared, replacement of the bromide by fluoride groups could not be accomplished. Diethylaminosulfur trifluoride fluorinates keto groups to the corresponding difluoromethylene groups.[15] Therefore, fluorination of a 1,3-diketone suitably functionalized at carbon 2 for subsequent manipulation seemed to be a convenient method for the preparation of $\alpha,\alpha,\alpha',\alpha'$-tetrafluoro ketones. The derivatized 1,3-diketone **6** was prepared from 1,3-dithiane[16] as described in Scheme I. However, all attempts to fluorinate **6** to the desired tetrafluoro derivative failed. In further work along this line, 4,6-nonadione derivatives functionalized at C-5 were treated with diethylaminosulfur trifluoride under a variety of conditions. The results, which are summarized in Table I, showed that either decomposition or fluorination of only one of the two carbonyl groups occurred. Further, in all cases the carbonyl function cis to the substituent at carbon 5 was fluorinated.[17]

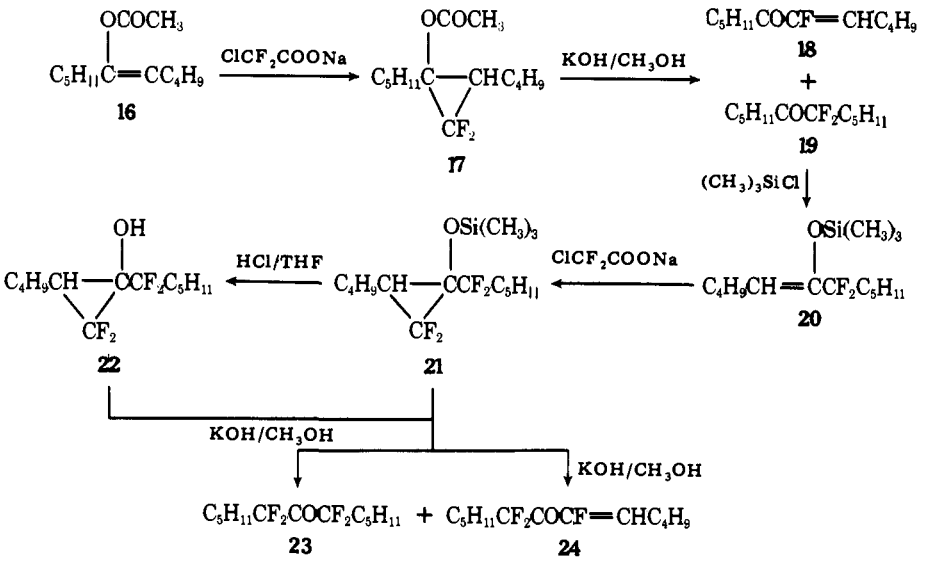
The tetrafluoro ketone **23** was prepared successfully by a method due to Crabbé et al.[18] Difluorocarbene, generated from sodium chlorodifluoroacetate in refluxing diglyme, added to the double bond of the enol acetate **16**, prepared from dipentyl ketone to form the difluorocyclopropyl acetate **17**. From the latter, the α,α-difluoro ketone **19** was generated by solvolytic ring opening in cold methanolic potassium hydroxide. It was separated from the side product, 6-fluorododec-5,6-en-7-one (**18**), by distillation and was obtained in 40% yield.

The newly introduced α,α-difluoromethylene group evidently exerted a strong influence on the reactivity of the carbonyl group such that the α,α-difluoro ketone **19** could no longer be converted to the enol acetate by the acid-catalyzed reaction used above for **17**. The enol acetate of **19** was obtained in 75% yield by treatment of the difluoro ketone **19** with acetic anhydride in refluxing pyridine. However, difluorocarbene failed to add to the resulting α,α-difluoroenol acetate, probably because of low electron density in the double bond due to the electron-withdrawing effects of both the acetoxy and the difluoromethylene groups. In an alternative approach, the trimethylsilyl enol ether **20** was prepared under very mild conditions and purified by distillation (80% yield). Addition of difluorocarbene to **20** occurred rapidly, although a part of the enol ether decomposed during the pyrolysis of sodium chlo-

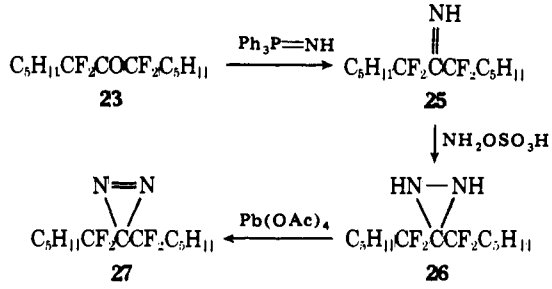
Scheme I



Scheme II



Scheme III



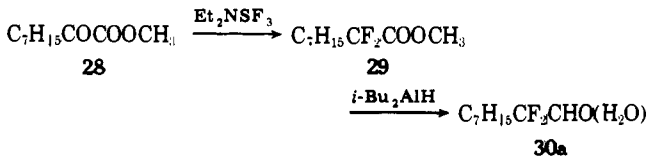
rodifluoroacetate.[19] The isolated yield of trimethylsilyl difluorocyclopropyl ether **21** was 58%. The latter was cleaved under acidic conditions to give the difluorocyclopropanol **22.** This, in turn, on KOH/CH_3OH treatment gave a mixture of the tetrafluoro ketone **23** and the trifluoro enone **24.** The ring opening of **21** to form **23** could be effected directly under basic conditions. No conditions could be found under which the formation of **24** could be completely avoided. On the other hand, the latter became the major product when the reaction temperature or the concentration of base was increased. The tetrafluoro ketone, which is readily hydrated, was easily separated from all less polar side products by chromatography on silicic acid. It can be dehydrated in ether over molecular sieves and then distilled to afford pure tetrafluoro ketone **23.** The overall yield from the starting material, di(*n*-pentyl) ketone, was 6%.

Preparation of the Diazirine 27 from the Tetrafluoro Ketone 23

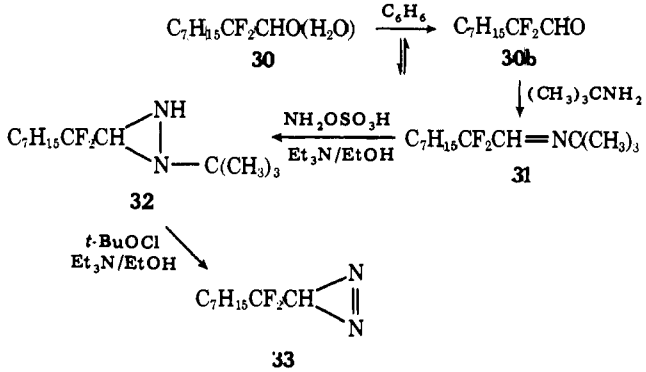
A number of methods have been used for the preparation of diazirines from aliphatic ketones,[20-22] aromatic aldehydes,[23] and hexafluoroacetone.[10,24,25] Because of the marked alteration in the reactivity of the ketone **23** due to the fluorine groups, a combination of methods from different sources was necessary. The tetrafluorodiazirine **27** was prepared successfully as shown in Scheme III.

The tetrafluoro ketone imine **25** was prepared by a Wittig type of reaction from the ketone **23** and triphenylphosphinimine.[26] It was purified by chromatography on silicic acid and by distillation and was obtained in a yield of 60%. The imine was surprisingly inert toward nucleophilic additions to the carbon atom. Thus, it did not add ammonia when kept in liquid ammonia for several hours. An attempt to prepare the ammonia adduct from the imine hydrochloride and ammonia failed. A product was formed which could not be characterized and which did not afford diazirine when treated with sodium hypochlorite.[27] Instead, the original ketone hydrate, formed probably by rapid exchange of ammonia with water, was obtained. The diaziridine **26** was formed when the imine **25** was treated with hydroxylamine-*O*-sulfonic acid in anhydrous diglyme. The diaziridine could then be oxidized with lead tetraacetate. The resulting diazirine **27** was purified by chromatography on silicic acid; it separated easily from unreacted tetrafluoro ketone hydrate. No attempts were made to improve the yield, which was 17% relative to the tetrafluoro ketone imine **25,** although possibilities for doing so can readily be conceived. After purification on silicic acid the tetrafluorodiazirine was 95% pure by analysis by gas chromatography. The impurities were the parent tetrafluoro ketone **23** and small

Scheme IV



Scheme V



amounts of the compounds which were later shown to be formed during photolysis. Pure samples could be obtained by preparative gas chromatography. The diazirine **27** has a UV absorption maximum with a double peak at 302 and 312 nm (ϵ_0 53) measured in cyclohexane. This spectrum was very similar to that of 3,3-bis(chlorodifluoromethyl)diazirine.[27]

Synthesis of the α,α-Difluoro Aldehyde 30 and the Corresponding Diazirine 33

Attempts to prepare an α,α-difluoro aldehyde by the method described above for the preparation of the tetrafluoro ketone failed. Vinyl acetate did not add difluorocarbene under the conditions described above. The vinyl trimethylsilyl ether added difluorocarbene. The resulting difluorocyclopropyl ether, however, was unstable at room temperature. It decomposed to give two compounds. One was identified as the α,β-unsaturated α-fluoro aldehyde. The second compound was tentatively identified as 2-fluoro-3-alkylcyclopropanone.[28]

A successful synthesis of the fluorinated aldehyde **30a** was achieved as shown in Scheme IV.

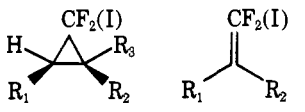
Methyl α-ketononanoate (**28**) was fluorinated with diethylaminosulfur trifluoride to afford the α,α-difluoro ester **29** in 77% yield. The α,α-difluoro aldehyde **30** was then prepared from the ester **29** by reduction with diisobutylaluminum hydride in ether.[29] The difluoro aldehyde hydrate **30a** obtained after workup was used directly for the preparation of the diazirine.

The difluorodiazirine **33** was prepared in 45% yield from the aldehyde, by a method used for the preparation of aromatic diazirines.[23] The aldehyde **30a** was first rendered anhydrous azeotropically by refluxing in benzene. Upon addition of *tert*-butylamine, the imine **31** formed spontaneously, and the latter on reaction with hydroxylamine-*O*-sulfonic acid in ethanol and triethylamine gave the *N*-*tert*-butyldiaziridine **32.** This was oxidized to the diazirine **33** with *tert*-butyl hypochlorite in ethanol in the presence of triethylamine.[30] The diazirine **33,** which was purified by chromatography on silicic acid, showed an absorption maximum with a triple peak at 306, 312, and 318 nm (ϵ_0 160).

Photochemical Reactions of the Tetrafluorodiazirine 27

When the diazirine **27** at a concentration of 0.02–0.2 M in cyclohexane, cyclohexene, or methanol was irradiated at 310 nm for 3 min, four major products were formed in a constant ratio which was independent of the solvent (cyclohexane, cyclohexene, methanol). They account for 97% of the starting material. Identification by spectroscopic properties showed the main product to be the valence isomer 6,6,8,8-tetrafluoro-7-diazotridecane (**35,** 56%). Consistent with the structure, it had a strong IR absorption at 2120 cm^{-1}, a finely structured UV absorption below 260 nm, and a weak UV maximum at around 400 nm (ϵ 12). Two additional products formed on photofragmentation of the diazirine were 1,1-difluoro-2-

Table II. ^{19}F NMR Chemical Shifts of the Substituted Difluorocyclopropanes and *gem*-Difluoro Olefins[a]



36/40 **37/39**

compd no.	R_1	R_2	R_3	δ_I		δ_{II}		$J_{I,I}$	$J_{II,II}$
36-*cis*	$C_5H_{11}CF_{2(II)}$	C_4H_9	H	121.40	152.61	91.2	98.2	162	254
36-*trans*	$C_5H_{11}CF_{2(II)}$	H	C_4H_9	137.55	138.55	94.9	100.9	166	252
40	C_6H_{13}	H	H	125	143			147	
37	$C_5H_{11}CF_{2(II)}$	C_5H_{11}		82.2	86.9		93.7	39	
39	C_7H_{15}	H		82	84			n.d.	

[a] The chemical shifts δ are in parts per million upfield relative to $CFCl_3$ (0.00 ppm) and the coupling constants J are in hertz.

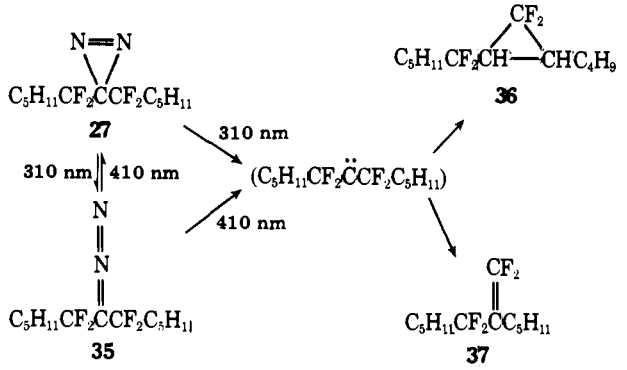


Figure 2.

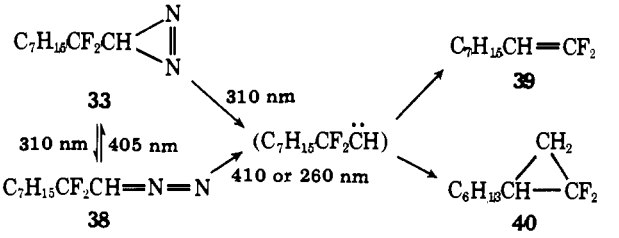


Figure 3.

(1,1-difluorohexyl)-3-butylcyclopropane (**36**) and 6,6-difluoro-7-difluoromethylenedodecane (**37**). The latter, a difluoro olefin, accounted for 13% of the products. It was evidently formed by rapid 1,2 alkyl chain migration following primary carbene formation. It showed a strong IR absorption at 1750 cm^{-1}, characteristic of difluoro olefins,[13] and a ^{19}F NMR spectrum with signals at 82 and 87 ppm as expected from the olefinic fluorines and at 94 ppm from the vinylic fluorines (Table II), in agreement with spectra of similar compounds.[31] The cis and trans difluorocyclopropyl compounds **36** evidently arose by intramolecular insertion of the carbene into the C-H bonds α to the difluoromethylene groups. The two cis and trans isomers accounted for 6 and 21%, respectively, of the photolysis products. The ^{19}F NMR characteristics of the isomers are given in Table II and the Experimental Section. These are completely as expected, and chemical shifts of the photoproducts (Table II) are in good agreement with those of the two isomers of 1,1-difluoro-2,3-dimethylcyclopropane.[32] Preferential formation of the trans isomer can be expected because of less steric interference between the alkyl substituents of the cyclopropyl ring and consequently lower free energy.

The tetrafluorodiazirine **27** is stable in glacial acetic acid for at least several hours. When photolyzed in 1 M acetic acid in cyclohexane, the product composition remains unchanged. However, during irradiation in glacial acetic acid the tetrafluorodiazo compound is not formed. Instead, the difluoro olefin **37** and the difluorocyclopropane **36** are the major products with a large number of products with longer retention times on gas chromatography observed.

When the reaction mixture, following complete photolysis of the tetrafluorodiazirine **27** at 310 nm in cyclohexane or methanol, was irradiated for 15 h at 410 nm, the UV absorbance of the tetrafluorodiazo isomer **35** at 400 nm disappeared and the UV absorption band at 310 nm, typical of the diazirine **27**, reappeared with an intensity of about 25% of the original absorbancy, measured at the start of the irradiation at 310 nm. Gas chromatographic analysis confirmed the disappearance of the diazo isomer **35** and the reappearance of the diazirine **27** together with the above-described products derived from the carbene (Figure 2). Integration of the peak areas on the gas chromatogram indicated that about 50% of the diazo isomer **35** had been reconverted to the diazirine **27**. Irradiation of the above mixture produced by photolysis at 310 nm, at 260 nm instead of 410 nm, showed only photofragmentation and no isomerization to the diazirine.

Photochemistry of the Diazirine 33

Irradiation of the difluorodiazirine **33** at 310 nm in cyclohexane or methanol gave three products (Figure 3). Infrared absorption at 2120 cm^{-1}, a finely structured UV absorption below 260 nm, and a very weak UV absorption around 400 nm all indicated the presence of α,α-difluorodiazononane (**38**). However, no diazo compound could be isolated by gas chromatography. This was probably because of its thermal instability (less stable than the tetrafluorodiazo compound **27**). Instead, two products in the ratio of 1:2 were separated and identified by their spectroscopic properties. The minor product, 1,1-difluorononene (**39**), had a ^{19}F NMR spectrum very similar to that of the difluoro olefin **37** obtained from the tetrafluorodiazirine **27** (Table II). The ^1H NMR and IR spectra were identical with those of an authentic sample of 1,1-difluorooctene prepared according to published procedures.[33] The major product was identified as 1,1-difluoro-2-hexylcyclopropane (**40**) by its ^{19}F NMR spectrum, which closely resembled those obtained from the difluorocyclopropanes **36** (Table II). Compounds **38** (IR at 2120 cm^{-1}) and **39** (IR at 1760 cm^{-1}) appeared and increased during photolysis at the same rate. This indicates that these two products and probably product **40** are all products of photolysis and not of thermolytic cleavage during gas chromatographic analysis.

In an experiment analogous to that performed with the tetrafluorodiazirine **27**, the difluorodiazirine **33** was irradiated first at 310 nm and then at 410 nm. Only about 6% of the original absorbance at 310 nm reappeared.

Photolysis of 3,3-Bis(chlorodifluoromethyl)diazirine

On photolysis of 3,3-bis(chlorodifluoromethyl)diazirine (**41**)[27] the corresponding diazo isomer formed (detected by a strong IR absorption at 2120 cm^{-1}).

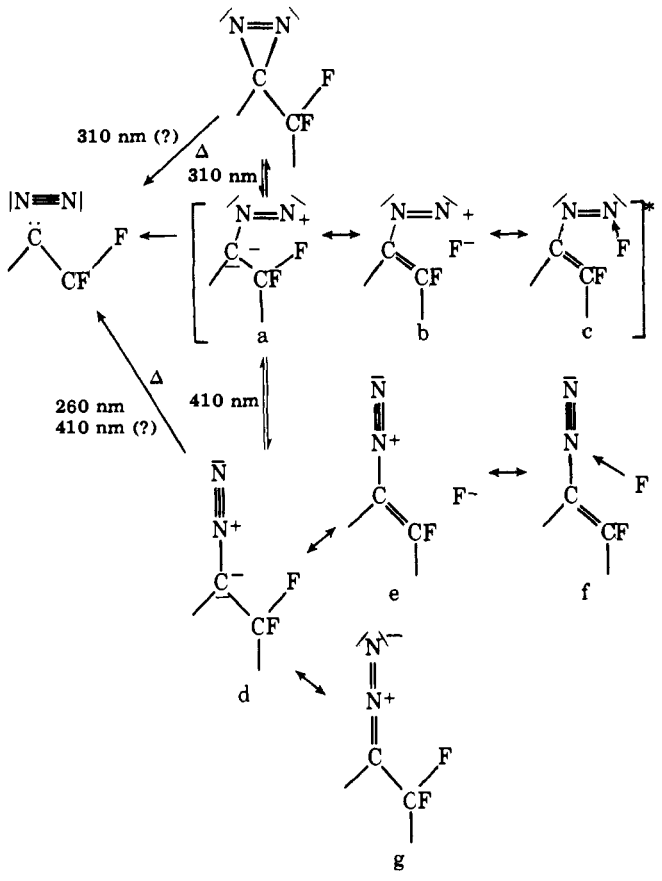
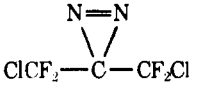


Figure 4.



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When the bis(chlorodifluoromethyl)diazomethane was irradiated at 400 nm for 3 h, all absorbance at 400 nm disappeared and about 10% of the original absorbance at 310 nm was recovered. Measurements with the diazo isomer are complicated, because it is slowly photolyzed itself during the irradiation of the diazirine at 310 nm, probably because of spectral overlap between the short-wavelength absorption of the diazo isomer and the absorption of the diazirine.

Discussion

The most significant finding has been the wavelength-dependent, reversible isomerization of the three-membered diazirine ring and its linear diazo isomer. Further, both isomers have remarkable thermal and chemical stability. Stability and photochemical properties can be explained by the manner in which fluorine affects the reactivity of adjacent chemical bonds. Thus, in the case of the $\alpha,\alpha,\alpha',\alpha'$-tetrafluorodiazirine, because of the inductive electron-withdrawing effect of the difluoromethylene groups, additional canonical structures with a negative charge localized on the diazo carbon (d, Figure 4) or on one of the four fluorine atoms (structure e) can be postulated. Moreover, the inductive withdrawal of electron density from the diazo system can be counteracted by return of electron density from the fluorines into the diazo system by p-π or p-p interactions (canonical structure f) in analogy to a formalism proposed for trifluoromethylbenzene.[11,34] Such π-p interaction between the π orbital of the fluorine could further explain the marked blue shift of the absorption of the fluorinated diazirines **27** and **33** (310 nm) relative to that of nonfluorinated diazirines (340-360 nm[35]). If these bands can be assigned to a $\pi^* \leftarrow \pi$ transition, the energy of the π orbital (highest occupied molecular orbital) would be lowered relative to that of the π^* orbital (lowest unoccupied molecular orbital) under the influence of fluorine participation, and in consequence the energy difference between the two orbitals would be increased.

A similar explanation for the stability of the fluorinated diazo compound can help rationalize the observed isomerization of the diazo compound **35** to the diazirine **27**. Interaction between the positively polarized nitrogen and an electron pair of a fluorine could stabilize a transition state as represented by the canonical structures a-c (Figure 4). Its conformation and charge distribution could facilitate the attack of the negatively polarized diazo carbon at the positively polarized nitrogen (canonical structure a). In this way, the probability of ring closure relative to fragmentation could be increased to allow the observed 50% isomerization.

There are other reports of the reversible isomerization of diazo compounds and diazirines.[36,37] Further, there are several cases of unidirectional isomerization from the stable diazirine to the labile diazo compounds.[23,38,39] Because of the chemical lability of these diazo compounds, the extent of isomerization was estimated by trapping the intermediate with a nucleophile.[23,38] Yet the results thus obtained agree surprisingly well with our finding of 54-58% photoisomerization of the tetrafluorodiazirine.

While the mechanism of thermal decomposition of diazirines has been investigated,[40] little is known about the mechanism of its light-induced decomposition. From studies with cycloalkane spirodiazirines,[38] photolytic ring opening of the diazirine has been postulated to occur by two competing routes, one in which only one C-N bond is broken to afford the diazo compound, and the second in which both C-N bonds are broken to give a carbene and molecular nitrogen. Evidence for the latter comes from the observation that photolysis of the diazo compound leads to a product composition different from that for the diazirine. In the present work, no significant difference in product composition was observed when the fluorinated diazirine **27** or the fluorinated diazo compound **35** were photolyzed. This could mean that excitation of both the diazirine and the diazo compound leads to the same transition state (canonical structures a-c) which can either fragment into carbene and molecular nitrogen, react by ring closure, or relax to the diazo isomer. However, qualitative and quantitative differences in product composition were observed when the diazirine **27** was pyrolyzed. Fragmentation without isomerization occurred, and the ratio of difluorocyclopropyl products to difluoro olefin was increased relative to that measured after photolysis at 310 nm. This could mean that thermal activation of the diazirine leads to an excited state, which results in the formation of the carbene in a one-step process by concerted cleavage of both C-N bonds.

Experimental Section

General Procedures. IR spectra were obtained on a Beckman Model 4210 spectrophotometer. ^{1}H NMR spectra were recorded using a Varian T-60 spectrometer or on a JEOL JNM-FX60 Q Fourier transform NMR spectrometer on samples in $CDCl_3$. Chemical shifts are reported in δ (ppm) with Me_4Si as an internal standard. ^{19}F NMR spectra were recorded at 56 MHz on a Hitachi Perkin-Elmer NMR spectrometer R-20B or at 254 MHz using a Bruker spectrometer. The high-field ^{19}F Fourier-transform NMR spectra were performed by Dr. D. Ruben at the F. Bitter National Magnet Laboratory, Massachusetts Institute of Technology. The shielding values for fluorine are reported in parts per million relative to fluorotrichloromethane as an internal standard.

Low-resolution mass spectra were determined on a Varian MAT 44 mass spectrometer by Ms. J. Owens. Exact molecular weights were determined on a CEC 110B Mattauch-Herzog (Du Pont Instruments) high-resolution mass spectrometer by Dr. C. E. Costello, Massachu-

setts Institute of Technology. UV spectra were recorded in cyclohexane with a Cary Model 15 spectrophotometer. Products were usually purified by chromatography on silicic acid columns or thin layer plates. Gas chromatographic (GC) product analysis, separation, and purification were performed on a Perkin-Elmer gas chromatograph 990 fitted with an effluent splitter. Glass columns (6 or 12 ft) packed with 3% SE-30 Gas Chrom Q were used throughout. Samples were collected into glass vials through glass capillaries cooled with dry ice.

Preparation and Photolysis of [1-^{14}C]Palmitoyl-2-(10-azistearoyl)phosphatidylcholine (3). Methyl 10-azistearate was prepared from methyl 10-ketostearate according to published procedures.[20] IR: 1750 and 1590 cm^{-1}. NMR: 3.7 (s, 3), 2.3 (t, 2), 1.2 and 0.9 ppm (t, 3). UV (CCl_4): ϵ_{365} 58, ϵ_{353} 55, and ϵ_{348} 68. The phospholipid **3** was prepared from the fatty acid anhydride and [1-^{14}C]palmitoyl-*sn*-glycero-3-phosphocholine in CCl_4 with a catalytic amount of 4-(dimethylamino)pyridine.[3] Vesicles were prepared by sonication of the phospholipid in aqueous buffer as previously described.[3] Photolysis of the vesicles was done at room temperature in an open cuvette at 365 nm, using an Oriel monochromatic irradiator (1000-W xenon-mercury lamp). The phospholipids were extracted[41] and separated by gel permeation chromatography (LH-20, 2.5 × 100 cm) into two well-separated fractions. The first fraction contained 7% of the total radioactivity as phospholipid dimers. The second contained the non-cross-linked phospholipids. Each fraction was transesterified in methanol containing sodium methoxide. Chromatography of the methyl esters on LH-20 gave only one peak, corresponding in elution volume to methyl palmitate.[4] No dimers formed by chemical cross-linking between the photoreactive fatty acid and [^{14}C]palmitic acid could be observed.

2,2-Bis-*n*-heptanoyl-1,3-dithiane (6). To a solution of 1,3-dithiane (10 g, 0.083 mol) in dry THF, cooled to −40 °C, was added with stirring *n*-BuLi (0.087 mol of a 2.4 M solution). After 2 h at −20 °C, the solution was transferred under N_2 pressure through a stainless-steel needle into a dropping funnel. It was added over a period of 2 h to a stirred solution, at −78 °C, of methyl heptanoate (6.8 mL, 0.0416 mol) in THF (12 mL). After the addition of lithium dithiane was complete, the reaction mixture was allowed to warm to room temperature over 2 h. It was then cooled again to −20 °C and heptanoyl chloride (13.4 mL, 0.087 mol) was added with vigorous stirring. The reaction mixture was allowed to warm to room temperature and after 4 h it was poured into ice water. The aqueous phase was extracted with ether and the organic phase was washed successively with 1 M KOH, 0.1 M HCl, and water. The organic solvents were then evaporated and the unreacted dithiane was removed by sublimation (70 °C, 0.1 mmHg, 3 h). To remove low-boiling material, the viscous solution was kept under a vacuum (100 °C, 0.1 mmHg, 10 h). After chromatography on silicic acid (260 g, petroleum ether–ether, 9:1) 88% of pure diheptanoyldithiane (**6**, 6 g, 40% yield) was obtained. Preparative thin layer chromatography afforded a 95% pure compound. IR: 1730, 1670, 1620, and 1370 cm^{-1}. NMR: 2.8 (m, 4, CH_2CO), 2.4 (m, 4, CH_2S), 2,2 (m, 2), 1.3 (16), and 0.9 ppm (t, 6). MS: *m/e* 344 (M^+), 232 ($M^+ - C_6H_{12}CO$), 85 (C_6H_{13}).

5-Bromo-4,6-nonadione (7). A mixture of 4,6-nonadione (3 g, 0.019 mol), *N*-bromosuccinimide (3.6 g, 0.02 mol), and 2,2′-azobis(2-methylpropionitrile) (0.03 g) in $CHCl_3$ (60 mL) was stirred for 1 h at room temperature. The solid succinimide was removed by filtration and the solvent was evaporated under vacuum. The product, bromononadione **7** (4.5 g, 100%), was initially obtained as a colorless liquid which turned brown after standing for some time. IR: 1750 and 1720 cm^{-1} (broad). NMR: 4.8 (s, 1, CHBr), 2.7 (t, 4, CH_2CO), 1.7 (m, 4, CH_2), and 0.95 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 234, 236 (M^+), 191, 193 ($M^+ - C_3H_7$), 164, 166 ($M^+ - C_3H_6CO$), 155 (M^+ − Br), 71 (C_3H_2CO).

5-Phthalimido-4,6-nonadione (8). 5-Bromo-4,6-nonadione (**7**, 0.5 g, 0.002 13 mol) and potassium phthalimide (0.395 g, 0.002 13 mol) were added to dimethylformamide (5 mL) at 15 °C and the mixture was stirred for 30 min. The reaction mixture, which turned dark yellow immediately, was then poured into a mixture of ether and water. The organic layer was washed with water, dried, and evaporated to dryness. To extract the product, benzene (2 × 5 mL) was added to the solid residue, and the mixture was heated to reflux and cooled. The clear solution was separated from the insoluble material by suction. Benzene was evaporated and the partially solid product was taken up in a minimum amount of ether. The solution was passed through silicic acid (18 g, petroleum ether–ether, 4:1) and afforded the phthalimidononadione **8** as a yellow oil (0.38 g, 60%, about 90% pure) which solidified on standing. IR: 1795 (sharp) and 1735 cm^{-1} (broad). NMR: 8.05 (d, 4, aromatic), 7.4 (s, 1, $HC(CO)_2N$), 2.2 (t, 4, $(CH_2CO)_2$), 1.6 (m, 4, $(CH_2)_2$), and 0.85 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 301 (M^+), 258 ($M^+ - C_3H_7$), 231 ($M^+ - C_3H_6CO$), 43 (C_3H_7).

5-Oximino-4,6-nonadione (9). Method A. Isoamyl nitrite (2.72 mL, 0.02 mol) was added dropwise to a stirred solution of nonadione (3 g, 0.019 mol) in anhydrous ether (25 mL) through which HCl gas was bubbled slowly at 10 °C. After 1 h, crushed ice and water were added and after separation of the phases the aqueous phase was washed with ether. The pooled organic phase was washed with saturated aqueous $NaHCO_3$, then water, and finally dried. Evaporation of the solvent gave a crude product which was purified on silicic acid (90 g, eluted with 250 mL each of petroleum ether–ether, 9:4 and 5:2) to give pure oximinononadione **9** (2.6 g, 73%).

Method B. Sodium nitrite (4.8 g, 0.07 mol) in water (6 mL) was added dropwise to a well-stirred solution of 4,6-nonadione (10 g, 0.064 mol) in acetic acid (30 mL). The temperature was kept below 15 °C during the reaction, which was complete in 1 h. Workup was as described above. Short-path distillation afforded the 5-oximino-4,6-nonadione (8.6 g, 73%) as a pale yellow liquid, bp 111 °C (0.5 mmHg). IR: 3400 (broad), 3040 (w), 1725/1695 (vs), 1420 (vs), and 1000 cm^{-1} (s). NMR: 9.9 (s, 1, OH), 2.7 (t, 4, $(CH_2CO)_2$), 1.65 (m, 4, $(CH_2)_2$), and 0.9 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 185 (M^+), 168 (M^+ − OH), 156 ($M^+ - C_2H_5$), 139 ($M^+ - C_2H_5$, OH).

5-Acetoximino-4,6-nonadione (10). Acetic anhydride (3.5 mL, 0.034 mol) was added dropwise to a stirred solution of the oximino diketone **9** (5.7 g, 0.031 mol) in pyridine (20 mL). After the usual workup, chromatography on silicic acid (150 g) gave a fraction containing 85% pure 5-acetoximino-4,6-nonadione (**10**, 3.4 g, 51%). An analytically pure sample was prepared by GC. IR: 1805 (s), 1730 (s), 1705 (w), and 1180 cm^{-1} (s). NMR: 2.95 (t, 2, CH_2CO), 2.6 (t, 2, CH_2CO), 2.2 (s, 3, CH_3CO), 1.7 (m, 4, $(CH_2)_2$), and 1.0 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 227 (M^+), 185 ($M^+ - CH_2CO$), 156 ($M^+ - C_3H_7CO$).

5-Methoximino-4,6-nonadione (11). Silver oxide (0.97 g, 0.0042 mol) was added in small portions over a period of 6 h to a well-stirred solution of the oximino diketone **9** (1.5 g, 0.0081 mol) and methyl iodide (1.5 mL, 0.0234 mol) in anhydrous ether (10 mL). After 8 h, the reaction mixture was diluted with $CHCl_3$, and the solution filtered and then evaporated. The residue containing the crude product was chromatographed on silicic acid (45 g, petroleum ether–ether, 3:2) and yielded pure methoximino diketone **11** (1.13 g, 70%). IR: 1740 (s), 1700 (s), and 1040 cm^{-1} (s). NMR: 4.1 (s, 3, OCH_3), 2.8 and 2.6 (2 t, 4, $(CH_2CO)_2$), 1.65 (m, 4, $(CH_2)_2$), and 1.0 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 199 (M^+), 168 ($M^+ - OCH_3$), 156 ($M^+ - C_3H_7$), 128 ($M^+ - C_3H_7CO$).

5-Benzylidene-2,4-nonadione (12). Prepared exactly as described,[42] the compound was obtained in 50% yield after chromatography on silicic acid with petroleum ether–ether, 9:1 and 5:1, followed by distillation under reduced pressure, bp 123–124 °C (0.1 mmHg). IR: 3060, 3040, 2900, 1710, 1665, 1620, 1580, and 1500 cm^{-1}. NMR: 7.45 (s, 1 =CHPh), 7.30 (m, 5, aromatic), 2.75 (t, 2, CH_2CO), 2.45 (t, 2, CH_2CO), 1.7 (m, 4), 1.0 (t, 3), and 0.85 ppm (t, 3). MS: *m/e* 244 (M^+), 201 ($M^+ - C_3H_7$), 173 ($M^+ - C_3H_7CO$), 131 ($C_6H_5CH{=}CHCO$), 102 ($C_6H_5CH{=}C$).

4,4-Difluoro-5-acetoximino-6-nonanone (13). Diethylaminosulfur trifluoride (1.5 mL, 0.012 mol) was added under N_2 to a stirred solution of the acetoximino diketone **10** (2.3 g, 0.01 mol) in CH_2Cl_2 (20 mL). After 16 h the reaction mixture was diluted with $CHCl_3$ and the solution washed with saturated $NaHCO_3$ and water. The organic solution was dried, the solvent evaporated under reduced pressure, and the residue purified on silicic acid (75 g, eluted with 100 mL each of petroleum ether–ether, 4:1, 3:1, and 1:1) and gave the difluoro monoketone **13** (0.74 g, 30%) as a yellow liquid. IR: 1810 (vs), 1735 (s), and 1180 cm^{-1} (s). NMR: 2.7 (t, 2, CH_2CO), 2.2 (s, 3, CH_3CO), 1.7 (m, 4, $(CH_2)_2$), and 1.0 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 249 (M^+), 207 ($M^+ - CH_2CO$), 187 (M^+ − HF, CH_2CO), 158 (M^+ − HF, C_3H_7CO), 115 (C_4H_6CFCNO), 93 ($C_3H_7CF_2$). Further elution of the silicic acid column yielded a mixture (0.6 g) containing 60% starting material and 13% difluoro monoketone **13**. When the reaction mixture was refluxed in the presence of a fivefold excess of the fluorinating agent, no tetrafluorinated product could be detected. However, the yield of the difluoro ketone **13** was greatly reduced.

4,4-Difluoro-5-methoximino-6-nonanone (14). Methoximino diketone **11** (0.47 g, 0.002 36 mol) and diethylaminosulfur trifluoride

(0.85 mL, 0.007 mol) were kept in CH_2Cl_2 (2 mL) for 4 days at room temperature. Workup as described above and purification by TLC (silicic acid, petroleum ether-ether, 5:1) yielded 40 mg (R_f 0.46) of the starting material and a pure sample of the difluoro ketone **14** (80 mg, R_f 0.64). IR: 1735 cm^{-1} (s). NMR: 4.0 (s, 3, OCH_3), 2.65 (t, 2, CH_2CO), 2.3-1.4 (m, 4), and 0.95 ppm (t, 6, $(CH_3)_2$). MS: *m/e* 221 (M^+), 201 (M^+ − HF), 150 (M^+ − C_3H_7CO), 115 ($C_2H_5CH{=}CFCNO$), 93 ($C_3H_7CF_2$), 71 (C_3H_7CO).

4,4-Difluoro-5-benzylidene-6-nonanone (15). Benzylidenenonadione (**12**, 1.2 g, 0.0078 mol) was heated under reflux in benzene for 50 h. During this time diethylaminosulfur trifluoride (3 mL, 0.024 mol) was added in portions. After this time, an aliquot of the reaction mixture was removed, worked up, and purified on TLC with petroleum ether-ether (5:1) as the solvent. A pale yellow liquid (R_f 0.58) was thus obtained. IR: 3060, 3040, 2980, 1710, 1210, and 1180 cm^{-1}. NMR: 7.35 (m, 5, aromatic), 7.1 (t, 1, PhCH=), 2.3 (t, 2), 1.5 (m, 6), 1.0 (t, 3), and 0.8 ppm (t, 3). MS: *m/e* 266 (M^+), 247 (M^+ − F), 223 (M^+ − C_3H_7), 203 (M^+ − HF, C_3H_7), 183 (M^+ − 2HF, C_3H_7), 155 (M^+ − C_3H_7CO, 2HF).

6-Acetoxy-5-undecene (16). A mixture of 6-undecanone (69 g, 0.4 mol), isopropenyl acetate (140 mL), benzene (50 mL), and *p*-toluenesulfonic acid (3 g) was heated overnight in an oil bath at 130 °C. The solvent and the reactants volatile at this temperature were allowed to distill into a receiver (90 mL of distillate after 16 h). The temperature was then raised to 170°C to complete the reaction and the mixture was cooled and poured into cold saturated $NaHCO_3$. The organic layer was washed with water and dried and after removal of the solvent the product was distilled through a 15-cm Vigreux column. The yield of the enol acetate **16** was 74 g (86%), bp 74-76 °C (0.1 mmHg). NMR: 5.05, 5.15 (t, 1, CH=), 2.15 (s, 3, CH_3CO), 2.1 (m, 4, CH_2CH=), 1.35 (m, 10), and 0.9 ppm (t, 6).

5,6-Difluoromethylene-6-acetoxyundecane (17). To a well-stirred solution of the enol acetate **16** (70 g, 0.33 mol) under reflux in diglyme (350 mL, dried over CaH_2 and $LiAlH_4$ and freshly distilled at reduced pressure) was added dropwise over a period of 2.5 h a suspension of sodium chlorodifluoroacetate (80 g, 0.53 mol, dried overnight over P_2O_5 at 0.5 mmHg) in diglyme (150 mL). The volume of the reaction mixture was kept constant by allowing the increase in solvent to distill slowly into a receiver. The resulting black solution was cooled to room temperature and filtered. Excess diglyme was removed by distillation under reduced pressure. The product was purified by distillation through a 15-cm Vigreux column. The difluorocarbene adduct **17** was obtained as an almost colorless liquid (71 g, 80%), bp 71 °C (0.1 mmHg). IR: 1770 cm^{-1}. NMR: 2.1 ppm (s, 3, CH_3CO). MS: *m/e* 263 (M^+ + 1), 242 (M^+ − HF), 219 (M^+ − CH_3CO), 206 (M^+ − C_5H_{11}), 163 (M^+ − CH_3CO,C_5H_{11}), 144 (M^+ − CH_3CO, C_5H_{11}, F).

7,7-Difluoro-6-dodecanone (19). To an ice-cold, well-stirred solution of the difluorocyclopropyl acetate **17** (40 g, 0.153 mol) in methanol (200 mL) was added dropwise over a period of 30 min potassium hydroxide (8.6 g, 0.155 mol) in methanol (80 mL). After 2 h the reaction mixture was concentrated by removal of solvent under reduced pressure and then poured into pentane-water. The organic layer was washed with water, dried, and evaporated under reduced pressure. A yellow liquid (29 g, 85%) was thus obtained which on being distilled through a 15-cm Vigreux column yielded 93% pure α,α-difluoro ketone **19** (20 g, 60%), bp 55-59 °C (0.5 mmHg), and a fraction (6 g, bp 62-75 °C) containing 65% *trans*-7-fluorododec-8-en-6-one (**18**). Difluoro ketone **19**: IR 1760 cm^{-1}; ^1H NMR 2.7 (t, 2, CH_2CO), 2.1-1.2 (m, 14), and 0.9 ppm (t, 6, CH_3); ^{19}F NMR 101 ppm (t, J_{HF} = 16.2 Hz). Fluoro enone **18**: IR 1770, 1700, and 1660 cm^{-1}; ^1H NMR 6.05 (sextet, 1, CH=CH, J_{HF} = 34, J_{HH} = 8 Hz), 2.6 (t, 2, CH_2CO), 2.1-1.2 (m, 12), and 0.9 ppm (t, 6, CH_3). MS: *m/e* 200 (M^+), 172 (M^+ − CO), 144 (M^+ − C_4H_8), 129 (M^+ − C_5H_{11}).

6-Trimethylsilyloxy-7,7-difluoro-5-dodecene (20). To a well-stirred solution of chlorotrimethylsilane (10.4 g, 0.096 mol) in dry DMF (33 mL) at room temperature was added triethylamine (19.6 g, 0.192 mol) followed by the difluoro ketone **19** (17.5 g, 0.08 mol). The temperature was increased to 100 °C over a period of 30 min. After this time the reaction was complete. The reaction mixture was cooled to 4 °C, diluted with cold pentane (60 mL), washed three times (100 mL each) with ice-cold $NaHCO_3$, 1 M HCl, $NaHCO_3$, and water, and dried. After removal of the solvent, the residual oil was distilled through a 15-cm Vigreux column. Trimethylsilyl enol ether **20** (18.7 g, 80%) was obtained in 95% purity, bp 71-75 °C (0.5 mmHg). IR: 1690, 1260, and 850 cm^{-1}. NMR: 5.2 (t, 1, CH=), 2.0 (m, 4), 1.3 (m, 10), 0.85 (t, 6), and 0.15 ppm (s, 9, $Si(CH_3)_3$).

5,6-Difluoromethylene-6-trimethylsilyloxy-7,7-difluorododecane (21). Sodium chlorodifluoroacetate (20 g, 0.128 mol) in diglyme (50 mL) was added to a stirred solution of the trimethylsilyl enol ether **20** (18.7 g, 0.064 mol) in diglyme (100 mL) exactly as described for **16**. Distillation through a 15-cm Vigreux column gave difluoro ketone **18** (3 g) and the difluorocarbene adduct **21** (11.7 g, 58%, bp 71-78 °C (0.1 mmHg)) of 85% purity.

5,6-Difluoromethylene-6-hydroxy-7,7-difluorododecane (22). The trimethylsilyl difluorocyclopropyl ether **21** (0.43 g) was heated under reflux for 6 h in THF (5 mL) containing 37% HCl (0.25 mL). The cooled reaction mixture was diluted with pentane, and the organic phase was washed with $NaHCO_3$ and water and dried. After removal of the solvent, the product was purified on silicic acid (18 g, petroleum ether-ether-CH_2Cl_2, 20:1:2) to yield the difluorocyclopropanol **22** (70 mg). IR: 3600, 3450, 1470, 1160, 1130, and 1030 cm^{-1}. NMR: 2.45 (OH), 2.1-1.2 (m, 15), and 0.95 ppm (t, 6).

6,6,8,8-Tetrafluoro-7-tridecanone (23). Treatment of either the difluorocyclopropanol **22** or the trimethylsilyl difluorocyclopropyl ether **21** with 0.15 equiv of KOH in ice-cold MeOH for 30 min gave two main products, the tetrafluoro ketone **23** and 6,8,8-trifluoro-5-tridecen-7-one (**24**), and a number of minor products. The tetrafluoro ketone **23** was separated as its hydrate from the less polar side products by chromatography on silicic acid. The latter materials were first washed off with petroleum ether-ether (5:1) and the tetrafluoro ketone hydrate was then eluted with ether. It was dehydrated in ether over molecular sieves (Lindé A4) and then distilled at reduced pressure, bp 58 °C (0.07 mmHg). IR: 1770 cm^{-1}. UV (cyclohexane): λ_{max} 315 nm, ϵ_0 ca. 60. MS: *m/e* 250 (M^+ − HF). The trifluorotridecenone was characterized as follows. IR: 1715, 1655, 1480, 1180, and 1125 cm^{-1}. ^1H NMR: 6.4 (sextet, 1, CH=CF, J_{HF} = 34, J_{HH} = 7.7 Hz), 2.35 (m, 4), 1.4 (m, 10), and 0.9 ppm (t, 6).

6,6,8,8-Tetrafluoro-7-tridecanonimine (25). Excess liquid ammonia, dried over sodium, was condensed over amidotriphenylphosphonium hydrogen sulfate[43] (3.75 g, 0.01 mol). The suspension was stirred for 15 min, ammonia was then evaporated, and benzene (10 mL, dried over Na) was added. The suspension was well stirred for 5 min and then filtered under nitrogen into a second flask. To this solution of triphenylphosphinimine[43] in benzene was added dropwise with stirring and cooling in an ice bath 6,6,8,8-tetrafluoro-7-tridecanone (1.66 g, 0.0062 mol). The reaction mixture was stirred at room temperature overnight. Benzene was evaporated and the solid residue was extracted twice with refluxing pentane. The pentane was evaporated and the crude product was purified on silicic acid (17 g) with petroleum ether-ether, 9:1, as eluent. After elution of the imine **25**, elution with ether gave unreacted ketone hydrate **23** (20%). Short-path distillation afforded pure tetrafluoro ketone imine **25** (1.16 g, 70%), bp 71 °C (0.1 mmHg). IR: 3300 (weak), 1670 (very weak), 1470, and 1210 cm^{-1}. NMR: 10.8 (broad, 1, exchanges slowly with D_2O), 2.4-1.9 (m), 1.4 (m), and 0.9 ppm (t). MS: *m/e* 269 (M^+), 254 (M^+ − NH), 250 (M^+ − F), 199 (M^+ − C_5H_{10}), 148 (M^+ − $C_5H_{11}CF_2$). UV (cyclohexane): λ_{max} 245 nm (ϵ_0 160).

3,3-Bis(1,1-difluoro-*n*-hexyl)diaziridine (26). To a solution of hydroxylamine-*O*-sulfonic acid (0.735 g, 0.0065 mol) in dry diglyme (4 mL, distilled freshly from $LiAlH_4$) was added with stirring at 4 °C 6,6,8,8-tetrafluoro-7-tridecanonimine (**25**, 1.18 g, 0.0048 mol). The reaction mixture was stirred overnight at room temperature, when a small precipitate formed. Pentane was added, followed by saturated aqueous $NaHCO_3$. The organic layer was washed five times with water and dried over $MgSO_4$. Removal of solvent yielded crude diaziridine **26** (0.7 g) containing tetrafluoro ketone hydrate. TLC (ether-petroleum ether, 1:1, silicic acid) showed a single spot (I_2 staining) moving slightly slower than the imine **25**. IR: 3300 (broad) and 1470 cm^{-1}.

3,3-Bis(1,1-difluoro-*n*-hexyl)diazirine (27). The crude diaziridine **26** (0.7 g) was dissolved in benzene (1 mL) and the solution added dropwise with stirring to an ice-cooled solution of lead tetraacetate (1.1 g) in benzene (4 mL). The reaction mixture was stirred at room temperature for 30 min. It was filtered, washed with water and saturated sodium bicarbonate, and dried over potassium carbonate. After removal of solvent at reduced pressure, the crude product was purified by chromatography on silicic acid (15 g, petroleum ether-ether, 9:1) to afford the diazirine **27** (0.18 g, 17%, 90% pure on GC). At this stage the product still had a slightly blue color. Pure samples could be prepared by gas chromatography. No decomposition of the diazirine occurred, if the injector and column temperature were kept below 150

°C. IR: 1590 and 1460 cm^{-1}. ^{19}F NMR: 88 ppm (t, J_{HF} = 16.5 Hz). M^+ not observed. $M^+ - N_2$: HF 234.1589 (calcd for $C_{13}H_{21}F_3$, 234.1595). $M^+ - N_2$, HF, C_4H_9: 177.0910 (calcd for $C_9H_{12}F_3$, 177.0891). 163.0799 (calcd for $C_8H_{10}F_3$, 163.0735). 113.0755 (calcd for $C_7H_{10}F_1$, 113.0766). UV (cyclohexane): λ_{max} 302, 312 nm (ϵ_0 53).

Methyl α-Ketononanoate (28). The procedure was based on that described for α-ketoglutaric acid.[44] Sodium (3.8 g, 0.165 mol) was dissolved in dry ethanol (200 mL). Excess of ethanol was then removed by distillation at reduced pressure until a thick slurry formed. Toluene (100 mL) was added to the slurry and it was distilled off at reduced pressure to remove residual ethanol. The slurry was cooled and dry ether (100 mL) was added followed by diethyl oxalate (18 g, 0.125 mol). After the ethoxide had completely gone into solution, ethyl octanoate (14 g, 0.082 mol) was added quickly. The reaction mixture was heated under reflux for 16 h. It was then cooled and poured into 70 mL of water and the layers were separated. The ether layer was extracted twice with 50 mL of water. The aqueous extracts were pooled, acidified with concentrated HCl, and extracted three times with 60 mL of ether each time. Ether was evaporated and the residual oil was heated under reflux with vigorous stirring in 4 M HCl (40 mL) for 12 h. The solvent was evaporated at reduced pressure and the residual black oil was heated under reflux for 2 h in methanol (100 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid. After concentration to a smaller volume, the reaction mixture was diluted with ether (100 mL) and extracted three times with 20% potassium carbonate. The ether solution was dried and evaporated. Distillation of the residue through a 15-cm Vigreux column gave the α-keto ester **28** (6.6 g, 46%) which was 83% pure, bp 96 °C (6 mmHg). IR: 1760 (shoulder) and 1740 cm^{-1}. NMR: 3.8 (s, 3), 2.75 (t, 2), 1.4 (10), and 0.9 ppm (t, 3).

Methyl α,α-Difluorononanoate (29). To an ice-cooled solution of methyl α-ketononanoate (6.6 g, 0.384 mol) in CH_2Cl_2 (40 mL) was added with stirring diethylaminosulfur trifluoride (6.6 g, 0.41 mol) and the reaction mixture was kept at room temperature overnight. Crushed ice was then added, followed by careful addition of solid $NaHCO_3$, in small portions, until the aqueous layer maintained alkaline pH. The layers were separated, the aqueous phase was extracted twice with CH_2Cl_2, and the pooled organic extracts were washed with water. The dried organic solution was evaporated and the residue distilled through a 15-cm Vigreux column to give the α-difluoro ester **29** (5.7 g, 77%), bp 71-75 °C (7 mmHg). IR: 1790 cm^{-1}. ^{19}F NMR: 103 ppm (t, J_{HF} = 15.8 Hz).

α,α-Difluorononaldehyde Hydrate (30a). To a solution of the α,α-difluoro ester **29** in ether, cooled to −76 °C, was added portionwise over a period of 1 h with vigorous stirring 1.2 equiv of a 25% solution of diisobutylaluminum hydride (DIBAL-H, Aldrich) in toluene. The reaction mixture was allowed to warm to room temperature over a period of 3 h. It was then diluted with ether and extracted with 4 M H_2SO_4. The organic layer was washed with $NaHCO_3$ and dried. Removal of solvent afforded the difluoro aldehyde hydrate. An analytically pure sample of dehydrated difluoro aldehyde **30b** was prepared on GC (3% SE-30, 80 °C). IR: 1770 cm^{-1}. MS: *m/e* 149 (M^+ − COH), 129 (M^+ − COH, − HF).

3-(1,1-Difluorooctyl)-3*H*-diazirine (33). The difluoro aldehyde hydrate **30a** (1.35 g, 0.007 mol) was heated under reflux in benzene for 2 h. The condensing vapors were rendered anhydrous by letting them flow back into the reaction flask via an addition funnel which was filled with molecular sieves. The solution was then cooled, *tert*-butylamine (0.84 mL, 0.008 mol) was added, and the reaction mixture was allowed to sit overnight. The *tert*-butylimine **31** was freed of solvents. Ethanol (7.0 mL) and triethylamine (3.5 mL) were added. To the ice-cooled, stirred reaction mixture was then added hydroxylamine-*O*-sulfonic acid (0.0105 mol, 1.2 g). After 1 h, the reaction mixture was concentrated at reduced pressure and diluted with ether and the ethereal solution extracted with water. It was dried and evaporated and the crude *tert*-butyldiaziridine **32** was redissolved in ethanol (7 mL) and triethylamine (1 mL). To the ice-cooled, stirred solution *tert*-butyl hypochlorite (0.0077 mol, 0.87 mL) in *tert*-butyl alcohol (1 mL) was added. After 1 h, the reaction mixture was concentrated, redissolved in pentane, and washed successively with solutions of NaS_2O_5 (10%), $NaHCO_3$ (10%), and saturated NaCl. After evaporation of solvents, the crude diazirine was purified on silicic acid (40 g, petroleum ether-ether, 6:1). The diazirine **33** was eluted as a slightly yellow liquid (0.6 g, 45%) which was at least 95% pure, as analyzed on GC. IR: 1600 cm^{-1}. ^1H NMR: 1.9 (m, 1, CHN), 1.6 (m, 2, CH_2CF_2), 1.3 (10), and 0.9 ppm (t, 3). ^{19}F NMR: 99 ppm (triplet of doublets, J_{HF} 14.7 and 5.7 Hz). UV (cyclohexane): λ_{max} 306, 312, 318 nm ($\epsilon_{306-318}$ 160).

1-*tert*-Butyl-3-(1,1-difluoro-*n*-octyl)-3*H*-diaziridine (32). A pure sample was prepared by GC. IR: 3280, 1480, 1365, and 1220 cm^{-1}. ^1H NMR: 3.1 (1, m, CH_2CH), 2.2 (exchanges with D_2O), 1.6, 1.3 (12), 1.0 (s, 9, $(CH_3)_3C$), and 0.9 ppm (t, 3). MS: *m/e* 233 (M^+ − CH_3), 213 (M^+ − HF, CH_3), 191 (M^+ − *t*-Bu).

Photochemical Reactions. In a typical photolysis experiment 1-50 μL of the diazirine in 0.1-1.0 mL of solvent was irradiated with an Oriel monochromatic irradiator (1000-W xenon-mercury lamp) for up to 14 h at temperatures between 8 °C and room temperature. The progress of the reaction was followed by monitoring the IR and UV spectra and by analysis on GC. The product ratios were determined from the peak areas on the gas chromatogram and from the relative extinctions of products with specific UV spectra. The reaction products were identified spectroscopically following preparation of pure samples by GC. Pyrolysis was done by injecting the diazirine into the gas chromatograph with the injector temperature set at 300 °C.

When the tetrafluorodiazirine **27** was irradiated at 310 nm in cyclohexane, cyclohexene, methanol, or 1 M acetic acid in cyclohexane, GC analysis (column temperature 110-140 °C, injector temperature 150 °C) gave in order of retention time the following four compounds in a ratio 13:21:6:54.

6,6-Difluoro-7-difluoromethylenedodecane (37). IR: 1750 and 1470 cm^{-1}. ^1H NMR: 2.0 (m), 1.35 (m), and 0.9 ppm (t). ^{19}F NMR: 82.2 (m, $=CF_2$), 86.8 (doublet of triplet, J_{FF} = 39, J_{XF} = 10 Hz, $=CF_2$), and 93.6 ppm (m, $-CF_2-$). MS: *m/e* 254 (M^+), 235 (M^+ − F), 234 (M^+ − HF), 214 (M^+ − 2HF), 164 (M^+ − F − C_5H_{11}), 163 (M^+ − HF − C_5H_{11}). M^+ 254.1665 (calcd for $C_{13}H_{22}F_4$, 254.1658).

1,1-Difluoro-2-(1,1-difluoro-*n*-hexyl)-3-*n*-butylcyclopropane (36). The identification was based on the following properties. IR: 1490 and 1470 cm^{-1}. ^1H NMR: 1.35-1.5 (m) and 0.9 ppm (t). ^{19}F NMR (trans isomer): 94.9 (doublet of multiplets, J_{FF} = 252 Hz, exocyclic CF_2), 100.9 (doublet of multiplets, J_{FF} = 252 Hz, exocyclic CF_2), 137.55 (doublet of multiplets, J_{FF} = 166 Hz, endocyclic $-CF_2-$), and 138.55 ppm (doublet of multiplets, J_{FF} = 166 Hz, endocyclic CF_2). (cis isomer): 91.2 (doublet of multiplets, J_{FF} = 254 Hz, exocyclic CF_2), 98.2 (doublet of multiplets, J_{FF} = 254 Hz, exocyclic CF_2), 121.4 (doublet of multiplets, J_{FF} = 162 Hz, endocyclic CF_2), and 152.6 ppm (doublet of multiplets, J_{FF} = 162 Hz, endocyclic CF_2). MS: *m/e* 235 (M^+ − F), 234 (M^+ − HF), 214 (M^+ − 2HF), 164, 163; M^+ not observed. $M^+ - C_3H_7HF$: 191.1037 (calcd for $C_{10}H_{14}F_3$, 191.1048). $M^+ - C_4H_9$: HF 177.0881 (calcd for $C_9H_{12}F_3$, 177.0891). $M^+ - C_5H_{11}$: HF, 163.0748 (calcd for $C_8H_{10}F_3$, 163.0735).

6,6,8,8-Tetrafluoro-7-diazotridecane (35). The identification was based on the following properties. IR: 2120 cm^{-1}. ^{19}F NMR: 87.9 (t, J_{HF} = 16.5 Hz). MS: *m/e* 254 ($M^+ - N_2$), 234, 214, 164, 163. UV (cyclohexane): λ_{max} 390 (ϵ_0 ca. 12).

When the difluorodiazirine **33** was irradiated in cyclohexane or methanol at 310 nm, a strong IR absorption at 2120 cm^{-1} indicated the presence of α,α-difluorodiazononane **38**. GC analysis gave in order of retention time the following two products in a ratio of 1:2.

1,1-Difluorononene (39). IR: 1760 cm^{-1}. ^1H NMR: 4.1 (doublet, J_{HF} = 25 Hz, of triplets, J_{HH} = 7.6 Hz, of doublets, J_{HF} = 3.17 Hz, 1, $-CH=CF_2$) 1.95 (m, 2, $-CH_2C=$), 1.3 (m, 10), and 0.88 ppm (t, 3). ^{19}F NMR: 84 and 82 ppm ($=CF_2$, J_{FF} not determined).

1,1-Difluoro-2-*n*-hexylcyclopropane (40). ^1H NMR: 1.35 (13), 0.9 ppm (t, 3). ^{19}F NMR: 125 (d, J_{FF} = 39 Hz, endocyclic $-CF_2-$) and 143 ppm (d, J_{FF} = 39 Hz). M^+ not observed. M^+ − HF: 142.1166 (calcd for $C_9H_{15}F$, 142.1158). $M^+ - CF_2$: 112.1247 (calcd for C_8H_{16}, 112.1252). $M^+ - C_3H_3F_2$: 85.1016 (calcd for C_6H_{13}, 85.1017). $M^+ - C_6H_{12}$: 78.0285 (calcd for $C_3H_4F_2$, 78.0281). $M^+ - C_5H_{11}$: HF 71.0314 (calcd for C_4H_4F, 71.0297).

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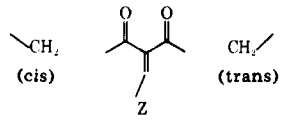
(17) The carbonyl groups, cis and trans, to the substituent 7 at the olefinic double bond



can be distinguished by the different chemical shifts of their α-methylene protons. The δ value of the protons cis to Z is increased relative to that of the trans protons because of interatomic, diamagnetic deshielding by the substituent Z. Through comparison of the chemical shifts before and after fluorination it is possible to deduce which of the two carbonyl groups is fluorinated. The data in Table I show the disappearance of the resonance at lower field of the methylene protons on the cis side. This seems to indicate that the carbonyl on the sterically more hindered cis side is fluorinated and that stereoelectronic rather than steric factors determine the reactivity of the carbonyl groups in conjugation with an olefinic bond.
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(27) The *sym*-dichlorotetrafluoroacetonimine was prepared according to Middleton, W. J.; Carlson, H. D. *Org. Synth.* **1970**, *50*, 81: bp 75 °C; IR 1690 cm^{-1}; ^1H NMR 11.5 ppm. The diamine (bp 146 °C) and the diazirine were prepared according to Bekker, R. A.; Melikyan, G. G.; Dyatkin, B. L.; Knunyants, I. L. *Zh. Org. Khim.* **1975**, *11*, 1604: bp 34 °C; IR 1640 cm^{-1}; ^{19}F NMR 53.5 ppm; UV λ_{max} 293 and 304 nm (ϵ_0 56).
(28) Decomposition of the difluorocyclopropyl ether could be initiated by traces of hydrofluoric acid. The difluorocyclopropanol thus formed could then further react by loss of the hydroxyl proton, followed by ring opening and fluoride elimination to form 2-fluorooct-2-enal: IR 3460 (weak), 1710, and 1670 cm^{-1}; ^1H NMR 9.4 (d, 1, J_{HF} = 18 Hz, CHO), 5.9 (doublet of triplets, 1, J_{HF} = 33 Hz, CH=CF), 2.4 (2, m), 1.4 (6), 0.9 (t, 3); ^{19}F NMR 63 ppm (d); MS *m/e* 124 (M^+ − HF), 115 (M^+ − COH), 95 (M^+ − HF, COH), 73 (M^+ − C_5H_{11}). Alternatively, elimination of hydrogen fluoride would give fluorocyclopropenol. The latter could then isomerize either via a hypothetical fluoro ketene to the α-fluoro aldehyde or to the stable 2-fluoro-3-pentylcyclopropanone: IR 1805, 1485, 1185, and 1140 cm^{-1}; ^1H NMR 4.3 (m, 1, J_{HF} 18 Hz, -CHF-), 3.7 (m, 1, -CHC=O), 1.5 (8), and 0.9 ppm (t, 3). This compound could be converted to the above α,β-unsaturated α-fluoro aldehyde by mild acid treatment.
(29) From the α,α-difluoro ester **29** the following compounds were further prepared by standard methods: α,α-difluoro alcohol by reduction with lithium aluminum hydride, α,α-difluoro amide by treatment with refluxing ammonia, and the α,α-difluoro amine by reduction of the amide with lithium aluminum hydride. The α,α-difluorononaldehyde oxime was prepared by a method analogous to that reported by Kissinger, L. W.; McGuistion, W. E.; Schwartz, M. *Tetrahedron, Suppl. 1* **1963**, *19*, 137: IR 3600 (w, sharp), 3280 (s, broad) and 1665 cm^{-1} (vw); ^1H NMR 8.2 (s, 1, exchanges with D_2O), 7.4 (t, 1, J_{HF} = 5.5 Hz), 1.3-2.0 (12), and 0.9 ppm (t, 3); ^{19}F NMR 95 ppm, J_{HF} = 15.4 (CH_2CF_2), J_{HF} = 5.6 Hz (CF_2CH=N); *m/e* 294 (M^+ + 1).
(30) If the *tert*-butylimine or the tritylimine were reacted with hydroxylamine-*O*-sulfonic acid in diglyme, only the aldehyde oxime could be isolated after aqueous workup. The *p*-toluenesulfonyl oxime was unstable in the presence of triethylamine, while the α,α-difluoronitrile was formed spontaneously.
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