When a mixture of *cis*- and *trans*-8 was allowed to react at 110 °C with the triazolinedione, NMR signals for the trans adduct 14 appeared together with those for the two cis compounds (13a,b). ^{19}F NMR ($CDCl_3$) for 14: 104.5 (F gem to Cl, distal to N), 113.5 (F gem to Cl, proximal to N), ~144 (vinyl F's, overlap with 13a,b signals), ~176 ppm (bridgehead F's, overlap with 13b signal).

Acknowledgment. We thank the Air Force Office of Scientific Research and the National Science Foundation for generous financial support.

1,2-Cycloadditions to *cis*-5,6-Dichlorohexafluorocyclohexa-1,3-diene[1]

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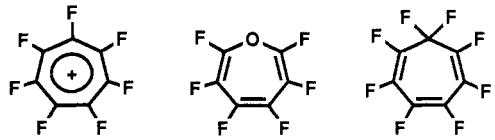
Addition of difluorocarbene to the title compound (7) at temperatures of 160–190 °C yielded rearranged monoadducts having the norbornene and bicyclo[3.2.0]hept-2-ene skeletons. Dechlorination of these compounds gave octafluoronorbornadiene (21) and octafluorobicyclo[3.2.0]hepta-2,6-diene (22). Though attempts to transform 22 into tropylium ion 1 met with failure, norbornadiene 21 was so transformed, as elaborated elsewhere. Addition of chlorofluorocarbene to 7 at 130 °C gave a stereoisomeric mixture of cyclopropanes (1:1 adducts), which were stable under the reaction conditions. Treatment of 7 with peroxytrifluoroacetic acid yielded a single monoepoxide (36). Reduction of 36 under mild conditions gave not the expected benzene oxide 2 but pentafluorophenol.

Introduction

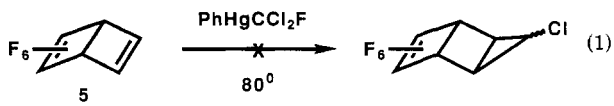
The work described in this paper was stimulated by a desire to synthesize the heptafluorotropylium ion (1) and hexafluorooxepin (2). An appropriate precursor for 1,



1 2 3

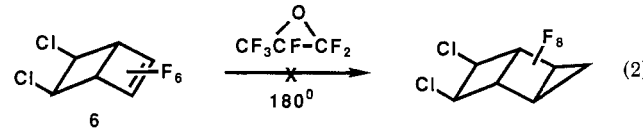
octafluorocycloheptatriene (3), had been synthesized previously by Tatlow's group,[2] but by a very long and low-yield route. A more practical method was needed, and the relatively inexpensive hexafluorobenzene (4) was an appealing starting material.

Direct addition of difluorocarbene to hexafluorobenzene requires violent conditions and yields only insertion products, octafluorotoluene and others.[3] Thus a hexafluorobenzene synthon, far more reactive than the compound itself, was required. At the outset, we envisioned carbene addition to the synthon hexafluoro Dewar benzene (5), which is available in excellent yield from the benzene by vapor-phase irradiation.[4] The resulting adduct was to be ring opened thermally to give the desired cycloheptatriene skeleton. Unfortunately, attempts to add chlorofluorocarbene to 5 at temperatures below 80 °C, where ring opening to 4 becomes fairly rapid, met with failure (eq 1). Halogenation of one of the double bonds of 5 results in greatly increased thermal stability,[5] thus



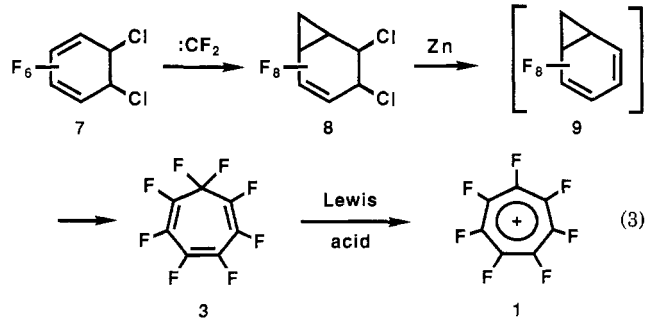
5 (1)

extending the temperature range available for carbene addition. It was found, however, that 5,6-dichlorobicyclo[2.2.0]hex-2-ene 6 resists addition of difluorocarbene (generated by pyrolysis of hexafluoropropylene oxide) even at temperatures around 180 °C (eq. 2).



6 (2)

We discovered that Dewar benzene 5 was also inert to peroxytrifluoroacetic acid at room temperature, but that a perfluorinated cyclohexa-1,3-diene underwent epoxidation under these conditions. These observations suggested that the cyclohexadiene 7 formed by thermal ring opening of bicyclohexene 6 might be capable of cyclopropanation with fluorinated carbenes. If so, 7 might serve as a hexafluorobenzene synthon en route to the heptafluorotropylium ion (1). Reductive dechlorination of the adduct 8 would yield via octafluoronorcaradiene (9) the triene 3,[6] which should be easily transformed by a Lewis acid into the ion 1 (eq 3).



7 8 9 3 1 (3)

As described in a previous paper,[7] we have developed a synthesis of 7 from the benzene 4 in 63% overall yield. Here we present the results of cyclopropanation and epoxidation experiments on this compound.

(1) This paper is based principally on the Ph.D. Dissertation of W. P.D., Dartmouth College, 1983.

(2) Dodsworth, D. J.; Jenkins, C. M.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc. Chem. Commun.* **1972**, 803–4.

(3) Vorozhtsov, N. N.; Ermolenko, N. V.; Mazalov, S. A.; Osina, O. M.; Platonov, V. E.; Tyurin, V. S.; Yakobson, G. C. *J. Gen. Chem. USSR (Engl. Trans.)* **1969**, 195.

(4) Camaggi, G.; Gozzo, F.; Cevidalli, G. *J. Chem. Soc. Chem. Commun.* **1966**, 313–4. Haller, I. *J. Am. Chem. Soc.* **1966**, *88*, 2070–1.

(5) Harrison, E., III, Senior Thesis, Dartmouth College, 1981. Lawlor, D., unpublished results.

(6) For the parent norbornadiene and its relationship to cycloheptatriene, see: Rubin, M. *J. Am. Chem. Soc.* **1981**, *103*, 7791–2.

(7) Dailey, W. P.; Correa, R. A.; Harrison, E., III; Lemal, D. M. *J. Org. Chem.*, previous paper in this issue.

0022-3263/89/1954-5516$01.50/0

Results and Discussion

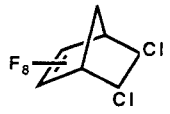
Addition of Difluorocarbene to Diene 7. Hexafluoropropylene oxide (HFPO) is an excellent source of difluorocarbene in the temperature range 170–200 °C.[8,9] Thus, the reaction of diene **7** with this reagent was explored in the presence of calcium carbonate, an acid scavenger that minimizes the rearrangements to which the diene is susceptible at elevated temperatures. With 2 equiv of HFPO at 190 °C, a 2:1:1 mixture of three major difluorocarbene adducts was obtained in 50% yield. The remaining mixture was composed mostly of rearranged dienes. Only two monoadducts, *syn*- and *anti*-**8**, are derivable from **7** without rearrangement. Further chemical transformation, described below, revealed that none of the three adducts was a cyclopropane and that rearrangement of initially formed cyclopropanes must have taken place.

In the hope of precluding rearrangement by carrying out the addition under milder conditions, a lower temperature source of difluorocarbene was sought.[8] Seyferth's organomercurial **10** was unsuitable since it requires the use of iodide ion,[10] which would reduce diene **7** to hexafluorobenzene. Trimethyl(trifluoromethyl)tin (**11**), for which Burton and Kesling have developed a relatively convenient synthesis,[11] releases difluorocarbene at temperatures above 150 °C. Reaction of diene **7** with 1 equiv of **11** at 160 °C for 2 h gave difluorocarbene adducts in 30% yield together with unreacted diene (45%) and rearranged dienes. Three major adducts, identical with those from the HFPO reaction, were present in the ratio 2:1:1. Milder conditions yet for difluorocarbene addition are being explored at the present time.

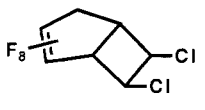
$PhHgCF_3$ $(CH_3)_3SnCF_3$

10 **11**

GC/MS analysis of these adducts revealed a parent peak at *m/e* 306 and a base peak at *m/e* 174 ($C_5F_6^+$) for all three compounds. Difluorocyclopropanes usually do not exhibit a parent peak.[9] The complete mass spectra for all three compounds were almost identical except for the inclusion of a peak at *m/e* 147 ($C_3F_4Cl^+$) in the spectra of the two smaller components. These data, together with subsequent chemical transformation, led us to propose that the major adduct was the norbornene **12** and the minor components were the two stereoisomeric bicyclo[3.2.0]hept-2-enes **13** and **14**. Both ring systems could give the hexafluoro-



12



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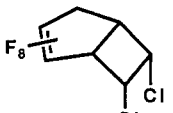
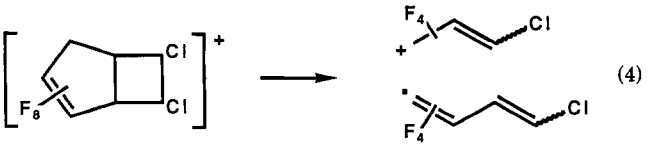


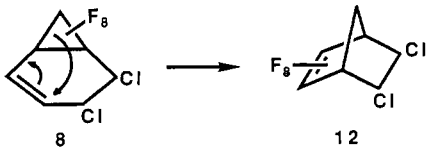
14

cyclopentadiene cation as a mass spectral fragment, and the bicyclo[3.2.0]heptenes could yield a stable *m/e* 147 fragment as in eq 4.



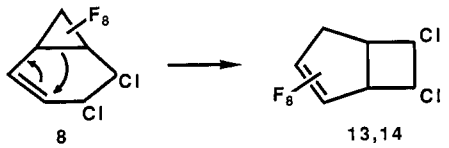
(4)

Although difluorocarbene is known to undergo 1,4-cycloaddition to some dienes,[12] all three compounds **12–14** probably arise from initially formed cyclopropanes that undergo a vinylcyclopropane rearrangement. The formation of norbornene **12** appears to be favored by orbital overlap considerations, for the cyclopropane bond that must migrate to form **12** is (or can easily become) well aligned with the double bond (eq 5). Though the cyclo-



(5)

8 **12**

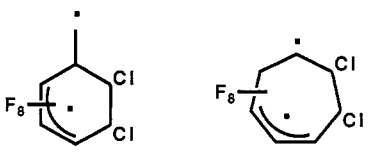


(6)

8 **13,14**

propane bond that must break en route to **13** and **14** has poorer overlap with the double bond, this bond is weakened by the geminal fluorines on the opposite carbon of the cyclopropane ring (eq 6).[13] Thus, inherent bond strength considerations favor formation of the [3.2.0] ring system. Apparently still other stereoelectronic factors play a role in determining the product composition, as discussed below.

The stereochemistry of adducts **12–14** is intriguing. Why should only a single norbornene stereoisomer be found when the syn and anti isomers of the bicyclo[3.2.0] system, **13** and **14**, are produced in equal amount? In the initial addition, formation of both *syn*- and *anti*-**8** would be expected, perhaps in roughly equal amounts. Vinylcyclopropane rearrangements of these adducts presumably proceed via biradical intermediates, as they are orbital topology-forbidden in the only geometrically feasible mode.[14a,15] Whatever its stereochemistry, a biradical of structure **15** can give only a single norbornene; in contrast, biradical **16**, which leads to the [3.2.0] system, can close



15 **16**

to give either anti (**13**) or syn (**14**) product and apparently does so indiscriminately. The question that remains is why only one of the two stereoisomeric biradicals of structure **15** would be formed in significant amount. For optimum overlap of the breaking cyclopropane bond with the π bond, transition states for ring opening of **8** are presumably twisted. One helix sense leads to **15**, the other to **16**. Examination with models of the two oppositely twisted transition states for *syn*-**8** reveals that one is destabilized by a 1,6-nonbonded interaction between fluorine and the chlorine at C_4, as shown in **17**. Since this transition state would lead to **16**, the implication is that *syn*-**8** opens to biradical **15** and thus yields norbornene **12**. In *anti*-**8** the

(8) For reviews on fluorinated carbenes, see: Seyferth, D. In *Carbenes*; Moss, R. A., Jones, M., Eds.; Wiley: New York, 1975. See also: Burton, D. J.; Hahnfeld, J. L In *Fluorine Chemistry Reviews*; Dekker: New York, 1977; Vol. 8.

(9) Sargeant, P. B. *J. Org. Chem.* **1970**, *35*, 678–82.

(10) Seyferth, D.; Hopper, S. P. *J. Organomet. Chem.* **1971**, *26*, C62–4.

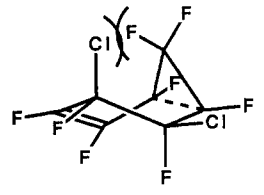
(11) Burton, D. J.; Kesling, H. S., unpublished results. We thank Professor Burton for informing us about this work.

(12) See, for example: Jefford, C. W.; Kabengle, T.; Kovaco, J.; Burger, V. *Tetrahedron Lett.* **1974**, 257–60. Jefford, C. W.; Mareda, J.; Gehet, J. C. E.; Kabengle, T.; Graham, D.; Burger, V. *J. Am. Chem. Soc.* **1976**, *98*, 2585–93.

(13) Dolbier, W. R. *Acc. Chem. Res.* **1981**, *14*, 195–200.

(14) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; a) pp 121–2.

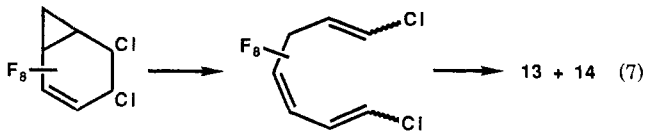
(15) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; pp 81–7.



17

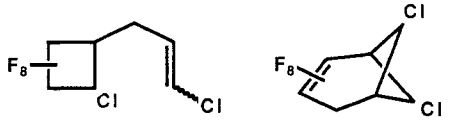
corresponding nonbonded interaction is between fluorines and is less severe because of the difference in both the size of the halogen at C_4 and the length of the carbon–halogen bond.[16] We suggest that *anti*-8 opens preferentially to **16**, therefore yielding **13** and **14**. If this analysis is correct, the chlorines in **12** are oriented exo.[17]

A priori, the formation of **13** and **14** might take an entirely different course, involving orbital topology-allowed disrotatory ring opening of the initial adduct **8** to triene **18** followed by a stepwise [2 + 2] cycloaddition of the ends (eq 7).[14] We regard this possibility as unlikely on several



8 18 13 + 14 (7)

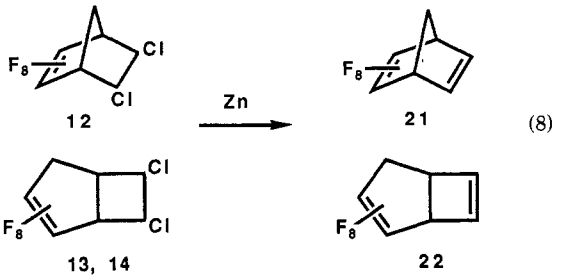
grounds, among them our expectation that the triene and/or cyclobutene **19** with which it might equilibrate would be stable under the reaction conditions. If [2 + 2] cyclization were to occur, the crosswise cyclization product **20** would be expected, as its formation would entail a stabler biradical than that leading to **13** and **14**.



19 20

The unpurified mixture from the HFPO reaction was dechlorinated with zinc in boiling diglyme,[18] and the products were swept into a cold trap with a slow stream of argon as the reaction progressed. A 54% overall yield (based on diene **7**) was obtained, consisting mainly of octafluoronorbornadiene (**21**, 33%), octafluorobicyclo[3.2.0]hepta-2,6-diene (**22**, 34%), hexafluorobenzene (9%), chloropentafluorobenzene (6%), and starting material (6%) (eq 8). The valence isomers **21** and **22** were easily separated by preparative GC.

Octafluoronorbornadiene had double-bond stretching bands in the infrared at 1774 and 1756 cm^{-1} (vapor), in reasonable agreement with the literature values. Its deceptively simple ^{19}F NMR spectrum (in acetonitrile-d_3) revealed signals at 131.6 (quintet of triplets, J_{app} = 5.5, 1.5 Hz) (F_7, F_8), 151.6 (triplet of triplets, J_{app} = 5.5, 1.5 Hz) (F_2, F_3, F_5, F_6), 216.3 ppm (septet, J_{app} = 1.5 Hz) (F_1, F_4).[19] The sole reported route to this diene started from hexa-

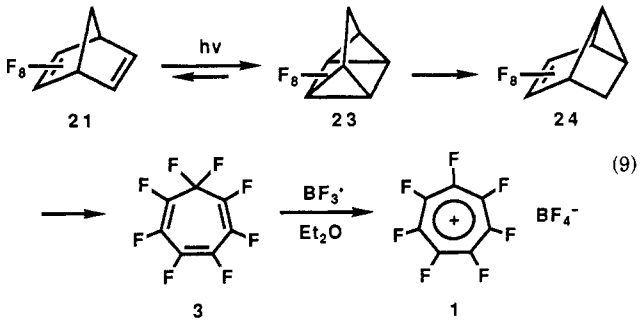


12 21 (8)

13, 14 22

chlorocyclopentadiene and gave overall yields for the seven steps of up to 9%. The present route gave a comparable overall yield from hexafluorobenzene.[20]

Through the intervention of serendipity, we were able to transform octafluoronorbornadiene into the original target species, the heptafluorotropylium ion (**1**). As described elsewhere,[21] this synthesis entailed low-temperature photocyclization of **21** to octafluoroquadricyclane (**23**), which upon warming spontaneously rearranged in remarkable fashion via tricycloheptene **24** to octafluorocycloheptatriene (**3**). As anticipated, treatment of **3** with boron trifluoride etherate generated the ion **1** as its tetrafluoborate salt (eq 9).



21 23 24 3 1 (9)

Like **23** and **24**, octafluorobicyclo[3.2.0]hepta-2,6-diene (**22**) is another new C_7F_8 valence isomer. Its infrared spectrum revealed double-bond stretching bands at 1787 and 1760 cm^{-1}. The ^{19}F NMR spectrum was nicely resolved in acetonitrile-d_3 solution, where it comprised a set of complex multiplets at these chemical shifts: 111.5; 112.75 and 116.75 (AB quartet, J = 264 Hz); 122.5; 139.6; 154.0; 177.2; 187.9 ppm. This spectrum has not been fully analyzed, but it is clear that the 111.5 and 122.5 signals correspond to four-membered-ring vinyl F's, the AB quartet to the geminal F's, the 139.6 and 154.0 signals to five-membered-ring vinyl F's, and the 177.2 and 187.9 ppm multiplets to the bridgehead F's.

At the outset it seemed likely that diene **22**, like norbornadiene **21**, could serve as a precursor for the heptafluorotropylium ion (**1**). Pyrolysis of **22** might be expected to lead to octafluorocycloheptatriene (**3**) by analogy with the parent hydrocarbon **25**, which ring opens with an activation energy of 39.5 kcal/mol (eq 10).[22] Khalil, Stephens, and Tatlow have described a similar reaction with the closely related molecule **26**, albeit under very vigorous conditions (eq 11).[23]

Diene **22** was extremely resistant to ring opening. Heating a dilute acetonitrile solution to 280 °C for 90 min gave a small amount of reaction but no identifiable prod-

(16) The C–Cl bond is about 0.4 Å longer than the C–F bond, and the van der Waals radius of the chlorine atom is about 0.45 Å greater than that of fluorine. Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; pp 107, 109.

(17) Heating the mixture of adducts **12–14** at 250 °C for 30 min gave no appreciable change in composition. After 20 min at 350 °C, all three components had diminished and a large assortment of other compounds had formed. While not definitive, the first of these observations indicates that adducts **12–14** do not interconvert under the conditions of their formation (190 °C, 2 h).

(18) Banks, R. E.; Haszeldine, R. N.; Prodgers, A. *J. Chem. Soc. Perkin Trans. I* **1973**, 596–8.

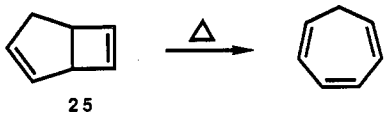
(19) The signal shapes reported in the literature were an 11-line multiplet, a triplet, and a singlet, respectively.[18]

(20) Our route produced an overall yield of 11%, but that figure is the product of an isolated yield for cyclohexadiene **7** (63%) and a GC yield (18%) for conversion of **7** to the norbornadiene.

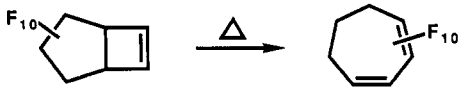
(21) Dailey, W. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 1169–70.

(22) Willcott, M. R.; Goerland, E. *Tetrahedron Lett.* **1966**, 6341–5.

(23) Khalil, E. M. M.; Stephens, R.; Tatlow, J. C. *J. Fluor. Chem.* **1983**, *22*, 43–50.

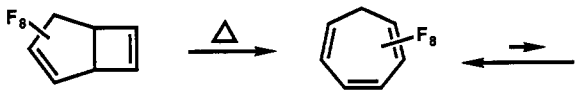


25 (10)

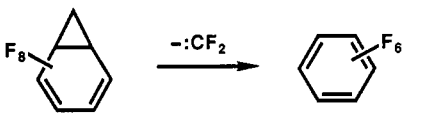


26 (11)

ucts. Pyrolysis in a glass-helix-packed hot tube at 330 °C using a carrier gas (residence time ~20 s) gave hexafluorobenzene as the only isolable product. The benzene probably arises via the desired cycloheptatriene, which would exist in equilibrium with a small amount of its norcaradiene valence isomer **27**. Extrusion of difluorocarbene from this compound should be facile, as judged from the thermal behavior of other *gem*-difluorocyclopropanes (eq 12).[13,24]

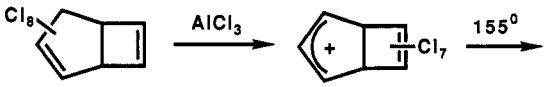


22 3

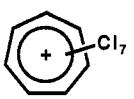


27 (12)

In principle, thermolysis of **22** in the presence of a strong Lewis acid could lead to the heptafluorotropylium ion directly. This is, in fact, the method by which heptachlorotropylium ion (**30**) has been prepared. Chloride abstraction from **28** generates intermediate cation **29**, which ring opens to **30** at 155 °C (eq 13).[25]

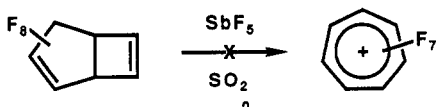


28 29



30 (13)

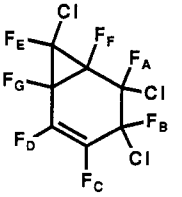
In practice, treatment of an acetonitrile solution of **22** with boron trifluoride etherate at 200 °C for 2 h gave no reaction by ^{19}F NMR. Likewise, treatment of a methylene chloride solution of **22** with anhydrous boron trifluoride at 200 °C for 1 h gave unchanged diene. Finally, reaction of a sulfur dioxide solution of **22** with 2 equiv of antimony pentafluoride at 100 °C for 20 min destroyed the starting material completely (eq 14). Addition of water to this mixture gave no hexafluorotropone or any other fluorocarbon identifiable by ^{19}F NMR analysis.



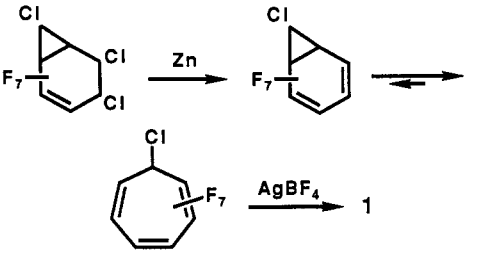
22 1 (14)

Addition of Chlorofluorocarbene to Diene 7. Since the destabilization of cyclopropane rings increases with the number of fluorine substituents, it seemed likely that adducts of chlorofluorocarbene[8] with diene **7** would be significantly stabler than the labile difluorocarbene adducts. If such adducts could be isolated, the direct route to ion **1** outlined in eq 15 might be realizable.

Table I. Tentative ^{19}F Chemical Shift Assignments for Adducts 31 and 32 ($CDCl_3$)

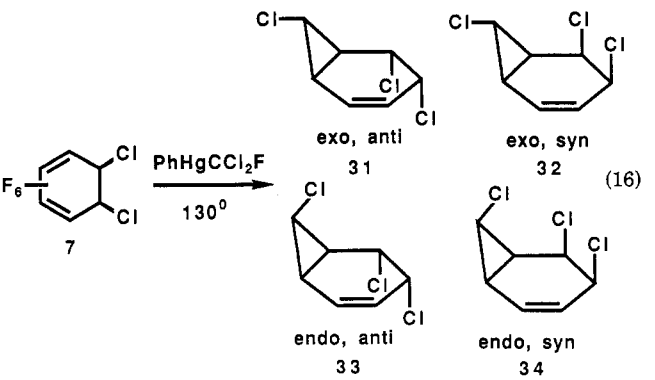


fluorine	31, ppm	32, ppm	fluorine	31, ppm	32, ppm
A	119.7	109.2	E	151.8	148.9
B	134.6	113.2	F	180.0	195.7
C	135.3	137.0	G	206.5	208.2
D	144.6	141.1			



(15)

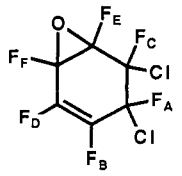
Phenyl(dichlorofluoromethyl)mercury[26] and a 2-fold excess of diene **7** heated neat at 130 °C for 1 h gave in yields up to 50% (based on mercurial) the cyclopropanes **31–34** (eq 16). The most abundant adduct (60%) appears to have the exo,anti configuration **31**. This conclusion is based in part on the mass spectrum, which does not show a parent peak but has a base peak at m/e 82 (CF_2Cl^+). When juxtaposed with results for adduct **32**, this finding argues for the anti configuration. Tentative ^{19}F NMR assignments for **31** are shown in Table I. The complex spectrum has not been fully analyzed, but a large coupling between F_A and F_E indicates through-space interaction and thus points to the exo orientation for the cyclopropyl chlorine. The other major adduct (30%) appears to be **32**. The base peak in the mass spectrum of this molecule at m/e 101 ($CFCl_2^+$) suggests that the cyclopropane ring is syn to the chlorine atoms on the six-membered ring. Consistent with this conclusion is the absence of strong coupling between F_A and F_E in **32**. The ^{19}F NMR spectrum has been tentatively assigned but not completely analyzed



(16)

(24) Birchall, J. M.; Haszeldine, R. N.; Roberts, D. W. *J. Chem. Soc. Perkin Trans. I* **1973**, 1071–8.
(25) West, R.; Kusuda, K. *J. Am. Chem. Soc.* **1968**, *90*, 7354–5. West, R. *Pure Appl. Chem.* **1971**, *28*, 379–98.
(26) Seyferth, D.; Murphy, G. J. *J. Organomet. Chem.* **1973**, *49*, 117–24.

Table II. Tentative ^{19}F Chemical Shift and Coupling Assignments for 36 ($CDCl_3$)



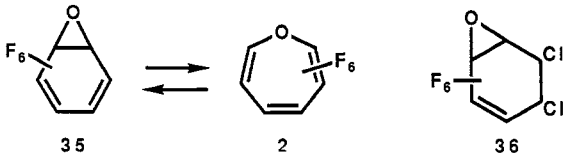
fluorine	ppm	coupling constants, Hz
A	109.6	J_{AB} = 23.5, J_{AC} = J_{AD} = 11.0
B	139.0	J_{BC} = 4.2, J_{BD} = 1.2, J_{BF} = 13.0
C	142.6	J_{CE} = 14.6
D	145.5	J_{DE} = 1.2, J_{DF} = 14.0
E	161.8	J_{EF} = 22.0
F	170.1	

(see Table I). The remaining two stereoisomeric adducts, believed to have endo chlorine at C_7, are present in very minor amount. Steric repulsion in the transition states for their formation would account for this observation.

Attempts to dechlorinate this mixture of cyclopropanes (**31–34**) have not been rewarding. Treatment with lithium amalgam required heating for reaction to occur and gave no volatile products. Interestingly, reductions carried out with zinc and with chromous ion under certain conditions yielded small amounts of octafluorocycloheptatriene (**3**). Finding **3** suggested that some of the desired tropylium ion **1** had been formed and had been trapped by fluoride ion present in the reaction mixture. Addition of fluoride ions before the start of the reaction failed to enhance the yield of **3** significantly, however.

In summary, our objective at the outset of synthesizing the heptafluorotropylium ion (**1**) has been achieved via carbene addition to diene **7**, but by a less direct route than had been planned. Efforts to improve the overall yield of **1** by utilizing the byproduct **22** were unavailing, as were attempts to develop a more direct route by substituting chlorofluorocarbene for difluorocarbene. Presently, efforts are underway to add difluorocarbene to diene **7** under conditions which the adducts can survive: the original synthetic plan may yet be reduced to practice.

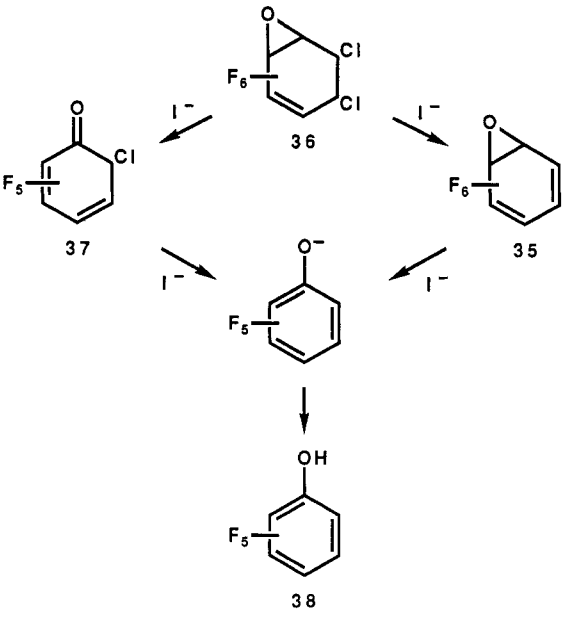
Epoxidation of Diene 7. Interest in hexafluorobenzene oxide (**35**) and its valence isomer hexafluorooxepin (**2**) stimulated us to try epoxidation of the hexafluorobenzene synthon **7**. We hoped to learn how substitution of fluorine for hydrogen changes the character of benzene oxide and oxepin and how it influences their equilibrium.[27] When **7** was subjected to the action of peroxytrifluoroacetic acid at room temperature, a single epoxide (**36**) was obtained



35 **2** **36**

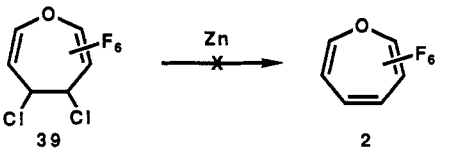
in fair yield.[28,29] Its configuration is assigned as anti on steric grounds, but without proof. The compound displayed a band at 1747 cm^{-1} in the vapor-phase infrared spectrum, and its ^{19}F NMR spectrum comprised six well-separated multiplets. Chemical shifts, coupling constants, and their tentative assignments are given in Table II.

Scheme I. Possible Reduction Pathways for Epoxide 36



Attempts to reduce epoxide **36** to hexafluorobenzene oxide using a variety of reagents were unsuccessful. Treatment of **36** with zinc dust in ethanol, Rieke zinc,[30] and lithium amalgam all gave reaction, but no volatile products. Zinc dust in acetic acid or sodium iodide in acetone gave pentafluorophenol (**38**). The phenol could be formed via dienone **37** (Scheme I) if the epoxide ring, whose considerable strain is presumably exacerbated by fluorine substitution, is cleaved more easily than a C–Cl bond. Alternatively, the desired benzene oxide may be formed by vicinal dechlorination but then reduced to **38** under the reaction conditions.

Barlow, Haszeldine, and Peck synthesized a dichloro epoxide (**39**) similar to **36** as a precursor for the oxepin valence isomer of **35**.[31] Like our efforts, their attempts to dechlorinate it to hexafluorooxepin (**2**) were unsuccessful (eq 17). It appears that the perfluorinated benzene oxide/oxepin valence isomer system is very vulnerable to reducing conditions. A synthetic approach to this system is planned in which the culminating step does not entail reduction.



39 **2** (17)

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Solids were analyzed in the infrared as potassium bromide disks, liquids as neat films between sodium chloride disks, and volatiles as gas-phase samples contained in a 10-cm evacuated gas cell equipped with sodium chloride windows. The ^{19}F NMR spectra were obtained at 56.2 MHz on a JEOL FX60Q Fourier transform instrument with fluorotrichloromethane (Freon 11) as an internal standard. Chemical shifts are reported in ppm upfield from the reference. Unless otherwise indicated, deuteriochloro-

(27) For the parent system, see: Vogel, E.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385–401.

(28) Since the epoxide appears to be unstable to strong acid, the presence of a buffer may improve this reaction.

(29) For a review of fluorinated epoxides, see: Tarrant, P.; Allison, C. G.; Barthold, K. P.; Stump, E. C. In *Fluorine Chemistry Reviews*; Dekker: New York, 1971; Vol. 5.

(30) Rieke, R. D.; Li, P. T.; Burns, T. P.; Uhm, S. Y. *J. Org. Chem.* **1981**, *46*, 4323–4.

(31) Barlow, M. G.; Haszeldine, R. N.; Peck, C. J. *J. Chem. Soc. Chem. Commun.* **1980**, 158–9.

form was used as solvent. Analytical gas chromatograms were obtained with a Hewlett-Packard Model 5880A gas chromatograph using a flame ionization detector and electronic integration. Peak areas were not corrected for differential detector response. Glass pyrolysis tubes were silylated by adding a few drops of *N,O*-bis(trimethylsilyl)acetamide (Aldrich) and heating the tube over a Bunsen flame in the hood while the liquid made contact with all inner surfaces. The tube was cooled slightly, washed out with two portions of carbon tetrachloride, and dried under vacuum. The Kugelrohr motor (Aldrich), which was used as a bomb rocker, had been modified by interchanging the two gears, thus reducing its arc from 300° to about 20°.

All solvents and reagents used in this work were reagent grade unless otherwise noted. Hexafluoropropylene oxide was a gift from du Pont. Perfluorobenzene was purchased from Fairfield Chemical and zinc dust from Fisher Scientific. The zinc was activated by being stirred with 1 N hydrochloric acid for 5 min, washed with water, and dried under a vacuum; it was stored under argon. Microanalytical data were obtained from Galbraith Labs, Knoxville, TN.

Trimethyl(trifluoromethyl)tin (11). The following is a modification of the procedure of Burton and Kesling.[11] It is important that all reagents and glassware be dry. [*Warning*: *Like other trimethyltin derivatives, this compound is expected to be highly toxic*!]

A 2-L three-neck flask was equipped with an overhead Teflon paddle stirrer and a reflux condenser connected to an argon inlet. To this were added 197 g (0.75 mol) of triphenylphosphine and 700 mL of freshly distilled (from sodium benzophenone ketyl) triglyme. Stirring for 15 min produced a clear, very light yellow solution. Dibromodifluoromethane (SCM Specialty Chemicals), 160 g (0.76 mol), was vacuum transferred to a 250-mL round-bottom flask cooled to −78 C. After the triglyme solution had been cooled to 0 °C, the dibromodifluoromethane was quickly added to the well-stirred solution by using a precooled 100-mL syringe. After 1 min, a white precipitate formed. The mixture was allowed to warm to room temperature and stirred for 1 h, then recooled to 0 °C. Trimethyltin chloride (Aldrich; *poison*!), 49.0 g (0.246 mol), was added via a solids addition tube. Anhydrous potassium fluoride, 136 g (2.34 mol), which had been dried overnight at $300_{0.05}$ °C, was added in three portions to the mixture via the flame-dried addition tube. The white mixture quickly turned brown and after 10 min was dark brown. It was stirred at 0 °C for 8 h and then at room temperature for 18 h.

The dark brown mixture was transferred under argon to a dry nitrogen-filled glovebag that contained a 2-L flask fitted with a 600-mL coarse-fritted funnel containing $^1/_2$ in. of Filter Cel and attached to an aspirator. A 1-L round-bottom flask containing 200 mL of dry triglyme was also present. The dark brown solution was suction filtered in the glovebag to give a dark brown filtrate. The funnel, which was almost completely filled with salt, was washed with dry triglyme (2 × 100 mL). The combined dark filtrate was poured into the 1-L round-bottom flask, which was then sealed with a rubber septum.

This flask was fitted for vacuum distillation into a dry ice/acetone-cooled receiver and the system was pumped down to 0.5 Torr. Distillation was carried out by immersing the pot in a preheated (75 °C) oil bath. After 30 min the distillation was halted and the crude distillate, 28.8 g, was short-path distilled under argon. After a small forerun, 3 g (bp 38–97 °C), the main fraction was collected at 98–102 °C as 20.8 g (36%) of colorless liquid, which was transferred under vacuum to a storage bulb. GC analysis (25-m methylsilicone capillary column, 70 °C, 15 psi, 175 °C injection and detection temperature) revealed that the product was 97% pure.

Reaction of Diene 7 with Trimethyl(trifluoromethyl)tin (11). A 4-mL freshly silylated, heavy-walled Pyrex ampule was filled with 1.10 g (4.7 mmol) of trimethyl(trifluoromethyl)tin and 1.56 g (6.0 mmol) of diene **7**. The tube and its contents were subjected to 2 freeze–pump–thaw cycles, frozen, and sealed. The mixture was heated in an oil bath at 160 °C for $2\ ^1/_2$ h. After being frozen in liquid nitrogen, the tube was cracked open and the volatiles were dynamically transferred into a U-trap and then statically transferred to a storage bulb (1.9 g). A large amount of white crystalline trimethyltin fluoride remained in the reaction tube. GC analysis of the volatiles (25-m methylsilicone capillary column, 14 psi, 40 °C) revealed 36% starting diene **7**, 12% **12**, 6% **13**, 6% **14**, and the remainder as rearrangement products of diene **7**.

Octafluoronorborna-2,5-diene (21) and Octafluorobicyclo[3.2.0]hepta-2,6-diene (22). A heavy-walled Pyrex ampule was filled with 5.2 g (20.3 mmol) of diene **7**, 6.5 g (39.1 mmol) of hexafluoropropylene oxide, and 1.0 g of calcium carbonate. The tube was frozen, evacuated, and sealed with a flame. It was placed in a metal pipe wrapped with a heating tape; this assembly was held horizontal by a clamp attached to a Kugelrohr motor. A thermocouple was attached with asbestos tape to the tube and the temperature was controlled with use of an Omega Model 149 temperature control unit. The tube was heated to 185–190 °C with gentle rocking for 2 h. [*Caution*: One tube exploded with considerable force.] The tube was cooled and then frozen and cracked open. The volatiles were dynamically transferred to a U-bulb and the extreme volatiles were statically transferred from there at 0 °C to a storage bulb. This bulb was opened in the hood and gaseous products were allowed to escape. The small amount of material that did not evaporate at room temperature was added to the remaining less volatile fraction, 5.5 g total. GC/MS analysis of this mixture revealed three major difluorocarbene adducts in 25%, 12%, and 12% yield, respectively. The remaining products were rearranged starting material **7** and derived compounds. All three adducts had extremely similar mass spectra. MS: major adduct **12** *m/e* 306 (M^+), 271, 252, 236, 221, 202, 186, 174 (100, $C_5F_6^+$), 155, 132; minor adducts **13** and **14** (identical mass spectra) *m/e* 306 (M^+), 271, 252, 236, 221, 202, 186, 174 (100, $C_5F_6^+$), 155, 147 ($C_3F_4Cl^+$), 132. This mixture was not further characterized and was used in the following reaction without any further purification.

The general dechlorination procedure of Banks, Haszeldine, and Prodger was followed.[18] Zinc dust, 30.0 g (0.45 mol), was activated by being stirred with 50 mL of 1 N hydrochloric acid for 5 min followed by a water wash (2 × 30 mL) and drying under vacuum. It was stored under dry argon.

A 250-mL three-necked round-bottom flask was fitted with a small pressure-equalizing dropping funnel and a reflux condenser that was attached to a dry ice/2-propanol-cooled U-trap. The U-trap outlet was connected to a bubbler. Freshly distilled (from Na) diglyme (40 mL) and the zinc dust were placed in the flask, vigorously stirred magnetically, and heated to boiling. A stream of dry nitrogen admitted through the dropping funnel (~20 mL/min) purged the system. A solution of 5.5 g of the reaction mixture from difluorocarbene addition in 10 mL of diglyme was added dropwise to the mixture over the course of 30 min. The mixture turned dark and foamed during the addition. After an additional 30 min at reflux, the reaction was halted. The product that had collected in the U-trap was statically transferred to a storage bulb to give 2.7 g of distillate. GC analysis (25-m methylsilicone capillary column, 14 psi, 40 °C) revealed 33% octafluoronorbornadiene, 33% octafluorobicyclo[3.2.0]hepta-2,6-diene, hexafluorobenzene (12%), chloropentafluorobenzene (12%), and unreacted starting materials (~6%). Short-path distillation (oil bath at 85 °C, head to 60 °C) gave 0.9 g of volatile material, which proved to be 63% octafluoronorbornadiene (**21**) and 30% octafluorobicyclo[3.2.0]hepta-2,6-diene (**22**). This fraction was further purified by preparative GC (10 ft × $^1/_4$ in. 10% SF-96 on Chromasorb W HP 80/100, 25 °C, 80 mL/min, 15 μL per injection). The retention times of **21** and **22** were 3.2 and 4.0 min, respectively. This procedure gave ~0.45 g of 99% pure octafluoronorbornadiene (**21**). IR (vapor phase): 1774, 1756 cm^{-1}. ^{19}F NMR (CD_3CN): 131.6 (2 F, quintet of triplets, J_{app} = 5.5, 1.5 Hz), 151.6 (4 F, triplet of triplets, J_{app} = 5.5, 1.5 Hz), 216.3 ppm (2 F, septet, J_{app} = 1.5 Hz). Also collected was ~0.25 g of 99% pure perfluorobicyclo[3.2.0]hepta-2,6-diene (**22**), bp 71_{740} °C (inverted capillary). IR (vapor phase): 1787, 1760 cm^{-1}. ^{19}F NMR (CD_3CN): 111.5, 112.75 and 116.75 (AB quartet, J = 264 Hz), 122.5, 139.6, 154.0, 177.2, 187.9 ppm. Anal. Calcd: C, 35.59; F, 64.41. Found: C, 35.51; F, 64.29.

More of both products could be obtained from the undistilled fraction that contained 16% octafluoronorbornadiene and 36% octafluorobicyclo[3.2.0]hepta-2,6-diene. If the reaction sequence were run on a larger scale, adequate separation should be achievable with a spinning band column. This preparation gave octafluoronorbornadiene and octafluorobicyclo[3.2.0]hepta-2,6-

diene in 18% yield each by GC analysis, starting with diene 7.

Addition of Chlorofluorocarbene to Diene 7. A 4-mL heavy-walled freshly silylated Pyrex ampule was filled with 0.5 g (1.3 mmol) of phenyl(dichlorofluoromethyl)mercury[26] and 0.64 g (2.5 mmol) of diene 7. The tube was frozen at 77 K, evacuated, and sealed with a flame. The white slurry was heated to 130–135 °C for 1 h in a rocker bomb. After cooling, the bomb was cracked open and the volatiles were dynamically transferred to a U-bulb to yield 0.7 g of colorless oil. GC analysis (25-m methylsilicone capillary column, 15 psi, 40 °C for 15 min and then 10°/min to 100 °C) revealed starting material (74%) and products 31–34 (26%, 50% yield based on mercurial). Also found was a significant amount of benzene, apparently present in the starting mercurial. The mixture was purified by preparative GC (10 ft × $^1/_4$ in. 10% SF-96 on Chromasorb W HP, 100 °C, 160 °C injection and detection temperature, 160 mL/min). The four desired products were collected together and had retention times of 5 to 6 min. Boiling point of mixture: 158_{755} °C (inverted capillary). IR (vapor phase): 1750, 1370, 1325, 1200 cm^{-1}. ^{19}F NMR (CD_3CN): **31** (60% of mixture) 119.7, 134.6, 135.3, 144.6, 151.8, 180.0, 206.5 ppm; **32** (30% of mixture) 119.2, 113.2, 137.0, 141.1, 148.9, 195.7, 208.2 ppm. MS: **31** *m/e* 252 ($-CF_2Cl$), 237, 221, 202, 186, 85 (CF_2Cl^+, 100); **32** *m/e* 221 ($-CFCl_2$), 202, 186, 101 ($CFCl_2^+$, 100). Anal. of mixture. Calcd: C, 26.00; F, 41.10; Cl, 32.90. Found: C, 26.18; F, 41.10; Cl, 32.49.

***cis*-6,7-Dichlorohexafluoro-2-oxabicyclo[4.1.0]hept-4-ene (36).** To an ice-cooled mixture of 1.0 mL of 80% H_2O_2 (23 mmol) in 10 mL of methylene chloride was added dropwise with good stirring 5.7 mL (39 mmol) of trifluoroacetic anhydride over the course of 10 min. After it had warmed to room temperature, 10 mL of this approximately 2.0 M solution of peroxytrifluoroacetic acid solution was vigorously stirred with 1.5 g of 85% diene 7 (5 mmol) for 24 h. The light yellow solution was diluted with Freon 11 and washed with saturated sodium bisulfite solution followed by saturated sodium bicarbonate solution. After drying, the solvent was removed and the product was purified by preparative GC (10 ft × $^1/_4$ in. 10% SF-96 on Chromasorb W HP 80/100, 50 °C, 160 mL/min) to give 0.30 g (22%) of colorless liquid. IR (gas phase): 1745, 1385, 1225, 995, 885 cm^{-1}. ^{19}F NMR: 109.6, 139.0, 142.6, 145.5, 161.8, 170.1 ppm. MS: *m/e* 272 (M^+), 237, 225, 209, 171 (100). Anal. Calcd: C, 26.38; F, 41.77. Found: C, 26.50; F, 42.01.

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Synthesis of 19,19,20,20,20-Pentadeuteriolipoxin A_4 Methyl Ester and 19,19,20,20,20-Pentadeuterioarachidonic Acid. Agents for Use in the Quantitative Detection of Naturally Occurring Eicosanoids

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19,19,20,20,20-Pentadeuteriolipoxin A_4 methyl ester (**2**) was synthesized from key intermediates **31** and **32**. 19,19,20,20,20-Pentadeuterioarachidonic acid (**1**) and its methyl ester (**24**) were also synthesized by sequential coupling of intermediates **12**, **22**, and **23**. With use of the pentadeuterated derivative **2**, a gas-chromatography–mass spectroscopy (GC-MS) method for the quantitative detection of lipoxin A_4 was developed.

Introduction

Arachidonic acid is an essential fatty acid that, when released from cellular stores, can be transformed to a variety of biologically active products.[1,2] The lipoxins are a novel series of oxygenated products of arachidonic acid that were first isolated from human leukocytes.[2,3] These compounds display a unique profile of biological activities that are different from those of either prostaglandins or leukotrienes (for reviews, see ref 4). Therefore, the detection and quantitation of the lipoxins, which, like other products of arachidonic acid metabolism, may be present in low levels in human fluids, is of considerable interest.

Since it is now clear that radioimmunologic detection of eicosanoids may, with complex biological fluids, give misleading results, the use of stable isotopes has become extremely helpful in the quantitative analysis of eicosanoids from biological samples.[5] In particular, deuterium-containing stable isotopes were used to quantitate both prostaglandins and thromboxanes in biological samples by methods utilizing gas chromatography–mass spectrometry detection.[5]

In order to assist in studies of the arachidonic acid cascade, and to develop analytical techniques (as in ref 5 and 6) that utilize mass spectroscopy for detection of products of arachidonic acid metabolism, in particular lipoxin A_4, we undertook the syntheses of 19,19,20,20,20-pentadeuterioarachidonic acid (**1**), its methyl ester (**24**), as well as 19,19,20,20,20-pentadeuteriolipoxin A_4 methyl ester (**25**). The present findings will permit the detection of LXA_4, which may be present in various biological sources (i.e., including patient-derived samples), by selected ion monitoring on gas chromatography–mass spectroscopy.

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