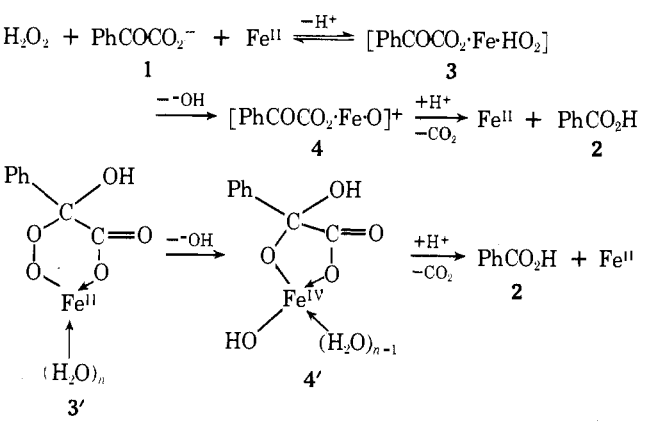
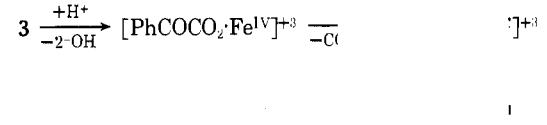
Scheme I



Scheme II



carboxylation of **1** may be rate limiting. That the slow step involves formation of a reactive iron oxidant (mechanism C) is supported by the following observations:[17] (1) iron catalyzes the decarboxylation of other α-keto acids and exhibits a value for k_{cat} that is insensitive to the structure of the α-keto acid and (2) the rate for iron-catalyzed loss of hydrogen peroxide (through either disproportionation or decarboxylation) is independent of the presence or absence of the α-keto acid.

Based on the observed metal ion specificity for rate enhancement, we favor mechanisms such as those shown in Schemes I and II[16] in which iron participates in the actual electron-transfer process (mechanism C).[18] Further support for this conclusion comes from the observation that iron also exhibits strong catalysis in the presence of peroxyacetic acid and *tert*-butyl hydroperoxide. If mechanism B were operative, internal delivery of a peroxo group chelated to iron would likely be possible only with the "double ended" oxidant, HOOH. If one of the hydrogens were replaced by an acyl or *tert*-butyl group, nucleophilic attack on **1** by a peroxide molecule coordinated to iron through a hydroxyl group would be blocked. All three peroxide derivatives are, however, capable of oxidizing iron to form a common reactive metal species, such as **4′**, that can convert **1** into **2**, as shown in the schemes. Moreover, highly oxidized iron species have been previously suggested as oxidants in other reactions.[20] Although both of these mechanisms are speculative in detail, each incorporates the formation of an iron(IV) species consistent with our observations. A major difference in these pathways lies in the presence (Scheme I) or absence (Scheme II) of an oxygen, perhaps derived from the peroxide, that is associated with the iron in the actual decarboxylation step. Additional studies to characterize this catalytic process more fully are in progress.

Acknowledgment. The authors are grateful for generous support of this work by The University of Minnesota Graduate School, The Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and The National Institutes of Health under Grant AM-21975.

References and Notes

(1) This work was presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 1978.
(2) In contrast to the widespread use of iron as a redox element in biological systems, there are relatively few applications of iron-promoted oxidations in organic synthesis.[3]
(3) For examples, see T. Matsuura, *Tetrahedron*, **33**, 2869 (1977), and L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–6, Wiley, New York, 1977.
(4) For a review, see C. Walling, *Acc. Chem. Res.*, **8**, 125 (1975), and references therein.
(5) For an overview, see "Organic Peroxides", D. Swern, Ed., Wiley-Interscience, New York, 1971. We thank a referee for stressing this ramification of our investigation.
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(7) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).
(8) To compare first-, second-, and third-order rate processes, the higher order rate constants have been normalized to 1 M standard states.
(9) (a) C. A. Bunton, *Peroxide React. Mech., Pap. Conf., 1960*, 16 (1962); (b) G. A. Hamilton, *Prog. Bioorg. Chem.*, **1**, 83 (1971).
(10) EDTA is ethylenediaminetetraacetic acid.
(11) We have observed that the rate of hydrogen peroxide disproportionation by iron is increased in the presence of EDTA over the pH range 0–4.
(12) Although EDTA could act as a radical trap[4] to retard the decarboxylation of **1**, such a mechanism seems unlikely in view of the similar rate dimunition induced by fluoride, phosphate, and several carboxylate salts (see text).
(13) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed., Wiley-Interscience, New York, 1972.
(14) The apparent difference between our observations of significant iron catalysis and an early report by Bunton which claims that added iron "does not readily decarboxylate", 1 may be explained, if the earlier experiments were carried out in the presence of a sequestering agent. See C. A. Bunton, *Nature (London)*, **163**, 444 (1949); see also H. Wieland and W. Franke, *Justus Liebigs Ann. Chem.*, **457**, 1 (1927).
(15) Metal ion coordination promotes the nonoxidative decarboxylation of β-keto acids through coordinative stabilization of the enol-like transition state. For a review, see R. Steinberger and F. H. Westheimer, *J. Am. Chem. Soc.*, **71**, 4158 (1949); **73**, 429 (1951).
(16) An issue raised by one referee. We also thank this referee for the suggestion of Scheme II.
(17) B. Siegel and J. Lanphear, unpublished results.
(18) Since many of the metal ions studied (for example manganese and tin) are able to generate ·OH through the decomposition of hydrogen peroxide, the unique catalytic ability of iron provides further evidence against a hydroxyl radical path.[4,19]
(19) For a review, see S. W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill, New York, 1960, p 596, and references therein.
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(21) (a) Dupont Young Faculty Fellow; (b) University of Minnesota Institute of Technology Corporate Fellow, 1977–1978.

Brock Siegel,*[21a] Jane Lanphear[21b]
Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455
Received July 28, 1978

Carboxylic and Phosphate Esters of α-Fluoro Alcohols[1]

Sir:

Fluorine substituted substrate analogues have played an increasingly important role in the elucidation and rational perturbation of biological processes.[2,3] The exceptional utility of fluorine stems from its high electronegativity and small size, its Van der Waals radius (~1.35 Å) not greatly exceeding that of hydrogen (~1.10 Å).[4] This dimensional parity is particularly important in biological situations, where binding of substrates to sterically defined macromolecular sites is a prerequisite to fruitful interaction, although the unique electronic properties of fluorine also make it a standard tool in the study of chemical transformations. Owing to the absence of methods for their preparation, however, the rich potential of carboxylic and phosphate esters of α-fluoro alcohols as chemical and biochemical probes has never been exploited.[5] Although a few carboxylic esters of perfluorinated, and consequently atypical, alcohols have been reported,[6] to our knowledge no phosphorus ester of an α-fluoro alcohol has ever been prepared.

The most common synthesis of esters, the reaction of alcohols with esterifying reagents, is not viable with α-difluoro alcohols owing to their inherent instability. Thus, trifluoromethanol, the only simple α-fluoro alcohol which has been isolated, undergoes exothermic loss of HF at temperatures above −20 °C.[7,8] Furthermore, although α-fluorinated ethers

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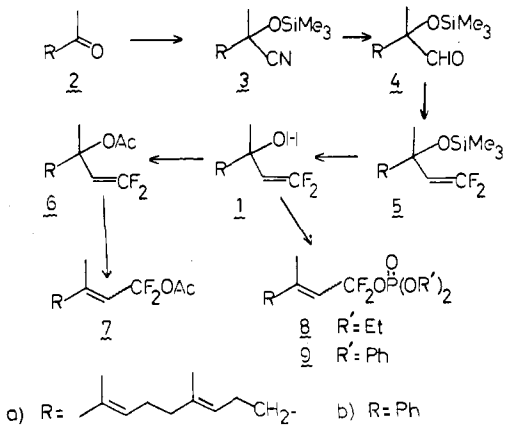
are prepared by addition of alkoxides to fluoro olefins,[4] this route is not available for the synthesis of esters owing to the attenuated nucleophilicity of carboxylate and phosphate anions. Finally, the lability of phosphate esters, particularly those derived from allylic alcohols, is incompatible with the available direct fluorination methods.[4,9] We report here the first potentially general synthesis of carbon and phosphorus esters of α-fluoro alcohols, using an allylic transposition of functionality to introduce an already esterified oxygen at a terminal difluorovinyl carbon. The preparation of 1,1-difluorofarnesol esters has been chosen as a prototypical system, not only because of the potential utility of the products in investigations of terpene biosynthesis, but also because the penchant of the farnesyl skeleton to undergo cationic cyclization reactions[10] makes it a challenging model for the development of versatile methodology.

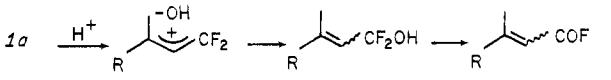
The synthesis of difluoroallyl alcohol units, key intermediates in our approach to α-fluoro alcohol esters, is illustrated by the synthesis of 1,1-difluoronerolidol (**1a**) from geranylacetone (**2a**). The first step in the sequence, conversion of a ketone to a protected α-hydroxyaldehyde, is accomplished by a general procedure developed in this laboratory.[11] Thus, reaction of geranylacetone with 1.1 equiv of *freshly* distilled trimethylsilyl cyanide (TMSCN) under HgI_2 catalysis[12] proceeded exothermically to give **3a** (90% isolated yield).[13] This intermediate, however, was not usually isolated but was directly reduced after vacuum removal of excess TMSCN, by reaction with i-Bu_2AlH (1.5 equiv) in THF at −20 °C. It is

Scheme I



essential to use THF in this reduction, since reaction in hydrocarbons or other solvents of low complexing ability results in overreduction of the nitrile to an amine.[11,12] Using THF, aldehyde **4a** was obtained in 88% yield (from geranylacetone) after aqueous workup and distillation. Reaction of aldehyde **4a** with CF_2Br_2 (2.2 equiv) and trisdimethylaminophosphine (4.5 equiv) in THF, according to the method of Naae and Burton,[14] furnished **5a** in 79% isolated yield. Finally, 1,1-difluoronerolidol (**1a**)[15] was obtained quantitatively on removal of the protecting group from **5a** by stirring with NaOH (1.5 equiv) in 5:1 MeOH–H_2O at 50 °C. The generality of this sequence of steps is demonstrated by analogous preparation of **5b** from acetophenone in similar yield. However, in contrast to 1,1-difluoronerolidol, alcohol **1b,** obtained from **5b** by hydrolysis, is unstable, an observation consistent with the fact that difluorovinylarylcarbinols were not isolated from the reaction of aryl aldehydes with 2,2-difluorovinyllithium.[16]

Treatment of tertiary allylic alcohols with acetic anhydride in the presence of p-toluenesulfonic acid has been shown to provide the corresponding allylically transposed acetates.[17] Linalool, the ten-carbon analogue of nerolidol, is an exception, primarily yielding cyclized products.[17a] Nevertheless, exposure of 1,1-difluoronerolidol to acetic anhydride containing p-toluenesulfonic acid at 25 °C resulted in the following product mixture (by GLC analysis): 1,1-difluorofarnesyl acetate (**7a,** 66%, ~3:1 2E–2Z isomer mixture by ^{19}F NMR), 1,1-difluoronerolidyl acetate (**6a,** 3%), farnesoyl fluoride (30%), and starting alcohol **1a** (1%). Primary acetate **7a,** however, could only be isolated in ~40% yield after silica gel chromatography. Since the most attractive rationale for the formation of farnesoyl fluoride is acid-catalyzed transposition of the hydroxyl group, followed by loss of HF, we investigated the use of preformed 1,1-difluoronerolidyl acetate (**6a**) as the starting point for the rearrangement. This tertiary acetate was obtained in 98% yield by reaction of **1a** with a mixture of acetic anhydride (4 equiv), 4-dimethylaminopyridine (1.1 equiv),[18] and triethylamine (1.5 equiv) in ether. The acetate was not formed



in the absence of 4-dimethylaminopyridine. Tertiary acetate **6a** did not rearrange to primary acetate **7a** on warming in benzene (80 °C, 24 h), providing instead a complex product mixture even in the presence of KOAc and 18-crown-6.[19] However, reaction of **6a** in acetic anhydride with a catalytic amount of p-toluenesulfonic acid provided **7a**[20] in 75% yield after purification by low pressure chromatography on silica gel. Analogously, although the instability of **1b** did not permit initial acetylation, direct reaction of the alcohol with acetic anhydride and p-toluenesulfonic acid gave **7b**[13] in 24% isolated yield.

Subsequent to a series of unpromising exploratory experiments, including examination of the reactions of 1,1-difluorofarnesyl bromide and chloride with phosphate silver salts,[21] our efforts to prepare a phosphate ester of 1,1-difluorofarnesol focused on the synthesis of a dialkyl phosphate derivative of 1,1-difluoronerolidol. Diethyl phosphochloridate (1.1 equiv) was therefore added (25 °C) to the alkoxide generated by treatment of **1a** with n-BuLi (1 equiv) in hexane at −78 °C. To our delight, low pressure chromatographic separation of the products gave, not the tertiary phosphate, but a mixture of the 2E and 2Z isomers of 1,1-difluorofarnesyl diethyl phosphate (**8a,** 30% yield).[22] The same reaction in benzene, however, primarily gave 1,1-difluorofarnesyl chloride rather than the diethyl phosphate. A high yield of primary phosphate was obtained with a different phosphorylation procedure. Stirring diphenyl phosphochloridate (2.4 equiv), 4-dimethylaminopyridine (2.4 equiv), triethylamine (2.2 equiv), and 1,1-difluoronerolidol in THF for 48 h led to the isolation of **9a** (2:1 2E–2Z isomer mixture) in 80% yield. The 2E[13] and 2Z[13] isomers could be separated in this instance by low pressure chromatography on silica gel.

The acetyl (**7a**), diethyl phosphate (**8a**), and diphenyl phosphate (**9a**) derivatives of 1,1-difluorofarnesol are stable structures which survive brief exposure to dilute aqueous acid or base and which can be stored in the refrigerator if pure. The remarkable thermal stability of the phosphate derivatives is emphasized by the observation of parent ions in their chemical ionization mass spectra. Extension of the present methodology to the preparation of monofluorinated functionalities is in progress.

Acknowledgments. The experimental collaboration of Ms. K. S. Prickett and the generous assistance of Dr. G. B. Matson with ^{19}F NMR studies greatly facilitated this work. This research was supported by National Institutes of Health Grants HL15476 and T32-GM07175, by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by a grant from the Research Corporation. P.R.O.M. is an Alfred P. Sloan Fellow. The U.C.S.F. NMR facility is supported in part by National Institutes of Health Grant RR 00892.

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(12) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.
(13) All structural assignments are consistent with complete spectroscopic and analytical data, including, where applicable, ^{19}F NMR data.
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(15) Compound **1a**: ^1H NMR ($CDCl_3$) 1.43 (d, J = 2 Hz, 3 H, Me at C-3), 1.63 and 1.72 (2 s, 9 H, allylic Me), 2.05 (br m, 8 H, allylic CH_2), 2.15 (s, H, OH), 4.43 (d of d, J = 26, 6 Hz, H, $CH{=}CF_2$), 5.20 ppm (m, 2 H, vinyl H); ^{19}F NMR ($CFCl_3$ reference) 84.9 (d of d, J = 46, 26 Hz, cis F), 86.3 ppm (d of d, J = 46, 6 Hz, trans F); CIMS m/e 241 ($MH^+ - H_2O$). Anal. Calcd for $C_{15}H_{24}F_2O$: C, 69.73; H, 9.36. Found: C, 69.63; H, 9.12.
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(20) Compound **7a**: ^1H ($CDCl_3$) 1.63 and 1.70 (2 s, 9 H, allylic Me), 1.88 (m, 3 H, Me at C-3), 2.07 (br m, 8 H, allylic CH_2), 2.15 (s, 3 H, MeCO), 5.17 (m, 2 H, vinyl H), 5.60 ppm (t, J = 10 Hz, H, C-2 proton); ^{19}F NMR ($CFCl_3$ reference) 63.3 and 63.7 ppm (2 d, J = 10 Hz each, 2*E* and 2*Z* isomers); CIMS m/e 241 ($MH^+ - HOAc$). Anal. Calcd for $C_{17}H_{26}F_2O_2$: C, 67.97; H, 8.73. Found: C, 68.36; H, 8.75.
(21) Vinson, W. A. Ph.D. Thesis, University of California at San Francisco, Sept 1978.
(22) Compound **8a** (*E*): ^1H NMR ($CDCl_3$) 1.38 (d of t, J = 1, 7 Hz, 6 H, ethoxy Me), 1.63 and 1.70 (2 s, 9 H, allylic Me), 1.92 (m, 3 H, Me at C-3), 2.02 (m, 6 H, allylic CH_2), 2.13 (m, 2 H, C-4 protons), 4.25 (q, J = 7 Hz, 4 H, OCH_2), 5.15 (m, 2 H, vinyl), 5.58 ppm (t, J = 10 Hz, H, C-2 proton); ^{19}F NMR ($CFCl_3$ reference) 55.06 ppm (br m); CIMS m/e 395 (MH^+), 375 ($MH^+ - HF$). Anal. Calcd for $C_{19}H_{33}F_2PO_4$: C, 57.85; H, 8.43; P, 7.85. Found: C, 58.11; H, 8.28; P, 7.76.

Paul R. Ortiz de Montellano,* Wayne A. Vinson

Department of Pharmaceutical Chemistry
School of Pharmacy, University of California
San Francisco, California 94143

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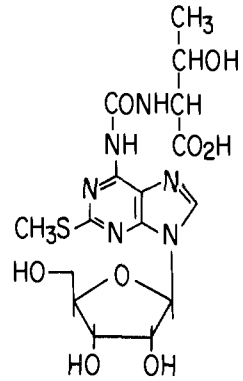
Structure Elucidation by High Resolution Mass Spectrometry of a Highly Modified Nucleoside from Mammalian Transfer RNA. *N*-[(9-β-D-Ribofuranosyl-2-methylthiopurin-6-yl)carbamoyl]threonine

Sir:

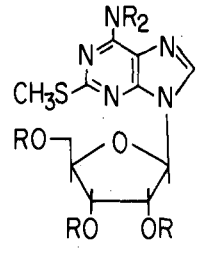
The chemical and conformational properties of modified nucleosides in tRNA, particularly those in the anticodon region, are thought to play a role in the biological functions of transfer RNA.[1,2] As interest in structure and function of eukaryotic tRNA grows, the structure elucidation of new nucleosides becomes more difficult owing to the complexity of structures encountered[2] and limitations in sample quantity. We report here the structure of the title compound as **1**,[3] based on mass spectrometry carried out on 35 μg of material.



1, 458.1203 (–1.7)

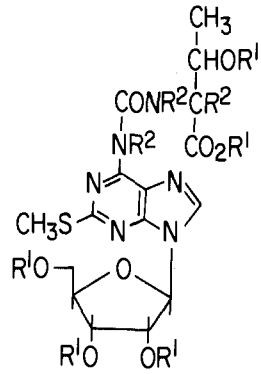
Unfractionated rabbit liver tRNA (5 g) was incubated with nuclease P_1 (pH 5.0, 37 °C, 2 h) and the resulting hydrolysate fractionated by DEAE-cellulose (DE-52) with a linear NaCl gradient (0–0.2 M, pH 7.5) in the presence of 7 M urea. Fractions containing the unknown nucleoside N as pNpA were converted into mononucleotides (snake venom phosphodiesterase, pH 7.5, 37 °C, 18 h) which were separated by DEAE Sephadex A-25 (pH 7.8, 0.1–0.7 M, triethylammonium bicarbonate gradient). Nucleotide pN (6 A_{260} units) was purified by two-dimensional paper electrophoresis and chromatography (first run, 30 V/cm for 5 h with 5% acetic acid (adjusted to pH 3.5 by pyridine); second run, isobutyric acid–0.5 M NH_3 (5:3 v/v)) and then dephosphorylated by alkaline phosphomonoesterase.[4]

Permethylation of the unknown nucleoside using methylsulfinyl carbanion with CD_3I or CH_3I[5] each yielded two



2, R = CD_3, 398.2558 (0.1)
3, R = CH_3, 383.1611 (–1.6)
8, R = H, 313.0831 (–1.4)

products which were completely fractionated by vaporization from the mass spectrometer probe at 100 (**2, 3**) and 150 °C (**4, 5**), while trimethylsilylation[6] produced a single derivative ($Si(CH_3)_3$, **6**; $Si(CD_3)_3$, **7**).



4, $R^1 = R^2 = CD_3$
5, $R^1 = R^2 = CH_3$, 570.2448 (–2.4)
6, R^1 = Me_3Si (TMS), R^2 = H, 818.3184 (–1.2)

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