Oxidation of Fluoroalkyl-Substituted Carbinols by the Dess–Martin Reagent

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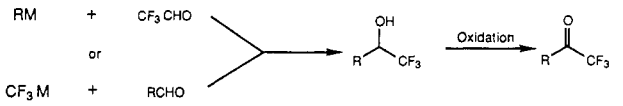
Received August 10, 1988

The efficient oxidation of mono-, di-, tri-, and perfluoroalkyl-substituted carbinols has been accomplished by the Dess–Martin periodinane oxidant. A variety of functional groups are compatible with the oxidation procedure. Monitoring the oxidation by ^{19}F NMR indicated that a discreet periodinane intermediate is formed during the course of the reaction. Nonnucleophilic or sterically encumbered α-thiofluoro carbinols were readily oxidized; however, a nucleophilic α-thio-substituted trifluoromethyl carbinol was not. A *tert*-butyl alcohol modified periodinane oxidant was ultimately employed to achieve oxidation in this example.

Fluorinated compounds have been of great interest to synthetic and medicinal chemists for a considerable time due to the unique physical and biological properties imparted by fluorine.[1] The synthesis of specifically fluorinated materials is an ongoing area of research, which has led to innovative methods for introducing fluorine in an electrophilic and nucleophilic fashion.[2] Currently, one subset of fluorinated compounds of great interest are fluorinated ketones, especially trifluoromethyl ketones, due to the remarkable ability of these compounds to function as enzyme inhibitors.[3]

The synthesis of fluoro ketones has not been trivial.[1b,2] Traditional early approaches involved the addition of Grignard species to trifluoroacetic acid or amide derivatives.[4] This approach was necessarily limited to functional groups compatible with Grignard or organolithium reagent preparation. Although recent work has improved upon this approach for the synthesis of trifluoromethyl ketones,[5] the method remains of limited general synthetic value. The alternative approach of preparing a fluoroalkyl-substituted carbinol, and subsequent oxidation to the ketone, has also been problematic. Condensation reactions of fluoroalkyl carbanions with aldehydes or ketones were initially quite difficult, especially for the trifluoromethyl anion.[6] However, within the past few years, trifluoromethyl organometallic reagents have been developed, which provide a useful source of this anion.[7] Perfluoroalkyl ($\geq$C2) substituted carbinols are more readily obtained by condensation reactions of the corresponding organometallic derivatives.[8] Trifluoroacetaldehyde undergoes condensation with a variety of nucleophiles, generating the carbinol in good yield.[9] Abeles has employed trifluoroacetaldehyde in condensation reactions with nitro-stabilized carbanions in an approach to α-amino trifluoromethyl ketones.[10]



Difluoro[11] and monofluoro[12] substituted carbinols are readily prepared via Reformatsky reactions. All of the condensation approaches provide fluoro carbinols efficiently; however, oxidation of the carbinol to the ketone has been very difficult. For example, the oxidation of an allylic trifluoromethyl-substituted alcohol using a large excess of manganese dioxide was very sluggish, requiring a prolonged reaction time.[13] Oxidation of simple alkyl-substituted trifluoromethyl carbinols has been accomplished, but only under rather severe conditions.[10] More recently, several investigators have employed the Swern oxidation (or other modified DMSO oxidations) in the preparation of difluoroalkyl-substituted ketones;[3a,g] however, these reactions also required a large excess of the oxidant (10–15 equiv). In our experience, the Swern oxidation procedure proved to be problematic and not easily repeatable. In peptidyl fluoro ketone enzyme inhibitor synthesis, Abeles has employed basic aqueous potassium permanganate oxidations;[3e,10] however, this oxidation procedure also suffers the limitation of poor reproducibility. We have also found that fluoroalkyl carbinols that are not soluble in aqueous solution were resistant to permanganate oxidation.

(1) (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: New York, 1976. (b) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier: New York, 1982. (c) Gerstenberger, M. R. C.; Haos, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

(2) (a) Filler, R. In *Organofluorine Chemicals and their Industrial Applications*; Banks, R. F., Horwood, E., Eds.; Halstead: New York, 1979. (b) *Synthesis of Fluoroorganic Compounds*; Knunyants, I. L., Yakobson, G. G., Eds.; Springer-Verlag: Berlin, 1985. (c) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 111. (d) Purrington, S. T.; Kagan, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, 997. (e) Prestwich, G. D. *Pestic. Sci.* **1986**, *37*, 430.

(3) For recent examples of fluorocarbonyl compounds as inhibitors of enzymes, see the following references and references therein: (a) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080. (b) Imperali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760. (c) Abdel-Aal, Y. A. I.; Hammock, B. D. *Science* **1986**, *223*, 1073. (d) Stein, R. L.; Strimpler, A. M.; Edwards, P. D.; Lewis, J. J.; Manger, R. C.; Swartz, J. A.; Stein, M. M.; Trainor, D. A.; Wildonger, R. A.; Zottola, M. A. *Biochemistry* **1987**, *26*, 2682. (e) Imperiali, B.; Abeles, R. H. *Biochemistry* **1987**, *26*, 4474. (f) Liang, T.-C.; Abeles, R. H. *Biochemistry* **1987**, *26*, 7603. (g) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071.

(4) (a) McBee, E. T.; Pierce, O. R.; Meyer, D. D. *J. Am. Chem. Soc.* **1955**, *77*, 917. (b) Dishart, K. T.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 2268. Also note ref 1a and 2b.

(5) (a) Salvador, R. L.; Saucier, M. *Tetrahedron* **1971**, *27*, 1221. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (c) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1981**, *18*, 117. (d) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026. (e) Beque, J. P.; Mesureur, D. *J. Fluorine Chem.* **1988**, *39*, 271.

(6) (a) Pierce, O. R.; McBee, E. T.; Judd, G. F. *J. Am. Chem. Soc.* **1954**, *76*, 474. (b) Haszeldine, R. N. *J. Chem. Soc.* **1954**, 1273.

(7) (a) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186. (b) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014. (c) O'Reilly, N. J.; Maruta, M.; Ishikawa, N. *Chem. Lett.* **1984**, 517.

(8) For pentafluoroethyllithium, see: Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481. For a perfluoroalkyl Grignard, see: Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1984**, *26*, 341.

(9) Ishikawa, N.; Koh, M. G.; Kitazume, T.; Choi, S. W. *J. Fluorine Chem.* **1984**, *24*, 419. Other examples can be found in ref 1a.

(10) Imperiali, B.; Abeles, R. H. *Tetrahedron Lett.* **1986**, *27*, 135. For an alternative approach to α-amino trifluoromethyl ketones, see: Kolb, M.; Barth, J.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 1579.

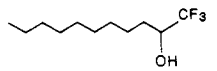
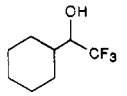
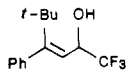
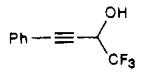
(11) Hallinan, E. A.; Fried, J. *Tetrahedron Lett.* **1984**, *25*, 2301. Burton, D. J.; Easdon, J. C. *J. Fluorine Chem.* **1988**, *38*, 125. Lang, R. W.; Schaub, B. *Tetrahedron Lett.* **1988**, *29*, 2943.

(12) Brandange, S.; Dahlman, O.; Morch, L. *J. Am. Chem. Soc.* **1981**, *103*, 4452.

(13) For examples of oxidations see ref 1a, 3a,b,g, 10, and Hanzawa, Y.; Yamada, A.; Kobayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 2881.

0022-3263/89/1954-0661$01.50/0

Table I. Oxidation of Trifluoromethyl-Substituted Carbinols by the Dess-Martin Periodinane

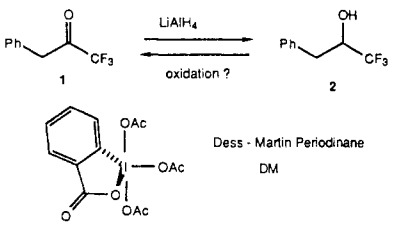
entry	carbinol structure (number)		^{19}F NMR, alcohol[a]	% yield,[b] ketone	^{19}F NMR, ketone
1		(2)	d, −79.7	95	s, −78.6
2		(3)	d, −81.0	93	s, −80.1
3		(4)	d, −76.7	75	s, −78.8
4		(5)	d, −79.2	76	s, −72.8
5		(6)	d, −80.1	85	s, −79.8
6		(7)	d, −80.2	90	s, −79.0

[a] ^{19}F NMR chemical shifts are reported as ppm relative to $CFCl_3$. Upfield shifts are designated as negative. [b] Isolated yield after purification of the crude reaction product.

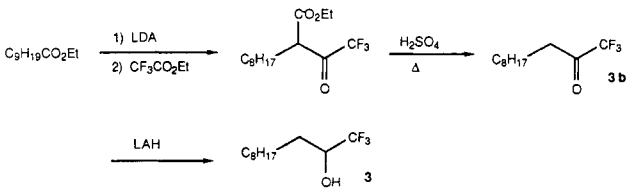
During our initial investigations into this problem, we had two goals in mind, an oxidation procedure, which would occur under mild reaction conditions without requiring a large excess (10–15 equiv) of oxidant, and a reproducible procedure, which would be applicable to a variety of functionalized fluoroalkyl-substituted carbinols. Given the potential application of this chemistry to the synthesis of enzyme inhibitors, we chose to survey oxidants that had been employed in the preparation of nonfluorinated enzyme inhibitors. Our attention was drawn to a report by Hanson and Lindberg[14] on the application of the Dess–Martin periodinane[15] to the synthesis of a keto vinyl isostere angiotension inhibitor. The oxidation was carried out on an optically active amido (nonfluorinated) carbinol to provide the corresponding ketone without racemization. We have recently reported an efficient method for the oxidation of trifluoromethyl-substituted carbinols by using the Dess–Martin periodinane[15] and would now like to present the full details of this procedure for mono-, di-, tri-, and perfluoroalkyl-substituted carbinols.[16]

Results and Discussion

Initial studies focused on the oxidation of trifluoromethyl carbinol **2**, which was prepared by lithium aluminum hydride reduction of the corresponding ketone **1**.[16] We arbitrarily chose to determine the optimal stoichiometry for the oxidation of **2** by the Dess–Martin (DM) reagent in methylene chloride at room temperature for 3 h. The reaction progress was monitored by GC analysis



of the crude reaction product after aqueous sodium thiosulfate workup.[15,16] Interestingly, no oxidation of **2** was observed during the 3-h time period in which 1.1–3.3 equiv of the periodinane was used, while 3.7 equiv of the oxidant resulted in complete conversion of **2** to **1**. In the experiments in which oxidation had not occurred, the alcohol was recovered in excellent material balance. A time course study was then pursued using 1.1 equiv of DM. An apparent induction period for the oxidation of 3 h was noted with the yield of **1** increasing to 65% after 6 h and 72% after 48 h (isolated yields). A series of trifluoromethyl carbinols was then prepared to begin to ascertain the scope and limitations of the oxidation procedure (Table I). The preparation of 1,1,1-trifluoroundecan-2-ol (**3**) is noteworthy. Several attempts to prepare the ketone precursor by the Grignard method[4] met with no success, nor could the required ketone be prepared by Collman's procedure.[17] Trifluoroacylation of the lithium enolate of ethyl undecanoate by ethyl trifluoroacetate followed by acid-catalyzed deesterification and decarboxylation provided **3b** in 50–55% overall yield. This method provided a general



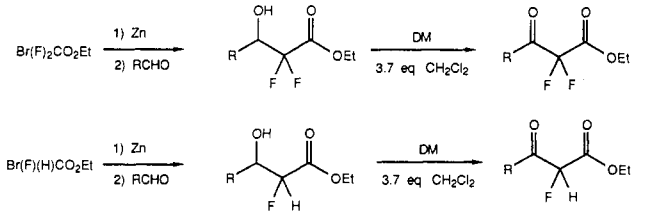
route to several simple trifluoromethyl ketones in reasonable yield.[18] Each of the alcohols **3–7** (Table I) were obtained by reduction of the corresponding ketones and were then subjected to the optimized oxidation conditions (3.7 equiv of DM, CH_2Cl_2, room temperature, 3 h). The ketones were isolated in good to excellent yield (Table I). Aliphatic, allylic, benzylic, and propargylic substrates were all readily oxidized.

The apparent induction period for the oxidation cannot be readily explained. The molar concentration of the periodinane oxidant or that of the substrate had no discernable effects on the reaction rate. This question was not pursued in any further detail. The need for 3.7 equiv of the oxidant is also quite unusual. Attempts to reduce

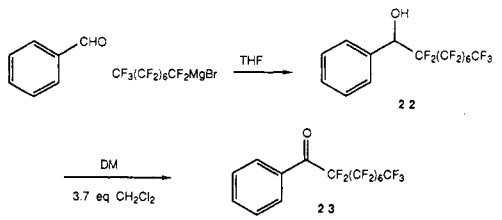
(14) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399.
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(16) Linderman, R. J.; Graves, D. M. *Tetrahedron Lett.* **1987**, *28*, 4259.
(17) Collman, J. P.; Hoffman, N. W. *J. Am. Chem. Soc.* **1973**, *95*, 2689.
(18) Leazer, J. M.S. Thesis, North Carolina State University, 1986. For related approaches see also: McBee, E. T.; Pierce, O. R.; Kilbourne, H. W.; Wilson, E. R. *J. Am. Chem. Soc.* **1953**, *75*, 3152. Joshi, K. C.; Joshi, B. S. *J. Fluorine Chem.* **1986**, *32*, 229.

the number of equivalents of oxidant in reactions with allylic trifluoromethyl-substituted carbinols also resulted in reduced yields. We cannot speculate on the reasons for this specific stoichiometry. Interestingly, this phenomenon (stoichiometry) was not observed with nonfluorinated substrates.[14,15]

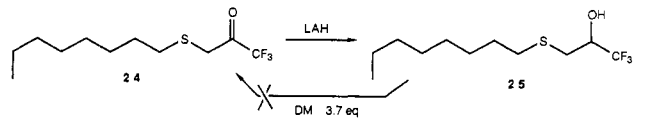
A second series of substrates for oxidation was then prepared via the Reformatsky approach.[11,12] In these examples (Table II), the DM oxidation procedure proved to be very efficient, generating the α-mono- or difluoro-β-keto esters in very good yield. Sterically hindered alcohols were



oxidized as readily as unhindered alcohols (entries 1–3 and 6–8, Table II). To further illustrate the generality of this oxidation method, perfluorooctyl-substituted alcohol **22** was prepared as illustrated.[19] Oxidation under the optimized reaction conditions provided an 86% isolated yield of the perfluoroctyl ketone **23**.



Esters, olefins, and aromatic (including heteroaromatic) functionality was readily tolerated. Note that the pyridyl, thienyl, and furyl moieties were compatible with the oxidation procedure (entries 12–14, Table II). In order to determine what other functionality might be present without interfering in the oxidation, 1,1,1-trifluoro-3-(octylthio)propan-2-ol **25** was prepared from the corresponding ketone **24**.[20] Upon reaction of **25** with 3.7 equiv of the DM reagent followed by aqueous sodium thiosulfate workup, none of the ketone **24** was obtained, nor was the starting alcohol recovered. We reasoned that a salt might



have formed by interaction of the nucleophilic sulfur atom with the oxidant and that the complex had been lost in the aqueous workup due to the failure of the salt to decompose. A ^{19}F NMR investigation was then undertaken to test this possibility.

Initial ^{19}F NMR studies were carried out using the model alcohol **2**, which exhibited an ^{19}F NMR resonance at −79.8 (d) ppm.[21] When **2** was combined with 3.7 equiv of the DM reagent and the ^{19}F NMR spectrum was recorded after 15 min, two new doublets were observed at −76.7 and −77.6

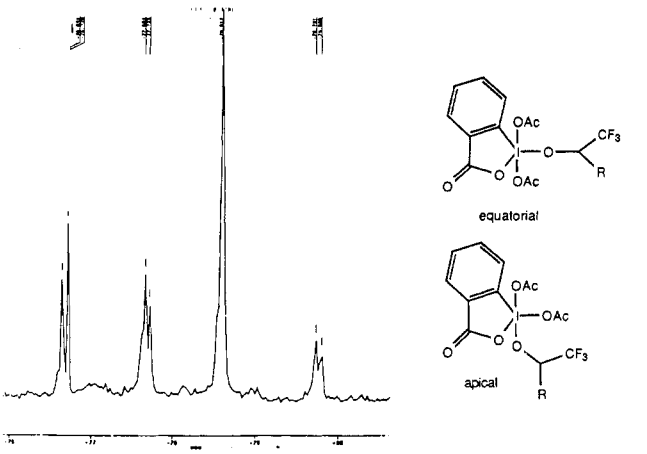
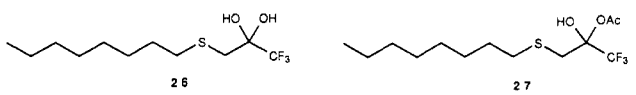


Figure 1. The ^{19}F NMR spectrum of **2** and 3.7 equiv of the DM reagent after 20 min. The starting alcohol **2** was observed at −79.8 ppm, the product **1** at −78.6 ppm, and two new doublets at −76.7 and −77.6 ppm. The new signals are attributed to the intermediate periodinanes A and B; however, no specific assignment of the signals has been made.

ppm in addition to the starting material doublet at −79.8 ppm and a singlet at −78.6 ppm, which corresponded to the ketone product (Figure 1). The new doublets and the signal for the starting material disappeared over time with a concomitant increase in the ketone signal. The doublets at −76.7 and −77.6 ppm were presumed to be discreet periodinane intermediates in which the alcohol had displaced an apical or equatorial acetate on the nearly trigonal-bipyramidal periodinane. Displacement of the benzoate substituent at iodine is also possible and cannot be ruled out by these studies. An intermediate periodinane species had not been previously observed (by ^1H NMR spectroscopy) in the reaction of nonfluorinated carbinols with the DM reagent, and the exact mechanism of oxidation was unknown.[14] This study clearly indicates that an activated periodinane intermediate plays a role in the oxidation.

The reaction of **25** and the DM reagent was then examined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum was very complex, showing at least 15 signals between −72.0 and −80.0 ppm. A signal corresponding to the product ketone **24** at −76.2 ppm was observed; however, this signal gradually diminished during the 3-h reaction period. Interestingly, a new signal appeared at −83.0 ppm, which is in the same range of chemical shift as the hydrated ketone (−86.2 ppm) **26**.[22] This signal (−83.0 ppm) increased substantially when glacial acetic acid was added to the reaction mixture, indicating that the initial product may be the acetate hemiketal **27**. However, **27** could not be



isolated from the reaction mixture. In a control experiment, ketone **24** and excess glacial acetic acid provided a clean ^{19}F NMR spectrum of the free ketone (−76.0 ppm) and the hemiketal (−85.8 ppm). Since the alcohol **25** was totally consumed in the reaction and apparently oxidized, the alcohol **25** itself does not form a nonoxidized water-soluble complex. Examination of the interaction of the ketone **24** and the DM reagent by ^{19}F NMR indicated that these two species immediately produced a complex spectrum analogous to that observed in the reaction of **25** and

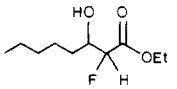
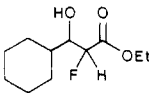
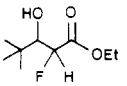
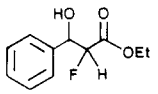
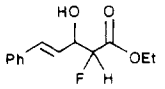
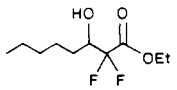
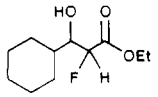
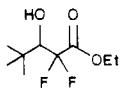
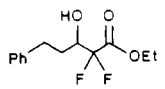
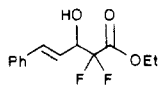
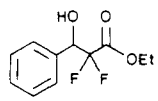
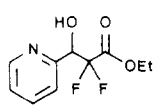
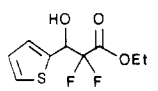
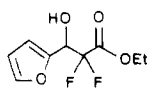
(19) Denison, D. D.; Smith, C. F.; Tamborski, C. *J. Fluorine Chem.* **1973/74**, 247. For a recent example of the reactions of perfluoroalkyl Grignards, see also: Noreau, P.; Naji, N.; Commeyras, A. *J. Fluorine Chem.* **1987**, *34*, 421.

(20) Abdel-Aal, Y. A. I.; Hammock, B. D. *Insect Biochem.* **1985**, *15*, 111.

(21) Chemical shifts are reported relative to $CFCl_3$, 0.0 ppm. Upfield shifts are reported as negative values.

(22) Fluoro ketones readily hydrate upon exposure to water. Ritchie, C. D. *J. Am. Chem. Soc.* **1984**, *106*, 7187.

Table II. Oxidation of β-Hydroxy-α-mono- or -α,α-difluoro Esters by the Dess-Martin Periodinane

entry	hydroxy ester structure (number)		^{19}F NMR, hydroxy ester[a]	% yield, ketone[b]	^{19}F NMR keto ester
1		(8)	dd, −198.8 dd, −206.8	90	d, −196.2
2		(9)	dd, −197.3 dd, −209.2	87	d, −196.0
3		(10)	dd, −190.2 dd, −208.5	76	d, −192.2
4		(11)	dd, −197.0 dd, −202.3	82	d, −189.8
5		(12)	dd, −200.1 dd, −204.4	80	d, −195.0
6		(13)	dd, −114.6 dd, −124.5	79	s, −114.6
7		(14)	dd, −111.3 dd, −125.1	86	s, −114.0
8		(15)	dd, −107.8 dd, −122.3	78	s, −108.8
9		(16)	dd, −115.4 dd, −123.7	90	s, −115.4
10		(17)	dd, −113.5 dd, −122.0	79	s, −114.5
11		(18)	dd, −113.5 dd, −122.0	85	s, −108.2
12		(19)	dd, −111.6 dd, −125.0	80	s, −113.2
13		(20)	dd, −113.5 dd, −122.2	95	s, −109.0
14		(21)	dd, −114.0 dd, −121.8	91	s, −111.0

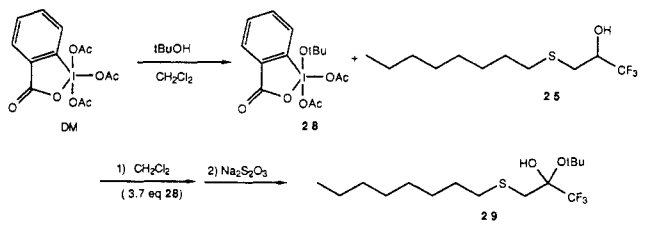
21

[a] ^{19}F NMR chemical shifts are reported as ppm relative to $CFCl_3$. Upfield shifts are designated as negative. The β-hydroxy esters were obtained as a mixture of erythro and threo isomers. [b] Isolated yields after purification on the crude reaction product.

the DM reagent. None of the ketone **24** could be recovered from the oxidation reaction mixture, leading to the conclusion that the product ketone **24** was incompatible with the oxidant. Analogous problems were encountered when 1:1 stoichiometry of **24** or **25** and the DM reagent was employed.

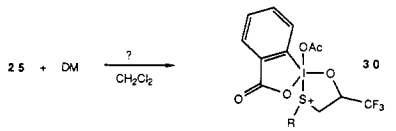
An attempt to deter complex formation by **24** or **25** with the DM reagent by modifying the oxidant was then carried out. An equivalent of *tert*-butyl alcohol was added to the periodinane at room temperature to provide the modified oxidant **28**.[23] The modified oxidant rapidly oxidized alcohol **2** to ketone **1** in >90% isolated yield. Upon combination of alcohol **25** and 3.7 equiv of oxidant **28** and observation of the ^{19}F NMR spectrum after 10 min, two predominant signals were observed, corresponding to the alcohol **25** and the ketone **24**. Several additional signals of lower intensity were also present. After 3 h at room temperature, the signal for the alcohol was absent. Surprisingly, after aqueous sodium thiosulfate workup, the

(23) Martin[15] also prepared this modified periodinane and had shown it to be an effective oxidant for nonfluorinated alcohols.

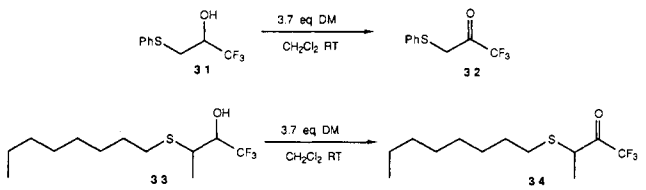


tert-butyl hemiketal **29** was isolated in 80% yield. Therefore, the DM oxidation method can be applied to α-thio-substituted fluoro carbinols if the periodinane is modified by the addition of a bulky, nonoxidizable alcohol.

The problems discussed above were presumably due to the fact that the α-S atom displaced an additional acetate of the periodinane, leading to a salt such as **30**. The



modified oxidant **28** reduced, but did not completely eliminate, this problem. To further verify this hypothesis, fluoro carbinols **31**[24] and **33**[25] were prepared. The S atom of **31** should be less nucleophilic than that of **25** and potentially more sterically hindered than **25** due to the ortho protons of the aromatic ring. Compound **33** would be expected to encounter greater steric interactions in the formation of a salt such as **30** than **25**. Indeed, alcohol **31** was cleanly and rapidly oxidized to ketone **32** in 96% yield by using 3.7 equiv of the unmodified DM periodinane. ^{19}F



NMR analysis of the oxidation indicated that the reaction was sufficiently rapid to preclude observation of any periodinane intermediates. In addition, in contrast to compound **24**, **32** was stable to the oxidant. In a similar fashion, **33** underwent clean oxidation to **34** in 79% isolated yield.

As further indication that the Dess–Martin periodinane is the reagent of choice for fluoroalkyl carbinol oxidations, the recent report of the oxidation of a peptidyl trifluoromethyl-substituted carbinol to the corresponding ketone by an ICI group[26] illustrates that this procedure can be carried out in the presence of amide groups. More importantly, the oxidation[26] of the fluoro carbinol proceeded without racemization of an adjacent chiral center. Our independent studies described herein coupled with these of the ICI group indicate that there are few limitations for the Dess–Martin periodinane procedure in the preparation of fluoroalkyl-substituted ketones.

In conclusion, an efficient and general synthetic procedure for the oxidation of fluoroalkyl-substituted carbinols has been developed. The scope and limitations have been addressed, indicating that a sterically unencumbered nucleophilic heteroatom in the α-position cannot be tolerated in the reaction due to complex or salt formation. However, this problem can be at least partially circumvented by modifying the DM oxidant with *tert*-butyl alcohol. Sterically biased or modestly nucleophilic α-heteroatom substitution presents no problem in the oxidation. ^{19}F NMR studies have provided insight into the course of the reaction, demonstrating that a periodinane/alcohol intermediate complex is formed.

Experimental Section

General Procedures. Infrared spectra were recorded on a Perkin Elmer 1430 ratio recording spectrophotometer. ^1H NMR spectra were obtained on either a Varian EM390 or Brucker WM250 spectrometer with tetramethylsilane as an internal standard. ^{19}F NMR spectra were obtained on either a Varian EM390 or an IBM 100 spectrometer with freon as an internal standard. Capillary gas chromatographic analyses were carried out using a Hewlett-Packard 5890 gas chromatograph. All analyses were carried out on a SE-30, 25 m fused silica column with use of a temperature ramp program. Ether and tetrahydrofuran (THF) were freshly distilled from lithium aluminum hydride (LAH) or sodium/benzophenone. All anionic reactions were carried out in flame-dried glassware under an inert atmosphere. Grignard reagents were prepared from freshly distilled alkyl or aryl halide precursors. Ethyl di- and trifluoroacetate were purchased from PCR and used without further purification. Alkyllithium reagents were purchased from Aldrich. Dess–Martin reagent and all other organic reagents were purchased from Aldrich. Flash chromatography were performed on silica gel 60, 230–400 ASTM, obtained from American Scientific Products. All chromatography solvents were distilled prior to use. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA.

Preparation of Trifluoromethyl-Substituted Carbinols. In general, the alcohol intermediates were not subjected to elemental analysis. Complete analytical data was obtained for the corresponding ketone.

3-Phenyl-1,1,1-trifluoropropan-2-ol, 2. An ether solution (10 mL) of 3-phenyl-1,1,1-trifluoropropan-2-one[27] (3.75 g, 19.9 mmol) was added dropwise to a suspension of LAH (300 gm, 7.91 mmol) in 20 mL of ether at 0 °C (ice bath). The resulting mixture was stirred for 1 h at 0 °C and then quenched by the addition of 50 mL of 10% aqueous sulfuric acid. After being warmed to room temperature, the layers were separated, and the aqueous phase was extracted with ether (3 × 25 mL). The combined organic fractions were washed with 25 mL of 5% aqueous sodium bicarbonate. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent then removed under reduced pressure. The crude product required no further purification: 3.41 g (90%); ^1H NMR (CCl_4) δ 2.6 (s, 1 H), 2.7 (t, 2 H, J = 3 Hz), 3.8 (m, 1 H), 7.3 (m, 5 H); ^{19}F NMR (CCl_4) δ −80.7 (d, J_{HF} = 5.1 Hz); IR (neat) (cm^{-1}) 3350, 3060, 1150.

1,1,1-Trifluoroundecan-2-ol, 3. A THF solution (10 mL) of ethyl decanoate (2.0 g, 2.32 mL, 10 mmol) was added dropwise to a solution of lithium diisopropylamide (LDA) (15 mmol) in 30 mL of THF at −78 °C (CO_2/acetone). The mixture was stirred for 30 min at −78 °C prior to the addition of a solution of ethyl trifluoroacetate (2.84 g, 2.38 mL, 20 mmol) in 10 mL of THF. The reaction mixture was allowed to gradually warm to room temperature and stirred for a period of 26 h. The reaction was then quenched at room temperature by the addition of 40 mL of 5% aqueous hydrochloric acid. The layers were then separated, and the organic phase was washed with water (2 × 15 mL) and saturated aqueous sodium chloride (2 × 15 mL). The combined aqueous layers were then back extracted with ether (1 × 25 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was then removed under reduced pressure. The crude reaction product (2.83 g, 96% crude yield) was then dissolved in 20 mL of 40% aqueous sulfuric acid. The solution was then refluxed for 94 h. The reaction mixture was allowed to cool to room temperature and then extracted with ether (3 × 30 mL). The combined organic phases were washed with

(24) Yamazaki, T.; Asai, M.; Ohnogi, T.; Lin, J. T.; Kitazume, T. *J. Fluorine Chem.* **1987**, *35*, 53.

(25) Linderman, R. J.; Leazer, J.; Venkatesh, K.; Roe, R. M. *Pestic. Biochem. Physiol.* **1987**, *29*, 266.

(26) See ref 3d and Bergeson, S. H.; Edwards, P. D.; Krell, R. D.; Shaw, A.; Stein, R. L.; Stein, M. M.; Strimpler, A. M.; Trainor, D. A.; Wildonger, R. A.; Wolanin, D. J. 193rd National Meeting of the American Chemical Society, Denver, CO, MEDI-1, April 5–10, 1987.

(27) Trabelski, H.; Bertrina, B.; Cambon, A. *Can. J. Chem.* **1985**, *63*, 426.

saturated aqueous sodium bicarbonate (2 × 25 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was then removed under reduced pressure. The crude product was purified by Kugelrohr distillation (72–75 °C at 5 mmHg), 1.08 g (50%).

The ketone (1.00 g, 4.46 mmol) was then added dropwise as a solution in 5 mL of ether to a suspension of LAH (0.17 g, 4.5 mmol) in 5 mL of ether of 0 °C (ice bath). The reaction mixture was then was allowed to warm to room temperature and stirred for 4 h. The reaction was then quenched by the dropwise addition of 2 mL of water followed by 1 mL of a 10% aqueous sodium hydroxide solution. The resulting precipitate was filtered off (suction through Celite), and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was then removed under reduced pressure. The crude product was purified by Kugelrohr distillation: 0.61 g (60%); ^1H NMR (CCl_4) δ 0.9 (t, 3 H, J = 6 Hz), 1.3 (m, 16 H), 3.9 (m, 1 H); ^{19}F NMR (CCl_4) δ −81.0 (d, J_{HF} = 5.6 Hz); IR (neat) (cm^{-1}) 3310, 2860, 1150.

2-Cyclohexyl-1,1,1-trifluoroethan-2-ol, 4. An ether solution (12 mL) of 2-cyclohexyl-1,1,1-trifluoroethan-2-one[28] (4.9 g, 27.19 mmol) was added dropwise to a suspension of LAH (0.83 g, 22.0 mmol) in 25 mL of ether at 0 °C (ice bath). The procedure described above was then followed. The crude product was purified by Kugelrohr distillation: 3.32 g (67%); ^1H NMR (CCl_4) δ 1.2–1.8 (m, 11 H), 2.3 (s, 1 H), 3.7 (m, 1 H); ^{19}F NMR (CCl_4) δ −76.7 (d, J_{HF} = 10.1 Hz); IR (neat) (cm^{-1}) 3320, 2890, 1150.

2-Phenyl-1,1,1-trifluoroethan-2-ol, 5. The known[29] alcohol was obtained from the corresponding ketone by LAH reduction as described above in 40% yield: ^1H NMR (CCl_4) δ 2.9 (d, 1 H, J = 4 Hz), 4.8 (q, 1 H, J = 4 Hz), 7.4 (m, 5 H); ^{19}F NMR (CCl_4) δ −79.2 (d, J_{HF} = 5.4 Hz); IR (neat) (cm^{-1}) 3320, 3080, 1150.

5,5-Dimethyl-4-phenyl-1,1,1-trifluorohex-3-en-2-ol, 6. A THF solution (2.5 mL) of 5,5-dimethyl-4-phenyl-1,1,1-trifluorohex-3-en-2-one[30] (0.3 g, 1.17 mmol) was cooled to 0 °C (ice bath) and treated dropwise with 1.76 mL of a 1 M THF solution of diisobutylaluminum hydride (1.76 mmol). The reaction mixture was stirred for 2 H at 0 °C (ice bath) before being quenched by the addition of 20 mL of 10% aqueous sulfuric acid. The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic phases were washed with 10 mL of 5% aqueous sodium bicarbonate, dried over anhydrous $MgSO_4$, and filtered, and the solvent was then removed under reduced pressure. The crude product was purified by Kugelrohr distillation (97–100 °C/5 mmHg): 0.27 g (89%); ^1H NMR (CCl_4) δ 1.2 (s, 9 H), 1.8 (s, 1 H), 3.6 (q, 1 H, J = 3 Hz), 5.3 (d, 1 H, J = 4 Hz), 7.2 (m, 5 H); ^{19}F NMR (CCl_4) δ −80.1 (d, J_{HF} = 6.0 Hz); IR ($CDCl_3$) (cm^{-1}) 3100, 2975, 1210.

4-Phenyl-1,1,1-trifluorobut-3-yn-2-ol, 7. The alcohol was obtained by the condensation of lithium phenylacetylide with trifluoroacetaldehyde:[9] ^1H NMR (CCl_4) δ 3.2 (s, 1 H), 4.8 (s, 1 H), 7.4 (m, 5 H); ^{19}F NMR (CCl_4) δ −80.2 (d, J_{HF} = 7.5 Hz); IR (neat) (cm^{-1}) 3240, 2900, 2220, 1150.

Preparation of Mono- and Difluoro-β-hydroxy Esters: General Procedures. For the difluoro compounds a procedure analogous to that reported by Fried[11] was employed. Zinc dust (235.3 mg, 3.6 mmol) (activated by successive washes with 20% aqueous hydrochloric acid, water, acetone, and anhydrous ether) was suspended in 6 mL of THF and heated to reflux. Ethyl bromodifluoroacetate (730.8 mg, 3.6 mmol) was then added to the refluxing suspension neat. Within 1 min, the aldehyde (3.0 mmol) was added, and refluxing was then continued for 15 min. The reaction mixture was cooled to room temperature and then poured into a mixture of ethyl acetate (100 mL), 1 M aqueous sodium hydrogen sulfate (25 mL), and saturated aqueous sodium bicarbonate (25 mL). After being stirred for 15 min, the layers were separated, and the aqueous layer was extracted with 50 mL of ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was then removed under reduced pressure.

For the monofluoro compounds a procedure similar to that reported by Bradange[12] was employed. Ethyl bromomonofluoroacetate (1.02 g, 5.50 mmol), activated zinc dust (0.654 g, 10 mmol), and the aldehyde (5.0 mmol) were combined in 11 mL of THF and heated to reflux. After refluxing for 10 min, the reaction mixture was cooled to room temperature and poured into a mixture of ethyl acetate (100 mL), 1 M aqueous sodium hydrogen sulfate (25 mL), and saturated aqueous sodium bicarbonate (25 mL). After being stirred for 15 min, the mixture was filtered through a pad of Celite, the layers were separated, and the aqueous layer was extracted with ether (2 × 75 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The products were obtained as mixtures of erythro/threo isomers as evidenced by ^{19}F NMR spectroscopy.

Ethyl 2-Fluoro-3-hydroxyoctanoate, 8. Crude product was purified by flash chromatography (SiO_2, 10% ethyl acetate/hexane): 77%; ^1H NMR (CCl_4) δ 0.95 (m, 3 H), 1.4 (m, 11 H), 2.75 (s, 1 H), 3.9 (m, 1 H), 4.25 (q, 2 H, J = 6 Hz), 4.7 (dd, 1 H, J = 48 Hz and J = 3 Hz), ^{19}F NMR (CCl_4) δ −198.5 (dd, J_{HFgem} = 49 Hz, J_{HF} = 18 Hz), −207.3 (dd, J_{HFgem} = 48 Hz, J_{HF} = 25 Hz); IR (neat) (cm^{-1}) 3480, 2940, 1760, 1210.

Ethyl 3-Cyclohexyl-2-fluoro-3-hydroxypropanoate, 9. Crude product was purified by flash chromatography (SiO_2, 10% ethyl acetate/hexane): 58%; ^1H NMR (CCl_4) δ 1.2 (m, 7 H), 1.8 (m, 6 H), 2.3 (s, 1 H), 3.4 and 3.8 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz), 4.6 and 5.1 (d, dd, 1 H, J = 8 Hz, J = 48 Hz, and J = 3 Hz); ^{19}F NMR (CCl_4) δ −197.3 (dd, J_{HFgem} = 49 Hz, J_{HF} = 17 Hz), −209.2 (dd, J_{HFgem} = 49 Hz, J_{HF} = 23 Hz).

Ethyl 4,4-Dimethyl-2-fluoro-3-hydroxypentanoate, 10.[12] Crude product was purified by Kugelrohr distillation: 71%; ^1H NMR (CCl_4) δ 1.00 (s, 9 H), 2.8 (s, 1 H), 4.3 (q, 2 H, J = 7 Hz), 3.6 and 5.1 (d, dd, 1 H, J = 6 Hz and J = 48 Hz), 3.6 and 5.0 (dd, 1 H, J = 48 Hz and J = 2 Hz); ^{19}F NMR (CCl_4) δ −190.2 (dd, J_{HFgem} = 48 Hz, J_{HF} = 16 Hz), −208.5 (dd, J_{HFgem} = 49 Hz, J_{HF} = 30 Hz); IR ($CDCl_3$) (cm^{-1}) 3600, 2970, 1750, 1210.

Ethyl 3-Phenyl-2-fluoro-3-hydroxypropanoate 11.[12] Crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexane): 65%; ^1H NMR (CCl_4) δ 1.2 (t, 3 H, J = 7 Hz), 3.5 (s, 1 H), 4.1 (q, 2 H, J = 7 Hz), 5.2 (s, 1 H), 7.3 (s, 5 H); ^{19}F NMR (CCl_4) δ −197.0 (dd, J_{HFgem} = 50 Hz, J_{HF} = 16 Hz), −202.0 (dd, J_{HFgem} = 50 Hz, J_{HF} = 21 Hz).

Ethyl 2-Fluoro-3-hydroxy-5-phenylpent-4-enoate, 12. Crude product was purified by flash chromatography (SiO_2, 25% ethyl acetate/hexane): 78%; ^1H NMR (CCl_4) δ 1.2 (t, 3 H), 3.4 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz), 5.1 (t, 1 H, J = 7 Hz), 6.2 (dd, 1 H, J = 48 Hz and J = 5 Hz), 6.8 (dd, 1 H, J = 48 Hz and J = 3 Hz), 7.3 (m, 5 H); ^{19}F NMR (CCl_4) δ −200.1 (dd, J_{HFgem} = 48 Hz, J_{HF} = 19 Hz), −204.4 (dd, J_{HFgem} = 47 Hz, J_{HF} = 23 Hz); IR (neat) (cm^{-1}) 3210, 2940, 1720, 1100.

Ethyl 2,2-Difluoro-3-hydroxyoctanoate, 13.[11] Crude product was purified by flash chromatography (SiO_2, 5% ethyl acetate/hexane): 56%; ^1H NMR (CCl_4) δ 1.00 (t, 3 H, J = 6 Hz), 1.6 (m, 12 H), 2.3 (s, 1 H), 3.9 (m, 1 H), 4.3 (q, 2 H); ^{19}F NMR (CCl_4) δ −114.6 (dd, J_{FF} = 264 Hz, J_{HF} = 8 Hz), −124.5 (dd, J_{FF} = 263 Hz, J_{HF} = 15 Hz); IR (neat) (cm^{-1}) 3220, 2910, 1745, 1150.

Ethyl 3-Cyclohexyl-2,2-difluoro-3-hydroxypropanoate, 14. Crude product was purified by Kugelrohr distillation: 54%; ^1H NMR (CCl_4) δ 1.2 (m, 7 H), 1.8 (m, 6 H), 2.2 (s, 1 H), 3.5 (m, 1 H), 3.7 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz); ^{19}F NMR (CCl_4) δ −111.3 (dd, J_{FF} = 263 Hz, J_{HF} = 8 Hz), −125.1 (dd, J_{FF} = 263 Hz, J_{HF} = 18 Hz); IR ($CDCl_3$) (cm^{-1}) 3600, 2940, 1760, 1150.

Ethyl 4,4-Dimethyl-2,2-difluoro-3-hydroxypentanoate, 15. Crude product was purified by Kugelrohr distillation: 74%; ^1H NMR (CCl_4) δ 1.00 (s, 9 H), 1.3 (t, 3 H, J = 6 Hz), 2.3 (s, 1 H), 3.5 (dd, 1 H, J = 21 Hz and J = 9 Hz), 4.3 (q, 2 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −107.8 (dd, J_{FF} = 261 Hz, J_{HF} = 6 Hz), −122.3 (dd, J_{FF} = 261 Hz, J_{HF} = 20 Hz); IR (neat) (cm^{-1}) 3240, 2920, 1750, 1075.

Ethyl 2,2-Difluoro-3-hydroxy-5-phenylpentanoate, 16. Crude product was purified by Kugelrohr distillation: 55%; ^1H NMR (CCl_4) δ 1.42 (t, 3 H, J = 6 Hz), 2.00 (q, 2 H, J = 6 Hz), 2.9 (t, 2 H, J = 6 Hz), 3.95 (m, 1 H), 4.35 (q, 2 H, J = 6 Hz), 7.25 (s, 5 H); ^{19}F NMR (CCl_4) δ −115.4 (dd, J_{FF} = 266 Hz, J_{HF} = 8 Hz), −123.7 (dd, J_{FF} = 266 Hz, J_{HF} = 14 Hz); IR (neat) (cm^{-1}) 3485, 2980, 1720, 1150.

Ethyl 2,2-Difluoro-3-hydroxy-5-phenylpent-4-enoate, 17. Crude product was purified by flash chromatography (SiO_2, 15%

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ethyl acetate/hexane): 61%; ^{1}H NMR (CCl_4) δ 1.2 (t, 3 H, J = 6 Hz), 3.5 (m, 1 H), 4.3 (q, 2 H, J = 6 Hz), 4.6 (br s, 1 H), 6.2 (dd, 1 H, J = 48 Hz and J = 6 Hz), 6.8 (br d, 1 H, J = 16 Hz), 7.3 (m, 5 H); ^{19}F NMR (CCl_4) δ −113.5 (dd, J_{FF} = 263 Hz, J_{HF} = 8 Hz), −122.0 (dd, J_{FF} = 263 Hz, J_{HF} = 14 Hz); IR (neat) (cm^{-1}) 3150, 2940, 1740, 1050.

Ethyl 2,2-Difluoro-3-hydroxy-3-phenylpropanoate, 18.[11] Crude product was purified by flash chromatography (SiO_2, 10% ethyl acetate/hexane): 99%; ^{1}H NMR (CCl_4) δ 1.2 (t, 3 H, J = 7 Hz), 2.9 (d, 1 H, J = 9 Hz), 4.2 (q, 2 H, J = 7 Hz), 5.0 (m, 1 H), 7.3 (s, 5 H); ^{19}F NMR (CCl_4) δ −113.5 (dd, J_{FF} = 261 Hz, J_{HF} = 8 Hz), −122.0 (dd, J_{FF} = 261 Hz, J_{HF} = 16 Hz); IR (neat) (cm^{-1}) 3480, 2960, 1730, 1150.

Ethyl 2,2-Difluoro-3-hydroxy-3-(2-pyridyl)propanoate, 19. Crude product was purified by flash chromatography (SiO_2, 25% ethyl acetate/hexane): 75%; ^{1}H NMR (CCl_4) δ 1.4 (t, 3 H, J = 7 Hz), 4.4 (q, 2 H, J = 7 Hz), 4.95 (t, 1 H, J = 7 Hz), 5.25 (d, 1 H, J = 12 Hz), 7.6 (m, 3 H), 8.65 (d, 1 H, J = 3 Hz); ^{19}F NMR (CCl_4) δ −111.6 (dd, J_{FF} = 262 Hz, J_{HF} = 5 Hz), −125.0 (dd, J_{FF} = 260 Hz, J_{HF} = 17 Hz); IR (neat) (cm^{-1}) 3500, 2990, 1725, 1150. Anal. Calcd for $C_{10}H_{11}F_2NO_3$: C, 51.95; H, 4.80. Found: C, 51.91; H, 4.83.

Ethyl 2,2-Difluoro-3-hydroxy-3-(2-thienyl)propanoate, 20. Crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexane): 70%; ^{1}H NMR (CCl_4) δ 1.4 (t, 3 H, J = 9 Hz), 3.25 (d, 1 H, J = 6 Hz), 4.45 (q, 2 H, J = 9 Hz), 5.5 (m, 1 H), 7.2 (m, 2 H), 7.5 (d, 1 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −113.5 (dd, J_{FF} = 262 Hz, J_{HF} = 8 Hz), −122.2 (dd, J_{FF} = 262 Hz, J_{HF} = 14 Hz); IR (neat) (cm^{-1}) 3480, 3120, 2990, 1705, 1150. Anal. Calcd for $C_9H_{10}F_2O_3S$: C, 45.76; H, 4.27. Found: C, 45.83; H, 4.28.

Ethyl 2,2-Difluoro-3-hydroxy-3-(2-furyl)propanoate, 21. Crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexane): 53%; ^{1}H NMR (CCl_4) δ 1.3 (t, 3 H, J = 8 Hz), 3.4 (s, 1 H), 4.3 (q, 2 H, J = 8 Hz), 5.1 (m, 1 H), 6.4 (m, 2 H), 7.4 (d, 1 H, J = 1 Hz); ^{19}F NMR (CCl_4) δ −114.0 (dd, J_{FF} = 264 Hz, J_{HF} = 9 Hz), −121.8 (dd, J_{FF} = 263 Hz, J_{HF} = 14 Hz); IR ($CDCl_3$) (cm^{-1}) 3580, 2980, 1760, 1150.

Perfluoro-Substituted Carbinol Preparation.[19] **1-Phenylperfluorooctan-1-ol, 22.** Perfluorooctyl iodide (3.11 g, 5.70 mmol) in ether (60 mL) was cooled to −70 °C (internal temperature). An ether solution of phenylmagnesium bromide (5.70 mmol) was then added to the iodide at a rate that maintained an internal temperature below −60 °C. Upon complete addition of the Grignard solution, the mixture was stirred for 15 min and then cooled to −70 °C (internal). Benzaldehyde (1.21 g, 1.16 mL, 11.4 mmol) was then added dropwise (neat), and the mixture stirred for 15 min at −70 °C before being gradually warmed to room temperature over a 1-h time period. The reaction was quenched with 50 mL of 5% aqueous hydrochloric acid, the layers were separated, and the aqueous layer was then extracted with ether (3 × 40 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was then removed under reduced pressure. The crude product was purified by recrystallization from pentane: 60%; mp 67–68 °C (uncorrected); ^{1}H NMR ($CDCl_3$) δ 5.2 (m, 1 H), 7.4 (s, 5 H); ^{19}F NMR ($CDCl_3$) δ −81.2 (t, J_{FF} = 10 Hz), −116.2, −126.8 (d, J_{HF} = 285 Hz), −121.5, −122.2, −123.5, −126.5; IR ($CDCl_3$) (cm^{-1}) 3520, 3060, 1225, 1150.

Dess–Martin Periodinane[15] Oxidation: General Procedure. The fluoro carbinol was added to a 0.16 M solution of the Dess–Martin (DM) reagent in methylene chloride, and the mixture was stirred at room temperature for 3 h. A typical reaction employed 0.79 mmol of the fluoro carbinol and 2.92 mmol of the oxidant. The reaction mixture was then diluted with 20 mL of ether and poured into a 0.26 M solution of sodium thiosulfate in saturated aqueous sodium bicarbonate. The volume of the thiosulfate solution was calculated by using a 7-fold excess of $Na_2S_2O_3$ to DM, typically 60 mL. The layers were then separated, and the organic phase was washed sequentially with saturated aqueous sodium bicarbonate (2 × 25 mL) and water (2 × 25 mL). The combined aqueous washes were then back extracted with ether (2 × 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered, and the solvent was then removed under reduced pressure.

1,1,1-Trifluoro-3-phenylpropan-2-one, 1:[27] obtained from **2** in 95% yield as pure material; ^{1}H NMR (CCl_4) δ 3.9 (s, 2 H), 7.3 (m, 5 H); ^{19}F NMR (CCl_4) δ −79.2 (s); IR (neat) (cm^{-1}) 3060, 1765, 1150.

1,1,1-Trifluoroundecan-2-one, 3b: obtained from **3** in 93% yield after Kugelrohr distillation (72–74 °C/5 mmHg); ^{1}H NMR (CCl_4) δ 0.8 (t, 3 H, J = 6 Hz), 1.2 (m, 14 H), 2.6 (t, 2 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −80.1 (s); IR (neat) (cm^{-1}) 2960, 1760, 1150. Anal. Calcd for $C_{11}H_{19}F_3O$: C, 58.91; H, 8.54. Found: C, 58.80; H, 8.58.

Trifluoromethyl cyclohexyl ketone,[28] **4b:** obtained from **4** in 75% yield as pure material; ^{1}H NMR (CCl_4) δ 1.5 (m, 10 H), 3.5 (m, 1 H); ^{19}F NMR (CCl_4) δ −78.8 (s); IR (neat) (cm^{-1}) 2960, 1755, 1150.

Trifluoromethyl phenyl ketone,[31] **5b:** obtained from **5** in 76% yield as pure material; ^{1}H NMR (CCl_4) δ 7.4 (m, 5 H); ^{19}F NMR (CCl_4) δ −72.8 (s).

5,5-Dimethyl-4-phenyl-1,1,1-trifluorohex-3-en-2-one,[30] **6b:** obtained from **6** in 85% yield as pure material; ^{1}H NMR (CCl_4) δ 1.2 (s, 9 H), 6.2 (s, 1 H), 7.2 (m, 5 H); ^{19}F NMR (CCl_4) δ −79.8 (s); IR (neat) (cm^{-1}) 2940, 1710, 1570, 1150. Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.61; H, 5.90. Found: C, 65.64; H, 5.93.

4-Phenyl-1,1,1-trifluorobut-3-yn-2-one,[32] **7b:** obtained from **7** in 90% yield as pure material: ^{1}H NMR (CCl_4) δ 7.5 (m, 5 H); ^{19}F NMR (CCl_4) δ −79.0 (s); IR (neat) (cm^{-1}) 2910, 2200, 1695, 1150. Anal. Calcd for $C_{10}H_5F_3O$: C, 64.10; H, 8.07. Found: C, 64.18; H, 8.10.

Ethyl 2-fluoro-3-oxooctanoate, 8b: obtained from **8** in 90% yield as pure material; ^{1}H NMR (CCl_4) δ 0.9 (t, 3 H, J = 6 Hz), 1.3 (t, 3 H, J = 6 Hz), 1.3 (m, 6 H), 2.5 (m, 2 H), 4.3 (q, 2 H, J = 6 Hz), 4.95 (d, 1 H, J = 48 Hz); ^{19}F NMR (CCl_4) δ −196.2 (d, J_{HF} = 50 Hz). Anal. Calcd for $C_{10}H_{17}FO_3$: C, 58.81; H, 8.39. Found: C, 58.88; H, 8.39.

Ethyl 3-cyclohexyl-2-fluoro-3-oxopropanoate, 9b: obtained from **9** in 87% yield as pure material; ^{1}H NMR (CCl_4) δ 1.3 (m, 7 H), 1.9 (m, 6 H), 2.8 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz), 5.1 (d, 1 H, J = 50 Hz); ^{19}F NMR (CCl_4) δ −196.0 (d, J_{HF} = 49 Hz); IR ($CDCl_3$) (cm^{-1}) 2970, 1770, 1740, 1130. Anal. Calcd for $C_{11}H_{17}FO_3$: C, 61.09; H, 7.93. Found: C, 60.98; H, 7.98.

Ethyl 4,4-dimethyl-2-fluoro-3-oxopentanoate, 10b: obtained from **10** in 76% yield as pure material; ^{1}H NMR (CCl_4) δ 1.1 (s, 9 H), 1.2 (t, 3 H, J = 7 Hz), 4.3 (q, 2 H, J = 7 Hz), 5.3 (d, 1 H, J = 50 Hz); ^{19}F NMR (CCl_4) δ −192.2 (d, J_{HF} = 50 Hz); IR ($CDCl_3$) (cm^{-1}) 2980, 1760, 1720, 1100. Anal. Calcd for $C_9H_{15}FO_3$: C, 58.63; H, 7.95. Found: C, 56.80; H, 7.96.

Ethyl 2-fluoro-3-oxo-3-phenylpropanoate, 11b: obtained from **11** in 82% yield as pure material; ^{1}H NMR (CCl_4) δ 1.3 (t, 3 H, J = 6 Hz), 4.2 (q, 2 H, J = 6 Hz), 5.6 (d, 1 H, J = 50 Hz), 7.4 (t, 3 H, J = 6 Hz), 8.1 (d, 2 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −189.8 (d, J_{HF} = 48 Hz); IR (neat) (cm^{-1}) 2940, 1745, 1705, 1130. Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.28. Found: C, 62.72; H, 5.36.

Ethyl 2-fluoro-3-oxo-5-phenylpent-4-enoate, 12b: obtained from **12** in 80% yield as pure material: ^{1}H NMR (CCl_4) δ 1.3 (t, 3 H, J = 8 Hz), 4.3 (q, 2 H, J = 8 Hz), 5.3 (d, 1 H, J = 50 Hz), 6.95 (d, 1 H, J = 2 Hz), 7.2 (d, 1 H), 7.5 (m, 5 H); ^{19}F NMR (CCl_4) δ −195.0 (d, J_{HF} = 49 Hz); IR ($CDCl_3$) (cm^{-1}) 2990, 1750, 1695, 1130. Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 65.95; H, 5.62.

Ethyl 2,2-difluoro-3-oxooctanoate, 13b: obtained from **13** in 79% yield as pure material; ^{1}H NMR (CCl_4) δ 0.9 (t, 3 H, J = 6 Hz), 1.4 (m, 9 H), 2.7 (t, 2 H, J = 6 Hz), 4.4 (q, 2 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −114.6 (s); IR ($CDCl_3$) (cm^{-1}) 2940, 1765, 1740, 1150. Anal. Calcd for $C_{10}H_{16}F_2O_3$: C, 54.04; H, 7.26. Found: C, 54.13; H, 7.26.

Ethyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate, 14b: obtained from **14** in 86% yield as pure material; ^{1}H NMR (CCl_4) δ 1.3 (m, 7 H), 1.9 (m, 6 H), 2.9 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz); ^{19}F NMR (CCl_4) δ −114.0 (s); IR ($CDCl_3$) (cm^{-1}) 2940, 1770, 1730, 1150. Anal. Calcd for $C_{11}H_{16}F_2O_3$: C, 56.40; H, 6.89. Found: C, 56.37; H, 6.90.

Ethyl 2,2-difluoro-4,4-dimethyl-3-oxopentanoate, 15b: obtained from **15** in 78% yield as pure material; ^{1}H NMR (CCl_4) δ 1.3 (s, 9 H), 1.4 (t, 3 H, J = 6 Hz), 4.3 (q, 2 H, J = 6 Hz); ^{19}F

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NMR (CCl_4) δ −108.8 (s); IR ($CDCl_3$) (cm^{-1}) 2980, 1770, 1720, 1150. Anal. Calcd for $C_9H_{14}F_2O_3$: C, 51.92; H, 6.78. Found: C, 52.03; H, 6.79.

Ethyl 2,2-difluoro-3-oxo-5-phenylpentanoate, 16b: obtained from **16** in 90% yield as pure material; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 6 Hz), 3.0 (m, 4 H), 4.3 (q, 2 H, J = 6 Hz), 7.3 (s, 5 H); ^{19}F NMR (CCl_4) δ −115.4 (s); IR ($CDCl_3$) (cm^{-1}) 2980, 1770, 1740, 1150. Anal. Calcd for $C_{13}H_{14}F_2O_3$: C, 60.93; H, 5.51. Found: C, 60.70; H, 5.61.

Ethyl 2,2-difluoro-3-oxo-5-phenylpent-4-enoate, 17b: obtained from **17** in 79% yield as pure material; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 8 Hz), 4.3 (q, 2 H, J = 8 Hz), 7.1 (dd, 1 H, J = 15 Hz and J = 1 Hz), 7.5 (m, 5 H), 7.9 (d, 1 H, J = 15 Hz); ^{19}F NMR (CCl_4) δ −114.5 (s); IR ($CDCl_3$) (cm^{-1}) 2980, 1770, 1700, 1150. Anal. Calcd for $C_{13}H_{12}F_2O_3$: C, 61.42; H, 4.76. Found: C, 61.52; H, 4.79.

Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 18b: obtained from **18** in 85% yield after purification by flash chromatography (SiO_2, 4% ethyl acetate/hexane); ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 7 Hz), 4.3 (q, 2 H, J = 7 Hz), 7.4 (t, 3 H, J = 6 Hz), 8.1 (d, 2 H, J = 6 Hz); ^{19}F NMR (CCl_4) δ −108.2 (s); IR ($CDCl_3$) (cm^{-1}) 2995, 1770, 1705, 1150. Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 57.98, H, 4.43.

Ethyl 2,2-difluoro-3-oxo-3-(2-pyridyl)propanoate, 19b: obtained from **19** in 80% yield as pure material; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 7 Hz), 4.3 (q, 2 H, J = 7 Hz), 7.6 (m, 1 H), 8.1 (m, 2 H), 8.7 (d, 1 H, J = 4 Hz); ^{19}F NMR (CCl_4) δ −113.2 (s); IR (neat) (cm^{-1}) 3000, 1780, 1740, 1150. Anal. Calcd for $C_{10}H_9F_2NO_3$: C, 52.40; H, 3.96. Found: C, 52.32; H, 4.00.

Ethyl 2,2-difluoro-3-oxo-3-(2-thienyl)propanoate, 20b: obtained from **20** in 95% yield as pure material; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 6 Hz), 4.3 (q, 2 H, J = 6 Hz), 7.2 (t, 1 H, J = 4 Hz), 7.8 (d, 1 H, J = 4 Hz), 8.1 (d, 1 H, J = 1 Hz); ^{19}F NMR (CCl_4) δ −109.0 (s); IR (neat) (cm^{-1}) 3000, 1770, 1680, 1150. Anal. Calcd for $C_9H_8F_2O_3S$: C, 46.15; H, 3.44. Found: C, 45.04; H, 3.39.

Ethyl 2,2-difluoro-3-(2-furyl)-3-oxopropanoate, 21b: obtained from **21** in 91% yield as pure material; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, J = 6 Hz), 4.3 (q, 2 H, J = 6 Hz), 6.6 (dd, 1 H, J = 2 Hz and J = 1 Hz), 7.4 (d, 1 H, J = 2 Hz), 7.7 (s, 1 H); ^{19}F NMR (CCl_4) δ −111.0 (s); IR ($CDCl_3$) (cm^{-1}) 2980, 1770, 1690, 1150. Anal. Calcd for $C_9H_8F_2O_4$: C, 49.55; H, 3.70. Found: C, 49.45; H, 3.70.

Perfluorooctyl phenyl ketone, 23: obtained from **22** in 86% yield as pure material; ^1H NMR (C_3D_6O) δ 7.6 (m, 3 H), 8.1 (m, 2 H); ^{19}F NMR (C_3D_6O) δ −82.0 (t, J_{FF} = 10 Hz), −113.5 (s), −121.5, −122.8, −123.5, −127.0; IR (neat) (cm^{-1}) 3080, 1710, 1200. Anal. Calcd for $C_{15}H_5F_{17}O$: C, 34.37; H, 0.96. Found: C, 34.51; H, 1.04.

α-Thio-Substituted Fluoro Carbinols: Preparation and Oxidations. 3-(Octylthio)-1,1,1-trifluoropropan-2-ol, 25: prepared from 3-(octylthio)-1,1,1-trifluoropropan-2-one[20,25] by LAH reduction (as described for the preparation of **2**) in 89% yield; ^1H NMR (CCl_4) δ 0.90 (t, 3 H, J = 6 Hz), 1.3 (br m, 12 H), 2.5 (t, 2 H, J = 6 Hz), 2.8 (d, 2, H, J = 3 Hz), 3.4 (m, 1 H), 4.8 (br s, 1 H); ^{19}F NMR (CCl_4) δ −80.1 (d, J_{HF} = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.81, 22.46, 28.59, 28.95, 29.34, 31.63, 32.46, 68.75 (q, J_{CF} = 31 Hz), 124.3 (q, J_{CF} = 282 Hz); IR (neat) (cm^{-1}) 3430, 2940, 1150. Anal. Calcd for $C_{11}H_{21}F_3OS$: C, 51.14; H, 8.19 Found: C, 51.28; H, 8.22.

Attempted Oxidation of 25, Preparation of 29. The modified periodinane oxidant **28** was prepared by adding dry *tert*-butyl alcohol (159.2 mg, 0.21 mL, 2.15 mmol) to a suspension of the DM reagent (0.911 g, 2.15 mmol) in 14 mL of dry CH_2Cl_2 at room temperature. After the mixture was stirred for 25 min, alcohol **25** (0.150 g, 0.58 mmol) was then added, and the heterogeneous mixture was stirred for 3 h. The reaction mixture was then worked up as described above for the general oxidation procedure.

Periodinane 28: ^1H NMR ($CDCl_3$) δ 1.6 (s, 9 H), 2.0 (s, 6 H), 7.8 (t, 1 H, J = 8 Hz), 8.0 (t, 1 H, J = 8 Hz), 8.2 (d, 1 H, J = 8 Hz), 8.3 (d, 1 H, J = 8 Hz).

Hemiketal 29: ^1H NMR (CCl_4) δ 0.8 (m, 3 H), 1.3 (12 H), 1.6 (s, 9 H), 2.8 (m, 4 H), 6.1 (br, 1 H, D_2O exchangeable); ^{19}F NMR (CCl_4) δ −76.7 (s) (ketone), −84.0 (s) (hemiketal).

3-(Phenylthio)-1,1,1-trifluoropropan-2-ol, 31:[24] prepared by LAH reduction of 3-(phenylthio)-1,1,1-trifluoropropan-2-one (**32**)[20,24] as described for the preparation of **2**; ^1H NMR (CCl_4) δ 3.0 (m, 1 H), 3.2 (d, 2 H, J = 3 Hz), 3.9 (br s, 1 H), 7.35 (m, 5 H); ^{19}F NMR (CCl_4) δ −80.0 (d, J_{HF} = 4.5 Hz); IR (neat) (cm^{-1}) 3440, 3080, 1150. Anal. Calcd for $C_9H_9F_3OS$: C, 48.64; H, 4.08. Found: C, 48.56; H, 4.10.

3-(Phenylthio)-1,1,1-trifluoropropan-2-one, 32:[24] obtained from **31** by using the DM oxidation procedure in 96% yield as pure material; ^{19}F NMR (CCl_4) δ −77.5 (s).

3-(Octylthio)-1,1,1-trifluorobutan-2-ol, 33: prepared by LAH reduction of 3-(octylthio)-1,1,1-trifluorobutan-2-one (**34**)[25] as described above: ^1H NMR (CCl_4) δ 0.90 (t, 3 H, J = 6 Hz), 1.3 (m, 12 H), 1.5 (d, 3 H, J = 6 Hz), 2.5 (t, 2 H, J = 6 Hz), 3.1 (s, 1 H), 3.3 (m, 1 H), 3.7 (m, 1 H); ^{19}F NMR (CCl_4) δ −77.2 (d, J_{HF} = 6.0 Hz), −76.8 (d, J_{HF} = 7.1 Hz) (mixture of erythro/threo isomers); IR (neat) (cm^{-1}) 3460, 2940, 1150. Anal. Calcd for $C_{12}H_{23}F_3OS$: C, 52.91; H, 8.51. Found: C, 53.01; H, 8.54.

3-(Octylthio)-1,1,1-trifluorobutan-2-one, 34:[25] obtained from **33** by using the DM oxidation procedure in 79% yield as pure material: ^{19}F NMR (CCl_4) δ −75.8 (s).

Acknowledgment. We would like to thank the United States Department of Agriculture (Grant 87-CRCR-1-2417) and the Herman Frasch Foundation (Grant 0145-HF) for financial support.