Hz, 2 H); IR (neat) 3300 (O–H) cm^{-1}.

2,6-Dimethyl-2,3,8-octanetriol (5): ^1H NMR δ 3.11 (t, J = 5.7 Hz, 2 H), 2.91–2.71 (m, 1 H), 1.45–1.07 (m, 7 H), 1.05 (s, 3 H), 0.95 (s, 3 H), 0.78 (d, J = 5.1 Hz, 3 H); IR (neat) 3300 (O–H) cm^{-1}.

Cholestane-3,5,6-triol (6) (Entry 6, Table I). A reaction mixture consisting of cholesterol (1 mmol), $K_3Fe(CN)_6$ (10 mmol), K_2CO_3 (10 mmol), and OsO_4 (0.05 equiv) all dissolved in *tert*-butyl alchol (30 mL) and water (30 mL) was stirred for 24 h at 40 °C. After workup as above the residue was purified by column chromatograpy (silica gel, ether–acetone, 5:1) to give **6** in 19% yield: ^1H NMR (400 MHz, pyridine-d_5) δ 4.72 (tt, J = 12 and 6 Hz, 3α-H), 4.00 (dd, J = 12 and 4 Hz, 6-H), 3.02 (dd, J = 12 and 4 Hz, 4α-H), and 2.11 (td, J = 12 and 2 Hz, 4β-H);[26] IR (KBr) 3300 (O–H) cm^{-1}.

Influence of the Amine on the Oxidation of Cholesterol. The procedure was the same as that described above except the added amine (1 mmol) to the reaction mixture (see Table II).

Qualitative Kinetic Studies of the Vicinal Hydroxylation of 1-Decene in the Presence of Quinuclidine and DABCO. To each of *tert*-butyl alcohol–water (1:1 v/v, 40 mL), which contains 1-decene (0.281 g, 2 mmol), $K_3Fe(CN)_6$ (1.980 g, 6 mmol), K_2CO_3 (0.830 g, 6 mmol), and undecane (0.100 g, as an internal standard), was added quinuclidine (0.0556 g, 0.5 mmol), DABCO (0.0560 g, 0.5 mmol), or none (a standard solution). Initiation of the hydroxylation was brought about by mixing each solution with the OsO_4 solution (0.5 mL, 0.0125 equiv). The reaction mixture was kept at 25 ± 1 °C. Progress of the reaction was monitored by the decrease of 1-decene (vs undecane) in a given intervals (10 min) by GLC analysis. The required reaction times at 50% conversion were 30 min (quinuclidine), 50 min (DABCO), and 390 min (no added amine), respectively.

Registry No. 1, 27607-33-6; 2, 4422-05-3; 3, 17131-14-5; 4, 1119-86-4; 5, 31558-25-5; 6, 35089-25-9; DABCO, 280-57-9; $PhCH_2CH{=}CH_2$, 300-57-2; $H_2C{=}CH(CH_2)_7CH_3$, 872-05-9; OsO_4, 20816-12-0; $K_3Fe(CN)_6$, 13746-66-2; cyclooctene, 931-88-4; cyclododecene, 1501-82-2; 3,7-dimethyl-6-octenol, 106-22-9; cholesterol, 57-88-5; quinuclidine, 100-76-5.

(26) ^1H NMR data were exactly identical with the reported data: Fujimoto, Y.; Yamada, T.; Ikekawa, N. *Chem. Pharm. Bull.* **1985**, *33*, 3129. We thank Mr. H. Yamada of this Department for the measurement of 400-MHz NMR spectrum.

Difluorination of Esters. Preparation of α,α-Difluoro Ethers

William H. Bunnelle,* Bradley R. McKinnis, and B. A. Narayanan

Department of Chemistry, University of Missouri—Columbia, Columbia, Missouri 65211

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Due to the extraordinary biological, physical, and chemical properties of organofluorine compounds,[1] methods for the tactical placement of fluorine into organic structures are of considerable interest. Since many of the available fluorinating agents are difficult to handle and/or require specialized apparatus, much of organofluorine chemistry remains outside the mainstream of synthetic methodology. The development and subsequent commercial availability of diethylaminosulfur trifluoride (DAST)[2] and its relatives has opened the field of organic fluorination to the general synthetic community, since these materials can be handled using standard techniques and apparatus.

A particularly useful transformation effected by DAST is the geminal difluorination of aldehydes and ketones under mild conditions. An analogous reaction with esters would provide easy access to α,α-difluoro ethers, but DAST does not react readily with esters. The more reactive sulfur tetrafluoride converts certain perfluorinated esters to the corresponding ethers, but hydrocarbon esters are cleaved to trifluoromethyl species.[3] The conversion of esters to α,α-difluoro ethers has been accomplished with chlorine monofluoride,[4] but overfluorination interferes, and ClF is an inconvenient reagent for general use. We describe here a mild, efficient, and general procedure for the geminal difluorination of esters.

We reasoned that the nonreactivity of esters toward DAST was due to the lowered electrophilicity of the carbonyl system which inhibits transfer of nucleophilic fluorine. Thioesters are much more electrophilic than are esters; moreover, fluorodesulfurization has ample precedent.[5] Indeed, we have found that thione esters react readily with DAST under mild conditions to provide cleanly and in good yield the corresponding α,α-difluoro ethers. The results are gathered in Table I.

The thioesters were prepared from the carboxylic esters using the Lawesson[6] reagent in refluxing toluene (see table for reaction time). Best results were obtained with material prepared according to the reported procedure[7] and stored in a dessicator. In several cases, a small amount of the starting material remained even after prolonged reflux, presumably due to decomposition of the thionating agent under the reaction conditions. Since large excesses of Lawesson reagent did not improve the conversion enough to justify the increased effort necessary for purification of the thione esters, the reactions were run with 1 mol (2 equiv) of Lawesson reagent per mole of ester. After the prescribed reaction period, any unreacted ester was removed from the less polar thioester by flash chromatography. In the case of 2-naphthyl acetate (entry 8), the lone enol ester studied, the conversion was low even after prolonged reflux and could not be improved by addition of fresh Lawesson reagent. Nevertheless, the reaction is clean, and the unconsumed starting material could be recovered efficiently. We made no special effort to optimize the conditions for this reaction. For the THP-protected ethyl β-hydroxybutyrate (entry 10), no thione ester was obtained. Instead, the starting material decomposed slowly to unidentified products. Similar difficulty in preparing thioesters when other oxygen-containing functional groups are present has been noted previously.[8] For some of the esters, notably α-benzyl-γ-butyrolactone (entry 9) and, to a lesser extent, (trimethylsilyl)methyl cinnamate (entry 7), thionation is accompanied by partial rearrangement to the thiol ester. Subsequent thionation then leads to the corresponding dithioester as a major side product, accounting for nearly one quarter of the reaction

(1) (a) *Preparation, Properties, and Industrial Applications of Organofluorine Compounds*; Banks, R. E., Ed.; Ellis Horwood, Ltd.: West Sussex, 1982. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.

(2) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Hudlicky, M. *Org. React.* **1988**, *35*, 513.

(3) Wang, C. J. *Org. React.* **1985**, *34*, 319.

(4) Boguslavskaya, L. S.; Panteleeva, I. Y.; Chuvatkin, N. N. *J. Org. Chem. USSR* **1982**, *18*, 198.

(5) (a) Harder, R. J.; Smith, W. C. *J. Org. Chem.* **1961**, *83*, 3422. (b) Yagupol'skii, Y. L.; Kerzhner, B. K.; Yagupol'skii, L. M. *J. Org. Chem. USSR* **1976**, *12*, 2148. (c) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787. (d) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1976**, *41*, 3107. (e) Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.

(6) (a) Pederson, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S.-O. *Bull. Chem. Soc. Belg.* **1978**, *87*, 293. (b) Cava, M. P.; Levinson, M. L. *Tetrahedron* **1985**, *41*, 5061.

(7) Thomson, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.

(8) Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831.

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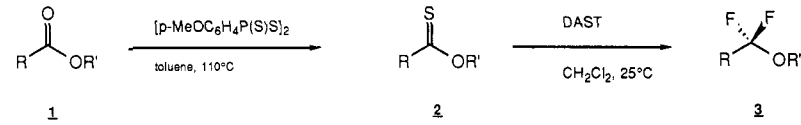
Table I. Conversion of Esters to Difluoro Ethers



1 2 3

			thionation			fluorination					
entry	R	R′		time, h	yield, %		yield, %	bp, °C (Torr)	m/e or anal. (calcd)	δ CF_2, ppm	$^1J_{C-F}$, Hz
1	n-C_7H_{15}	Me	**2a**	36	72	**3a**	77	59–60 (108)	160.1264 (160.1264)[a]	125.9	263
2	cyclohexyl	Me	**2b**	26	74	**3b**	81	45–46 (108)	164.1013 (164.1002)	126.5	264
3	1-adamantyl	Me	**2c**	34	88	**3c**	68	48–51 (0.35)	C, 66.64; H, 8.39 (C, 66.31; H, 8.43)	127.2	266
4	Ph	Me	**2d**	26	80	**3d**	53	50–51 (109)	158.0543 (158.0538)	126.5	264
5	PhCH=CH	Et	**2e**	22	81	**3e**	53	66–67 (19)	198.0856 (198.0844)	122.2	252
6	Ph	$CH_2Si(Me)_3$	**2f**	36	76	**3f**	81	36–37 (0.45)	127.0359 (127.0359)[b]	123.2	256
7	PhCH=CH	$CH_2Si(Me)_3$	**2g**	24	72	**3g**	74	63–64 (27)	256.1095 (256.1071)	122.5	253
8	Me	2-naphthyl	**2h**	38	29	**3h**	72	54–55 (0.30)	208.0700 (208.0711)	124.5	262
9	α-benzyl-γ-butyrolactone		**2i**	12	71[c]	**3i**	<10	–	–	–	–
10	$CH_3CH(OTHP)CH_2$	Et	–	20	0	–	–	–	–	–	–

[a] M − HF. [b] M − $TMSCH_2O$. [c] A 23% yield of the corresponding dithiolactone accompanies this product.

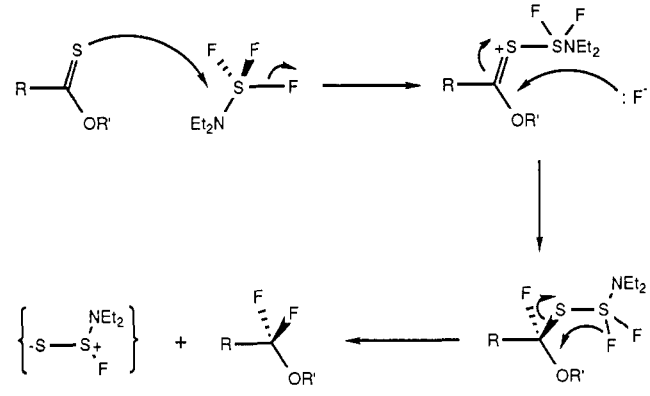
in entry 9. This material, too, was easily separated from the desired thione ester by chromatography.

Each of the thioesters thus obtained was smoothly converted to the corresponding α,α-difluoro ether on treatment with DAST in dichloromethane at 25 °C. Preparative-scale reactions were carried out using 2 mol equiv of DAST per mole of thioester; subsequent work has shown that nearly complete consumption of thioester is effected with 1 equiv of DAST. The reactions were complete within 6 h, and no other volatile products were observed in significant amounts. The difluorinated ethers were obtained in good purity after bulb-to-bulb distillation of the crude product. The smaller isolated yields of some of the fluorinated ethers (e.g., entry 3) are a consequence of their relatively high volatility and reflect losses during distillation rather than inefficient reaction. Of particular interest is the observation that the (trimethylsilyl)methyl esters[9] (entries 6 and 7) carry through the process with the silyl group intact. Unfortunately, the method does not appear to work well with lactones (entry 9). In this case, the thiolactone reacts rapidly with DAST to give a complex mixture of products. A small amount (<10%) of the cyclic difluoro ether was tentatively identified on the basis of GC–MS, but we were unable to obtain enough pure material to assure its characterization. The reaction was monitored by low-temperature NMR; even at −40 °C, consumption of the thiolactone is rapid, but the difluoro ether is, at best, a minor component.

The α,α-difluoro ethers are reasonably stable and can be kept for months at 0 °C in the absence of moisture. Hydrolysis returns the starting ester, and some of the ethers show a propensity for slow decomposition at ambient temperature, with apparent loss of HF (evidenced by etching of glass vials).

We have not explored the mechanism of the geminal difluorination, but assume that it is analogous to that proposed for aldehydes and ketones (Scheme I). The enhanced Lewis basicity of the thione toward DAST complexation, and the consequent increased electrophilicity at the thioacyl carbon, facilitating fluoride transfer, are then the key features of this process.[10] Speculation beyond this stage is premature, since we have not yet identified the sulfur-containing byproduct(s) of the reaction.[11]

Scheme I



Nevertheless, the overall process constitutes a selective and convenient method for the fluorination of esters and fills a void in organofluorine methodology.

Experimental Section[12]

The following general procedures were used. Some of the relevant properties of the new compounds have been listed in the

(9) The preparation of these compounds will be reported in due course.

(10) A similar mechanism has been proposed for the fluorination of thiones by SF_4. See ref 5a.

(11) The sulfur-containing byproduct is relatively nonvolatile and can be isolated by pumping away the solvent and difluoro ether. IR shows evidence for S–F bond (ν 716 cm^{-1}). The ^1H NMR spectrum of this material has signals for the diethylamino group. The material is hydrolytically unstable, and hydrolysis causes disappearance of the IR band at 716 cm^{-1}. From the proposed mechanism, one would predict a structure $Et_2NS(F)S$, analogous to the more stable isomer of S_2F_2, or the rearranged structure Et_2NSSF, as found for other S_2X_2. See: Seel, F. *Adv. Inorg. Chem. Radiochem.* **1974**, *16*, 297.

(12) Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Listed "boiling points" are the air bath temperatures for bulb-tobulb distillation at the specified pressure. ^1H NMR spectra of solutions in $CDCl_3$ were obtained at 90 MHz on a JEOL FX90Q spectrometer. Chemical shifts are referenced to internal tetramethylsilane. Proton-decoupled ^{13}C NMR spectra were taken at 22.5 MHz on the same instrument, and chemical shifts are referenced to the center line of the $CDCl_3$ multiplet (77.0 ppm). IR spectra of neat liquids between NaCl plates were recorded on a Nicolet 20 DXB FTIR; selected bands of interest are reported. Mass spectra were obtained using an HP 5790B mass-selective detector interfaced with an HP 5890 gas chromatograph. Elemental analyses were determined by Desert Analytics, Tucson, AZ. Exact mass spectra were obtained on a Kratos MS 25 spectrometer. Toluene was dried by distillation over sodium metal and stored over 4-Å molecular sieves. Dichloromethane was distilled over calcium hydride and stored over sieves. The Lawesson reagent was prepared according to the published procedure[7] and stored in a tightly capped bottle in a dessicator. A 1 M stock solution of diethylaminosulfur trifluoride (DAST, Aldrich) in dichloromethane was used for all of the fluorinations—this solution was kept in a sealed Nalgene bottle in a refrigerator. Flash chromatography was performed with Merck Kieselgel 60 (230–400 mesh), eluting with 50–50 (v/v) dichloromethane–petroleum ether.

table. Complete spectral data for characterization is available as supplementary material.

Thioesters. General Procedure. A solution of ester (4.0 mmol) in toluene (15 mL) was placed in a dry, 50-mL round-bottom flask with stir bar and reflux condenser. Lawesson reagent (1.61 g, 4.0 mmol, 2 equiv) was added, and the mixture was stirred at reflux (115 °C oil bath) under nitrogen for the specified reaction time (see table). The reaction mixture was cooled to room temperature and diluted with a 60/40 benzene–petroleum ether solution (35 mL). The precipitated solids were removed by filtration through glass wool, and the reddish-orange filtrate was concentrated at the rotary evaporator. The residue was purified by flash chromatography.

Fluorination. General Procedure. A solution of thioester (1.0 mmol) in dry dichloromethane (5 mL) was placed in a round-bottom flask with stir bar and rubber septum cap. The solution was stirred at room temperature under a nitrogen atmosphere as a solution of DAST in dichloromethane (1 M, 2.0 mL, 2 equiv) was added by syringe. Stirring was continued for 6 h, at which time the reaction mixture was cooled in an ice water bath and quenched by addition of saturated $NaHCO_3$ (15 mL). The organic layer was separated, and the aqueous phase was extracted twice with dichloromethane (5 mL). The combined organic solutions were dried over Na_2SO_4, and the bulk of the solvent was removed by distillation through a Vigreux column at the steam bath. The residual oil was purified by bulb-to-bulb distillation.

Acknowledgment. We are grateful to the University of Missouri Research Council for partial support of this work. The NSF provides partial support of the NMR (PCM-815599) and MS (PCM-8117116) facilities at the University of Missouri—Columbia.

Registry No. 1 (R = n-C_7H_{15}, R′ = Me), 111-11-5; 1 (R = cyclohexyl, R′ = Me), 4630-82-4; 1 (R = 1-adamantyl, R′ = Me), 711-01-3; 1 (R = Ph, R′ = Me), 93-58-3; 1 (R = PhCH=CH, R′ = Et), 103-36-6; 1 (R = Ph, R′ = $CH_2Si(Me)_3$), 17998-87-7; 1 (R = PhCH=CH, R′ = $CH_2Si(Me)_3$), 123933-28-8; 1 (R = Me, R′ = 2-naphthyl), 1523-11-1; 1 (R,R′ = $-CH_2CH_2CH(CH_2Ph)-$), 61129-28-0; 1 (R = $CH_2CH(OTHP)CH_3$, R′ = Et), 104372-23-8; **2a**, 123933-29-9; **2b**, 91923-30-7; **2c**, 123933-30-2; **2d**, 5873-86-9; **2e**, 73818-80-1; **2f**, 123933-31-3; **2g**, 123933-32-4; **2h**, 123933-33-5; **2i**, 105688-51-5; **3a**, 123933-34-6; **3b**, 123933-35-7; **3c**, 123933-36-8; **3d**, 123933-37-9; **3e**, 123933-38-0; **3f**, 123933-39-1; **3g**, 123933-40-4; **3h**, 123933-41-5; **3i**, 123933-42-6; DAST, 38078-09-0; α-benzyl-γ-butyrodithiolactone, 119018-57-4.

Supplementary Material Available: Listings of physical (boiling point or melting point) and spectral (IR, ^1H NMR, ^{13}C NMR, MS) data for compounds **2a-i** and **3a-h** (4 pages). Ordering information is given on any current masthead page.

The Effect of β-Dialkylamino Substitution on Ketone Enolization

Norman E. Pratt and Kim F. Albizati*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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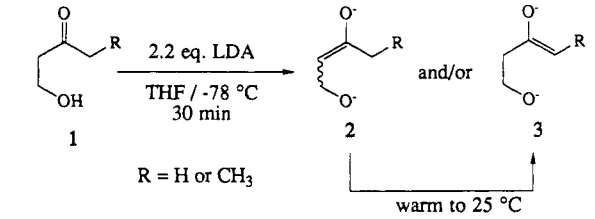
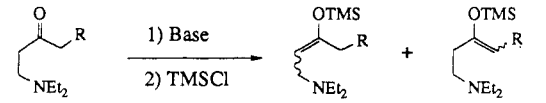
In previous work in these laboratories, we examined the effect of a β-hydroxy group on ketone enolization.[1] It was found that a dianionic species (an "aldolate dianion", **2** or **3**) could be generated when β-hydroxy ketones were treated with more than 2 equiv of a strong base at low temperature. It was determined that the ratio of distal (**3**) to proximal (**2**) enolates was temperature dependent and that the enolate ratios changed with time, indicating an equilibrating species, contrary to conventional ketone enolates. If the enolate was allowed to warm to 25 °C the distal enolate **3** was the preferred, and sometimes exclusive, isomer as indicated by trapping of the resulting enolate mixture with chlorotrimethylsilane (TMSCl). These findings encouraged us to examine other β-heteroatomic groups.



1 2 3

To our knowledge, there has not been a systematic study of the effects of β-amino groups on enolization.[2c] In an effort to gain insight in this area, we have studied the enolizations of *N,N*-diethyl-3-oxobutylamine (**4**) and *N,N*-diethyl-3-oxopentylamine (**5**).

These compounds were prepared by the conjugate addition of diethylamine to the corresponding enone as described by Ross and Levine.[3] The enolates were formed under a variety of conditions and trapped with TMSCl as shown in eq 1. The deprotonations were carried out with



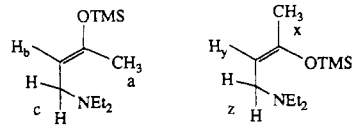
(1)

4 R = H
5 R = CH_3

proximal enol silane
6 R = H
8 R = Me

distal enol silane
7 R = H
9 R = Me

2.4 equiv of base, with the exception of runs employing lithium diisopropylamide (LDA) where only 1.25 equiv was used. In all cases the solution of the amide base was cooled to −78 °C, and the ketone was added as a neat liquid. Three methods were used to study the enolization process. In the first (method A, internal quench[1,4]) the silylating agent was added to the amide bases prior to the addition of the ketone. In this method only 1.25 equiv of TMSCl was used to trap the resulting enolates. Using the classical method (B) the ketone was added to a cooled solution of the base and held for 1 h, after which time 2.4 equiv of TMSCl was added. Method C involved warming the enolate solution (as formed in method B) to 25 °C for 15 min before quenching with TMSCl. The ratios of the resulting enol silane products were determined by capillary gas chromatography and/or by 300-MHz ^1H NMR analysis. The assignment of the *E* and *Z* isomers was made by analysis of ^1H NMR chemical shifts and the relative magnitudes of the allylic and homoallylic coupling constants.[5] For example, in the isomer pair **6E** and **6Z**, the



6E **6Z**

(1) Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1988**, *53*, 5986.

(2) (a) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307. (b) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *Tetrahedron Lett.* **1978**, 2671. (c) McGarvey, G. J.; Hiner, R. N.; Williams, J. M.; Matasubara, Y.; Poarch, J. W. *J. Org. Chem.* **1986**, *51*, 3742. McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matasubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

(3) Ross, N.; Levine, R. *J. Org. Chem.* **1964**, *29*, 2346.

(4) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

0022-3263/90/1955-0770$02.50/0