



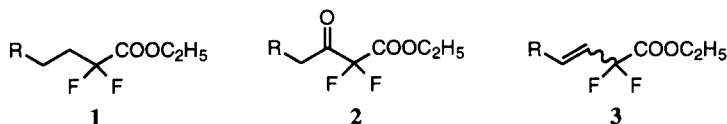
A Novel Synthetic Approach to the Preparation of Various α,α -Difluoroesters

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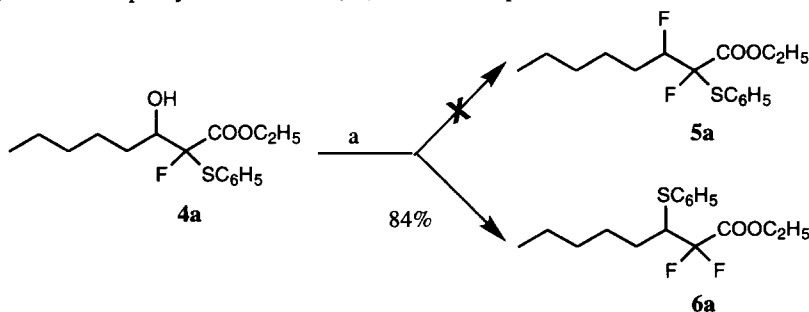
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Abstract : Treatment of readily available α -fluoro- β -hydroxy- α -phenylthioesters **4** with DAST afforded α,α -difluoro- β -phenylthioesters **6** which are of interest to synthesize gem-difluorinated derivatives. Copyright © 1996 Elsevier Science Ltd

Gem-difluorinated derivatives have been widely used as enzyme inhibitors or to modify properties of biologically active products¹. In this publication, we wish to report a synthetic method giving access to α,α -difluoroesters **1**, α,α -difluoro- β -ketoesters **2** or α,α -difluoro- β,γ -unsaturated esters **3**.



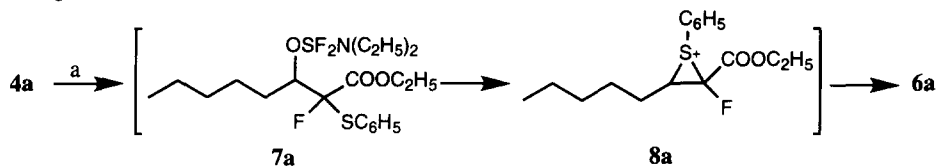
These findings originated from an unexpected reaction of ethyl 2-fluoro-3-hydroxy-2-phenylthiohexanoate (**4a**) with diethylaminosulfur trifluoride (DAST). **4a** treated with 1.5 equivalent of DAST in methylene chloride at -78°C during 30 minutes did not give the expected 2,3-difluoro derivative **5a**², but yielded ethyl 2,2-difluoro-3-phenylthiohexanoate (**6a**)¹² as the sole product (84 %) (scheme 1).



a) DAST (1.5 eq.), CH_2Cl_2 , -78°C , 30min.

Scheme 1

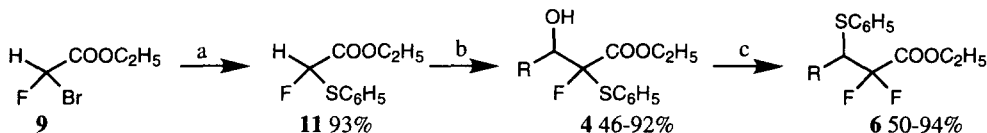
This surprising result can be explained by the participation of the phenylthio group during **4a** reaction with DAST, leading to the episulfonium **8a**³. The fluoride ion added preferentially to the carbon α to the ester, yielding **6a**¹² (scheme 2).



a) DAST (1.5 eq.), CH_2Cl_2 , -78°C , 30min.

Scheme 2

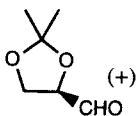
This rearrangement was found to be general for α -fluoro- β -hydroxy- α -phenylthio esters **4** with the exception of ethyl 2-fluoro-3-hydroxy-2-phenylthiohydrocinnamate (**4c**) which gave exclusively the non-rearranged product **5c**¹². The synthetic sequence for the preparation of **6** is simple and gives good yields from commercially available compounds : ethyl bromofluoroacetate (**9**) and aldehydes **10** (scheme 3-Table 1).



a) $\text{C}_2\text{H}_5\text{ONa}$, $\text{C}_2\text{H}_5\text{OH}$, $\text{C}_6\text{H}_5\text{SH}$; b) LDA (1eq.), THF, -78°C ; then RCHO, THF;
c) DAST (1.5eq.), CH_2Cl_2 .

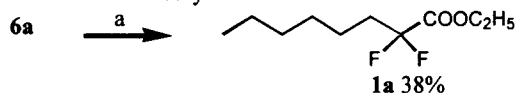
Scheme 3

Table 1

Entry	Aldehyde 10	Alcohol 4 ^c (yield %)	6 (conditions and yield %)
a	$n\text{-C}_5\text{H}_{11}\text{CHO}$	86	-78°C , 30 min, (84)
b	CH_3CHO	52	-78°C , 30 min, (94)
c	$\text{C}_6\text{H}_5\text{CHO}$	71	-78°C , 30 min, (0) ^a
d	$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	18 ^b	-78°C , 60 min, (50)
e	$c\text{-C}_6\text{H}_{11}\text{CHO}$	46	-78°C , 30 min, (81)
f		92	0°C , 180 min, (80)

a) Only ethyl 2,3-difluoro-3-phenyl-2-phenylthiopropionate (**5c**)¹² was isolated (86%). b) The low yield is due to enolization of the aldehyde **10d** which competed with addition on carbonyl. c) Mixture of diastereomers.

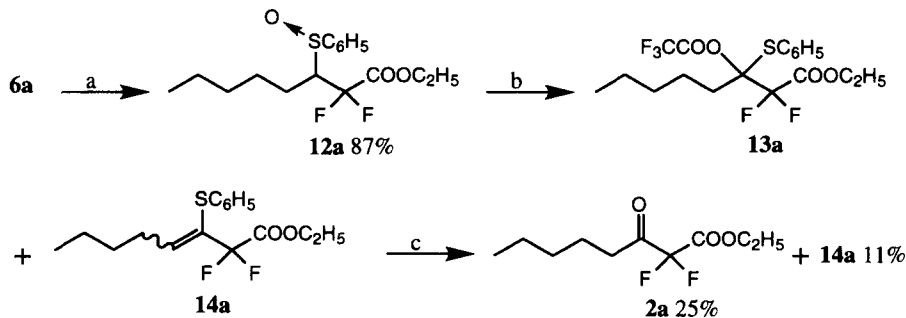
6a desulfurization was carried out using tri-*n*-butyltinhydride in refluxing toluene with a catalytic amount of AIBN⁴ to yield **1a**¹² (Scheme 4). Such derivatives are usually obtained by DAST fluorination of α -ketoester or copperdifluoroacetate alkylation⁶.



a) $n\text{-Bu}_3\text{SnH}$ (1.3 eq.), AIBN (cat.), toluene, reflux 24h.

Scheme 4

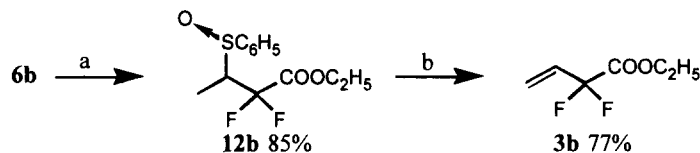
Oxidation of sulfide **6a** with meta-chloroperoxybenzoic acid⁷ gave the sulfoxide **12a**. Pummerer rearrangement on **12a** using trifluoroacetic anhydride with collidine⁸ gave the hemithiotrifluoroacetal **13a** along with vinylthioether **14a**. Treatment of the mixture without isolation by mercuric chloride afforded, after purification, ketoester **2a**¹² (25%) and sulfide **14a** (11%) (Scheme 5). Compounds of type **2** are obtained by Reformatsky reaction of ethyl bromodifluoroacetate with a suitable aldehyde, followed by oxidation⁹ of the obtained alcohol. Thus, the above method in some cases could be a useful alternative to the Reformatsky-oxidation sequence.



a) *m*-CPBA (1eq.), CH_2Cl_2 ; b) $(\text{CF}_3\text{CO})_2\text{O}$ (2eq.), 2,4,6-collidine (2eq.), 0°C , 12h; c) HgCl_2 (1.4eq.), CH_3CN , 0°C , 3h.

Scheme 5

Sulfoxides of type **12** can give access to α,α -difluoro- α,β -unsaturated esters **3**. Thus, pyrolysis of **12b** in a short path distillation apparatus yielded, after elimination of sulfenic acid¹⁰, **3b**¹² (77%) (Scheme 6). This method is an alternative to the available method using the reaction between ethyl copperdifluoroacetate and a vinylic iodide⁶ which requires the use of ethyl difluoroiodoacetate, not readily available¹¹.



a) *m*-CPBA (1eq.), CH_2Cl_2 ; b) Δ 120°C , neat, Kugelrohr distillation.

Scheme 6

REFERENCES AND NOTES

- Filler, R. *J. Fluorine Chemistry* **1986**, *33*, 361-374; Welch, J.T. *Tetrahedron* **1987**, *43*, 3123-3194; Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley ; New York, 1991.
- Hudlicky, M. *Organic Reactions* **1988**, *35*, 513-637.
- Kil'disheva, O.V.; Lin'kova, M.G.; Rasteikiene, L.; Zabelaite, V.; Pociute, N.; Knunyants, I.L. *Dokl Akad. Nauk. SSSR* **1972**, *203*, 1072-1074 ; Brownbridge, P. ; Warren, S. *J.C.S. Perkin I* **1977**, 1131-1141.
- Gutierrez, C.G. ; Summerhays, L.R. *J. Org. Chem.* **1984**, *49*, 5202-5213.
- Erni, B.; Khorana, H.G. *J. Am. Chem. Soc.* **1980**, *102*, 3888-3896 ; Gerskenberger, M.C., Haas, A. *Angew Chem. Int. Ed. Engl.* **1981**, *20*, 647-667.
- Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehava, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103-6106 ; Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Chem. Lett.* **1989**, 389-392.
- Oae, S. *Organic Sulfur Chemistry : Structure and Mechanism*; Doi, J.T. Ed.; CRC Press Inc.; Boca Raton, **1991**; pp 253-254.
- Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881; Arnone, A.; Bravo, P.; Frigerio, M.; Salami, G Viani, F. *Tetrahedron* **1994**, *50*, 13485-13492.
- Peet, N.P.; Burkhart, M.R.; Angelastro, M.R.; Giroux, E.L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394-407.
- Grieco, P.A.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1181-1183; Reutrakul, V.; Rukachaisirikul, V. *Tetrahedron Lett.*, **1983**, *24*, 725-728.
- Kumai, S; Samejima, S.; Munekata, S.; Yamabe, M. *Asahi Garasu Kenkyu Hokoku* **1983**, *33*, 127-133; *Syntheses of Fluoroorganic compounds* ; Knunyants, I.L.; Yakobson G.G. Eds.; Springer-Verlag Berlin; **1985**; pp 63-64.
- All new compounds gave analytical and spectroscopic data in agreement with the assigned structure; **1a** ^{19}F NMR δ (282 MHz, CDCl_3 , C_6F_6) 55.78 (2F, t, $J_{\text{HF}}=15\text{Hz}$); ^1H NMR δ (300 MHz, CDCl_3 , TMS) 0.89 (3H, t, $J_{\text{HH}}=7\text{Hz}$, O-C- CH_3), 1.30-1.55 (8H, m, $\text{H}_{4,5,6,7}$), 2.00-2.10 (2H, m, H_3), 4.32 (2H, q, $J_{\text{HH}}=7\text{Hz}$, O- CH_2 -C); $\text{MNH}_4^+=226$. **2a** ^{19}F NMR δ (282 MHz, CDCl_3 , C_6F_6) 47.88 (2F, s); ^1H NMR δ (300 MHz, CDCl_3 , TMS) 0.88 (3H, t, $J_{\text{HH}}=7\text{Hz}$, H_8), 1.25-1.70 (9H, m, $\text{H}_{5,6,7}$, O-C- CH_3), 2.71 (2H, t, $J_{\text{HH}}=7\text{Hz}$, H_4), 4.34 (2H, q, $J_{\text{HH}}=7\text{Hz}$, O- CH_2 -C); $\text{MNH}_4^+=240$; IR $\nu(\text{C}=\text{O})=1750, 1781\text{ cm}^{-1}$. **3b** ^{19}F NMR δ (282 MHz, CDCl_3 , C_6F_6) 55.94 (2F, d, $J_{\text{HF}}=10\text{Hz}$); ^1H NMR δ (300 MHz, CDCl_3 , TMS) 1.35 (3H, t, $J_{\text{HH}}=7\text{Hz}$), 4.33 (2H, q, $J_{\text{HH}}=7\text{Hz}$, O- CH_2 -C), 5.55-6.20 (3H, m, $\text{H}_{3,4}$); $\text{MNH}_4^+=168$. **5c** ^{19}F NMR δ (282 MHz, CDCl_3 , C_6F_6)-11.7 (1F, dd, $J_{\text{FF}}=19\text{Hz}$, $J_{\text{HF}}=43\text{Hz}$, F_3), 8.85 (1F, t, $J_{\text{HF}}=J_{\text{FF}}=19\text{Hz}$, F_2); ^1H NMR δ (300 MHz, CDCl_3 , TMS) 1.02 (3H, t, $J_{\text{HH}}=7\text{Hz}$, O-C- CH_3), 4.00 (2H, q, $J_{\text{HH}}=7\text{Hz}$, O- CH_2 -C), 6.05 (1H, dd, $J_{\text{HF}}=19\text{Hz}$, $J_{\text{HF}}=43\text{Hz}$, H_3), 7.20-7.65 (10H, m, H aromatic); $\text{MNH}_4^+=340$. **6a** ^{19}F NMR δ (282 MHz, CDCl_3 , C_6F_6), 47.64 (1F, dd, $J_{\text{FF}}=255\text{Hz}$, $J_{\text{HF}}=20\text{Hz}$), 59.84 (1F, dd, $J_{\text{FF}}=255\text{Hz}$, $J_{\text{HF}}=10\text{Hz}$); ^1H NMR δ (300 MHz, CDCl_3 , TMS) 0.90 (3H, $J_{\text{HH}}=7\text{Hz}$, H_8), 1.24 (3H, t, $J_{\text{HH}}=7\text{Hz}$, O-C- CH_3), 1.25-1.40 (4H, m, $\text{H}_{6,7}$), 1.45-1.60 (2H, m, $\text{H}_{4a,5a}$), 1.75-1.95 (2H, m, $\text{H}_{4b,5b}$), 3.45 (1H, ddt, $J_{\text{HF}}=20\text{Hz}$, $J_{\text{HF}}=10\text{Hz}$, $J_{\text{HH}}=10\text{Hz}$, $J_{\text{HH}}=3\text{Hz}$, H_3), 4.05-4.30 (2H, 2m, O- CH_2 -C); $\text{MNH}_4^+=334$.

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