A New Method for the Synthesis of α,α-Difluoro-β-hydroxy Esters through the Enolization of *S*-*tert*-Butyl Difluoroethanethioate

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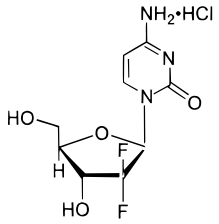
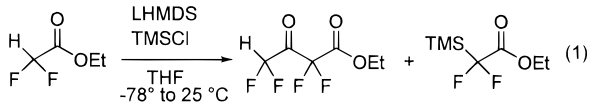
The need for dependable methods to introduce fluorine atoms into organic molecules has grown tremendously as the medicinal chemistry community searches for unique biological activity through substitution of hydrogen atoms with fluorine.[1] For example, 2-deoxy-2,2-difluorocytidine (gemcitabine, **1**), a novel anticancer agent which possesses a geminal difluoromethylene group, has been synthesized through construction of an α,α-difluoro-β-hydroxy ester, which provides the carbohydrate portion of the nucleoside.[2] The geminal difluoromethylene moiety may be obtained via several methods, which include Reformatsky reaction of halodifluoroacetate esters,[3] *gem*-difluoroallylation,[4] difluorovinyl anion additions,[5] intramolecular trapping of *gem*-difluoroalkyl radicals,[6] difluoroketene silyl acetal condensations,[7] and direct fluorination.[8] In the original synthesis of gemcitabine achieved by Hertel and co-workers, a Reformatsky reaction utilizing ethyl bromodifluoroacetate and 2,3-*O*-isopropylidene-D-glyceraldehyde provided the desired difluororibonic ester as a mixture of diastereomers.[2]

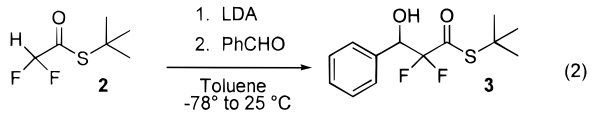


gemcitabine, **1**

We set out to develop a general synthesis of α,α-difluoro-β-hydroxy esters which does not rely upon expensive halodifluoroacetate esters as the fluorine source and which avoids formation of a stoichiometric amount of zinc waste. An aldol condensation utilizing the lithium enolate of ethyl difluoroacetate would meet these criteria, and indeed Easdon has investigated the synthesis of this enolate (eq 1).[9] Unfortunately, this species is not stable and results in formation of a β-keto ester via a self-condensation reaction. In an attempt to form the difluoroketene silyl acetal from the enolate in the presence of chlorotrimethylsilane, carbon silylation was observed along with defluorination of the ester. Given the known differences in electronic structure, acidity, and reactivity of thiolesters versus esters,[10] we decided to investigate the enolization of *S*-*tert*-butyl difluoroethanethioate (**2**) and its subsequent reaction with electrophiles. We also explored the formation and reactivity of difluoroketene *O*,*S*-acetals.



As a means to test the stability and reactivity of the lithium enolate of **2**, its reaction with benzaldehyde was investigated. Accordingly, the desired α,α-difluoro-β-hydroxy ester **3** was obtained in 70% isolated yield by the addition of LDA (1.1 equiv) to a solution of **2** (0.1 M in toluene) at −78 °C followed by addition of benzaldehyde (1.1 equiv) and warming to 25 °C (eq 2). The major byproducts, as determined by ^{19}F NMR spectroscopy of the reaction mixture, were unreacted **2** (5%) and the self-condensation product $HF_2CC(O)CF_2C(O)S$-*t*-Bu (10%).



In order to explore the scope of this reaction, several other electrophiles were screened to afford condensation products **3**−**12** in moderate to good yield (Table 1). Anisaldehyde, hexanal, isobutyraldehyde, and pivalaldehyde gave rise to the expected secondary alcohols **4**−**7**, while acetophenone yielded tertiary alcohol **8**. The double addition product **9** was obtained from benzoyl chloride, presumably through formation of an intermediate ketone upon chloride displacement. Additionally, cyclohex-2-en-1-one reacted via 1,2-addition to form **10**.

An intermediate suitable for the synthesis of gemcitabine was obtained by aldol condensation of **2** with 2,3-*O*-(3-pentylidene)-D-glyceraldehyde (**13**), which afforded compounds **11** and **12** as an 85/15 mixture of diastereomers. The erythro isomer **11** is the major compound, as predicted by the Felkin−Ahn model of asymmetric induction.[11] The relative stereochemistry was assigned by

(1) Taylor, N. F., Ed. *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*, ACS Symposium Series 374; American Chemical Society: Washington, DC, 1988.

(2) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406.

(3) (a) Hallinan, E. A.; Fried, J. *Tetrahedron Lett.* **1984**, *25*, 2301. (b) Burton, D. J.; Easdon, J. C. *J. Fluorine Chem.* **1988**, *38*, 125. (c) Shen, Y.; Qi, Y. *J. Fluorine Chem.* **1994**, *67*, 229. (d) Hanzwa, Y.; Inazawa, K.; Kon, A.; Aoki, H.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 659. (e) Lang, R. W.; Schaub, B. *Tetrahedron Lett.* **1988**, *29*, 2943.

(4) (a) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 1037. (b) Seyferth, D.; Simon, R. M.; Sepeiak, D. J.; Klein, H. *J. Am. Chem. Soc.* **1983**, *105*, 4634. (c) Hiyama, T.; Obayashi, M.; Sawahata, M. *Tetrahedron Lett.* **1983**, *24*, 4113.

(5) (a) Percy, J. *Tetrahedron Lett.* **1990**, *31*, 3931. (b) Bennett, A. J.; Percy, J.; Rock, M. H. *Synlett* **1992**, 483. (c) Ichikawa, J.; Minami, T. *Tetrahedron Lett.* **1992**, *33*, 3779. (d) Ichikawa, J.; Hamada, S.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 337.

(6) (a) Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459. (b) Morikawa, T.; Uejina, M.; Kobayaski, Y.; Taguchi, T. *J. Flourine Chem.* **1993**, *65*, 79. (c) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 4676. (d) Okano, T.; Takakura, N.; Nakano, Y.; Eguchi, S. *Tetrahedron Lett.* **1992**, *33*, 3491.

(7) (a) Greuter, H.; Lang, R. W.; Romann, A. *Tetrahedron Lett.* **1988**, *29*, 3291. (b) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803. (c) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahderon Lett.* **1988**, *29*, 5291. (d) Matsumura, Y.; Fujii, H.; Nakayama, T.; Morizawa, Y.; Yasuda, A. *J. Fluorine Chem.* **1992**, *57*, 203.

(8) (a) Frogier, P. R. T.; Tran, T. T.; Viani, S.; Condom, R.; Guedj, R. *Antiviral Chem. Chemother.* **1994**, *5*, 372. (b) York, C.; Prakash, G. K. S.; Wang, Q.; Olah, G. A. *Synlett* **1994**, 425. (c) Kornilov, A. M.; Sorochinsky, A. E.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1994**, *5*, 1015. (d) Xu, Z.-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Fluorine Chem.* **1992**, *58*, 71. (e) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505.

(9) Easdon, J. C. Ph.D. Thesis, The University of Iowa, Iowa City, IO, 1987.

(10) Suckling, K. E.; Suckling, C. J. *Biological Chemisty: The Molecular Approach to Biological Systems*; Cambridge University Press: Cambridge, England, 1980; pp 76−79. (b) Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186 and references therein.

(11) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eissenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(12) Chou, T. S.; Heath, P. C.; Patterson, L. E.; Poteet, L. M.; Lakin, R. E.; Hunt, A.H. *Synthesis* **1992**, 565.

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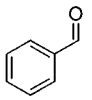
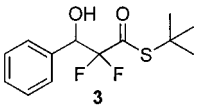
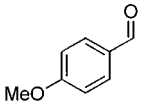
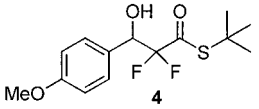
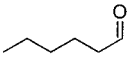
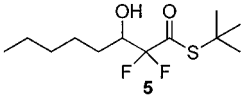
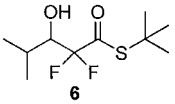
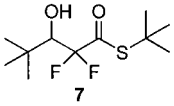
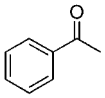
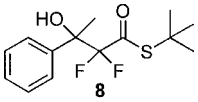
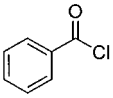
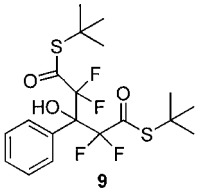
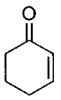
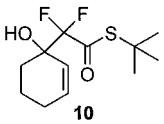
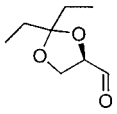
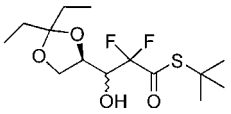
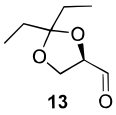
Table 1. Reactions of the Lithium Enolate of 2 with Various Electrophiles

run	substrate	product	yield (%)
1		 **3**	70
2		 **4**	62
3		 **5**	61
4		 **6**	44
5		 **7**	42
6		 **8**	69
7		 **9**	77
8		 **10**	65
9	 **13**	 **11/12** Anti/Syn = 85/15	64

hydrolysis, cyclization, and benzoylation of **11** to give the known gemcitabine intermediate, 2-deoxy-2,2-difluoro-D-*erythro*-pentofuranos-1-ulose 3,5-dibenzoate (**14**).[12]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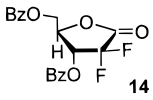
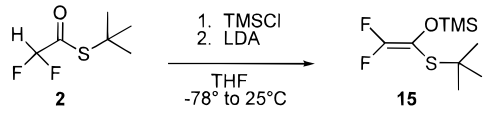
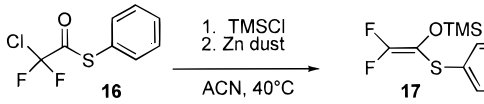

14

Difluoroketene silyl acetal additions to glyceraldehyde derivatives have been reported to proceed with high diastereoselectivities, in contrast to their Reformatsky counterparts.[13] Therefore we desired to synthesize a difluoroketene *O,S*-acetal and investigate its reaction with aldehyde **13**. To this end, thiolester **2** was enolized with LDA in the presence of TMSCl at −78 °C (eq 3). Upon examination of the reaction mixture by ^{19}F NMR spectroscopy, only one product was observed, which has been assigned as acetal **15**.[14] No evidence of carbon silylation or Claisen reaction was detected, which is in contrast with the behavior observed by Easdon for difluoroesters (*vide supra*).


2 **15** (3)

Acetal **15** reacted with aldehyde **13** in the presence of $BF_3{\cdot}OEt_2$ at low temperature to afford **11** and **12** in 74% isolated yield (95/5, erythro/threo). The alcohols were presumably formed as the TMS ethers and were desilylated on workup. The diastereoselectivity observed upon condensation with **13** increased from 85/15 (lithium enolate) to 95/5 (ketene silyl *O,S*-acetal); this trend parallels that observed by Kobayashi for condensations between 2,3-*O*-isopropylidene-D-glyceraldehyde and methyl iododifluoroacetate: 65/35 (Reformatsky reaction); 90/10 (ketene silyl acetal).[13] We ascribe the greater erythro selectivity of the thiolester enolate and acetal to lower reaction temperatures and the steric bulk of the *S*-*tert*-butyl versus methyl ester.

In a search for alternate routes to difluoroketene silyl *O,S*-acetals, we investigated the reduction of *S*-phenyl chlorodifluoroethanethioate (**16**) in the presence of TMSCl. Ester **16** was reacted with zinc dust and TMSCl in CH_3CN at 40 °C to yield a single product, which was identified as difluoroketene silyl *O,S*-acetal (**17**) by ^{19}F NMR spectroscopy and MS data (eq 4).[15] Acetal **17** could be isolated but is extremely hydrolytically sensitive and decomposed over several days at room temperature. Halodifluoro *thiol*ester **16** proved to be a superior precursor to difluoroketene silyl acetals, when compared with halodifluoroesters, due to the absence of side reactions and its ease of reduction. For example, compound **16** undergoes rapid zinc reduction in CH_3CN, while halodifluoroesters require use of the less available and more expensive bromo or iodo derivatives to afford reaction.[2,6]


16 **17** (4)

In summary, we have reported a new synthesis of α,α-difluoro-β-hydroxy esters which is operationally simple and does not produce heavy metal waste. For instance, the lithium enolate of **2** adds to aldehyde **13** with good diastereoselectivity, which could be enhanced by use of the difluoroketene silyl *O,S*-acetal **15** to provide an intermediate in the synthesis of the anticancer agent gemcitabine. Although alcohols **3**−**8** and **10** were produced as racemates, we note the possibility of enantioselectivity utilizing the work of Mukaiyama and others.[16] We have also demonstrated the synthesis of difluoroketene silyl *O,S*-acetal **17** through reduction of a chlorodifluoroethanethioate ester.

Acknowledgment. The author gratefully acknowledges the contributions of Mr. Ross Johnson for analyzing the NMR spectral data.

Supporting Information Available: Experimental procedures and physical data (^{1}H NMR spectra) for compounds **2**−**12** and **16**−**17** (19 pages).

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(13) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803.

(14) ^{19}F NMR (C_6D_6) δ −97.1 (d, J = 47 Hz), −108.6 (d, J = 47 Hz). Acetal **15** was not isolated due to its great hydrolytic instability and was generated in situ for subsequent reactions.

(15) ^{19}F NMR (C_6D_6) δ −96.8 (d, J = 47 Hz), −109.5 (d, J = 47 Hz); APCI MS (positive ion mode, m/z) 261 $[M + 1]^+$.

(16) For leading references, see: Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653.