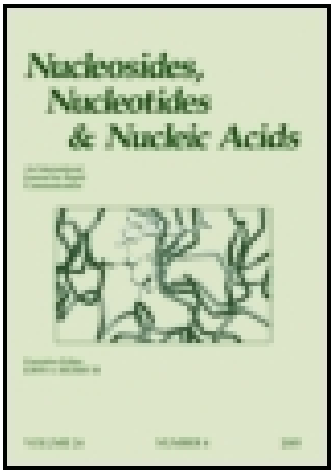


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

The "β-Fluorine Effect" in the Non-Metal Hydride Radical Deoxygenation of Fluorine-Containing Nucleoside Xanthates

Maqbool A. Siddiqui [a] , John S. Driscoll [a] , Elie Abushanab [a b] , James A. Kelley [a] , Joseph J. Barchi Jr. [a] & Victor E. Marquez [a]

[a] Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, NIH , Bethesda, MD, 20892, U.S.A.

[b] The University of Rhode Island

Published online: 24 Sep 2006.

To cite this article: Maqbool A. Siddiqui , John S. Driscoll , Elie Abushanab , James A. Kelley , Joseph J. Barchi Jr. & Victor E. Marquez (2000) The "β-Fluorine Effect" in the Non-Metal Hydride Radical Deoxygenation of Fluorine-Containing Nucleoside Xanthates, Nucleosides, Nucleotides and Nucleic Acids, 19:1-2, 1-12, DOI: 10.1080/15257770008032993

To link to this article: http://dx.doi.org/10.1080/15257770008032993

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(1&2), 1–12 (2000)

THE "β-FLUORINE EFFECT" IN THE NON-METAL HYDRIDE RADICAL DEOXYGENATION OF FLUORINE-CONTAINING NUCLEOSIDE XANTHATES

Maqbool A. Siddiqui, John S. Driscoll, Elie Abushanab,+ James A. Kelley, Joseph J. Barchi Jr. and Victor E. Marquez*
Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, NIH, Bethesda, MD 20892 U.S.A.

Dedicated to the memory of Dr. Gertrude B. Elion

ABSTRACT. An alternative method to conduct a Barton-McCombie deoxygenation in nucleosides is described. The utility of the procedure is limited to structures with an electronegative substituent, particularly fluorine, in the β-position relative to the radical center. The process is radical in nature and triggered by peroxides. The abstraction of hydrogen from the solvent is favorably influenced by the presence of a β-fluorine.

Introduction.

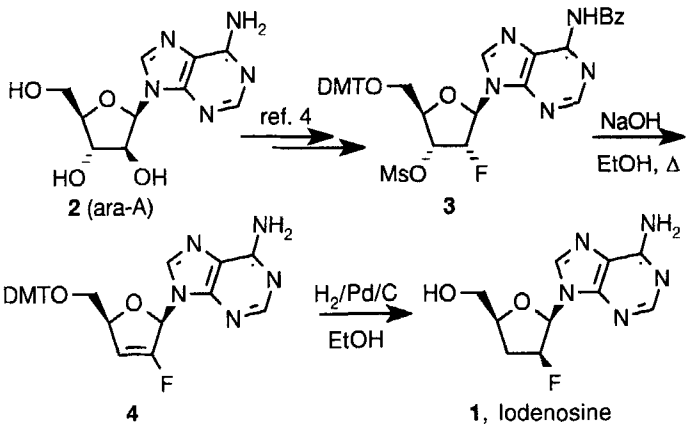
Lodenosine [9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-9*H*-purine, FddA, **1**] is a new promising antiretroviral agent that has shown effectiveness against HIV strains resistant to zidovudine (AZT), zalcitabine (ddC) and didanosine (ddI).[1] Lodenosine is currently in phase II clinical trials for the treatment of AIDS as a single agent[2] and as a key component of a triple therapy protocol.[3] The anticipated demand for the drug has prompted a search for alternative methods for synthesis improvement.

We have recently described a new synthesis of lodenosine from the readily available precursor 9-(β-D-arabinofuranosyl)adenine (ara-A, **2**) that was based on the stereospecific hydrogenation of fluoroolefin **4** (SCHEME 1).[4] This fluoroolefin was obtained after fluorine incorporation at C2'(ribo configuration) via a base-catalyzed *trans*-elimination of the corresponding C3'-methylsulfonate ester **3**.

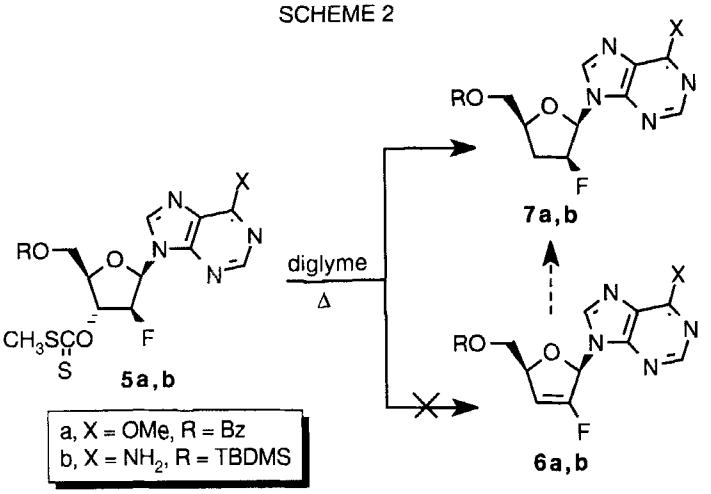
Alternatively, we considered obtaining the comparable fluoroolefins **6a** and **6b** (SCHEME 2) from the corresponding 3'-*O*-S-methyl xanthates **5a** and **5b**. The latter 3'-*O*-S-methyl xanthate is currently used for the large-scale synthesis of lodenosine.[5] Under

+ On sabbatical leave from the University of Rhode Island.

SCHEME 1



SCHEME 2



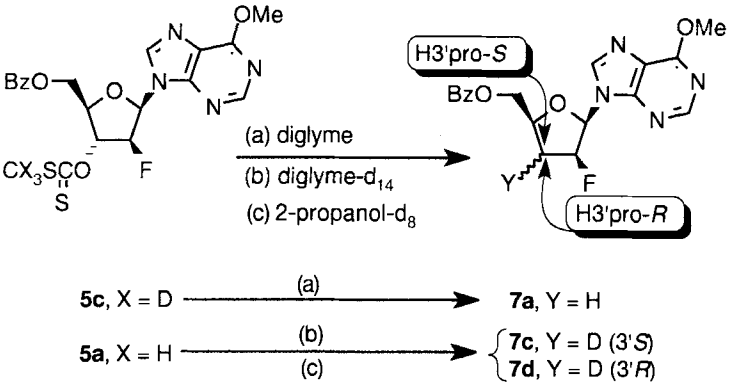
Barton-McCombie deoxygenation conditions,[6] these xanthates react readily with tri-*n*-butyltin hydride to give the corresponding deoxygenated products **7a** and **7b**, which are one step away from lodenosine.[7] Since in terms of safety, cost, and efficiency, tri-*n*-butyltin hydride is not an ideal reagent,[8] the conversion of **6a,b** to **7a,b** by catalytic hydrogenation seemed very attractive. Hence, a thermal Ei *syn*-elimination (Chugaev reaction) to obtain olefin **6a** from xanthate **5a** in biphenyl and other high-boiling point hydrocarbons was attempted.[9] Unfortunately, the outcome of this reaction ranged from recovery of unreacted starting material to extensive decomposition. Because of its high boiling point and solvent capacity, diglyme was considered as an alternative solvent.

However, instead of the Chugaev product, we obtained the deoxygenated material (**7a**), identical to the one resulting from the Barton-McCombie deoxygenation with tri-*n*-butyltin hydride. Other radical precursors such as the 3'-*O*-thiocarbonylimidazolide[10] or the 3'-*O*-phenoxythiocarbonyl ester[11] were less efficient and the yield of reduced product (**7a**) was significantly lower (58% and 39%, respectively).

Nature of the Reducing Agent.

Under the same standard conditions (see experimental), reactions performed with a deuterated methyl xanthate substrate (**5c**, SCHEME 3) and with the unlabeled substrate **5a** in fully deuterated diglyme (diglyme-d_{14})[12] demonstrated that the source of hydrogen was the diglyme itself. The stereochemistry of hydrogen transfer and the preferred 3'*R*:3'*S* ratio will be discussed later. Since the diglyme used tested positive for peroxides, it is not surprising that hydrogen abstraction from diglyme took place under radical conditions. Indeed, removal of peroxides from diglyme slowed the speed of the reaction significantly from 4 to 24 h to achieve completion. Furthermore, addition of benzoquinone (0.28 molar equivalents) as a radical scavenger completely abolished the reaction.

SCHEME 3



Other Reducing Systems

A. Ethers and ether/peroxide mixtures

In an attempt to expand the scope of the reaction, a number of ethers were investigated with the standard substrate (**5a**) under refluxing conditions (ethyl ether, bp 35 °C; THF, bp 65 °C; dioxane, bp 101 °C; 1,1-diethoxyethane, bp 102 °C; 1,2-diethoxyethane, bp 121 °C; 2-methoxytetrahydropyran, bp 129 °C; 1-methoxy-2-*t*-butoxyethane, bp 131 °C; anisole, bp 154 °C; diglyme, bp 162 °C; phenetole, bp 169 °C; and diethyleneglycol ethyl ether, bp 202 °C) and formation of **7a** was monitored by tlc.

Because of the radical nature of the reaction, all ethers were tested for radical-initiating hydroperoxide (and/or peroxide) content. The ease of reduction correlated roughly with the amount of naturally occurring peroxides/hydroperoxides present. For example, anisole and phenetole, which were peroxide-free, did not act as reducing agents except when radical inducers were added to the reaction mixtures. 1,4-Dioxane was ineffective despite its high content of peroxides/hydroperoxides perhaps due to the stability of its hydroperoxide.[13] The addition of various radical initiators (i.e., benzoyl peroxide, *t*-butylhydroperoxide, triethylborane, etc.) allowed dioxane and other low-boiling ethers, such as tetrahydrofuran or ethyl ether, to participate in the reduction (data not shown); however, the yields were generally lower than with diglyme. Based on these results diglyme was selected as the best reducing agent.

B. 2-Propanol/dilauroyl peroxide

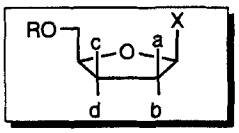
While our work was in progress, Quiclet-Sire and Zard reported comparable yields (40—90%) in the reduction of carbohydrate xanthates in refluxing 2-propanol with dilauroyl peroxide as radical initiator.[14] Therefore, a direct comparison between diglyme and 2-propanol as hydrogen sources was performed with **5a** and a number of additional xanthates available from known starting materials (TABLE).[7,11,15-18]

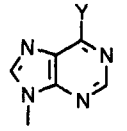
Structure-Reactivity Relationship: β-Oxygen versus β-Fluorine Effect.

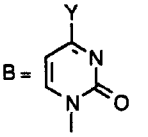
In 1982 Barton observed that thionocarbonyl esters bearing alkoxy and/or acyloxy groups in the β-position[19] underwent deoxygenation at lower temperatures than the corresponding species lacking these substituents.[20] Despite Crich's report casting doubt on the nature of the so-called β-oxygen effect,[21] differences in reactivity can be explained in terms of an enhanced electrophilic character of the radical resulting from the β-oxygen effect.[14] Since fluorine is oxygen's heterosubstituent par excellence, we decided to investigate the reduction of several fluorine-containing nucleoside xanthates (TABLE) to test the influence of the more electronegative β-fluorine in facilitating hydrogen abstraction from diglyme and 2-propanol. In all the fluorine-containing substrates (TABLE, entries 1-5 and 7-9) the fluorine is β relative to the xanthate.[19] These compounds, therefore, should provide a good opportunity to study how the strong polar effect induced by the more electronegative fluorine influences the electrophilic character of the generated radical.

The results showed significant differences between the two reducing systems (TABLE). The diglyme reaction was quite sensitive to the stereochemical disposition of the fluorine and the xanthate. When the relative stereochemistry changes from *trans* to *cis* (compare entries 3 and 4) the reaction becomes very inefficient. The position of the

TABLE. Substrates for the diglyme- and 2-propanol-mediated deoxygenations



A = 

B = 

C = OMe

no.	cpd.	X	Y	R	a	b	c	d	Yield (%) Diglyme	Yield(%) *i*-propanol dilauroyl peroxide
1	**5a**[7]	A	OMe	PhC(=O)-	F	H	H	MeSC(=O)O-	74 (50)	81 (78)
2	**8**[7]	A	OMe	*t*-BuCMe$_2$Si-	F	H	H	MeSC(=O)O-	91	94
3	**5b**[7]	A	NH_2	*t*-BuCMe$_2$Si-	F	H	H	MeSC(=O)O-	31	86
4	**9**[15]	A	NH_2	*t*-BuCMe$_2$Si-	H	F	H	MeSC(=O)O-	7	84 (52)
5	**10**[16]	A	OMe	PhC(=O)-	H	MeSC(=O)O-	F	H	64	82
6	**11**[17]	A	NH_2	*t*-BuCMe$_2$Si-	H	H	H	MeSC(=O)O-	6	63
7	**12**[7]	A	Cl	PhCO-	F	H	H	MeSC(=O)O-	76	ND
8	**13**[16]	B	OMe	PhCO-	H	MeSC(=O)O-	F	H	71	ND
9	**14**[18]	C	—	PhCO-	F	H	H	MeSC(=O)O-	42	77
10	**15**[11]	A	NH_2	*i*-Pr$_2$Si(O)—	H	MeSC(=O)O-	H	—O~Si-*i*-Pr$_2$	23	75
11	**16**[11]	B	NH_2	*i*-Pr$_2$Si(O)—	H	MeSC(=O)O-	H	—O~Si-*i*-Pr$_2$	traces	64 (60)

Values in parenthesis are yields using fully deuterated reagents. ND = not determined

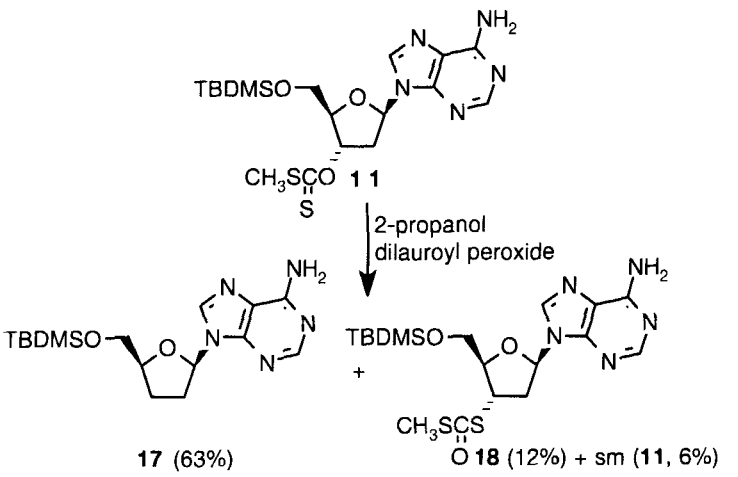
fluorine on the sugar, however, was irrelevant. Indeed, whether the fluorine was at C2' (entries 1-3, 7 and 9) or C3' (entries 5 and 8), the diglyme reduction worked reasonably well as long as the fluorine and the xanthate are *trans*. The 2-propanol/dilauroyl peroxide system works uniformly well regardless of the relative stereochemical disposition of the fluorine and the xanthate (entries 1-5 and 9). The presence of fluorine, even in the more efficient 2-propanol/dilauroyl peroxide system, plays a measurable role since the yields are lower when the fluorine atom is absent (compare entries 4 and 6). The nature of the purine substituent appears to have an important impact on the diglyme reaction as well. An intact amino group (entries 3, 4 and 6) results in poor yields, whereas direct precursors to it, such as MeO (entries 1, 2, 5 and 8) and Cl (entry 7), are compatible with the reaction. As far as 5'-*O*-protection, two of the most commonly used groups in nucleoside chemistry (benzoyl and *tert*-butyldimethysilyl) are compatible with both reactions. The nature of the heterocyclic base (purine or pyrimidine) does not appear to be a factor in the diglyme reduction as long as the conditions described above are met (entry 8). The 2-propanol/dilauroyl peroxide procedure gives acceptable yields with plain fluorosugars and even with nucleosides lacking fluorine; however, the yields tend to be ca. 10-20% lower (entries 9, 10 and 11). The last two substrates containing either a purine (entry 10) or a pyridimidine (entry 11) aglycon gave useful yields of the corresponding 2'-deoxy nucleosides when the compounds were protected as 3',5'-*O*-(1,1,3,3-tetra-isopropyldisilox-1,3-diyl)nucleosides.[22]

During these reductions, a thermal *O*- to *S*- transposition can occur to varying degrees.[14] In our hands, confirmation of this rearrangement was feasible only with the less efficient reactions. However, even this was complicated by the fact that the unreacted starting material and the rearranged product comigrated on tlc. Therefore, identification of the product and its extent of formation was determined by ^{1}H NMR analysis of the isolated mixture of starting material and rearranged product. In 2-propanol, the non-fluorinated substrate (**11**, entry 6 TABLE and SCHEME 4) gave a 63% yield of reduced product (**17**) and an 18% yield of a mixture of rearranged (**18**) and unrearranged (**11**) products. Integration of the SMe singlets corresponding to rearranged product (δ 2.05) and starting material (δ 2.70) demonstrated a 2:1 preponderance of the former.

Stereochemistry of the Reduction.

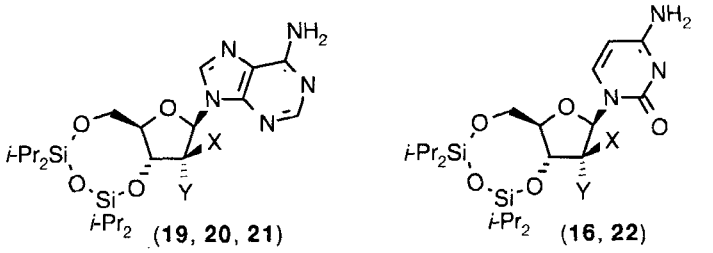
From a mechanistic point of view it was of interest to study the stereochemistry of hydrogen transfer from diglyme-d_{14} and 2-propanol-d_8. In similar radical-initiated homolytic deoxygenations with tri-*n*-butyltin deuteride, Robins et al. have shown that for the phenoxythiocarbonyl esters of 9-[2-*O*-phenoxycarbonyl-3,5-*O*-(1,1,3,3-tetra-isopropyldisiloxy-1,3-diyl)-β-D-ribofuranosyl]adenine (**19**) and 9-[2-*O*-phenoxy-

SCHEME 4



carbonyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxy-1,3-diyl)-β-D-arabinofuranosyl]adenine (**20**) (SCHEME 5), the ratio of 2'*R*:2'*S* deuterium substitution obtained from either starting material was ~ 88:12.[11] This suggested that hydrogen transfer from the bulky tributylstannane to the radical center occurred with high stereoselectivity on the less hindered ribo face. Later, Ishido et al. were successful in obtaining even higher stereoselectivity (i.e., 99:1) employing a triethylborane-induced tin deuteride system or a deuterated tris(trimethylsilyl)silane system on structurally similar substrates.[24-26] Our results show a similar preference for the ribo face of the nucleoside, since formation of the 3'*R* [3'-D] diastereoisomer was dominant (SCHEME 3, entry 1, TABLE). The 3'*R*:3'*S* deuterium substitution ratios (**7d/7c**) obtained were, respectively, 84:16 and 89:11 for the diglyme-d_{14} and 2-propanol-d_8/lauroyl peroxide reduction (FIGURE). Yields were also

SCHEME 5



19, X = H, Y = OCOPh
20, X = OCOPh, Y = H
ref. 11 → **21**, X = H, Y = D (2'*R*:2'*S* = 88:12)

16, X = H, Y = OCSMe
2-propanol-d_8 → **22**, X = H, Y = D (2'*R*:2'*S* = 88:12)

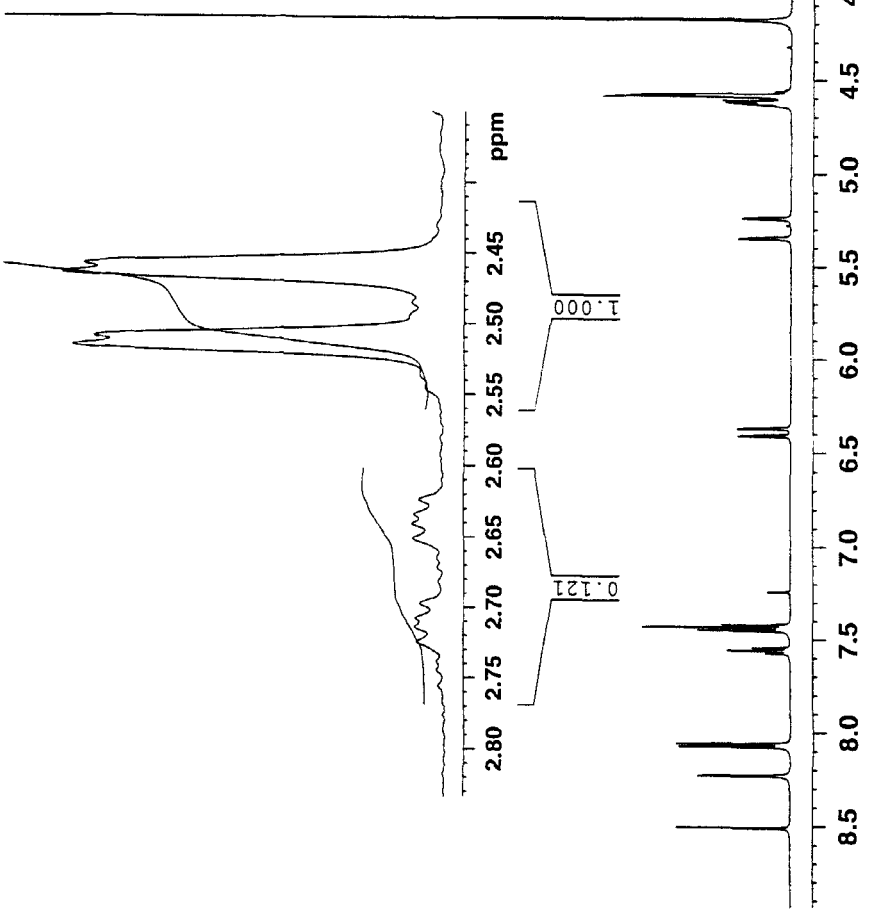


FIGURE. One-dimensional ^{1}H NMR spectrum of the product mixture **7d/7c** from the reaction of **5a** with 2-propanol-d_8/lauroyl peroxide (SCHEME 3). The major resonance between 2.45 and 2.55 ppm (dd) corresponds to the 3'-*R* deuterated product (**7d**). The minor peaks between 2.65 and 2.75 ppm (dm) are derived from the 3'-*S* isomer (**7c**), and the residual signals adjacent to the larger peaks correspond to the protonated product (**7a**).

lower for the diglyme-d_{14} reaction (50%) compared to the 2-propanol-d_8/lauroyl peroxide system (78%) (entry 1, TABLE). The amount of non-deuterated reduced product was minimal for the 2-propanol-d_8/lauroyl peroxide system, which according to FAB mass spectral analysis gave a 96:4 ratio of deuterium incorporation in the isolated product. The 2-propanol-d_8/lauroyl peroxide system appears to be just as stereoselective with a non-fluorinated substrate. For example, the reaction in entry 11 (SCHEME 5, TABLE) gave a 2'*R*:2'*S* deuterium substitution ratio of 88:12, identical to that reported by Robins et al. for the phenoxythiocarbonyl esters **19** and **20**.[11]

Despite the fact that deuterium incorporation takes place preferentially on the ribo face, the stereochemical disposition of the fluorine relative to the xanthate has an impact on the stereochemistry and extent of deuterium incorporation in these reductions. For the reaction in entry 4 (TABLE), where the fluorine and the xanthate are *cis*, the yield of labeled compound using the 2-propanol-d_8/lauroyl peroxide system was significantly reduced (52%). In addition, the ratio of deuterium incorporation by FAB mass spectral analysis was only 79:21, and the 3'*R*:3'*S* deuterium substitution ratio was just 67:33 (data not shown). This clearly shows that the β-fluorine effect on radical electrophilicity is rather complex and appears to be sensitive to the stereochemical disposition of the fluorine relative to the radical center.

One can conclude that the 2-propanol/dilauroyl peroxide reduction is very efficient for this class of compounds and constitutes an environmentally attractive, metal-free alternative to the tri-*n*-butyltin hydride reduction.[8] In addition, the enhanced reactivity observed in the presence of a single fluorine β to the radical center confirms the importance of polar effects in these radical deoxygenations.[14,23] The diglyme reduction, on the other hand, has a more modest range of substrates and its outcome is sensitive to the relative stereochemistry between the fluorine and the xanthate. In those cases where the diglyme reaction works well (entries 1, 2, 5, 7 and 8, TABLE) the method is much simpler and requires no addition of lauroyl peroxide or collidine. The latter base is sometimes necessary in the 2-propanol/dilauroyl peroxide procedure to avoid cleavage of acid-sensitive groups by the lauric acid formed during the reaction.[14]

EXPERIMENTAL

General. All chemical reagents were commercially available. Column chromatography was performed on silica gel 60, 230-400 mesh (E. Merk), and analytical tlc was performed on Analtech Uniplates silica gel GF. Proton NMR spectra were recorded on a Bruker AMX-500 instrument. Spectra were referenced to the solvent in which they were run

(7.24 ppm for $CDCl_3$). Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix and ionization was effected by a beam of xenon atoms. All ethers were tested for radical-initiating hydroperoxide (and/or peroxide) content by the formation of iodine from a 10% KI solution. The reaction conditions for all reductions employing the 2-propanol/lauroyl peroxide system are described in ref. 14.

General conditions for the diglyme (and other ethers) reduction. All reactions were performed in a ca. 0.5 mmol scale reaction. Xanthates were dissolved in 15 mL of diglyme and heated over a temperature range of 75 °C to reflux (162 °C). It was established that for the standard xanthate substrate **5a**, a temperature of 100 °C was sufficient to achieve completion of the reaction in just 4 h. These conditions were applied uniformly to all other ethers. The reactions were monitored by tlc (silica gel, CH_2Cl_2:MeOH, 25:1). The same standard reaction conditions were used with the deuterated methyl xanthate substrate (**5c**) and with the unlabeled substrate **5a** in fully deuterated diglyme (diglyme-d_{14}).

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