Synthesis of 2′,3′-Dideoxy-2′-Fluoro-4′-Thionucleosides from a Fluoroxanthate

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Abstract: The synthesis of a thiobutyrolactone as precursor of modified nucleosides is reported from a fluoroxanthate and a protected allylic alcohol. This approach opens a new and straightforward route for the synthesis of 2′,3′-dideoxy-2′-fluoro-4′-thiothymidine derivatives in few steps, including the formation of a fluorothiolactone and a Vorbrüggen thymine base alkylation reaction.

Key words: fluorine, free radical, nucleosides, lactones

Modified nucleosides have been introduced several years ago to develop new anticancer and antiviral agents.[1] One of the limitations in the use of such drugs lies in their possible degradation by nucleoside phosphorylases. To enhance the length of their half-life, a variety of modifications have been introduced in order to stabilize the nucleosidic bond. Among them, the replacement of the 4′-oxygen atom by a sulfur atom,[2] or the introduction of fluorine atoms at the 2′-C carbon atom,[3] have conferred resistance to nucleoside cleavage, as in the case of the 4′-thiothymidine and the gemcitabine.[4] It has been established that these modifications contributed to the destabilization of the carbocation involved in the nucleoside degradation, and consequently produced metabolically stable nucleoside analogues.[5]

The synthesis of fluoro- or thionucleosides is not trivial and some difficulties appeared during the coupling reaction between the sugar moiety and the purine or the pyrimidine heterocycle under the Vorbrüggen conditions. From 2′-difluoronucleosides the displacement of the intermediate acetate derivative is difficult due to the strong electron-withdrawing character of the difluoromethylene group. In this case the use of a more reactive alkylsulfonate derivative is required for the success of the reaction.[4] In contrast the presence of only one fluorine atom at the 2′-position affects moderately the acetate-group reactivity and the introduction of the nucleic base is easier.[6] In order to prepare novel drug candidates resistant to nucleoside cleavage, the introduction of both sulfur and fluorine atoms appeared attractive. In connection with our current interest in the preparation of fluorinated nucleosides,[7] the present work was focused on the development of a straightforward route to synthesize 2′-fluoro- and 2′,3′-difluoro-4′-thionucleosides. This approach would be useful to prepare sulfur-containing analogues of the antiviral drugs FddA and FMAU, such as 4′S-FddA and 4′S-dFMAU (Figure 1).[8] In this paper is described a free-radical approach for the preparation of a fluorothiolactone and its derivation into nucleoside analogues.

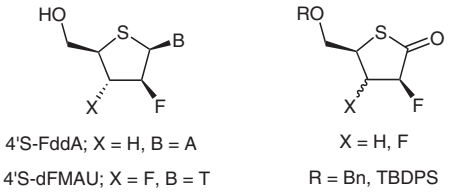
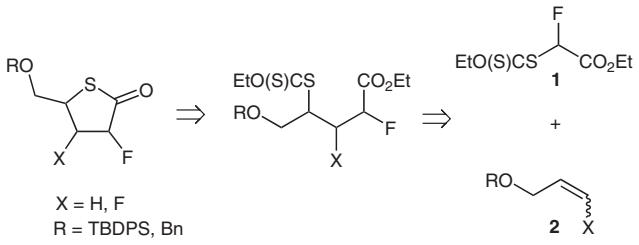


Figure 1

Fluorothionucleosides synthesis is often difficult and several steps are usually required to obtain the target compound. Among the reported methods, some involved the use of carbohydrates as starting materials to afford, after chemical-group transformations, the intermediate thiolactones as precursors of thionucleosides. Fluorine atoms are commonly introduced by using electrophilic or nucleophilic fluorinating reagents to produce the corresponding mono- or difluorothionucleosides.[9] Other approaches included the fluorination of oxo- or hydroxy-tetrahydrothiophene intermediates, followed by nucleic-base introduction via the Vorbrüggen reaction,[10] or a Pummerer-like reaction.[11] A recent straightforward synthesis of thiolactone intermediates has been reported by using a free-radical chemistry approach.[12] In this latter, carboxymethyl xanthate added onto allylic phosphonate afforded after intramolecular cyclization a thiolactone as thionucleoside precursors. Inspired by this unique example, this approach was selected to explore the preparation of 2-fluoro- and 2,3-difluoro-thiolactones from the xanthate **1** and a protected allylic alcohol **2** (Scheme 1).



Scheme 1

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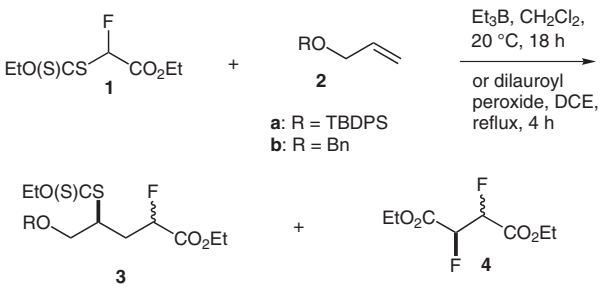
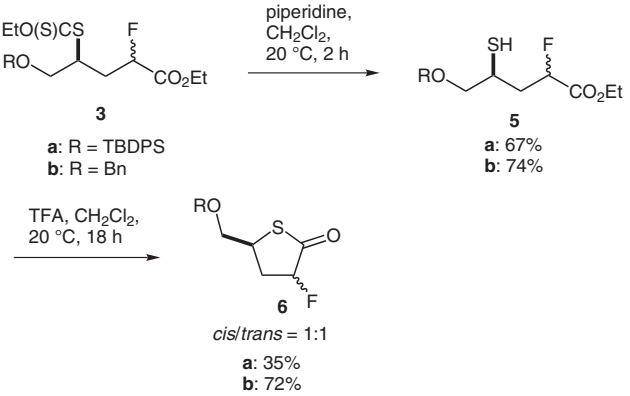
The xanthate **1** was prepared from the commercially available ethyl bromofluoroacetate, and we have reported previously its reaction with a large variety of alkenes by using dilauroyl peroxide or triethylborane as initiators.[7b] Triethylborane (1 M in *n*-hexane) was first tested as radical initiator. The reaction of the protected alcohol **2a** with **1** in dichloromethane afforded the desired fluoroester **3a** (Scheme 2). The reaction was slower than those reported from simple alkenes and needed at least overnight at room temperature to reach completion. However, in this case the reaction was not reproducible and the formation of the product **3a** is strongly depending on the quality of the triethylborane solution. In some case the presence of the dimeric product **4** was observed up to 30%.[13] Attempts to limit its formation by changing the nature of the solvent, the concentration of the alkene or the rate of the addition were unsuccessful. In contrast, the use of dilauroyl peroxide as initiator in refluxing 1,2-dichloroethane afforded exclusively the expected ester **3a**. A slow addition of a solution of dilauroyl peroxide (0.3 equiv) to a mixture of alkene **2a** and xanthate **1** over two hours followed by 30 minutes of stirring gave reproducible results. The ester **3a** was isolated by flash column chromatography in 65–70% yield as a 1:1 mixture of diastereomers. From the *O*-benzyl alcohol **2b** similar results were obtained, and the adduct **3b** was exclusively formed and isolated in 62% yield.[14] No traces of the dimer **4** were detected.



Scheme 2

The formation of the corresponding thiol by sulfur–carbon bond cleavage of the dithiocarbonate function is usually realized by using primary amine. However, the presence of the fluorine atom enhances the electrophilic character of the ester function, and competitive addition of the amine onto the ester could occur.[15] Indeed, treatment of the dithiocarbonate **3a** with a primary amine, such as the ethylene diamine, afforded a mixture of the desired thiol and other products (presumably the corresponding amides),[16] even at –20 °C. At lower temperature (–78 °C) no reaction occurred. The use of a secondary amine, such as piperidine, allowed us to avoid this competitive reaction,[17] and thiol **5** was exclusively formed. Flash column chromatography of the crude yielded a diastereomeric mixture of **5a** and **5b** in 67% and 74%, respectively (Scheme 3). Due to its rapid degradation at room temperature, **5** was directly involved in the next step. The ring-closure reaction was performed in the presence of an excess of TFA over 18 hours at 20 °C. Purification of the crude product afforded the γ-thiobutyrolactone **6b** in 72% yield. Both diastereomers were separated by flash column chromatography. The consistency of their NMR data with those reported in the literature,[18] permitted the identification of the *cis* and *trans* isomers.[19] In contrast, moderate yield (30–40%) was obtained from **5a** due to a partial cleavage of the silylether protecting group in **6a**.

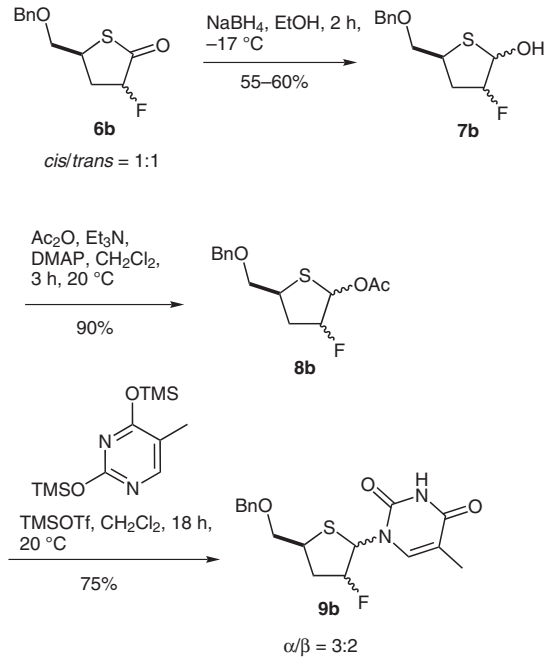


Scheme 3

Reduction of the thiolactone **6b** with DIBAL-H (1 M in *n*-hexane) at –40 °C or 0 °C afforded a mixture of fluorinated products, while $NaBH_4$ gave better results at –17 °C. In these conditions, the thiolactol **7b** was obtained in 55–60% yield (Scheme 4). In this case, one major isomer was formed in a 85:15 ratio, when the reduction was conducted separately from both *cis*- and *trans*-thiolactones **6b**. This selective reduction was probably due to the steric demand of the *O*-benzylether group, leading preferentially to the β-isomer as major isomer. It is worthy of note that scrupulous control of the reaction temperature is needed during the reduction of **6b** to avoid any ring-opening reaction by the solvent. Acetylation of **7b** afforded **8b** in 90% yield, which was ready to be involved in the Vorbrüggen reaction with the bistrimethylsilylthymine. A stoichiometric amount of $SnCl_4$ was used to introduce the thymine base from the acetate **8b** (Scheme 4). By working either under refluxing acetonitrile or at 20 °C, a total degradation of the starting acetate **8b** was observed. No reaction occurred at lower temperatures. In contrast, in the presence of freshly distilled TMSOTf the reaction reached completion after 18 hours at 20 °C under stirring.[9a] The crude mixture was purified by flash column chromatography, and afforded the thionucleoside analogue **9b** in 75% yield.[20] The NMR analysis of the mixture presented the four isomers: the 2′,4′-*cis* and -*trans* isomers in 3:2 α/β ratio.

The α/β ratio was deduced from the {^{19}F}-^{1}H HOESY NMR experiment. The assignment of the spatial proximity between the fluorine atom and the hydrogen atoms H1′, H4′, or H6 for each diastereomer is depicted in Figure 2.

This approach was transposed to the synthesis of 2′,3′-difluorothionucleoside by trapping the free radical with a terminal monofluoroalkene.[21] However, no expected free-



Scheme 4

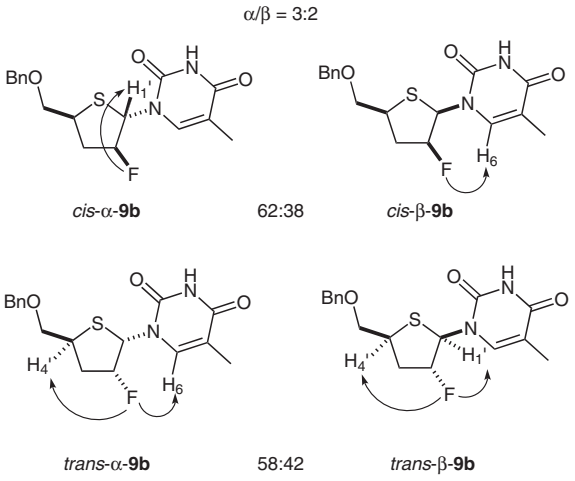


Figure 2

radical addition occurred, the dimer **4** was exclusively formed. Current investigations to solve this problem are under way.

In conclusion, the synthesis of 2′,3′-dideoxy-2′-fluoro-4′-thionucleosides is reported in six steps from the fluoroxanthate **1** and a protected allylic alcohol. We have shown that this approach is flexible and can be applied to the preparation of fluorothionucleosides. This additional example illustrates the continuous growing of the xanthate chemistry in synthesis.[22] However, some limitations of this method appeared as described by our failure when attempting to trap the free radical with the terminal fluoroalkene analogue of **2**. The debenzylation and the HPLC separation of the four isomers of **9b** are in progress in order to evaluate their biological activity.

Acknowledgment

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(14) **Experimental for 3b**
A solution of *O*-benzyl allylic alcohol **2b** (1.08 g, 7.28 mmol, 1.1 equiv), and xanthate **1** (1.50 g, 6.62 mmol, 1 equiv) in deoxygenated DCE (80 mL) was heated at 85 °C (oil bath). A solution of lauroyl peroxide (0.79 g, 1.99 mmol, 0.3 equiv) in deoxygenated DCE (20 mL) was added dropwise (over 2 h by using a syringe pump), then the mixture was stirred 30 min. The solution was cooled to r.t., and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (pentane–EtOAc, 95:5) to afford **3b** as a mixture of diastereomers (1.54 g, 62%, 1:1) as a light yellow liquid.^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 [t, 6 H, $^3J_{HH}$ = 7.1 Hz, CH_3 (2 dia)], 1.40 [t, $^3J_{HH}$ = 7.1 Hz, 6 H, CH_3 (2 dia)], 2.12–2.75 [m, 4 H, C*H*$_2$CHF (2 dia)], 3.80–3.99 [m, 4 H, CH_2O (2 dia)], 4.03–4.16 [m, 2 H, C*H*S (2 dia)], 4.27 [q, $^3J_{HH}$ = 7.1 Hz, 4 H, CH_2 (2 dia)], 4.56 [s, 4 H, $PhCH_2O$ (2 dia)], 4.59 [q, $^3J_{HH}$ = 7.1 Hz, 2 H, CH_2 (dia 1)], 4.60 [q, $^3J_{HH}$ = 7.1 Hz, 2 H, CH_2 (dia 2)], 5.00 [ddd, $^2J_{HF}$ = 49.0 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 4.1 Hz, 1 H, CHF (dia 1)], 5.08 [ddd, $^2J_{HF}$ = 49.0 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 2.9 Hz, 1 H, CHF (dia 2)], 7.25–7.35 [m, 10 H, Ph (2 dia)]. ^{19}F NMR (235 MHz, $CFCl_3$, $CDCl_3$): δ = –191.46 [ddd, $^2J_{HF}$ = 49.0 Hz, $^3J_{HF}$ = 28.0 Hz, $^3J_{HF}$ = 20.0 Hz, 1 F, (dia 1)], –191.42 [ddd, $^2J_{HF}$ = 49.0 Hz, $^3J_{HF}$ = 36.0 Hz, $^3J_{HF}$ = 16.0 Hz, 1 F, (dia 2)]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.7, 13.1 (s, CH_3), 32.85 [d, $^2J_{CF}$ = 20.6 Hz, CH_2 (dia 1)], 32.2 [d, $^2J_{CF}$ = 20.9 Hz, CH_2 (dia 2)], 44.9, 45.4 (s, CHS), 60.7, 69.1, 69.2, 69.6, 70.7, 71.9 (s, OCH_2), 85.8 [d, $^1J_{CF}$ = 184.5 Hz, CF (dia 1)], 85.9 [d, $^1J_{CF}$ = 184.8 Hz, CF (dia 2)], 126.6, 126.7, 127.1, 136.7 (s, Ph), 168.3 [d, $^2J_{CF}$ = 23.9 Hz, C=O (dia 1)], 168.5 [d, $^2J_{CF}$ = 23.3 Hz, C=O (dia 2)], 211.7 [C=S (dia 1)], 211.8 [C=S (dia 2)]. MS (ESI, 9 eV): *m/z* 375 (73) $[M + H]^+$, 329 (18), 269 (26), 267 (61), 251 (49), 223 (100), 207 (25), 163 (35), 91 (20). ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}FO_4S_2$: 375.1100; found: 375.1099.
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(16) The ^{19}F NMR spectra of the crude mixture revealed two multiplets: –188.2 (dddd, $^2J_{FH}$ = 49.4 Hz, $^3J_{FH}$ = 25.9 Hz, $^3J_{FH}$ = 21.2 Hz, $^4J_{F–NH}$ = 4.7 Hz) and –191.0 (dddd, $^2J_{FH}$ = 49.4 Hz, $^3J_{FH}$ = 40.0 Hz, $^3J_{FH}$ = 16.5 Hz, $^4J_{F–NH}$ = 4.7 Hz).
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(19) **Typical Procedure: Preparation of the γ-Thiobutyrolactone 6b**
Trifluoroacetic acid (1 mL, 13.46 mmol) was added to a solution of thiol **5b** (0.20 g, 0.7 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 18 h at 20 °C, then poured into a sat. aq NaCl soln (10 mL). The aqueous layer was extracted twice with CH_2Cl_2 (10 mL), and the organic layer was dried ($MgSO_4$) then the solvent was evaporated. The crude product was purified by flash column chromatography on silica (pentane–EtOAc, 95:5) to afford the less polar isomer 2,4-*trans*-**6b** (68 mg, 0.28 mmol, 40%) and the more polar isomer 2,4-*cis*-**6b** (52 mg, 0.22 mmol, 31%).
γ-Thiobutyrolactone 2,4-*trans*-**6b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30–2.40 (m, 2 H, H_3), 3.50–3.75 (m, 2 H, H_5), 4.20 (m, 1 H, H_4), 4.50 (s, 2 H, OCH_2Ph), 5.15 (ddd, $^2J_{HF}$ = 51.2 Hz, $^3J_{HH}$ = $^3J_{HH}$ = 6.8 Hz, 1 H, H_2) 7.15–7.35 (m, 5 H, Ph). ^{19}F NMR (235 MHz, $CFCl_3$, $CDCl_3$): δ = –184.65 (ddd, $^2J_{HF}$ = 51.2 Hz, $^3J_{HF}$ = $^3J_{HF}$ = 18.8 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 32.6 (d, $^2J_{CF}$ = 20.8 Hz, C_3), 42.0 (d, $^3J_{CF}$ = 5.9 Hz, C_4), 71.2, 75.0, 93.0 (d, $^1J_{CF}$ = 190.2 Hz, C_2), 127.5, 128.0, 128.9, 137.5 (s, Ph), 200.7 (d, $^2J_{CF}$ = 17.4 Hz, C_1).
γ-Thiobutyrolactone 2,4-*cis*-**6b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.18 (m, 1 H, H_3), 2.71 (m, 1 H, $H_{3'}$), 3.62 (m, 1 H, H_5), 3.80 (m, 1 H, $H_{5'}$), 3.95 (m, 1 H, H_4), 4.57 (s, 2 H, OCH_2Ph), 5.10 (ddd, $^2J_{HF}$ = 50.4 Hz, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1 H, H_2), 7.15–7.35 (m, 5 H, Ph). ^{19}F NMR (235 MHz, $CFCl_3$, $CDCl_3$): δ = –183.7 (ddd, $^2J_{HF}$ = 50.4 Hz, $^3J_{HF}$ = 18.8 Hz, $^3J_{HF}$ = 9.4 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 33.6 (d, $^2J_{CF}$ = 19.6 Hz, C_3), 42.6 (d, $^3J_{CF}$ = 7.2 Hz, C_4), 71.7, 74.8, 93.3 (d, $^1J_{CF}$ = 196.2 Hz, C_2), 127.5, 127.9, 128.9, 137.6 (s, Ph), 201.7 (d, $^2J_{CF}$ = 17.6 Hz, C_1). IR (NaCl): ν = 1714 (C=O) cm^{-1}. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{13}FNaO_2S$: 263.0518; found: 263.0525.
(20) **Selected Analytical Data for the Four Isomers of 9b**
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79 [s, 3 H, CH_3 (dia 1)], 1.86]s, 3 H, CH_3 (dia 2)], 1.93 [s, 3 H, CH_3 (dia 3)], 1.97 [s, 3 H, CH_3 (dia 4)], 1.75–2.62 [m, 8 H, C*H*$_2$CHF (4 dia)], 3.58–4.10 (m, 12 H, C*H*CH_2OBn and CH_2OBn (4 dia)], 4.48–4.56 [m, 8 H, CH_2Ph (4 dia)], 5.18 (br d, $^2J_{HF}$ = 49.4 Hz, 2 H, $H_{2'}$ (2 dia)], 5.20 (br d, $^2J_{HF}$ = 54.1 Hz, 2 H, $H_{2'}$ (2 dia)], 6.17 (dd, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H, $H_{1'}$ (dia 1)], 6.19 (dd, $^3J_{HF}$ = 10.6 Hz, $^3J_{HH}$ = 1.4 Hz, 1 H, $H_{1'}$ (dia 2)], 6.40 (dd, $^3J_{HF}$ = 19.9 Hz, $^3J_{HH}$ = 4.2 Hz, 1 H, $H_{1'}$ (dia 3)], 6.44 (dd, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 3.7 Hz, 1 H, $H_{1'}$ (dia 4)], 7.19–7.34 [m, 20 H, Ph (4 dia)], 7.59 [s, 2 H, C*H*CH_3 (2 dia)], 7.93 [s, 2 H, C*H*CH_3 (2 dia)] 9.40–9.70 (br s, 4 H, NH). ^{19}F NMR (235 MHz, $CFCl_3$, $CDCl_3$): δ = –171.54 [m (dia 1)], –175.88 [dddd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HF}$ = 40.0 Hz, $^3J_{HF}$ = 14.1 Hz, $^3J_{HF}$ = 10.6 Hz (dia 2)], –187.00 [m (dia 3)], –190.75 [ddddd, $^2J_{HF}$ = 54.1 Hz, $^3J_{HF}$ = 42.4 Hz, $^3J_{HF}$ = 23.5 Hz, $^3J_{HF}$ = 12.5 Hz, $^4J_{HF}$ = 2.4 Hz (dia 4)]. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}FN_2O_3S$: 351.1179 $[M + H]^+$; found: 351.1180 $[M + H]^+$.
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