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An Expedient Radical Based Approach to Difluorophosphonate Analogues of Thionucleosides

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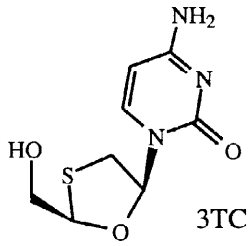
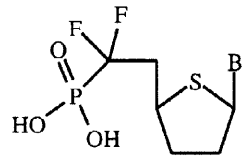
Abstract : An expedient approach to difluorophosphonate analogues of thionucleosides of general structure 1 is described; the key step is a radical xanthate transfer chain reaction on diethyl 1,1-difluoro-3-butenylphosphonate.

Nucleosides with a sulfur atom in place of the tetrahydrofuranyl oxygen have attracted increasing attention since their first appearance in 1964.[1] Thus, several recent publications describe the synthesis and biological evaluation of numerous thionucleoside derivatives as part of a vast search for cytotoxic and antiviral compounds.[2,3] Some members have indeed proved efficaceous against infections by retroviruses; 3TC® (lamivudine), for example, has recently been approved for clinical use as an anti-HIV agent.[3]

Small modifications in the structure can cause a significant change in the biological activity of these substances;[2f,g] it seemed therefore interesting, with these considerations in mind, to replace the 5'-oxygen with a geminal difluoromethylene linkage as shown in general structure **1**. A difluoromethylene moiety is a good mimic of the oxygen atom in a phosphate, both in terms of steric bulk and charge distribution.[4] By analogy with oligonucleotides containing a phosphonate group instead of a phosphate, such derivatives would be expected to be resistant to nucleases which cleave the phosphorus-5'-oxygen bond in the natural series.[5]



3TC



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The most common route to α,α-difluoromethylphosphonates is by means of reactions based on diethyl (difluorolithiomethyl)phosphonate or, more recently, by addition of a phosphorus centered radical onto a difluoroalkene, both processes being used late in the synthetic sequence.[6] In our case, we decided to introduce this unit as well as the sulfur atom at the very start of the synthesis, in contrast to earlier work in

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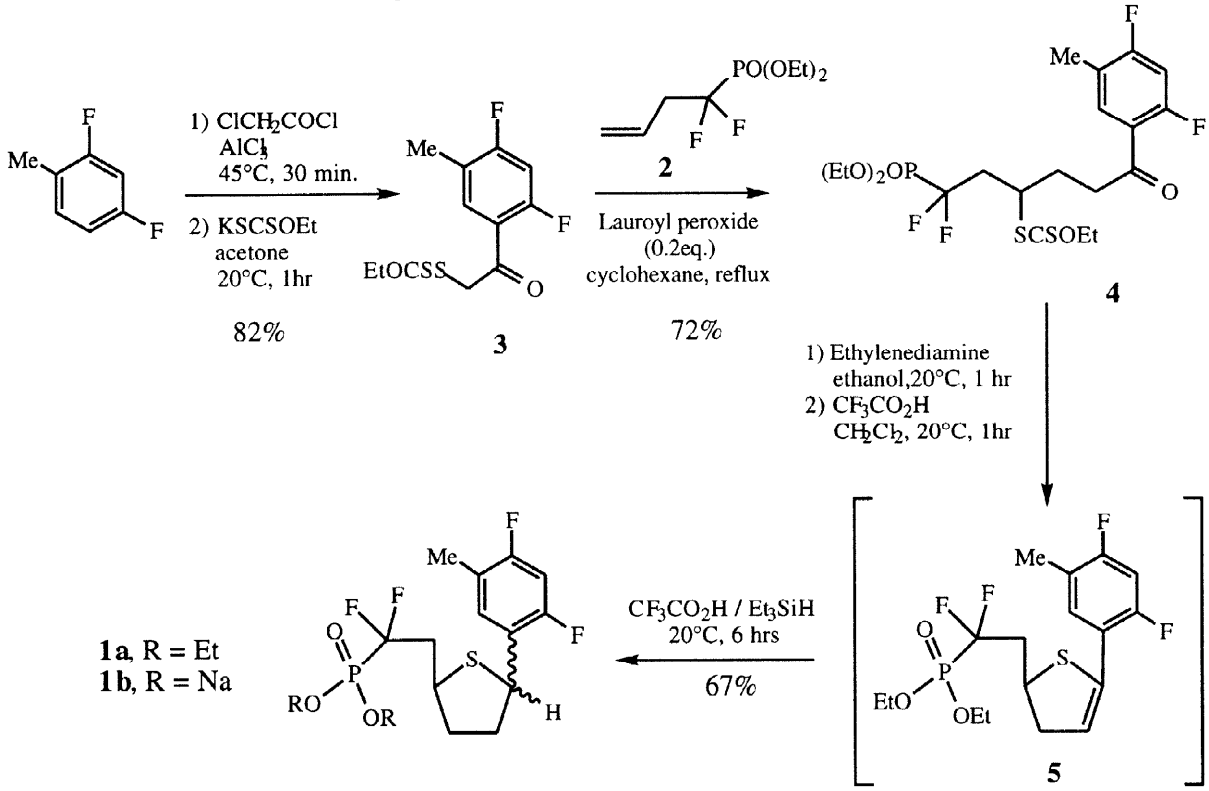
this area. This strategy was dictated by our desire to exploit a powerful xanthate transfer reaction we have discovered which, unlike most other radical generating systems, allows radical additions to unactivated olefins.[7] By carrying therefore a radical addition onto 1,1-difluoro-3-butenylphosphonate, the sulfur appears naturally in the product under the guise of a xanthate group. We adopted two different approches depending on whether a nitrogen base or an aromatic mimic thereof was to be incorporated in the final product

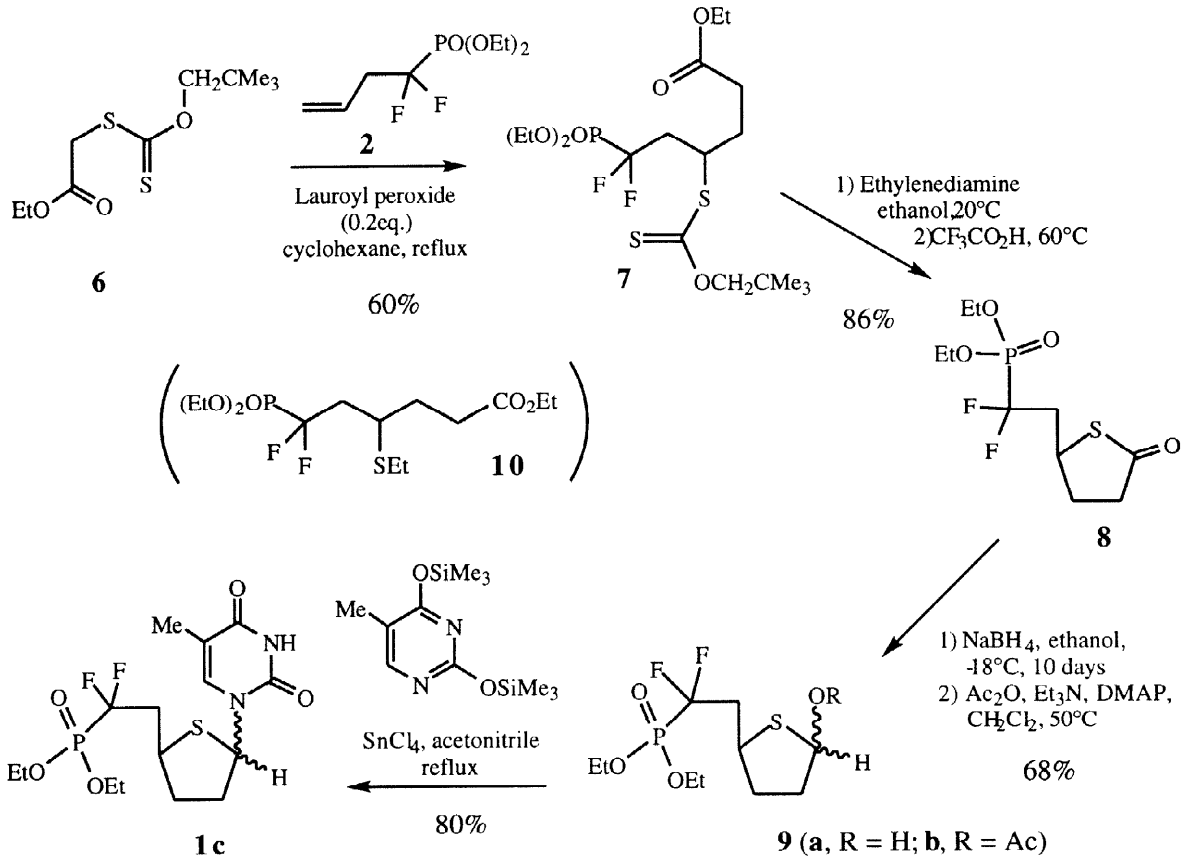
Recent studies by E. Kool and his collaborators[8] have indicated that 2,4-difluorotoluene is a good replacement for thymine. We therefore designed the synthesis displayed in Scheme 1 to access thionucleoside **1a** containing such an aromatic ring. Friedel-Crafts chloroacetylation of 2,4-difluorotoluene followed by treatment with potassium *O*-ethyl xanthate in acetone provided the xanthate partner **3** in 82% overall yield. The olefinic component, 1,1-difluoro-3-butenylphosphonate **2**, was itself obtained by the action of diethyl bromodifluoromethylphosphonate and zinc on allyl bromide according to the procedure of Burton *et al.*[9] The key radical addition took place smoothly upon heating a solution of xanthate **3** and 2 equivalents of olefin **2** in refluxing cyclohexane with the initiator, lauroyl peroxide (0.2 eq.), added portionwise. The expected adduct **4** was thus obtained in 72% yield.



Scheme 1

The xanthate group was cleaved by exposure to excess ethylenediamine in ethanol under an inert atmosphere and the resulting thiol extracted and immediately converted into the corresponding dihydrothiophene **5** by trifluoroacetic acid in dichloromethane in the dark. Finally, the solvent was evaporated and the residue reduced by a combination of triethylsilane and trifluoroacetic acid to give the penultimate precursor of **1a** as a 7:3 mixture of epimers (by nmr)[10] and in 67% yield for the three steps, without any purification of the intermediates. The ethyl groups in the side-chain can be removed with bromotrimethylsilane[6] and the crude phosphonic acid purified by chromatography on Sephadex DEAE A-25 (HCO_3^-) then on Dowex 50W X8 (Na^+) to give the target sodium salt **1b**.

For the thymine containing analogue, a Vorbrüggen type coupling[7,11] appeared better suited. We therefore applied the sequence depicted in Scheme 2. Xanthate **6** was made in 67% yield by treating ethyl bromoacetate with sodium *O*-neopentyl xanthate. The key radical addition to olefin **2** proceeded with reasonable efficiency (60% yield) under conditions similar to those used above. Cleavage of the adduct xanthate **7** with ethylenediamine and exposure of the crude thiol to hot trifluoroacetic acid (60°C) provided thiolactone **8** in high yield (86%). Curiously, in preliminary experiments with the corresponding*O*-ethyl xanthate (made of course by using *O*-ethyl analogue of xanthate **6**), variable but significant amounts of ethylsulfide **10** were isolated. Such sulfides are occasionally encountered in xanthate chemistry[12] and appear to arise by a substitution reaction of the thiol with the xanthate through an ionic chain mechanism. The reason for the special propensity of this particular substrate to undergo such a transformation is not clear but the problem was circumvented by using the neopentyl derivative where steric hindrance at the neopentylic centre blocks the substitution step.



Scheme 2

With thiolactone **8** in hand, the next step was partial reduction to the thiohemiacetal (**9a**), and this turned out not to be trivial. Conditions involving $LiAlH_4$ recommended by Rassu *et al.*[13] failed because of extensive attack at the difluorophosphonate side-chain.[14] After some experimentation, we eventually found that keeping the thiolactone for 10 days in the freezer at -18°C with sodium borohydride in ethanol followed by acetylation furnished the desired precursor **9b** in 68% yield. Finally, Vorbrüggen coupling of this derivative in acetonitrile with silylated thymine in the presence of tin (IV) chloride provided the end product in 80% yield as a 55:45% mixture of epimers.[10]

This preliminary work demonstrates the possibility of building thionucleoside analogues in a quite efficient manner and using readily available reactants. More functionalised derivatives can in principle be obtained by modifying the olefin and / or the xanthate at the beginning of the synthesis, or by exploiting the intrinsic reactivity of the intermediates (for example vinyl sulfide **5** in Scheme 1). Although the stereocontrol at the "anomeric" position is not high, it can be certainly improved[15] if needed, pending the results of the biological testing.

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10. NMR data for **1a** and **1c** (both as an inseparable mixture of *cis* and *trans* isomers): **1a** ^{1}H NMR ($CDCl_3$) δ 1.40 (t,6H, J=7Hz), 1.60-2.10 (m, 2H), 2.23 (s, 3H), 2.26-2.66 (m, 4H), 3.85 (m, 0.3H, 4'H of *trans* isomer), 4.02 (m, 0.7H, 4'H of *cis* isomer), 4.26 (dq,4H, J=7Hz, J_{HP}=7Hz), 4.75 (t,0.3H, J=6.5Hz, 1'H of *trans* isomer), 4.85 (dd, 0.7H, J=5.5Hz, 9.5Hz, 1'H of *cis* isomer), 6.70 (m, 1H), 7.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.3,36.4, 37.25, 38.5, 38.8, 40.7 (m),41.8, 44.8, 64.86, 104.4 (t,J_{CF}=27Hz), 120.3 (m), 130.8, 160.6 (dd, J=12 Hz, 255Hz), 163.7 (dd, J=11Hz, 256Hz). The major isomer appears to be the *cis* isomer by analogy with results in ref. 8 where the 1'H in the *trans* isomer appears as a triplet whereas that for the *cis* appears as a double doublet (signals at δ 4.75 and 4.85 ppm in our case).
1c: ^{1}H NMR ($CDCl_3$) δ 1.38-1.43 (m, 6H), 1.68-1.90 (m, 2H), 1.97 (s, 3H), 2.10-2.64 (m, 5H), 3.76-3.84 (m, 1H, 4'Ha), 4.00-4.06 (m, 0.5H, 4'Hb), 4.26-4.35 (m, 4H), 6.26 (dd, 0.5H, J=3 Hz, 6Hz, 1'Ha), 4.95 (t, 0.5H, J=7 Hz, 1'Hb), 7.51 (d, 0.5H, J=1 Hz, Ha), 7.61 (d, 0.5H, J=1 Hz, Hb), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.64, 12.76, 16.35, 35.20, 36.52, 36.85, 37.26, 40.15 (m), 42.29, 42.83, 63.08, 64.38, 64.74, 64.80, 110.66, 111.56, 119.52 (ddd, J_{CP}=215 Hz, J_{CF}= 261 Hz), 136.06, 136.22, 150.86, 163.72, 163.81.
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15. See for example: Tse, A.; Mansour, T. S. *Tetrahedron Lett.* **1995**, *36*, 7807-7810.