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A DIASTEREOSELECTIVE SYNTHESIS OF (S,S)-α-FLUORO-2,2-DIMETHYL-1,3-DIOXOLANE-4-PROPANOIC ACID METHYL ESTER, A KEY INTERMEDIATE FOR THE PREPARATION OF ANTI-HIV EFFECTIVE FLUORODIDEOXYNUCLEOSIDES

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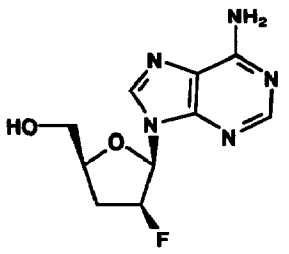
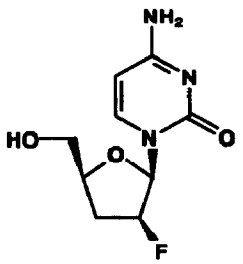
Abstract. (S,S)-α-fluoro-2,2-dimethyl-1,3-dioxolane-4-propanoic acid methyl ester (**10**), a key intermediate for the preparation of anti-HIV active 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-adenine (**1**, FddA) and 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (**2**, FddC) was prepared via the diastereoselective fluorination of the chiral imide enolate obtained from **8** with N-fluorobenzenesulfonimide. The overall yield of **10** from the readily available 1,2:5,6-di-O-isopropylidene-D-mannitol was 25% (*de* 93%).

Despite the active search for alternative modes of inhibiting HIV replication, dideoxynucleoside inhibitors of reverse transcriptase (RT) continue to play the major role as potential drugs for the treatment of AIDS.[1] Investigations on the biological activity and chemical stability of fluorine-substituted dideoxynucleosides that function as RT inhibitors have led to the discovery of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) as a promising candidate for the treatment of AIDS.[2] As a consequence, our laboratory developed a reasonably expedient approach for the synthesis of FddA[3] which is currently in use to meet the demands of drug required for preclinical studies. However, despite the advantages of this method[3] over previous approaches,[2,4] the process is still expensive and the search for a more economical alternative procedure became desirable.



1 (FddA)



2 (FddC)

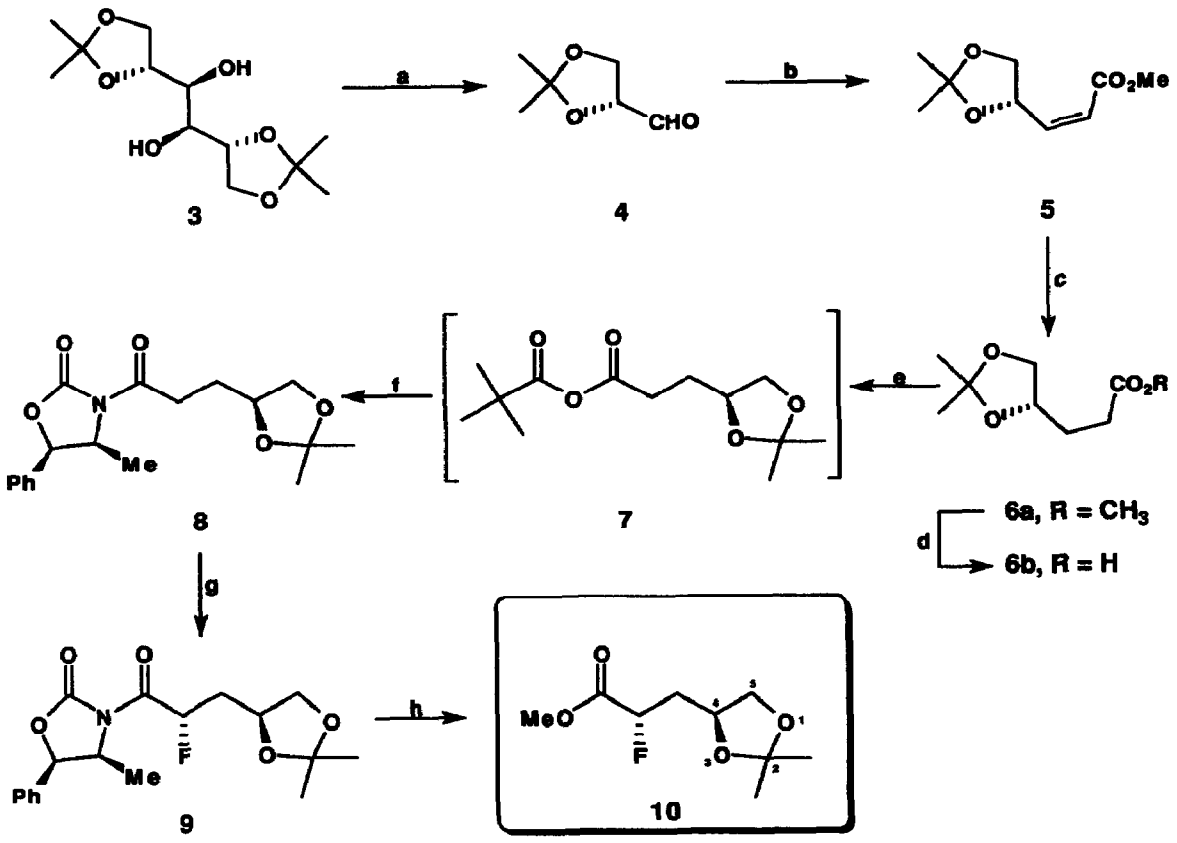
With a similar intent, Okabe, et al. (Hoffman-La Roche) produced (S,S)-α-fluoro-2,2-dimethyl-1,3-dioxolane-4-propanoic acid methyl ester (**10**) as a key intermediate precursor for the synthesis of 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (**2**, FddC).[5] Although the synthesis of **10** started

with the inexpensive sugar D-xylose, the introduction of fluorine was performed by leaving group displacement with fluoride ion which caused a loss of stereochemical control and led to a mixture of diastereoisomers that required enrichement of the desired diastereoismer by chemical or enzymatic means.[5] Since intermediate **10** also could be useful for the synthesis of FddA, we initiated a search for alternative methods to produce this compound more efficiently and with complete stereochemical control. Herein, we report a new approach to this key precursor (**10**, Scheme 1) where the fluorine atom is introduced diastereoselectively on an intermediate derived from mannitol via the reaction of a chiral enolate with an electrophilic fluorinating reagent. This type of fluorination has not, to our knowledge, been applied to the preparation of fluorinated sugars.[6]

Following the procedure of Mann, Partlett and Thomas,[7] 2,3-O-isopropylidene-D-(R)-glyceraldehyde (**4**) generated from the periodate cleavage of 1,2:5,6-di-O-isopropylidene-D-mannitol (**3**) reacted with the stabilized ylide, carbomethoxymethylene triphenylphosphorane,[8] to give methyl (S)-(Z)-4,5-O-isopropylidenepent-2-enoate (**5**), together with a small amount of the *trans* alkene. The presence of the minor isomer was irrelevant since the double bond was reduced in the following step to give methyl (S)-4,5-O-isopropylidenepentanoate (**6a**) in a combined yield of 69% over the first three steps. The ensuing hydrolysis of the methyl ester with LiOH afforded acid **6b** after neutralization. Evans' chiral auxiliary, (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone,[9,10] was reacted as the lithium salt with the mixed anhydride **7** to give (4S,5R)-3-[(S)-2,2-dimethyl-1,3-dioxolane-4-propanoyl]-4-methyl-5-phenyl-2-oxazolidinone (**8**) in excellent yield. Then, using a similar procedure to that described by Davis and Han,[11] compound **8** was converted to the corresponding sodium enolate with sodium bis(trimethylsilyl)amide and reacted with commercially available N-fluorobenzenesulfonimide[12] to give the α-fluoro compound **9** with complete diastereoselectivity (>99% *de*).[13] In their method, Davis and Han used the bicyclic fluorinating reagent N-fluoro-*o*-benzenedisulfonimide[14] which they prepared; however, for this synthesis we limited ourselves exclusively to the use of commercially available reagents. The complete diastereoselectivity obtained with the use of chiral auxiliaries is not unprecedented,[15] and in this case, it could be enhanced by the concerted directing effect of the chiral auxiliary oxazolidinone and the isopropylidene moiety in **8** blocking the same Re-face of the molecule in the transition state. The final step, which consisted of a mild magnesium methoxide methanolysis[16] of **9** proceeded to give the desired methyl ester **10** and the reusable chiral auxiliary. After this hydrolysis, however, we detected a partial loss of the stereochemical integrity at C-α which occurred due to the acidity of the α-fluoro proton. After this step, the diastereoselectivity dropped to 93% *de*, as estimated by integration of the areas of the α-protons for both diastereoisomers in the ^{1}H NMR spectrum.[17] Despite this drop in *de*, our value compares favorably with the 83.5% *de* reported by Okabe and coworkers in their synthesis of **10**.[5] The improved diastereoselectivity of the method, combined with an overall yield of 25% from **3** demonstrates the advantages of this approach when compared with a 9.7% overall yield of **10** obtained from D-xylose.[5]

Following the same chemistry reported by Okabe et al.,[5] we successfully completed the synthesis

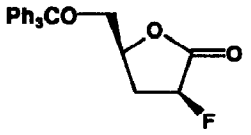
Scheme 1



Reagents and Conditions.

a. Reference 7 (92%). b. Reference 7 (87%). c. H_2, 10% Pd/C, EtOH (86%). d. LiOH, MeOH:H_2O (3:1), rt, 48 h (97%). e. Me_3CCOCl, Et_3N, THF, –78 °C. f. (4S,5R)-4-methyl-5-phenyl-2-oxazolidinone, n-BuLi, THF, –78 °C 1 h (85% from **6b**). g. $NaN(Me_3Si)_2$, THF, –78 °C, then N-fluorobenzenesulfonimide, THF, –78 °C (56%). h. MeMgBr/MeOH, 0 °C (84%).

of fluorolactone **11** and (2R,3S,5S)-2-chloro-3-fluoro-5-[(triphenylmethoxy)methyl]tetrahydrofuran (**12**) in comparable yields. Compound **12** is an immediate precursor to both FddC and FddA. The successful synthesis of FddA from **12** was achieved in our laboratory through the coupling reaction of **12** with the sodium salt of adenine. This synthesis is currently being optimized and will be the subject of a separate communication.



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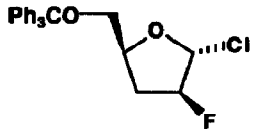

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13. *De* was determined by ^{1}H NMR. Compound **9**: clear oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 3 H, oxazolidinone 4-Me), 1.32 and 1.45 (s, 3 H, CH_3), 1.90-2.40 (m, 2 H, H-β), 3.65 (dd, J = 8.3, 6.3 Hz, 1 H, H-5_a), 4.15 (ddd, J = 8.3, 5.8, 0.7 Hz, 1 H, H-5_b), 4.40 (m, 1 H, H-4), 4.75 (m, 1 H, oxazolidinone H-4), 5.70 (d, J = 7.3 Hz, 1 H, oxazolidinone H-5), 6.15 (ddd, J = 49.4, 9.2, 3.6 Hz, 1 H, H-α), 7.20-7.50 (m, 5 H, Ph). Anal. Calcd. for $C_{18}H_{22}FNO_5$: C, 61.53; H, 6.31; N, 3.98. Found: C, 61.65; H, 6.38; N, 3.99.
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17. The ^{1}H NMR spectra of **10** (*anti*-isomer) and its *syn*-isomer are reported in reference 5. In **10**, the α-fluoro proton appears as a ddd, whereas the same proton appears as a dt in the *syn*-isomer. This is exactly what we observed, and when the spectra was recorded in benzene-d_6 the two sets of signals from each isomer were perfectly separated (*anti*:*syn* = 26:1, *de* 93%).

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