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A concise synthesis of anti-viral agent F-ddA, starting from (*S*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone

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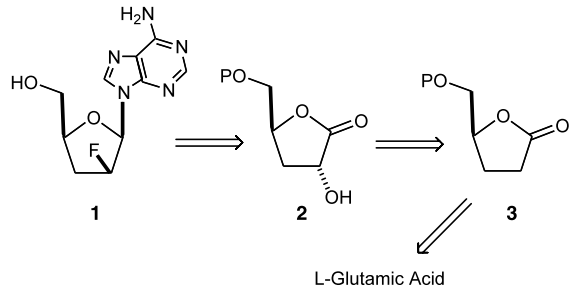
Abstract—Anti-HIV agent β-F-ddA (**1**) has been synthesized starting from readily available non-sugar, (*S*)-(+)-Dihydro-5-(hydroxymethyl)-2-(3*H*)-furanone (**4**). A highly *syn*-stereoselective fluorination of the hydroxy lactone **2** generates the key intermediate fluorolactone **5** in a short and concise synthetic sequence. Reduction of **5** followed by bromination generates the aglycon which is glycosylated to generate F-ddA by amination and deprotection. Steric bulk of the 5-protecting group has minimal effect on the steric course of glycosylation.

9-(2,3-Dideoxy-2-fluoro-β-D-threo-pentofuranosyl)-adenine (F-ddA, **1**) is a potent nucleoside-based HIV reverse transcriptase inhibitor[1] which is effective against HIV strains resistant to AZT, ddC and ddI. This nucleoside has a β-fluoro group, that is critical for its biological activity as well as stability of the molecule to either chemical or enzymatic hydrolysis.[2] Since its discovery in 1987, many syntheses of F-ddA have been reported in the literature.[1–6] Basically it has been pursued from two directions. One of the approaches starts from structurally related nucleosides, where the synthetic manipulations are mainly directed to achieve the introduction of the desired fluoro group at C-2 position with β stereochemistry, and to remove the undesired 3-hydroxyl functional group from the sugar segment.[1,3,4] The second approach, which is rather more flexible, heavily relies upon the successful glycosidic bond formation of an appropriately substituted sugar unit with the desired adenine.[5,6] While the key challenge in those syntheses has been the critical adjustment of the fluoro group stereochemistry, several synthetic steps are generally required to achieve this goal. Therefore most of the reported methods are not suitable from a process standpoint regarding scalability and cost. Recently we have reported a hydrogenation controlled scalable synthesis of F-ddA staring from mannitol.[6] In spite of its elegance and scalability, several synthetic steps including an expensive Wittig reagent were required to generate the aglycon precursor. As a part of the program, our objective was to look for an alternate and facile synthesis of the aglycon amenable for large-scale synthesis.

In this communication, we disclose our efforts towards a non-sugar based approach for the synthesis of F-ddA (**1**) starting from commercially available (*S*)-dihydro-5-(hydroxymethyl)-2-(3*H*)-furanone, which is easily accessible from inexpensive and readily available L-glutamic acid. A highly *syn* selective fluorination of the 2-OH group has been achieved using DAST as the fluorinating reagent to generate the desired flluoro-sugar. To best of our knowledge this synthesis of fluorolactone (**5**) is the shortest and the synthetic sequence is novel among the reported methods in the literature.[1–6]



Scheme 1.

Keywords: nucleosides; purines; β-fluorolactone; α-hydroxylactone.

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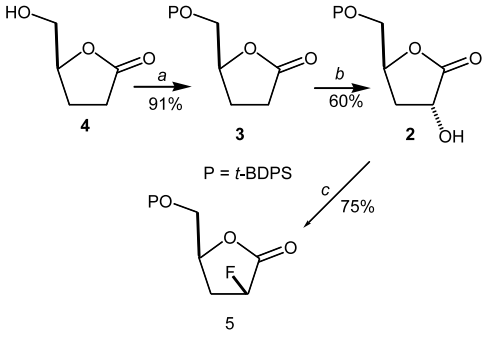
Several years ago, Hannesian and co-workers demonstrated the versatile utility of L-glutamic acid[7a] as a key material in the synthesis of many chiral intermediates, which could serve as building blocks to other asymmetric molecules. One such compound is (*S*)-(+)-dihydro-5-(hydroxymethyl)-3-hydroxy-2(3*H*)-furanone **2** (Scheme 1), a synthon which we envisioned to find application in a practical and scalable synthesis of F-ddA (**1**). Our retrosynthetic rationalization was that molecule **2**, that possesses the required stereochemistry for the hydroxymethyl group at C-5, would serve as the sugar unit in F-ddA. The lactone functionality could be manipulated for the desired glycosidic bond formation, and it also is devoid of unnecessary functional group at C-3, which needs to be removed in other sugar based synthetic approaches. More importantly, the crucial β-fluoro bond can likely be introduced via a S_N2 displacement of the α-hydroxyl group at the C-2 position[8] (Scheme 1).

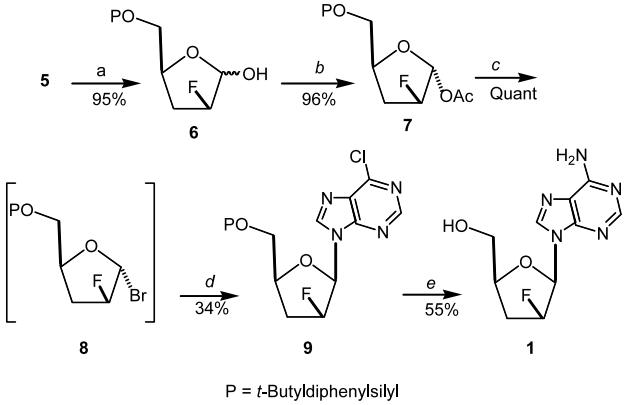
We therefore focused our attention on the synthesis of **5** (Scheme 2). Following Hanessian's protocol, reaction of (*S*)-(+)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**4**) with *t*-BDPS-Cl in the presence of imidazole afforded a 91% yield of TBDPS-ether **3**.[9] While this steric requirement was necessary to control the diastereoselection of the enolate oxidation in the next step, we were interested but were unaware of the effect of the steric bulk of 5-protection on the key glycosylation step.

The oxidation of the lithium enolate of **3** using MoOPH reproducibly gave an 80% solution yield with a 7:1 diastereoselectivity.[7a] The desired major diastereomer was readily crystallized from the reaction mixture and isolated in 60% yield. Attempts to replace MoOPH[7b] with other oxidizing agents to improve the oxidation step was investigated. Oxidation of enolate of **3** using Davis reagent (camphor-derived oxaziridine)[10] also resulted in a 7:1 ratio of diastereomers (the major diastereomer being the desired one). The separation of the desired material from camphor residue was tedious. In a preliminary scouting Thornton's protocol[11] using Jacobsen's salen catalyst gave a very high stereoselectivity of the desired product (25:1) but with low (25–30%) isolated chemical yield. The low yield resulted from the facile de-silylation of the enolsilylether during the reaction to give the starting material **3**. Rubottom oxidation[12] of the silyl enol ether also was not successful, largely giving starting material back. The next task was the key fluorination of the 3-OH group of **2**. Treatment of hydroxylactone **2** with 1 equiv. of DAST at −78°C followed by warming to room temperature generated fluorolactone **5** as a crystalline solid[13] which was isolated in 75% yield with no detectable epimer by ^{19}F NMR indicating a highly *syn* stereoselective fluorination. It should be noted that a successful DAST mediated fluorination on the epimeric lactone derived from L-ribose[14a] has been demonstrated, where fluorination takes place *anti* to the bulky C-5 protected *t*-butyldimethylsilyl group. Moreover, Liotta et. al also have reported an electrophilic *anti* fluorination on the Li enolate of the lactone **3**.[14b] *Despite our skepticism, we were pleased to see a syn fluorination in* ***2*** *which gives the requisite stereochemistry for our intermediate.*



Scheme 2. *Reagents and conditions*: (a) *t*-butyl diphenylsilylchloride, imidazole, CH_2Cl_2; (b) $Li(HMDS)_2$, THF, −78°C, MoOPH; (c) DAST, CH_2Cl_2, −78°C to rt.

The reduction of the lactone functionality (Scheme 3) was achieved using DIBAH at −78°C producing an inseparable mixture of lactols **6** in 95% isolated yield.[15] Acetylation of this mixture with Ac_2O/pyridine afforded 96% yield of α-acetate **7** as the dominant stereoisomer (>98%). We were then set to glycosylate the requisite purine base in presence of a bulky 5-TBDPS group.[5a] The stereodirecting ability of 2-F substituent in this type of glycosylation has several precedents in the literature, placing the nucleoside base in the desired β-sense.[16] The α-acetate was converted to bromide **8** (>98% of α-bromide measured by ^{19}F NMR) in-situ by using TMSBr with a catalytic of $BiBr_3$.[17] From preliminary investigation, it seems the regio and stereochemistry of the glycosylation depends on the choice of solvent and temperature, although this needs to be further explored and optimized. Using dichloromethane as the solvent, the glycosylation resulted in a 34% isolated yield[18] of the desired product **9** as an α/β mixture (N9/β:N9/α = 8:1) along with the undesired regioisomeric (i.e. due to nucleophilic attack of N7 nitrogen of the adenine segment) product mixture (N7/β:N7/α = 8:1, N7β = 8.5%). With a 2:1 mixture of aceto-



Scheme 3. *Reagents and conditions*: (a) DIBAL-H, −78°C, α:β (4:1); (b) Ac_2O, Py; (c) TMSBr/cat. BiBr; (d) 9-TMS-6-Cl-purine. CH_2Cl_2, overnight; (e) i. TBAF, THF; ii. NH_3 in MeOH, 100°C, 18 h.

nitrile: dichloroethane, almost identical isolated desired product yield (**9**, 33%) along with a 13% of the undesired N7β product were obtained. Comparing the stereodirecting effect of 5-*t*-BDPS protecting group versus 5-*p*-methylbenzoyl on the glycosylation step[6] (CH_3CN, rt, 16 h, N9/β:N9/α = 5:1, N7β = 10–15%, Ref. 6), it is safe to say that the steric bulk of the 5-protecting group has a minimal influence on the topology of glycosylation step under similar reaction conditions. The *t*-butyldiphenylsilyl protecting group was removed using TBAF/THF and treatment of the crude with NH_3/MeOH at 100°C for 18 h generated F-ddA (**1**) in 55% overall yield in two steps and in a one-pot sequence.

In conclusion we have demonstrated that the hydroxy lactone **2** (obtained from commercially available **4** in two short steps), can be converted to fluorolactone **5** in high yield and selectivity. The subsequent glycosylation with silylated base followed by deprotection of *t*-TBDPS group and subsequent amination generated F-ddA. With several asymmetric enolate oxidation protocols in literature and availability of DAST substitutes, this sequence presents a promising future for F-ddA synthesis.

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This paper is dedicated to Professor Ralph F. Hirschmann on the occasion of his 80th birthday. We thank Tom Neiss and Barbara Stephens for analytical support. This work was carried out at DuPont Pharmaceuticals.

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13. Spectral data for compound **5**: (3*S*,5*S*)-3-fluoro-5-(*tert*-butyldiphenylsiloxy)pentan-4-olide (**5**): white solid, mp 101°C; ^{1}H NMR ($CDCl_3$): δ 7.68–7.64 (m, 4H), 7.47–7.38 (m, 6H), 5.25(dt, J = 8.8 and 51.28 Hz, 1H), 4.53–4.47 (m, 1H), 3.92 (ddd, J = 1.26, 3.53 and 11.62 Hz, 1H), 3.73 (dd, J = 11.62, 3.79 Hz, 1H), 2.71–2.62 (m, 1H), 2.59–2.45 (m, 1H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.2 (d, J = 21.06 Hz), 135.6, 135.5, 132.7, 132.4, 130, 129.97, 127.9, 85.8 (d, J = 192.8 Hz), 76.3 (d, J = 6.13 Hz), 63.9, 30.3 (d, J = 19.74 Hz), 26.7, 19.2; ^{19}F NMR ($CDCl_3$): δ −193.5 (ddd, J = 6.88, 24.66 and 51.63 Hz). HRMS calcd for $C_{21}H_{25}O_3FSi$ [M+H] 373.1635, found 373.1636.
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18. To a solution of compound **6** (3.8 g, 10.2 mmol) in 30 mL of dichloromethane was added pyridine (1.8 mL, 22.3 mmol) followed by acetic anhydride (2.1 mL, 22.3 mmol). The reaction mixture was stirred for 3 days. Standard work-up provided the crude acetate **7** (3.9 g) as an oily product. ^{1}H NMR ($CDCl_3$): δ 7.68–7.64 (m, 4H), 7.42–7.35 (m, 6H), 6.32 (d, J = 9 Hz, 1H), 5.13 and 4.95 (ddt, 1H, J = 55.88, 5.4, 1.2 Hz), 4.47–4.8 (m, 1H), 3.83–3.64, m, 2H), 2.49–2.1 (m, 2H), 2.05 (s, 3H), 1.05 (s, 9H). To a solution of compound **7** (1.02 g, 2.45 mmol) in dichloromethane at 0°C was added $BiBr_3$ (50 mg) followed by TMSBr (1.3 mL). The solution was stirred in ice bath until the absence of **7** was observed

by TLC. The mixture was quenched with saturated aqueous sodium bicarbonate then washed with and finally water. The solution was concentrated in vacuo to give crude **8** (1.03 g) as an oil. Separately 6-chloropurine (760 mg, 8.3 mmol) and ammonium sulfate (20 mg) were suspended in 20 mL of hexamethyldisilazane, heated to reflux and held for 3 h. The solution was concentrated in vacuo to a crude solid which was dissolved in dichromethane (8 mL) and treated with crude bromide **8**. After stirring overnight at rt the mixture was concentrated in vacuo then chromatographed on silica gel with EtOAc/hexane to give compound **9** (400 mg, 34%) as a white solid. ^{1}H NMR ($CDCl_{13}$): δ 8.73 (s, 1H), 8.37 (s, 1H), 7.71–7.67 (m, 5H), 7.45–7.37 (m, 5H), 6.42–6.33 (m, 1H), 5.41–5.2 (m, 1H), 4.4–4.32 (m, 1H), 3.94–3.84 (m, 2H), 2.62–2.47 (m, 2H), 1.09 (s, 9H).