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(2*R*,3*S*,5*S*)-2-Acetoxy-3-fluoro-5-(*p*-toluoyloxymethyl)tetrahydrofuran: a key intermediate for the practical synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA)

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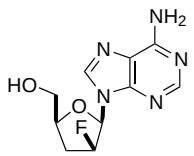
Abstract—A highly efficient synthesis of (2*R*,3*S*,5*S*)-2-acetoxy-3-fluoro-5-(*p*-toluoyloxymethyl)tetrahydrofuran (**2a**) was developed. As a key intermediate, **2a** was effectively applied to the synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA), thus, providing a practical synthetic approach to FddA.

9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA, **1**) is a novel drug candidate for the treatment of AIDS.[1–3] One major developmental issue of this compound is the lack of a practical, commercial process. Although extensive efforts have been devoted to the discovery of new synthetic approaches,[1,2,4–9] the challenge of identifying a scalable process for FddA still remains. Several methods for the synthesis of FddA have been reported based on the modification of non-fluorinated nucleosides such as cordycepin.[4,5] However, the ineffective introduction of the fluorine atom in the required β-orientation of the aglycone renders these methods impractical for a large scale synthesis. Though attractive in principal, more convergent approaches[2,6,10] consisting of coupling a fluorosugar, especially a 3-deoxy fluorosugar (**2**), with the purine base remain problematic due to the inefficient coupling reaction and the difficult synthesis of the fluorosugar. Our intensive research efforts on this problem have led to the development of a scalable process for FddA based on the key intermediate **2a**. Herein, we would like to report our results.



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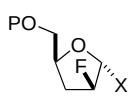

2

2a: P = *p*-$CH_3C_6H_4CO$
X = OAc

Patrick et al. reported a synthesis of (*S*)-(−)-2-fluoro-4-(hydroxymethyl)-2-buten-4-olide (**3**)[11] and its application to the preparation of 1-(2′-fluoro-2′,3′-dideoxy-β-D-*threo*-pentofuranosyl)thymine.[12] Recognizing the potential of **3** as a feasible precursor of a variety of 3-deoxy fluorosugars **2** and the potential key role a suitable 3-deoxy fluorosugar might play in the FddA process development, we were attracted to the conversion of **3** into FddA through the intermediacy of a reliable 3-deoxy fluorosugar. To this end, we have developed a highly efficient synthesis of 3-deoxy fluorosugar **2a** (Scheme 1).

Toluoylation of the fluoroolefin **3** gave **4** as a crystalline solid in an excellent yield (95%). The highly crystalline nature of **4** made it possible to prepare this compound directly from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol without purifying any intermediates in a yield of 65%. Compound **4** was hydrogenated to **5**[13] in the presence of Pd-C in quantitative yield but, surprisingly, with a diastereoselectivity which

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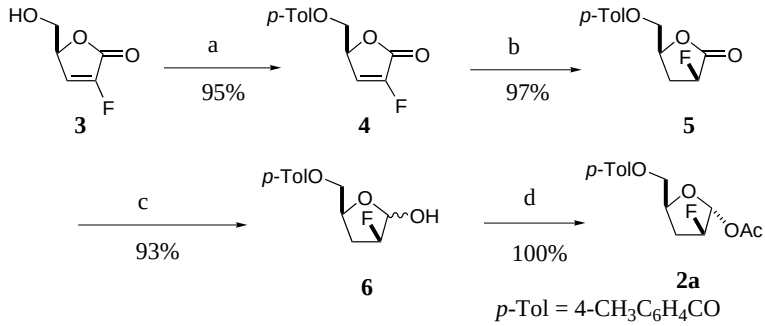
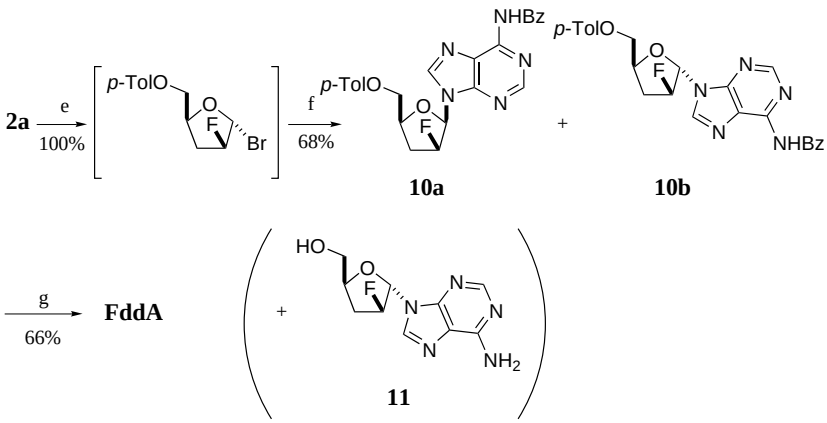


Scheme 1. *Reagents and conditions*: (a) *p*-TolCl, Py, CH_2Cl_2, 0°C–rt; (b) 5% Pd-C, H_2 (10 psi), EtOAc, rt; (c) red-Al, 2-hydroxypyridne, THF, −30°C; (d) Ac_2O, cat. conc. H_2SO_4, CH_2Cl_2, rt.

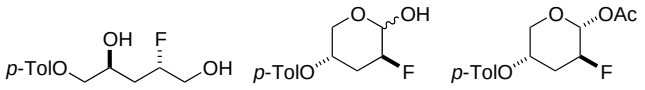
is dependent on the hydrogen pressure. When the hydrogenation was conducted at a hydrogen pressure of 40 psi, a moderate diastereoselectivity (79.5% de) was observed; however, at 20 psi the diastereoselectivity was increased to 90%. A satisfactorily high diastereoselectivity (98%) was achieved at a H_2 pressure of 10 psi. The structure of **5** was determined by single-crystal X-ray crystallography.

Although reduction of a γ-lactone to the corresponding lactol is a common transformation,[14–20] conversion of **5** into **6** was initially found to be problematic. When **5** was treated with DIBAL-H at −78°C in CH_2Cl_2, the desired lactol **6** was obtained in a yield of only 40% after quenching with MeOH. A significant amount of the over-reduction product **7** (30%) was isolated along with the tetrahydropyran **8** (15%), which was characterized by conversion into its corresponding acetate **9**. This pyranose presumably results from migration of the toluoyl group. Indeed, investigation into the formation of pyranose **8** indicated that it was mainly generated during the work-up. It was further observed that exposure of **6** to bases such as Et_3N or aqueous NaOH leads to a partial conversion into **8**, suggesting that **8** results from a base-induced toluoyl group migration of **6**. Based on these observations, we eliminated the formation of **8** by quenching the reduction under acidic conditions with acetic acid rather than under basic conditions using MeOH or H_2O. To selectively reduce **5** to the desired lactol **6**, a wide array of reducing reagents with varying degrees of reducing ability such as $NaBH_4$,[15] L-Selectride,[16] red-Al,[17] disiamylborane,[18] Vitride solution[19] and $LiAlH(Ot\text{-}Bu)_3$[20] were screened to effect this reduction, but all failed to give satisfactory results. We reasoned that a selective reducing reagent should possess the ability to efficiently stabilize the lactoxide intermediate so that an over-reduction can be prevented. Thinking along this line, we tried a combination of LAH with various alcohols of varying p*K*as such as phenol, MeOH, EtOH, CF_3CH_2OH, aiming to lower the reducing ability of LAH while, in the meantime, to increase its coordination ability with the lactoxide. As expected, we observed that the lower the p*K*a of the alcohol, the more selective its combination with LAH. When the alcohol was phenol and at a reaction temperature of −78°C, **6** was obtained in an isolated yield of 93% with less than 4% of by-product **7**. Excellent selectivity can also be achieved by the combination of LAH with other alcohols such as hydroxypyridine, or combination of other aluminum hydride such as red-Al with alcohols. A more impressive combination which offers practical advantage over the combination of LAH and phenol is that of red-Al with 2-hydroxypyridine. This reducing reagent allows **5** to be converted into **6** at higher temperature (−30°C) with a comparable efficiency and selectivity. Finally, a quanti-



Scheme 2. *Reagents and conditions*: (e) AcOH–HBr, CH_2Cl_2; (f) *N*-benzoylaminopurine, NaH, THF, reflux; (g) MeONa, MeOH, reflux.

tative conversion of **6** into **2a** was achieved by treatment with Ac_2O and catalytic concentrated H_2SO_4.



7 **8** **9**

With a highly efficient and economically feasible synthesis of **2a** developed, we then studied its conversion to FddA as shown in (Scheme 2). Coupling of a 3-deoxyfluorosugar with a purine base has been plagued by low yields and poor β/α selectivity, necessitating a tedious separation of the desired β anomer.[6] To improve the β/α selectivity, a 3-deoxyfluorosugar is usually converted into its corresponding 1-α-halosugar which is then coupled with a base under conditions favoring an SN_2 nucleophilic displacement. To define a process for coupling **2a** with a purine base suitable for large-scale synthesis of FddA, we screened different derivatives of purine bases. For the coupling reaction, **2a** was first converted into the corresponding α-bromosugar stereoselectively in quantitative yield by treatment with HBr/HOAc. The bromosugar was then reacted with a purine base either as its persilylated analog or the sodium salt. We found that coupling of the sodium salt of 6-*N*-benzoylpurine with **2a** in THF gave a cleaner reaction and better β/α selectivity than using purine or 6-chloropurine. Thus, after conversion into its corresponding α-bromide, **2a** was treated with the sodium salt of 6-*N*-benzoylpurine generated by reaction of 6-*N*-benzoylpurine with NaH in refluxing THF to afford the desired coupling product **10a** and its anomer **10b** in a yield of 68% and with a β/α ratio of 8 to 1. Although separation of **10a** from **10b** at this stage proved difficult, a facile recrystallization after hydrolysis easily yielded pure FddA free of the corresponding hydrolysis product of **10b**, the α-anomer of FddA (**11**). In this manner, we converted **2a** into FddA in an overall yield of 45% after recrystallization.

In conclusion, we have developed a highly efficient synthesis of the 3-deoxy fluorosugar **2a** and converted it into FddA via an efficient process. The high efficiency in each step and simplicity of the purification of the intermediates and the final product render this route practical for large-scale synthesis of FddA. In addition, the intermediate **2a** should prove to be a useful building block for the synthesis of other 3-deoxyfluoro nucleosides.

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13. Spectral data for compound **5** and its α-epimer. (*3R*,*5S*)-3-Fluoro-5-(*p*-toluoyloxymethyl)-2-tetrahydrofuranone (**5**): white solid, mp 138–140°C; ^{1}H NMR ($CDCl_3$) δ 2.39 (m, 1H), 2.40 (s, 3H), 2.86 (m, 1H), 4.42 (dd, J=11.0, 4.8, 1H), 4.60 (dd, J=12.0, 3.0, 1H), 4.80 (m, 1H), 5.30 (dt, J=50.9, 8.8, 1H), 7.24 (d, J=8.1, 2H), 7.92 (d, J=8.1, 2H); ^{19}F NMR ($CDCl_3$) δ −193.2 (m); MS (ESI) m/z (relative intensity %), 253 (M+1, 100); Anal. calcd for $C_{13}H_{13}FO_4$: C, 61.90; H, 5.20. Found: C, 61.90; H, 5.13. (*3S*,*5S*)-3-Fluoro-5-(*p*-toluoyloxymethyl)-2-tetrahydrofuranone (α-epimer of **5**): white solid, mp 68–70°C. ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.57–2.76 (m, 2H), 4.52 (m, 2H), 5.06 (m, 1H), 5.36 (ddd, J=52.0, 7.3, 6.6, 1H), 7.27 (d, J=8.1, 2H), 7.86 (d, J=8.1, 2H); ^{19}F NMR ($CDCl_3$) δ −190.3 (m); MS (ESI) m/z (relative intensity %), 253 (M+1, 100). Anal. calcd for $C_{13}H_{13}FO_4$: C, 61.90; H, 5.20. Found: C, 61.85; H, 5.19.
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