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Tetrahedron 60 (2004) 3445–3449
Tetrahedron

A stereoselective synthesis of 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine, a potentially useful intermediate for ribonucleoside synthesis☆,☆☆

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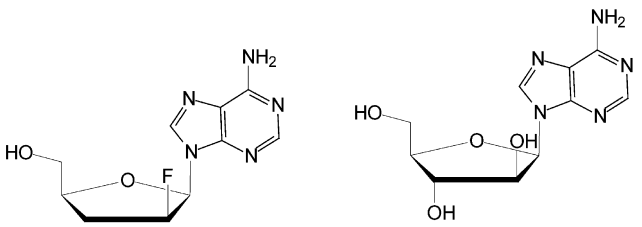
Received 2 December 2003; revised 17 February 2004; accepted 17 February 2004

Abstract—A novel synthesis for preparing 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (**6**) has been developed which does not require sub zero temperatures or exotic reagents. A key step in this synthesis is the selective protection of the 3′-OH of ara-A with a benzyl group. The 5′-OH is then selectively protected with DHP to yield **6**, a potentially useful intermediate. A synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA), an anti-viral compound, is given to illustrate the utility of this new approach.

1. Introduction

Purine nucleosides bearing fluorine at C2′ have been studied intensely the past few years because of their biological activity. For example, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) has been investigated for its anti-viral activity against HIV.[1] Several methods for synthesizing **1** have been reported,[1b,2] all of which take one of two general approaches: (1) coupling of a fluorinated sugar with a purine base,[1a,2a] and (2) fluorination and transformation of a pre-formed nucleoside derivative.[2b–g] A key step in the latter, more attractive synthetic approach is the selective protection of 3′-OH of the ribonucleosides prior to fluorination at the 2′ position. The similar reactivity of the 2′ and 3′-OH groups of ribonucleosides makes selective protection of either of these functionalities difficult. There are a limited number of selective methods for protecting 3′-OH of purine ribonucleosides.[3] Herein is reported a new way to conveniently protect 9-(β-D-arabinofuranosyl)adenine (**2**, ara-A) at 3′-OH. Once 3′-OH is selectively protected the 5′-OH can be easily protected with a different blocking group to afford a useful intermediate for nucleoside synthesis. This intermediate was used in a convenient method for preparing **1**.



1 (FddA) **2 (ara-A)**

2. Results and discussion

Commercially available **2** is easily converted to 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**3**) in high yield.[4a–c] Nucleophiles such as acetate[4c] and azide[4d] preferentially attack the α-face of **3** at C3′ yielding 3′-substituted adenine arabinosides (**4a**-**b**, Scheme 1). We have now demonstrated that when a salt of benzyl alcohol is employed for the nucleophilic ring-opening, 9-(3-*O*-benzyl-β-D-arabinofuranosyl)adenine (**4c**) is obtained in 74% yield. The preparation of **4c** is performed in benzyl alcohol solvent with the sodium salt of benzyl alcohol, as generated by NaH or *t*-BuONa. The sodium counter ion seems to give the best results but potassium and magnesium have also been used successfully. Desired isomer **4c** is formed preferentially over the 2′-*O*-benzyl isomer (**5c**) in a ratio of ~6:1. This manipulation effectively provides ara-A that is blocked by a benzyl group at 3′-OH. The benzyl fragment is an excellent

☆ CDRI Communication No. 6414.

☆☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2004.02.033

Keywords: Fluororibonucleoside; Ara-A; 9-(3-*O*-Benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine; 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine; FddA.
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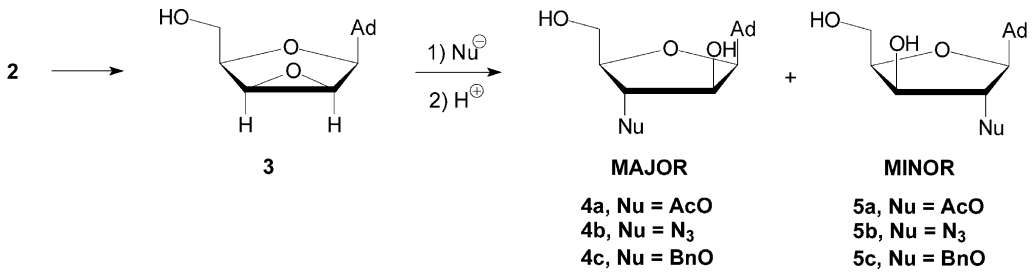
doi:10.1016/j.tet.2004.02.033



Scheme 1.

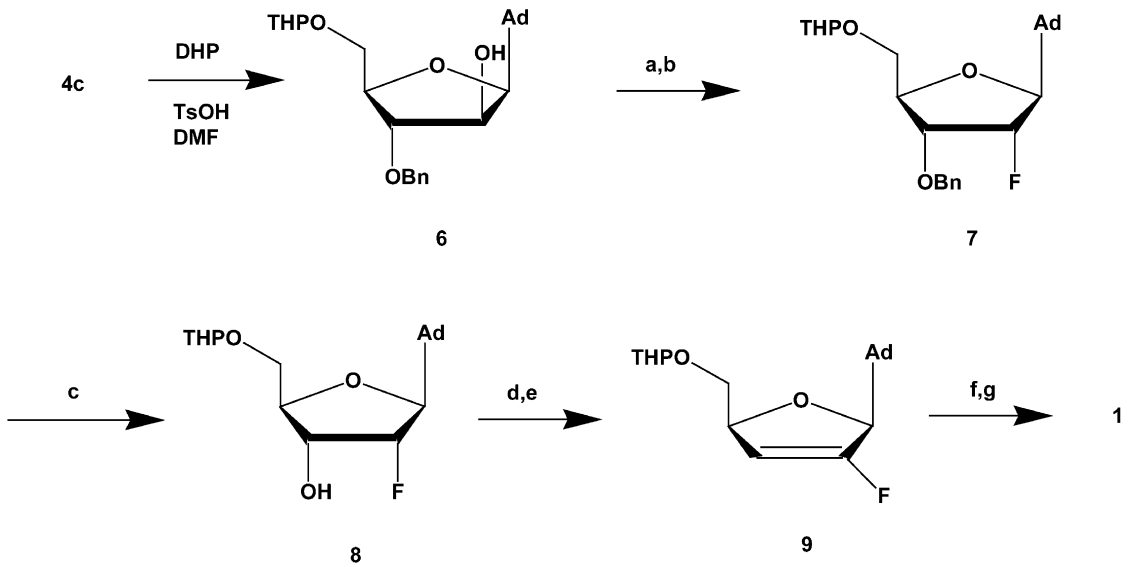
protecting group for preparing 2′-fluororibonucleosides because it will survive fluorination conditions, will not migrate, as is often seen for acetyl and benzoyl groups, and can be selectively removed.

With the 3′-OH blocked, the primary 5′-OH can be protected easily and selectively to leave only the 2′-OH free for fluorination. A variety of reagents can be used to block 5′-OH but dihydropyran (DHP) appears to be the most amenable to the downstream chemistry for preparing **1**. The resulting tetrahydropyranyl group will not be removed under the hydrogenation conditions used to remove the benzyl-protecting group and will not be affected by the fluorination conditions. Hence, when **4c** is reacted with DHP in DMF at 0 °C, the desired 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (**6**) is obtained in 85% yield after column chromatography. Thus, ara-A derivatives bearing different protecting groups on 3′-OH and 5′-OH are easily obtainable. The presence of different protecting groups at 3′ and 5′ provides synthetic flexibility because it allows selective removal of either group.

Once the 3′- and 5′-OH groups have been blocked, the 2′-OH can be converted to a leaving group and displaced by fluoride. Fluorination of purine nucleosides by S_N2 displacement at the β-face of C2′ is notoriously difficult[1b,2f–g] while fluorination from the α-face is readily accomplished.[5] Marquez, et al.[2c] took advantage of this behavior in their synthesis of **1** by fluorinating a protected ara-A derivative from the α-face, eliminating to a vinyl fluoride intermediate and selectively hydrogenating. By this sequence, they were able to effectively invert the stereochemistry at C2′ while deoxygenating C3′ to produce **1**. The same general approach can be used to transform **6** into **1** (Scheme 2).

Fluorination of **6** was accomplished by converting the 2′-OH to the triflate and displacing with tetrabutylammonium fluoride in THF to yield **7** in 65% yield after column chromatography to remove the elimination co-product and ammonium salts. The benzyl protecting group of **7** can be removed, without affecting the THP group, by hydrogenolysis using Pearlman's catalyst and cyclohexene as a hydrogen donor.[6] Thus, **7** was refluxed in ethanol and cyclohexene in the presence of 20–40% (based on weight of **7**) dry Pearlman's catalyst to afford **8** in 81% isolated yield. Interestingly, Pd/C and hydrogen at 150 °C and 180 psi removed only the THP group. Under these conditions, the hydrogenation catalyst may behave like a Lewis acid causing transketalation of the THP group with the ethanol solvent.

Reaction of **8** with Tf_2O in the presence of DMAP and pyridine was rapid and clean. The reaction mixture was washed with 10% Na_2CO_3 (aq.) and concentrated to isolate



Scheme 2. Key: (a) Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; (b) TBAF, THF, 0 °C; (c) $Pd(OH)_2/C$ (20%), cyclohexene, EtOH, reflux; (d) Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; (e) *t*-BuOK, DMSO, rt; (f) H_2, Pd/C (10%), THF; (g) pyridinium DOWEX 50, EtOH, MeOH.

the triflate intermediate, which is quite stable. The crude triflate was dissolved in DMSO and treated with potassium *tert*-butoxide at ambient temperature. The vinyl fluoride, **9**, was isolated in 85% yield. Hydrogenation of **9** was performed in a non-protic solvent in order to avoid removal of the THP group at this point. The THP group lends solubility to the reduced product, **10**, which aids in its removal from the hydrogenation catalyst support. After filtering and washing the catalyst, the THP group was removed using the mild deprotection method of Uesugi, et al.[7] The solution is stirred with pyridinium DOWEX 50. After a few hours, the THP group is removed cleanly. FddA, **1**, is thus obtained in 80% yield from **9**.

3. Conclusion

We have developed a simple and efficient method to selectively protect and deprotect 3′- and 5′-OH of ara-A (**2**) which is potentially useful for the synthesis of a variety of adenosine derivatives. This ability of selective protection of ara-A with different blocking groups allows great synthetic flexibility. This methodology has been employed to prepare FddA (**1**) from commercially available ara-A (**2**) by a relatively short synthetic sequence in 28% overall yield without the use of expensive protecting groups or undesirable fluorinating reagents.

4. Experimental

4.1. General

All new compounds were determined to be >95% pure by HPLC and NMR.

4.1.1. 9-(3-*O*-Benzyl-β-D-arabinofuranosyl)adenine (4c). Fresh sodium *tert*-butoxide (81.0 g, 0.843 mol) was added to benzyl alcohol (700 mL). After stirring 10 min., the yellow solution was cooled to room temperature. Dry 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**3**)[4d] (70.0 g, 0.281 mol) was added to the solution over a 5 min period. The tan slurry was heated to 65 °C for 7 h. The resulting brown solution was cooled to 25 °C and quenched with acetic acid (51.0 g) and water (200 mL). The upper, organic layer was separated and concentrated in vacuo. The residue was purified by silica gel column chromatography to give **4c** (74.34 g, 74% yield) and **5c** (12.25 g, 12% yield) as off-white solids.

Compound **4c**. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.19 (1H, s, HC_8), 8.12 (1H, s, HC_2), 7.25–7.48 (5H, m, Ph), 7.24 (2H, br.s, H_2N), 6.24 (1H, d, HC_1', J=4.9 Hz), 5.81 (1H, d, HOC_2', J=4.9 Hz), 5.19 (1H, t, HOC_5', J=5.3 Hz), 4.70 (1H, d, H′C–Ph, J=11.8 Hz), 4.62 (1H, d, H″C–Ph, J=11.8 Hz), 4.36 (1H, m, HC_2'), 4.13 (1H, dd, HC_3', J_1=J_2=3.8 Hz), 3.98 (1H, ddd, HC_4', J_1=3.8 Hz, J_2=J_3=5.1 Hz), 3.65 (2H, m, H_2C_5'). Signal assignment was made on the basis of the COSY experiment. ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 155.9, 152.5, 149.3, 140.2, 138.1, 128.3 (2C), 127.6 (3C), 118.2, 83.8, 83.4, 82.4, 73.7, 70.9, 61.2. MS (high res.) actual 357.1425, calculated 357.1437.

Compound **5c**. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.26 (1H, s, HC_8), 8.18 (1H, s, HC_2), 7.43 (2H, br.s, H_2N), 7.22–7.33 (5H, m, Ph), 6.08 (1H, br.s, HC_1'), 5.99 (1H, br.s, HOC_3'), 4.82 (1H, br.s, HOC_5'), 4.68 (2H, br. s, H_2C–Ph), 4.26 (2H, m, HC_3'+HC_2'), 4.13 (1H, m, HC_4'), 3.78 (1H, dd, H″C_5', J_1=5.1 Hz, J_2=10.9 Hz), 3.68 (1H, dd, H′C_5', J_1=6.26 Hz, J_2=10.9 Hz). Signal assignment was made on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 152.2, 148.5, 139.5, 137.6, 128.3 (2C), 127.7, 127.7 (2C), 118.9, 88.3, 87.6, 84.0, 72.8, 71.0, 59.3. Column chromatography can be avoided if crude **4c** is recrystallized from 3:1 methanol/water. The yield from two crops is 49%.

4.1.2. 9-(3-*O*-Benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (6). To a 0 °C solution of **4c** (33.0 g, 0.092 mol) and dried *p*-toluenesulfonic acid (35.3 g, 0.205 mol) in anhydrous *N*,*N*-dimethylformamide (500 mL) was added 3,4-dihydro-2*H*-pyran (77.7 g, 0.923 mol). The reaction progress was monitored by HPLC. After <5% **4c** remained, the reaction mixture was treated with 10% $NaHCO_3$ (aq, 300 mL). The mixture was diluted with water (1.2 L) and extracted with chloroform (2×1 L). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed through a column of silica gel. Fractions containing the product were combined and concentrated to afford **6** as an off-white solid (34.5 g, 85% yield). There are two diastereomers with a ratio 1:1 due to a non-stereoselective attachment of the THP group. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–8.18 (2H, 4 separate s, HC_8+HC_2), 7.36–7.26 (5H, m, Ph), 6.36 (1/2H, d, H_1C_1', J=3.7 Hz), 6.34 (1/2H, d, H_2C_1', J=3.7 Hz), 6.30 (2H, H_2N), 5.60 (1H, br.s, HO), 4.77 (1/2H, d, H_1'C–Ph, J=11.6 Hz), 4.76 (1/2H, d, H_2'C–Ph, J=11.6 Hz), 4.67 (1/2H, m, H_1CO_2–THP), 4.65 (1H, d, H_1''C–Ph, J=11.6 Hz), 4.65 (1H, d, H_2''C–Ph, J=11.6 Hz), 4.59 (1/2H, m, H_2CO_2–THP), 4.53 (1/2H, dd, H_1C_2', J_1=2.87 Hz, J_2=3.7 Hz), 4.54 (1/2H, dd, H_2C_2', J_1=2.9 Hz, J_2=3.7 Hz), 4.29 (1/2H, m, H_1C_4'), 4.28 (1/2H, m, H_2C_4'), 4.25 (1/2H, dd, H_1C_3', J_1=2.9 Hz, J_2=3.3 Hz), 4.19 (1/2H, dd, H_2C_2', J_1=2.9 Hz, J_2=3.7 Hz), 4.07 (1/2H, dd, $H_2'C_5'$, J_1=3.6 Hz, J_2=10.8 Hz), 3.97 (1/2H, dd, $H_1'C_5'$, J_1=3.6 Hz, J_2=10.8 Hz), 3.81 (1/2H, m, H_2'CO–THP), 3.71 (1/2H, dd, $H_2''C_5'$, J_1=3.6 Hz, J_2=10.8 Hz), 3.69 (1/2H, m, H_1'CO–THP), 3.58 (1/2H, dd, $H_2''C_5'$, J_1=3.59 Hz, J_2=10.8 Hz), 3.49 (1H, m, H_2CO–THP), 1.8–1.5 (6H, m, THP). Signal assignment was made on the basis of the COSY experiment of a recrystallized sample that has some enrichment of one stereoisomer. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (1C), 153.2 (1/2C), 153.1 (1/2C), 150.0 (1/2C), 149.9 (1/2C), 140.9 (1/2C), 140.7 (1/2), 137.6 (1/2C), 137.5 (1/2C), 128.9 (2C), 128.4 (1C), 128.1 (1C), 128.1 (1C), 119.6 (1/2C), 119.5 (1/2C), 99.38 (1/2C), 99.35 (1/2C), 86.1 (1C), 84.06 (1/2C), 83.95 (1/2C), 82.1 (1/2C), 82.0 (1/2C), 74.5 (1/2C), 74.4 (1/2C), 72.3 (1C), 67.24 (1/2C), 67.19 (1/2C), 62.53 (1/2C), 62.49 (1/2C), 30.26 (1/2C), 30.24 (1/2C), 25.4 (1/2C), 25.1 (1/2C), 19.4 (1/2C), 19.3 (1/2C). MS (high res.) actual 442.2072, calculated 442.2090.

4.1.3. 9-(3-*O*-Benzyl-2-deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (7). 4-Dimethylaminopyridine (21.6 g, 0.177 mol), pyridine (37 mL), and **6** (24.0 g, 0.054 mol) were dissolved in CH_2Cl_2 (1,440 mL)

and cooled to 0 °C under nitrogen. Trifluoromethanesulfonic acid anhydride (25.1 g, 0.089 mol) was added dropwise over 20 min. After 1 h., the reaction mixture was poured into sat. $NaHCO_3$ (aq., 1.8 L). The organic layer was removed and the aqueous washed with CH_2Cl_2 (3×350 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated at below 25 °C. The residue was taken up in THF (100 mL) and evaporated to remove all traces of CH_2Cl_2. The residue was dissolved in THF (550 mL) and cooled, under nitrogen, to 0 °C. A solution of 1 M tetrabutylammonium fluoride in THF (109 mL, 0.109 mol) was added over 30 min. The reaction progress was monitored by HPLC. After 18 h the reaction was finished. The solvent was stripped on a rotary evaporator and the residue was dissolved in CH_2Cl_2 (500 mL) and washed with sat. NaCl (aq., 3×250 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed through a column of silica gel. The desired product, **7**, was obtained as a pale yellow solid (15.7 g, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (1/2H, s, H_1C_8), 8.32 (1/2H, s, H_2C_8), 8.20 (1/2H, s, H_1C_2), 8.18 (1/2H, s, H_2C_2), 7.40–7.25 (5H, m, Ph), 6.34 (1/2H, dd, $H_1C'_1$, J_1=1.9 Hz, J_2=11.7 Hz), 6.29 (1/2H, dd, $H_2C'_1$, J_1=1.9 Hz, J_2=11.7 Hz), 5.90 (2H, br.s, H_2N), 5.46 (1H, dm, HCF, J=51.6 Hz), 4.79 (1H, dd, H′C–Ph, J_1=5.0 Hz, J_2=11.7 Hz), 4.62 (1H, m, H″C–Ph), 4.67–4.38 (3H, m, HC′3+HC′4+HCO_2–THP), 4.17 (1/2H, dd, $H'_1C'_5$, J_1=2.2 Hz, J_2=11.5 Hz), 3.98 (1/2H, dd, $H'_2C'_5$, J_1=2.9 Hz, J_2=11.5 Hz), 3.82 (1/2H, dd, $H''_2C'_5$, J_1=2.4 Hz, J_2=11.5 Hz), 3.79 (1/2H, m, H'_1CO–THP), 3.69 (1/2H, m, H'_2CO–THP), 3.53 (1/2H, dd, $H''_1C'_5$, J_1=3.35 Hz, J_2=11.5 Hz), 3.48 (1H, m, H''_1CO–THP+H''_2CO–THP), 1.80–1.40 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.64 (1/2C), 155.63 (1/2C), 153.36 (1/2C), 153.31 (1/2C), 149.44 (1/2C), 149.35 (1/2C), 139.4 (1/2C), 139.2 (1/2), 137.17 (1/2C), 137.16 (1/2C), 128.73 (1C), 128.71 (1C), 128.5 (1/2C), 128.4 (1/2C), 128.3 (1C), 128.2 (1C), 120.2 (1/2C), 120.1 (1/2C), 99.3 (1/2C), 99.2 (1/2C), 91.9 (1/2C, d, C'_2–F, J=190.4 Hz), 91.7 (1/2C, d, C''_2–F, J=189.8 Hz), 87.8 (1/2C, d, C'_1–F, J=33.2 Hz), 87.5 (1/2C, d, C''_1–F, J=32.7 Hz), 81.3 (1/2C), 81.0 (1/2C), 75.2 (1/2C, d, C'_3–F, J=33.0 Hz), 75.0 (1/2C, d, C''_3–F, J=33.0 Hz), 73.1 (1/2C), 73.0 (1C), 65.7 (1/2C), 65.4 (1/2C), 62.5 (1/2C), 62.3 (1/2C), 30.6 (1/2C), 30.4 (1/2C), 25.4 (1/2C), 25.3 (1/2C), 19.6 (1/2C), 19.4 (1/2C). ^{19}F NMR (282.3 MHz, $CDCl_3$): δ −202.58 (F_1, ddd, J_1=16.9 Hz, J_2=18.8 Hz, J_3=52.6 Hz), −203.30 (F_2, ddd, J_1=15.9 Hz, J_2=18.8 Hz, J_3=55.5 Hz). MS (high res.) actual 444.2042, calculated 444.2047.

4.1.4. 9-(2-Deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (8). Pearlman's catalyst (0.20 g, 20% Pd by wt. on a dry basis, 57% water) was dried by slurrying in absolute EtOH (25 mL) and concentrating to dryness. The dried catalyst was added to a solution of **7** (0.20 g, 0.45 mmol) in absolute EtOH (14 mL) and cyclohexene (2 mL). The reaction mixture was refluxed for 18 h at which time **8** was essentially gone. The catalyst was filtered and washed well with hot EtOH (3×10 mL) and THF (15 mL). The filtrate was concentrated to dryness and the residue was passed through a short column of silica gel eluting with $CHCl_3$/MeOH (15:1). The appropriate fractions were combined and concentrated to afford **8** as a white, foamy solid (0.13 g, 81% yield). The first product fractions contained one stereoisomer: ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.29 (1H, s, HC_8), 8.14 (1H, s, HC_2), 7.35 (2H, br.s, H_2N), 6.23 (1H, dd, HC'_1, J_1=1.7 Hz, J_2=18.0 Hz), 5.79 (1H, d, HO, J=6.5 Hz), 5.43 (1H, ddd, HC'_2–F, J_1=1.9 Hz, J_2=4.1 Hz, J=52.9 Hz), 4.60 (2H, m, HC'_3+HCO_2–THP), 4.08 (1H, m, HC'_4), 3.79 (1H, dd, H′C'_5, J_1=4.1 Hz, J_2=11.5 Hz), 3.70 (1H, dd, H″C'_5, J_1=2.6 Hz, J_2=11.5 Hz), 3.68 (1H, m, H′CO–THP), 3.41 (1H, m, H″CO–THP), 1.73–1.37 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 156.0, 152.8, 148.8, 139.0, 118.9, 97.7, 93.5 (d, C'_2–F, J=185.8 Hz), 85.9 (d, C'_1–F, J=33.8 Hz), 79.2, 68.3 (d, C'_3–F, J=16.1 Hz), 65.1, 61.0, 30.0, 24.9, 18.8. ^{19}F NMR (282.3 MHz, Me_2SO-d_6): δ −202.19 (ddd, J_1=17.8 Hz, J_2=21.7 Hz, J_3=52.5 Hz). The last few main product fractions contained the second stereo-isomer: ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.32 (1H, s, HC_8), 8.14 (1H, s, HC_2), 7.35 (2H, br.s, H_2N), 6.22 (1H, dd, HC'_1, J_1=1.9 Hz, J_2=18.7 Hz), 5.80 (1H, d, HO, J=6.2 Hz), 5.42 (1H, ddd, HC'_2–F, J_1=1.9 Hz, J_2=4.5 Hz, J=55.1 Hz), 4.62 (2H, m, HC'_3+HCO_2–THP), 4.10 (1H, m, HC'_4), 3.98 (1H, dd, H′C'_5, J_1=2.4 Hz, J_2=11.5 Hz), 3.64 (1H, m, H′CO–THP), 3.58 (1H, dd, H″C'_5, J_1=5.0 Hz, J_2=11.5 Hz), 3.41 (1H, m, H″CO–THP), 1.73–1.37 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 156.1, 152.8, 148.8, 139.2, 119.0, 98.1, 93.6 (d, C'_2–F, J=185.6 Hz), 86.0 (d, C'_1–F, J=33.5 Hz), 81.5, 68.4 (d, C'_3–F, J=16.0 Hz), 66.0, 61.0, 29.9, 24.9, 18.8. ^{19}F NMR (282.3 MHz, Me_2SO-d_6): δ −201.94 (ddd, J_1=18.9 Hz, J_2=22.0 Hz, J_3=52.5 Hz). MS (high res.) actual 353.1483, calculated 353.1499.

4.1.5. 9-(2,3-Deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-*glycero*-pent-2-enofuranosyl)adenine (9). 4-Dimethylaminopyridine (0.79 g, 6.5 mmol), pyridine (1.4 mL), and **8** (0.70 g, 2.0 mmol) were dissolved in CH_2Cl_2 (52 mL) and cooled to 0 °C under nitrogen. Trifluoromethanesulfonic acid anhydride (0.92 g, 3.3 mmol) was added dropwise over 5 min. After 2 h, the reaction mixture was poured into sat. $NaHCO_3$ (aq., 50 mL) and extracted with EtOAc (3×15 mL). The extracts were combined and dried over $MgSO_4$. The residual oil was dissolved in DMSO (63 mL) and treated with potassium *tert*-butoxide (0.44 g, 4.0 mmol). The solution immediately became dark red. After 30 min, NH_4OAc (0.38 g, 4.0 mmol) was added to quench the mixture. The DMSO solvent was stripped in vacuo to leave a yellow oil. The oil was purified by silica gel column chromatography to yield **9** as a white solid (0.56 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (1/2H, s, H_1C_8), 8.38 (1/2H, s, H_2C_8), 8.29 (1/2H, d, H_1C_2, J=1.0 Hz), 8.24 (1/2H, d, H_2C_2, J=0.7 Hz), 6.95 (1H, m, HC'_3), 6.34 (1H, td, $H_1C'_1$, J_1=1.2 Hz, J_2=7.2 Hz), 5.68 (2H, br.s, H_2N), 5.09 (1H, m, HC'_4), 4.62 (1/2H, dd, H_1CO–THP, J_1=2.9 Hz, J_2=3.9 Hz), 4.56 (1/2H, dd, H_2CO–THP, J_1=2.9 Hz, J_2=4.8 Hz), 3.99 (1H, m, H′C'_5), 3.79 (1H, m, HCO–THP), 3.61 (1H, m, H″C'_5), 3.50 (1H, m, HCO–THP), 1.92–1.45 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.40 (1/2C), 155.37 (1/2C), 153.45 (1/2C, d, C'_2–F, J=283.4 Hz), 153.44 (1C), 152.4 (1/2C, d, C'_2–F, J=283.4 Hz), 150.7 (1C), 139.4 (1/2C), 139.0 (1/2C), 119.5 (1C), 106.0 (1/2C,d, J=8.3 Hz), 105.0 (1/2C, d,

J=8.3 Hz), 99.6 (1/2C), 99.5 (1/2C), 81.9 (1/2C, d, J=28.9 Hz), 81.8 (1/2C), 81.7 (1/2C, d, J=28.9 Hz), 81.6 (1/2C), 68.5 (1/2C), 68.1 (1/2C), 62.9 (1/2C), 62.4 (1/2C), 30.4 (1/2C), 30.3 (1/2C), 25.3 (1/2C), 25.1 (1/2C), 19.8 (1/2C), 19.4 (1/2C). ^{19}F NMR (282.3 MHz, $CDCl_3$): δ −136.06 (F_1, ddd, J_1=1.4 Hz, J_2=J_3=5.3 Hz), −136.29 (F_2, ddd, J_1=2.7 Hz, J_2=J_3=5.1 Hz). MS (high res.) actual 335.1405, calculated 335.1394.

4.1.6. 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-adenine (1, FddA). A solution of **9** (1.24 g, 3.7 mmol) in THF (150 mL) was charged into a shaker bottle with 10% Pd/C (0.62 g). The mixture was hydrogenated at room temperature and 70 psi H_2 pressure. The reaction was monitored by LC/MS. After 55 h the reaction was complete so the catalyst was filtered and washed with THF (25 mL). The solvent was removed with a rotary evaporator to leave 1.08 g of a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (1H, s, HC_8), 8.20 (1/2H, d, H_1C_2, J=2.6 Hz), 8.17 (1/2H, d, H_2C_2, J=2.9 Hz), 6.38 (1/2H, dd, H_1C_1', J_1=3.6 Hz, J_3=17.2 Hz), 6.33 (1/2H, dd, H_2C_1', J_1=3.4 Hz, J_2=18.4 Hz), 6.00 (2H, br.s, H_2N), 5.29 (1H, dm, HCF, J=53.4 Hz), 4.71 (1H, m, HCO_2–THP), 4.45 (1H, m, HC_4'), 3.98 (1H, m, $H_1'C_5'$), 3.88 (1H, m, H′CO–THP), 3.69 (1H, m, $H_1''C_5'$), 3.56 (1H, m, H″CO–THP), 2.48 (2H, m, $C_3'H_2$), 1.90–1.50 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0 (1C), 153.5 (1C), 150.2 (1C), 140.5 (1/2C), 140.4 (1/2C), 119.5 (1C), 99.6 (1/2C), 99.5 (1/2C), 91.2 (1/2C, d, C_2'–F, J=190.9 Hz), 91.1 (1/2C, d, C_2''–F, J=190.2 Hz), 85.1 (1/2C, d, C_1'–F, J=16.6 Hz), 84.9 (1/2C, d, C_1''–F, J=16.6 Hz), 76.49 (1/2C), 76.48 (1/2C), 69.7 (1/2C), 69.2 (1/2C), 62.8 (1/2C), 62.7 (1/2C), 34.2 (1/2C, d, C_3', J=20.6 Hz), 33.8 (1/2C, d, C_3'', J=20.6 Hz), 30.9 (1/2C), 30.8 (1/2C), 25.7 (1C), 19.8 (1/2C), 19.7 (1/2C). ^{19}F NMR (282.3 MHz, $CDCl_3$): δ −186.8 (F_1, m), −187.4 (F_2, m). MS (high res.) actual 337.1550, calculated 337.1550. The crude solid was dissolved in 5:1 MeOH/EtOH (42 mL) and stirred with pyridinium DOWEX 50 W×2–100[8] for 2 h. The resin was filtered and washed with MeOH (25 mL), 1:1:1 pyridine/triethylamine/water (100 mL) and MeOH (25 mL). The solution was distilled to dryness to leave 0.75 g of **1** (80% from **9**). An analytical sample, which is identical to a standard sample of **1**, can be prepared by recrystallizing from EtOH (50 mL).

5. Supplementary information

NMR spectral data and high resolution mass spectra are available for each new compound.

Acknowledgements

This work was made possible by the hard work and advice of Dan Devido (LC, LC/MS) and Dallas Hallberg (NMR). We gratefully acknowledge US Bioscience, Inc. for supplying a sizable quantity of ara-A for our studies and an analytical standard of FddA. Pearlmans catalyst was generously supplied by Degussa Corp.

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8. Prepared by stirring DOWEX 50W×2–100 (2.2 g) with pyridine (10 mL) for 5 min and decanting the excess pyridine. The resin was then washed several times with MeOH.