Synthesis of 3′-Fluoro-3′-deoxyadenosine Starting from Adenosine

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A new synthesis of 3′-fluoro-3′-deoxyadenosine is described. Starting from adenosine via a suitably protected intermediate by triflate activation and nucleophilic displacement with sodium acetate, the "xylo" epimer is obtained in two cases with different silyl groups protecting the 2′-position. Treatment of the xylo derivatives with diethylaminosulphur trifluoride gives the corresponding 3′-fluoro derivatives with inversion of the configuration. The reaction sequence affords protected derivatives allowing selective deblocking of the 5′ or 2′-position.

3′-Fluoro-3′-deoxyadenosine **(11)** is a recently synthesized compound[1-3] with antiviral properties. Both the known synthetic routes start from a suitably protected xylofuranose but differ in the way of introduction of fluorine into the sugar moiety. The Herdewijn's route[2] is suitable for large scale preparation but involves more than ten steps. These steps start from commercially available D-xylose[4] that, properly protected, undergoes first coupling with adenine to a xylofuranosyladenine derivative. This is followed by a laborious change of the protective groups[5] and then fluorination at 3′-position by diethylaminosulphur trifluoride (DAST). Finally low yield deprotection affords **11**.[1,2,6] Similarly D-xylose is the starting material for the Asahi group synthesis[3] in which fluorination is first performed at the properly protected sugar (by displacement with tetraalkylammonium fluoride) and then the fluoro sugar undergoes coupling with the heterocyclic base and final deblocking to **11**.

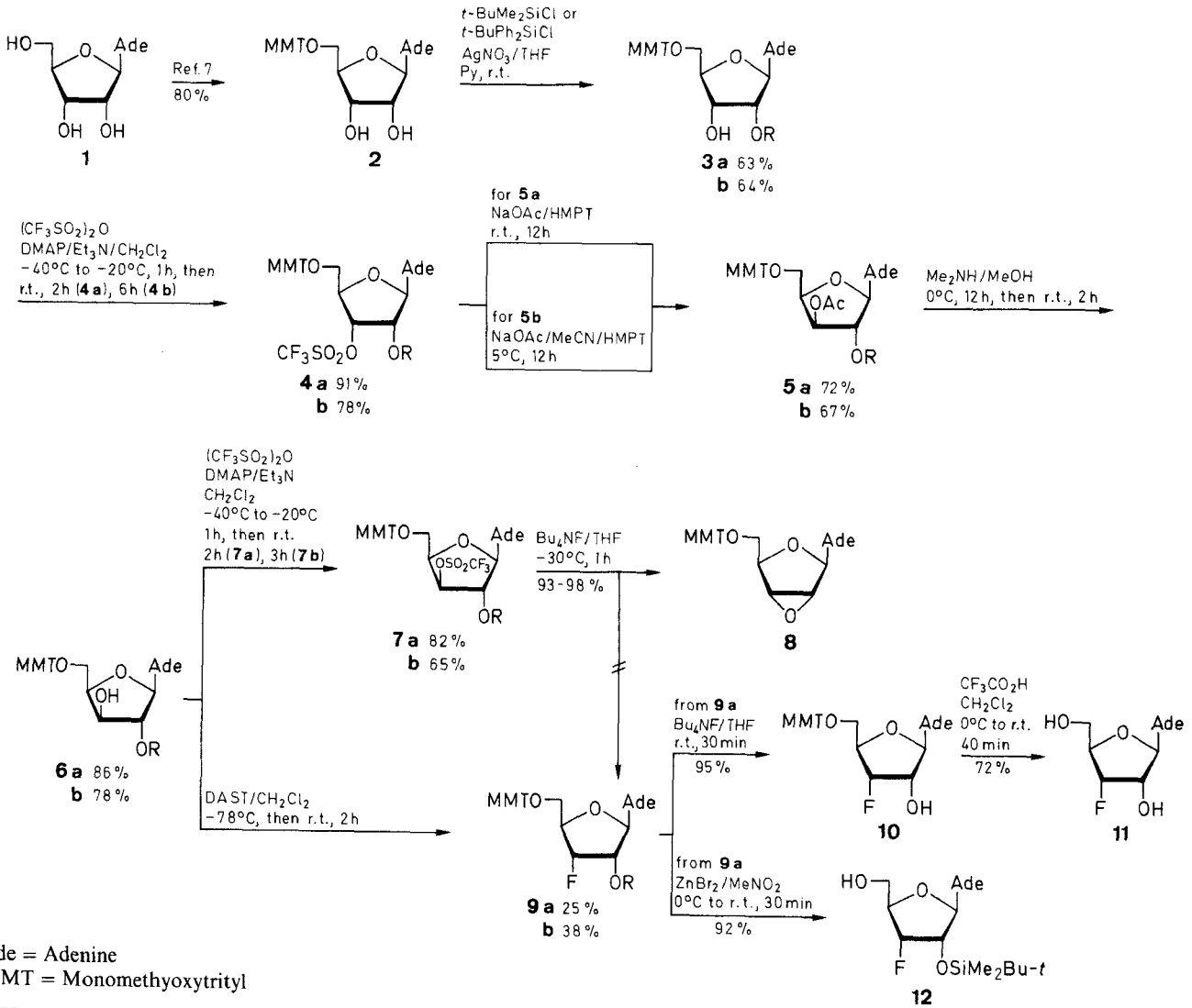
For our synthetic purposes we were interested in a shorter synthetic route to a 3′-fluoro-3′-deoxyadenosine derivative with selectively removable protecting groups at the 5′- and 2′-positions. This induced us to synthesize **11** starting from a suitable protected adenosine by reversing the configuration at the 3′-position and then introducing the fluorine atom by nucleophilic displacement. For our purpose the adenosine derivative to be utilized as substrate for 3′-inversion is 5′-*O*-monomethoxytrityl-2′-*O*-*tert*-butyldimethylsilyladenosine **(3a)**, which is easily obtained in 50% overall yield from adenosine **(1)** by 5′-*O*-tritylation to **2** and subsequent selective 2′-*O*-silylation under silver nitrate catalysis.[7,8] The inversion of the 3′-hydroxyl group configuration could be performed in nucleosides by reduction of the corresponding 3′-keto derivative.[9] However, at the beginning of this work, only one case was reported for the preparation of xylofuranosyladenine, this with a very low yield and scanty stereoselectivity.[10] Quite recently, while this work was in progress, another paper reported improved yields and stereoselectivity for the same transformation.[11] We also considered the possibility of performing the inversion by reaction with diethylazodicarboxylate and triphenylphosphine in the presence of benzoic acid although unfavorable results would be expected in the case of purine nucleosides when the nucleophile is a weak one.[12] Anyway, it is possible to reduce the expected nucleophilic attack of N-3 to C-3′ by protecting N^6 with a benzoyl group in order to decrease the nucleophilic character of N-3 atom,[13] but in this case two further steps are introduced into the synthesis.

Thus, we chose to perform the inversion of the 3′-hydroxyl groups via an *O*-triflyl derivative and subsequent reaction with sodium acetate to the epimeric ester. This was followed by hydrolysis to the xyloderivative. As recently reported for other nucleosides,[14] triflation of compound **3a** was accomplished by treating the alcohol with trifluoromethanesulfonic anhydride in dichloromethane, in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine, at room temperature, giving the 3′-triflate **4a** in 91% yield. Treatment of **4a** with sodium acetate in hexamethylphosphoric triamide (HMPT) at room temperature afforded the ester **5a** in 72% yield. The absence of detectable amounts of the analogous "ribo" acetate indicates that the reaction proceeds with complete inversion of the configuration under these conditions. An indicative feature of the "xylo" configuration for the product **5a** is the chemical shift of acetoxy group protons, which are shifted to an unusually high field ($\delta = 1.69$), as observed for analogous Neplanocine A derivatives,[14] probably due to the anisotropic effect of the pyrimidine ring of the adenine portion. Aminolysis of **5a** with methanolic dimethylamine at room temperature overnight afforded the crystalline deacetylated compound **6a**, recrystallized from ethyl acetate/hexane to give 86% yield of the pure alcohol. No migration of the protecting silyl group from 2′-*O* to 3′-*O* has been detected under the basic reaction conditions in this "xylo" system in contrast to that reported for "ribo" derivatives.[15] Moreover an unambiguous assignment of the compounds stereochemistry was provided by comparison of Nuclear Overhauser Effect (NOE) measurements on the product **6a** and the starting material **3a**. Thus, for the starting "ribo configuration" NOE's were observed between H-2′ and H-3′: irradiation of 2′ generated a 9,6% enhancement of H-3′. On the other hand, the same experiment performed on the compound **6a** gave rise to a 5,5% enhancement of H-3′ irradiating H-2′ (irradiation of H-3′ generated a 5,5% enhancement of H-2′). Moreover, irradiation of H-3′ generated a 10.3% enhancement of H-4′, while no similar effect was observed for the starting **3a**. These results are consistent with the assigned structure **6a** for the obtained compound.

To achieve the subsequent step, namely the introduction of fluorine atom into the sugar moiety, we initially attempted to subject the triflate **7a**, obtained by esterification of **6a** with trifluoromethanesulfonic anhydride, to nucleophilic displacement by equimolar amount of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran at −78 °C. We tried this because the selective reaction of TBAF with triflate in the presence of *tert*-butyldiphenylsilyl group without concurrent desilylation was reported.[16,17] However, we obtained 5′-*O*-(monometh-

oxytrityl)-2',3'-anhydroadenosine **(8)** in almost quantitative yield instead of the desired 3'-fluoro derivative **9a**.

The same compound was also obtained by employing different temperatures of reaction (– 50 °C, – 30 °C), or replacing the 2'-*O*-*tert*-butyldimethylsilyl group with the 2'-*O*-*tert*-butyldiphenylsilyl group. The 2'-*O*-*tert*-butyldiphenylsilyl derivative **7b** was prepared analogously to **7a**. Therefore, we explored a different route. Diethylaminosulphur trifluoride (DAST)[18,19] is a widely employed reagent to effect the conversion of alcohol into alkyl fluoride. The reaction generally proceeds with inversion of configuration at the reacting carbon centre, with the exception of substrates in which neighbouring-group participation can lead to partial or complete retention of configuration.[19,20] DAST has been largely used in carbohydrate chemistry[21] and more recently its use has appeared in nucleoside chemistry,[6,22] where the very mild conditions required for a DAST-promoted reaction and the inertness of this reagent towards acid sensitive substances proved to be very promising. The unexpected compatibility of DAST with the tetraisopropyldisiloxane protecting group, which has been recently reported,[23,17] prompted us to explore the stability of the protective *tert*-butyldimethylsilyl group to this reagent. During the last part of this work, problems have been reported[1] related to an analogous situation for fluorinating the 2'-position. Reaction of the alcohol **6a** with DAST in dichloromethane was complete after 3 hours at room temperature. TLC analysis (ethyl acetate) of the reaction mixture showed one product to be present, at an R_f-value slightly higher than the starting material, accompanied by a small spot moving with the solvent front (tritanol product) and a considerable amount of compound remaining at the base line. Attempts to move the last one from the base line by more polar solvents (dichloromethane/methanol mixtures) produced an undefined mixture of products. None of the spots corresponded to the deblocked fluorinated compounds **10** or **11**. Aqueous workup and silica gel flash chromatography (hexane/ethyl acetate) afforded compound **9a** in 25% yield. Incorporation of the fluorine atom at C-3' in compound **9a**



Ade = Adenine
MMT = Monomethyoxytrityl

3–7, 9	a	b
R	*t*-$BuMe_2Si$	*t*-$BuPh_2Si$

was clearly indicated by ^{1}H-NMR spectrum, and the significant data are reported in the Table. The relative stereochemistry of the substituents on the ring was confirmed by conversion to the unprotected derivative. The fluorine substituted compound **9a** was desilylated by means of tetrabutylammonium fluoride in tetrahydrofuran to give product **10** in 95% yield and this was subsequently converted to 3'-fluoro-3'-deoxyadenosine **(11)** by trifluoroacetic acid detritylation in 70% yield. Comparison of ^{1}H-NMR spectrum of the compound (data in agreement with those reported in literature[1]) with that of its epimer, 9-(3'-fluoro-3'-deoxy-β-D-xylofuranosyl) adenine[24] (see Table), confirms the assigned stereochemistry of 3'-fluoro-3'-deoxyadenosine **(11)**, and hence of its protected precursor **9a**. Selective zinc bromide promoted detritylation of the intermediate **9a** led to the 5'-*O*-unblocked intermediate **12**. We explored the same route by using a different protective group for the 2'-position. Actually fluorination of the *tert*-butyldiphenylsilyl derivative **6b** slightly improved the yield (from 25% to 37%) under the same reaction conditions, affording the fluoro derivative **9b** that can be readily deblocked selectively at 5'- or 2'-position analogously to **9a**.

Table. ^{1}H-NMR Data for **9a** and **11**

Compound	Chemical Shift δ, J(Hz)			
	H-4' ($J_{4',F}$)	H-3' ($J_{3',F}$, $J_{3',2'}$, $J_{3',4'}$)	H-2' ($J_{2',F}$, $J_{2',3'}$, $J_{2',1'}$)	H-1' ($J_{1',2'}$)
9a	4.45 (26)	5.02 (54.5, 4.4, 1.6)	5.26 (20.6, 4.4, 6.4)	6.01 (6.4)
11	4.28 (27.6)	5.05 (54.3, 4.4, 0)	4.88 (26.3, 4.4, 7.9)	5.92 (7.9)
3' epimer of **11**[a]	4.36 (28)	5.13 (54, 2.3, 2.5)	4.78 (16, 2.3, 2.3)	6.04 (2.3)

[a] Data from ref. 24.

Melting points were determined with a Buchi 510 apparatus and are uncorrected.

UV spectra were measured using a SP8-200 PYE-UNICAM spectrophotometer. $[\alpha]_D$ were measured at 20°C using a Jasco DIP-140 polarimeter.

^{1}H-NMR spectra were determined with a Varian VXR-200 or VXR-400. Field desorption mass spectra (FDMS) were recorded by a Varian MAT 311-A mass spectrometer equipped with a combined FI/FD/EI ion source and with an Ion Tech FAB atom gun. In FD mode PhCN activated emitters were used. The total potential difference between the field emitter anode and the cathode was 9 KV. The emitter heating current (EHC) was in the range of 14–18 mA and the source temperature was 200°C. FAB mass spectrum of the sample **11** was obtained using Xenon as bombarding gas with a kinetic energy of 9 KeV; a mixture of dithiothreitol/dithioerythritol (5:1, w/w) was used as matrix and the source was kept at r.t. Precoated Merck silica gel F254 plates were used for TLC, the spots were examined with UV light and $H_2SO_4/(NH_4)_2MoO_4/(NH_4)_2Ce(SO_4)_3$ spray. Flash chromatography was carried out using Carlo Erba Kieselgel 60, 230–400 mesh. THF was distilled from $LiAlH_4$, pyridine was refluxed on KOH and then distilled, CH_2Cl_2 was refluxed on P_4O_{10} and distilled. HMPT was treated with molecular sieves and stored overnight before being employed. Organic solvents from aqueous workup were routinely dried ($MgSO_4$ or Na_2SO_4). Satisfactory microanalyses were obtained for compounds **4–12**: C ± 0.36, H ± 0.20, N ± 0.20; except **5b** (C + 0.71), **6b** (C − 0.54), **10** (C − 0.47), and **11** (N − 0.43).

5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)adenosine (3a):[8]

Prepared from adenosine **(1)** (Fluka, AC) in 50% overall yield by a two-step procedure as described;[7] mp 167–168°C (Lit.[7] 164–167°C).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = −0.02, −0.14 (2 s, 6H, $Si(CH_3)_2$), 0.83 (s, 9H, $(CH_3)_3C$), 3.38 (dd, 1H, J = 3.9, 10.5 Hz, H-5'a), 3.51 (dd, 1H, J = 3.2, 10.0 Hz, H-5'b), 3.78 (s, 3H, OCH_3), 4.25 (ddd, 1H, J = 3.2, 3.7, 3.9 Hz, H-4'), 4.34 (ddd, 1H, J = 3.7, 3.7, 5.2 Hz, H-3'), 4.99 (dd, 1H, J = 5.2, 5.4, H-2'), 5.61 (br s, 2H, NH_2), 6.02 (d, 1H, J = 5.4 Hz, H-1'), 7.5–6.8 (m, 14H_{arom}), 8.26, 8.01 (2 s, 2H, Adenine H's).

5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)-3'-*O*-(trifluoromethanesulfonyl)adenosine (4a):

A solution of **3a** (4.8 g, 7.4 mmol) and DMAP (0.9 g, 7.4 mmol) in dry CH_2Cl_2 (150 mL) is cooled at −40°C, under a dry N_2 atmosphere, Et_3N (1.1 mL, 7.8 mmol) is added dropwise. The solution is then treated with $(CF_3SO_2)_2O$, also added dropwise. The resulting mixture is stirred at −20°C for 1 h, and then allowed to attain r.t. over a 2 h period. The mixture is quenched in ice/water (50 mL), and stirred for 10 min. The organic layer is separated, washed with cold H_2O, dried and evaporated under vacuum to afford a yellow solid. The crude product is chromatographed on silica gel (hexane/EtOAc, 6:4) to give the triflate **4a** as a colorless solid; yield: 5.3 g (91%); mp 91–93°C (Et_2O/hexane).

TLC: (hexane/EtOAc, 1:1), R_f = 0.4; $[\alpha]_D$ −12.0° (c = 1, $CHCl_3$)

UV: λ_{max} = 259 nm (log ε = 4.19; abs EtOH).

$C_{37}H_{42}F_3N_5O_7SSi$ (785.9) FDMS: m/z (%) = 786 (46 $[MH]^+$), 514 (100 $[MMT + 2H]^+$).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = −0.45, −0.05 (2 s, 6H, $Si(CH_3)_2$), 0.73 (s, 9H, $(CH_3)_3C$), 3.35 (dd, 1H, J = 3.9, 10.8 Hz, H-5'a), 3.70 (dd, 1H, J = 5.2, 10.8 Hz, H-5'b), 3.78 (s, 3H, OCH_3), 4.43 (dd, 1H, J = 3.9, 5.2 Hz, H-4'), 5.29 (d, 1H, J = 4.7 Hz, H-3'), 5.45 (dd, 1H, J = 4.7 Hz, H-2'), 5.64 (br s, 2H, NH_2), 5.90 (d, 1H, J = 7.4 Hz, H-1'), 7.58–6.8 (m, 14H_{arom}), 8.17, 7.90 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)-3'-*O*-acetyl-β-D-xylofuranosyl]adenine (5a):

To a solution of **4a** (3.5 g, 4.45 mmol) in HMPT (80 mL), NaOAc (0.820 g, 10 mmol) is added, the resulting suspension stirred at r.t. for 12–14 h and then poured into ice-water (300 g). The resulting slurry is then extracted several times with EtOAc and the organic layers are collected and washed with H_2O, dried and evaporated under vacuum to a yellow oil. The crude reaction product is chromatographed over silica gel, washing first with hexane and then eluting the product with hexane/EtOAc (1:1). Compound **5a** is obtained as colorless crystals; yield: 2.2 g (72%); mp 181°–183°C (CH_2Cl_2/hexane); TLC (EtOAc) R_f = 0.5; $[\alpha]_D$ −40.6° (c = 1, $CHCl_3$).

It is noteworthy that the "xylo"-acetate is more polar than the corresponding "ribo"-triflate (TLC: EtOAc R_f = 0.7).

$C_{38}H_{45}N_5O_6Si$ (695.9) FDMS: m/z (%) = 695 (100, M^+)

UV: λ_{max} = 259 nm (log ε = 4.21, abs EtOH).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 0.16, 0.15 (2 s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $(CH_3)_3C$), 1.69 (s, 3H, CO_2CH_3), 3.34 (dd, 1H, J = 5.4, 10.0 Hz, H-5'a), 3.56 (dd, 1H, J = 6.3, 10.0 Hz, H-5'b), 3.79 (s, 3H, OCH_3), 4.54 (dd, 1H, J = 1.3, 1.7 Hz, H-2'), 4.71 (ddd, 1H, J = 3.8, 5.4, 6.3 Hz, H-4'), 5.10 (dd, 1H, J = 1.7, 3.8 Hz, H-3'), 5.64 (br s, 2H, NH_2), 6.05 (d, 1H, J = 1.3 Hz, H-1'), 7.5–6.8 (m, 14H_{arom}), 8.30, 7.86 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]adenine (6a):[5]

Compound **5a** (2 g, 2.8 mmol) is dissolved in MeOH (20 mL). To this ice-cooled solution methanolic Me_2NH (3 mL, 13% w/w) is

added dropwise. The resulting solution is stirred at 0°C for 12–14 h and then for 2 h at r.t. The resultant product is evaporated under vacuum to afford the crude crystalline **6a** that gives the pure alcohol after crystallization from hexane/EtOAc; yield: 1.5 g (86%); mp 105–106°C (Lit.[5] 103°C); TLC (EtOAc) R_f = 0.4; (CH_2Cl_2/MeOH, 94:6) R_f = 0.3.

$C_{36}H_{43}N_5O_5Si$ (653.8) FDMS: *m/z* (%) = 653 (100, M^+).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 0.06, 0.03 (2 s, 6H, $Si(CH_3)_2$), 0.88 (s, 6H, $(CH_3)_3C$), 3.6–3.5 (m, 2H, CH_2-5'), 3.76 (s, 3H, OCH_3), 3.97 (dd, 1H, J = 3.2, 10.3 Hz, H-3'), 4.30 (m, 1H, H-4'), 4.47 (d, 1H, J = 1.4 Hz, H-2'), 5.71 (d, 1H, J = 1.4 Hz, H-1'), 5.48 (br s, 2H, NH_2), 6.8 (d, 1H, J = 10.3 Hz, OH-3'), 7.5–6.7 (m, 14H_{arom}), 8.24, 7.91 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)-3'-*O*-trifluoromethanesulfonyl-β-D-xylofuranosyl]adenine (7a):

A solution of **6a** (180 mg, 0.27 mmol) and DMAP (33 mg, 0.27 mmol) in dry CH_2Cl_2 (10 mL) is cooled at −40°C and Et_3N (0.038 mL, 0.28 mmol) is added. To the obtained solution, under dry N_2 atmosphere, $(CF_3SO_2)_2O$ (0.045 mL) is added dropwise at −40°C. The resulting mixture is stirred for 1 h at −20°C, and then for 2 h at r.t. The mixture is then quenched in ice-water (5 g) and stirred for 10 min. The organic layer is separated, washed with cold H_2O, and then dried and concentrated under vacuum to leave a pale yellow product that is chromatographed over silica gel (EtOAc/hexane, 8:2). The triflate **7a** is sufficiently pure (TLC) for the subsequent steps; yield: 173 mg (82%); TLC (EtOAc/hexane, 1:1) R_f = 0.51.

5'-*O*-(Monomethoxytrityl)-2',3'-anhydroadenosine (8):[25]

A solution of the triflate **7a** (150 mg, 0.19 mmol) in dry THF (8 mL), is cooled at −78°C, under a dry N_2 atmosphere, then 1 M Bu_4NF (TBAF) solution in THF (0.22 mL, 0.22 mmol), is slowly added. The resulting solution is allowed to attain −20°C over 1 h. A TLC (CH_2Cl_2/MeOH, 95:5) analysis of the mixture shows all the starting material is converted to a slower moving product (R_f = 0.4). Addition of H_2O (10 mL) to the dark mixture followed by EtOAc extraction and under vacuum evaporation of the solvent, affords a coloured but chromatographically homogeneous, viscous product that gives after short column chromatography (EtOAc) the epoxide **8**; yield: 97 mg (98%); TLC (EtOAc): R_f = 0.11. Crystallization of **8** was unsuccessful, $[\alpha]_D$ +23.1° (c = 0.5, $CHCl_3$).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 3.28 (m, 2H, CH_2-5'), 3.77 (s, 3H, OCH_3), 4.09 (d, 1H, J = 2.7 Hz, H-3'), 4.45 (d, 1H, J = 2.7 Hz, H-2'), 4.50 (m, 1H, H-4'), 5.60 (br s, 2H, NH_2), 6.13 (s, 1H, H-1'), 7.3–6.7 (m, 14H_{arom}), 8.17, 7.79 (2 s, 2H, Adenine H's).

Spectroscopic data are identical with those described in the literature.[25]

The same compound is obtained performing the above reported reaction at −50°C for 1 h, and direct aqueous quenching, or at −30°C for 1 h. Increasing the temperature does not change the obtained product but decreases the yield.

5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldimethylsilyl)-3'-fluoro-3'-deoxyadenosine (9a):

A solution of the hydroxy compound **6a** (2.6 g, 4 mmol) in dry CH_2Cl_2 (10 mL) is slowly added to a solution of DAST (1.06 mL, 8 mmol), in dry CH_2Cl_2 (70 mL), at −78°C, under a dry N_2 atmosphere. The solution is allowed to attain r.t. and stirred at this temperature for further 2 h.

TLC analysis (EtOAc) of the mixture shows all the starting material (R_f = 0.4) converted into a faster moving product (R_f = 0.58) and UV detectable base line material. The dark red solution is then cooled to −50°C and poured into the mixture of ice and $NaHCO_3$ (5%). The resulting pale yellow solution is stirred for 30 min, the aqueous phase separated and extracted with CH_2Cl_2. The combined organic phases are dried and evaporated under reduced pressure. The orange syrup obtained is chromatographed over silica gel by eluting with hexane/EtOAc (1:1) to give compound **9a** as a colorless solid; yield: 0.65 g (25%); mp 149–152°C (Et_2O/hexane); TLC (CH_2Cl_2/MeOH/aq NH_3, 94.5:5:0.5): R_f = 0.38; $[\alpha]_D$ −35.5° (c = 1, $CHCl_3$).

$C_{36}H_{42}FN_5O_4Si$ (655.8) FDMS: *m/z* (%) = 655 (100, M^+).

UV: λ_{max} = 259 nm (log ε = 4.21, abs EtOH).

^{1}H-NMR (400 MHz; $CDCl_3$/TMS): δ = −0.02, −0.19 (2 s, 6H, Si$(CH_3)_2$), 0.77 (s, 9H, $(CH_3)_3C$), 3.35 (dd, 1H, $J_{5'-5'}$ = 10,6 Hz, $J_{4'-5'}$ = 3.6 Hz, H-5'a), 3.57 (dd, 1H, $J_{5'-5'}$ = 10.6 Hz, $J_{4'-5'}$ = 4 Hz, H-5'b), 4.45 (ddd, 1H, $J_{4'-F}$ = 26 Hz, $J_{4'-5'}$ = 4 Hz, 3.6 Hz, $J_{4'-3'}$ = 1.6 Hz, H-4'), 5.02 (ddd, 1H, $J_{3'-F}$ = 54.5 Hz, $J_{3'-2'}$ = 4.4 Hz, $J_{3'-4'}$ = 1.6 Hz, H-3'), 5.26 (ddd, 1H, $J_{2'-F}$ = 20.6 Hz, $J_{2'-3'}$ = 4.4 Hz, $J_{2'-1'}$ = 6.4 Hz, H-2'), 6.01 (d, 1H, 6.4 Hz, H-1'), 5.60 (br s, 2H, NH_2), 7.51–6.8 (m, 14H_{arom}), 8.23, 7.97 (2 s, 2H, Adenine H's).

5'-*O*-(Monomethoxytrityl)-3'-fluoro-3'-deoxyadenosine (10):

A solution of **9a** (600 mg, 0.91 mmol) in THF (30 mL), is treated at r.t. with 1 M TBAF solution in THF (1.8 mL, 1.8 mmol). The resulting dark amber solution is then stirred at r.t. for 30 min. H_2O is added to this solution and the mixture is evaporated *in vacuo*. The residue is partitioned between EtOAc (30 mL) and brine (10 mL); the aqueous phase is then back extracted with EtOAc (2 × 10 mL) and the collected organic phases dried and evaporated under reduced pressure. The residue is chromatographed over silica gel using CH_2Cl_2/MeOH (95:5) as eluent to give the alcohol **10** as a colorless solid; yield: 470 mg (95%); mp 170–172°C (hexane/EtOAc); TLC (CH_2Cl_2/MeOH/aq NH_3 86:10:0.6) R_f = 0.49.

UV: λ_{max} = 259 nm (log ε = 4.19, abs EtOH).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 3.35 (m, 2H, H-5'), 3.78 (s, 3H, OCH_3), 4.58 (dt, 1H, J = 24 Hz, J = 3.4 Hz, H-4'), 5.02 (ddd, 1H, J = 21, 6.8 Hz, H-2'), 5.11 (dd, 1H, J = 52.7, 4.3 Hz, H-3'), 5.68 (br s, 2H, NH_2), 5.99 (d, 1H, J = 7 Hz, H-1'), 7.5–6.7 (m, 14H_{arom}), 8.32, 8.09 (2 s, 2H, Adenine H's).

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-fluoro-3'-deoxyadenosine (12):

To an ice-cooled solution of $ZnBr_2$ (500 mg, 2.2 mmol) in $MeNO_2$ (20 mL), compound **9a** (mg 186, 0.28 mmol) dissolved in $MeNO_2$ (8 mL) is added dropwise, under dried N_2 atmosphere. The deep-yellow solution obtained is allowed to warm to r.t. (30 min.), and then poured into an ice-cooled 1 M solution of NH_4OAc. The mixture is diluted with EtOAc (40 mL), the organic phase separated and the aqueous layer back extracted with EtOAc (2 × 20 mL). The collected organic phase is dried, evaporated under reduced pressure and the residue chromatographed over silica gel eluting with CH_2Cl_2/MeOH (98:2) to remove fast moving impurities. The polarity is then increased (90:10) to obtain the pure compound **12**; yield: 100 mg (92%); mp 202–203°C (Et_2O); TLC (CH_2Cl_2/MeOH/aq NH_3, 94.5:5:0.5): R_f = 0.30.

UV: λ_{max} = 259 m (log ε = 4.17, abs EtOH).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = −0.12, −0.3 (2 s, 6H, Si$(CH_3)_2$), 0.75 (s, 9H, $(CH_3)_3C$), 3.85 (m, 2H, H-5'), 4.51 (dt, 1H, J = 24, 1 Hz, H-4'), 5.05 (dd, 1H, J = 47.5, 3.7 Hz, H-3'), 5.10 (ddd, 1H, J = 22.5, 6.2, 3.7 Hz, H-2'), 5.81 (d, 1H, J = 6.2 Hz, H-1'), 5.85 (br s, 2H, NH_2), 8.32, 7.83 (2 s, 2H, Adenine H's).

3'-Fluoro-3'-deoxyadenosine (11):

To an ice-cooled solution of **10** (120 mg, 0.22 mmol) in dried CH_2Cl_2 (20 mL), CF_3CO_2H (0.2 mL) is added dropwise, under dried N_2 atmosphere and at 0°C. The resulting red solution is allowed to warm to r.t. over 40 min and then cautiously poured into a stirred, ice-cooled solution of 5% $NaHCO_3$ (20 mL). CH_2Cl_2 is evaporated under reduced pressure and the aq. residue is washed with Et_2O (3 × 5 mL). The resulting aqueous phase is chromatographed over a Lichroprep RP-C18 pre-packed column (size B, Merck). The column is washed first with H_2O and then eluted with H_2O/MeOH (90:10), to afford the pure **11**. Fractions containing the product are analyzed by HPLC, collected and freeze-dried to give **11**; yield: 45 mg (72%); mp 197–198°C (Lit. 205.6°C[3], 164°C[1]); TLC (CH_2Cl_2/MeOH/aq NH_3 86:10:0.6): R_f = 0.21; $[\alpha]_D$ −93.5° (c = 0.5, MeOH); HPLC (10% MeOH/0.1 M NH_4OAc; flow 2 mL/min; column: Wathman Partisphere 5 C18): R_t = 10.29 min.

$C_{10}H_{12}FN_5O_3$ (269.2) FABMS: *m/z* (%) = 270 (97, MH^+), 136 (100, [Adenine + H]$^+$).

UV: λ_{max} = 259 nm (log ε = 4.17, abs EtOH).

^{1}H-NMR (400 MHz; DMSO-d_6): δ = 3.64 (m, 2H, CH_2-5'), 4.28 (m, 1H, *J* = 27.6, 3 Hz, H-4'), 4.88 (ddd, 1H, *J* = 26.3, 4.4 Hz, 7.9 Hz, H-2'), 5.05 (dd, 1H, *J* = 54.3, 4.4 Hz, H-3'), 5.92 (d, 1H, *J* = 7.9 Hz, H-1'), 7.40 (br s, 2H, NH_2), 8.13, 8.35 (2 s, 2H, Adenine H's).

5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldiphenylsilyl)adenosine (3b):

Compound **3b** is obtained from adenosine by a two-step procedure as described for compound **3a**, in 56% overall yield. Using *t*-$BuPh_2SiCl$ instead of *t*-$BuMe_2SiCl$, longer reaction times are used in the silylation step (48 h, r.t.) and some amount of unreacted starting material (8%) is isolated. In this case no 2',3'-disilylated isomer is detected (TLC). The crude mixture of regioisomers is separated by chromatography over silica gel (hexane/EtOAc, 60:40) to give the faster moving 2'-silylated isomer in 64% yield. Increasing the polarity of the eluent (90:10) enables the slow moving 3'-silylated isomer (27%) to be recovered. It is noteworthy that the 3'-silylated isomer can be easily isomerized into almost a 1:1 mixture of 2'/3' isomers by stirring its methanolic solution, containing a few drops of Et_3N, at r.t. for 12–14 h, giving further crops of 2'-silylated compound.

Title compound **3b**: TLC: (EtOAc) R_f = 0.48; mp 124–125°C (Et_2O).

UV: λ_{max} = 260 nm (log ε = 4.19, abs EtOH).

$C_{46}H_{47}N_5O_5Si$ (778.0) FDMS: *m/z* (%) = 778 (100, MH^+).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 1.03 (s, 9H, $(CH_3)_3C$), 2.85 (br s, 1H, OH-3'), 3.25 (dd, 1H, *J* = 3.8, 10 Hz, H-5'a), 3.37 (dd, 1H, *J* = 3.2, 10 Hz, H-5'b), 3.75 (s, 3H, OCH_3), 4.22 (m, 2H, H-3', H-4'), 5.05 (dd, 1H, *J* = 4.6, 6.0 Hz, H-2'), 5.58 (br s, 2H, NH_2), 6.02 (d, 1H, *J* = 6.0 Hz, H-1'), 7.6–6.7 (m, 24 H_{arom}), 7.53, 8.11 (2 s, 2H, Adenine H's).

5'-O-(Monomethoxytrityl)-3'-O-(tert-butyldiphenylsilyl)-adenosine: TLC (EtOAc): R_f = 0.37.

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 1.10 (s, 9H, $(CH_3)_3C$), 2.68 (dd, 1H, *J* = 5, 11 Hz, H-5'a), 3.12 (dd, 1H, *J* = 5, 11 Hz, H-5'b), 3.73 (s, 3H, OCH_3), 4.12 (m, 1H, H-4'), 4.52 (m, 1H, H-3'), 4.66 (t, 1H, *J* = 6 Hz, H-2'), 6.10 (d, 1H, *J* = 6 Hz, H-1'), 5.77 (br s, 2H, NH_2), 7.6–6.7 (m, 24 H_{arom}), 8.24, 7.95 (2 s, 2H, Adenine H's).

5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldiphenylsilyl)-3'-*O*-trifluoromethanesulfonyladenosine (4b):

The title compound is prepared from **3b** (2.0 g, 2.57 mmol) by the same procedure as described for the preparation of **4a**, with the exception that a longer reaction time is required (6 h, r.t.). The crude product is chromatographed over silica gel eluting with EtOAc/hexane (80:20) to afford pure **4b** as a colorless foam; yield: 1.82 g (78%); TLC (CH_2Cl_2/MeOH/aq NH_3, 94.5:5:5:0.5): R_f = 0.37 (starting material R_f = 0.33).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 0.98 (s, 9H, $(CH_3)_3C$), 3.28 (dd, 1H, *J* = 4.4, 10.6 Hz, H-5'a), 3.57 (dd, 1H, *J* = 6.5, 10.6 Hz, H-5'b), 3.76 (s, 3H, OCH_3), 4.22 (dd, 1H, *J* = 4.4, 6.5 Hz, H-4'), 5.43 (d, 1H, *J* = 4.6 Hz, H-3'), 5.44 (br s, 2H, NH_2), 5.53 (dd, 1H, *J* = 4.6, 7.3 Hz, H-2'), 5.92 (d, 1H, *J* = 7.3 Hz, H-1'), 7.4–6.7 (m, 24 H_{arom}), 7.84, 8.02 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldiphenylsilyl)-3'-*O*-acetyl-β-D-xylofuranosyl]adenine (5b):

The reaction is carried out from **4b** (1.8 g, 1.98 mmol) as described for compound **5a**, but using mixture of MeCN/HMPT (1:1) as solvent and maintaining the reaction temperature at + 5°C for 14 h. In the reaction, conducted at r.t. in HMPT only, the desidered product is accompained by small amounts of the acetate of "ribo" configuration. After workup of the mixture as described for compound **5a** and column chromatography over silica gel (EtOAc/hexane, 1:1), chromatographically homogeneous **5b** is obtained as a colorless foam. All attempts of crystallizing **5b** failed; yield: 1.1 g (67%); TLC (CH_2Cl_2/MeOH/aq NH_3, 94.5:5:0.5): R_f = 0.40.

$C_{48}H_{49}N_5O_6Si$ (820.0) FDMS: *m/z* (%) = 820 (100, MH^+).

^{1}H-NMR (400 MHz; $CDCl_3$/TMS): δ = 1.12 (s, 9H, $(CH_3)_3C$), 1.64 (s, 3H, CO_2CH_3), 3.27 (dd, 1H, *J* = 6.0, 9.8 Hz, H-5'a), 3.46 (dd, 1H, *J* = 5.7, 9.8 Hz, H-5'b), 3.81 (s, 3H, OCH_3), 4.68 (m, 1H, H-2'), 4.72 (m, 1H, H-4'), 5.34 (m, 1H, H-3'), 5.56 (br s, 2H, NH_2), 6.18 (d, 1H, *J* = 2.5 Hz, H-1'), 6.8–7.6 (m, 24 H_{arom}), 7.67, 8.26 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldiphenylsilyl)-β-D-xylofuranosyl]adenine (6b):

The reaction is conducted from **5b** (1.0 g, 1.22 mmol) as described for compound **6a** to give, after column chromatography (EtOAc/hexane, 1:1), compound **6b** as a colorless foam. All attempts to crystallize **6b** failed; yield: 0.74 g (78%); TLC (EtOAc): R_f = 0.58.

UV: λ_{max} = 260 nm (log ε = 4.22, abs EtOH).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 1.09 (s, 9H, $(CH_3)_3C$), 3.53 (dd, 1H, *J* = 3.2, 10.0 Hz, H-5'a), 3.60 (dd, 1H, *J* = 6.9, 10.0 Hz, H-5'b), 3.75 (s, 3H, OCH_3), 4.18 (dd, 1H, *J* = 3.2, 11.3 Hz, H-3'), 4.37 (ddd, 1H, *J* = 3.2, 4.2, 6.9 Hz, H-4'), 4.57 (d, 1H, *J* = 1.2 Hz, H-2'), 5.53 (d, 1H, *J* = 1.2 Hz, H-1'), 5.59 (br s, 2H, NH_2), 7.06 (d, 1H, *J* = 11.3 Hz, OH-3'), 6.7–7.6 (m, 24 H_{arom}), 7.80, 8.10 (2 s, 2H, Adenine H's).

9-[5'-*O*-(Monomethoxytrityl)-2'-*O*-(*tert*-butyldiphenylsilyl)-3'-*O*-trifluoromethanesulfonyl-β-D-xylofuranosyl]adenine (7b):

To a solution of **6b** (400 mg, 0.51 mmol), in dry CH_2Cl_2, cooled at −40°C, DMAP (74.5 mg, 0.61 mmol) and Et_3N (0.085 mL, 0.61 mmol) are added. To the resulting solution $(CF_3SO_2)_2O$ (0.1 mL, 0.61 mmol) is added dropwise. The suspension is stirred at r.t. for 3 h and worked up as described for compound **7a**. The resulting triflate **7b** is obtained after column chromatography (EtOAc/hexane, 80:20) as a pale yellow foam; yield: 300 mg (65%); TLC (hexane/EtOAc, 2:8): R_f = 0.70.

$C_{47}H_{46}F_3N_5O_7Si$ (910.0) FDMS: *m/z* (%) = 910 (100, MH^+).

^{1}H-NMR (200 MHz; $CDCl_3$/TMS): δ = 1.11 (s, 9H, $(CH_3)_3C$), 3.39 (dd, 1H, *J* = 5.8, 10.3 Hz, H-5'a), 3.69 (dd, 1H, *J* = 6.3, 10.3 Hz, H-5'b), 3.79 (s, 3H, OCH_3), 4.50 (ddd, 1H, *J* = 3.0, 5.8, 6.3 Hz, H-4'), 4.96 (m, 1H, H-2'), 5.18 (d, 1H, *J* = 3.0 Hz, H-3'), 5.52 (br s, 2H, NH_2), 6.08 (d, 1H, *J* = 1.6 Hz, H-1'), 6.8–7.6 (m, 24 H_{arom}), 8.22, 8.36 (2 s, 2H, Adenine H's).

5'-*O*-(Monomethoxytrityl)-2',3'-anhydroadenosine (8) from 7b:

The triflate **7b** is then dissolved in dry THF (10 mL), and treated with 1 M solution of Bu_4NF (TBAF) in THF (0.33 mL) at − 30°C for 1 h H_2O (0.1 mL) is added, and the resulting amber solution is worked up as previously described to yield the epoxide **8** (160 mg, 93%). Analytical data are the same as described above.

5'-O-(Monomethoxytrityl)-2'-O-(*tert*-butyldiphenylsilyl)-3'-deoxy-3'-fluoroadenosine (9b).

Reaction is carried out starting from **6b** (0.7 g, 0.9 mmol) as described for **9a**. TLC analysis (EtOAc) of the mixture shows the reaction to be complete after 2 h at r.t. After workup as described for **9a** and column chromatography (CH_2Cl_2/MeOH, 98:2), **9b** is isolated as a colorless solid; yield: 0.265 g (37.7%); mp 114–116°C (hexane/Et_2O); TLC (EtOAc): R_f = 0.63; (CH_2Cl_2/MeOH/aq NH_3, 94.5:5:0.5): R_f = 0.45.

UV: λ_{max} = 260 nm (log ε = 4.17, abs EtOH)

^{1}H-NMR (400 MHz; $CDCl_3$/TMS): δ = 0.99 (s, 9H, $(CH_3)_3C$), 3.77 (s, 3H, OCH_3), 4.36 (ddd, 1H, *J* = 3.5, 4.2, 30.0 Hz, H-4'), 4.58 (dd, 1H, *J* = 4.1, 54.6 Hz, H-3'), 5.10 (ddd, 1H, *J* = 4.1, 7.6, 21.6 Hz, H-2'), 5.59 (br s, 2H, NH_2), 6.16 (d, 1H, *J* = 7.6 Hz, H-1'), 6.7–7.6 (m, 24 H_{arom}), 7.76, 8.11 (2 s, 2H, Adenine H's).

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