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Towards the preparation of 2″-deoxy-2″-fluoro-adenophostin A. Study of the glycosylation reaction

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ABSTRACT

The synthesis of 2″-deoxy-2″-fluoro-adenophostin A framework starting from tri-*O*-acetylglucal and adenosine is described. The key steps are the formation of the 2-deoxy-2-fluoroglycosyl donor by electrophilic fluorination of tri-*O*-acetylglucal and the stereoselective glycosylation of a suitable adenosine derivative. The glycosylation reaction was optimized affording the desired 2″-deoxy-2″-fluoro-glycoside with excellent α-stereoselectivity and in good yields, taking into account that glycosylations using nucleosides as glycosyl acceptors do not usually give excellent results. In that sense, an improvement of the glycosylation step with respect to that of the reported adenophostin synthesis, using adenosine derivatives as glycosyl donors, has been made.

1. Introduction

The fluorination of biologically active organic compounds often leads to dramatic changes in their biological activity, stability and bioavailability. Thus, many fluorine-containing pharmaceuticals have been developed over the past few decades.[1] The incorporation of fluorine into a drug allows for simultaneous modulation of electronic, lipophilic and steric parameters, all of which can critically influence both the pharmacodynamic and the pharmacokinetic properties of a drug.

Fluorinated carbohydrates derivatives, and particularly 2-deoxy-2-fluoro nucleosides, have received great attention because they exhibit fascinating biological activities in antiviral therapies,[2] cancer imaging diagnosis[2d,3] and antitumour applications.[2d,3a,4] Fluorinated carbohydrates have been used as well to probe the mechanism and specificity of various enzymes[5] as they can modify the activity of substrates and stabilize the glycosidic linkage against hydrolysis.[6]

The van der Waals radius of fluorine (1.47 Å) falls between that of oxygen (1.52 Å) and that of hydrogen (1.20 Å), making it a versatile element for bioisosteric replacements. A C–F moiety can mimic a C–OH moiety, because its polarity is similar, especially when fluorine and oxygen are involved in polar interactions with strongly positively charged polarized centres, such as lateral chains of basic amino acids.[7] Moreover, F is the smallest substituent that can replace H, and therefore, a C–F bond can often substitute a C–H bond with minimal structural consequences.[8]

On the other hand, adenophostins A and B (Fig. 1) are a new class of glyconucleosides isolated in 1993 from a culture of *Penicillium brevicompactum*.[9]

These compounds have been shown to be the most potent agonists of inositol 1,4,5-trisphosphate receptor (IP_3R) discovered to date with affinities between 10- and 100-fold higher than inositol 1,4,5-trisphosphate (IP_3) itself.[10] Thus, they mobilize Ca^{2+}, as IP_3, from intracellular stores by binding to IP_3R and causing its intrinsic Ca^{2+} channel to open. Many cellular processes are controlled by the generation of these internal calcium signals.

These findings, in combination with our group's experience in the field of fluorinated carbohydrates and nucleosides[11] led us to believe that incorporating a fluorine atom at the adenophostin

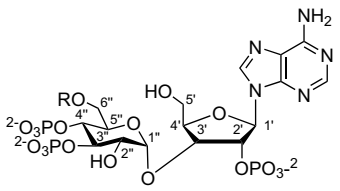

Figure 1. Structure of adenophostins A and B.

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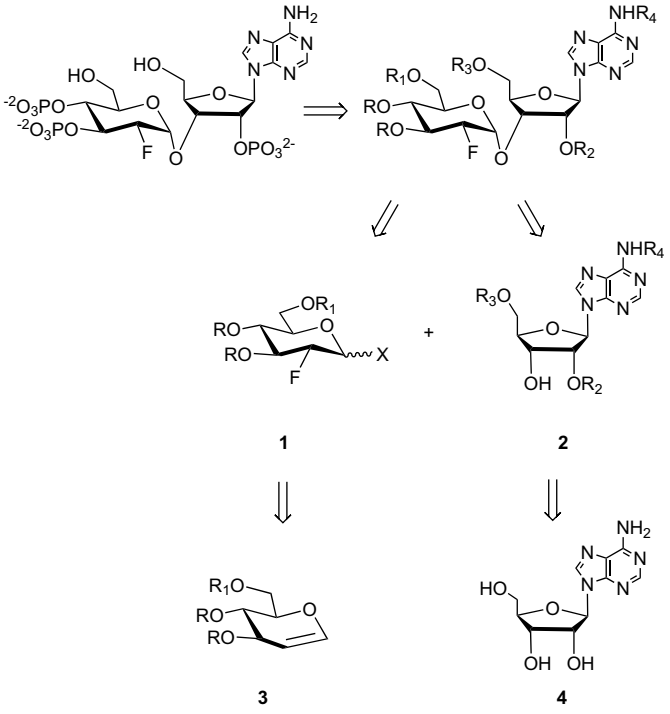
2″-position while maintaining all of the essential functionality for activity would create a good candidate analogue. Thus, the resulting analogue would be more resistant to enzymes that metabolize IP_3 and fluorination would aid in elucidating the role of the natural product's 2″-OH.

The proposed retrosynthetic analysis (Scheme 1) involves the stereoselective glycosylation of suitable adenosine derivative **2** with 2-deoxy-2-fluoroglycosyl donor **1**. The donor could be obtained from an appropriately protected *D*-glucal **3** via electrophilic fluorination. Product **2** can be obtained in turn from the selective protection of adenosine **4**.



Scheme 1. Retrosynthetic analysis of 2″-deoxy-2″-fluoro-adenophostin A.

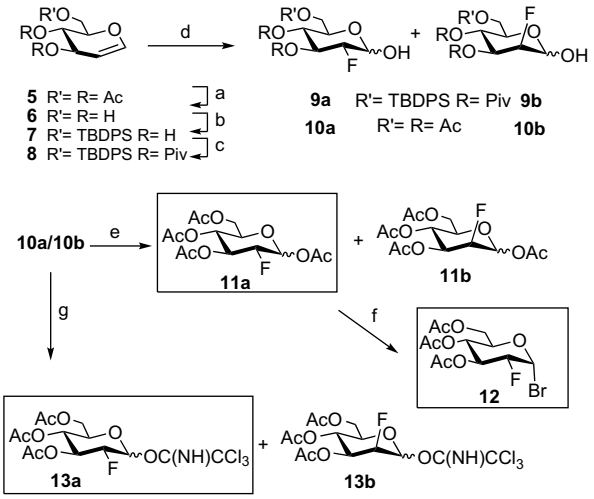
We expected a difficult activation of glycosyl donor because of the presence of fluorine at position 2. Moreover, taking into account that glycosylations using nucleosides as glycosyl acceptors do not usually give excellent results,[12] and that a good α-stereoselectivity is needed to get the 2″-fluoro analogue of the natural product, a careful optimization of the glycosylation reaction must be performed. In fact, the only reported synthesis of adenophostins using an adenosine derivative as glycosyl donor[13] described a yield of only 48% for the glycosylation reaction. Thus, in this work we report a study of the glycosylation of derivative **2** with **1**, a key step in the synthesis of 2″-deoxy-2″-fluoro-adenophostin A.

2. Results and discussion

2-Deoxy-2-fluoro derivative **1** could be obtained from the electrophilic addition of fluorine to the double bond of a *D*-glucal derivative **3**, using Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazonium bicycle[2.2.2]octane tetrafluoroborate) as a fluorine source.[14]

Dax et al. reported that the stereoselectivity of this class of reactions mainly depended on the protecting groups present on the glycal.[15] Starting from peracetylated D-glucal, equimolar mixtures of diastereoisomers were obtained (61% yield, *gluco*/*manno*: 1.3:1). When pivaloyl protecting groups were used, however, the formation of *gluco* derivatives was favoured (85%, *gluco*/*manno*: 9:1).

Taking into account that adenophostin synthesis involves selective phosphorylation at positions 3″ and 4″ in the last steps of the synthesis and Dax's results, we prepared the glucal **8** in 74% global yield by quantitative deprotection of tri-*O*-acetyl-D-glucal,[16] selective protection of the primary alcohol with *tert*-butyldiphenylsilyl chloride[17] and esterification using pivaloyl chloride (Scheme 2). In the last protection step the described yield (52%)[18] was improved until 93% maintaining the reaction for 36 h in DMF.



Scheme 2. Synthesis of glycosyl donors **11a**, **12** and **13**. (a) Ref. 16. (b) Ref. 17. (c) PivCl, Py, DMAP, DMF, 0 °C to r.t., 36 h, 93%. (d) Selectfluor, CH_3NO_2:/H_2O (5:1), 12 h at r.t., 30 min reflux, 56% for **9a**/**9b** (18:/1), Ref. 15 for **10a**/**10b** (1.3:/1). (e) Ac_2O, Py, 12 h, r.t., quantitative. (f) HBr, AcOH, CH_2Cl_2, 5 h, r.t., quantitative. (g) NaH, CCl_3CN, CH_2Cl_2, 2 h, r.t., 85% for **13a**.

Subsequent electrophilic fluorination of **8** led to an anomeric mixture of diastereoisomers **9a** and **9b** in a *gluco*/*manno* ratio of 18:1. Although the diastereoisomeric ratio observed was, as expected high, the *gluco* derivative could not be separated from the mixture and that was only possible after deprotection of the primary hydroxyl group. Thus, this approach was discarded because it supposes additional protection–deprotection steps.

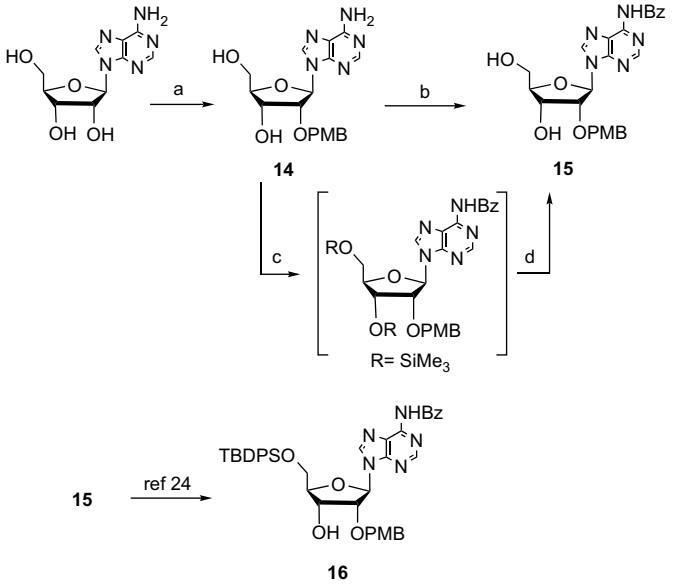
Taking into account these results, we decided to obtain the glucoside fragment by direct electrophilic fluorination of commercially available 3,4,6-tri-*O*-acetyl-D-glucal **5** (Scheme 2), which gave a mixture of compounds **10a** and **10b**,[15] separable after subsequent anomeric acetylation. With acetyl glycosides **11a**[18] in hand, glycosyl bromide **12**[19] was obtained quantitatively by reaction with HBr/AcOH in CH_2Cl_2.

In addition to acetate **11a** and bromide **12**, trichloroacetimidate derivative **13a**[20] was also prepared in order to test the effect of different glycosyl donors. Thus, a mixture of **10a** and **10b** was reacted with trichloroacetonitrile in the presence of NaH. As a result of fluorine being present at C-2, the trichloroacetimidate products proved stable enough to tolerate chromatographic purification to give *gluco* derivatives **13a** in an 85% yield.

The convergent synthesis required synthesizing building block **2**. Most of the syntheses of adenophostin or its analogues described in the literature use a suitable protected riboside as a glycosyl acceptor.[21] The base moiety is usually incorporated later via Vorbrüggen glycosylation.[22] We decided to perform the glycosylation with the corresponding protected adenosine directly. Using this methodology, the synthesis is simplified and is more convergent.

Thus, starting from commercially available adenosine, product **15** was obtained following the methodology of Takaku et al.:[23] selective protection of the 2′-hydroxyl by using PMBCl and NaH, perbenzoylation by benzoyl chloride and selective hydrolysis of the benzoate ester (Scheme 3, a, b). In our hands however, the synthesis

did not meet the expectations for efficiency set by the literature. After some modifications of the described methodology the best yield of **14** (75%) was obtained when the reaction was held at room temperature for 12 h, but formation of significant amounts of 3′-OPMB adenosine could not be avoided and the selective alcohol deprotection led to a mixture of products and modest yield (55%). Finally, reaction of **15** with *tert*-butyldiphenylsilyl chloride gave the desired glycosyl acceptor **16**[24] in 36% global yield from adenosine. The inversion of the sequence (selective protection of primary alcohol in **14** and subsequent benzoylation and 3′-ester hydrolysis) did not improve the result (20% global yield).



Scheme 3. Synthesis of glycosyl aceptoracceptor **16**. (a) NaH, PMBCl, DMF, 12 h, −5 °C to r.t., 75%. (b) (i). BzCl, Py, 0 °C to r.t., (ii). NaOH (1%), MeOH, 55 %. (c) Me_3SiCl, py, 2 h, r.t. (d) (i). BzCl, py, 3 h, r.t., (ii). DOWEX-H^+, 81%.

To increase the efficiency of the process, **14** was subjected to temporary TMS protection at positions 3′ and 5′[25] (Scheme 3, c), in situ benzoylation and subsequent hydrolysis with Dowex H^+ to give benzoylated adenosine **15** in good yield (81%) improving the reported procedure. After TBDPS protection at position 5′ the desired glycosyl acceptor **16** was obtained in 53% overall yield.

With **16** in hand, we centred on the study of the key glycosylation reaction. Treatment of acetate glycosyl donor **11a** with 3.5–6.0 equiv of $BF_3\cdot Et_2O$ in CH_2Cl_2 gave no reaction and only starting material was recovered (Table 1, entries 1 and 2). We examined also the use of $Sc(OTf)_3$, which was found to be an efficient catalyst for C- and O-glycosylation using glycosyl acetates under mild conditions.[26] Nevertheless, no reaction was observed again (Table 1, entry 3).

Unexpectedly, trichloroacetimidate **13a** did not react (Table 1, entry 4), and prolonging reaction time (more than 48 h) led only to decomposition of glycosyl acceptor **16** and a little amount of product resulting of trichloroacetimidate hydrolysis was detected. We presumed that the presence, in the glycosyl donor, of a fluorine atom at position 2 prevents the activation of the anomeric position because of its electron-withdrawing properties. When the reaction conditions are forced activation can happen, but glycosyl acceptor is not nucleophilic enough and traces of water can compete in the reaction.

Taking into account these results, attention was focused on glycosyl bromide **12**. The activation using AgOTf together with NEt_3 in CH_2Cl_2 gave only a 5% yield of the undesirable β-glycosylated product (Table 1, entry 5). The effects of solvent on the stereochemical outcome of glycosylation reactions are well documented. The application of ethereal solvents such as dioxane or diethyl ether generally results in the formation of the thermodynamic product, the axial glycoside.[27] Thus, the use of THF and Et_2O was tested, obtaining in the last case the desired α-product **17** with complete stereoselectivity but only in a 30% yield (Table 1, entry 7).

The best results were finally obtained when the glycosylation reaction was performed using AgOTf with Ag_2CO_3 as a base in a 3:1 mixture of Et_2O and CH_2Cl_2.[28] These conditions afforded compound **17** in 58% yield (Table 1, entry 8) with complete α stereochemistry, confirmed by H1″–H2″ coupling constant (J=4.0 Hz). The ^{19}F NMR spectrum showed only a doublet of doublets at −201.25 ppm ($^2J_{F-H2''}$=48.8, $^3J_{F-H3''}$=12.0 Hz), which confirmed a *trans*-diequatorial F2″–H1″ configuration. Amount of silver triflate was increased to 1.1 equiv in order to improve glycosylation yield, but no significant improvement was observed (61%, Table 1, entry 9).

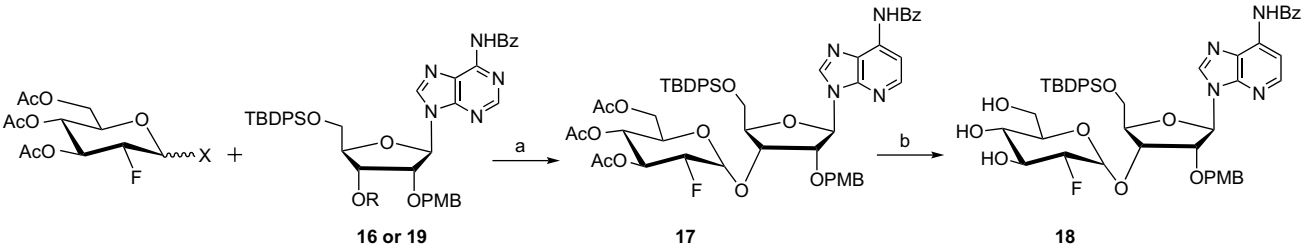
Reaction times, extended from 24 h to 5 days, did not increase the yields. Moreover, hydrolyzed glycosyl donor was always recovered after work-up. This indicated that activation of glycosyl bromide had taken place, but the glycosyl acceptor **16** was not sufficiently reactive. Since the major obstacle to glycosylation was the nucleophilicity of the 3′-OH, the stannylether derivative was used as a glycosyl acceptor instead.[29] Formation of 3′-stannylether was carried out with either bis-tributyltin oxide in toluene in a Dean–Stark apparatus,[30] or TfOH-catalyzed allyltriphenyltin in CH_2Cl_2.[31] After 32 h, yields were low, only 15% of the glycosylated product was obtained (Table 1, entry 10). This result could be attributed to the increased steric hindrance of stannylether formed.

The hydrolysis of acetyl groups was needed to obtain pure enough product for a physical characterization. Thus, after treatment of fully protected 2′-deoxy-2-fluoro-adenophostin A with NaOMe/MeOH, compound **18** was obtained (Scheme 4). Surprisingly, subsequent selective protection of the 6″-OH was no trivial. Thus, when **18** was reacted with TBDPSCl, TBDMSCl or TBDMSOTf in CH_2Cl_2 or pyridine in the presence of bases, Et_3N, DMAP or 2,6-lutidine, no reaction was observed. Treatment of **18** with TESCl in

Table 1
Glycosylation assays

Entry	Glycosyl donor (X)	Glycosyl acceptor (R)	Activator[a]	Base	Solvent	Result, yield %	Ratio α:β
1	**11a** (OAc)	**16** (H)	$BF_3\cdot Et_2O$ (3.5 equiv)	—	CH_2Cl_2	No reaction[b]	
2	**11a** (OAc)	**16** (H)	$BF_3\cdot Et_2O$ (6.0 equiv)	—	CH_2Cl_2	No reaction[b]	
3	**11a** (OAc)	**16** (H)	$Sc(OTf)_3$ (3.0–6.0 equiv)	—	CH_2Cl_2	No reaction[b]	
4	**13a** ($OC(NH)CCl_3$)	**16** (H)	TMSOTf (0.75 equiv)	—	CH_2Cl_2	No reaction[b]	
5	**12** (Br)	**16** (H)	AgOTf (1.2 equiv)	NEt_3 (1.2 equiv)	CH_2Cl_2	5	0:1
6	**12** (Br)	**16** (H)	AgOTf (1.5 equiv)	DTBMP (3 equiv)	THF	No reaction[b]	
7	**12** (Br)	**16** (H)	AgOTf (1.5 equiv)	DTBMP (3 equiv)	Et_2O	30	1:0
8	**12** (Br)	**16** (H)	AgOTf (0.3 equiv)	Ag_2CO_3 (1 equiv)	Et_2O/CH_2Cl_2 (3:1)	58	1:0
9	**12** (Br)	**16** (H)	AgOTf (1.1 equiv)	Ag_2CO_3 (1 equiv)	Et_2O/CH_2Cl_2 (3:1)	61	1:0
10	**12** (Br)	**19** ($SnBu_3$)	AgOTf (1.1 equiv)	Ag_2CO_3 (1 equiv)	Et_2O/CH_2Cl_2 (3:1)	15	1:0

[a] All reactions were carried out with 4 Å M.S.
[b] No reaction was observed after 48 h at room temperature.



Scheme 4. Glycosylation and further step to 2″-deoxy-2″-fluoro-Aadenophostin A framework. (a) See Table 1. (b) NaMeO, MeOH, 4 h, r.t. 70%.

DMF at 80 °C in the presence of DMAP afforded 6″-*O*-TES derivative in only 6% yield.

3. Conclusions

Product **18**, a key intermediate towards the synthesis of 2″-deoxy-2″-fluoro-adenophostin A has been obtained from tri-*O*-acetylglucal and adenosine. The key glycosylation reaction was optimized obtaining the desired 2″-deoxy-2″-fluoroglycoside with excellent α-stereoselectivity and in good yields, considering the difficult glycosylation of the nucleoside used as glycosyl acceptor.

4. Experimental section

4.1. General methods

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using VARIAN GEMINI 300 and VARIAN MERCURY 400 spectrometers and are reported in parts per million (δ). In ^{1}H NMR spectra TMS was used as an internal reference. In the ^{13}C NMR spectra, the residual solvent signal was used as an internal reference ($CDCl_3$, triplet at 77.23 ppm). ^{19}F NMR spectra were referenced to $CFCl_3$ as external standard. Elemental analyses were performed with a Carlo Erba EA 1108 Analyser. Optical rotations were recorded on a Perkin–Elmer 241 MC polarimeter in a 1 dm cell at 20 °C.

All reactions were performed under a nitrogen atmosphere in glassware dried under high vacuum. Flash column chromatography was performed with silica gel 60 (E. Merck, 40–63 μm). Medium-pressure liquid chromatography (MPLC) was carried out on silica gel 60 ACC (SDS, 6–35 μm). Radial chromatography was performed on 1, 2 or 4 mm plates of Kieselgel 60 PF_{254} silica gel (E. Merck), depending on the amount of product. Solvents were purified using standard procedures. For thin layer chromatography (TLC) aluminium sheets coated with silica gel 60 F_{254} (E. Merck) were used. Compounds were visualized by UV (254 nm) and also by spraying the TLC plates with 6% H_2SO_4 in ethanol, followed by charring at 150 °C for few minutes.

4.2. Synthesis of 6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-fluoro-3,4-di-*O*-pivaloyl-D-*gluco* and *manno*pyranoses (9a and 9b)

Selectfluor© (1.2 g, 3.39 mmol) was added to a 10% solution of glucal **8** (1.50 g, 2.71 mmol) in CH_3NO_2/H_2O (5:1, 15 mL). The solution was stirred at rt, and after consumption of starting material (15 h), the mixture was heated to reflux for 45 min. Then the solvents were evaporated under vacuum, the residue was redissolved in CH_2Cl_2. The resulting mixture was washed with an aqueous solution of $NaHCO_3$ (5%). The organic phase was dried with $MgSO_4$ and concentrated to dryness. The syrup was applied to a silica gel column. An inseparable mixture of anomers of *manno*/*gluco* (1:18) derivatives was obtained (0.90 g, 56% yield). Product **9a**. Data for α anomer extracted from the diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.67–7.39 (m, 10H), 5.62 (dt, 1H, J=12.0, 9.6 Hz), 5.46 (dd, 1H, J=3.6, 3.2 Hz), 5.18 (dd, 1H, J=10.0, 9.6 Hz), 4.49 (ddd, J=50.0, 9.6, 3.2 Hz), 4.13 (m, 1H), 3.69 (m, 2H), 2.82 (d, 1H, J=3.6 Hz), 1.18 (s, 18H), 1.06 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 177.7, 176.6, 135.8–127.7, 90.4 (d, J=21.5 Hz), 88.4 (d, J=193.2 Hz), 70.6 (d, J=19.1 Hz), 69.8, 67.4 (d, J=6.8 Hz), 62.1, 38.8, 38.6, 27.0, 27.0, 26.8, 19.2; ^{19}F NMR (376.4 MHz, $CDCl_3$, 25 °C) δ −201.6 (dd, J=50.0, 12.0 Hz). Data for β anomer extracted from the diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.67–7.39 (m, 10H), 5.33 (ddd, 1H, J=14.0, 9.6, 9.2 Hz), 5.08 (t, 1H, J=9.6 Hz), 4.78 (ddd, 1H, J=8.0, 5.6, 2.8 Hz), 4.22 (ddd, 1H, J=53.2, 9.2, 8.0 Hz), 4.13 (m, 1H), 3.66 (m, 2H), 2.92 (d, 1H, J=5.6 Hz), 1.17 (s, 18H), 1.04 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 177.7, 176.4, 135.8–127.7, 94.4 (d, J=22.2 Hz), 91.0 (d, J=196.0 Hz), 74.7, 72.9 (d, J=19.1 Hz), 67.5, 62.4, 38.8, 38.6, 27.0, 27.0, 26.8, 19.2; ^{19}F RMN (376.4 MHz, $CDCl_3$, 25 °C) δ −200.7 (ddd, J=53.2, 14.0, 2.8 Hz). Product **9b**. Data for β anomer extracted from the diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.67–7.39 (m, 10H), 5.33 (m, 1H), 4.75 (dt, 1H, J=50.4, 2.2 Hz), 4.13 (m, 1H), 3.77 (dd, 1H, J=11.8, 5.4 Hz), 3.66 (m, 1H), 2.65 (m, 1H), 1.18 (s, 18H), 1.06 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 177.9, 176.6, 135.8–127.7, 91.7 (d, J=29.2 Hz), 87.5 (d, J=178.7 Hz), 71.1, 70.1 (d, J=16.9 Hz), 65.3, 62.6, 38.8, 38.6, 27.0, 27.0, 26.8, 19.2; ^{19}F RMN (376.4 MHz, $CDCl_3$, 25 °C) δ −205.2 (ddd, J=50.4, 28.0, 5.3 Hz).

4.3. Synthesis of 2′-*O*-*p*-methoxybenzyl adenosine (14)

A suspension of adenosine (2.00 g, 7.48 mmol) in DMF (67.5 mL) was cooled down to −5 °C. Then NaH (60% in mineral oil, 400 mg, 9.73 mmol) was added to the solution. The mixture was stirred for further 1 h at −5 °C. Then 4-methoxybenzyl chloride (1.3 mL, 8.98 mmol) was added dropwise during 1 h. After addition was complete, the reaction was let to reach rt, and stirred for 12 h. When TLC (CH_2Cl_2/MeOH, 9:1) showed no further evolution, DMF was evaporated under vacuum. The residual oil obtained was applied to a silica gel column, affording **14** (2.20 g, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.31 (s, 1H), 8.08 (s, 1H), 7.38 (br s, 2H), 7.06 (d, 2H, J=8.8 Hz), 6.72 (d, 2H, J=8.8 Hz), 6.02 (d, 1H, J=6.4 Hz), 5.51 (dd, 1H, J=7.6, 4.4 Hz), 5.32 (d, 1H, J=5.2 Hz), 4.57 (d, 1H, J=12.0 Hz), 4.53 (dd, 1H, J=6.4, 4.8 Hz), 4.36 (d, 1H, J=12.0 Hz), 4.34 (m, 1H), 4.02 (m, 1H), 3.68 (s, 3H), 3.67 (m, 1H), 3.56 (ddd, 1H, J=12.0, 7.6, 3.6 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C) δ 158.7, 156.2, 152.3, 148.8, 139.8, 129.6, 129.1, 119.4, 113.4, 86.7, 86.3, 79.7, 70.7, 69.0, 61.6, 55.0. The ^{1}H NMR spectrum of this product was consistent with the literature data.[22] Anal. Calcd for $C_{18}H_{21}N_5O_5$: 55.81%, C; 5.46%, H; 18.08%, N. Found: 55.82%, C; 5.44%, H; 18.12%, N.

4.4. Synthesis of N^6-benzoyl-2′-*O*-*p*-methoxybenzyl adenosine (15)

Compound **14** (2.20 g, 5.68 mmol) was dissolved in dry pyridine. Then Me_3SiCl (4.7 mL, 37.49 mmol) was added. The reaction mixture was stirred for 2 h. After that time, BzCl (1.98 mL, 7.04 mmol)

was added, and the solution was stirred for further 3 h. When TLC (CH_2Cl_2/MeOH, 9:1) showed no further evolution the reaction was quenched with NH_4OH (30%, 15 mL) and the mixture was stirred for 15 min. After that time, the solution was poured into a water/ice bath, and then extracted with CH_2Cl_2. The organic phase was washed, dried with $MgSO_4$, and evaporated under vacuum. The reaction crude was redissolved in methanol and Dowex H^+ was added (4 g). The suspension was stirred until complete disappearing of the starting material was observed. Then the solution was filtered, concentrated under vacuum, and the residue redissolved in CH_2Cl_2, washed with an aqueous solution of $NaHCO_3$ (×3), dried with $MgSO_4$, evaporated and purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) affording **15** (3.36 g, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 11.26 (s, 1H), 8.70 (s, 1H), 8.67 (s, 1H), 8.05–7.56 (m, 5H), 7.09 (d, 2H, J=8.7 Hz), 6.75 (d, 2H, J=8.7 Hz), 6.18 (d, 1H, J=6.0 Hz), 5.41 (d, 1H, J=5.0 Hz), 5.21 (t, 1H, J=5.0 Hz), 4.63 (d, 1H, J=11.6 Hz), 4.59 (d, 1H, J=6.0 Hz), 4.44 (d, 1H, J=11.6 Hz), 4.38 (dd, 1H, J=7.5, 5.0 Hz), 4.04 (dd, 1H, J=7.5, 3.8 Hz), 3.72–3.59 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C) δ 165.5, 158.5, 151.3, 151.3, 150.2, 142.8, 133.1, 132.3, 128.3, 125.6, 129.2, 128.9, 116.0, 113.2, 86.2, 85.8, 79.6, 70.6, 68.6, 60.9, 54.7. The ^{1}H NMR spectrum of this product was consistent with the literature data.[22] Anal. Calcd for $C_{25}H_{25}N_5O_6$: 61.09%, C; 5.13%, H; 14.25%, N. Found: 61.02%, C; 5.14%, H; 14.02%, N.

4.5. Synthesis of 3′-*O*-(3″,4″,6″-tri-*O*-acetyl-2″-deoxy-2″-fluoro-α-D-glucopyranosyl)-N^6-benzoyl-5′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-*p*-methoxybenzyl adenosine (17)

Glycosyl acceptor (**16**) (280 mg, 0.38 mmol), Ag_2CO_3 (116 mg, 0.42 mmol) and AgOTf (30 mg, 0.11 mmol) were placed in a flask, then 2 mL of dry toluene was added and evaporated to dryness (three times), finally 4 Å M.S. (200 mg) were put in and the flask was protected from light. A similar procedure was followed for glycosyl donor (**12**, 200 mg). Then both acceptor and donor were placed in a dryer with P_2O_5 and left under vacuum for 24 h. After that time dry Et_2O (1.2 mL) was added to acceptor flask. Then glycosyl bromide was dissolved in dry CH_2Cl_2 (0.4 mL) and transferred to acceptor flask. The mixture was stirred for 48 h at rt. After 2 days the solution was filtered through Celite, and the solvents were evaporated to dryness. The crude reaction was applied to a silica gel column using a gradient of hexane/ethyl acetate (1:1, 1:2, 1:4) as elution system. After purification **17** was afforded (224 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 9.31 (s, 1H), 8.63 (s, 1H), 8.10 (s, 1H), 8.02–7.35 (m, 15H), 7.06 (d, 2H, J=8.8 Hz), 6.66 (d, 2H, J=8.8 Hz), 6.15 (d, 1H, J=6.0 Hz), 5.63 (dt, 1H, J=12.0, 9.6 Hz), 5.27 (d, 1H, J=4.0 Hz), 5.06 (dd, 1H, J=10.0, 9.6 Hz), 4.91 (dd, 1H, J=6.0, 5.2 Hz), 4.62 (d, 1H, J=11.6 Hz), 4.58 (m, 1H), 4.54 (ddd, 1H, J=48.8, 9.6, 4.0 Hz), 4.42 (m, 1H), 4.40 (d, 1H, J=11.6 Hz), 4.17 (dd, 1H, J=12.4, 4.4 Hz), 4.11 (m, 1H), 4.04 (ddd, 1H, J=10.0, 4.4, 2.4 Hz), 3.93 (dd, 1H, J=12.4, 2.4 Hz), 3.85 (dd, 1H, J=11.6, 3.6 Hz), 3.72 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 170.6, 170.2, 169.8, 164.8, 159.5, 152.6, 149.6, 142.3, 135.7–113.8, 123.4, 96.1 (d, J=20.5 Hz), 87.2 (d, J=196.8 Hz), 87.5, 83.6, 78.0, 74.8, 72.4, 70.6 (d, J=19.9 Hz), 68.2, 67.9 (d, J=6.8 Hz), 63.1, 61.6, 55.4, 27.1, 20.9, 20.8, 29.4; ^{19}F NMR (376.4 MHz, $CDCl_3$, 25 °C) δ −201.25 (dd, J=48.8, 12.0 Hz).

4.6. Synthesis of 3′-*O*-(2″-deoxy-2″-fluoro-α-D-glucopiranosyl)-5′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-*p*-methoxybenzyl adenosine (18)

A solution of compound **17** (214 mg, 0.21 mmol) was dissolved in dry methanol (0.2 mL). Then sodium methoxide (62 mg, 1.15 mmol) was added to the solution. The reaction mixture was stirred at rt for 4 h. The solution was neutralized with acetic acid, and concentrated under vacuum. Then the crude was diluted and washed with an aqueous solution of $NaHCO_3$. The organic layer is dried, filtered and evaporated to dryness. The crude was purified by column chromatography (elution system CH_2Cl_2/MeOH, 10:0, 9.5:0.5, 9:1) affording **18** (116 mg, 70% yield). ^{1}H NMR (300 MHz, CD_3OD, 25 °C) δ 8.25 (s, 1H), 7.91 (s, 1H), 7.63–7.33 (m, 10H), 7.06 (d, 1H, J=8.7 Hz), 6.68 (d, 1H, J=8.7 Hz), 6.19 (d, 1H, J=6.3 Hz), 5.85 (br s, 2H), 5.08 (d, 1H, J=3.6 Hz), 4.70 (m, 1H), 4.59 (d, 1H, J=11.7 Hz), 4.51–4.16 (m, 4H), 4.01 (dd, 1H, J=11.4, 4.5 Hz), 4.00–3.93 (m, 2H), 3.45 (t, 1H, J=9.2 Hz), 3.80–3.65 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C) δ 160.9, 151.8, 149.6, 143.2, 136.9–128.9, 123.4, 114.6, 98.1 (d, J=20.5 Hz), 91.6 (d, J=190.3 Hz), 88.9, 86.4, 80.4, 75.2, 74.6, 73.4, 73.0 (d, J=17.1 Hz), 71.1 (d, J=7.3 Hz), 65.3, 62.2, 55.9, 27.6, 20.3; ^{19}F NMR (376.4 MHz, CD_3OD, 25 °C) δ −202.77 (dd, J=50.4, 13.9 Hz). Anal. Calcd for $C_{40}H_{48}FN_5O_9Si$: 60.82, C; 6.12, H; 8.87, N. Found: 60.79, C; 6.11, H; 8.90, N. $[\alpha]_D^{20}$ +32.3 (*c* 0.3, MeOH).

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