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Synthetic Studies towards New Nucleoside Analogues: Preparation of (±)-1′,4′-Dimethyladenosine

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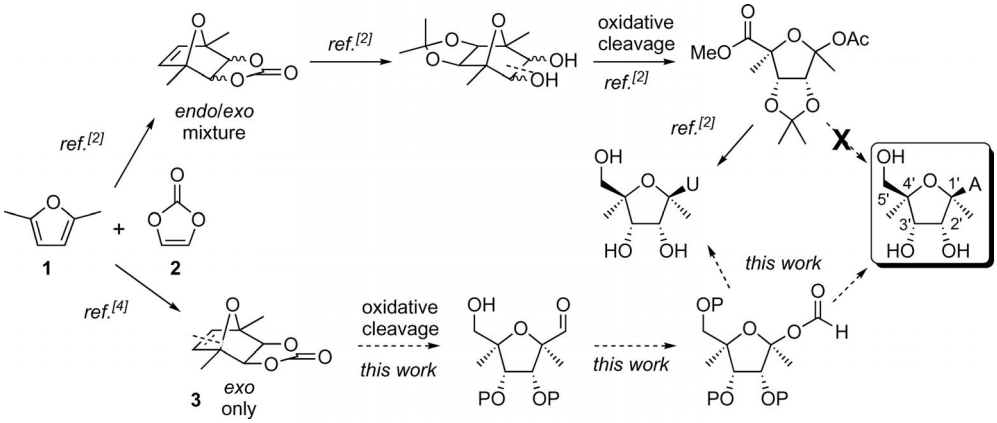
Racemic 1′,4′-dimethyladenosine was prepared according to a stereoselective sequence from 2,5-dimethyl furan and vinylene carbonate. This sequence is short and efficient (nine steps) and relies on the desymmetrization of a *meso* diol, followed by the glycosylation of the anomeric position. The latter reaction was thoroughly studied, as it is the key step of the sequence, and very particular reactivity of the 1′,4′-dimethylated sugars was observed. Secondary reactions took place according to original mechanisms and delivered original byproducts.

Introduction

Nucleoside analogues constitute an important class of biologically active compounds, and the synthesis of new molecules of this class with original substitution patterns remains a challenge for therapeutic chemists.[1] During the course of our synthetic studies towards 1′,4′-disubstituted nucleoside analogues, we developed a synthesis of 1′,4′-dimethyl uridine, starting from 2,5-dimethyl furan (**1**) and vinylene carbonate (**2**).[2] This synthetic route is efficient, as it overcomes the poor selectivity of the initial Diels–Alder reaction. However, we found it is limited to the synthesis of pyrimidine analogues, as the acetonide deprotection in the purine series was unsuccessful, probably because of a greater sensitivity of these substrates to the required acidic conditions. It is of key importance to circumvent this severe drawback, as purine derivatives, and especially adenosine analogues, are relevant for biological studies.[3] During our studies on the Diels–Alder reaction between **1** and **2**, we evidenced that prolonged heating leads to clean conversion of the *endo*/*exo* mixture into *exo* adduct **3** only, enabling large-scale production of the latter on a preparative scale after direct crystallization.[4] Therefore, we decided to exploit this result to design another route to 1′,4′-dimethyl nucleoside analogues, which is both shorter and suitable for purine synthesis (Scheme 1). It is the purpose of this communication to report our first results regarding this approach.



Scheme 1. Envisioned pathways towards 1′,4′-disubstituted adenosine analogues.

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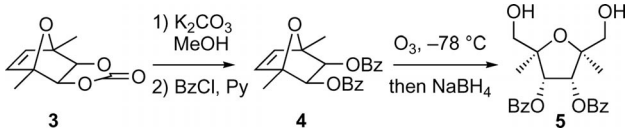
Results and Discussion

Our synthetic analysis is very simple (Scheme 1): oxidative cleavage of the olefinic double bond in **3** should reveal the 5′-hydroxy group, as well as an aldehyde, which would, after Baeyer–Villiger reaction, lead to a sugar bearing an activated anomeric center for heterocyclic base introduction. Thus, *exo* Diels–Alder adduct **3** possesses the correct relative configurations at the 2′- and 3′-oxygen atoms of the desired nucleoside analogues.

There are several possibilities to deliver directly the desired aldehyde moiety with an oxidative cleavage. We examined several ozonolysis methods, including unsymmetrical versions.[5] However, none gave satisfactory results on our substrate. Even the classical Me_2S- or PPh_3-based quenches did not lead to the corresponding dialdehyde on several substrates of this family in a clean manner. Therefore, we performed ozonolysis followed by $NaBH_4$ reduction, which proved to be very efficient.

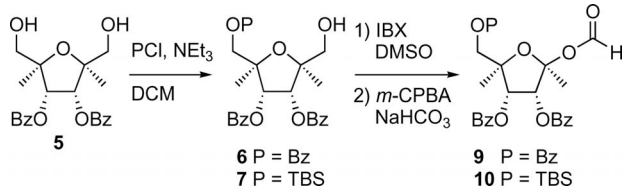
On a first attempt, we tried to keep the cyclic carbonate as a protecting group. However, this group did not withstand the reductive conditions, and most of the product was lost during treatment in the aqueous layer, probably in a tetraol form. Thus, we hydrolyzed the carbonate of **3** with potassium carbonate in methanol, then protected the resulting diol as a bis-benzoate with benzoyl chloride in pyridine, with an excellent yield (87%) after crystallization (Scheme 2). Ozonolysis of **4** in DCM/MeOH at –78 °C followed by immediate treatment with $NaBH_4$ delivered diol **5** in 72% yield after crystallization. On a small scale, a better yield (87%) can be obtained after purification by silica gel chromatography.



Scheme 2. Preparation of *meso* diol **5**.

Diol **5** is also a very interesting intermediate: it is a *meso* compound, and several methods are described regarding the enantiotopic differentiation of both alcohol groups on such substrates. Lipase-catalyzed acylation is envisioned for an enantioselective synthesis based on this work.[6] Before studying this point, we wanted to prove that the synthetic pathway could efficiently deliver the desired nucleoside analogues. Therefore, we pursued a racemic synthesis, employing either a benzoate or a *tert*-butyldimethylsilyl (TBS) protecting group (Scheme 3).

Monoprotection of diol **5** with a benzoate group was performed by using a slight deficiency of the protecting agent, which allowed almost complete avoidance of bis-benzoylation. Using benzoyl chloride (0.9 equiv.), 22% of the starting diol was easily recovered after purification by silica gel chromatography, delivering tribenzoate **6** in 83% corrected yield. On the other hand, the same method was less



Scheme 3. Preparation of activated sugars **9** and **10**.

efficient when silylating agents were used. The second silylation was more rapid, producing a large amount of bis-silylated compound. Thus, employing TBSCl (1.0 equiv.), we isolated desired product **7** in 37% yield, along with starting diol (23%) and bis-silylated product **8** (28%). The corrected yield for **7** is 48%, and the three compounds can be separated easily by flash column chromatography on silica gel thanks to the large difference in their R_f values. However, it is clear that a preparative-scale process cannot be designed from these sole results, although bis-silylated derivative **8** can be easily recycled into starting diol **5** after fluoride-mediated deprotection.[7]

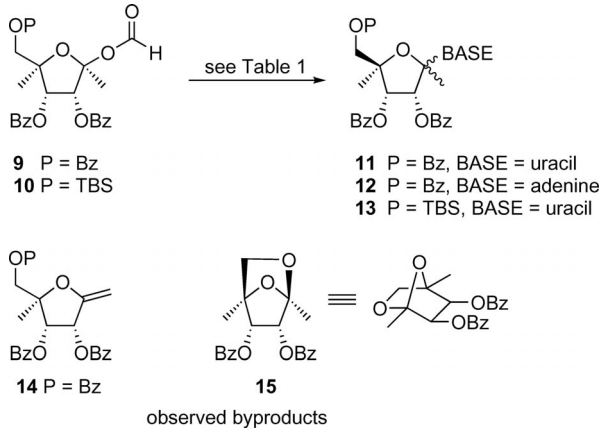
With monoprotected alcohols **6** and **7** in hand, we studied the transformation of the remaining hydroxymethyl group into a formate group to deliver the protected activated sugar required for heterocyclic base introduction. The oxidation of the alcohol moiety into the corresponding aldehyde was best effected with IBX in DMSO.[8] The yield was moderate and variable (60 to 75%) but counterbalanced by the quantitative Baeyer–Villiger oxidation on the same aldehyde (Scheme 3). Furthermore, we demonstrated that no purification of the intermediate aldehyde is required. Thus, compound **9** was obtained in 66% yield over the two steps starting from benzoate **6**, and **10** was obtained in 72% yield from TBS derivative **7**. The formate can be purified by chromatography on silica gel, and it is stable for several months when stored in the freezer. On the other hand, analysis by mass spectrometry did not reveal the peak corresponding to the product. However, under the mass spectrometry conditions, that is, electrospray ionization (ESI), the sample must be heated to a minimum of 250 °C, a temperature at which the compound is not stable, even in the neutral mode. The moderate yield for this transformation can be explained by the ease of over-oxidation of the aldehyde: the latter could not be isolated with a purity greater than 90% and showed decomposition to a baseline product by 2D TLC analysis. Basic aqueous treatment at the Baeyer–Villiger step may then lead to the loss of the corresponding carboxylic acid.

With activated sugars **9** and **10** in hands, we studied the introduction of various heterocyclic bases (Scheme 4 and Table 1). Among the numerous possibilities, we first focused on Vorbrüggen coupling, employing a silylated base with Lewis acid activation.[9] This method is widely applicable, as it usually gives high yield and high selectivity. First, we studied the introduction of the uracil moiety. As noticed during our previous studies,[2] we had to work at low temperature, in contrast to the generally encountered operating

Table 1. Glycosylation results on substrates **9** and **10**.

Entry	Conditions	Product	Yield [%]	β/α selectivity
1	bis-silylated uracil (2.0 equiv.), **9**, TMSOTf (1.0 equiv.), –20 °C, 1 h	**11**	70	3:1
2	bis-silylated uracil (2.0 equiv.), **9**, TMSOTf (1.0 equiv.), –20 °C to r.t.	**11**	35	3:1
		14	25	
3	bis-silylated uracil (2.0 equiv.), **9**, TMSOTf (1.0 equiv.), –20 to 70 °C	**14**	50	
4	bis-silylated uracil (2.0 equiv.), **10**, TMSOTf (1.0 equiv.), –20 °C, 1 h	**13**	27	3:1
5	bis-silylated N^6-Bz-Adenine (2.0 equiv.), **9**, TMSOTf (1.0 equiv.), –20 °C, 1 h	**12** (Bz)	43	2:1
6	adenine (2.0 equiv.), $SnCl_4$ (4.0 equiv.), **9**, –20 °C, 1 h	**12**	63	1:1
7	adenine (2.0 equiv.), $SnCl_4$ (4.0 equiv.), **10**, –20 °C to r.t.	**15**	48	

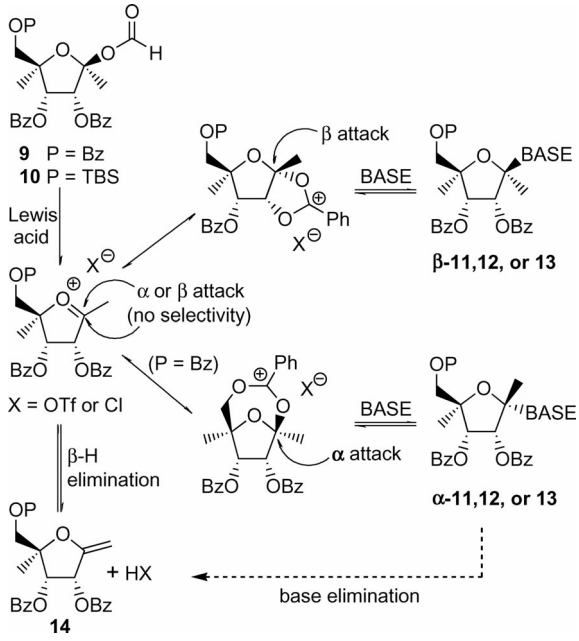
conditions. Also, to optimize the yield and selectivity of the reaction, we studied the impact of the different parameters on the Vorbrüggen reaction outcome.



Scheme 4. Glycosylation of **9** and **10**.

The only parameter to have a real influence on the reaction was the temperature (Table 1). We showed that at low temperature (below –30 °C) that the reaction is sluggish and that starting material is still present. The best conversion was achieved at –20 °C (70% isolated yield; Table 1, Entry 1). When warming to room temperature, a new spot was detected after TLC analysis of the reaction mixture. Isolation of this compound, followed by spectroscopic analysis revealed the formation of *exo* methylene **14** (Scheme 4; Table 1, Entry 2). Further warming of the reaction medium leads to an increase in the formation of this compound and to the complete disappearance of Vorbrüggen adducts **11** (Table 1, Entry 3).

Such a compound can result from β-hydrogen elimination on the intermediate carbocation, probably induced by the Lewis acid conjugated base (Scheme 5). Examining the mass spectrum of formate **9**, we noticed that the peak corresponding to elimination product **14** is also present, suggesting its easy formation. We eventually showed that heating formate **9** at 80 °C in the presence of silica gel leads to relatively clean conversion directly into **14**. Such a direct transformation on ketose derivatives was never reported before to the best of our knowledge, as it usually requires activation with a better leaving group and base catalysis.[10]



Scheme 5. Proposed mechanism of glycosylation of **9** and **10**.

The stability of *exo*-glycal **14** is striking compared to the ease of hydrolysis of common *exo*-glycals on silica gel.[11] 2D TLC analysis showed absolutely no degradation of **14** on standard chromatography silica gel. We propose two reasons for this stability: the electron-withdrawing effect of three benzoate protecting groups can significantly lower the electrophilicity of the enol ether, and also the steric hindrance on the furanose ring, mainly the presence of the 4′-quaternary center, may disfavor sp^3 hybridization of the 1′-carbon to avoid 1,3-diaxial interactions. Both reasons are also invoked in the discussion on the selectivity of the reaction.

Regarding the selectivity, these results are somehow disappointing: we observed a modest selectivity in favor of the β anomer (3:1). The configuration of the anomeric center was further confirmed after deprotection of the benzoate protecting groups: the obtained compound was identical to the derivative prepared by our first route (see below). This behavior during a Vorbrüggen reaction is noteworthy. Usually, the accepted mechanism proposes a thermodynamic equilibration, favoring the β anomer, through a bridged oxonium with the 2′-benzoate group.[12] Also, the intramo-

lecular participation of the 5′-benzoate, through a β-face-bridged oxonium, which then induces preferred α attack, was already reported on similar substrates.[13] Both intermediates are depicted in Scheme 5.

The β/α ratio we observe does not vary meaningfully with the temperature, suggesting that the reaction stays under kinetic control. Any attempt to reach a thermodynamic equilibration led instead to *exo* methylene adduct **14**. *exo*-Glycal **14** appears thus to be the thermodynamic well of the reaction, and we do not think that it is an intermediate en route to protected nucleosides **11**–**13**, as described before during the synthesis of complex disaccharides.[14] It is not possible to completely exclude that compound **14** results from the elimination of the heterocyclic base from compound **11**, **12**, or **13**. However, treatment of formate **9** with TMSOTf alone in acetonitrile (at –20 °C to r.t.) leads predominantly to *exo*-glycal **14**, albeit accompanied by several side products of the same polarity. These conditions may be slightly too harsh and lead to partial degradation of compound **14** but also suggest its direct formation from the intermediate carbocation through β-hydrogen elimination (Scheme 5). Such a reaction is entropically favored, in contrast to base condensation, and we thus propose that any attempt at α to β equilibration on protected nucleosides **11**–**13** will eventually lead to **14**. This behavior is specific to our 1′,4′-dimethylated substrates and has never been observed before, to the best of our knowledge.

We then studied the same coupling with a 5′-silyl group, a typical nonparticipating group. The reaction was run with silyl derivative **10**, but the selectivity was exactly the same (3:1) at –20 °C (Table 1, Entry 4). Thus, we think that on the substrates we are studying, the steric bulk on the β face of the molecules is important and counterbalances to some extent the shielding of the α face by the benzoate group. We modeled the (simplified) intermediate carbocations with DFT calculations by using Gaussian (B3LYP/6-31G**), and it appeared that the 5′-group prefers to lie in an axial position to avoid 1,2- or 1,3-diaxial interactions between the 4′-methyl and the 3′- and 2′-benzoate group, respectively (Figure 1). The shielding of the β face in the case of the benzoate group is enhanced by the preferred conformation where the carbonyl group lies above the C1′ center. The last result gives consistence to the above proposed 5′-benzoate assistance, which leads to a seven-membered ring (Scheme 5).

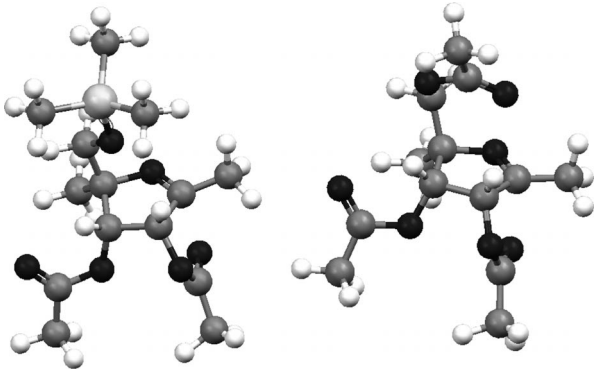
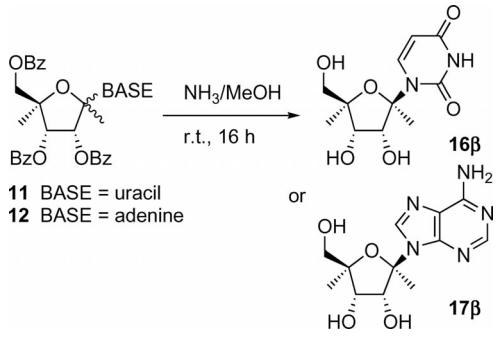


Figure 1. Optimized geometry of the intermediate carbocations encompassing a 5′-acetate or a 5′-trimethylsilyl group (B3LYP/6-31G**).

To complete the synthesis, the three benzoate groups of **11** can be cleanly removed simultaneously after treatment with NH_3 in MeOH (Scheme 6). Desired isomer **16β** is obtained pure after column chromatography on silica gel in 64% yield (β isomer only). NMR spectroscopic analysis shows identical properties as the compound obtained by our previously described route, bearing all the correct relative stereochemistries. Thus, the route described in this article is three steps shorter (9 steps instead of 12 starting from **1** and **2**) and gives slightly higher yields (9% global yield vs. 7%).



Scheme 6. Completion of the synthesis.

We then tried to apply this route to the synthesis of purine nucleoside analogues. With bis-silylated N^6-benzoylated adenine as a base, Vorbrüggen coupling of formate **9** was quite sluggish (Table 1, Entry 5). A poor yield was obtained (43%) with a low selectivity (2:1). Therefore, we also employed Saneyoshi's conditions with unsilylated adenine and $SnCl_4$ catalysis. Unfortunately, there was no β/α selectivity (Table 1, Entry 6). Analysis of the ^1H NMR spectrum of the crude reaction mixture showed no other signal in the 4.0 to 6.5 ppm region, which can be attributed to the 2′- or 3′-protons of other regioisomers such as *N*7 adducts. TLC analysis also showed that no starting material remained, but several low polarity products were detected; amongst them *exo*-glycal **14** was present. The yield remains good regarding this type of coupling and reflects the lower reactivity of the purine heterocycles compared to that of the pyrimidines.

However, deprotection of the benzoate groups led to a separable mixture of both β and α anomers. β Anomer **17β** was thus obtained in 31% yield and was fully characterized (Scheme 6). Nuclear Overhauser effect (nOe) studies confirmed the relative configuration of the stereocenters: we performed nOe difference experiments, which revealed that the adenine ring, the 5′-group, and the 2′- and 3′-protons are on the same side of the molecule (Figure 2). As with the uracil derivative, we did not observe a nOe between the methyl groups, suggesting a pseudoequatorial conformation for both groups.

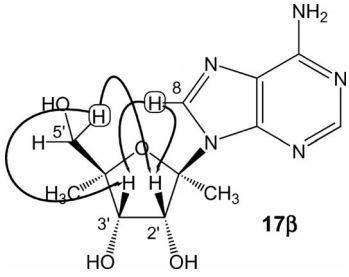
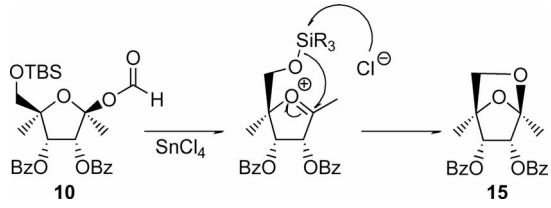


Figure 2. Observed nOe interactions on compound **17β**.

Finally, we also tried Saneyoshi's conditions[15] with silylated derivative **10** (Table 1, Entry 7). To our surprise, no coupling adduct was obtained, but a clean cyclization reaction took place to afford bicyclic product **15** (Scheme 4). The structure of **15** was fully established by IR spectroscopy, which showed no free hydroxy band. Other spectroscopic data, such as ^1H and ^{13}C NMR spectroscopy and MS, are in full agreement with this structure. Such a cyclization implies either nucleophilic attack of the TBS ether onto the intermediate carbocation or prior deprotection of the silyl ether, followed by addition of the resulting oxide onto the same carbocation. As TBS groups are described to be stable under $SnCl_4$ treatment at 0 °C[16] and because they are poorly nucleophilic, we propose a concerted mechanism, where chloride-mediated desilylation is favored by the activation of the silicon oxygen bond through oxygen lone pair interaction with the carbocationic center (Scheme 7).



Scheme 7. Proposed mechanism for the formation of **15**.

This cyclization proves that the presence of the methyl groups tends to induce the adoption of a bicyclic structure; thus, the 5′-protected hydroxy group strongly prefers an axial position. This point could explain the low selectivity observed during Vorbrüggen coupling: the bridging of the oxonium with the 5′-benzoate should be favored by the conformation of the molecule.

Conclusions

As a conclusion, we described here another route to 1′,4′-dimethylated nucleoside analogues. This route is advantageous, as it enables access to both pyrimidine and purine derivatives with a short reaction sequence and good yields. This study also revealed the unique behavior of this family of substrates during glycosylation. Further studies will be devoted to the study of the structural parameters influencing the selectivity of this reaction, as well as to the final design of an enantioselective route. Finally, we will be able to study this new family of 1′,4′-disubstituted nucleoside analogues and their biological applications.

Experimental Section

General Procedures: Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, acetonitrile, and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed by using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed by using 0.25 mm silica gel plates (Merck). Melting points were determined in open capillary tubes with a Büchi-545. UV spectra were recorded with a Uvikon 931 (Kontron). Infrared spectra were recorded with a Perkin–Elmer Paragon 1000 FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded at 300 K with Bruker 300 Avance and DRX 400 spectrometers in solutions in the indicated solvent. Chemical shifts are expressed in parts per million downfield from tetramethylsilane and are referenced to the residual solvent peak (^1H NMR: $CHCl_3$, δ = 7.26 ppm; [D_6]DMSO, δ = 2.50 ppm) or the deuterated solvent peaks (^{13}C NMR: $CDCl_3$, δ = 77.16 ppm; [D_6]DMSO, δ = 39.52 ppm). When possible, hydroxy groups were identified by D_2O swap. FAB mass spectra were recorded in the positive-ion or negative-ion mode with a JEOL SX 102. The matrix was a mixture (50:50) of glycerol and thioglycerol (G/T). Electrospray ionization (ESI) mass spectra and high-resolution mass spectra were obtained with a Waters Q-TOF.

1,4-Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-diyl Dibenzoate (4): To a solution of carbonate **3** (4.65 g, 25.6 mmol) in methanol (50 mL) was added K_2CO_3 (3.90 g, 28.1 mmol, 1.1 equiv.), and the resulting slurry was stirred for 2 h at room temperature, then filtered, and concentrated in vacuo. The resulting solid was diluted in DCM (24 mL) and pyridine (16 mL) and cooled to 0 °C. To the resulting solution was added benzoyl chloride (6.5 mL, 56.3 mmol, 2.2 equiv.) dropwise; a white precipitate appeared. The resulting mixture was stirred at room temperature for 3 h. After dilution with AcOEt (50 mL), the mixture was quenched with a saturated aqueous NH_4Cl solution (40 mL), and the layers were separated. The organic layer was washed successively with water (40 mL), 1 N HCl (2 × 40 mL), water (40 mL), and brine (40 mL). It was then dried with $MgSO_4$, filtered, and concentrated in vacuo. Crystallization (petroleum ether/ether, 2:1) yielded a white solid (8.15 g, 69%). M.p. 136–137 °C. IR (neat): $\tilde{\nu}$ = 3061, 2980, 2936, 1728, 1601, 1584, 1491, 1451, 1382, 1354, 1317, 1283, 1177, 1120, 1071, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 6 H, Me), 5.32 (s, 2 H, 2-H and 3-H), 6.39 (s, 2 H, 5-H and 6-H), 7.24 (m, 4 H, Ar-H), 7.46 (m, 2 H, Ar-H), 7.89 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 140.8, 133.2, 129.8, 129.5, 128.2, 87.5, 73.2, 14.6 ppm. MS (ESI+): *m*/*z* = 365 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{22}H_{21}O_5$ $[M + H]^+$ 365.1389; found 365.1382.

2,5-Bis(hydroxymethyl)-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (5): A $O_3/O_2/N_2$ stream was bubbled at –78 °C into a solution of dibenzoate **4** (5.4 g, 14.8 mmol) in DCM/MeOH (5:1, 120 mL) with a drop of Sudan red solution (0.6 mg in 2 mL MeOH) until complete disappearance of the red color (approx. 30 min). Then, solid $NaBH_4$ (5.6 g, 150 mmol, 10 equiv.) was added

portionwise, and the resulting mixture was stirred at room temperature until H_2 bubbling stopped. Then the mixture was diluted with DCM (150 mL), quenched slowly with a saturated aqueous NH_4Cl solution (60 mL), and the layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo. The obtained solid was triturated with petroleum ether/AcOEt (1:1), filtered, and washed with the same solvent (2×). Diol **5** was obtained as a white solid (3.7 g, 72%). M.p. 124–125 °C. IR (neat): $\tilde{\nu}$ = 3422, 3058, 2976, 2924, 1726, 1601, 1451, 1315, 1279, 1124, 1067 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 6 H, Me), 3.71 (s, 4 H, 2-CH_2 and 5-CH_2), 3.87 (s, 2 H, OH), 5.97 (s, 2 H, 3-H and 4-H), 7.34–7.39 (m, 4 H, Ar-H), 7.50–7.58 (m, 2 H, Ar-H), 7.90–7.97 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 133.5, 129.8, 129.5, 128.6, 84.6, 74.3, 68.2, 20.2 ppm. MS (ESI+): *m*/*z* = 401 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{22}H_{25}O_7$ $[M + H]^+$ 401.1600; found 401.1606.

2-[(Benzoyloxy)methyl]-5-(hydroxymethyl)-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (6): To a solution of diol **5** (947 mg, 2.4 mmol) in DCM (15 mL) at 0 °C was added NEt_3 (1.0 mL, 7.1 mmol, 3.0 equiv.), DMAP (15 mg, 0.12 mmol, 5 mol-%), and BzCl (250 µL, 2.1 mmol, 0.9 equiv.) dropwise. A white precipitate formed, and the resulting mixture was stirred at room temperature for 2 h. The reaction medium was diluted with AcOEt (50 mL) and quenched with MeOH (2 mL), then with a saturated aqueous NH_4Cl solution (15 mL). The layers were separated, the organic layer was washed with water (2 × 15 mL) and brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/AcOEt, 70:30 to 50:50) yielded product **6** as a colorless oil (772 mg, 65%) and starting material **5** (212 mg, 22%). IR (neat): $\tilde{\nu}$ = 3492, 3063, 2984, 2936, 2976, 1721, 1601, 1451, 1379, 1263, 1176, 1095, 1067, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 3 H, Me), 1.57 (s, 3 H, Me), 2.80 (dd, *J* = 8.3, 5.2 Hz, 1 H, OH), 3.54–3.67 (m, 2 H, 5-CH_2), 4.41 (d, *J* = 11.6 Hz, 1 H, 2-CH_2), 4.56 (d, *J* = 11.6 Hz, 1 H, 2-CH_2), 5.94 (d, *J* = 6.1 Hz, 1 H, 3-H or 4-H), 5.98 (d, *J* = 6.1 Hz, 1 H, 3-H or 4-H), 7.33–7.42 (m, 3 H, Ar-H), 7.43–7.49 (m, 3 H, Ar-H), 7.51–7.62 (m, 3 H, Ar-H), 7.93–7.99 (m, 4 H, Ar-H), 8.10–8.15 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.4, 165.2, 133.5, 133.5, 133.4, 129.9, 129.8, 129.7, 129.7, 129.4, 129.3, 128.7, 128.6, 128.6, 84.8, 82.9, 74.3, 73.4, 69.2, 67.4, 20.6, 19.8 ppm. MS (ESI+): *m*/*z* = 505 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{29}H_{29}O_8$ $[M + H]^+$ 505.1862; found 505.1859.

2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(hydroxymethyl)-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (7): To a solution of diol **5** (452 mg, 1.1 mmol) in dry DMF (4 mL) at 0 °C was added imidazole (390 mg, 5.6 mmol, 5.0 equiv.) and TBSCl (170 mg, 1.1 mmol, 1.0 equiv.) portionwise. A white precipitate formed, and the resulting mixture was stirred at room temperature for 24 h. The reaction medium was quenched with MeOH (2 mL), then diluted with AcOEt (50 mL), and a saturated aqueous NH_4Cl solution (10 mL) was added. The layers were separated, and the organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/AcOEt, 80:20 to 40:60) yielded bis-protected compound **8** (229 mg, 28%), product **7** as a colorless oil (192 mg, 37%), and starting material **5** (105 mg, 23%). Data for **7**: IR (neat): $\tilde{\nu}$ = 3447, 2931, 2858, 1727, 1451, 1314, 1275, 1260, 1122, 1094, 1068, 1025, 837, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, Si-Me), 0.09 (s, 3 H, Si-Me), 0.87 (s, 9 H, Si-CMe_3), 1.26 (s, 3 H, 2-Me or 5-Me), 1.29 (s, 3 H, 2-Me or 5-Me), 3.38 (dd, *J* = 9.6, 3.2 Hz, 1 H, 2-CH_2 or 5-CH_2), 3.45–3.59 (m, 3 H, OH and 2-CH_2 and/or 5-CH_2), 3.62 (d, *J* = 9.6 Hz, 1 H, 2-CH_2 or 5-CH_2), 5.78 (d, *J* = 5.8 Hz, 1 H, 3-H or 4-H), 5.88 (d, *J* = 5.8 Hz, 1 H, 3-H or 4-H), 7.19–7.30 (m, 4 H, Ar-H), 7.37–7.46 (m, 2 H, Ar-H), 7.79–7.88 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 165.1, 133.3, 133.2, 129.7, 129.6, 129.5, 128.5, 128.4, 84.8, 84.2, 74.7, 73.3, 68.6, 68.5, 26.0, 20.4, 20.0, 18.6, –5.3, –5.5 ppm. MS (ESI+): *m*/*z* = 515 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{28}H_{39}O_7Si$ $[M + H]^+$ 515.2465; found 515.2463. Data for **8**: IR (neat): $\tilde{\nu}$ = 2954, 2929, 2857, 1729, 1451, 1314, 1275, 1258, 1092, 1068, 837, 775, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 12 H, Si-Me), 0.91 (s, 18 H, Si-CMe_3), 1.43 (s, 6 H, 2-Me and 5-Me), 3.57 (d, *J* = 10.2 Hz, 2 H, 2-CH_2 and 5-CH_2), 3.67 (d, *J* = 10.1 Hz, 2 H, 2-CH_2 and 5-CH_2), 5.86 (s, 2 H, 3-H and 4-H), 7.32–7.53 (m, 6 H, Ar-H), 7.92–7.95 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 133.1, 129.9, 129.7, 128.4, 83.8, 74.7, 69.1, 26.0, 20.4, 18.4, –5.2, –5.3 ppm. MS (ESI+): *m*/*z* = 629 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{34}H_{53}O_7Si_2$ $[M + H]^+$ 629.3330; found 629.3311.

2-[(Benzoyloxy)methyl]-5-(formyloxy)-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (9): To a solution of alcohol **6** (772 mg, 1.5 mmol) in DMSO (15 mL) at 15 °C was added 2-iodoxybenzoic acid (IBX, 857 mg, 3.0 mmol, 2.0 equiv.) portionwise over 10 min. The resulting solution was stirred for 2 h at 35 °C, then cooled to room temperature, quenched with water (30 mL), and diluted with AcOEt (50 mL). A white precipitate formed, and the mixture was filtered through a sintered funnel. The layers were separated, and the organic layer was washed with water (3 × 15 mL) and brine (15 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude aldehyde was taken into DCM (25 mL) at 0 °C. Solid $NaHCO_3$ (252 mg, 3.0 mmol, 2.0 equiv.) was added all at once, and then *m*-CPBA (70% purity, 550 mg, 2.25 mmol, 1.5 equiv.) was added portionwise over 10 min. The resulting mixture was stirred for 15 min at room temperature. It was then quenched with an aqueous thiosulfate solution (10 mL), and AcOEt (50 mL) was added. The layers were separated, and the organic layer was washed with an aqueous thiosulfate solution (20 mL), an aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/AcOEt, 80:20) yielded formate **9** as a colorless oil (513 mg, 66%). IR (neat): $\tilde{\nu}$ = 3067, 2996, 2943, 1722, 1601, 1451, 1380, 1261, 1175, 1091, 1068, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, Me), 1.92 (s, 3 H, Me), 4.42 (d, *J* = 11.7 Hz, 1 H, 2-CH_2), 4.59 (d, *J* = 11.7 Hz, 1 H, 2-CH_2), 6.05 (d, *J* = 6.1 Hz, 1 H, 3-H or 4-H), 6.08 (d, *J* = 6.1 Hz, 1 H, 3-H or 4-H), 7.30–7.38 (m, 3 H, Ar-H), 7.40–7.48 (m, 3 H, Ar-H), 7.51–7.66 (m, 3 H, Ar-H), 7.85–7.88 (m, 4 H, Ar-H), 8.02–8.06 (m, 2 H, Ar-H), 8.33 (s, 1 H, $H_{formate}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.0, 164.7, 159.2, 133.8, 133.7, 133.3, 129.8, 129.8, 129.8, 129.7, 129.0, 128.8, 128.6, 128.5, 110.6, 85.5, 76.4, 72.5, 68.6, 20.9, 20.4 ppm. MS (ESI+): *m*/*z* = 473 $[M + H – HCOOH]^+$. HRMS (ESI+): calcd. for $C_{28}H_{25}O_7$ $[M + H – HCOOH]^+$ 473.1600; found 473.1594.

2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(formyloxy)-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (10): To a solution of alcohol **7** (373 mg, 0.7 mmol) in DMSO (7 mL) at 15 °C was added 2-iodoxybenzoic acid (IBX, 408 mg, 1.4 mmol, 2.0 equiv.) portionwise over 5 min. The resulting solution was stirred for 2 h at 35 °C, then cooled to room temperature, quenched with water (15 mL), and diluted with AcOEt (30 mL). A white precipitate formed, and the mixture was filtered through a sintered funnel. The layers were separated, and the organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude aldehyde was taken into DCM (10 mL) at 0 °C. Solid

$NaHCO_3$ (122 mg, 1.4 mmol, 2.0 equiv.) was added all at once, and then *m*-CPBA (70% purity, 270 mg, 1.1 mmol, 1.5 equiv.) was added portionwise over 5 min. The resulting mixture was stirred for 15 min at room temperature. It was then quenched with an aqueous thiosulfate solution (5 mL), and AcOEt (30 mL) was added. The layers were separated, and the organic layer was washed with an aqueous thiosulfate solution (10 mL), an aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/AcOEt, 85:15) yielded formate **10** as a colorless oil (277 mg, 72%). IR (neat): $\tilde{\nu}$ = 2928, 2857, 1729, 1452, 1256, 1093, 1069, 835, 779, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, Si-Me), 0.01 (s, 3 H, Si-Me), 0.79 (s, 9 H, Si-CMe_3), 1.37 (s, 3 H, 2-Me or 5-Me), 1.78 (s, 3 H, 2-Me or 5-Me), 3.57 (d, J = 10.6 Hz, 1 H, 2-CH_2), 3.64 (d, J = 10.6 Hz, 1 H, 2-CH_2), 5.87 (s, 2 H, 3-H and 4-H), 7.17–7.51 (m, 6 H, Ar-H), 7.76–7.79 (m, 2 H, Ar-H), 7.88–7.90 (m, 2 H, Ar-H), 8.20 (s, 1 H, $H_{formate}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.6, 159.8, 133.6, 133.3, 129.8, 129.7, 129.2, 128.6, 128.4, 110.3, 87.5, 77.0, 72.3, 68.3, 25.9, 21.7, 19.9, 18.4, –5.4 ppm. MS (ESI+): m/z = 483 [M + H – HCOOH]$^+$.

Glycosylation According to the Vorbrüggen Procedure

2-[(Benzoyloxy)methyl]-5-[2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (11): To a solution of compound **9** (140 mg, 0.27 mmol) in dry acetonitrile (3 mL) was added uracil (60 mg, 0.54 mmol, 2.0 equiv.) and *N*,*O*-bis-trimethylsilyl acetamide (280 µL, 1.1 mmol, 4.2 equiv.). The resulting suspension was stirred at 50 °C until clear (1 h). The resulting solution was cooled to –20 °C, and TMSOTf (50 µL, 0.27 mmol, 1.0 equiv.) was added dropwise. The temperature was maintained at –20 °C for 1 h, and the reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution (5 mL), and diluted with CH_2Cl_2 (40 mL). The layers were separated, and the organic layer was washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/AcOEt, 50:50) yielded compound **11** (3:1 mixture of isomers) as a colorless oil (110 mg, 70%). UV (EtOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 262 (11300) nm. IR (neat): $\tilde{\nu}$ = 3269, 3061, 2360, 2341, 1731, 1693, 1601, 1451, 1377, 1267, 1177, 1105, 1069, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (major isomer italicized when identified) = 1.60 (s, 2.25 H, *2-Me or 5-Me*), 1.60 (s, 0.75 H, 2-Me or 5-Me), 1.88 (s, 2.25 H, *2-Me or 5-Me*), 1.86 (s, 0.75 H, 2-Me or 5-Me), 4.27 (d, J = 12.2 Hz, 0.75 H, *2-CH_2*), 4.29 (d, J = 12.0 Hz, 0.25 H, 2-CH_2), 4.71 (d, J = 12.2 Hz, 0.75 H, *2-CH_2*), 4.73 (d, J = 12.2 Hz, 0.25 H, 2-CH_2), 5.48 (d, J = 8.4 Hz, 0.75 H, *6′-H*), 5.83 (d, J = 8.4 Hz, 0.25 H, 6′-H), 6.02 (d, J = 5.7 Hz, 0.75 H, *3-H or 4-H*), 6.15 (d, J = 5.2 Hz, 0.25 H, 3-H or 4-H), 6.27 (d, J = 5.2 Hz, 0.25 H, 3-H or 4-H), 6.57 (d, J = 5.7 Hz, 0.75 H, *3-H or 4-H*), 7.33–7.63 (m, 9 H, Ar-H), 7.77–8.08 (m, 6 H, Ar-H and 5′-H), 8.18 (s, 0.75 H, *Ar-H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (major isomer italicized when identified) = 165.8, *165.7*, *164.8*, *164.8*, 164.3, 163.7, *163.4*, 163.3, *149.5*, 149.4, 139.7, *139.2*, 133.8, 133.6, 133.6, 133.4, 133.3, 129.7, 129.6, 129.6, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, *101.6*, 100.9, *98.4*, 95.8, *85.9*, 84.7, *76.6*, 75.6, *73.9*, 70.7, *67.8*, 67.1, 26.4, *24.4*, 19.6, 19.4 ppm. MS (ESI+): m/z = 585 [M + H]$^+$. HRMS (ESI+): calcd. for $C_{32}H_{29}N_2O_9$ [M + H]$^+$ 585.1873; found 585.1871.

2-[(Benzoyloxy)methyl]-2-methyl-5-methylenetetrahydrofuran-3,4-diyl Dibenzoate (14): This compound was obtained as a byproduct (colorless oil) of this procedure (see Table 1 for details). IR (neat): $\tilde{\nu}$ = 3075, 2960, 2925, 2857, 1723, 1601, 1451, 1378, 1259, 1176, 1093, 1068, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 3 H, 2-Me), 4.37 (m, 1 H, 5-CH_2), 4.42 (d, J = 11.8 Hz, 2 H, 2-CH_2), 4.54 (d, J = 11.8 Hz, 2 H, 2-CH_2), 4.62 (m, 1 H, 5-CH_2), 5.86 (d, J = 6.0 Hz, 2 H, 3-H or 4-H), 6.32 (d, J = 6.0 Hz, 2 H, 3-H or 4-H), 7.34–7.41 (m, 2 H, Ar-H), 7.42–7.48 (m, 2 H, Ar-H), 7.51–7.61 (m, 2 H, Ar-H), 7.94–7.98 (m, 2 H, Ar-H), 8.06–8.10 (m, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.3, 165.2, 157.4, 133.6, 133.5, 133.4, 129.9, 129.6, 129.3, 129.0, 128.6, 128.6, 128.5, 86.5, 85.0, 72.5, 71.3, 68.3, 18.8 ppm. MS (ESI+): m/z = 473 [M + H]$^+$. HRMS (ESI+): calcd. for $C_{28}H_{25}O_7$ [M + H]$^+$ 473.1600; found 473.1590.

Glycosylation According to the Saneyoshi Procedure

2-(6-Amino-9*H*-purin-9-yl)-5-[(benzoyloxy)methyl]-2,5-dimethyltetrahydrofuran-3,4-diyl Dibenzoate (12): To a solution of compound **9** (161 mg, 0.31 mmol) in dry acetonitrile (3 mL) was added adenine (84 mg, 0.62 mmol, 2.0 equiv.). The resulting solution was cooled to –20 °C, and $SnCl_4$ (150 µL, 1.25 mmol, 4.0 equiv.) was added dropwise. The reaction mixture turned yellow and was stirred at the same temperature for 1 h, then quenched with dry pyridine (1.5 mL), and diluted with CH_2Cl_2 (40 mL). A white precipitate formed, and the mixture was filtered through a Celite pad. The organic layer was washed with an aqueous $NaHCO_3$ solution (10 mL), water (10 mL), and brine (3 × 10 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (DCM/MeOH, 95:5) yielded compound **12** (1:1 mixture of isomers) as a white solid (115 mg, 53%). UV (EtOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 231 (26500), 261 (9800) nm. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 3 H, 2-Me or 5-Me), 1.68 (s, 3 H, 2-Me or 5-Me), 2.03 (s, 3 H, 2-Me or 5-Me), 2.17 (s, 3 H, 2-Me or 5-Me), 2.36 (s, 2 H, NH_2), 4.42 (d, J = 12.0 Hz, 1 H, 5-CH_2), 4.43 (d, J = 11.9 Hz, 1 H, 5-CH_2), 4.66 (d, J = 12.0 Hz, 1 H, 5-CH_2), 4.71 (d, J = 11.9 Hz, 1 H, 5-CH_2), 5.85 (s, 1 H, 3′-H), 5.88 (s, 1 H, 3′-H), 6.04 (d, J = 5.5 Hz, 1 H, 3-H or 4-H), 6.15 (d, J = 5.4 Hz, 1 H, 3-H or 4-H), 6.42 (d, J = 5.4 Hz, 1 H, 3-H or 4-H), 7.10 (d, J = 5.5 Hz, 1 H, 3-H or 4-H), 7.13–7.63 (m, 18 H, Ar-H), 7.69–7.78 (m, 4 H, Ar-H), 7.86–7.91 (m, 3 H, Ar-H), 8.07–8.18 (m, 7 H, Ar-H), 8.18 (s, 1 H, 8′-H), 8.38 (s, 1 H, 8′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.9, 165.0, 164.9, 164.8, 164.4, 155.5, 155.4, 152.9, 152.5, 149.9, 149.3, 148.7, 138.7, 138.3, 136.0, 133.7, 133.7, 133.6, 133.6, 133.4, 133.3, 129.9, 129.8, 129.6, 129.4, 129.2, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 120.6, 120.5, 96.5, 95.3, 85.6, 85.2, 76.0, 75.8, 73.3, 72.6, 68.5, 68.2, 27.4, 25.5, 20.3, 19.5 ppm. MS (ESI+): m/z = 608 [M + H]$^+$. HRMS (ESI+): calcd. for $C_{33}H_{30}N_5O_7$ [M + H]$^+$ 608.2145; found 608.2157.

1,4-Dimethyl-2,7-dioxabicyclo[2.2.1]heptane-5,6-diyl Dibenzoate (15): This compound was obtained as a byproduct (white solid) of this procedure (see Table 1 for details). M.p. 133–135 °C. IR (neat): $\tilde{\nu}$ = 2925, 1731, 1651, 1453, 1288, 1126, 1010 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 3 H, Me), 1.70 (s, 3 H, Me), 3.53 (d, J = 7.2 Hz, 1 H, 3-H), 3.79 (d, J = 7.2 Hz, 1 H, 3-H), 5.38 (d, J = 6.0 Hz, 1 H, 5-H or 6-H), 5.52 (d, J = 6.0 Hz, 1 H, 5-H or 6-H), 7.21–7.31 (m, 4 H, Ar-H), 7.44–7.52 (m, 2 H, Ar-H), 7.86–7.91 (m, 4 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 165.3, 133.3, 133.3, 129.8, 129.1, 129.0, 128.3, 128.3, 107.6, 85.0, 75.5, 71.6, 14.8, 12.6 ppm. MS (ESI+): m/z = 369 [M + H]$^+$. HRMS (ESI+): calcd. for $C_{21}H_{21}O_6$ [M + H]$^+$ 369.1338; found 369.1343.

Deprotection with NH_3/MeOH

(±)-1′,4′-Dimethyl-1′,4′-didehydroadenosine (17β): Tribenzoate **12** (83 mg, 0.14 mmol) was introduced into a screw cap vessel, and dry MeOH saturated with NH_3 (4 mL) was added. The vessel was closed, and set at room temperature for 16 h. The vessel was slowly opened, and the medium was degassed with argon for 10 min. The

resulting product was taken into DCM and concentrated in vacuo. Purification by flash chromatography on silica gel (DCM/MeOH, 90:10) yielded compound **17β** as a white solid (13 mg, 31%) and isomer **17α** still contaminated with a residual amount of **17β**. M.p. 191–193 °C (decomp.). UV (EtOH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 260 (10600) nm. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.19 (s, 3 H, 1′-Me or 4′-Me), 1.73 (s, 3 H, 1′-Me or 4′-Me), 3.25–3.28 (m, 1 H, 5′-H), 3.42 (dd, J = 11.8, 5.3 Hz, 1 H, 5′-H), 3.96 (t, J = 5.8 Hz, 1 H, 2′-H or 3′-H), 4.77 (t, J = 5.3 Hz, 1 H, 2′-H or 3′-H), 4.93 (d, J = 6.1 Hz, 1 H, OH), 5.54 (t, J = 5.8 Hz, 1 H, OH), 5.62 (d, J = 5.3 Hz, 1 H, OH), 7.25 (s, 2 H, NH_2), 8.10 (s, 1 H, 3-H), 8.33 (s, 1 H, 8-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 156.6, 152.1, 148.3, 139.6, 120.5, 96.9, 87.5, 75.9, 71.1, 67.0, 24.1, 19.9 ppm. MS (ESI+): m/z = 296 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{12}H_{18}N_5O_4$ $[M + H]^+$ 296.1359; found 296.1353.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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