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Synthesis and antiviral activity of 3′-*C*-branched-3′-deoxy analogues of adenosine [1]

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Abstract

The synthesis of some 3′-*C*-branched-3′-deoxy adenine nucleosides is described. Starting from the known 3-deoxy-3-*C*-(hydroxymethyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (**1**), a versatile glycosylating agent, namely 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-*C*-(mesyloxymethyl)-β-D-ribofuranose (**6**), was prepared in three steps. Condensation of the latter with bis(trimethysilylated) N^6-benzoyladenine in the presence of tin(IV) chloride gave the N^9-β-nucleoside **7**. Compound **7** was converted into (*i*) 9-[3-*C*-(azidomethyl)-3-deoxy-β-D-ribofuranosyl]adenine (**10**), (*ii*) 9-[3-*C*-(azidomethyl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]adenine (**14**) and 9-[2-azido-3-*C*-(azidomethyl)-2,3-dideoxy-β-D-arabinofuranosyl]adenine (**15**), and (*iii*) 9-[3-deoxy-2-*O*,3-*C*-(methylene)-β-D-ribofuranosyl]adenine (**16**). None of the tested nucleosides showed marked cytostatic or antiviral activity in vitro. © 1996 Elsevier Science Ltd.

Keywords: 3′-Branched-3′-deoxy sugars; Adenine nucleosides; Adenosine analogues; Synthesis; Antiviral activity

1. Introduction

In the last few years, the 3′-branched-3′-deoxy nucleoside analogues have received much attention as potential chemotherapeutic agents [2–10] as well as in antisense

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[1] For a preliminary report, see ref. [1].

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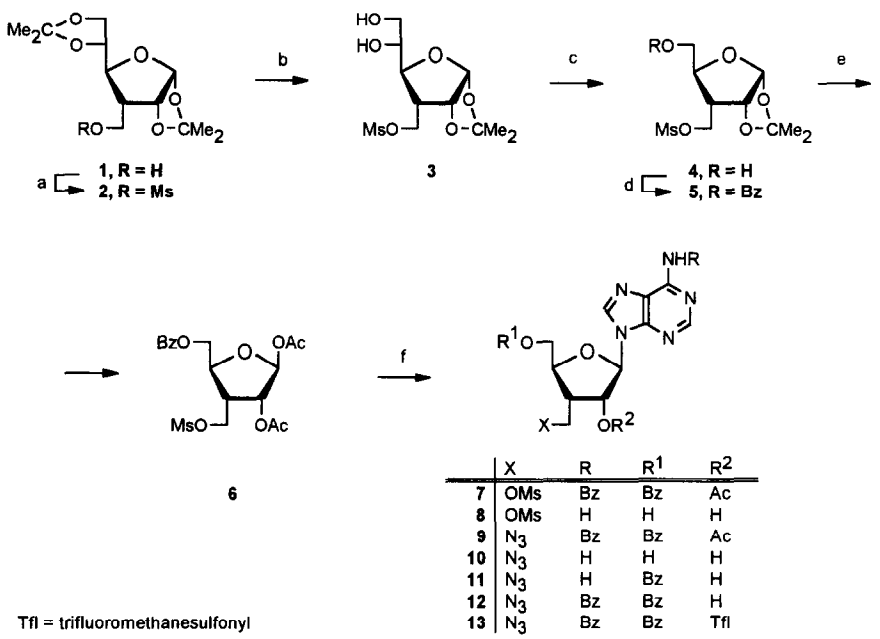
oligonucleotide research [11]. Some of these analogues have been shown to display a very interesting spectrum of antiviral [3–5] and anticancer [12,13] activities. For example, 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)adenosine showed moderate anti-HIV activity [6], whereas the cytosine analogue was found to be a potent inhibitor of HIV-1 and a broad range of DNA viruses [4].

In continuation of our search for new sugar-modified nucleosides of antiviral potential [14], the present report describes the synthesis and antiviral evaluation of some 3′-branched adenine nucleosides.

2. Results and discussion

Our approach was to synthesize first the 3′-deoxy-3′-hydroxymethyl functionalized carbohydrate precursor **6** and then to prepare the key intermediate nucleoside **7** (see Scheme 1). Starting from D-glucose, a 3′-homologue **1** of 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose was obtained as previously described [13]. Mesylation of **1** in pyridine



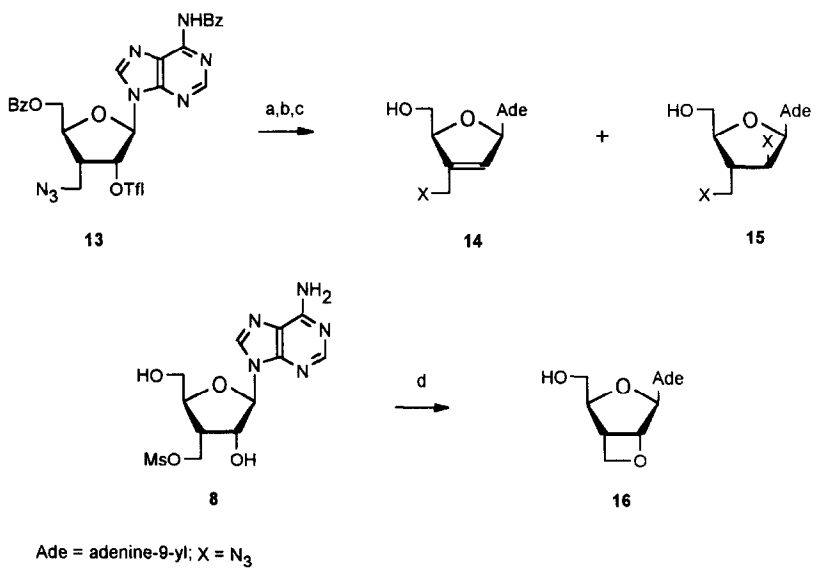
	X	R	R^1	R^2
7	OMs	Bz	Bz	Ac
8	OMs	H	H	H
9	N_3	Bz	Bz	Ac
10	N_3	H	H	H
11	N_3	H	Bz	H
12	N_3	Bz	Bz	H
13	N_3	Bz	Bz	Tfl

Scheme 1. (a) MsCl, pyridine, 0 °C, 16 h (71%); (b) 75% aq HOAc, 20 °C, 20 h (98%); (c) $NaIO_4$, EtOH-saturated aq $NaHCO_3$ (15:1, v/v), 20 °C, 4 h, $NaBH_4$, 20 °C, 1 h (90%); (d) BzCl, pyridine, 20 °C, 20 h (85%); (e) 10.0:1.0:0.55 HOAc–Ac_2O–H_2SO_4, 20 °C, 48 h (80%); (f) **6**–persilylated N^6-benzoyladenine–$SnCl_4$ (1.0:0.99:2.4, mol), 1,2-dichloroethane, 20 °C, 20 h (69.5%); (g) **7** → **8** and **9** → **10**, saturated at 0 °C methanolic ammonia, 20 °C, 48 h (**8**, 73%; **10**, 75%); (h) **7** → **9**, NaN_3, DMF, 20 °C, 96 h (80%); (i) **8** → **10**, NaN_3, DMF, 20 °C, 120 h, reflux for 8 h, (82%); (j) **9** → **11**, 85% aq hydrazine hydrate, pyridine–HOAc (4:1, v/v), 20 °C, 26 h (80%); (k) **11** → **12**, Me_3SiCl, pyridine, 20 °C, 8 h, BzCl, 20 °C, 20 h, concd aq NH_4OH, 0 °C, 1 h (32%); (l) **12** → **13**, $(CF_3SO_2)_2O$, CH_2Cl_2, DMAP, 0 °C, 2 h (75%).

gave the crystalline mesylate **2**. Selective removal of the 5,6-*O*-isopropylidene group from the latter to give crystalline **3** was readily effected with 75% aq acetic acid. Treatment of **3** with sodium metaperiodate and then with sodium borohydride furnished **4** as an oil. Benzoylation of the latter compound gave crystalline **5**. Acetolysis of the 1,2-*O*-isopropylidene protecting group in 10:1 glacial acetic acid–acetic anhydride in the presence of a small amount of concd sulfuric acid afforded the crystalline β-acetate **6**. The β-configuration of **6** was apparent from its ^{1}H NMR spectrum since H-1 appeared as a singlet [15,16]. The overall yield for this five-step conversion of **1** to **6** was 42%.

In order to prevent the formation of N^7-adenine nucleoside, persilylated N^6-benzoyladenine was glycosylated with the acetate **6** in the presence of an excess of tin(IV) chloride (1:1:2.4, mol) in 1,2-dichloroethane at room temperature [17,18]. After column chromatography on silica gel, the fully blocked N^9-glycoside **7** was obtained in 70% yield as a foam. The formation of the N^7-isomer was not observed under these reaction conditions. Treatment of **7** with methanolic ammonia at room temperature led to the nucleoside **8** (73%). Nucleophilic displacement of the mesyloxy group in **7** by treatment with sodium azide in DMF at room temperature, followed by column chromatography, afforded the azide **9** in 80% yield, the standard deprotection of which gave **10** (75%).

Treatment of **9** with hydrazine hydrate in 4:1 pyridine–acetic acid [19], followed by column chromatography, furnished **11** (80%). Selective N^6-benzoylation by a transient protection protocol of Jones et al. [20] afforded, somewhat unexpectedly, a complex mixture of reaction products, the chromatography of which gave the desired compound **12** in 32% yield. The latter was converted (see Scheme 2) into its 2′-*O*-triflyl derivative **13** via reaction with triflic anhydride in methylene chloride in the presence of 4-(dimethylamino)pyridine (DMAP) at 0 °C. After flash chromatography on silica gel, the



Scheme 2. (a) LiN_3, HMPA, 20 °C, 4 h; (b) saturated at 0 °C methanolic ammonia, 20 °C, 16 h; (c) Dekker column chromatography (**14**, Σ35%; **15**, Σ11%); (d) $Bu_4NF \cdot 3H_2O$, MeCN, 20 °C, 24 h, 70 °C, 18 h (53%).

crude **13** (oil, 75%) was allowed to react at room temperature with an excess of lithium azide in hexamethylphosphoramide for 4 h. Following work-up and debenzoylation with methanolic ammonium hydroxide, the 2′,3′-unsaturated nucleoside **14** and the arabinoside **15** were obtained as the main products. These compounds, however, had very similar TLC mobilities and could not be separated by column chromatography on silica gel. Moreover, the 2′,3′-olefin **14** was found to be unstable during column chromatography. The separation was effected by the use of the Dekker column chromatography [21] (Dowex AG 1×2, OH^--form; linear gradient elution: water → 80% MeOH) giving pure nucleosides **14** and **15** in yields of 35 and 11%, respectively. It is noteworthy that the formation of didehydro derivatives was not observed in closely related reactions [22,23].

Attempted nucleophilic displacement of the mesyloxy group of **8** by a fluoride ion under the action of tetrabutylammonium fluoride trihydrate in anhyd acetonitrile resulted, however, in the isolation of the oxetane derivative **16** in 53% yield. Steric considerations would suggest that intramolecular nucleophilic attack of O-2′ at the C-3′ methylene carbon atom would be preferred, although smooth closure of the oxetane ring was somewhat unexpected. In contrast to this, the reaction of **8** with sodium azide in anhyd DMF afforded the azide **10** in high yield; the oxetane **16** was not detected (TLC). It is noteworthy that deblocked mesylate **8** reacted more slowly than **7** and the reaction required prolonged heating of the reactants to obtain **10** in high yield.

The assignment of structure of fully deblocked nucleosides was based on the ^1H NMR data (Tables 1 and 2) and, to a certain extent, on CD spectra (see Fig. 1 and the Experimental section). The values of $J_{1',2'}$, $J_{2',3'}$, and $J_{3',4'}$ for **8** and **10** are consistent [24] with the predominant population of *N*-type conformer of the furanose rings. Thus, the bulky 3′-*C*-substituents display strong preference for a pseudoequatorial orientation (cf., e.g., refs. [5,25]). The rather rigid conformation of the furanose moiety of **16** induced by the oxetane ring resulted in (*i*) a characteristic reduction of both $J_{1',2'}$ and $J_{3',4'}$, and (*ii*) the expected downfield shifts of the furanose ring protons (cf. the data for the related 2′,3′-*ribo*-epoxides [26] and for 2′,3′-di-*O*-isopropylidene derivatives [27,28]). The ^1H NMR spectrum of **14** showed the absence of a 3′-proton and the presence of only a single vinylic 2′-proton at 6.10 ppm as an unresolved multiplet (cf., e.g., ref. [29]). The couplings (all are < 1.0 Hz) of a 2′-proton to H-1′, H-4′, and the 3′-methylene group were confirmed by homodecoupling experiments. As might be expected [30,31], the conversion of **10** to **15** is accompanied by a substantial downfield shift of the H-1′ proton.

Despite the obvious conformational similarity of the furanose rings of **8** and **10**, the CD spectra show substantial differences. Like adenosine [31], both analogues display a minimum at 261 nm; however, their intensities are increased two- to three-fold. Moreover, **8** and **10** exhibit the negative CD band in the 215–225 nm region with molar ellipticities of 28.6×10^{-3} and 14.2×10^{-3}, respectively, while adenosine [31] shows a positive band in this region. Unexpectedly, mesylate **8** has a 292 nm positive Cotton effect, which is missing in the azide **10**. The CD spectrum of the oxetane **16** is similar in shape to that of **8**, albeit the 259 nm minimum has very low ellipticity. The 2′,3′-olefin **14** shows a positive Cotton effect in the 260–240 (as opposed to adenosine) and 225–215 nm regions; the spectrum resembles that of 2′,3′-dideoxy-2′,3′-didehydro-

Table 1
^{1}H NMR spectral data of sugars and nucleosides [a] (δ)

Compound	(H-2; H-8)	H-1 (H-1′)	H-2 (H-2′)	H-3 (H-3′)	H-4 (H-4′)	H-5,5′ (H-5′,5″)	CH_2-3 (CH_2-3′)	Others
2		5.81d	4.77t	2.41m	3.69dd	3.99m	4.64dd 4.36t	4.11 (dd, H-6); 3.92 (dd, H-6′); 3.05 (s, Ms); 1.53, 1.40, and 1.34 (s, 2 × iPr)
3		5.83d	4.78t	2.48m	3.80dd	3.74– 3.54m	4.67dd 4.30t	3.74–3.54 (m, H-6,6′, H-5); 3.03 (s, Ms); 1.50 and 1.32 (s, iPr)
4		5.85d	4.74dd	2.56m	4.01 br dt	3.90dd 3.63dd	4.49dd 4.29dd	3.05 (s, Ms); 1.49 and 1.32 (s, iPr)
5		5.90d	4.78t	2.46m	4.24m	4.62dd 4.44dd	4.55dd 4.39dd	8.06–7.43 (m, Bz); 3.05 (s, Ms); 1.54 and 1.35 (s, iPr)
6		6.09s	5.29d	2.92m	4.60 ⟷		4.22m	8.03–7.35 (m, Bz); 2.98 (s, Ms); 2.08, 1.90 (s, 2Ac)
8	8.40s; 8.14s	5.94d	4.64m	2.84m	4.13dt	3.73dd 3.56dd	4.46dd 4.34dd	7.30 (br s, NH_2); 6.12 (d, 2′-OH); 5.31 (t, 5′-OH); 3.22 (s, Ms)
10	8.40s; 8.15s	5.93d	4.58m	2.64m	4.02dt	~ 3.76 ~ 3.56	3.66dd 3.46dd	7.29 (br s, NH_2); 6.07 (d, 2′-OH); 5.25 (t, 5′-OH)
11	8.26s; 8.12s	5.97d	4.85m	3.00m	4.36m	4.61dd 4.47dd	3.77dd 3.55dd	7.90–7.45 (m, Bz); 7.31 (br s, NH_2); 6.12 (d, 2′-OH)
12	8.61s; 8.20s	6.02d	5.02m	2.78m	4.74 ⟷	4.49m	3.81dd 3.64dd	9.11 (br s, NH); 8.00–7.32 (m, 2Bz)
14	8.22s; 8.18s	7.02 br s	6.10 br s	–	4.86 br s	3.64 br d	4.30d 4.19d	7.24 (br s, NH_2); 5.44 (t, 5′-OH)
15	8.40s; 8.15s	6.41d	4.68dd	2.68m	3.90m	3.81 ⟷	3.66m	7.29 (br s, NH_2); 5.28 (t, 5′-OH)
16	8.19s; 8.14s	6.23s	5.92d	3.56m	4.59m	3.27t	~ 4.88dd 4.38dd	7.25 (br s, NH_2); ~ 4.85 (m, 5′-OH + CH-3′)

[a] The spectra of sugars and blocked nucleosides were taken in $CDCl_3$; the spectra of deblocked nucleosides were measured in Me_2SO-d_6.

Table 2
Coupling Constants (J, Hz) for the ^{1}H NMR data of sugars and nucleosides

Compound	1,2 [1′,2′]	2,3 [2′,3′]	3,4 [3′,4′]	4,5 [4′,5′]	4,5′ [4′,5′]	3,CH [a] [3′,CH [a]]	3,CH [b] [3′,CH [b]]	Others
2	4.2	4.2	10.8	7.8	n.d. [c]	4.8	10.8	6.0 (5,6); 5.4 (5,6′); 8.4 (6,6′); 10.8 (*gem* CH_2-3)
3	3.6	3.6	10.8	7.2	n.d.	4.8	9.6	9.6 (*gem* CH_2-3)
4	3.6	4.0	9.6	3.0	3.6	8.4	6.6	10.8 (*gem* CH_2-3); 12.6 (5,5′)
5	3.6	5.4	10.2	2.5	5.4	7.8	6.6	10.2 (*gem* CH_2-3); 12.0 (5,5′)
6	< 1.0	5.0	n.d.	n.d.	n.d.	n.d.	n.d.	
8	2.5	5.8	8.0	2.8	3.5	7.0	6.0	9.5 (*gem* CH_2-3′); 5.5 (5′,5′,OH); 12.0 (5′,5′); 5.0 (2′,OH)
10	2.0	5.0	8.5	~ 3.0	~ 3.0	8.0	5.5	12.0 (*gem* CH_2-3′); 5.5 (5′,5′,OH); 12.0 (5′,5′); 4.8 (2′,OH)
11	1.5	~ 5.0	~ 9.0	2.0	4.5	7.5	6.0	12.6 (*gem* CH_2-3′); 5.0 (2′,OH); 12.0 (5′,5′)
12	2.8	~ 6.0	n.d.	n.d.	n.d.	7.0	6.5	12.6 (*gem* CH_2-3′)
14	< 1.0	< 1.0	< 1.0	~ 1.2	~ 1.2	–	–	15.6 (*gem* CH_2-3′)
15	6.2	9.3	9.3	2.4	2.4	n.d.	n.d.	
16	< 1.0	5.4	1.8	6.0	6.0	~ 7.0	~ 4.0	6.2 (*gem* CH_2-3′); 5.8 (5′,5′,OH)

[a] For low-field signal.
[b] For high-field signal.
[c] n.d. = not determined.

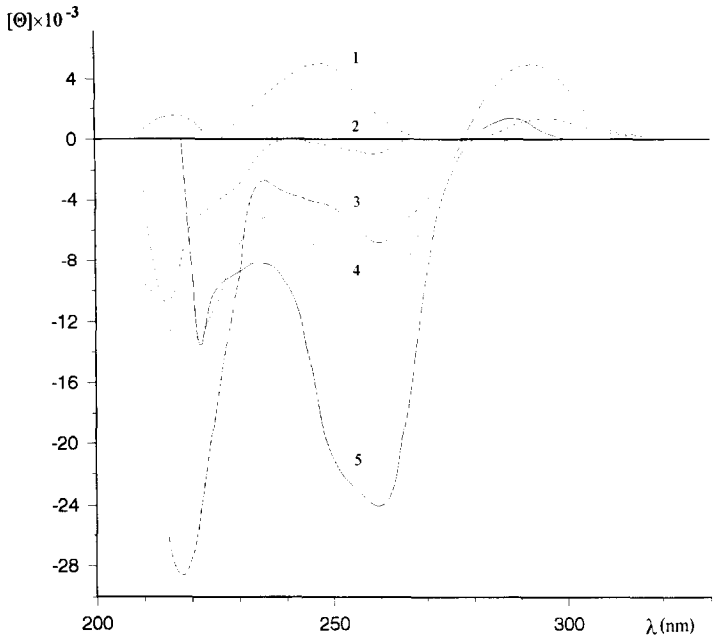


Fig. 1. Experimental CD spectra of adenine nucleosides **8** (3), **10** (4), **14** (1), **15** (5), and **16** (2) in ethanol at 20 °C.

adenosine [32,33] in appearance. It is noteworthy that theoretical considerations have revealed a strong dependence of the rotational strength on base conformation about the glycosidic bond and changes in the puckered conformations of the ribofuranose residue [34]. Therefore, a more detailed conformational analysis is needed to interpret the CD data for the nucleosides **8**, **10**, and **16**. The arabinoside **15** displays negative Cotton effects at 259 and 234 nm, the former possessing an unusually large molar ellipticity in comparison with that of 9-(β-D-arabinofuranosyl)adenine (ara-Ade) [31] and its 2′-azido congener (2′-N_3-ara-Ade) [30]. One of possible explanations could be the consequence of differences in the puckered conformations of the arabinofuranose residue of **15** versus ara-Ade and 2′-N_3-ara-Ade resulting in changes of the sugar–base torsion angle and/or of the base–azide group interaction.

3. Biological properties

The test compounds **10**, **14**, **15**, and **16** were evaluated for their inhibitory effects on the replication of HSV-1 (KOS, TK^- B2006 and TK^- VMW1837), HSV-2 (G), and vaccinia virus in E_6SM cells, the vesicular stomatitis virus in E_6SM and HeLa cells, the parainfluenza-3 virus, retrovirus-1, Sindbis virus, and Semliki forest virus in Vero cell cultures, the Coxsackie virus B4 in Vero and HeLa cell cultures, and the polio virus-1 in HeLa cell cultures, as well as for their inhibitory effects on proliferation of the above

cells. None of the compounds proved inhibitory to virus replication or cell viability or proliferation at concentrations up to 200–400 μg/mL.

Compounds **14** and **15** were evaluated for their inhibitory effect on HIV-1- and HIV-2-induced cytopathicity in human T-lymphocyte (CEM/0) cells: none of them are active at subtoxic concentrations.

4. Experimental

General methods.—The UV and IR spectra were recorded on Specord M-400 and UR-20 instruments (Carl Zeiss, Germany), respectively. ^{1}H NMR spectra were measured at 200.13 MHz at 23 °C on an AC-200 spectrometer equipped with an Aspect 3000 data system (Bruker, Germany) with Me_4Si as an internal standard; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments. CD spectra and $[\alpha]_D$ were obtained on a J-20 (JASCO, Japan) spectropolarimeter. Standard (1) Silufol UV_{254} (Czechoslovakia) and (2) Kieselgel 60 F_{254} (E. Merck, Germany) plates were used for thin layer chromatography (TLC) of sugars and nucleosides, respectively; as solvent systems were used (v/v): 19:1 (A) and 9:1 (B) $CHCl_3$–MeOH. Column chromatography of sugars and nucleosides was performed on Silica Gel L (Chemapol, Czechoslovakia) 100/400 and 40/100 μ, respectively. Tetrabutylammonium fluoride trihydrate and trifluoromethanesulfonic anhydride were purchased from Fluka (Switzerland). The solutions of compounds in organic solvents were dried with anhyd Na_2SO_4 for 4 h. Except where otherwise indicated, the reactions were carried out at 20 °C.

3-Deoxy-1,2;5,6-di-O-isopropylidene-3-C-(mesyloxymethyl)-α-D-allofuranose (**2**).—To a stirred solution of **1** [12] (3.5 g, 12.77 mmol) in pyridine (40 mL) at 0 °C, mesyl chloride (1.41 mL, 2.08 g, 18.2 mmol) was added, the mixture was stirred at 0 °C for 16 h, and then poured into ice–water (100 mL). A precipitate that formed was filtered off, washed with cold water (0 °C), and dried. Crystallization from 15:1 MeOH–water mixture gave **2** (3.2 g, 71%); mp 102–103 °C; $[\alpha]_D^{20}$ +37.0° (*c* 1.0, MeOH); R_f 0.43 (1,A). Anal. Calcd for $C_{14}H_{24}O_8S$: C, 47.72; H, 6.87; S, 9.10. Found: C, 47.70; H, 6.92; S, 9.06.

3-Deoxy-1,2-O-isopropylidene-3-C-(mesyloxymethyl)-α-D-allofuranose (**3**).—A solution of **2** (7.5 g, 21.3 mmol) in 75% aq HOAc was stirred for 20 h, evaporated, and co-evaporated with toluene (4 × 50 mL) to yield homogeneous (TLC) crystalline **3** (6.5 g, 98%) which was used in the next step without additional purification. An analytical sample was crystallized from 10:1 MeOH–toluene, mp 106–107 °C; $[\alpha]_D^{20}$ +68.1° (*c* 1.0, EtOH); R_f 0.07 (1,A). Anal. Calcd for $C_{11}H_{20}O_8S$: C, 42.30; H, 6.46; S, 10.27. Found: C, 42.43; H, 6.46; S, 10.10.

3-Deoxy-1,2-O-isopropylidene-3-C-(mesyloxymethyl)-α-D-ribofuranose (**4**).—To a solution of **3** (6.5 g, 20.8 mmol) in EtOH (150 mL), saturated aq $NaHCO_3$ (10 mL) was added, and then, under vigorous stirring, a water solution (150 mL) of $NaIO_4$ (4.94 g, 23.09 mmol). After stirring for 4 h, $NaBH_4$ (2.34 g, 61.85 mmol) was added portionwise (~ 0.8 g) at 30 min intervals and the mixture was stirred for 1 h. Then, it was cooled to 0 °C, neutralized with HOAc to pH 7, and evaporated to dryness leaving a residue that

was partitioned between $CHCl_3$ (300 mL) and saturated aq $NaHCO_3$ (50 mL). The $CHCl_3$ extract was washed with water (2 × 50 mL), dried, and evaporated. The residue was purified by column chromatography on silica gel (300 mL), and eluted successively with diethyl ether (300 mL), $CHCl_3$ (400 mL), and EtOH (500 mL) to yield **4** (5.3 g, 90%) as a TLC homogeneous pale yellow syrup; $[\alpha]_D^{20}$ +53.2° (*c* 1.15, EtOH); R_f 0.21 (1,A).

5-O-Benzoyl-3-deoxy-1,2-O-isopropylidene-3-C-(mesyloxymethyl)-α-D-ribofuranose (**5**).—To a solution of **4** (5.3 g, 18.8 mmol) in pyridine (23 mL) at 0 °C, benzoyl chloride (3.0 mL, 3.64 g, 25.87 mmol) was added and the mixture was stirred for 20 h before allowing it to warm to room temperature. The mixture was poured into ice–water (100 mL), a precipitate that formed was filtered off, washed with cold water (50 mL), and dried. Crystallization from 7:1 EtOH–water gave **5** (6.2 g, 85%); mp 99–100 °C; $[\alpha]_D^{20}$ +4.0° (*c* 0.5, MeOH); R_f 0.33 (1,A). Anal. Calcd for $C_{17}H_{22}O_8S$: C, 52.84; H, 5.74; S, 8.30. Found: C, 52.97; H, 5.78; S, 7.94.

1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-3-C-(mesyloxymethyl)-β-D-ribofuranose (**6**).—Concd H_2SO_4 (6 mL) was added under stirring to the solution of **5** (7.0 g, 18.1 mmol) in 10:1 HOAc–Ac_2O (120 mL) at 0 °C, the mixture was allowed to warm to room temperature, stirred for 48 h, and then poured into a mixture of ice (300 mL) and saturated aq $NaHCO_3$ (1 L). It was then extracted with $CHCl_3$ (3 × 200 mL), the organic extracts were combined, washed with water (100 mL), dried, and evaporated. The residue was crystallized from 3:1 $CHCl_3$–diethyl ether to yield the acetate **6** (6.2 g, 80%); mp 123–124 °C; $[\alpha]_D^{20}$ −25.0° (*c* 1.0, $CHCl_3$); R_f 0.36 (1,A). Anal. Calcd for $C_{18}H_{22}O_{10}S$: C, 50.23; H, 5.15; S, 7.45. Found: C, 50.13; H, 4.99; S, 7.77.

9-[3-Deoxy-3-C-(mesyloxymethyl)-β-D-ribofuranosyl]adenine (**8**).—To a stirred solution of the bis(trimethylsilyl) derivative of N^6-benzoyladenine [obtained from 3.5 g (14.6 mmol) of N^6-benzoyladenine] and **6** (6.2 g, 14.4 mmol) in anhyd 1,2-dichloroethane (122 mL), a solution of $SnCl_4$ (4 mL, 8.92 g, 34.2 mmol) in anhyd 1,2-dichloroethane (25 mL) was added, the mixture was stirred for 20 h, and then poured into saturated aq $NaHCO_3$ (500 mL). It was then extracted with $CHCl_3$ (2 × 500 mL), the combined organic extracts were washed with 5% aq $NaHCO_3$ (2 × 200 mL), and water (400 mL), dried, and evaporated. The residue was purified by silica gel (500 mL) column chromatography, using a 49:1 $CHCl_3$–EtOH mixture as eluent to yield TLC homogeneous **7** (6.0 g, 69.5%) as a foam; R_f 0.28 (2,A). ^{1}H NMR ($CDCl_3$), δ 9.18 (br s, 1 H, N*H*), 8.70 and 8.10 (2 × s, 2 H, H-8 and H-2), 8.06–7.40 (m, 10 H, *arom.*), 6.04 (s, 1 H, H-1′), ≈ 6.05 (d, 1 H, H-2′), 4.80–4.40 (m, 5 H, H-4′, H-5′, H-5′, and 3′-CH_2), 3.78 (center of m, 1 H, H-3′), 3.14 (s, 3 H, SO_2CH_3), 2.10 (s, 3 H, $COCH_3$).

A solution of **7** (0.124 g, 0.2 mmol) in MeOH (25 mL), saturated with ammonia at 0 °C, was kept for 48 h and evaporated. The residue was triturated with diethyl ether (50 mL), the precipitate was filtered off and crystallized from water to yield the mesylate **8** (52 mg, 73%); mp 173–175 °C; $[\alpha]_D^{25}$ −13° (*c* 1.285, 1:1 H_2O–DMF); R_f 0.21 (2,B); λ_{max} (EtOH) 260.1 nm (ε 14500); CD (EtOH), λ nm ($\Theta \times 10^{-3}$): 219 (−28.6), 261 (−6.8), 295 (+4.8), 329 and 278 (0). Anal. Calcd for $C_{12}H_{17}N_5O_6S \cdot 0.75H_2O$: C, 38.66; H, 5.00; N, 18.78; S, 8.60. Found: C, 38.58; H, 5.00; N, 19.07; S, 8.14.

9-[3-C-(azidomethyl)-3-deoxy-β-D-ribofuranosyl]adenine (**10**).—*Procedure A.* To a solution of **7** (2.6 g, 4.26 mmol) in anhyd DMF (150 mL), NaN_3 (1.53 g, 23.53 mmol)

was added and the heterogeneous mixture was stirred for 96 h. The precipitate was filtered off, washed with DMF (50 mL) and benzene (10 mL). The combined filtrates were evaporated, the residue was purified by silica gel (300 mL) column chromatography, using a linear EtOH gradient (0 → 2%, v/v; 2 × 1 L) in $CHCl_3$ to afford 1.9 g (80%) of TLC homogeneous azide **9** as a foam; R_f 0.33 (2,A); λ_{max} (EtOH) 280 nm; ν_{max} (film) 2110 (N_3) cm^{-1}. ^1H NMR ($CDCl_3$), δ 8.96 (br s, 1 H, N*H*), 8.70 and 8.08 (2 × s, 2 H, H-8 and H-2), 7.99–7.37 (m, 10 H, *arom.*), 6.03 (s, 1 H, H-1′), ≈ 6.01 (d, 1 H, H-2′), 4.82–4.45 (m, 3 H, H-4′, H-5′, and H-5″), 3.82–3.57 (m, 3 H, H-3′ and 3′-CH_2), 2.23 (s, 3 H, COCH_3).

Standard deprotection of 0.2 g (0.36 mmol) of **9** followed by crystallization from MeOH yielded the azide **10** (83 mg, 75%); mp 187 °C; $[\alpha]_D^{25}$ −36° (*c* 1.16, 1:1 H_2O–DMF); R_f 0.16 (2,B); ν_{max} (KBr) 2120 (N_3) cm^{-1}; λ_{max} (EtOH) 260.4 nm (ε 13800); CD (EtOH), λ nm ($\Theta \times 10^{-3}$): 218 (−14.2), 261 (−10.6), 210 and 288 (0). Anal. Calcd for $C_{11}H_{14}N_8O_3$: C, 43.14; H, 4.61; N, 36.58. Found: C, 43.53; H, 4.61; N, 36.40.

Procedure B. To a solution of **8** (0.1 g, 0.27 mmol) in anhyd DMF (5.0 mL), NaN_3 (0.1 g, 1.54 mmol) was added, the heterogeneous mixture was stirred for 120 h and then refluxed for 8 h. After cooling to room temperature, the precipitate was filtered off, washed with DMF (2.0 mL) and the combined filtrates were evaporated. The residue was chromatographed on the silica gel column (50 mL), by elution with a linear MeOH gradient (0 → 17%, v/v; 2 × 400 mL) in $CHCl_3$, to yield the azide **10** (62 mg; 82% based on the consumed **8**) and the starting mesylate **8** (9 mg).

*9-[3-*C*-(Azidomethyl)-5-*O*-benzoyl-3-deoxy-β-*D*-ribofuranosyl]adenine* (**11**).—To a solution of **9** (1.7 g, 3.05 mmol) in 4:1 pyridine–HOAc (26 mL), 85% aq hydrazine hydrate (1 mL) was added and the mixture was stirred for 26 h. Then, acetone (10 mL) was added, stirring was continued for 3 h and the mixture was evaporated. The residue was dissolved in $CHCl_3$ (300 mL) and washed with saturated aq $NaHCO_3$ (100 mL) and water (100 mL). The organic phase was dried and evaporated. The residue was purified by column chromatography on silica gel (150 mL), using a linear EtOH gradient (0 → 5%, v/v; 2 × 850 mL) in $CHCl_3$ to afford 1.0 g (80%) of TLC homogeneous **11** as a foam: R_f 0.10 (2,A); λ_{max} (EtOH) 259 nm.

*9-[3-*C*-(Azidomethyl)-5-*O*-benzoyl-3-deoxy-β-*D*-ribofuranosyl]-*N*^{6}-benzoyladenine* (**12**).—To a solution of **11** (1.0 g, 2.44 mmol) in pyridine (20 mL), trimethylchlorosilane (1.7 mL, 1.45 g, 13.4 mmol) was added and the mixture was stirred for 8 h. After cooling to 0 °C, benzoyl chloride (0.6 mL, 0.72 g, 5.1 mmol) was added, the mixture was allowed to warm to room temperature and stirred for 20 h. After cooling to 0 °C, 25% NH_4OH (10 mL) was added, the mixture was stirred at 0 °C for 1 h, then poured into water at +4 °C and extracted with $CHCl_3$ (2 × 250 mL). The combined organic extracts were dried, evaporated and co-evaporated with toluene (2 × 50 mL). The residue was chromatographed on the silica gel (150 mL) column, using a linear MeOH gradient (0 → 4%, v/v; 2 × 1 L) in $CHCl_3$. The fractions containing the benzoate **12** were collected and evaporated to yield 0.4 g (32%) of homogeneous (TLC) product as a foam; R_f 0.25 (2,A); λ_{max} (EtOH) 280 nm.

*9-[3-*C*-(Azidomethyl)-2,3-dideoxy-β-*D*-*glycero*-pent-2-enofuranosyl]adenine* (**14**) *and 9-[2-azido-3-*C*-(azidomethyl)-2,3-dideoxy-β-*D*-arabinofuranosyl]adenine* (**15**).—To a

suspension of **12** (0.3 g, 0.58 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, DMAP (0.25 g, 2.05 mmol) and then triflic anhydride (0.12 mL, 0.21 g, 0.74 mmol) were added, the mixture was stirred at 0 °C for 2 h. Ice (2.0 g) was then added, the stirring was continued for 1 h and the mixture was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with water (1 mL), dried, and evaporated. The residue was purified by flash-chromatography and eluted with $CHCl_3$ to afford the triflate **13** (0.25 g, 75%); R_f 0.29 (2,A).

The crude **13** was dissolved in HMPA (1 mL), LiN_3 (0.1 g, 1.92 mmol) was added and the mixture was stirred for 4 h. Then, water (5 mL) was added and the mixture was extracted with EtOAc (2 × 5 mL). The combined extracts were washed with saturated aq NaCl solution (2 × 2 mL), water (5 mL), dried, and evaporated. The residue was dissolved in MeOH (20 mL), saturated with ammonia at 0 °C, kept for 16 h, and evaporated. The residue was treated with diethyl ether, the precipitate was filtered off, washed with diethyl ether, dissolved in water (10 mL), and applied onto a Dowex AG 1 × 2 (100–200 mesh, OH^--form, equilibrated in H_2O; 100 mL) column. Elution with a linear MeOH gradient (0 → 80%, v/v; 2 × 500 mL) in water separated two products.

Compound **14**, 59 mg (35%), mp 112–114 °C (from H_2O), R_f 0.33 (2,B); ν_{max} (KBr) 2110 cm^{-1} (N_3); λ_{max} (EtOH) 260.4 nm (ε 15200); CD (EtOH), λ nm ($\Theta \times 10^{-3}$): 249 (+4.5), ~217 (~ +2.0), 225 and 271 (0). Anal. Calcd for $C_{11}H_{12}N_8O_2$: C, 45.83; H, 4.20; N, 38.87. Found: C, 45.42; H, 4.22; N, 38.36.

Compound **15**, 22 mg (11%), mp 185–187 °C (from MeOH), $[\alpha]_D^{25}$ −153.8° (*c* 0.253, 1:1 H_2O–DMF); R_f 0.32 (2,B); ν_{max} (KBr) 2125 cm^{-1} (N_3); λ_{max} (EtOH) 260.1 nm (ε 14400); CD (EtOH), λ nm ($\Theta \times 10^{-3}$): 234 (−7.12), 259 (−24.33), 218 and 286 (0). Anal. Calcd for $C_{11}H_{13}N_{11}O_2$: C, 39.88; H, 3.95; N, 46.51. Found: C, 39.46; H, 4.06; N, 46.24.

*9-[3-Deoxy-2-O,3-C-(methylene)-β-*D*-ribofuranosyl]adenine* (**16**).—To a suspension of **8** (0.2 g, 0.54 mmol) in anhyd MeCN (15 mL), tetrabutylammonium fluoride trihydrate (0.6 g, 1.9 mmol) was added, the mixture was stirred for 24 h and then at 70 °C for 18 h, and evaporated. The residue was purified by column chromatography on silica gel (50 mL), and eluted with 19:1 $CHCl_3$–MeOH to afford after crystallization from MeOH 90 mg (53%) of **16**; mp 223–225 °C; $[\alpha]_D^{25}$ −170° (*c* 0.47, 1:1 H_2O–DMF); R_f 0.23 (2,B); λ_{max} (EtOH) 259.3 nm (ε 13,000); CD (EtOH), λ nm ($\Theta \times 10^{-3}$): 214 (−10.7), 259 (−0.89), ~295 (+1.33), ~320, 266, and 239 (0). Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 49.60; H, 4.22; N, 27.08.

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