

Nucleic acid related compounds. 63.

Synthesis of 5'-deoxy-5'-methyleneadenosine and related Wittig-extended nucleosides¹

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Treatment of the purified 5'-aldehyde (**2a**) (derived from 6-*N*-benzoyl-2',3'-*O*-isopropylideneadenosine (**1a**)) with methylentriphenylphosphorane and successive deprotection with ammonia and acid gave 9-(5,6-dideoxy-β-*D*-ribo-hex-5-enofuranosyl)adenine (5'-deoxy-5'-methyleneadenosine) (**4**). Oxidation of **1a** or 2',3'-*O*-isopropylideneadenosine (**1b**) and treatment of the crude 5'-aldehydes (**2a** or **2b**) with (*p*-toluenesulfonylmethylene)triphenylphosphorane gave high yields of the 5'-deoxy-5'-tosylmethylene derivatives (**5a** or **5b**). Removal of the tosyl group from **5b** to give **3b** was effected with tributylstannyl lithium, but sulfone cleavage by the usual reductive methods failed. Reduction and deprotection of **5a** or **5b** gave 9-[5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-*D*-ribo-hexofuranosyl]adenine (**6b**). Isomerization of the vinyl tosyl (**5b**) to a 4',5'-unsaturated allylic tosyl derivative (**7**) occurred under cleavage conditions and in solutions of aqueous or organic bases.

Key words: adenosine, 5'-deoxyadenosine, 5'-methylene-5'-deoxyadenosine, nucleosides.

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La réaction du 5'-aldéhyde purifié (**2a**) (obtenu à partir de la 6-*N*-benzoyl-2',3'-*O*-isopropylidèneadénosine (**1a**)) avec le méthylentriphénylphosphorane, suivie d'une déprotection à l'aide d'ammoniac et d'acide, conduit à la 9-(5,6-didésoxy-β-*D*-ribo-hex-5-énofuranosyl)adénine (5'-désoxy-5'-méthylèneadénosine) (**4**). L'oxydation de **1a** ou de la 2',3'-*O*-isopropylidèneadénosine (**1b**), suivie d'une réaction des 5'-aldéhydes bruts (**2a** ou **2b**) avec le (*p*-toluènesulfonylméthylène)triphénylphosphorane fournit les dérivés 5'-désoxy-5'-tosylméthylènes (**5a** ou **5b**) avec d'excellents rendements. On a effectué l'enlèvement des groupements tosyles du produit **5b** à l'aide de tributylstannyl lithium et on a obtenu le produit **3b**; toutefois le clivage de la sulfone par les méthodes réductrices habituelles s'est avéré inefficace. La réduction et la déprotection des produits **5a** ou **5b** a fourni la 9-[5,6-didésoxy-6-(*p*-toluènesulfonyl)-β-*D*-ribo-hexofuranosyl]adénine (**6b**). L'isomérisation du dérivé vinyl tosyl (**5b**) en un dérivé tosylé allylique 4',5'-insaturé (**7**) se produit dans les conditions de clivage ainsi qu'en solutions aqueuses ou organiques de bases.

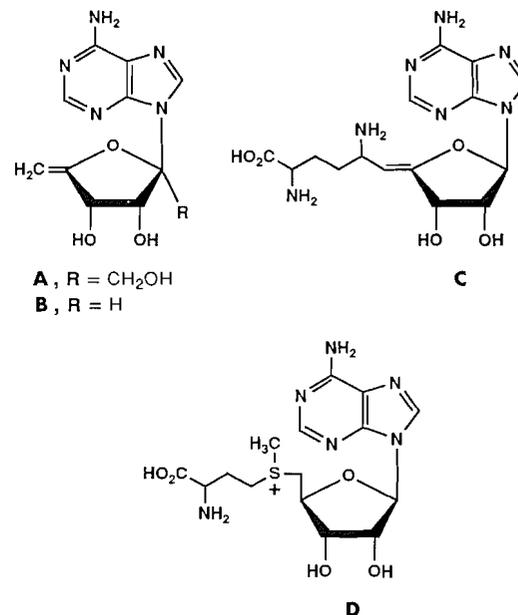
Mots clés : adénosine, 5'-désoxyadénosine, 5'-méthylène-5'-désoxyadénosine, nucléosides.

[Traduit par la rédaction]

Introduction

Examples of naturally occurring 4',5'-unsaturated nucleosides include the antibiotics angustmycin A (decoyinine) (**A**) (1-3) and A9145C (**C**), a 4',5'-didehydrosinefungin derivative (**4**). Synthetic 5'-deoxy-4',5'-didehydroadenosine (**B**) (**3**) was found to be accepted by *S*-adenosylhomocysteine hydrolase as an alternative substrate (**5**). Sinefungin and antibiotic A9145C (**C**) are inhibitors of methyl transferase enzymes, and this inhibition can be reversed by the addition of *S*-adenosylmethionine (**D**) (**4**). We are developing inhibitors of enzymes utilized in pathways involving *S*-adenosylmethionine metabolism and wanted to examine nucleoside analogues with unsaturated groups at C5'.

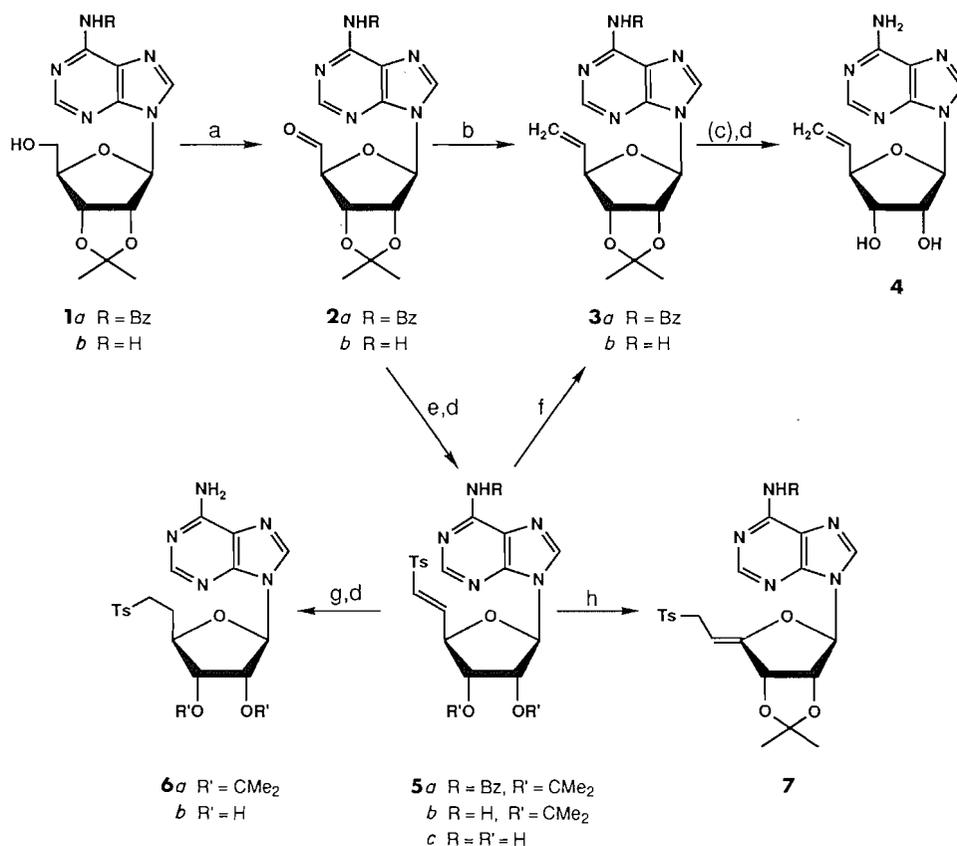
Chain extensions and other carbon-carbon bond-forming reactions at C5' of nucleosides have generally involved oxidation to 5'-aldehyde derivatives and treatment with Wittig-type reagents, or conversions with 5'-deoxy-5'-halonucleosides (**6**). Wittig-type reactions of nucleoside 5'-aldehydes with electro-negatively substituted ylides have provided several 6'-substituted-5',6'-unsaturated hexofuranosyl nucleosides (**7-11**). However, direct introductions of alkylidene groups (particularly the methylene group) at C5' have met with limited success, presumably owing to the instability of the 5'-aldehyde (or intermediates/products) under the experimental conditions (**8, 10**). Ueda and co-workers reported successful Wittig reactions of 3',5'-*O*-(1,1,3,3-tetraisopropylidisiloxan-1,3-diyl)-2'-keto adenosine (**12**) and uridine (**13**) derivatives with methylene-



triphenylphosphorane to give 2'-deoxy-2'-methylene nucleosides. We also have developed efficient procedures for syntheses of purine and pyrimidine 2'-deoxy-2'-methylene and 3'-deoxy-3'-methylene nucleoside analogues with direct Wittig reactions (**14**). Seebach's silyl nitronate (nitro-aldol) methodology has been used in an efficient variation of the Henry reaction for chain extension of aldehyde sugars including a uridine 5'-aldehyde derivative (**15**). Barton *et al.* have developed a radical-mediated strategy that has been applied to the synthesis

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(a) Cl₂CHCO₂H/DCC/DMSO. (b) Ph₃PCH₂Br/NaOC₅H₁₁/Et₂O/C₆H₆/THF. (c) NH₃/MeOH. (d) CF₃CO₂H/H₂O. (e) Ph₃P=CHTs. (f) Bu₃SnLi/THF. (g) NaBH₄/MeOH/H₂O. (h) DBU/THF or NaOH/H₂O/CH₃CN.

SCHEME 1

of chain-lengthened nucleoside phosphonates and vinyl sulfonates (16).

A multistep synthesis of 5'-deoxy-5'-methyleneadenosine (9-(5,6-dideoxy-β-D-ribo-hex-5-enofuranosyl)adenine) (**4**) (Scheme 1) by conversion of D-allose to methyl 2,3-di-O-benzoyl-5,6-dideoxy-β-D-ribo-hex-5-enofuranoside, activation, coupling with the chloromercury salt of 6-benzamido-purine, and deprotection was reported in 1978 (17). We now describe two Wittig-based syntheses of **4** from adenosine, and transformations of related vinyl sulfone intermediates.

Results and discussion

Adenosine was protected, oxidized, and purified as described (18) to give the 6-N-benzoyl-2',3'-O-isopropylidene-5'-aldehyde derivative (**2a**). Treatment of **2a** with methylenetriphenylphosphorane (generated (14, 19) from methyltriphenylphosphonium bromide and sodium 2-methyl-2-butoxide in benzene/ether) in tetrahydrofuran at -20°C resulted in formation of 6-N-benzoyl-9-(5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5-enofuranosyl)adenine (**3a**) in 58% yield. The ¹H nmr spectrum of **3a** had characteristic peaks for H6' and H6'' at δ 5.17 and 5.27 as doublets of triplets with $J_{6'-6''} = J_{6'/6''-4'} = 1.3$ Hz, $J_{6'-5'} = 10.4$ Hz (*cis*), and $J_{6''-5'} = 17.2$ Hz (*trans*). Removal of the benzoyl group from **3a** with methanolic ammonia, treatment of the resulting **3b** with aqueous trifluoroacetic acid, and purification on a column of Dowex 1 × 2 (OH⁻) resin gave **4** in 36% overall yield from **2a**.

Our second approach utilized the Wittig reaction of **2a** with a stabilized ylid, (*p*-toluenesulfonylmethylene)triphenylphos-

phorane (**20**, **21**), to give the vinyl sulfone product (**5a**) in 85% yield. The large vinyl coupling constant ($^3J_{6'-5'} = 15$ Hz) indicated an *E* configuration for **5a**. Treatment of crude **2a** (from Moffatt oxidation (7, 22) of 6-N-benzoyl-2',3'-O-isopropylideneadenosine) with (*p*-toluenesulfonylmethylene)triphenylphosphorane gave the same high yield (86%) of **5a**. Analogous oxidation of 2',3'-O-isopropylideneadenosine (**1b**) and treatment of crude **2b** with the stabilized Wittig reagent gave **5b** in 63% yield. It was hoped that removal of the sulfone group from **5a** or **5b** could be readily effected to provide a more efficient route to 5'-deoxy-5'-methyleneadenosine (**4**).

Methods for the reductive cleavage of carbon-sulfur bonds in saturated (23, 24) and α,β-unsaturated (25-27) sulfones have been reported. Unfortunately, our attempted application of these procedures to remove the *p*-toluenesulfonyl group from **5a** or **5b** failed to give significant quantities of **3a** or **3b**. The Corey sulfone cleavage (23) with sodium (24) or aluminum (25) amalgam, and the sodium dithionite procedure of Julia (26, 27) resulted primarily in rearrangement of the vinyl to allylic sulfones and recovery of starting material. Formation of more complex mixtures was observed under more vigorous conditions. Isomerization of the vinyl sulfone **5b** to a single allylic sulfone (**7**, tentatively assigned the *Z* configuration with a less-hindered exocyclic 4'-5' double bond) occurred under basic conditions. Formation of the allylic sulfone **7** was conveniently monitored by ultraviolet absorption spectroscopy. A major bathochromic shift and hypochromic effect were observed as the conjugated vinyl sulfone **5b** (λ_{\max} 236 nm (ϵ 23 500)) was converted into the allylic sulfone **7** (λ_{\max} 258 nm

(ϵ 15 200)) in solutions of aqueous sodium hydroxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile or THF.

Desulfonylation of **5b** was effected (61% yield) via conjugate addition of tributylstannyl lithium (28). However, ^1H nmr spectra of the crude product showed contamination by the allylic sulfone **7** (5–10%). Treatment of this mixture with aqueous trifluoroacetic acid and purification on a column of Dowex 1 \times 2 (OH^-) resin gave pure **4** (39%). The contaminating allylic sulfone **7**, with 4'-5' unsaturation, suffers acid-catalyzed decomposition as expected (3) from its exocyclic vinyl ether skeleton.

Treatment of **5b** with sodium borohydride in aqueous methanol resulted in conjugate reduction of the vinyl sulfone to give **6a** (~75% yield). Deprotection of **6a** with aqueous trifluoroacetic acid gave 9-[5,6-dideoxy-6-(*p*-toluenesulfonyl)- β -D-ribo-hexofuranosyl]adenine (**6b**, 83%). Parallel treatment of the 6-*N*-benzoyl derivative (**5a**) gave an equivalent yield of **6b**. Deprotection of **5b** proceeded without incident in aqueous trifluoroacetic acid to give 9-[5,6-dideoxy-6-(*p*-toluenesulfonyl)- β -D-ribo-hex-5(*E*)-enofuranosyl]adenine (**5c**, 89%).

Thus, direct Wittig treatment of the protected adenosine 5'-aldehyde (**2a**) with methylenetriphenylphosphorane provided the most efficient sequence to 5'-deoxy-5'-methyleneadenosine (**4**). This route circumvented complications inherent in the multistep preparation of unsaturated sugar derivatives and coupling with a nucleobase (17). A sulfonyl-stabilized Wittig reagent gave high yields of protected vinyl sulfone intermediates, but removal of the *p*-toluenesulfonyl group proved to be difficult.

Experimental

Uncorrected melting points were determined on a microstage block. The uv spectra were recorded on a Beckman Acta M IV spectrophotometer. The ^1H nmr spectra were recorded on Bruker WH-200 or Varian Gemini-200 spectrometers. Mass spectra (ms) were obtained with AEI MS-12 or Jeol JMS-D-100 instruments. Elemental analyses were determined by the microanalytical laboratories of the University of Alberta or Adam Mickiewicz University, Poznań. Reagents and solvents were of commercial reagent quality. Diethyl ether and tetrahydrofuran (THF) were dried by distillation from sodium benzophenone ketyl. Acetonitrile was dried by distillation from P_4O_{10} . (*p*-Toluenesulfonylmethylene)triphenylphosphorane (73% (crystallized from CH_2Cl_2 /hexane), mp 182–183°C (lit. (20) mp 186–187°C; (21) mp 182–184°C) was prepared (20) from bromomethyl *p*-tolyl sulfone (21) and triphenylphosphine. Tributylstannyl lithium was prepared by treatment of tributyltin chloride with excess lithium in anhydrous THF under N_2 at ambient temperature (29). 6-*N*-Benzoyl-2',3'-*O*-isopropylideneadenosine 5'-aldehyde (**2a**, 55%, as the dehydrated aldehyde) was prepared from 6-*N*-benzoyl-2',3'-*O*-isopropylideneadenosine (**1a**) with isolation of the crystalline 1,3-diphenylimidazolidine intermediate (18). Sodium 2-methyl-2-butoxide was prepared by refluxing *tert*-amyl alcohol with excess sodium beads in benzene under N_2 for 10 days (30).

6-*N*-Benzoyl-9-(5,6-dideoxy-2,3-*O*-isopropylidene- β -D-ribo-hex-5-enofuranosyl)adenine **3a**

To a magnetically stirred suspension of methyltriphenylphosphonium bromide (464 mg, 1.3 mmol) in dry Et_2O (75 mL) in a flame-dried flask under N_2 was added a solution of sodium 2-methyl-2-butoxide (1.115 mL of a 1.13 M solution in benzene, 1.26 mmol). The bright yellow solution was stirred for 1.5 h at ambient temperature and cooled to -40°C . Dehydrated **2a** (18) (258 mg, 0.63 mmol) in anhydrous THF (50 mL) was added by syringe and stirring continued at -20°C for 2 h and overnight at $\sim 0^\circ\text{C}$. $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ was added, the layers separated, and the aqueous layer extracted with CHCl_3 . The two organic fractions were washed separately with $\text{NaHCO}_3/\text{H}_2\text{O}$ and

$\text{NaCl}/\text{H}_2\text{O}$, dried (Na_2SO_4), and evaporated. The combined residues were purified by silica column chromatography (EtOAc). Evaporation of appropriately pooled fractions gave 149 mg (58%) of **3a** as a white solid foam: uv (MeOH): max 278, 229 nm (ϵ 20 100, 14 100), min 246 nm (ϵ 12 200); ^1H nmr (CDCl_3) δ : 1.43 and 1.57 (s,s; 3,3; CH_3 's), 4.71–4.78 (m, 1, H_4'), 5.04 (dd, $J_{3'-2'}$ = 6.2 Hz, $J_{3'-4'}$ = 3.4 Hz, 1, H_3'), 5.17 (dt, $J_{6'-4'}$ = 1.3 Hz, $J_{6'-5'}$ = 10.4 Hz (*cis*), $J_{6'-6''}$ = 1.3 Hz, 1, H_6'), 5.27 (dt, $J_{6'-4'}$ = 1.3 Hz, $J_{6'-5'}$ = 17.2 Hz (*trans*), 1, H_6''), 5.58 (dd, $J_{2'-1'}$ = 2 Hz, 1, H_2'), 5.90 (ddd, $J_{5'-4'}$ = 6.9 Hz, 1, H_5'), 6.20 (d, 1, H_1'), 7.5–7.7 (m, 3, Bz), 8.05–8.16 (m, 2, Bz), 8.12 (s, 1, H_2), 8.82 (s, 1, H_8), 9.15 (s, 1, NH); ms m/z : 407 (34, M^+), 378 (100), 277 (79). Anal. calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}_4$ (407.4): C 61.91, H 5.20, N 17.19; found: C 61.82, H 5.32, N 17.28.

9-(5,6-Dideoxy- β -D-ribo-hex-5-enofuranosyl)adenine (5'-deoxy-5'-methyleneadenosine) **4**

Removal of the benzoyl group

Saturated NH_3/MeOH (15 mL) was added to a solution of **3a** (203 mg, 0.5 mmol) in MeOH (15 mL) and stirring was continued at $\sim 4^\circ\text{C}$ overnight. Thin-layer chromatography (tlc) ($\text{MeOH}/\text{CHCl}_3$, 7:93) showed a new polar compound and the absence of **3a**. Evaporation of the solution gave 198 mg of crude **3b**, which can be deprotected directly in the next step. For spectroscopic characterization this material was purified by chromatography on silica ($\text{MeOH}/\text{CHCl}_3$, 1:49) to give 140 mg (92%) of **3b** as a white solid foam: ^1H nmr (CDCl_3) δ : 1.40 and 1.65 (s,s; 3,3; CH_3 's), 4.64–4.72 (m, 1, H_4'), 5.00 (dd, $J_{3'-2'}$ = 6.2 Hz, $J_{3'-4'}$ = 3.2 Hz, 1, H_3'), 5.13 (dt, $J_{6'-4'}$ = 1.3 Hz, $J_{6'-5'}$ = 10.4 Hz (*cis*), $J_{6'-6''}$ = 1.2 Hz, 1, H_6'), 5.25 (dt, $J_{6'-4'}$ = 1.3 Hz, $J_{6'-5'}$ = 17.2 Hz (*trans*), 1, H_6''), 5.50 (dd, $J_{2'-1'}$ = 1.8 Hz, 1, H_2'), 5.75 (br s, 2, NH_2), 5.90 (ddd, $J_{5'-4'}$ = 6.2 Hz, 1, H_5'), 6.10 (d, 1, H_1'), 7.89 (s, 1, H_2), 8.35 (s, 1, H_8); ms m/z : 303 (12, M^+), 277 (100).

Removal of the isopropylidene group

A solution of crude **3b** (198 mg) in $\text{CF}_3\text{CO}_2\text{H}/\text{H}_2\text{O}$ (17:3) was stirred for 20 min at $\sim 0^\circ\text{C}$ and evaporated. The residue was dissolved in EtOH, evaporated, dissolved in MeOH (5 mL), and applied to a column of Dowex 1-X2 (OH^-) resin. Elution was effected with $\text{MeOH}/\text{H}_2\text{O}$ (3:7, 500 mL; followed by 1:1, 500 mL). Evaporation of appropriately pooled fractions gave a colorless product that was recrystallized from $\text{Et}_2\text{O}/\text{EtOH}$ to give 87 mg (62% from **3a**) of **4**: mp 185–187°C (lit. (17) mp 190–191°C); uv (MeOH): max 259 nm (ϵ 15 300), min 226 nm (ϵ 2350); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 4.10 (ddd, $J_{3'-2'}$ = 5.0 Hz, $J_{3'-4'}$ = 4.6 Hz, $J_{3'-\text{OH}_3'}$ = 5.6 Hz, 1, H_3'), 4.28–4.34 (m, 1, H_4'), 4.65 (ddd, $J_{2'-1'}$ = 5.2 Hz, $J_{2'-\text{OH}_2'}$ = 5.7 Hz, 1, H_2'), 5.17 (dt, $J_{6'-4'}$ = 1.5 Hz, $J_{6'-5'}$ = 10.6 Hz (*cis*), $J_{6'-6''}$ = 1.5 Hz, 1, H_6'), 5.28 (dt, $J_{6'-4'}$ = 1.5 Hz, $J_{6'-5'}$ = 17.3 Hz (*trans*), 1, H_6''), 5.35 (d, 1, OH_3'), 5.52 (d, 1, OH_2'), 5.90 (d, 1, H_1'), 6.07 (ddd, $J_{5'-4'}$ = 6.8 Hz, 1, H_5'), 7.30 (br s, 2, NH_2), 8.15 (s, 1, H_2), 8.30 (s, 1, H_8); ms m/z : 263 (12, M^+), 178 (26), 104 (45), 136 (67), 135 (100), 108 (44). Anal. calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}_3$ (263.3): C 50.19, H 4.98, N 26.60; found: C 50.32, H 5.11, N 26.49.

6-*N*-Benzoyl-9-[5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)- β -D-ribo-hex-5(*E*)-enofuranosyl]adenine **5a**

Method A

A solution of **1a** (411 mg, 1 mmol) and dicyclohexylcarbodiimide (DCC, 619 mg, 3 mmol) in anhydrous Me_2SO (2.5 mL) was stirred with cooling (ice bath) while $\text{Cl}_2\text{CHCO}_2\text{H}$ (0.041 mL, 65 mg, 0.5 mmol) was added. Stirring was continued at ambient temperature for 90 min and then (*p*-toluenesulfonylmethylene)triphenylphosphorane (20, 21) (516 mg, 1.2 mmol) was added. After stirring overnight, tlc indicated complete conversion to a product that migrated faster than **1a**. Oxalic acid dihydrate (252 mg, 2 mmol) in MeOH (5 mL) was added (to hydrolyze excess DCC) and, after 20 min, *N,N'*-dicyclohexylurea was filtered and the filtrate evaporated *in vacuo*. The residue was partitioned ($\text{EtOAc}/\text{H}_2\text{O}$) and the organic layer washed with H_2O (3 \times 50 mL, to remove Me_2SO), $\text{NaHCO}_3/\text{H}_2\text{O}$, and $\text{NaCl}/\text{H}_2\text{O}$, dried (MgSO_4), and evaporated to give a slightly yellow foam. Silica column chromatography ($\text{MeOH}/\text{CHCl}_3$, 1.25:98.75) and "diffusion

crystallization" (31) from EtOH/pentane/hexanes gave 482 nm (86%) of **5a**: mp 106–108°C; uv (MeOH): max 279, 234 nm (ϵ 19 500, 29 700), min 256 nm (ϵ 12 800); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 1.34 and 1.56 (s,s; 3,3; CH_3 's), 2.38 (s, 3, PhCH_3), 4.95 (ddd, $J_{4'-3'} = 3.2$ Hz, $J_{4'-5'} = 5.6$ Hz, $J_{4'-6'} = 1.5$ Hz, 1, $\text{H}4'$), 5.26 (dd, $J_{3'-2'} = 6.2$ Hz, 1, $\text{H}3'$), 5.58 (dd, $J_{2'-1'} = 1.8$ Hz, 1, $\text{H}2'$), 6.40 (d, 1, $\text{H}1'$), 6.77 (dd, $J_{6'-5'} = 15$ Hz, 1, $\text{H}6'$), 6.91 (dd, 1, $\text{H}5'$), 7.40 (d, $J_{\text{H}_A-\text{H}_B} = 8.5$ Hz, 2, aromatic H_A), 7.55–7.68 (m, 5, H_B), 8.07 (d, 2, aromatic H_B), 8.60 (s, 1, $\text{H}2$), 8.63 (s, 1, $\text{H}8$), 11.2 (s, 1, NH); ms (CI, NH_3) m/z : 562 (22, $\text{M} + 1$). Anal. calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_5\text{O}_5\text{S}$ (561.6): C 59.88, H 4.85, N 12.47, S 5.71; found: C 60.18, H 4.86, N 12.71, S 5.58.

Method B

(*p*-Toluenesulfonylmethyl)triphenylphosphorane (537 mg, 1.25 mmol) in dry CH_3CN (20 mL) was added dropwise to a stirred solution of dehydrated **2a** (18) (0.41 g, 1 mmol) in dry CH_3CN (5 mL) under N_2 and stirring was continued at ambient temperature for 10 h. The solution was evaporated to give a white solid that was purified by silica column chromatography and crystallized as in Method A to give 477 mg (85%) of **5a** with identical physical and spectral data.

9-[5,6-Dideoxy-2,3-O-isopropylidene-6-(*p*-toluenesulfonyl)- β -D-ribo-hex-5(E)-enofuranosyl]adenine **5b**

Treatment of **1b** (307 mg, 1 mmol) by Method A (as described above for **5a**) gave 288 mg (63%) of **5b** (after diffusion crystallization (31) from EtOAc/hexanes): mp 114–116°C; uv (MeOH): max 257, 236 nm (ϵ 16 600, 23 500), min 252, 222 nm (ϵ 16 000, 16 500); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 1.32 and 1.53 (s,s; 3,3; CH_3 's), 2.40 (s, 3, PhCH_3), 4.88 (ddd, $J_{4'-3'} = 3.3$ Hz, $J_{4'-5'} = 6.0$ Hz, $J_{4'-6'} = 1.25$ Hz, 1, $\text{H}4'$), 5.20 (dd, $J_{3'-2'} = 6.0$ Hz, 1, $\text{H}3'$), 5.49 (dd, $J_{2'-1'} = 2.0$ Hz, 1, $\text{H}2'$), 6.26 (d, 1, $\text{H}1'$), 6.74 (dd, $J_{6'-5'} = 15$ Hz, 1, $\text{H}6'$), 6.90 (dd, 1, $\text{H}5'$), 7.34 (s, 2, NH_2), 7.39 (d, $J_{\text{H}_A-\text{H}_B} = 8.5$ Hz, 2, aromatic H_A), 7.58 (d, 2, aromatic H_B), 8.01 (s, 1, $\text{H}2$), 8.27 (s, 1, $\text{H}8$); ms m/z : 457.1406 (0.4, M^+ (calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_5\text{S} = 457.1419$)), 442.1172 (1.8, $\text{M} - \text{CH}_3$), 302.1254 (100, $\text{M} - \text{Ts}$). Anal. calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_5\text{S}$ (457.5): C 55.13, H 5.07, N 15.13; found: C 55.27, H 5.11, N 15.37.

Desulfonylation of **5b** to give 9-(5,6-dideoxy-2,3-O-isopropylidene- β -D-ribo-hex-5-enofuranosyl)adenine **4**

A solution of **5b** (183 mg, 0.4 mmol) in anhydrous THF (6 mL) was added to a stirred solution of tributylstannyl lithium (29) (1.2 mL of a 1 M solution in anhydrous THF, 1.2 mmol) under N_2 at -78°C . After 1 h, CHCl_3 (10 mL) and silica gel (0.9 g; Merck 60, 200–400 mesh) were added and the resulting mixture stirred at ambient temperature for 20 h. The silica gel was filtered, washed with CHCl_3 (2×10 mL), and the combined mother liquors shaken with $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ (15 mL) and CHCl_3 (10 mL). The organic layer was washed with $\text{NaHCO}_3/\text{H}_2\text{O}$ and $\text{NaCl}/\text{H}_2\text{O}$, dried (MgSO_4), and evaporated to give a yellow foam. Silica column chromatography ($\text{MeOH}/\text{CHCl}_3$, 1.75:98.25) of this material gave 74 mg (61%) of **3b** as a white solid foam. The ^1H nmr spectrum of this tlc-homogeneous product had peaks identical to those noted above for **3b**, but also had other peaks (5–10% integrated intensity) corresponding to the allyl-tosyl compound **7**. Deprotection of this material and purification (as described above for pure **3b**) gave 41 mg (39%) of **4** with identical physical and spectral data.

9-[5,6-Dideoxy-6-(*p*-toluenesulfonyl)- β -D-ribo-hex-5(E)-enofuranosyl]adenine **5c**

A solution of **5b** (137 mg, 0.3 mmol) in $\text{CF}_3\text{CO}_2\text{H}/\text{H}_2\text{O}$ (17:3, 5 mL) was stirred for 20 min at $\sim 0^\circ\text{C}$, evaporated, and coevaporated with EtOH. Crystallization and recrystallization of the residue from EtOH/hexanes gave 111 mg (89%) of **5c**: mp 128–130°C; uv (MeOH): max 259, 239 nm (ϵ 16 700, 22 800), min 256, 223 nm (ϵ 16 500, 14 800); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 2.38 (s, 3, PhCH_3), 4.26 (ddd, $J_{3'-2'} = 5.1$ Hz, $J_{3'-4'} = 4.1$ Hz, $J_{3'-\text{OH}3'} = 5.6$ Hz, 1, $\text{H}3'$), 4.57 (dd, $J_{4'-5'} = 4.7$ Hz, 1, $\text{H}4'$), 4.74 (ddd, $J_{2'-1'} = 5.4$ Hz, $J_{2'-\text{OH}2'} = 5.5$ Hz, 1, $\text{H}2'$), 5.58 (d, 1, $\text{OH}3'$), 5.60 (d, 1, $\text{OH}2'$), 5.94 (d, 1, $\text{H}1'$), 6.92 (d, $J_{6'-5'} = 15.1$ Hz, 1, $\text{H}6'$), 7.07 (dd, 1, $\text{H}5'$), 7.43 (d, $J_{\text{H}_A-\text{H}_B} = 8.8$ Hz, 2, aromatic H_A), 7.72 (d, 2, aromatic H_B), 7.91 (br s, 2, NH_2), 8.08 (s, 1, $\text{H}2$), 8.43 (s, 1, $\text{H}8$); ms m/z : 417 (1, M^+), 358 (3),

278 (10), 156 (14), 139 (32), 135 (100). Anal. calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5\text{S}$ (417.4): C 51.79, H 4.59, N 16.78; found: C 51.66, H 4.39, N 16.61.

9-[5,6-Dideoxy-2,3-O-isopropylidene-6-(*p*-toluenesulfonyl)- β -D-ribo-hexofuranosyl]adenine **6a**

To a magnetically stirred solution of **5b** (274 mg, 0.6 mmol) in $\text{MeOH}/\text{H}_2\text{O}$ (2:1, 30 mL) was added sodium borohydride (45 mg, 1.2 mmol). After stirring for 16 h at ambient temperature, the solution was concentrated to one-half volume and CHCl_3 (20 mL) and H_2O (10 mL) were added. The organic layer was separated and the aqueous layer washed with CHCl_3 (10 mL). The combined organic phase was washed with $\text{NaCl}/\text{H}_2\text{O}$ and H_2O , dried (MgSO_4), and evaporated to give a slightly yellow solid foam that was purified by silica column chromatography ($\text{MeOH}/\text{CHCl}_3$, 1.5:98.5). Evaporation of appropriately pooled fractions gave 208 mg (76%) of **6a** as a tlc-homogeneous white solid that could be deprotected directly in the next step; ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 1.20 and 1.42 (s,s; 3,3; CH_3 's), 1.80–1.98 (m, 2, $\text{H}5'$, $5''$), 2.33 (s, 3, PhCH_3), 3.10–3.45 (m, 2, $\text{H}6'$, $6''$), 4.08–4.16 (m, 1, $\text{H}4'$), 4.83 (dd, $J_{3'-2'} = 6.0$ Hz, $J_{3'-4'} = 3.0$ Hz, 1, $\text{H}3'$), 5.36 (dd, $J_{2'-1'} = 2.2$ Hz, 1, $\text{H}2'$), 5.99 (d, 1, $\text{H}1'$), 7.27 (s, 2, NH_2), 7.31 (d, $J_{\text{H}_A-\text{H}_B} = 8.5$ Hz, 2, aromatic H_A), 7.50 (d, 2, aromatic H_B), 7.97 (s, 1, $\text{H}2$), 8.16 (s, 1, $\text{H}8$); ms m/z : 459 (4, M^+), 444 (12), 401 (36), 304 (100).

Compound **5a** was reduced with NaBH_4 by the same procedure to give **6a** in the same yield.

9-[5,6-Dideoxy-6-(*p*-toluenesulfonyl)- β -D-ribo-hexofuranosyl]adenine **6b**

A solution of **6a** (161 mg, 0.35 mmol) in $\text{CF}_3\text{CO}_2\text{H}/\text{H}_2\text{O}$ (17:3, 5 mL) was stirred for 25 min at $\sim 0^\circ\text{C}$, evaporated, and coevaporated with EtOH to give an amorphous glass. Crystallization and recrystallization from MeOH gave 122 mg (83%) of **6b** (two crops): mp 158–160°C; uv (MeOH): max 261, 223 nm (ϵ 15 400, 15 600), min 240 nm (ϵ 7300); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 1.90–2.03 (m, 2, $\text{H}5'$, $5''$), 2.38 (s, 3, PhCH_3), 3.20–3.43 (m, 2, $\text{H}6'$, $6''$), 3.88–3.98 (m, 1, $\text{H}4'$), 4.09 (dd, $J_{3'-2'} = 5.6$ Hz, $J_{3'-4'} = 4.0$ Hz, 1, $\text{H}3'$), 4.59 (dd, $J_{2'-1'} = 4.8$ Hz, 1, $\text{H}2'$), 5.30 (br s, 2, $\text{OH}2'$, $\text{OH}3'$), 5.84 (d, 1, $\text{H}1'$), 7.41 (d, $J_{\text{H}_A-\text{H}_B} = 8.5$ Hz, 2, aromatic H_A), 7.76 (d, 2, aromatic H_B), 8.26 (s, 1, $\text{H}2$), 8.50 (s, 1, $\text{H}8$), 8.52 (s, 2, NH_2); ms m/z : 419 (0.5, M^+), 278 (8), 246 (100), 157 (18), 139 (30), 135 (42). Anal. calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_5\text{O}_5\text{S}$ (419.5): C 51.54, H 5.05, N 16.70; found: C 51.29, H 4.96, N 16.79.

9-[5,6-Dideoxy-2,3-O-isopropylidene-6-(*p*-toluenesulfonyl)- β -D-erythro-hex-4(Z)-enofuranosyl]adenine **7**

To a stirred solution of **5b** (183 mg, 0.4 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (4:1, 10 mL) was added 1 M $\text{NaOH}/\text{H}_2\text{O}$ (1 mL). (Alternatively, THF (10 mL) as solvent and DBU (0.06 mL, 60 mg, 0.4 mmol as base can be used.) After 4 h at ambient temperature, the solution was concentrated to one-half volume and EtOAc (10 mL) and $\text{HCl}/\text{H}_2\text{O}$ (0.05 M, 2 mL) were added. The organic layer was separated and the aqueous layer washed with EtOAc (2×10 mL). The combined organic phase was washed with $\text{NaHCO}_3/\text{H}_2\text{O}$, $\text{NaCl}/\text{H}_2\text{O}$, and H_2O , dried (MgSO_4), and evaporated to a white foam that was crystallized from EtOH/hexanes to give 163 mg (89%) of **7**: mp 115–116°C; uv (MeOH): max 258, 227 nm (ϵ 15 200, 13 900), min 240 nm (ϵ 9700); ^1H nmr (CDCl_3) δ : 1.39 and 1.48 (s,s; 3,3; CH_3 's), 2.35 (s, 3, PhCH_3), 3.83 (d, $J_{6'-5'} = 8$ Hz, 2, $\text{H}6'$, $6''$), 4.81 (t, 1, $\text{H}5'$), 5.19 (d, $J_{3'-2'} = 6$ Hz, 1, $\text{H}3'$), 5.62 (d, 1, $\text{H}2'$), 6.02 (s, 2, NH_2), 6.14 (s, 1, $\text{H}1'$), 7.16 (d, $J_{\text{H}_A-\text{H}_B} = 8.5$ Hz, 2, aromatic H_A), 7.67 (d, 2, aromatic H_B), 7.74 (s, 1, $\text{H}2$), 8.14 (s, 1, $\text{H}8$); ms m/z : 442.1178 (1.7, $\text{M} - \text{CH}_3$ [$\text{C}_{20}\text{H}_{20}\text{N}_5\text{O}_5\text{S}$] = 442.1185), 302.1257 (100, $\text{M} - \text{Ts}$). Anal. calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_5\text{S}$ (457.5): C 55.13, H 5.07, N 15.31, S 7.01; found: C 55.03, H 5.09, N 15.08, S 7.12.

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