Nucleic acid related compounds. 67. Synthesis of 5′-amino and 5′-methylthio chain-extended nucleosides from uridine[1]

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Treatment of 2′,3′-*O*-isopropylideneuridine-5′-aldehyde with the stabilized Wittig reagent, (*p*-toluenesulfonylmethylene)triphenylphosphorane, gave high yields of 1-[5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-*ribo*-hex-5(*E*)-enofuranosyl]uracil (**2**). This vinylsulfone (**2**) underwent isomerization readily in base to give the allylic sulfone, 1-[5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-*erythro*-hex-4(*Z*)-enofuranosyl]uracil (**3**). Treatment of **2** or **3** with aqueous trifluoroacetic acid gave the corresponding deprotected vinyl (**5**) or allylic (**6**) sulfones, and **5** was converted to **6** readily in basic solutions. Treatment of **2** with sodium borohydride, sodium thiomethoxide, or ammonia resulted in conjugate addition (at C5′ of the vinyl sulfone) to give the 5′-hydro, 5′-methylthio, or 5′-amino-5′,6′-dideoxy-6′-(*p*-toluenesulfonyl) nucleosides. The 5′-substituted diastereomers were deprotected, separated, and the configuration of a 5′-amino derivative was established by X-ray crystallography.

Key words: allylic sulfones, amino-nucleosides, 5′,6′-dideoxynucleosides, nucleosides, uridine, vinyl sulfones.

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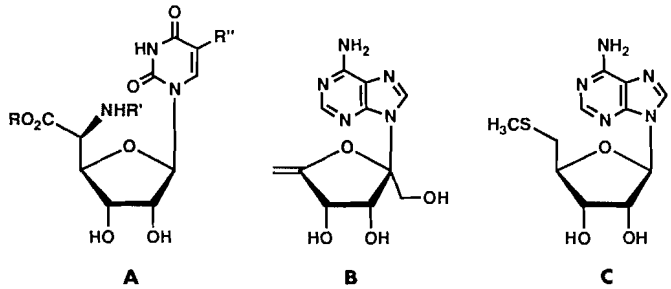
Le traitement du 2′,3′-*O*-isopropylidène-uridine-5′-aldéhyde avec le réactif de Wittig stabilisé, (*p*-toluènesulfonylméthylène)triphénylphosphorane, fournit des rendements élevés du 1-[5,6-didésoxy-2,3-*O*-isopropylidène-6-(*p*-toluènesulfonyl)-β-D-*ribo*-hex-5(*E*)-énofuranosyl]uracil (**2**). En présence de base, cette vinylcétone (**2**) subit une isomérisation conduisant à la sulfone allylique, 1-[5,6-didésoxy-2,3-*O*-isopropylidène-6-(*p*-toluènesulfonyl)-β-D-*érythro*-hex-4(*Z*)-énofuranosyl]uracil (**3**). Le traitement des composés **2** ou **3** avec de l'acide trifluoroacétique aqueux fournit les sulfones correspondantes déprotégées vinylique **5** et allylique **6**; le composé **5** est facilement transformé en produit **6** en solutions basiques. Le traitement du composés **2** par le borohydrure de sodium, du thiométhylate de sodium ou de l'ammoniac conduit à une addition conjuguée (en C5′ de la vinylcétone) et à la formation des 5′-hydro-, 5′-méthylthio- ou 5′-amino-5′,6′-didésoxy-6′-(*p*-toluènesulfonyl)-nucléosides. Les diastéréoisomères substitués en 5′ ont été déprotégés, séparés et la configuration d'un dérivé 5′-amino a été déterminé par diffraction des rayons-X.

Mots clés : sulfones allyliques, amino-nucléosides, 5′,6′-didésoxynucléosides, nucléosides, uridine, vinylsulfones.

[Traduit par la rédaction]

Introduction

Among the varied structural features present in nucleoside antibiotics (1*a*, 2*a*), the polyoxin and nikkomycin complexes (**A**) have a substituted 5′-amino-5′-deoxyhexofuranosyl uronic acid sugar backbone with a uracil or 5-substituted-uracil base (1*b*, 2*b*). Other nucleoside antibiotics (e.g., decoyinine (**B**)) have unsaturated sugar moieties and (or) further modifications at C5′ (1*c*, 2*c*). Methylthioadenosine phosphorylase catalyzes the glycosyl cleavage of 5′-*S*-methyl-5′-thioadenosine (**C**), and



A **B** **C**

the resulting 5-*S*-methyl-5-thioribose 1-phosphate is converted to methionine by salvage pathway enzymes (3). Pyrimidine nucleoside phosphorylases effect analogous cleavage of uridine nucleosides (4). Thus, the synthesis and biological evaluation of uridine nucleoside analogues modified at C5′ with amino or methylthio substituents is of current interest.

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 nucleophilic conversions with 5′-deoxy-5′-halonucleosides (5, 6). Wittig reactions of nucleoside 5′-aldehydes with stabilized ylides have provided 6′-substituted-5′,6′-unsaturated hexofuranosyl nucleosides (7–12). However, direct introduction of the methylene group at C5′ has met with limited success, and only recently has the direct synthesis of 5′-deoxy-5′-methyleneadenosine been reported (13). Seebach's silyl nitronate (nitro-aldol) methodology was used for chain extension of aldehyde sugars including a uridine 5′-aldehyde derivative (14). Barton *et al.* developed radical-mediated chemistry for the stereocontrolled synthesis of chain-lengthened nucleoside phosphonates (15*a*), vinyl sulfones (15*b*), and a phosphonate analogue of 3′-azido-3′-deoxythymidine 5′-monophosphate (AZTMP) (15*c*). A multistep synthesis of 5′-homo-AZT from 1,2;5,6-di-*O*-isopropylidene-3-*O*-mesyl-α-D-allofuranose (4% overall yield) was reported recently (16).

Chattopadhyaya and co-workers prepared 1-(2,3-dideoxy-3-*p*-toluenesulfonyl-β-D-*glycero*-pent-2-enofuranosyl)uracil and its adenine analogue (17) and the uracil 3′-phenylselenone analogue (18). These powerful Michael acceptors (vinyl 3′-sulfone or selenone) were utilized to functionalize the carbohydrate moiety of nucleosides. The chemistry of vinyl sulfones was reviewed recently (19). We now describe the efficient synthesis of a uridine vinylsulfone derivative (**2**), its use as a synthetic intermediate for Michael addition products, and its base-catalyzed rearrangement to the 4′,5′-unsaturated allylic sulfone (**3**).

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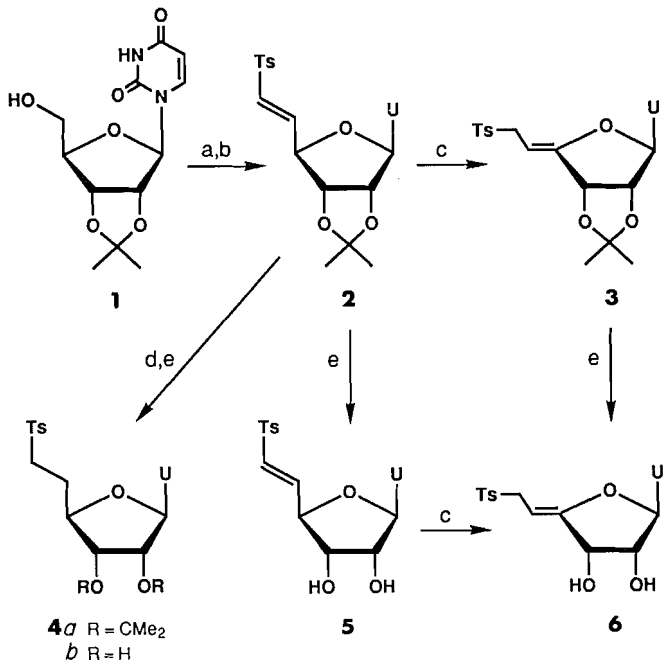


(a) DCC/DMSO/PTFA or DCC/DMSO/Cl_2CHCO_2H. (b) Ph_3P=CHTs. (c) NaOH/H_2O/CH_3CN or DBU/THF. (d) $NaBH_4$/MeOH/H_2O. (e) CF_3CO_2H/H_2O.

SCHEME 1

Results and discussion

Moffatt oxidation of 2′,3′-*O*-isopropylideneuridine (**1**, Scheme 1) (7, 20), followed by treatment of the resulting 5′-aldehyde with the stabilized ylid, (*p*-toluenesulfonylmethylene)triphenylphosphorane (21, 22), gave the vinyl sulfone, 1-[5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-*ribo*-hex-5(*E*)-enofuranosyl]uracil (**2**, 85%). The ^1H NMR spectrum of **2** in Me_2SO-d_6 had a "collapsed" broad singlet for H5′ and H6′ whereas its spectrum in $CDCl_3$ had two doublets of doublets. The large vinyl coupling constant ($^3J_{5'-6'}$ = 15.0 Hz) was in harmony with the *E* configuration. Deprotection of **2** with aqueous trifluoroacetic acid gave 1-[5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-*ribo*-hex-5(*E*)-enofuranosyl]uracil (**5**, 89%).

Attempted application of methods for the reductive cleavage of carbon–sulfur bonds in saturated (23–25) and α,β-unsaturated (26–29) sulfones to **2** failed to give 5′-deoxy-2′,3′-*O*-isopropylidene-5′-methyleneuridine. The Corey sulfone cleavage conditions (23) with sodium (24) or aluminum (26) amalgam resulted in rearrangement of the vinyl to allylic sulfones (**2** → **3**) and (or) recovery of starting material. Formation of more complex mixtures was observed under more vigorous conditions. Attempted desulfonylation of **2** via conjugate addition of tributylstannyllithium (29) also failed, possibly resulting from interactions between the reagent and the uracil ring, in contrast to results with the adenosine analogue (13). The sodium dithionite procedure of Julia and co-workers (27, 28) caused loss of UV absorption, presumably resulting from nucleophilic addition of the reagent to C6 of uracil as anticipated from sodium bisulfite addition studies of Shapiro *et al.* (30).

Base-catalyzed isomerization of the vinyl sulfone **2** to a single allylic sulfone (**3**, 91%, exocyclic double bond tentatively assigned the less hindered *Z* configuration) occurred by stirring **2** in aqueous sodium hydroxide in acetonitrile or in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF. The bathochromic shift (λ_{max} 237 to 258 nm) and hypochromic effect (ε 22 200 to 10 300) accompanying conversion of the conjugated vinyl sulfone (**2**) into the allylic sulfone (**3**) was monitored by UV spectroscopy.

Attempted deprotection of 1-[5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-*erythro*-hex-4(*Z*)-enofuranosyl]uracil (**3**) at ambient temperature resulted in the expected acid-catalyzed decomposition of the exocyclic vinyl ether (31, 32). However, treatment of **3** with aqueous trifluoroacetic acid at 0°C for 25 min afforded **3**, uracil, and 1-[5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-*erythro*-hex-4(*Z*)-enofuranosyl]uracil (**6**, 22%) after silica column purification. Longer reaction times resulted in formation of greater quantities of uracil. The deprotected vinyl sulfone (**5**) underwent clean isomerization to **6** (81%) in aqueous sodium hydroxide. This provides an efficient route to **6** (61% from **1**), which differs from the usual methodologies for preparation of 4′,5′-unsaturated nucleosides that involve elimination of hydrogen and an activated O5′ function or halide from C4′ and C5′ (5, 6, 31, 32).

Conjugate reduction of **2** occurred with sodium borohydride in aqueous methanol to give **4***a* (83%). Deprotection with aqueous trifluoroacetic acid gave 1-[5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-*ribo*-hexofuranosyl]uracil (**4***b*, 71%). Treatment of **2** with sodium thiomethoxide in THF gave the 5′-methylthio-5′,6′-dideoxy diastereomers **7** (~1:1, >70%, Scheme 2). One diastereomer crystallized preferentially (19:1) during "diffusion crystallization" (33) from hexane/ethyl acetate. The mother liquor was purified by silica column chromatography and the second diastereomer then crystallized predominantly (1:4). Deprotection of the two mixtures with aqueous trifluoroacetic acid and crystallization afforded **8** (5′*R*, mp 219–220°C) and **9** (5′*S*, mp 125–128°C), respectively. The 5′-stereochemistry is tentatively assigned by parallel ^{13}C NMR shifts of C5′ relative to spectra of the 5′-amino analogues whose configurations were defined by X-ray crystallography of **12***b*(5′*R*). The ^{13}C NMR peak for C5′ of **8**(5′*R*) was at 1.2 ppm higher field than that of **9**(5′*S*). Shifts for C5′ of **10***b* (0.8 ppm) and **12***b* (0.6 ppm) (5′*R*) also were at higher fields than those of their *S* isomers.

Treatment of **2** with methanolic ammonia or aqueous ammonia in ethanol gave the 5′-amino-5′,6′-dideoxy diastereomers **10***a*(5′*R*) and **11***a*(5′*S*) (~1:1, 77%) plus the isomerization product **3** (19%). Purification by silica column chromatography resulted in partial separation of **10***a* and **11***a*. Treatment of a mixture of these diastereomers with 4-dimethylaminopyridine/acetic anhydride (34) gave the 5′-*N*-acetylamino derivatives **12***a*(5′*R*) and **13***a*(5′*S*), which were separated readily by chromatography. Deprotection of separated **10***a* and **11***a*, and **12***a* and **13***a* with aqueous trifluoroacetic acid gave **10***b* and **11***b*, and **12***b* and **13***b*, respectively. X-ray crystallography established the *R* configuration at C5′ of **12***b*. Removal of the *N*-acetyl group from **13***b*(5′*S*) was effected by heating with 1 M hydrochloric acid at ~90°C for 30 h to give **11***b*(5′*S*).

Attempted removal of the *p*-toluenesulfonyl group from a mixture of **10***a*/**11***a* by heating at reflux with magnesium turnings in MeOH as described recently (25) gave low yields (~14%) of slightly less polar (TLC) products. Although this mixture could be shown (^1H NMR and MS) (13) to contain 5′-deoxy-2′,3′-*O*-isopropylidene-5′-methyleneuridine, it was contaminated (10–15%) with by-products and was not investigated further.

In summary, Moffatt oxidation of 2′,3′-*O*-isopropylideneuridine and Wittig treatment of the resulting 5′-aldehyde with (*p*-toluenesulfonylmethylene)triphenylphosphorane gave efficient conversion to the chain-extended (*E*)vinyl sulfone. This in-

TABLE 1. ^{1}H NMR spectral data[a,b]

Compound	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5'}$)	H5′[e] or H5′,5″ ($J_{5'-6'}$)	H6′ or H6′,6″	H5[c] (J_{5-6})	H6[c]	NH[f]	Aromatic[c] (J_{A-B})	Others[g]
2	5.80 (1.8)	5.12[e] (6.0)	4.88[e] (4.0)	4.66 (4.0)	6.93[f,h,i]		5.56 (8.0)	7.69	11.44	7.72, 7.44 (8.5)	1.26, 1.46 (CH_3's) 2.39 ($PhCH_3$)
3	5.84[g]	5.25[c] (6.3)	5.05[c]		4.45[j] (8.2)[k]	3.95[c]	5.59 (8.0)	7.68	11.42	7.71, 7.40 (8.5)	1.27, 1.29 (CH_3's) 2.37 ($PhCH_3$)
4*a*[l]	5.68 (2.2)	4.98[e] (6.2)	4.62[e] (5.0)	3.93[d] (6.5)[n]	1.91[m]	3.30[m]	5.60 (8.0)	7.66	11.40	7.74, 7.45 (8.5)	1.24, 1.42 (CH_3's) 2.41 ($PhCH_3$)
4*b*	5.62 (4.4)	4.03 (5.6)	3.77[m]	3.77[m]	1.93[m]	3.32[m]	5.59 (8.1)	7.56	11.40	7.78, 7.42 (8.5)	2.40 ($PhCH_3$) 5.13[c] (5.4,[o] OH3′) 5.35[c] (5.5,[o] OH2′)
5	5.72 (4.4)	4.16 (5.5)	3.99 (6.0)	4.39 (4.6)	6.98 (15.0)	6.87[c]	5.60 (8.0)	7.63	11.40	7.78, 7.44 (8.5)	2.40 ($PhCH_3$) 5.48[c] (6.2,[o] OH3′) 5.53[c] (5.3,[o] OH2′)
6	5.83 (4.8)	4.04 (5.1)	4.40[e]		4.53[j] (8.2)[k]	3.92[c]	5.58 (8.1)	7.10	11.42	7.72, 7.41 (8.5)	2.38 ($PhCH_3$) 5.56 (5.9,[o] OH3′) 5.63[c] (5.5,[o] OH2′)
7 (5′*R*)[p]	5.70[f]	5.05[c] (6.3)	4.89[e] (3.9)	3.96 (9.3)	3.18[d] (8.1)	[q]	5.61 (8.0)	7.67	11.40	7.73, 7.40 (8.5)	1.28, 1.45 (CH_3's) 1.92 (CH_3S) 2.38 ($PhCH_3$)
7 (5′*S*)[p]	5.68 (3.1)	4.98[e] (6.5)	4.79[e] (4.8)	4.13 (4.4)	3.22[d] (5.9)[k]	3.63[j]	5.67 (8.0)	7.61	11.41	7.80, 7.41 (8.5)	1.28, 1.46 (CH_3's) 2.03 (CH_3S) 2.38 ($PhCH_3$)
8 (5′*R*)[r]	5.78 (6.0)	4.22 (5.6)	4.16 (3.8)	3.98 (6.1)	3.21[d] (5.9)[k]	3.68[c]	5.75 (7.9)	7.74	11.42	7.89, 7.52 (8.5)	1.99 (CH_3S) 2.43 ($PhCH_3$) 5.34[c] (5.1,[o] OH3′) 5.50[c] (5.6,[o] OH2′)
9 (5′*S*)[r]	5.78 (5.8)	4.22[g]	4.17[g]	4.17[g] (6.0)	3.25[d] (6.0)[k]	3.74[c]	5.79 (8.0)	7.62	11.43	7.92, 7.54 (8.5)	2.07 (CH_3S) 2.44 ($PhCH_3$) 5.38[c] (4.8,[o] OH3′) 5.52[c] (5.1,[o] OH2′)
10*a* (5′*R*)	5.70 (3.0)	4.85[e] (6.5)	4.78[e] (5.0)	3.88 (3.0)	3.30[m]	3.30[m]	5.61 (8.0)	7.82	11.40	7.76, 7.43 (8.5)	1.24, 1.44 (CH_3's) 1.75[f] (NH_2) 2.38 ($PhCH_3$)
10*b* (5′*R*)	5.66 (6.3)	4.00[m]	4.00[m]	3.74[m]	3.50[m]	3.24[m]	5.62 (8.0)	7.93	11.40	7.79, 7.45 (8.5)	1.9[f] (NH_2) 2.40 ($PhCH_3$) 5.10[c] (5.0,[o] OH3′) 5.33[c] (5.4,[o] OH2′)
11*a* (5′*S*)	5.68 (2.0)	4.91[m]	4.91[m] (6.0)	3.74 (3.0)	3.25[m]	3.25[m]	5.54 (8.0)	7.66	11.32	7.72, 7.40 (8.5)	1.24, 1.43 (CH_3's) 1.8[f] (NH_2) 2.38 ($PhCH_3$)
11*b* (5′*S*)	5.68 (5.9)	4.04[m]	4.04[m]	3.61[m]	3.38[m]	3.19[m]	5.56 (8.0)	7.68	11.48	7.80, 7.43 (8.5)	1.9[f] (NH_2) 2.41 ($PhCH_3$)

termediate underwent Michael addition of hydrogen (sodium borohydride), thiomethanol, and ammonia to give the corresponding 5′-substituted-5′,6′-dideoxy derivatives. Removal of the isopropylidene group was effected with aqueous trifluoroacetic acid. Base-catalyzed isomerization of the vinyl sulfone to give a single geometric isomer of the 4′,5′-unsaturated allylic sulfone occurred readily. Attempted desulfonylation by various methods failed. New 5′-substituted-6′-*p*-toluenesulfonyl-5′,6′-dideoxy nucleoside analogues have been prepared and characterized, including determination of C5′ stereochemistry by X-ray crystallography. Biological testing results will be reported separately.

Single crystal X-ray structure determination

The single crystal structural study was performed with a Siemens R3m/V automated diffractometer that utilized graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The compound (**12***b*) crystallized in the orthorhombic space group $P2_12_12_1$ with $a = 7.302(2)$, $b = 11.352(4)$, and $c = 25.813(9)$ Å with $Z = 4$. A total of 2359 unique data points were taken of which 1443 were considered observed, $F > 3\sigma(F)$.

The structure was solved using direct methods and refined using a full-matrix least-squares procedure. All non-hydrogen atoms were refined anisotropically. Positional parameters for hydrogen atoms of the nucleoside were calculated using known stereochemical geometry or obtained from difference maps, and these parameters were not refined. The isotropic thermal parameter of each hydrogen atom was set equal to 1.2 times the equivalent isotropic thermal parameter of the atom to which it was bonded, and these parameters were not refined. The phenyl ring was refined as a rigid body with C—C bond lengths fixed at 1.395 Å and C—C—C angles fixed at 120°. A partial water of hydration was located in the difference map. Its oxygen atom was refined anisotropically with an occupancy factor of

TABLE 1 (*concluded*)

Compound	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5'}$)	H5′[e] or H5′,5″ ($J_{5'-6'}$)	H6′ or H6′,6″	H5[c] (J_{5-6})	H6[c]	NH[f]	Aromatic[c] (J_{A-B})	Others[g]
											5.10[c] (4.1,[o] OH3′) 5.32[c] (5.7,[o] OH2′)
12*a* (5′*R*)	5.72 (2.5)	5.01[e] (6.5)	4.61[e] (5.6)	3.98 (3.3)	4.47[m,s] (3.0)	[t]	5.70 (8.0)	7.70	11.45	7.75, 7.50 (8.5)	1.28, 1.52 (CH_3's) 1.64 (Ac) 2.38 ($PhCH_3$) 7.81[c] (8.5,[u] NH)
12*b* (5′*R*)	5.58 (5.5)	3.79[m]	3.79[m]	3.79[m] (3.0)	4.39[m,s] (2.6)	[v]	5.62 (8.0)	7.65	11.38	7.72, 7.43 (8.5)	1.63 (Ac) 2.40 ($PhCH_3$) 5.15[c] (5.2,[o] OH3′) 5.37[c] (5.7,[o] OH2′) 7.81[c] (8.2,[u] NH)
13*a* (5′*S*)	5.75 (2.0)	5.10[e] (6.5)	4.78[e] (4.7)	3.83 (7.2)	4.44[m,s] (9.0)	[w]	5.68 (8.0)	7.65	11.43	7.74, 7.48 (8.5)	1.30, 1.50 (CH_3's) 1.60 (Ac) 2.40 ($PhCH_3$) 7.92[c] (8.5,[u] NH)
13*b* (5′*S*)	5.66 (6.2)	4.03 (5.9)	3.86 (3.8)	3.56 (7.6)	4.31[m]	3.40[m]	5.61 (8.0)	7.38	11.40	7.66, 7.41 (8.5)	1.52 (Ac) 2.37 ($PhCH_3$) 5.16[c] (5.4,[o] OH3′) 5.41[c] (5.9,[o] OH2′) 7.84[c] (8.1,[u] NH)

[a]Chemical shifts at 200 MHz (Me_2SO-d_6 unless otherwise noted).
[b]"Apparent" first-order coupling constants (in parentheses).
[c]Doublet (unless otherwise noted).
[d]Doublet of doublets of doublets (unless otherwise noted).
[e]Doublet of doublets (unless otherwise noted).
[f]Broad singlet.
[g]Singlet (unless otherwise noted).
[h]"Collapsed" signals for H5′ and H6′.
[i]Spectrum in $CDCl_3$ revealed dd's at δ 6.48 ($J_{6'-5'}$ = 15 Hz, $J_{6'-4'}$ = 1.9 Hz, H6′), 7.05 ($J_{5'-4'}$ = 4.5 Hz, H5′).
[j]Triplet.
[k]($^3J_{5'-6',6''}$).
[l]Irradiation of the signal at δ 3.93 (H4′) simplified the multiplet at δ 1.91 (H5′,5″) into a triplet ($J_{5'-6'}$ = 8.0 Hz).
[m]Multiplet.
[n]($^3J_{4'-5',5''}$).
[o]($^3J_{HO-CH}$).
[p]Signals assigned from spectrum of diastereomeric mixture (correlated with integrated intensities).
[q]δ 3.66 (dd, $J_{6'-6''}$ = 15.2 Hz, H6′), 3.49 (dd, $J_{6''-5'}$ = 3.0 Hz, H6″).
[r]Spectrum at 500 MHz.
[s]ddd after D_2O exchange.
[t]δ 3.64 (dd, $J_{6'-6''}$ = 15.0 Hz, H6′), 3.51 (dd, $J_{6''-5'}$ = 9.0 Hz, H6″).
[u]($^3J_{5'-NH}$).
[v]δ 3.58 (dd, $J_{6'-6''}$ = 14.7 Hz, H6′), 3.36 (dd, $J_{6''-5'}$ = 9.6 Hz, H6″).
[w]δ 3.51 (dd, $J_{6'-6''}$ = 15.0 Hz, H6′), 3.43 (dd, $J_{6''-5'}$ = 2.0 Hz, H6″).

0.5. The water hydrogen atoms could not be located in difference maps and were not included in the refinement. The final R values were R = 0.0641 and R_w = 0.0574. All computer programs used in the structure solution, refinement, and display are included in the "SHELXTL PLUS" (35) program package. Standard atomic scattering factors (36) were used.

The drawing of the structure of **12***b* in Fig. 1 clearly established the R configuration at C5′. The pseudorotation angle of the furanose ring is 47.2°, indicating a $_4T^3$ conformation very close to $_4E$. The C6—N1–C1′—O4′ glycosyl torsion angle is 67.0(8)° and the C3′—C4′–C5′—N5′ torsion angle is 60.0(8)°. There are no intramolecular hydrogen bonds in the structure, but HO2′ and HN3 are involved in intermolecular hydrogen bonds. Also, HO3′ is hydrogen-bonded to the water of hydration. Details of the experimental procedure, structure solution, and refinement along with atomic positional and thermal parameters, bond lengths and angles, important torsion angles, and hydrogen bond data are included in the supplementary material.[3]

Experimental section

Uncorrected melting points were determined on a microstage block. UV spectra were recorded on a Hewlett Packard 8951A spectrophotometer. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Varian Gemini-200 spectrometer. ^1H spectra at 500 MHz were determined on a Varian VXR-500S spectrometer.

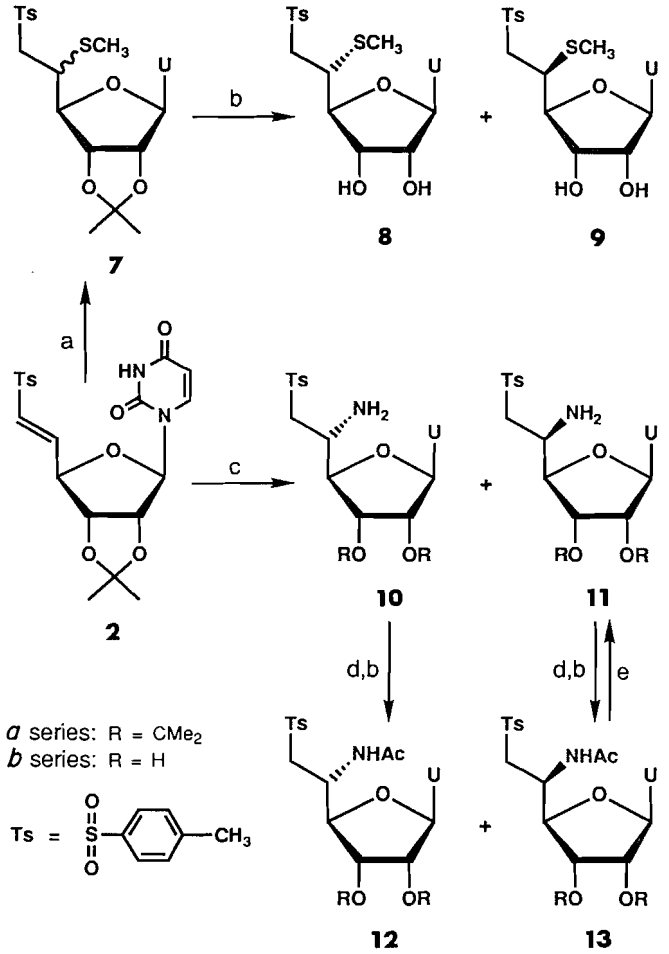
[3]Supplementary X-ray crystallography material may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0S2.

Tables of atomic coordinates, bond lengths and angles, and details of the structure determination have also been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

TABLE 2. ^{13}C NMR spectral data[a,b]

Compound	C2	C4	C5	C6	C1′	C2′,[c]	C3′,[c]	C4′	C5′	C6′	Aromatic C1″	Aromatic C2″	Aromatic C3″	Aromatic C4″	CH_3
4*b*	150.79	163.55	102.28	141.90	89.58	72.38[d]	72.38[d]	80.95	26.09	51.60	136.01	128.01	130.30	144.98	21.04
5	150.90	163.42	102.32	142.03[e]	90.32	73.13	72.39	81.08	142.50[e]	132.35	137.42	127.67	130.41	144.79	21.07
6	150.58	163.48	102.53	140.42	89.68	71.78	69.04	161.04	87.60	52.58	136.02	128.30	129.96	144.77	21.06
8 (5′*R*)[f]	150.98	163.58	102.42	141.91	88.91	71.74	70.26	84.83	41.94	55.91	136.88	128.12	130.19	145.03	21.10
9 (5′*S*)[f]	150.72	163.94	102.47	141.54	88.62	72.54	70.52	83.96	43.16	57.46	136.16	128.05	130.20	145.43	21.31
10*b* (5′*R*)	150.97	163.59	102.17	142.07	88.37	72.59	69.63	86.02	47.50	59.22	136.82	127.90	130.28	144.92	21.05
11*b* (5′*S*)	150.98	163.70	102.22	141.73	88.09	72.36	68.97	86.14	48.30	58.73	136.53	127.89	130.32	145.10	21.02
12*b* (5′*R*)[g]	150.94	163.75	102.04	142.21	88.76	72.30	69.44	84.71	45.32	55.94	136.17	128.15	130.10	145.03	21.01
13*b* (5′*S*)[h]	150.90	163.72	102.40	141.24	88.48	71.57	69.59	84.47	45.90	55.14	136.05	128.08	130.13	145.13	20.99

[a]Chemical shifts at 50 MHz.
[b]Proton-decoupled singlets.
[c]Assignments might be reversed.
[d]Peaks not resolved.
[e]Peak at δ 13.51 (CH_3S).
[f]Peak at δ 14.50 (CH_3S).
[g]Peaks at δ 22.23, 170.37 (Ac).
[h]Peaks at δ 22.14, 170.32 (Ac).



(a) $NaSCH_3$/THF. (b) CF_3CO_2H/H_2O. (c) NH_3/MeOH or NH_3/H_2O/EtOH. (d) DMAP/Ac_2O. (e) HCl/H_2O/Δ.

SCHEME 2

Mass spectra (MS) were obtained with an AEI MS-12 instrument. Elemental analyses were determined by the microanalytical laboratories of the University of Alberta, Adam Mickiewicz University, Poznan, or M-H-W Laboratories. Reagents and solvents were of reagent quality, and solvents were purified and dried before use. Diffusion crystallization was performed with the solvent combinations noted as described previously (33) except the diffusion solvent is listed first, and the dissolving solvent or mixture second, in the present paper. (*p*-Toluenesulfonylmethylene)triphenylphosphorane (73%, crystallized from CH_2Cl_2/hexane, mp 182–183°C (lit. (21) mp 186–187°C, (22) 182–184°C)) was prepared (21) from triphenylphosphine and bromomethyl *p*-toluylsulfone (22). Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} sheets with the following systems: S1 (MeOH/$CHCl_3$, 1:16), S2 ($Me_2CO/CHCl_3$, 1:3), S3 (EtOAc/*i*-PrOH/H_2O, 4:1:2, upper layer), S4 (MeOH/$CHCl_3$, 1:8), with sample observation under 254-nm light. Column chromatography was performed with Merck Kieselgel 60 (230–400 mesh).

*1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-*β*-D-ribo-hex-5*(E)*-enofuranosyl]uracil* **2**

Method A

A solution of **1** (2.84 g, 10 mmol), dicyclohexylcarbodiimide (DCC, 8.25 g, 40 mmol), and pyridinium trifluoroacetate (PTFA, 0.96 g, 5 mmol) in anhydrous Me_2SO (40 mL) was stirred at ambient temperature overnight. (*p*-Toluenesulfonylmethylene)triphenylphosphorane (21, 22) (5.17 g, 12 mmol) was added and stirring continued at ~35°C for 5 h. Me_2SO was evaporated *in vacuo* and the residue partitioned (EtOAc/H_2O). The organic phase was

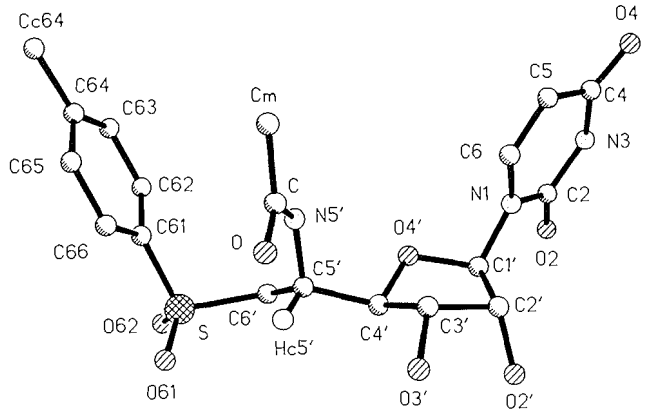


FIG. 1. Computer drawing of compound **12***b*. All hydrogen atoms except Hc5′ have been deleted for clarity and to emphasize the configuration at C5′.

washed (NaCl/H_2O), filtered (*N*,*N*′-dicyclohexylurea, DCU), dried ($MgSO_4$), evaporated, and the residue chromatographed (MeOH/$CHCl_3$, 1.5:98.5). Evaporation of appropriate fractions gave a white solid that was dissolved in $CH_2Cl_2/CHCl_3$ (20 mL, 1:1), filtered (traces of DCU), and the product precipitated with hexane. Recrystallization (MeOH) gave **2** (3.69 g, 85%) as white needles; mp 195–196°C; UV (MeOH) max: 237 nm (ε 22 200), min: 219 nm (ε 12 500); MS *m/z*: 434.1155 (1.6, M^+ = 434.1148). Anal. calcd. for $C_{20}H_{22}N_2O_7S$ (434.5): C 55.29, H 5.10, N 6.45, S 7.38; found: C 55.05, H 4.94, N 6.58, S 7.31.

Method B

A solution of **1** (4.26 g, 15 mmol) and DCC (12.36 g, 60 mmol) in anhydrous Me_2SO (60 mL) was stirred with cooling (ice-bath) while Cl_2CHCO_2H (0.62 mL, 0.97 g, 7.5 mmol) was added, and stirring was continued at ambient temperature for 2 h. (*p*-Toluenesulfonylmethylene)triphenylphosphorane (21, 22) (6.88 g, 16 mmol) was added and, after stirring overnight, TLC (S1) indicated complete conversion to a more rapidly migrating product. Oxalic acid dihydrate (5.67 g, 45 mmol) in MeOH (50 mL) was added and, after 30 min, DCU was filtered and the filtrate evaporated *in vacuo*. The residue was partitioned (EtOAc/H_2O) and the organic layer washed with H_2O (2 × 50 mL), $NaHCO_3/H_2O$, and NaCl/H_2O, dried ($MgSO_4$), and evaporated to give a yellow solid foam. Column chromatography (MeOH/$CHCl_3$, 1.5:98.5) and crystallization (MeOH) gave **2** (5.47 g, 84%) with identical data.

*1-[5,6-Dideoxy-6-(*p*-toluenesulfonyl)-β-D-*ribo*-hex-5(*E*)-enofuranosyl]uracil* **5**

A solution of **2** (217 mg, 0.5 mmol) in CF_3CO_2H/H_2O (9:1, 5 mL) was stirred at ~0°C for 25 min, evaporated, and coevaporated with EtOH. Crystallization of the residue (MeOH) gave **5** (175 mg, 89%) as white needles; mp 212–213°C; UV (MeOH) max: 238 nm (ε 21 000), shoulder: 260 nm (ε 9900), min: 221 nm (ε 12 600); MS *m/z*: 394 (1, M^+), 239 (25), 221 (100), 155 (43), 112 (56). Anal. calcd. for $C_{17}H_{18}N_2O_7S$ (394.4): C 51.77, H 4.60, N 7.10; found: C 51.79, H 4.65, N 7.03.

*1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-*erythro*-hex-4(Z)-enofuranosyl]uracil* **3**

To a stirred solution of **2** (217 mg, 0.5 mmol) in CH_3CN/H_2O (1:1, 15 mL) was added 1 M NaOH/H_2O (1 mL) (alternatively, DBU (0.075 mL, 76 mg, 0.5 mmol) in THF (10 mL) was used) and stirring was continued at ambient temperature for 4 h. TLC (S2) indicated complete conversion to one slightly slower migrating product. The solution was concentrated to half volume and EtOAc (30 mL) and 0.1 M HCl/H_2O (10 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 $NaHCO_3/H_2O$, NaCl/H_2O, dried ($MgSO_4$), and evaporated to a white foam that was diffusion crystallized (hexane/EtOH) to give **3** (198 mg, 91%) as a white solid; mp 119–121°C; UV (MeOH) max: 258 nm (ε 10 300), min: 241 nm (ε 8000); MS *m/z*: 419.0897 (3, M − CH_3 [$C_{19}H_{19}N_2O_7S$] = 419.0913), 279.0979 (100, M − Ts [$C_{13}H_{15}N_2O_5$] = 279.0981). Anal. calcd. for $C_{20}H_{22}N_2O_7S$ (434.5): C 55.29, H 5.10, N 6.45, S 7.38; found: C 55.41, H 5.12, N 6.51, S 7.49.

*1-[5,6-Dideoxy-6-(*p*-toluenesulfonyl)-β-D-*erythro*-hex-4(Z)-enofuranosyl]uracil* **6**

Method A

A solution of **5** (100 mg, 0.25 mmol) in MeOH/H_2O (1:1, 30 mL) was treated with 1 M NaOH/H_2O (1 mL) and stirred at ambient temperature for 8 h (TLC (S3) showed a single slightly more polar product). Dried Dowex 50W-X8 (H^+) resin (0.3 g, 200–400 mesh) was added, stirred for 1 h, filtered, and washed with MeOH (2 × 10 mL). The combined filtrates were evaporated and the residue crystallized (MeOH) to give **6** (71 mg, 71%). Evaporation of the mother liquor and diffusion crystallization (hexane/MeOH) of the residue gave a second crop of **6** (10 mg, 10%); mp 196–197°C (dec.); UV (MeOH) max: 260 nm (ε 10 200), min: 243 nm (ε 8100); MS *m/z* 239 (38, M − Ts), 221 (100), 156 (60), 112 (84), 92 (82). Anal. calcd. for $C_{17}H_{18}N_2O_7S$ (394.4): C 51.77, H 4.60, N 7.10; found: C 51.95, H 4.66, N 7.18.

Method B

A solution of **3** (100 mg, 0.23 mmol) in CF_3CO_2H/H_2O (22:3, 5 mL) was stirred at ~0°C for 25 min, evaporated (<10°C), and coevaporated with EtOH. TLC (S4) of the residue showed three components with R_f 0.8 (**3**, ~40%), 0.48 (**6**, ~35%), and 0.39 (uracil, ~25%), which were separated by column chromatography (MeOH/$CHCl_3$, 1:24). Evaporation of appropriately pooled fractions gave **6** (20 mg, 22%) with identical data.

Extension of the deprotection time to 45 min resulted in formation of additional uracil without complete consumption of **3**.

*1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil* **4**a

To a magnetically stirred solution of **2** (260 mg, 0.6 mmol) in MeOH/H_2O (1:1, 60 mL) was added sodium borohydride (45 mg, 1.2 mmol). TLC (S2, two developments) after 18 h at ambient temperature indicated ~95% conversion to a slightly more polar product. The solution was concentrated to half volume and the residue was partitioned ($CHCl_3/H_2O$). The organic layer was washed with NaCl/H_2O, H_2O, dried ($MgSO_4$), and evaporated to give a foam that was purified by column chromatography ($Me_2CO/CHCl_3$, 1:9). Evaporation of appropriately pooled fractions and diffusion crystallization (hexane/EtOH) gave **4***a* (218 mg, 83%) as an amorphous powder; mp 108–110°C; UV (MeOH) max: 258, 223 nm (ε 10 200, 14 700), min: 238, 212 nm (ε 5900, 12 900); MS *m/z*: 436.1309 (1.2, M^+ = 436.1304), 421.1063 (19, M − CH_3), 325.1106 (89, M − B). Anal. calcd. for $C_{20}H_{24}N_2O_7S$ (436.5): C 55.04, H 5.54, N 6.42, S 7.35; found: C 54.79, H 5.68, N 6.55, S 7.58.

*1-[5,6-Dideoxy-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil* **4**b

A solution of **4***a* (174 mg, 0.4 mmol) in CF_3CO_2H/H_2O (9:1, 8 mL) was stirred at ~0°C for 40 min, evaporated, and coevaporated with EtOH to give an amorphous glass. Column chromatography (MeOH/$CHCl_3$, 1:24) and diffusion crystallization (hexane//EtOAc/MeOH) gave **4***b* (112 mg, 71%); mp 177–179°C; UV (MeOH) max: 260, 224 nm (ε 9300, 14 600), min: 239 nm (ε 6100); MS *m/z*: 284 (5, M − BH), 246 (20), 156 (24), 112 (100). Anal. calcd. for $C_{17}H_{20}N_2O_7S$ (396.4): C 51.51, H 5.09, N 7.07; found: C 51.40, H 5.29, N 7.05.

*1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6,5-methylthio-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil 7(5′R/S)*

A solution of **2** (660 mg, 1.52 mmol) in anhydrous THF (20 mL) was added to a solution of sodium thiomethoxide (128 mg, 1.83 mmol) in anhydrous THF (10 mL) under N_2 and stirring was continued at ambient temperature for 7 h. Acetic acid (0.105 mL, 110 mg,

1.83 mmol) was added, the solution evaporated, and the residue partitioned ($CHCl_3$//$NaHCO_3/H_2O$). The organic layer was washed with $NaCl/H_2O$, dried ($MgSO_4$), evaporated, and the residue diffusion crystallized (hexane/EtOAc) to give **7** (210 mg, 29%, 5′(*R*/*S*) ~19:1) with mp 201–203°C; MS *m/z*: 467 (12, M − CH_3), 327 (100), 279 (82), 157 (91). Purification of the mother liquor by column chromatography ($Me_2CO/CHCl_3$, 1:9) and diffusion crystallization of the residue (hexane/EtOAc), gave **7** (325 mg, 44% 5′(*R*/*S*) ~1:4).

*1-[5,6-Dideoxy-5(*R*)-methylthio-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil {1-[6-deoxy-5-*S*-methyl-5-thio-6-(*p*-toluenesulfonyl)-α-L-talofuranosyl]uracil} **8**(5′R)*

A solution of **7** (150 mg, 0.31 mmol, 5′(*R*/*S*) ~19:1) in CF_3CO_2H/H_2O (9:1, 5 mL) was stirred at ~0°C for 30 min, evaporated, coevaporated with EtOH, and crystallized (EtOH, two crops) to give **8**(5′*R*) (116 mg, 85%) as fine white needles; mp 219–220°C; UV (MeOH) max: 260, 222 nm (ε 10 200, 15 400), min: 240 nm (ε 6100); MS *m/z*: 442 (1, M^+), 358 (24), 287 (93), 239 (72), 271 (58), 221 (100), 155 (52), 113 (66). Anal. calcd. for $C_{18}H_{22}N_2O_7S_2$ (442.5): C 48.86, H 5.01, N 6.33; found: C 48.84, H 5.07, N 6.36.

*1-[5,6-Dideoxy-5(*S*)-methylthio-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil {1-[6-deoxy-5-*S*-methyl-5-thio-6-(*p*-toluenesulfonyl)-β-D-allofuranosyl]uracil} **9**(5′S)*

A solution of **7** (200 mg, 0.41 mmol, 5′(*R*/*S*) ~1:4) in CF_3CO_2H/H_2O (9:1, 5 mL) was stirred at ~0°C for 30 min, evaporated, coevaporated with EtOH, and the resulting brown glass purified on a short silica column ($MeOH/CHCl_3$, 1:24). The residue was crystallized (hexane/EtOH) and recrystallized (MeOH, two crops) to give **9**(5′*S*) (114 mg, 63%) as cream-colored crystals; mp 125–128°C; UV (MeOH) max: 260, 224 nm (ε 9800, 14 500), min: 240 nm (ε 5900); MS *m/z*: 287 (28, M − Ts), 221 (45), 155 (100), 91 (82), 113 (52). Anal. calcd. for $C_{18}H_{22}N_2O_7S_2$ (442.5): C 48.86, H 5.01, N 6.33; found: C 48.71, H 5.19, N 6.42.

*1-[5-Amino-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **10**a(5′R)/**11**a(5′S)*

A solution of **2** (326 mg, 0.75 mmol) in anhydrous MeOH (30 mL) was treated with saturated NH_3/MeOH (30 mL) (or concentrated NH_3/H_2O (2 mL) in EtOH (20 mL)) and stirring was continued at ambient temperature for 4 h. TLC (S2) indicated complete consumption of **2** (R_f 0.53) with formation of more polar components (R_f 0.48 (**3**, minor), R_f 0.16/0.14 (**11***a*/**10***a*, ~1:1)). The reaction mixture was evaporated and subjected to column (80 g, 3.5 × 30 cm) chromatography. Slow elution ($Me_2CO/CHCl_3$, 3:22, 700 mL; followed by $MeOH/CHCl_3$, 1.5:98.5, 1200 mL) and evaporation of appropriately pooled fractions gave **3** (62 mg, 19%), **11***a* (115 mg, 34%), overlapping fractions of **11***a*/**10***a* (37 mg, 11%), and **10***a* (108 mg, 32%). The more rapidly eluted diastereomer was crystallized (MeOH) to give 1-[5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-allofuranosyl]uracil (**11***a*(5′*S*)) (96 mg, 28%); mp 230–231°C; UV (MeOH) max: 224, 258 nm (ε 16 600, 10 800), min: 239, 212 nm (ε 6100, 13 600); MS *m/z*: 436.1175 (2, M − CH_3 [$C_{19}H_{22}N_3O_7S$] = 436.1178), 296.1244 (15, M − Ts), 198.0590 (100, $TsCH_2CHNH_2$); MS (ci, NH_3) *m/z*: 452 (100, M + 1). Anal. calcd. for $C_{20}H_{25}N_3O_7S$ (451.5): C 53.21, H 5.58, N 9.31, S 7.10; found: C 53.26, H 5.58, N 9.26, S 7.14. The more slowly eluted 1-[5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-α-L-talofuranosyl]uracil (**10***a*(5′*R*)) failed to crystallize; UV (MeOH) max: 224, 258 nm (ε 16 000, 10 400), min: 239, 213 nm (ε 6100, 14 000); MS *m/z*: 436.1181 (1.8, M − CH_3 [$C_{19}H_{22}N_3O_7S$] = 436.1178), 296.1247 (13, M − Ts), 198.0592 (100, $TsCH_2CHNH_2$); MS (ci, NH_3) *m/z*: 452 (100, M + 1).

*1-[5(*R*)-Acetamido-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **12**a(5′R) and 1-[5(*S*)-acetamido-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **13**a(5′S)*

A mixture of **10***a*/**11***a* (~1:1, 157 mg, 0.35 mmol) in Ac_2O (1.5 mL) was treated with 4-dimethylaminopyridine (DMAP, 4 mg, 0.032 mmol) and stirred at ambient temperature for 5 h. TLC (S4) indicated complete consumption of **10***a*/**11***a* (R_f ~0.53) with formation of two well-resolved products (R_f 0.57 and 0.49). MeOH (3 mL) was added, the solution stirred for 1 h, evaporated *in vacuo*, and the residue partitioned ($CHCl_3$/($AcOH/H_2O$, 1:99)). The organic phase was washed with $NaHCO_3/H_2O$, $NaCl/H_2O$, dried (Na_2SO_4), evaporated, and the residue subjected to column chromatography ($MeOH/CHCl_3$, 1.5:98.5). Evaporation of sequentially pooled fractions and diffusion crystallization (hexane/EtOAc) gave 1-[5-*N*-acetyl-5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-α-L-talofuranosyl]uracil **12***a*(5′*R*) (81 mg, 47%); mp 110–115 (transition), 164–167°C; UV (MeOH) max: 258, 226 nm (ε 9800, 14 200), min: 240 nm (ε 5800); MS *m/z*: 478.1281 (7.7, M − CH_3 [$C_{21}H_{24}N_3O_8S$] = 478.1284), 338.1353 (11, M − Ts), 198.0589 (100, $TsCH_2CHNH_2$); MS (ci, NH_3) *m/z*: 494 (100, M + 1). Anal. calcd. for $C_{22}H_{27}N_3O_8S$ (493.5): C 53.54, H 5.51, N 8.51; found: C 53.61, H 5.58, N 8.49.

Further elution gave 1-[5-*N*-acetyl-5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-6-(*p*-toluenesulfonyl)-β-D-allofuranosyl]uracil **13***a*-(5′*S*) (79 mg, 46%); MS *m/z*: 493.1505 (0.3, M^+ [$C_{22}H_{27}N_3O_8S$] = 493.1518), 478.1279 (8, M − CH_3), 338.1351 (7, M − Ts), 198.0586 (100, $TsCH_2CHNH_2$). It was confirmed that acetylation of a purified sample of **11***a*(5′*S*) gave **13***a*(5′*S*).

*1-[5(R)-Amino-5,6-dideoxy-6-(p-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **10**b(5′R) and 1-[5(S)-amino-5,6-dideoxy-6-(p-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **11**b(5′S)*

Solutions of **10***a*(5′*R*) (55 mg, 0.12 mmol) and **11***a*(5′*S*) (60 mg, 0.13 mmol) in CF_3CO_2H/H_2O (9:1, 5 mL) were stirred at ~0°C for 7 h and 8 h, respectively. Evaporation and coevaporation (EtOH) gave amorphous products that were purified on dry-packed silica columns (S3) to give 1-[5-amino-5,6-dideoxy-6-(*p*-toluenesulfonyl)-α-L-talofuranosyl]uracil **10***b*(5′*R*) (41 mg, 83%) (MeOH/EtOAc); mp 196–198°C; UV (MeOH) max: 260, 224 nm (ε 10 200, 15 200), min: 240 nm (ε 5000); MS *m/z*: 394 (1, M − NH_3), 264 (2), 170 (36), 156 (18), 155 (20), 112 (52), 92 (100). Anal. calcd. for $C_{17}H_{21}N_3O_7S$ (411.4): C 49.63, H 5.14, N 10.21; found: C 49.53, H 5.14, N 10.11. The diffusion crystallized (hexane/MeOH/EtOAc) 1-[5-amino-5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-allofuranosyl]uracil **11***b*(5′*S*) (39 mg, 73%) had mp 203–206°C (dec.); UV (MeOH) max: 260, 224 nm (ε 9900, 15 100) min: 240 nm (ε 4900); MS *m/z*: 394 (1, M − NH_3), 264 (5), 239 (6), 198 (56), 156 (55), 112 (82), 92 (100). Anal. calcd. for $C_{17}H_{21}N_3O_7S$ (411.4): C 49.63, H 5.14, N 10.21; found: C 49.86, H 5.29, N 10.04.

*1-[5(R)-Acetamido-5,6-dideoxy-6-(p-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **12**b(5′R) and 1-[5(S)-acetamido-5,6-dideoxy-6-(p-toluenesulfonyl)-β-D-ribo-hexofuranosyl]uracil **13**b(5′S)*

Solutions of **12***a*(5′*R*) (65 mg, 0.13 mmol) and **13***a*(5′*S*) (60 mg, 0.12 mmol) in CF_3CO_2H/H_2O (9:1, 5 mL) were stirred at ~0°C for 3 h and 2 h, respectively. Evaporation and coevaporation (EtOH) gave amorphous products that were diffusion crystallized to give 1-[5-*N*-acetyl-5-amino-5,6-dideoxy-6-(*p*-toluenesulfonyl)-α-L-talofuranosyl]uracil **12***b*(5′*R*) (48 mg, 88%, hexane/MeOH/EtOAc); mp 259–260°C (dec.); UV (MeOH) max: 260, 226 nm (ε 9700, 14 100), min: 241 nm (ε 5100); MS *m/z*: 453 (2, M^+), 342 (11), 240 (31), 198 (94), 156 (38), 112 (100). Anal. calcd. for $C_{19}H_{23}N_3O_8S$ (453.5): C 50.33, H 5.11, N 9.27; found: C 50.13, H 5.05, N 9.05. For the X-ray study, this product was recrystallized (MeOH) to give near cubic crystals with mp 261–262°C. The 1-[5-*N*-acetyl-5-amino-5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-allofuranosyl]uracil (**13***b*(5′*S*)) (37 mg, 68%, MeOH two crops) had mp 166–169°C; UV (MeOH) max: 260, 224 nm (ε 9800, 14 500), min: 240 nm (ε 5100); MS *m/z*: 342 (15, M − B), 240 (22), 198 (42), 155 (32), 112 (100), 92 (78). Anal. calcd. for $C_{19}H_{23}N_3O_8S{\cdot}0.5H_2O$ (462.5): C 49.34, H 5.23, N 9.09; found: C 49.25, H 5.49, N 8.96.

*Deacetylation of **13**b(5′S) to **11**b(5′S)*

A solution of **13***b*(5′*S*) (45 mg, 0.1 mmol) in MeOH (0.5 mL) was treated with 1 M HCl/H_2O (4 mL) and heated at ~90°C for 30 h. The reaction mixture was cooled, neutralized to pH ~7 with solid

$NaHCO_3$, and evaporated. The residue was extracted (hot MeOH) and purified by column chromatography (S3) to give **11***b*(5′*S*) (25 mg, 61%) with data identical to those of the product of the reaction of **11***a*(5′*S*) → **11***b*(5′*S*) described above.

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1. (*a*) R. J. SUHADOLNIK. Nucleoside antibiotics. Wiley–Interscience, New York. 1970; (*b*) pp. 218–234; (*c*) pp. 115–119.
2. (*a*) R. J. SUHADOLNIK. Nucleosides as biological probes. Wiley–Interscience, New York. 1979; (*b*) pp. 30–37, 43–45; (*c*) pp. 279–281.
3. (*a*) F. SCHLENK. Adv. Enzymol. Relat. Areas Mol. Biol. **54**, 195 (1983); (*b*) R. W. MYERS and R. H. ABELES. J. Biol. Chem. **265**, 16913 (1990).
4. J. G. NIEDZWICKI, M. H. EL KOUNI, S. H. CHU, and S. CHA. Biochem. Pharmacol. **32**, 399 (1983).
5. J. G. MOFFATT. *In* Nucleoside analogues: chemistry, biology, and medical applications. *Edited by* R. T. Walter, E. De Clercq, and F. Eckstein. Plenum Press, New York. 1979. pp. 71–164.
6. T. UEDA. *In* Chemistry of nucleosides and nucleotides. Vol. 1. *Edited by* L. B. Townsend. Plenum Press, New York. 1988. pp. 1–112.
7. G. H. JONES and J. G. MOFFATT. J. Am. Chem. Soc. **90**, 5337 (1968).
8. P. HOWGATE, A. S. JONES, and J. R. TITTENSOR. Carbohydr. Res. **12**, 403 (1970).
9. J. A. MONTGOMERY, A. G. LASETER, and K. HEWSON. J. Heterocycl. Chem. **11**, 211 (1974).
10. R. A. SHARMA and M. BOBEK. J. Org. Chem. **43**, 367 (1978).
11. J. M. J. TRONCHET and M. J. VALERO. Helv. Chim. Acta, **62**, 2788 (1979).
12. J.-D. ZHANG and L.-H. ZHANG. Synthesis, 909 (1990).
13. S. F. WNUK and M. J. ROBINS. Can. J. Chem. **69**, 334 (1991).
14. O. R. MARTIN, F. E. KHAMIS, H. A. EL-SHENAWY, and S. P. RAO. Tetrahedron Lett. **30**, 6139 (1989).
15. (*a*) D. H. R. BARTON, S. D. GÉRO, B. QUICLET-SIRE, and M. SAMADI. J. Chem. Soc. Chem. Commun. 1000 (1989); (*b*) D. H. R. BARTON, S. D. GÉRO, B. QUICLET-SIRE, and M. SAMADI. J. Chem. Soc. Chem. Commun. 1372 (1988); (*c*) D. H. R. BARTON, S. D. GÉRO, B. QUICLET-SIRE, and M. SAMADI. Tetrahedron Lett. **30**, 4969 (1989).
16. J. HIEBL and E. ZBIRAL. Tetrahedron Lett. **31**, 4007 (1990).
17. J.-C. WU, T. PATHAK, W. TONG, J.-M. VIAL, G. REMAUD, and J. CHATTOPADHYAYA. Tetrahedron, **44**, 6705 (1988).
18. J.-C. WU and J. CHATTOPADHYAYA. Tetrahedron, **45**, 4507 (1989).
19. N. S. SIMPKINS. Tetrahedron, **46**, 6951 (1990).
20. K. E. PFITZNER and J. G. MOFFATT. J. Am. Chem. Soc. **87**, 5661 (1965).
21. A. J. SPEZIALE and K. W. RATTS. J. Am. Chem. Soc. **87**, 5603 (1965).
22. A. M. VAN LEUSEN, B. A. REITH, A. J. W. IEDEMA, and J. STRATING. Recl. Trav. Chim. Pays Bas, **91**, 37 (1972).
23. E. J. COREY and M. CHAYKOVSKY. J. Am. Chem. Soc. **87**, 1345 (1965).
24. B. M. TROST, H. C. ARNDT, P. E. STREGE, and T. R. VERHOEVEN. Tetrahedron Lett. **17**, 3477 (1976).
25. A. C. BROWN and L. A. CARPINO. J. Org. Chem. **50**, 1749 (1985).
26. V. PASCALI and A. UMANI-RONCHI. J. Chem. Soc. Chem. Commun. 351 (1973).
27. J. BREMNER, M. JULIA, M. LAUNAY, and J.-P. STACINO. Tetrahedron Lett. **23**, 3265 (1982).
28. M. JULIA, H. LAURON, J.-P. STACINO, J.-N. VERPEAUX, Y. JEANNIN, and Y. DROMZEE. Tetrahedron, **42**, 2475 (1986).
29. M. OCHIAI, T. UKITA, and E. FUJITA. J. Chem. Soc. Chem. Commun. 619 (1983).
30. R. SHAPIRO, R. E. SERVIS, and M. WELCHER. J. Am. Chem. Soc. **92**, 422 (1970).
31. J. P. H. VERHEYDEN and J. G. MOFFATT. J. Am. Chem. Soc. **88**, 5684 (1966).
32. J. R. MCCARTHY, JR., R. K. ROBINS, and M. J. ROBINS. J. Am. Chem. Soc. **90**, 4993 (1968).
33. M. J. ROBINS, R. MENGEL, R. A. JONES, and Y. FOURON. J. Am. Chem. Soc. **98**, 8204 (1976).
34. M. J. ROBINS, M. MACCOSS, S. R. NAIK, and G. RAMANI. *In* Nucleic acid chemistry. Improved and new synthetic procedures, methods and techniques. Vol. 3. *Edited by* L. B. Townsend and R. S. Tipson. Wiley–Interscience, New York. 1986. pp. 58–60.
35. G. M. SHELDRICK. SHELXTL PLUS™ Siemens Analytical X-ray Instruments, Inc., Madison, WI. 1990.
36. J. A. IBERS and W. C. HAMILTON (*Editors*). International tables for X-ray crystallography. Vol. 4. Kynoch Press, Birmingham, England. 1974. p. 99.
37. M. J. ROBINS, F. HANSSKE, S. F. WNUK, and T. KANAI. Can. J. Chem. **69**, 1468 (1991).