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Halo Sugar Nucleosides. 5.[1] Synthesis of Angustmycin A and Some Base Analogues

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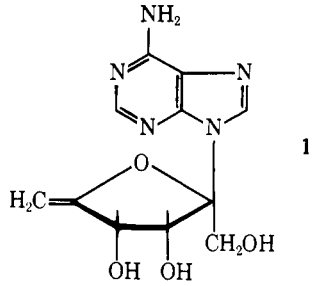
An efficient synthesis of 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**) is described via dehydrohalogenation of 5′-deoxy-5′-iodo-N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (**2c**) with either silver fluoride in pyridine or with DBN in DMF. The synthesis of 1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl bromide (**9**) was achieved starting with D-fructose via oxidation of the 1,2:4,5-di-*O*-isopropylidene derivative followed by borohydride reduction, acid-catalyzed isomerization to the psicofuranose derivative, and iodination by several different routes. Condensation of **9** with several derivatives of adenine provides the 9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl) nucleosides (**11**) together with lesser amounts of the α anomers **12**. Dehydrohalogenation of **11** followed by deblocking provides a total synthesis of the nucleoside antibiotic angustmycin A (**1**). Related sequences starting with condensations of **9** with cytosine or 3-methoxycarbonyl-1,2,4-triazole lead to the corresponding base analogues of angustmycin A, **16** and **21**. By appropriate manipulation of the intermediates in the above routes, syntheses of the β-D-psicofuranosyl derivatives of cytosine (**25a**) and of 1,2,4-triazole-3-carboxamide (**22**) are also described.

The nucleoside antibiotic angustmycin A,[3] which shows modest antimicrobial[4,6] and antitumor[5] activity, was originally isolated from *S. hygroscopicus* by Yüntsen et al.[6] and an incorrect structure was assigned.[7] Subsequently the antibiotic decoyinine was shown to be identical with angustmycin A, and, based upon spectroscopic evidence, the correct structure was shown to be 9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**1**).[8]



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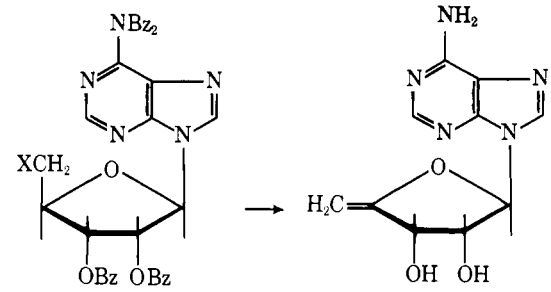
The structure of **1** is interesting since it is the only naturally occurring enofuranosyl nucleoside and at the same time is, together with the closely related antibiotic psicofuranine,[8] one of the few examples of nucleosides derived from ketose sugars. Considerable work has already appeared concerning the synthesis of ketohexose nucleosides derived from psicose,[9] fructose,[10] and sorbose,[11] and the structure of angustmycin A stimulated our own interest in the synthesis of 4′,5′-unsaturated ribonucleosides.[12] During the course of our work the conversion of psicofuranine to angustmycin A was described by McCarthy et al.[13] The key to this synthesis was the ingenious use of an orthoformate ester for the simultaneous and selective blocking of the 1′-, 3′-, and 4′-hydroxyl groups in the intact psicofuranine molecule. In the present paper we describe a totally different approach to the synthesis of angustmycin A in which the problem of selective protection is resolved in a key carbohydrate intermediate that can be efficiently condensed with a variety of heterocyclic bases, thus allowing the synthesis of analogues of **1**.

As a prelude to the synthesis of **1** itself we have first examined the synthesis of the somewhat simpler 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**). The lability of pent-4-enofuranosides toward acids precluded the use of the 2′,3′-*O*-isopropylidene group for protection of the adenosine sugar moiety. Subsequently, however, it was shown that the 2′,3′-*O*-ethoxymethylidene group could be removed without extensive hydrolysis of the vinyl ether.[13] We preferred to use base labile protecting groups for this purpose, and accordingly fully benzoylated 5′-*O*-trityladenosine giving the N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoate (**2a**)[14] in essentially quantitative yield. This compound was originally considered to be the N^1,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyl derivative but recent work has shown that fully benzoylated adenosine derivatives have both *N*-benzoyl groups at N^6.[15] Subsequent detritylation of **2a** with hydrogen chloride in chloroform then gave crystalline N^6,N^6,$O^{2'}$,O^3-tetrabenzoyladenosine (**2b**) in 86% yield without need for chromatography (cf. ref 14). Iodination of **2b** was readily achieved using methyltriphenoxyphosphonium iodide[16] which gave the crystalline 5′-iodo derivative **2c** in 87% yield after only a 10-min reaction at room temperature. It should be noted that attempted iodination of 2′,3′-*O*-isopropylideneadenosine with this reagent gave only an N^3,5′-cyclonucleoside.[16] Acylation of the adenine ring, however, is known to substantially reduce the tendency of adenosine derivatives to form such cyclonucleosides.[17] Treatment of **2c** with silver fluoride in pyridine, a reaction used extensively in the pyrimidine series,[12] was only modestly successful in effecting dehydrohalogenation. Following debenzoylation with methanolic ammonium hydroxide and ion exchange chromatography on a basic resin[18] crystalline **3** was obtained, but only in 15% overall yield. Much better results were obtained



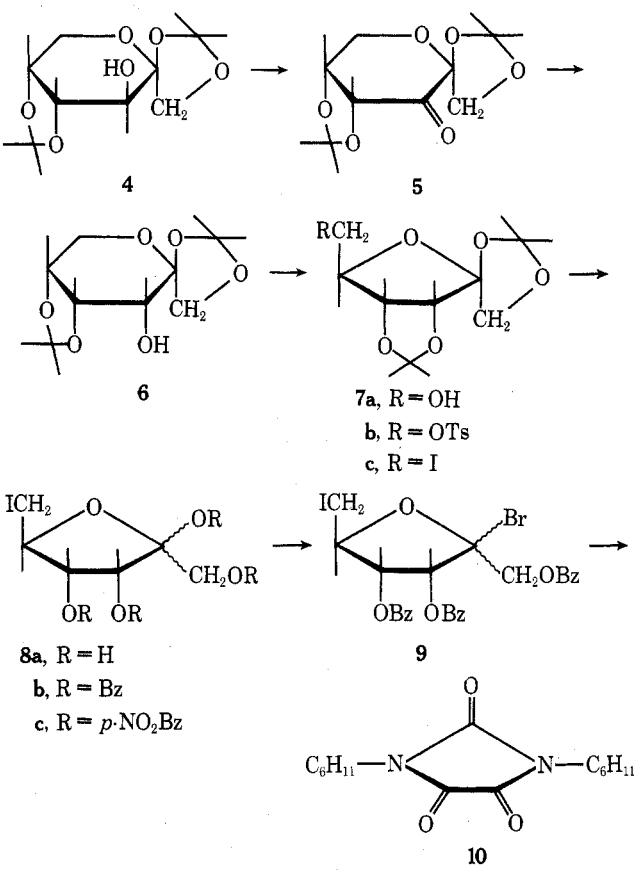
2a, X = Tr
b, X = OH
c, X = I

3

by treatment of **2c** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dimethylformamide, the overall conversion to crystalline **3** in this case being 72%. It may be noted that **3** has also been detected as a product from the treatment of coenzyme B_{12} with alkali.[19] The successful synthesis of **3** described above encouraged us to proceed with the planned synthesis of angustmycin A.

Our objective was the synthesis of a derivative of 6-deoxy-6-iodo-D-psicofuranose (e.g., **9**) suitable for condensation with a variety of heterocyclic bases, followed by dehydrohalogenation. While 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (**7a**) can be prepared via the diazo ketone derived from 2,3,4,5-tetra-*O*-acetylribonic acid chloride[9c,20] followed by mild acetonation,[21] a more convenient route involves the oxidation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**4**)[22] to the 2,3-hexodiulose **5**[23] followed by stereoselective reduction to 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**6**)[23] and acid-catalyzed acetal equilibration to the furanose form **7a**.[21b,23b,c,24] We have independently developed this route (**4** → **7a**) although the conditions used for the various steps differ somewhat from those that have been reported. In particular, we have used perchloric acid as the catalyst during preparation of **4** and obtained the pure, crystalline compound in 38% yield on a kilogram scale. The use of perchloric acid gives **4** and its 2,3:4,5-di-*O*-isopropylidene isomer in a ratio of roughly 3:1 by GLC analysis, but homogeneous **4** can be readily obtained by crystallization. The oxidation of **4** to **5** has been examined by others using dimethyl sulfoxide–acetic anhydride[23a,b,d] in yields of 44–70%, and using ruthenium tetroxide.[23c,d] We have done this oxidation using dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of pyridinium phosphate[25] and have isolated crystalline **5** in 85% yield on a 0.9-mol scale. It is interesting to note that a crystalline by-product of this reaction was isolated in low yield and identified as 1,3-dicyclohexylparabanic acid (**10**).[26] This compound must arise from an unrecognized condensation of dicyclohexylcarbodiimide with oxalic acid, a step that is used to destroy excess carbodiimide.[27] Reduction of the ketone **5** has been examined under a variety of conditions,[23] and we find the use of sodium borohydride in ethanol to be highly stereoselective, affording pure 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranoside (**6**) in 94% yield. Isomerization of **6** to its furanose isomer **7a** was accomplished using either perchloric or sulfuric acid in acetone and 2,2-dimethoxypropane. While **7a** could be isolated in 62% yield with 98% purity (GLC) by distillation, its crystallization was accomplished only with substantial losses and we have usually preferred to combine this step with suitable derivatization of the 6-hydroxyl group in order to handle crystalline compounds.

Our goal was the preparation of a 6-deoxy-6-iodo-D-psicofuranose derivative (e.g., **9**) which could be condensed with a variety of heterocyclic bases and then dehydrohalogenated to introduce the desired 5′,6′-olefinic function. With this objective in mind we examined a number of methods for the conversion of **7a** into the 6-iodo derivative **7c**. Direct iodination of pure **7a** using methyltriphenoxyphosphonium iodide[16] gave crystalline **7c** in 57% yield but required chromatography on silicic acid. Alternatively, iodination with this same reagent of the crude reaction product from acetonide equilibration of **6** and without purification of **7a** gave, after chromatography, crystalline **7c** in an overall yield of 44%. Alternatively, pure **7a** was converted to the 6-*O*-tosyl derivative (**7b**) and then treated with sodium iodide in dimethylformamide giving readily crystalline **7c** in overall yield of 59% from **6**. A similar sequence using the crude acetonide equilibration mixture led to **7c** in 57% yield from **6**. Finally, the best overall conversion of **6** to **7c** involved iodination of the crude acid equilibrated mixture, containing principally **7a**, with triphenylphosphine and iodine,[28] a reaction giving crystalline **7c** in 67% yield



without any need for chromatography. Thus the key intermediate (**7c**) was obtained in an overall yield of 20% from fructose and is, hence, readily available.

Hydrolysis of the isopropylidene functions from **7a** was readily accomplished using an acidic ion exchange resin giving crystalline 6-deoxy-6-iodo-D-psicofuranose (**8a**) in 74% yield. This compound exhibited a sharp melting point but its NMR spectrum in Me_2SO-d_6–D_2O did not permit an assignment of anomeric configuration. Since the intermediates **4**–**7c** all showed significant negative rotations while **8a** had $[\alpha]^{23}D$ 14.6°, it is tempting to suggest that **8a** is, in fact, the α anomer. It is interesting to note that we were unable to observe any mutarotation in water, or in a mixture of water and pyridine. Benzoylation of **8a** readily gave the tetrabenzoate **8b** in 82% yield as a roughly 2:1 mixture of anomers as judged by ^1H NMR analysis. This mixture could not be further resolved by chromatography on silicic acid and attempts to isolate a single anomer by crystallization were unsuccessful. On the other hand, the tetra-*O*-*p*-nitrobenzoyl derivative **8c** could be resolved into its anomers by chromatography and the major isomer was isolated in crystalline form in 59% yield.

Since the anomeric configuration of **8** was not significant for further work, the readily available mixed benzoates (**8b**) were converted to 1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl bromide (**9**) by reaction with anhydrous hydrogen bromide in methylene chloride. Without any attempt at purification, **9** was condensed with several different adenine derivatives. Firstly, N^6-hexanoyladenine[29] was treated with **9** in the presence of stannic chloride and an excess of mercuric cyanide, a mixture that was previously found to be effective as part of another project.[30] The use of N^6-octanoyladenine in order to increase the solubility of adenine has previously been reported.[31] By chromatography on silicic acid N^6-hexanoyl-9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)adenine (**11a**) and its α anomer (**12a**) were isolated in yields of 46 and 12%, respectively. It should be noted that condensations of perbenzoylated hexulofuranosyl bromides could, in principle, condense to give either α or β nucleosides

Table I. 100-MHz NMR Chemical Shifts (ppm)

Cpd	Solvent[a]	C_1 H_a	C_1 H_b	C_3 H	C_4 H	C_5 H	C_6 H_a	C_6 H_b	Other
1	P/D_2O	4.85 (d)	5.06 (d)	5.71 (d)	4.94 (m)		4.71 (dd)	4.82 (dd)	8.42, 8.44 (s, 1, C_2 H, C_8 H)
2a[b]	C	6.52 (d, C_1, H)		6.40 (dd)	6.11 (dd)	4.60 (dt)	3.62 (d)		8.30, 8.57 (s, 1, C_2 H, C_8 H), 7.1–8.1 (m, 35, Ar)
2b[b]	P	7.07 (d, C_1, H)		6.77 (dd)	6.48 (dd)	4.80 (dt)	4.30 (d)		8.78, 9.42 (s, 1, C_2 H, C_8 H), 7.3, 8.0 (m, 20, Ar)
2c[b]	C	6.48 (d, C_1, H)		6.29 (dd)	5.94 (dd)	4.54 (dt)	3.67 (d)		8.43, 8.70 (s, 1, C_2 H, C_8 H), 7.4, 7.9 (m, 20, Ar)
3[b]	D	6.17 (d)		4.85 (ddd)	4.73 (br dd)		4.21 (d)	4.32 (br d)	8.17, 8.38 (s, 1, C_2 H, C_8 H), 5.52, 5.56 (d, 1, OH), 7.32 (s, 2, NH_2)
4	C	3.98 (d)	4.21 (d)	3.68 (br d)	4.10 (m)	4.10 (m)	4.00 (m)	4.17 (m)	1.36, 1.44, 1.51, 1.52 (s, 3, CMe_2)
5	C	3.96 (d)	4.60 (d)		4.72 (d)	4.5 (m)	4.08 (dd)	4.40 (dd)	1.39 (s, 6), 1.44, 1.53 (s, 3, CMe_2)
6	C	4.01 (d)	4.25 (d)	3.73 (dd)	4.42 (dd)	~4 (m)	~4 (m)	~4 (m)	1.37, 1.41, 1.49, 1.54 (s, 3, CMe_2), 2.34 (d, 1, C_3OH)
7a	C	4.02 (d)	4.31 (d)	4.61 (d)	4.88 (dd)	4.25 (m)	5.05 (dd)	5.22 (dd)	1.31, 1.39, 1.43, 1.49 (s, 3, CMe_2)
7b	C	3.98 (d)	4.25 (d)	4.53 (d)	4.67 (d)	3.9–4.3 (m)	3.9–4.3 (m)		1.28, 1.36 (6 H), 1.39 (s, 3, CMe_2), 2.44 (ArMe), 7.31, 7.78 (m, 4, Ar)
7c	P	4.21 (d)	4.46 (d)	4.74 (d)	4.93 (dd)	4.55 (m)	3.49 (ABX)		1.31, 1.45 (6 H), 1.56 (s, 3, CMe_2)
8b[c]	C	4.53 (d)	4.67 (d)	5.71 (d)	5.50 (dd)	4.44 (dd)	3.50 (ABX)		7.2–8.1 (m, 20, Ar)
8b[d]	C	4.50 (d)	4.81 (d)	5.90 (d)	5.77 (dd)	4.5 (m)	3.50 (ABX)		7.2–8.1 (m, 20, Ar)
8c	C	4.98 (d)	5.43 (d)	6.36 (d)	5.92 (dd)	4.70 (ddd)	3.55 (d)		7.9–8.3 (m, 16, Ar)
11a	C	5.13 (d)	5.39 (d)	6.94 (d)	5.68 (dd)	4.73 (ddd)	3.51 (dd)	3.63 (dd)	8.55, 8.63 (s, 1, C_2 H, C_8 H), 0.8–1.9 (m, 9, Aliph), 2.90 (t, 2, $COCH_2$), 7.2–8.1 m, 15, Ar)
11b	C	5.17 (d)	5.44 (d)	6.97 (d)	5.70 (dd)	4.72 (ddd)	3.54 (dd)	3.66 (dd)	8.63 (s, 2, C_2 H, C_8 H), 7.2–8.1 (m, 20, Ar), 9.27 (s, 1, NH)
11c	C	5.10 (d)	5.35 (d)	7.01 (d)	5.69 (dd)	4.70 (ddd)	3.49 (dd)	3.62 (dd)	8.19, 8.37 (s, 1, C_2 H, C_8 H)
12a	C	5.17 (d)	5.35 (d)	6.51 (d)	5.85 (dd)	4.82 (ddd)	3.43 (dd)	3.54 (dd)	8.19, 8.55 (s, 1, C_2 H, C_8 H), 0.8–1.9 (m, 9, aliph), 2.83 (t, 2, $COCH_2$), 9.05 (s, 1, NH)
12c	C	5.12 (d)	5.32 (d)	6.49 (d)	5.83 (dd)	4.74 (ddd)	3.42 (dd)	3.54 (dd)	7.85, 8.28 (s, 1, C_2 H, C_8 H), 7.1–8.15 (m, 15, Ar), 5.68 (s, 2, NH_2)
13	P/D_2O	4.50 (d)	4.98 (d)	5.24 (d)	5.47 (m)		4.67 (dd)	4.80 (dd)	8.50, 8.59 (s, 1, C_2 H, C_8 H)
14	P/D_2O	3.72 (d)	5.13 (d)	5.19 (d)	4.83 (d)	4.69 (br s)	3.84 (br s)		8.36, 8.50 (s, 1, C_2 H, C_8 H)
15a	C	4.98 (d)	5.28 (d)	6.10 (d)	5.65 (dd)	4.57 (ddd)	3.37 (dd)	3.54 (dd)	5.95 (d, 1, C_5 H), 7.94 (d, 1, C_6 H), 7.1–8.0 (m, 15, Ar)
15b	C	5.06 (d)	5.36 (d)	6.50 (d)	5.62 (dd)	4.58 (ddd)	3.37 (dd)	3.55 (dd)	2.21 (s, 3, NAc), 8.35 (d, 1, C_6 H), 7.2–8.1 (m, 16, Ar and C_5H)
16	P/D_2O	4.67 (d)	5.22 (d)	5.54 (d)	4.8 (m)		4.64 (dd)	4.77 (dd)	6.02 (C_5 H), 7.83 (C_6 H), 3.58 (s, 1.5, MeOH)
17	C	7.57 (d)		6.74 (dd)	5.50 (dd)	4.55 (m)	3.41 (dd)	3.55 (dd)	7.1–8.0 (m, 15, Ar)
18a	C	4.84 (d)	5.37 (d)	6.46 (d)	5.65 (dd)	4.65 (ddd)	3.47 (dd)	3.59 (dd)	3.96 (s, 3, OMe), 8.75 (s, 1, C_5 H), 7.2–8.05 (m, 15, Ar)
18b	C	4.85 (d)	5.39 (d)	6.40 (d)	5.80 (dd)	4.89 (m)	3.79 (dd)	3.98 (dd)	3.95 (s, 3, OMe), 8.70 (s, 1, C_5 H), 7.2–8.05 (m, 15, Ar)
18c	C	4.80 (d)	5.30 (d)	6.52 (d)	5.74 (dd)	4.8 (m)	4.31 (dd)	4.47 (dd)	1.96 (s, 3, OAc), 3.95 (s, 3, OMe), 8.64 (s, 1, C_5 H), 7.1–8.1 (m, 15, Ar)
19	C	4.94 (d)	5.67 (d)	7.14 (d)	5.53 (dd)	4.68 (ddd)	3.23 (dd)	3.44 (dd)	4.04 (s, 3, OMe), 7.97 (s, 1, C_5 H), 7.1–8.05 (m, 15, Ar)
20	C	4.88 (d)	5.25 (d)	6.52 (d)	6.13 (ddd)		4.56 (dd)	4.90 (dd)	3.95 (s, 3, OMe), 8.56 (s, 1, C_5 H), 7.1–8.0 (m, 15, Ar)
21	P/D_2O	4.84 (s)		5.40 (d)	5.17 (ddd)		4.66 (dd)	4.78 (dd)	9.10 (s, 1, C_5 H)
22	P/D_2O	4.79 (br s)		5.32 (d)	4.79 (m)	4.79 (m)	4.10 (dd)	4.32 (dd)	9.41 (s, 1, C_5 H)
23	C	4.06 (d)	4.31 (d)	4.66 (d)	4.83 (d)	4.42 (m)	4.42 (m)	4.42 (m)	1.35 (s, 6, CMe_2), 1.43, 1.46 (s, 3, CMe_2), 7.45 (m, 3, Ar), 8.05 (dd, 2, Ar)
24b[c]	C	4.90 (d)	5.34 (d)	6.31 (d)	6.06 (dd)	4.85 (m)	4.60 (dd)	4.85 (m)	6.9–8.5 (m, 25, Ar)
25a	C	5.01 (d)	5.29 (d)	6.63 (d)	5.82 (dd)	4.8 (m)	4.47 (dd)	4.73 (dd)	5.71 (d, 1, C_5 H), 7.1–8.1 (m, 2, Ar and C_6 H)
25b	P/D_2O	3.75–4.1 (m)		4.50 (d)	3.4 (m)	3.9 (m)	3.3–3.6 (m)		5.63 (d, 1, C_5 H), 7.90 (d, 1, C_6 H)

[a] Solvents are designated as C ($CDCl_3$), P (pyridine-d_5), D (Me_2SO-d_6). [b] Compounds **2** and **3** are numbered as though they were β-D-psicofuranosides. Thus the normal $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'a}$ and $C_{5'b}$ protons are referred to in this table as $C_{3'}$ H, $C_{4'}$ H, $C_{5'}$ H, $C_{6'a}$ H and $C_{6'b}$ H, respectively. [c] Major isomer. [d] Minor isomer.

Table II. First-Order Coupling Constants (Hz)

Compd	$J_{1a,1b}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	Other
1	12	4.5				1.5	$J_{4,6a} = 1.5$, $J_{4,6b} \sim 0.5$
2a	$J_{1',2'} = 5.5$	5.5	4	4	4	0	
2b	$J_{1',2'} = 6$	6	3	3	3	0	
2c	$J_{1',2'} = 5.5$	5.5	5	5	5	0	
3	$J_{1',2'} = 5$	5				2	$J_{3',5'} \sim 0.5$, $J_{H,OH} = 5$
4	9	*a*	*a*	*a*	*a*	12	$J_{H,OH} = 5$
5	10		5.5	1.5	2	15	
6	9	4	6.5	*a*	*a*	*a*	$J_{H,OH} = 6.5$
7a	10	6	1	3.5	2.5	12.5	
7b	10	6	0	*a*	*a*	*a*	
7c	10	6	1	*a*	*a*	*a*	
8b[b]	12	6.5	3.5	4	4	*a*	
8b[c]	11.5	4.5	6.0	*a*	*a*	*a*	
8c	12	5	7	5	5	0	
11a	12	5.5	5.5	5	5	12	
11b	12	6	6	4	4	12	
11c	12	5.5	5.5	5	5	12	
12a	12	5	5	5	5	12	
12c	12	5.5	5.5	5	5	12	
13	12	5				1.5	$J_{4,6a} = 1.5$, $J_{4,6b} \sim 0.5$
14	10.5	6	0	~1	~1	0	
15a	12	6	6	5	5	12	$J_{5,6(\text{pyrimidine})} = 7.5$
15b	12	6	6	5	5	11	$J_{5,6(\text{pyrimidine})} = 7.5$
16	11.5	5				2	$J_{4,6a} = 1.5$, $J_{4,6b} =$ (a)
17		6	7	5.5	5	11	$J_{1,3} = 1.5$
18a	12	5.5	5	5	5	13	
18b	12	5.5	5.5	3	*a*	12	
18c	11.5	5	6	4	3	12	
19	12	5	7	6	5	11	
20	12	5.5				3	$J_{4,6a} = 1.5$, $J_{4,6b} = 1.5$
21	0	5				2	$J_{4,6a} = 2$, $J_{4,6b} = 2$
22	*a*	4	*a*	3	2	12	
23	10	5.5	0	*a*	*a*	*a*	
24b[b]	11.5	4.5	7	3	*a*	11	
25a	12	5.5	5.5	3.5	3	12	$J_{5,6(\text{pyrimidine})} = 7.5$
25b	*a*	4.5	*a*	*a*	*a*	*a*	$J_{5,6(\text{pyrimidine})} = 7.5$

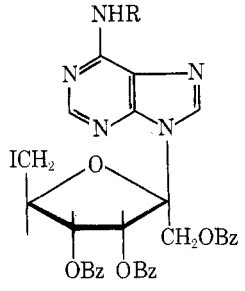
[a] Unresolved. [b] Major isomer. [c] Minor isomer.

since the relative degree of anchiomeric participation by the 1-*O*-benzoyl and 3-*O*-benzoyl groups is uncertain. In such furanose systems it has been found that the major product is, in fact, the anomer with a trans disposition to the 3-*O*-benzoate, indicating the predominant formation of a 2,3-*O*-benzoxoninium ion.[32] The absence of an anomeric proton in the resulting nucleosides makes the definitive assignment of configuration rather difficult and an examination of the ^{1}H NMR spectra of **11a** and **12a** (see Tables I and II) shows that the only significant differences lie in the chemical shifts of $C_{3'}$H and of one of the adenine ring protons. Unequivocal assignment of stereochemistry is, however, possible from subsequent transformations described below. It is interesting to note that the patterns for the benzoyl protons in **11a** and **12a** also differ markedly. Thus, in the major, β isomer (**11a**) the 15 aromatic protons appear as two groups of multiplets, the nine meta and para protons at 7.2–7.65 ppm and the six ortho protons at 7.7–8.1 ppm. In the α anomer (**12a**), however, 13 protons appear in the 7.0–7.65-ppm range and only two appear as a clean doublet of doublets ($J_{ortho} = 7.5$, $J_{meta} = 1.5$ Hz) at 8.04 ppm. Clearly, a single benzoyl group exists in an environment distinctly different from the other two, a situation that is compatible with the $C_{1'}$-*O*-benzoyl in the α anomer (**12a**). Alternatively, **9** was condensed with N^6-benzoylchloromercuriadenine[33] and, following chromatography on silicic acid, the β-psicofuranosyl derivative (**11b**) was isolated in 49% yield. The α nucleoside **12b** was not isolated. In this case the β configuration was apparent both from the conversion of **11b** to angustmycin A and from its NMR spectrum, the sugar portion of which was essentially identical with that of **11a**. The condensation of **9** with unsilylated adenine in the presence of stannic chloride and mercuric cyanide in acetonitrile was less efficient and led to the isolation of the β (**11c**) and α (**12c**) nucleosides in yields of 21 and 7%, respectively. In this reaction the adenine dissolved instantly upon addition of the stannic chloride, and while the yields are somewhat low, the direct formation of the *N*-glycoside from unprotected adenine is noteworthy. Once again, a 0.5-ppm downfield shift of the $C_{3'}$ proton in the β isomer and the presence of only two downfield benzoyl protons in the α anomer (**12c**) were the only significant differences in the NMR spectra of **11c** and **12c**. Presumably this consistent chemical shift difference for $C_{3'}$H is the consequence of not readily predictable differences in the anisotropic effects of the adjacent adenine or benzoyloxymethyl substituents. Some analogy for the effects of the heterocyclic ring on the chemical shift of $C_{4'}$H comes from an examination of the NMR spectra of the α and β anomers of $N^6,O^{2'},O^{3'},O^{5'}$-tetrabenzoyladenosine.[34] In the β-adenosine derivative $C_{1'}$ H and $C_{2'}$ H appeared at 5.92 ($J_{1',2'} = 4.5$ Hz) and 5.80 ppm ($J_{2',3'} = 5.5$ Hz), respectively, while the α anomer showed these protons at 6.42 ($J_{1',2'} = 5.5$ Hz) and 5.64 ppm ($J_{2',3'} = 5.5$ Hz). The deshielding of $C_{1'}$ H in the α anomer is well known[35] and, while the deshielding of $C_{2'}$ H (equivalent to $C_{3'}$ H in **11**) in the β anomer is smaller than that shown upon comparison of **11** and **12**, the shift is in the same direction.

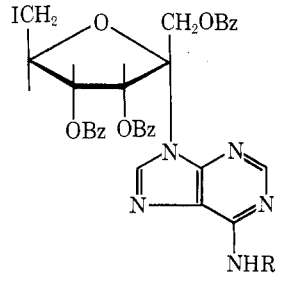
The dehydrohalogenation of **11** and **12** was first investigated using DBN. Treatment of **11b** with DBN in benzene under reflux for 45 min readily gave an olefin as shown by a positive test with dilute potassium permanganate spray on TLC plates. Following debenzoylation with methanolic ammonium hy-

droxide and chromatography on a column of Bio-Rad AG1 (X2) resin in the hydroxide form,[18] crystalline 9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**1**) was isolated in 48% yield as the hemimethanolate that had an identical melting point, mixture melting point, NMR spectrum, chromatographic mobility, and antimicrobial activity[4] with an authentic sample of decoyinine (angustmycin A) obtained through the courtesy of the Upjohn Co. Similar treatment of the α anomer **19a** with DBN in dimethylformamide at room temperature gave crystalline 9-(6-deoxy-α-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**13**), the α anomer of angustmycin A, in 64% yield. The structure of **13** was apparent from its NMR spectrum (see Tables I and II), which was similar to that of **1** and clearly showed the presence of the 5′,6′ olefin.

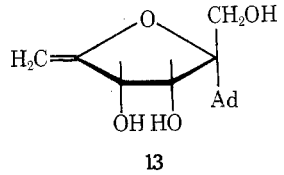
Alternatively, dehydrohalogenation and deacylation of **11a** could be efficiently achieved through treatment with methanolic sodium methoxide. In this case the product was purified by chromatography on silicic acid followed by crystallization from methanol giving pure **1** in 60% yield. It is interesting to note than an analytical sample crystallized from water was obtained in a nonsolvated form with mp 183.5–185 °C. Most previous reports on this substance have led to solvates, although nonsolvated decoyinine with mp 183–186 °C has been described in the patent literature.[36] Similar treatment of the α anomer **12a** with sodium methoxide led to the formation of two major products, the more abundant one of which did not contain an olefin as demonstrated by a negative test with permanganate spray. By chromatography on silicic acid these two substances were isolated in pure form. The minor component, isolated in crystalline form in only 13% yield, was identical with the α-angustmycin A (**13**) described above. The major crystalline component, isolated in 38% yield, was shown to have the same empirical formula as **13** but its NMR spectrum clearly confirmed that it was not an olefin. It did, however, give a positive test with the periodate–benzidine spray,[37] indicating the presence of a vicinal diol. While the NMR spectrum of this compound showed the usual magnetic nonequivalence of the $C_{1'}$ protons, the $C_{6'}$ protons were equivalent and appeared as a slightly broadened two-proton singlet (half-band width 3 Hz) at 3.84 ppm indicating very small coupling to $C_{5'}$ H ($J_{5',6'} \sim 1$ Hz) and a conformation rather different from other compounds in this series. The chemical shift of $C_{6'}$ H_2 suggests the presence of an oxygen substituent and this compound is considered to be 9-(1,6-anhydro-α-D-psicofuranosyl)adenine (**14**) arising from intramolecular displacement of the 6′-iodo function by the $C_{1'}$ oxygen anion. The formation of this substance provides unequivocal confirmation of the α configuration for **12a.**



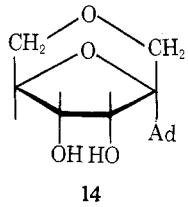
11a, R = $CO(CH_2)_4CH_3$
b, R = Bz
c, R = H



12a, R = $CO(CH_2)_4CH_3$
b, R = Bz
c, R = H



13



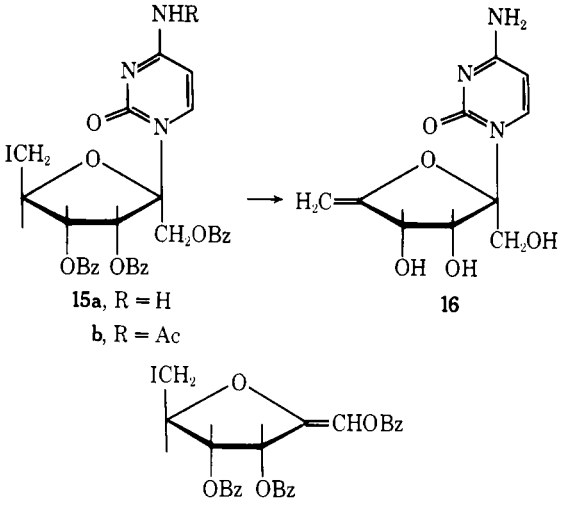
14

The successful synthesis of angustmycin A described above prompted us to also prepare several base analogues. The condensation of **9** with bis(trimethylsilyl)cytosine[38] in benzene in the presence of both stannic chloride and mercuric cyanide gave a crystalline nucleoside considered to be 1-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (**15a**) in 56% yield. This method of condensation is a hybrid of the well-known methods of Wittenburg[39] and of Niedballa and Vorbrüggen.[40] In the absence of stannic chloride the yield of **15a** fell to 17–31% under various conditions and several byproducts were formed. One of these was isolated in low yield by chromatography on silicic acid and proved to be 2,5-anhydro-1,3,5-tri-*O*-benzoyl-2,6-dideoxy-6-iodo-D-*ribo*-hex-1-enitol (**17**). We have not found any close precedent for the formation of such an exocyclic glycal derived from a ketosyl halide. Its structure, however, appears on safe ground from its NMR spectrum, which retains the typical ABX pattern for the iodomethyl group but lacks that of the C_1-*O*-benzoyl function found in other members of this series. In its place one finds only a single, isolated vinyl proton at 7.57 ppm, a position quite compatible with what would be expected for such a substituted enol benzoate. A considerably less efficient condensation between N^4-acetylbis(trimethylsilyl)cytosine[39] and **9** occurred in the presence of mercuric cyanide, **15b** being isolated as a foam in only 20% yield.

Dehydrohalogenation of **15a** and **15b** was achieved using both sodium methoxide and DBN in dimethylformamide. The former method proved to be more efficient and crystalline 1-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)cytosine (**16**), the cytosine analogue of angustmycin A, was obtained in 84% yield. It should be noted that with possession of only a single anomer of **15a,b** the assignment of anomeric configuration is not without difficulty. The chemical shift of $C_{3'}$ H, which was distinctly different in the two adenine anomers, does not appear to provide an unequivocal answer when applied to the cytosine derivatives **15a** and **15b.** The $C_{3'}$ protons in **15a** and **15b** appeared at 6.10 and 6.50 ppm, respectively, these positions being closer to those in the α-adenine derivatives (**12a,b**) than to the desired β anomers. An examination of the NMR spectra of a considerable number of acylated adenine and cytosine nucleosides available in these laboratories shows that $C_{2'}$ H (corresponding to $C_{3'}$ H in the psicofuranosyl derivatives) in the cytosine compounds consistently appears at higher field (~5.4–5.7 ppm for 2′-*O*-acetates and ~5.7–5.9 ppm for 2′-*O*-benzoates) in the cytidine series than in the adenosine counterparts (~5.9–6.1 ppm for acetates and 6.2–6.4 ppm for benzoates). This effect, which is presumably due to the proximity of the C^2 carbonyl group in the pyrimidine ring, makes it difficult to draw any firm conclusions with only a single cytosine anomer available. Also, the NMR spectrum of 2′,3′,5′-tri-*O*-benzoyluridine[41b] was compared with that of its α anomer.[41a] In the β isomer $C_{1'}$ H and $C_{2'}$ H appeared at 6.31 and 5.75 ppm, respectively, while in the α isomer these protons were at 6.61 and 6.11 ppm. Once again, the deshielding of $C_{1'}$ H in the α anomer was expected,[35] but, unlike the adenosine analogues mentioned earlier, $C_{2'}$ H also appeared further downfield in the β isomer. Hence the observed chemical shift of $C_{3'}$ H in the pyrimidine derivatives (**15**) is not unexpected.

Several other, indirect arguments strongly point to the desired β configuration for the cytosine nucleosides. Firstly, it has been established that the condensation of acylated psicofuranosyl bromides with trimethylsilylpyrimidines leads exclusively to β nucleosides[9c] and the presence of the 6-iodo function in **9** would not be expected to greatly change this tendency. Secondly, treatment of **15a** with sodium methoxide gave the crystalline olefin **16** in 84% yield while similar

treatment of the α anomer (**12a**) in the adenine series led predominantly to the 1,6-oxide (**14**). If **15a** had, in fact, the α configuration one would expect the formation of an appreciable amount of a similar anhydro compound, which was not the case. Thirdly, it was hoped that the 5′,6′-olefin function would not play an overriding role in determination of the nature of the ORD spectra of these compounds. If this were the case, then the sign of the Cotton effect would provide direct evidence as to the anomeric configuration.[42] Unfortunately neither **1** nor **13**, the only anomeric pair of exocyclic olefins of value to us, gave well-defined ORD spectra, the intensities being very low. This effect has previously been noted for **1** and **3**.[43] Thus, while the effect of the 4′,5′ olefin is not readily predictable, the well-defined positive Cotton effect shown by **16** and similar to those of cytidine[42] and 1-(β-D-psicofuranosyl)cytosine[9c] offers further tentative support for the assigned β configuration. Various attempts to convert **15a** into the known 1-(β-D-psicofuranosyl)cytosine via displacement of the 6′-iodo function with silver acetate in aqueous acetic acid, with tetramethylammonium acetate in benzene, or with lithium benzoate in hexamethylphosphoramide gave an olefinic product, presumably the tribenzoate of **16**, as the only identifiable new product. This same olefin was also obtained upon attempted conversion of **15a** into an O^2,5′-cyclonucleoside by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene in methylene chloride.[44]



15a, R = H
b, R = Ac

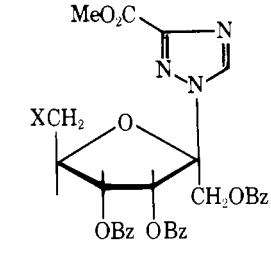
16

17

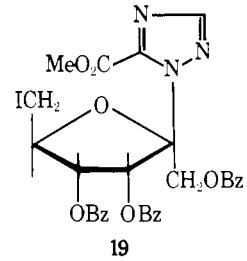
In view of the interesting antiviral properties exhibited by 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,[45] we have also decided to prepare several related psicosyl derivatives. Thus N-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole[45] and **9** were condensed in benzene in the presence of mercuric cyanide at 60 °C. Following chromatography of the products on a column of silicic acid one major and several minor products were isolated as foams that failed to crystallize. The major product, isolated in 49–51% yields, was expected to be the 1-(1,3,4-tri-O-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (**18a**) on the basis of the known preferential glycosidation of the nitrogen distal to the ester function in this triazole,[45,46] and the previously discussed predominant formation of β nucleosides from compounds related to **9**. ^{1}H NMR spectroscopy has recently been shown to provide a facile method for determination of the site of glycosidation in nucleosides derived from 3-methoxycarbonyl-1,2,4-triazole and related compounds.[46] The single triazole proton in the major product from the above reaction appeared at 9.15 ppm in Me_2SO-d_6, a position that assures the site of glycosidation as indicated for **18a**.[46]

Two other products were also isolated from the above reaction. The major of these, isolated as a foam in 19% yield, was isomeric with **18a** and was somewhat less polar. In contrast with **18a**, the NMR spectrum of this substance showed the single triazole proton as a singlet at 8.29 ppm in Me_2SO-d_6, allowing its assignment as the 1-glycosyl-5-methoxycarbonyl-1,2,4-triazole (**19**). There is no precedent for the formation of N^4-glycosyl derivatives from 3-methoxycarbonyl-1,2,4-triazoles. In another experiment, using a different preparation of **9** and giving **19** in 51% yield, a second byproduct was also isolated in 11% yield. The NMR spectrum of this substance was almost identical with that of **18a** except that the $C_{6'}$ protons were displaced 0.3–0.4 ppm downfield, and its mass spectrum clearly showed it to be the 6-chloro derivative **18b**. This compound must have arisen from some displacement of the iodo group during benzoylation of **8a** and points out that care must be taken in establishing the purity of **8b**. We have previously observed similar partial formation of chloro compounds during benzoylation of 5′-iodonucleosides.[47]

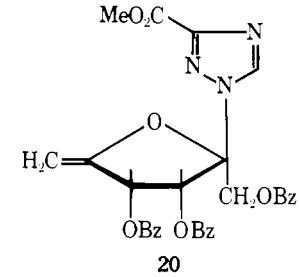
The treatment of **18a** with DBN in dimethylformamide at room temperature led to rapid dehydrohalogenation and crystalline 1-(1,3,4-tri-O-benzoyl-6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-3-methoxycarbonyl-1,2,4-triazole (**20**) was isolated in 58% yield. The NMR spectrum of **20** showed the typical features shown by other furanose exocyclic vinyl ethers,[12] the $C_{6'}$ protons being nonequivalent and showing small geminal (J_{gem} = 3 Hz) and allylic ($J_{4',6'}$ = 1.5 Hz) couplings. Subsequent treatment of **20** with methanolic ammonium hydroxide gave the desired 1-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-1,2,4-triazole-3-carboxamide (**21**) as an analytically pure foam in 85% yield. Once again the NMR spectrum of **21** showed C_5 H at 9.10 ppm in pyridine-d_5, this downfield position further supporting the



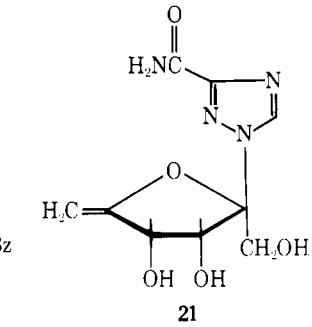
18a, X = I
b, X = Cl
c, X = OAc



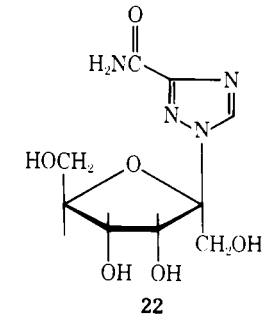
19



20



21



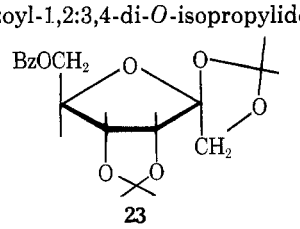
22

assigned site of glycosylation. It is interesting to note that, unlike the other compounds in this series, the $C_{1'}$ protons in **21** appear as a sharp singlet. It is not certain whether this is an indication of actual magnetic equivalence or the result of an AB pattern in which the central lines are adventitiously coincident and the outer lines vanishingly small.

While nucleophilic displacement of the 6-iodo function of **15a** with acetate anion was unsuccessful under a variety of conditions, the comparable displacement starting with **18a** could be achieved. Attempted displacements with lithium acetate or silver acetate in dimethylformamide under a variety of conditions led to fairly clean mixtures of the olefin **20** and the desired 6-*O*-acetyl derivative **18c** with the former usually predominating. Treatment of **18a** with 2 equiv of silver acetate in acetic acid–water (99:1) at 100 °C for 4.5 h, however, led predominantly to the desired acetate, which was isolated in 60% yield by chromatography. Surprisingly, in view of the acidic reaction conditions, the crystalline olefin **20** was also isolated in 5% yield. The structure of **18c** was obvious from its elemental analysis and NMR spectrum. Subsequent treatment of **18c** with methanolic ammonium hydroxide effected conversion to 1-(β-D-psicofuranosyl)-1,2,4-triazole-3-carboxamide (**22**) in 71% yield. The latter compound differs from the antiviral agent virazole (ribavarin)[45] only in the presence of an additional hydroxymethyl group at the anomeric center. This difference, however, is sufficient to render **22** biologically inactive with respect to antiviral, antibacterial, and antitumor activity.[48]

It was also of interest to consider the synthesis of some other β-D-psicofuranosyl nucleosides and the availability of **7a** would appear to provide a convenient intermediate for the preparation of the requisite 1,3,4,6-tetra-*O*-benzoyl-D-psicofuranosyl bromide (**24c**). Related psicofuranosyl halides have previously been prepared from psicose by different routes.[9] Our supply of **7a** was, however, exhausted and hence, in view of the successful nucleophilic displacement of the iodo function of **18a** by acetate, we considered a similar conversion of **8b** to the corresponding 6-*O*-acetyl derivative. This displacement was attempted under a number of conditions using silver acetate in acetic acid and when a reaction did occur, a plethora of unidentified products resulted. The use of tetrabutylammonium acetate in dimethylformamide was quite clean but the product was an olefin that was not further characterized. On the other hand, the 6-iodo diisopropylidene derivative (**7c**) reacted smoothly with lithium benzoate in dimethylformamide at 100 °C giving crystalline 6-*O*-benzoyl-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (**23**) in 90% yield. Acidic hydrolysis of the isopropylidene functions using a sulfonic acid ion exchange resin was essentially quantitative and the resulting anomeric mixture **24a** was benzoylated giving 1,2,3,4,6-penta-*O*-benzoyl-D-psicofuranose (**24b**). This too was a mixture of anomers with one component predominating. The NMR spectrum recorded in Tables I and II is that of the major anomer. Conversion of **24b** to the glycosyl bromide **24c** was achieved through treatment with hydrogen bromide in methylene chloride. Without purification the bromide was condensed with bis(trimethylsilyl)cytosine in the presence of mercuric cyanide giving homogeneous 1-(1,3,4,6-tetra-*O*-benzoyl-β-D-psicofuranosyl)cytosine (**25a**) in 33% yield. The same condensation could be more easily achieved using unsilylated cytosine, but in this case required stannic chloride and gave **25a** in an identical yield (33%). Debenzoylation of the latter compound then provided 1-(β-D-psicofuranosyl)cytosine (**25b**) as a crystalline dihydrate that lost water at 95–110 °C and then melted at 208–209 °C. The latter melting point and the ultraviolet spectrum of **25b** are identical with those reported for **25b** recently prepared via a different route.[9c] In view of the extensive studies of the Prague group on psicofuranosyl nucleosides[9c,d] we have not further extended this work.

It is clear from this paper that iodo sugars such as **9** provide versatile intermediates for the synthesis of angustmycin A and its base analogues. Subsequent papers will describe the synthesis of a number of other 4′,5′-unsaturated purine nucleosides,[49] some of which are useful starting materials for the synthesis of other natural products such as nucleocidin.[50]



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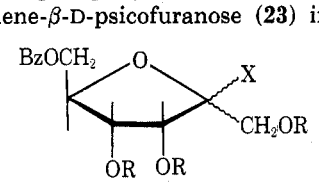
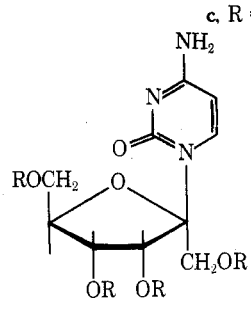


24a, R = H, X = OH
b, R = Bz, X = OBz
c, R = Bz, X = Br



25a, R = Bz
b, R = H

Experimental Section

General Methods. Proton magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and ^{13}C NMR spectra using a Bruker WH-90 spectrometer operating at 22.62 MHz. Spectra are recorded in parts per million downfield of an internal standard of tetramethylsilane. Gas–liquid chromatography was done using a Hewlett-Packard Model 402 instrument. Preparative thin layer chromatography and column chromatography were conducted on silica gel GF-254 from E. M. Laboratories, Elmsford, N.Y. Solutions were dried with $MgSO_4$ during workup. Melting points are corrected.

***N*⁶,*N*⁶,*O*²′,*O*³′-Tetrabenzoyladenosine (2b).** Benzoyl chloride (564 ml, 0.47 mol) was added dropwise to a stirred partial solution of 5′-*O*-trityladenosine (23.9 g, 47 mmol) in pyridine (300 ml) at 0 °C and the mixture was stored in the dark for 48 h. It was then added to ice water (4 l.) and extracted into chloroform. The organic phase was washed with aqueous sodium bicarbonate and water, dried, evaporated in vacuo, coevaporated with benzene, and then precipitated from chloroform with hexane giving 42.2 g (97%) of almost pure 5′-*O*-trityltetrabenzoyladenosine (**2a**):[14] λ_{max} (MeOH) 228 nm (ε 49 100), 272 (2700); $[\alpha]^{23}D$ −51.8° (*c* 0.5, $CHCl_3$); NMR (see Table I). This material (41.7 g, 45 mmol) was dissolved in a 0.56 M solution of hydrogen chloride in chloroform (230 ml) and stored at room temperature for 1 h. The solution was then evaporated and a solution of the residue in chloroform was washed with aqueous sodium bicarbonate and water, dried, and evaporated. Crystallization from chloroform–benzene gave 26.39 g (86%) of **2b** with mp 182–184 °C. An analytical sample had mp 183–185 °C (reported[14] mp 185 °C): λ_{max} (MeOH) 231 nm (ε 32 900), 273 (17 000); $[\alpha]^{23}D$ −20.3° (*c* 0.5, $CHCl_3$).

5′-Deoxy-5′-iodo-*N*⁶,*N*⁶,*O*²′,*O*³′-tetrabenzoyladenosine (2c). A solution of **2b** (3.41 g, 5 mmol) and methyltriphenoxyphosphonium iodide (3.35 g, 7.7 mmol)[16] in dimethylformamide (20 ml) was kept at 20 °C for 10 min. Following addition of methanol (0.5 ml), the solvent was evaporated and a chloroform solution of the residue was washed with aqueous sodium thiosulfate and water, dried, and evaporated. Crystallization from ethanol gave 3.40 g (87%) of **2c** with mp 188–189 °C: λ_{max} (MeOH) 231 nm (ε 43 800), 274 (22 800); $[\alpha]^{23}D$ −96.4° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{38}H_{28}N_5O_7I$ (793.55): C, 57.51; H, 3.55; I, 15.99. Found: C, 57.67; H, 3.78; I, 16.33.

9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (3). A. Using Silver Fluoride. Finely powdered silver fluoride (130 mg, 1 mmol) was added under nitrogen to a solution of **2c** (794 mg, 1 mmol) in pyridine (10 ml) and stirred in the dark at room temperature

for 3 days. The mixture was then diluted with ethyl acetate (200 ml) and filtered. The filtrate was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving a residue that was treated with methanol–concentrated ammonium hydroxide (1:1) at room temperature for 24 h and evaporated. The residue was coevaporated several times with ethanol and then applied in methanol–water (3:7) to a 1 × 15 cm column of Bio-Rad AG1 (X2) resin (OH^-).[18] The column was thoroughly washed with methanol–water (3:7) and then eluted with methanol–water (4.5:5.5) giving 5200 OD_{259} units (35%) of **3**. Crystallization from ethanol gave 36 mg (15%) of **3** with mp 185–186 °C (reported[13] mp 195 °C dec), λ_{max} (MeOH) 259 nm (ε 14 300).

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.24): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.38; H, 4.42; N, 27.94.

B. Using DBN. A solution of **2c** (0.79 g, 1 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.25 g, 2 mmol) in dimethylformamide (50 ml) was kept at room temperature for 18 h and then evaporated to dryness. The residue was hydrolyzed with methanolic ammonium hydroxide and chromatographed as in A above giving 11 560 OD_{259} units (77%) of **3**. Crystallization from ethanol gave 179 mg (72%) of pure **3** with mp 185–186 °C and identical with that above.

1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (4). A suspension of fructose (1235 g, 6.86 mol) in a mixture of acetone (12 l.), 2,3-dimethoxypropane (500 ml), and 70% perchloric acid (1.2 ml) was stirred at room temperature for 70 h. Analysis by GLC (3% OV-225 at 130 °C) showed the presence of a 3:1 mixture of **4** and its 2,3:4,5-di-*O*-isopropylidene isomer. Concentrated ammonium hydroxide (1 ml) was added and the mixture was evaporated leaving a crystalline residue that was dried in vacuo overnight and then dissolved in chloroform (3 l.). The solution was washed three times with water (1 l.) and the aqueous extracts were back-extracted with chloroform. The dried chloroform phases were evaporated and crystallized from chloroform–hexane giving 686 g (38.5%) of **4** with mp 117.5–118 °C (reported[22] mp 119 °C) and showing a single peak by GLC analysis: ^{13}C NMR ($CDCl_3$) C_1 (72.43), C_2 (104.71), C_3 (70.48), C_4 (77.37), C_5 (73.47), C_6 (60.89), CMe_2 (26.01, 26.37, 26.50, 27.99), CMe_2 (109.52, 111.96).

1,2:4,5-Di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (5). A solution of anhydrous phosphoric acid in dimethyl sulfoxide (5 M, 85 ml, 0.42 mol) was added to a solution of **4** (232 g, 0.9 mol) and dicyclohexylcarbodiimide (557 g, 2.7 mol) in a mixture of dimethyl sulfoxide (340 ml), ethyl acetate (112 ml), and pyridine (68 ml). After 10 min an exothermic reaction commenced and the mixture was stirred in ice for 5 min and then at room temperature for 24 h. The mixture was then filtered and the dicyclohexylurea was washed with ethyl acetate (1.2 l.). A solution of oxalic acid dihydrate in methanol (8 M, 316 ml, 2.5 mol) was added gradually to the combined filtrates and after gas evolution had ceased the mixture was filtered and the dicyclohexylurea was washed with ethyl acetate. The filtrates were washed twice with saturated aqueous sodium chloride (500 ml) and then with aqueous sodium bicarbonate (2 × 500 ml) and water (2 × 250 ml). The organic phase was dried, evaporated, and crystallized from ethanol, giving 189 g of **5** in two crops. The final mother liquors were evaporated and a solution of the residue in ethyl acetate was washed with water, dried, evaporated, and crystallized from ethanol, giving a third crop (31 g) of **5**. GLC analysis of the first crop showed the presence of an impurity which was removed by recrystallization from ethanol (1.5 l.) giving 23 g of 1,3-dicyclohexylparabanic acid (**10**) with mp 175–176 °C (reported[26] mp 174–175 °C): λ_{max} (MeOH) 223 nm (ε 1500), 263 (sh, 500); NMR ($CDCl_3$) 1.0–2.2 ppm (m, 20 aliphatic), 4.0 (m, 2, NCH); mass spectrum (70 eV) *m/e* 278 (M^+), 197 (M^+ – cyclohexene), 115 (*m/e* 197 – cyclohexene), 83 ($C_6H_{11}^+$). The mother liquors after removal of **10** were evaporated and the residue combined with crops 2 and 3 from above. Crystallization from hexane (750 ml) gave 184 g (80%) of pure **5** with mp 101–102.5 °C (reported[23b] mp 101.5–102.5 °C). By further crystallization of the mother liquors from several experiments as above the total yield of pure **5** was raised to 85%: ^{13}C NMR ($CDCl_3$) C_1 (70.12), C_2 (104.29), C_3 (197.17), C_4 (76.01), C_5 (78.05), C_6 (60.24), CMe_2 (26.07, 26.07, 26.56, 27.17), CMe_2 (110.73, 113.95).

1,2:4,5-Di-*O*-isopropylidene-β-D-psicopyranose (6). A solution of sodium borohydride (21 g, 0.55 mol) in ethanol (300 ml) was added over 30 min to a stirred solution of **5** (173 g, 0.67 mol) ethanol (2.2 l.) at 0 °C. After a further 15 min the solvent was removed in vacuo, the residue was partitioned between ether (2.8 l.) and water, and the aqueous phase was back-extracted with ether. The combined ether phases were dried and evaporated leaving a crystalline residue that was washed with cold pentane giving 164 g (94%) of **6** with mp 62–63 °C (reported mp 62–64,[23c] 68–69 °C[23d]) that gave a single peak by GLC analysis (3.8% UC-W column at 140 °C): ^{13}C NMR ($CDCl_3$) C_1 (73.08), C_2 (105.10), C_3 (68.89), C_4 (72.33), C_5 (72.04), C_6 (61.34), CMe_2 (25.16, 26.07, 26.20, 26.56), CMe_2 (109.56, 111.18).

1,2:3,4-Di-*O*-isopropylidene-β-D-psicofuranose (7a). A solution of **6** (10.3 g, 39.6 mmol) in a mixture of acetone (90 ml) and 2,2-dimethoxypropane (10 ml) containing 70% perchloric acid (0.15 ml) was kept at room temperature for 17 h and then made basic with concentrated ammonium hydroxide (0.3 ml) and evaporated to dryness. The residue was dissolved in chloroform, washed with water, dried, evaporated, and distilled in a Kugelrohr apparatus[51] at 10^{-3} mm. Acetone polymers were first removed at 40–50 °C and then **7a** distilled at 70 °C giving 6.4 g (62%) of ~98% pure (GLC on OV-101 at 130 °C) crystalline product. Recrystallization from chloroform–hexane gave mp 56–56.5 °C, but only with considerable loss (reported[23b] mp 56–57.5 °C).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-β-D-psicofuranose (7b). A. A solution of **7a** (1.80 g, 6.9 mmol) and *p*-toluenesulfonyl chloride (2.08 g, 10.9 mmol) in pyridine (30 ml) was kept at room temperature for 48 h, quenched with water, and evaporated to dryness. A solution of the residue in benzene was filtered and evaporated to dryness and the residue was crystallized from hexane giving 2.5 g (87%) of **7b** with mp 99.5–100 °C (reported[21b] mp 98–99 °C), $[\alpha]^{23}D$ −40.4° (*c* 1.0, $CHCl_3$).

B. A solution of **6** (40 g, 154 mmol) and concentrated sulfuric acid (2.4 ml) in acetone (1 l.) was kept at room temperature for 27 h and then made basic with concentrated ammonium hydroxide (10 ml), filtered, and evaporated to dryness. A solution of the residue in ether (600 ml) was washed with water (3 × 50 ml), dried, and evaporated. The residue was treated with *p*-toluenesulfonyl chloride (44.5 g, 232 mmol) in pyridine at room temperature for 24 h, worked up as in A, and crystallized from hexane giving 37.4 g (59% from **6**) of **7b** identical with that from A.

6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (7c). A. A solution of **7b** (18.0 g, 43.5 mmol) and sodium iodide (20.0 g, 133 mmol) in dimethylformamide (250 ml) was heated at 110 °C for 2.5 h and then cooled. After evaporation of the solvent the residue was stirred with hexane (400 ml) and filtered, the precipitate being once more extracted with hexane (200 ml). Evaporation of the filtrates left 15.7 g (98%) of pure crystalline **7c**. An analytical sample from aqueous methanol had mp 44–44.5 °C; $[\alpha]^{23}D$ −74.3° (*c* 0.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$) C_1 (69.83), C_2 (113.91), C_3 (85.63), C_4 (83.68), C_5 (86.25), C_6 (6.79), CMe_2 (26.59, 26.46, 26.46, 25.19), CMe_2 (113.00, 111.96).

Anal. Calcd for $C_{12}H_{19}O_5I$ (370.18): C, 38.93; H, 5.17. Found: C, 38.68; H, 5.09.

B. A solution of **7a** (7.8 g, 30 mmol) and methyltriphenoxyphosphonium iodide (16.3 g, 36 mmol) in a mixture of dimethylformamide (45 ml) and pyridine (5.8 ml) was kept at room temperature for 15 min. After addition of methanol (1 ml) the solvents were evaporated and a solution of the residue in chloroform was washed with aqueous sodium thiosulfate and water. The organic phase was evaporated and the residue was chromatographed on a column of alumina (450 g) (deactivated with 5% water) using benzene. Evaporation of the major product gave 6.30 g (57%) of crystalline **7c** that was homogeneous by GLC (3.8% UC-W at 160 °C) and identical with that from A.

C. The crude, undistilled product obtained by equilibration of pyranose **6** (10.3 g, 39.6 mmol) with perchloric acid as described for **7a** was treated with methyltriphenoxyphosphonium iodide (25 g, 55 mmol) and worked up as in B above. Following chromatography as above 6.38 g (44% from **6**) of crystalline **7c** was obtained.

D. A solution of **6** (225 g, 0.86 mol) in acetone (6.3 l.) was equilibrated and worked up as described in the preparation of **7a** giving 196 g of crude product. This was dissolved in a mixture of benzene (1.3 l.) and pyridine (75 ml) and to it was added triphenylphosphine (262 g, 1 mol) and iodine (254 g, 1 mol). After 11 h at room temperature, methanol (20 ml) was added, the mixture was filtered, and the precipitate was washed with benzene (1 l.). Following evaporation of the filtrates the residue was extracted four times with hexane (1 l.) and the combined extracts were washed with aqueous sodium thiosulfate and water. The aqueous phases were back-extracted with hexane and the combined hexane phases were dried and evaporated. Decolorization with charcoal and crystallization from aqueous methanol gave 215 g (67% from **6**) of **7c** identical with that above.

6-Deoxy-6-iodo-D-psicofuranose (8a). A suspension of **7c** (50 g, 135 mmol) and Bio-Rad AG 50W (H^+) resin (100 ml) in water (500 ml) was stirred at 60 °C for 4 h and then cooled and filtered. The filtrate was neutralized with barium carbonate and filtered at 5 °C, the precipitate being washed with acetone. The filtrates were evaporated and the residue was crystallized from acetone–chloroform giving 28.9 g (74%) of **8a** with mp 80.5–81 °C; $[\alpha]^{23}D$ 14.6° (*c* 1.0, H_2O) with no observed mutarotation.

Anal. Calcd for $C_6H_{11}O_5I$ (290.05): C, 24.84; H, 3.82. Found: C, 24.58; H, 3.71.

1,2,3,4-Tetra-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranose (8b). Benzoyl chloride (21 ml, 180 mmol) was added over 30 min to a stirred solution of **8a** (8.7 g, 30 mmol) in pyridine (150 ml) at 0 °C. After a further 24 h at room temperature, methanol (20 ml) was added and the mixture was evaporated. A solution of the residue in chloroform was washed with water, dried, and evaporated, leaving an orange syrup (23.5 g). This was chromatographed on a column of silicic acid (500 g) using benzene and benzene containing 5% and 10% ethyl acetate giving 17.44 g (82%) of **8b** as a TLC homogeneous foam that was a roughly 2:1 mixture of anomers by NMR. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (19:1) but no separation of anomers was possible.

Anal. Calcd for $C_{34}H_{27}O_9I$ (706.48): C, 57.80; H, 3.85. Found: C, 58.03; H, 4.08.

1,2,3,4-Tetra-*O*-*p*-nitrobenzoyl-6-deoxy-6-iodo-D-psicofuranose (8c). The reaction of **8a** (1.0 g, 3.4 mmol) with *p*-nitrobenzoyl chloride (5.1 g, 27 mmol) in pyridine (60 ml) at 3 °C for 2 days was worked up as for **8b**. Chromatography on a column of silicic acid (200 g) using benzene–ethyl acetate (97:3) led to a separation of anomers, the major, less polar isomer being then crystallized from chloroform–hexane, giving 1.79 g (59%) of **8c** with mp 173–174 °C, λ_{max} (dioxane) 257 nm (ϵ 53 200).

Anal. Calcd for $C_{34}H_{23}IN_4O_{17}$ (886.45): C, 46.06; H, 2.61; N, 6.32. Found: C, 45.95; H, 2.52; N, 6.49.

A small amount (443 mg, 14%) of the more polar anomer was eluted but not explored further.

1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl Bromide (9). Anhydrous hydrogen bromide was slowly passed through a solution of **8b** (10.59 g, 15 mmol) in methylene chloride (40 ml) at 0 °C for 1.25 h. The mixture was then evaporated to dryness and the residue was coevaporated four times with a 3:1 mixture of toluene and dichloromethane (30 ml) and then once with benzene. The resulting viscous semicrystalline syrup was used directly for condensation reactions.

N^6-Hexanoyl-9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)adenine (11a) and Its α Anomer (12a). Anhydrous stannic chloride (0.24 ml, 2 mmol) was added under nitrogen to a stirred solution of N^6-hexanoyladenine (350 mg, 1.5 mmol)[29] and mercuric cyanide (760 mg, 3 mmol) in acetonitrile. The mixture was stirred at 60 °C for 2 h and then evaporated leaving a residue that was dissolved in methylene chloride and filtered. The filtrate was washed with aqueous sodium bicarbonate, filtered through Celite, and further washed with 30% aqueous potassium iodide and then water. The organic phase was dried and evaporated leaving a yellow residue (780 mg) that was chromatographed on a column of silicic acid (70 g) using benzene–ethyl acetate (85:15) giving a clean separation of two anomeric products. Elution of the less polar, major isomer gave 373 mg (46%) of **11a** as a homogeneous foam: λ_{max} (MeOH) 231 nm (ϵ 43 000), 273 (23 100), 281 (17 200).

Anal. Calcd for $C_{38}H_{36}N_5O_8I$ (817.6): C, 55.82; H, 4.44; N, 8.57. Found: C, 55.94; H, 4.53; N, 8.42.

Continued elution with the same solvent gave 99 mg (12%) of the α anomer (**12a**) as a homogeneous white foam: λ_{max} (MeOH) 231 nm (ϵ 41 000), 273 (2000), 280 (sh, 15 700).

Anal. Calcd for $C_{38}H_{36}N_5O_8I$ (817.6): C, 55.82; H, 4.44; N, 8.57. Found: C, 55.65; H, 4.50; N, 8.60.

N^6-Benzoyl-9-(1,3,4-tri-*O*-benzoyl-5-deoxy-5-iodo-β-D-psicofuranosyl)adenine (11b). A suspension of N^6-benzoylchloromercuriadenine (1.42 g, 3 mmol)[33] and **9** (from 2.5 g, 3.5 mmol, of **8b** as above) in nitromethane was stirred at room temperature for 48 h and then evaporated to dryness. The residue was stirred with ethyl acetate and filtered, the filtrate then being washed with saturated aqueous sodium iodide and with water. The organic phase was dried, evaporated, and purified by preparative TLC on five plates using benzene–ethyl acetate (4:1). Elution of the major band gave 1.2 g (49%) of homogeneous (TLC, NMR) **11b** as a foam, $[\alpha]^{23}D$ −95.4° (*c* 0.14, $CHCl_3$).

Anal. Calcd for $C_{39}H_{30}N_5O_8I$ (823.58): C, 56.87; H, 3.67. Found: C, 56.60; H, 3.53.

9-(1,3,4-Tri-*O*-benzoyl-5-deoxy-5-iodo-β-D-psicofuranosyl)adenine (11c) and Its α Anomer (12c). Anhydrous stannic chloride (0.24 ml, 2 mmol) was added to a stirred mixture of adenine (200 mg, 1.5 mmol), **9** (from 1 mmol of **8b**), and mercuric cyanide (760 mg, 3 mmol) in acetonitrile (20 ml) at room temperature, leading to immediate dissolution of the adenine. The mixture was then heated at 60 °C for 2 h and evaporated. A suspension of the residue in chloroform was filtered and the filtrate was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water. It was then dried and evaporated leaving a yellow residue (570 mg) that was chromatographed on a column of silicic acid (60 g) using carbon tetrachloride–acetone (7:3). Elution of the less polar product gave 154 mg (21%) of **11c** as a white foam: λ_{max} (MeOH, H^+) 231 nm (ϵ 42 200), 258 (18 000), 265 (16 500).

Anal. Calcd for $C_{32}H_{26}N_5O_7I$ (719.5): C, 53.42; H, 3.64; N, 9.73. Found: C, 53.60; H, 3.76; N, 9.51.

Continued elution gave 48 mg (7%) of **12c** contaminated with a trace of **11c**. Crystallization from chloroform–hexane gave pure **12c** with mp 192–193 °C: λ_{max} (MeOH, H^+) 232 nm (ϵ 45 100), 258 (17 100), 264 (16 200).

Anal. Calcd for $C_{32}H_{26}N_5O_7I$ (719.5): C, 53.42; H, 3.64; N, 9.73. Found: C, 53.59; H, 3.78; N, 9.78.

9-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (1, Angustmycin A). A. A solution of **11a** (500 mg, 0.61 mmol) in 0.08 M methanolic sodium methoxide (38 ml) was heated under reflux for 3 h, then neutralized with glacial acetic acid and evaporated to dryness. The residue was partitioned between water and chloroform and the aqueous phase was evaporated leaving a reddish syrup (550 mg) that was dissolved in methanol (5 ml) containing silicic acid (2 g) and evaporated to dryness. The silica was then added to the top of a column of silicic acid (60 g) and the column was eluted with chloroform–methanol (85:15). Evaporation of the major peak followed by crystallization from methanol gave 102 mg (60%) of homogeneous (TLC and NMR) **1** with mp 178–180 °C. An analytical sample from water had mp 183.5–185 °C (reported multiple mp with final decomposition at 164.5–166.5[7] and 156–159 °C[13] for a hydrate and 183–186 °C for anhydrous[36]): $[\alpha]^{23}D$ 46.4° (*c* 0.46, H_2O); λ_{max} (MeOH, OH^-) 260 nm (ϵ 15 500).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.43; H, 4.51; N, 25.24.

B. A solution of **11b** (820 mg, 1 mmol) and DBN (0.2 ml, 1.5 mmol) in benzene (20 ml) was heated under reflux for 45 min and then cooled and decanted from a brown gum. The supernatant was evaporated and the residue was treated with methanol (20 ml) and concentrated ammonium hydroxide (2 ml) for 24 h at room temperature. Following evaporation of the solvent a solution of the residue in methanol–water (3:7) was applied to a 1 × 15 cm column of Bio-Rad AG1 (X2) resin in the hydroxide form. The column was washed with methanol–water (3:7) and then eluted with methanol–water (1:1). Evaporation of the major peak followed by crystallization from methanol gave 142 mg (48%) of **1** as the hemimethanolate which softened at 133 °C and melted with decomposition at 170 °C. The melting point and mixture melting point were identical with those of an authentic sample of **1** obtained from the Upjohn Co. and the NMR spectra were also identical and identical with that from A above.

9-(6-Deoxy-α-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (13) and 9-(1,6-Anhydro-α-D-psicofuranosyl)adenine (14). A. A solution of **12a** (82 mg, 0.1 mmol) and DBN (0.04 ml, 0.3 mmol) in dimethylformamide (0.5 ml) was kept at room temperature for 24 h. Methanol (0.5 ml) was then added and the solution was stored for a further 54 h. The solution was evaporated and the residue was purified by preparative TLC using chloroform–methanol (85:15). Elution of the major band followed by crystallization from methanol gave 18 mg (64%) of **13** with mp 193–194.5 °C, λ_{max} (MeOH, OH^-) 259 nm (ϵ 13 700).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.30; H, 5.04; N, 25.01.

B. A solution of **12a** (500 mg, 0.61 mmol) in 0.08 M methanolic sodium methoxide (38 ml) was heated under reflux for 8 h and then a further 2 mmol of sodium methoxide was added and heating was continued for 16 h. The cooled solution was neutralized with acetic acid and evaporated, and the residue was partitioned between chloroform and water. The aqueous phase was evaporated and the residue was adsorbed on silicic acid (3 g) and added to the top of a column of silicic acid (70 g). Elution with chloroform–methanol (9:1) gave a permanganate negative product that was crystallized from pyridine–ether giving 65 mg (38%) of **14** with mp 292–294 °C, λ_{max} (MeOH) 259 nm (ϵ 15 500).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.44; H, 4.75; N, 25.04.

Continued elution with chloroform–methanol (85:15) gave 50 mg of crude **13** contaminated with some **14**. Further purification by preparative TLC using chloroform–methanol (4:1) followed by crystallization from methanol gave 23 mg (13%) of **13** identical with that from A above.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (15a). A. A solution of sublimed bis(trimethylsilyl)cytosine (900 mg, 3.5 mmol),[38] **9** (from 2.1 g, 3 mmol, of **8b**), and stannic chloride (0.7 ml, 6 mmol) in benzene was stirred at 60 °C for 1.5 h in

the presence of finely powdered mercuric cyanide (2.3 g, 9 mmol). Following evaporation of the solvent the residue was suspended in chloroform and filtered. The filtrate was washed with saturated aqueous sodium bicarbonate, filtered, washed with 30% aqueous potassium iodide and with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (180 g) using chloroform–acetone (3:2). The major peak was evaporated giving 1.6 g (56%) of crystalline **15a** with mp 125–127 °C from chloroform–hexane. An analytical sample had mp 127–128 °C: λ_{max} (MeOH, H^+) 230 nm (ϵ 46 000), 276 (17 200), 281 (17 200).

Anal. Calcd for $C_{31}H_{26}N_3O_8I$ (695.45): C, 53.54; H, 3.77; N, 6.04. Found: C, 53.64; H, 3.64; N, 5.85.

B. In similar experiments using **9** (10 mmol), bis(trimethylsilyl)-cytosine (13 mmol), and mercuric cyanide (22 mmol) in benzene at 60 °C for 1.5 h in the absence of stannic chloride, the yield of crystalline **15a** was 31%, while after 24 h at room temperature **15a** was obtained in 25% yield. In these cases several less polar minor byproducts were also formed and one of these was isolated during chromatography giving 116 mg (2%) of **17** with mp 121.5–122 °C: λ_{max} (MeOH) 230 nm (ϵ 42 700), 260 (sh, 1900).

Anal. Calcd for $C_{27}H_{21}O_7I$ (584.35): C, 55.49; H, 3.62. Found: C, 55.45; H, 3.64.

N^4-Acetyl-1-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (15b). A solution of N^4-acetylbis(trimethylsilyl)cytosine (3.5 g, 11.8 mmol)[38] and **9** (from 10 mmol of **8b**) was heated in benzene at 60 °C for 19 h in the presence of finely powdered mercuric cyanide (5.1 g, 20 mmol) and then evaporated. A filtered solution of the residue in chloroform was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water. The dried solution was evaporated and the residue was chromatographed on a column of silicic acid (350 g) using benzene–ethyl acetate (3:2) giving 1.50 g (20%) of **15b** as a homogeneous foam: λ_{max} (MeOH) 231 nm (ϵ 46 000), 283 (8000), 298 (7700).

Anal. Calcd for $C_{33}H_{28}N_3O_9I$ (737.48): C, 53.74; H, 3.83; N, 5.70. Found: C, 54.20; H, 4.27; N, 5.55.

1-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)cytosine (16). A. A solution of **15a** (695 mg, 1 mmol) in 0.06 M methanolic sodium methoxide (53 ml) was heated under reflux for 2 h and then cooled, neutralized with acetic acid, and evaporated. The residue was partitioned between water and chloroform and the aqueous phase was evaporated and coevaporated in the presence of silicic acid (1 g). The dried silicic acid was added to the top of a column containing 60 g of silicic acid. Elution of the column with chloroform–methanol (4:1) gave 230 mg (84%) of homogeneous, crystalline **16** which upon recrystallization from methanol gave 176 mg (61%) of pure product as the hemimethanolate with mp 185–186 °C: λ_{max} (0.1 N NaOH) 229 nm (ϵ 8600), 272 (8700); ORD (H_2O) $[\Phi]^{pk}_{286}$ 11 000°, $[\Phi]_{268}$ 0°, $[\Phi]^{tr}_{250}$ −9400°.

Anal. Calcd for $C_{10}H_{13}N_3O_5 \cdot \frac{1}{2}MeOH$ (271.24): C, 46.49; H, 5.57; N, 15.49. Found: C, 46.41; H, 5.74; N, 15.39.

B. A solution of **15a** (695 mg, 1 mmol) and DBN (0.25 ml, 2 mmol) in dimethylformamide (5 ml) was kept at room temperature for 24 h and then evaporated. The residue was treated with methanol (5 ml) and concentrated ammonium hydroxide (5 ml) for 64 h at room temperature and then evaporated leaving a residue that was dissolved in water (15 ml) and washed three times with ethyl acetate. The aqueous phase was evaporated and chromatographed on silicic acid as in A and crystallized from methanol giving 150 mg (55%) of **16** identical with that from A.

C. A solution of **15b** (1.25 g, 1.7 mmol) and DBN (0.5 g, 4 mmol) in dimethylformamide (10 ml) was kept at room temperature for 1.5 h and then worked up as in B. Crystallization from methanol gave 190 mg (44%) of pure **16** identical with that above. In one experiment a monomethanolate with mp 144–146 °C was obtained.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (18a) and Its 5-Methoxycarbonyl Isomer 19. A solution of *N*-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole (5.42 g, 27.2 mmol)[45] and **9** (from 24.7 mmol of **8b**) in benzene (500 ml) was stirred at 60 °C for 2.5 h in the presence of finely divided mercuric cyanide (12.5 g, 49.4 mmol) and then evaporated. A filtered solution of the residue in chloroform was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water, dried, and evaporated. The residue (19.6 g) was chromatographed on a column of silicic acid (1.4 kg) using benzene–ethyl acetate (92:8). Evaporation of the major peak followed by treatment with charcoal gave 8.64 g (49%) of **18a** as a homogeneous white foam: λ_{max} (dioxane) 231 nm (ϵ 4300), 270 (3000), 275 (3200), 283 (2600); $[\alpha]^{23}D$ −69.1° (*c* 1.0, dioxane).

Anal. Calcd for $C_{31}H_{26}N_3O_9I$ (711.4): C, 52.23; H, 3.68; N, 5.91. Found: C, 52.49; H, 3.72; N, 5.56.

Evaporation of a significant peak that was eluted from the column before **18a** gave 3.38 g (19%) of the 5-methoxycarbonyl derivative **19** as a foam: λ_{max} (dioxane) 231 nm (ϵ 42 200), 275 (3200), 282 (2700); $[\alpha]^{23}D$ −27.1° (c 1.0, dioxane).

Anal. Calcd for $C_{31}H_{26}N_3O_9I$ (711.4): C, 52.23; H, 3.68; N, 5.91. Found: C, 52.14; H, 3.95; N, 6.05.

In a separate experiment similar to that described above and giving **19** in 51% yield, the 6-chloro derivative (**18b**) was also isolated as a slightly more polar foam in 11% yield: λ_{max} (dioxane) 229 nm (ϵ 43 300), 275 (3300), 282 (2700); $[\alpha]^{23}D$ −80.1° (*c* 1.0, dioxane); mass spectrum (70 eV) *m/e* 585 (MH − Cl), 584 (M − Cl), 493, 495 (M − base), 484, 486 (M − CH_2OBz), 457 (*m/e* 493, 495 − HCl), 371, 373 (*m/e* 495, 495 − C_6H_5COOH), 362, 364 (*m/e* 484, 486 − C_6H_5COOH), 335 (*m/e* 371, 373 − HCl).

Anal. Calcd for $C_{31}H_{26}N_3O_9Cl$ (620.00): H, 4.23; N, 6.78. Found: H, 4.34, N, 6.67.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-3-methoxycarbonyl-1,2,4-triazole (20). A solution of **18a** (2.9 g, 4.08 mmol) and DBN (1.0 ml, 8 mmol) in dimethylformamide (60 ml) was kept at room temperature for 30 min and then evaporated. A solution of the residue in chloroform was washed with aqueous sodium thiosulfate and water, dried, and evaporated. Crystallization of the residue from ethanol gave 1.38 g (58%) of **20** with mp 153–154 °C: λ_{max} (dioxane) 230 nm (ϵ 37 100), 268 (2400), 275 (2900), 283 (2300).

Anal. Calcd for $C_{31}H_{25}N_3O_9$ (583.53): C, 63.80; H, 4.32; N, 7.20. Found: C, 64.06; H, 4.26; N, 7.18.

1-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-1,2,4-triazole-3-carboxamide (21). A solution of **20** (1.38 g, 2.37 mmol) in a mixture of methanol (20 ml) and concentrated ammonium hydroxide (20 ml) was kept at room temperature for 21 h and then evaporated. The residue was dissolved in water, washed five times with ether, and evaporated to dryness. A solution of the residue in methanol was decolorized with charcoal, evaporated in the presence of silicic acid (3 g), and added to a column of silicic acid (50 g). Elution with chloroform–methanol (4:1) followed by decolorization with charcoal gave 513 mg (85%) of **21** as a homogeneous white foam: λ_{max} (MeOH) 207 nm (ϵ 12 000); ORD (H_2O), plain positive $[\Phi]_{230}$ 6500°.

Anal. Calcd for $C_9H_{12}N_4O_5$ (256.22): C, 42.19; H, 4.72; N, 21.87. Found: C, 42.25; H, 4.88; N, 21.64.

1-(6-*O*-Acetyl-1,3,4-tri-*O*-benzoyl-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (18c). A solution of **18a** (2.25 g, 3.16 mmol) in acetic acid (80 ml) and water (0.8 ml) was stirred at 100 °C for 4.5 h in the presence of silver acetate (1.06 g, 6.34 mmol) and then evaporated. A solution of the residue in chloroform was washed with aqueous sodium bicarbonate and water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (100 g) using benzene–ethyl acetate (4:1) giving 94 mg (5%) of crystalline **20** followed by 1.22 g (60%) of **18c** as a white foam: λ_{max} (dioxane) 212 nm (sh, ϵ 21 900), 230 (4600), 270 (sh, 3300), 275 (3100), 283 (2500).

Anal. Calcd for $C_{33}H_{29}N_3O_{11}$ (643.58): C, 61.58; H, 4.54; N, 6.53. Found: C, 61.72; H, 4.58; N, 6.23.

1-(β-D-Psicofuranosyl)-1,2,4-triazole-3-carboxamide (22). A solution of **18c** (1.3 g, 2 mmol) in methanol (15 ml) and concentrated ammonium hydroxide (15 ml) was kept at room temperature for 16 h and then evaporated. The residue was dissolved in water, washed with ether, and evaporated, leaving a residue that was chromatographed on silicic acid (50 g) using chloroform–methanol (3:1). The major peak was decolorized with charcoal and evaporated leaving 387 mg (71%) of **22** as a homogeneous foam that crystallized very slowly from ethanol at −18 °C with mp 66–68 °C dec, λ_{max} (0.1 N HCl) 208 nm (ϵ 1800).

Anal. Calcd for $C_9H_{14}N_4O_6$ (274.23): C, 39.42; H, 5.15; N, 20.43. Found: C, 39.39; H, 5.28; N, 20.28.

6-*O*-Benzoyl-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (23). A solution of **7c** (3.7 g, 10 mmol) and lithium benzoate (2.5 g, 20 mmol) in dimethylformamide (100 ml) was kept at 100 °C for 16 h and then evaporated. The residue was partitioned between ether (100 ml) and water (3 × 50 ml) and the ether layer was dried and evaporated. Crystallization of the residue from aqueous methanol gave 3.28 g (90%) of **23** with mp 72–72.5 °C.

Anal. Calcd for $C_{19}H_{24}O_7$ (364.38): C, 62.62; H, 6.64. Found: C, 62.70; H, 6.74.

6-*O*-Benzoyl-D-psicofuranose (24a). A mixture of **23** (29.5 g, 81 mmol) and Bio-Rad AG 50W (H^+) resin (60 ml) in water (300 ml) was stirred at 65 °C for 12 h, then stored at 5 °C for 18 h and filtered. The filtrates were adjusted to pH 6 with barium carbonate and filtered and the solids were washed with acetone. Evaporation of the filtrates left a residue that was coevaporated with toluene–ethanol (1:1) and dried under high vacuum giving 22.4 g (97%) of **24a** as a foam that was

sufficiently pure for direct use in the next step. An analytical sample was prepared by preparative TLC using chloroform–methanol (4:1), elution of the ultraviolet-absorbing band giving the mixed anomers of **24a** as a white foam.

Anal. Calcd for $C_{13}H_{16}O_7$ (284.26): C, 54.93; H, 5.67. Found: C, 54.88; H, 5.97.

1,2,3,4,6-Penta-*O*-benzoyl-D-psicofuranose (24b). Benzoyl chloride (100 ml, 0.86 mol) was added dropwise over 50 min to a stirred solution of **24a** (22.8 g, 80 mmol) in pyridine (500 ml) at 0 °C. After a further 24 h at room temperature, methanol (50 ml) was added and the mixture was evaporated to dryness. A solution of the residue in chloroform was washed with water, dried, and evaporated, leaving a residue that was largely freed from methyl benzoate by drying at 50 °C under high vacuum for 8 h. The product (69 g) was then purified by chromatography on a column of silicic acid (2.9 kg) using elution with benzene–ethyl acetate (98:2) until **24b** appeared followed by a gradient of ethyl acetate (2–7.5%) in benzene. Evaporation of the major peak left 32.59 g (58%) of pure **24b** as a foam. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (19:1).

Anal. Calcd for $C_{41}H_{32}O_{11}$ (700.67): C, 70.28; H, 4.60. Found: C, 70.05; H, 4.43.

1-(1,3,4,6-Tetra-*O*-benzoyl-β-D-psicofuranosyl)cytosine (25a). A. Anhydrous hydrogen bromide was passed through a solution of **24b** (3.5 g, 5 mmol) in dichloromethane (40 ml) at 0 °C for 15 min and the solution was then kept at 0 °C for 1.25 h and evaporated to dryness. The residue was coevaporated four times with a 3:1 mixture of toluene and dichloromethane (30 ml) leaving semicrystalline, crude **24c.** This material and bis(trimethylsilyl)cytosine (1.5 g, 6 mmol) were dissolved in benzene and stirred at 60 °C for 1.5 h in the presence of finely powdered mercuric cyanide (3.75 g, 15 mmol). The mixture was then evaporated and a solution of the residue in chloroform was filtered through Celite. The filtrate was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (250 g) using chloroform–acetone (3:2) and giving 1.13 g (33%) of **25a** as a TLC homogeneous foam. An analytical sample was prepared by preparative TLC using chloroform–methanol (98:2): λ_{max} (MeOH, H^+) 230 nm (ε 5700), 281 (15 300).

Anal. Calcd for $C_{38}H_{31}N_3O_{10}$ (689.65): C, 66.18; H, 4.53; N, 6.09. Found: C, 65.80; H, 4.81; N, 6.47.

B. To a solution of **24c** (obtained from 5 mmol of **24b** as described above) in acetonitrile (100 ml) were added cytosine (670 mg, 6 mmol), mercuric cyanide (3.75 g, 15 mmol), and stannic chloride (1.2 ml, 10 mmol). The reaction mixture was stirred at 60 °C for 1.5 h and the brown solution was then evaporated. The residue was dissolved in chloroform and filtered. A saturated solution of sodium bicarbonate was used to neutralize the filtrate and a light precipitate was removed by filtration. The organic layer was washed with 30% potassium iodide and water, dried, and evaporated. The residue (3 g) was purified by chromatography as described above and gave 1.33 g (33%) of **25a** as a TLC homogeneous foam identical with that above.

1-(β-D-Psicofuranosyl)cytosine (25b). A suspension of **25a** (1.0 g, 1.45 mmol) in a mixture of methanol (10 ml) and concentrated ammonium hydroxide (15 ml) was stirred at room temperature for 24 h and the mixture (from which crystalline **25b** had separated) was evaporated, leaving a crystalline residue that was thoroughly washed with ethyl acetate. Recrystallization from water gave 321 mg (72%) of **25b** as the dihydrate which lost water at 95–110 °C and melted at 208–209 °C dec, unchanged upon recrystallization (reported[9c] mp 207–208 °C): λ_{max} (0.1 N HCl) 214 nm (ε 9700), 281 (1000); λ_{max} (0.1 N NaOH) 226 nm (ε 9100), 273 (9400); $[\alpha]^{23}D$ −33.8° (*c* 1.0, Me_2SO)

Anal. Calcd for $C_{10}H_{15}N_3O_6 \cdot 2H_2O$ (309.27): C, 38.83; H, 6.19; N, 13.59. Found: C, 38.96; H, 6.15; N, 13.51.

Registry No.—**1,** 2004-04-8; **2a,** 58463-03-9; **2b,** 58463-04-0; **2c,** 58463-05-1; **3,** 20535-04-0; **4,** 25018-67-1; **5,** 18422-53-2; **6,** 18422-54-3; **7a,** 34626-95-4; **7b,** 58501-81-8; **7c,** 38084-06-9; **8a,** 58463-06-2; **8b,** 58463-07-3; **8c,** 58463-08-4; **9,** 58463-09-5; **10,** 3621-71-4; **11a,** 58463-10-8; **11b,** 58463-11-9; **11c** 58463-12-0; **12a,** 58463-13-1; **12c,** 58463-14-2; **13,** 58463-15-3; **14,** 58463-16-4; **15a,** 58463-17-5; **15b,** 58463-18-6; **16,** 58463-19-7; **17,** 58463-20-0; **18a,** 58463-21-1; **18b,** 58463-22-2; **18c,** 58463-23-3; **19,** 58463-24-4; **20,** 58463-25-5; **21,** 58463-26-6; **22,** 58463-27-7; **23,** 58501-82-9; **24a,** 58463-28-8; **24b,** 58463-29-9; **24c,** 54401-10-4; **25a,** 58463-30-2; **25b,** 53318-75-5; 5′-*O*-trityladenosine methyltriphenoxyphosphonium iodide methyl, 17579-99-6; methyltriphenoxyphosphonium iodide, 4167-91-3; fructose, 57-58-7; acetone, 67-64-1; *p*-toluenesulfonyl chloride, 98-59-9; sodium iodide, 7681-82-5; *p*-nitrobenzoyl chloride 122-04-3; N^6-hexanoyladenine, 21043-28-7; N^6-benzoylchloromercuriadenine, 17187-65-4; bis(trimethylsilyl)cytosine, 18037-10-0; N^4-acetylbis(trimethylsilyl)cytosine, 18027-23-1; *N*-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole, 40372-08-5.

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