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A new synthesis of L-talose and preparation of its adenine nucleosides

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Abstract

Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-β-D-allofuranoside, prepared by a route starting from D-glucose and its conversion to 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose and D-allose, has been used as the starting material for a new synthesis of L-talose. The configuration at C-5 was inverted with NaOAc in hot DMF, resulting in the L-talofuranoside derivative from which the acetyl groups were removed to give methyl 2,3-*O*-isopropylidene-α-L-talofuranoside. Hydrolysis of the latter yielded L-talose. Methyl 2,3-*O*-isopropylidene-α-L-talofuranoside was used as the starting material in a six-step synthesis of 9-α-L-talofuranosyladenine. L-Talose was acetylated and coupled with the base to give 9-α-L-talopyranosyladenine. 9-α-L-Talofuranosyladenine was a slow-reacting substrate for calf intestinal adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4) and an inhibitor of the growth of leukemia L1210 cells in vitro.

Key words: L-Talose; Nucleoside; Adenine; Adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4)

1. Introduction

L-Talose has been prepared in the past from D-galactonic acid by conversion to L-galactonic acid, epimerization of C-2 of the latter to L-talonic acid in pyridine, lactonization, and finally reduction with sodium-amalgam [1–3]. The total synthesis of L-talose has been achieved from noncarbohydrate precursors in several labora-

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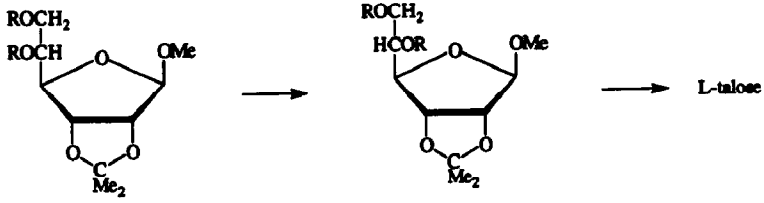
tories [4,5], and L-talono-1,4-lactone has been synthesized starting from L-ascorbic acid [6]. Furthermore, a number of 1,2-*O*-isopropylidene derivatives of L-talofuranose have been synthesized in multistep reaction sequences starting from D-glucose and going through L-idofuranose derivatives [7–9]. The present report describes a convenient synthesis of L-talose from D-glucose via D-allose or 1,2:5,6-di-*O*-isopropylidene-D-allose as the starting material.

2. Results and discussion

Previous work from this laboratory reported the conversion of D-allose to methyl 2,3-*O*-isopropylidene-β-D-allofuranoside (**1**, Scheme 1) from which the crystalline dimesylate **2** had been easily obtained [10]. Since inversion of configuration at C-5 would afford the L-talofuranoside derivative, an approach involving the conversion of the D-allofuranoside derivative **2** to the L-talofuranoside derivative **4** seemed worth investigating. The methodology used was based upon the conversion of D-mannose into L-gulose, as described by Evans and Parrish [11]. We also investigated the possibility of converting 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose directly into **1**, since it was an intermediate in the conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose to D-allose. Therefore, 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was subjected to the exact, same reaction conditions as D-allose: a boiling mixture of MeOH, 2,2-dimethoxypropane, and concd HCl, which resulted in a 41% yield of **1**. Since the yield of **1** from D-allose was 51–53%, and losses due to the formation and crystallation of free D-allose were not incurred, this yield is almost the same as that of the overall process from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose to D-allose to **1**, and it saves an unnecessary hydrolysis step.

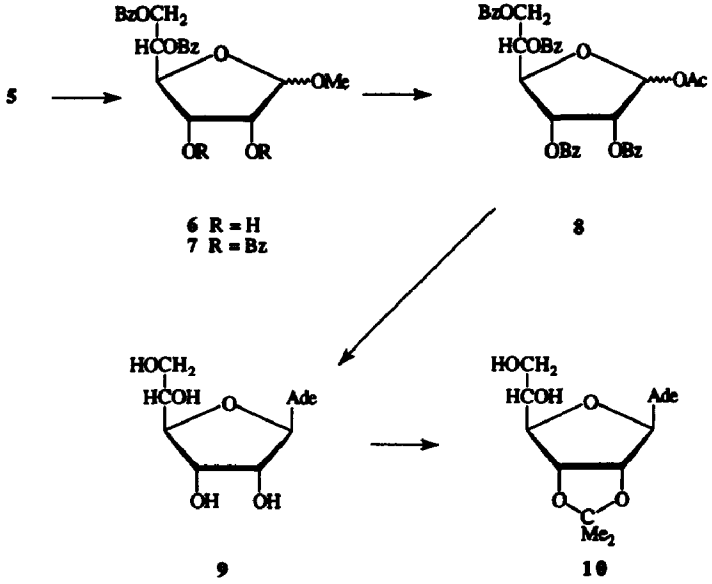
Treatment of the dimesylate **2** with NaOAc in hot DMF followed by removal of the acetyl groups from crude **3** and subsequent chromatographic purification, gave methyl 2,3-*O*-isopropylidene-α-D-talofuranoside (**4**). Acid hydrolysis gave L-talose, which was further characterized by the preparation of its *N*-methyl-*N*-phenylhydrazone derivative.



1 R = H
2 R = Ms

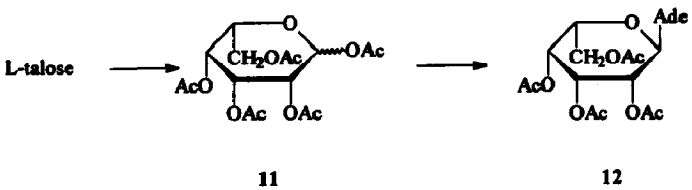
3 R = Ac
4 R = H
5 R = Bz

Scheme 1.



Scheme 2.

In a continuation of a long-term interest of this laboratory dealing with the preparation of hexofuranose and hexopyranose nucleosides, the synthesis of adenine nucleosides of the two ring forms of L-talose was carried out. Of special interest was the furanose form (**9**, Scheme 2), because it has a structure closely resembling adenosine and, therefore, was a good candidate for biological activity. Indeed, the structure of **9** suggested that it could be a substrate for adenosine deaminase, since it had the minimal stereochemical configurations required for activity [12,13]. Thus, compound **4** was benzoylated by standard procedures to give **5** as an analytically pure syrup. The isopropylidene group of **5** was removed to afford **6**, which was not characterized, but was immediately benzoylated to give the tetrabenzoate **7**. Acetolysis of **7** gave a mixture of the anomeric 1-acetates (**8**) as shown by the NMR spectra. *N*-Benzoyladenine was then coupled with **8** by the method of Niedballa and Vorbrüggen [14] as applied to purines [15]. The blocking groups were removed with NaOMe in MeOH, and upon neutralization with acid, 9-α-L-talofuranosyladenine (**9**) crystallized in good yield.



Scheme 3.

Acetylation of L-talose to give the pentaacetate **11** was followed by coupling to *N*-benzoyladenine as described above to afford, after catalytic removal of the blocking groups, 9-α-L-talopyranosyladenine (**12**) (Scheme 3).

The new nucleosides **9** and **12** had the same physical properties as the D forms except for the signs of the optical rotations. This automatically established the anomeric configuration of **12** as α-L because the D form had been unequivocally shown to be α-D [16]. This method had involved periodate oxidation of the carbohydrate ring, reduction of the aldehyde groups to primary alcohols, and determination of the optical rotation in comparison to standards derived in the same way from adenosine or 9-β-D-mannopyranosyladenine. ^{1}H NMR data in the present case shows $J_{1',2'} \simeq 8.2$ Hz, indicative of a trans-diaxial orientation of the hydrogen atoms at C-1 and C-2, further supporting the assigned configuration and a $^4C_1$ conformation.

In contrast to the D-pyranosyl nucleoside, the D-furanosyl nucleoside was not unequivocally proven to be α-D. Instead, the assignment of the anomeric configuration was argued on the basis of the coupling method used and a comparison of the molecular rotation to that of a series of known glycosides and nucleosides [17]. This was because furanose glycosides (and nucleosides) tend to overoxidize in the presence of periodate, causing severe discoloration, due in part to the liberation of elemental I_2. In fact, this behavior can be utilized as a test for the presence of a hexofuranose ring in either glycosides [18] or nucleosides [19]. In the present case, further evidence for the α-L configuration of **9** was sought using ^{1}H NMR spectroscopy. Unfortunately, $J_{1',2'}$ for the anomeric position was 6.3 Hz, a value that does not offer a solution. It has been demonstrated, however, that fusion of a second 5-membered ring, such as an isopropylidene group or a cyclic phosphate, will dramatically decrease the value of the coupling constant [20]. Therefore, nucleoside **9** was treated with acetone under acidic conditions to afford the 2',3'-*O*-isopropylidene derivative **10**. The ^{1}H NMR spectrum gave $J_{1',2'}$ 3.6 Hz, which would correspond to a dihedral angle of ~130°, supporting the α-L configuration. The alternative value of ~45° would cause too much distortion, considering that molecular models show that if the configuration were β-L, the dihedral angle should be ~0°. It is also of interest that the separation for the two signals for the two methyl groups of the 2',3'-*O*-isopropylidene group of **10** is 0.24 ppm. According to the empirical rule discovered by Imbach and co-workers [21], this $\Delta\delta$ value would be supportive of the assigned α-L configuration.

As predicted, nucleoside **9** was a substrate for adenosine deaminase, albeit a weak one. Under the conditions employed, **9** was completely deaminated in 30 min. In comparison, under the same conditions, the related 9-(6-deoxy-α-L-talofuranosyl)adenine was deaminated in just 3 min [22]. This difference in deamination rate between 6'-deoxyhexofuranosyladenine nucleosides and the 6'-hydroxymethyl nucleosides has been previously demonstrated [23]. The fact that **9** is a substrate for adenosine deaminase is also supportive of the assigned α-L configuration at the anomeric carbon. Nucleoside **12** was not a substrate for this enzyme. Studies with in vitro growing cultures of leukemia L1210 cells indicated that **9** inhibited growth by 50% (IC_{50}) at a concentration of 7×10^{-5} M. The nucleoside

apparently prevents cell division rather than killing the cells, for upon transfer of the cells to fresh media, normal growth was observed. Nucleoside **12** was an extremely weak inhibitor, with an IC_{50} value $> 10^{-4}$ M.

3. Experimental

General methods.—Melting points were determined with a Kofler hot stage and are corrected values. NMR spectra were obtained on a Bruker 250 MHz spectrometer, IR spectra on a Perkin–Elmer Model 21 spectrophotometer, UV spectra on a Beckman Model 25 spectrophotometer, and optical rotations with a Perkin–Elmer Model 141 polarimeter. Elemental analyses were performed at M-H-W Laboratories, Phoenix, AZ.

Paper chromatography was performed on Whatman No. 1 paper by a descending technique, and spots were located with a Mineralight lamp (254 nm). The R_{Adc} values reported are defined as the ratio of the distance the nucleoside migrated to the distance that adenine migrated. TLC was performed on 0.25-mm layers of Silica Gel G or GF_{254}, Type 60 (E. Merck, Darmstadt). Where applicable, spots were first located with a UV lamp, and then the plates were sprayed with chromic acid solution and heated in an oven at 110°C.

Drying of moist solutions was accomplished with anhyd Na_2SO_4, and evaporations were carried out under reduced pressure with a rotary evaporator at the bath temperatures indicated. The term petroleum ether refers to the 30–60°C boiling fraction.

N-Benzoyladenine was prepared as described by Kohn et al. [24]. It was converted to *N*-benzoyl-*N*,9-bis(trimethylsilyl) adenine as previously described and used without distillation [25].

Methyl 2,3-O-isopropylidene-β-D-allofuranoside (**1**).—1,2 : 5,6-Di-*O*-isopropylidene-α-D-allofuranose [10,26] (4.5 g, 17.3 mmol) was dissolved in a solution containing 2,2-dimethoxypropane (16 mL), acetone (10.5 mL), MeOH (10.5 mL), and concd HCl (0.35 mL). The mixture was heated at reflux for 2 h, cooled to room temperature, and poured into H_2O (32 mL). The organic solvents were evaporated (30°C), whereupon a white precipitate formed. MeOH (32 mL) and concd HCl (0.8 mL) were added, and the solution was stirred at room temperature for 3.5 h. The solution was made slightly alkaline with satd $NaHCO_3$ solution (25 mL), evaporated (30°C) to ~30 mL and extracted with $CHCl_3$ (4 × 30 mL). After drying and filtration, evaporation (30°C) of the $CHCl_3$ left an orange syrup (2.46 g). The product (**1**) was crystallized from EtOAc–petroleum ether in two crops (1.671 g, 41% yield); mp 100–100.5°C. The properties were the same as **1** prepared from D-allose [10].

Methyl 2,3-O-isopropylidene-α-L-talofuranoside (**4**).—A mixture containing methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methysulfonyl-β-D-allofuranoside [10] (**2**) (14.53 g, 37.2 mmol), anhyd NaOAc (15 g), and DMF (120 mL) was heated under reflux for 6 h, protected from moisture. Ac_2O (22.5 mL) was added, and refluxing

was continued for 1 h. The mixture was cooled to room temperature and evaporated (60°C) leaving a dark-brown residue, which was dissolved in MeOH (20 mL). Satd $NaHCO_3$ solution (75 mL) was added in small increments, and after 45 min, H_2O (210 mL) was used to dilute the solution. Continuous extraction with hexane (300 mL) for 44 h, followed by drying, filtration, and evaporation (40°C) gave a thin syrup (**3**), 9.20 g (78% yield).

The syrup was dissolved in MeOH (27 mL), N methanolic NaOMe (3 mL) was added, and the mixture was stirred at room temperature for 18 h. The solution was neutralized with Amberlite CG-120 (H^+) resin, and the MeOH was removed by evaporation (40°C), leaving a syrup, which was placed on a column (3.8 cm ID) consisting of silica gel on the bottom (60 g, 17 cm), and a mixture (9 g each) of Darco G-60, and Celite-545 on top. EtOAc (400 mL) was passed through the column, and the solvent was evaporated (40°C), leaving a deep-yellow syrup, 6.72 g (77% yield from **2**, 99% from **3**). TLC (G plate, 98:2 $CHCl_3$–MeOH) revealed two minor contaminants.

The syrup was dissolved in a small amount of $CHCl_3$ and placed on top of a column of silica gel (Baker, 60–200 mesh, 200 g, 20.5 × 6 cm). Elution was performed with 98:2 $CHCl_3$–MeOH, and 200-mL fractions were collected. Fractions 7–9 yielded **4**, 5.91 g; $[\alpha]_D^{25}$ − 44.2° (*c* 2.34, MeOH); R_f 0.18 (G plate, 98:2 $CHCl_3$–MeOH); IR (smear on NaCl plate) ν_{max} 3300 (OH), 1378 (gem-Me_2), 1104, 1082, 1062 cm^{-1} (C–O, C–O–C); ^1H NMR ($CDCl_3$): δ 4.95 (s, 1 H, H-1), 4.81 (d, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.56 (d, 1 H, $J_{3,2}$ 6.0 Hz, H-3), 4.46 (s, 1 H, H-4), 3.6–3.5 (m, 3 H, H-5, H-6_a,6_b), 3.42 (s, 3 H, OMe), 1.44, 1.28 (both s, 3 H each, gem-Me_2); ^{13}C NMR ($CDCl_3$): δ 112.2 (*C*Me_2), 110.3 (C-1), 88.2 (C-2), 85.2 (C-3), 82.2 (C-4), 71.9 (C-5), 64.2 (C-6), 56.0 (OMe), 26.2, 24.6 (C*Me*$_2$). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.34; H, 7.88.

L-*Talose*.—Amberlite IR-120 (H^+) ion-exchange resin (25 mL) was suspended in boiling H_2O for 15 min, and the H_2O was decanted. This process was repeated twice, and then the resin was added to a flask containing **4** (2.2 g, 9.4 mmol) dissolved in H_2O (130 mL). The mixture was heated under reflux for 1.5 h. TLC on a Silica Gel G plate (1:1 EtOAc–petroleum ether) showed that complete hydrolysis had occurred. The resin was removed by filtration, the filtrate was evaporated (40°C) to ~ 25 mL, and the yellow solution was treated with a small amount of Norit A. Evaporation (30°C) of the H_2O afforded a clear, colorless syrup. Abs EtOH (3 × 10 mL) was added and evaporated (30°C), and the syrup was placed in a desiccator over P_2O_5 and Drierite at 30 Torr for 7 days. The yield of L-talose was 1.61 g (95%); $[\alpha]_D^{24}$ − 17.6° (*c* 1.03, H_2O); lit. [4] $[\alpha]_D^{20}$ − 18.2° (*c* 1.0, H_2O).

L-*Talose*N-*methyl*-N-*phenylhydrazone*.—L-Talose (100 mg), MeOH (4 mL), and *N*-methyl-*N*-phenylhydrazine (0.075 mL) were mixed in a beaker and placed on a steam bath until the solvent had evaporated. An orange syrup remained, which upon cooling formed a crystalline mass. These crystals were recrystallized twice from MeOH (2 mL) in the refrigerator. The final yield was 76 mg (48%) in two crops; mp 155–156°C; $[\alpha]_D^{24}$ + 8.4° (*c* 1.00, MeOH); lit. [4] mp 153–154°C; $[\alpha]_D^{20}$ + 7.6° (*c* 1, MeOH).

Methyl 5,6-di-O-benzoyl-2,3-O-isopropylidene-α-L-talofuranoside (**5**).—A solution of **4** (1 g) in dry pyridine (10 mL) was chilled in an ice-bath, benzoyl chloride (1.4 mL) was added, and the mixture was stirred for 30 min at this temperature, then for 18 h at room temperature. When the mixture was poured into ice-satd $NaHCO_3$ (125 mL), a gum formed, which was dissolved in $CHCl_3$, washed with H_2O and dried. Evaporation (40°C) and coevaporation with toluene afforded a light-orange syrup (2.24 g), which was chromatographed on silica gel (Baker 60–200 mesh, 80 g, 23 × 3.5 cm) using 99:1 $CHCl_3$–MeOH as the elution solvent. Fractions (100 mL) were collected. Fractions 3 and 4, which were homogeneous on TLC (GF plate, 98:2 $CHCl_3$–MeOH), were combined and evaporated to afford 1.40 g (74% yield) of **5** as a gum: $[\alpha]_D^{23} - 51.0°$ (*c* 1.46, $CHCl_3$); R_f 0.71 (GF plate, 98:2 $CHCl_3$–MeOH); IR (smear on NaCl plate) ν_{max} 1732 (C=O), 1612, 1593 (phenyl ring), 1378 (d, gem-Me_2), 1116–1056 (plateau, C–O, C–O–C), 710 cm^{-1} (monosubstituted benzene); ^1H NMR ($CDCl_3$): δ 8.15–7.97, 7.56–7.36 (complex m, PhH), 3.37 (s, OMe), 1.50, 1.30 (both s, gem-Me_2). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.10; H, 5.86.

In a separate, larger-scale preparation, a 95% yield of **5** was obtained after column chromatography. This syrup was used for the synthesis of nucleoside **9**.

9-α-L-Talofuranosyladenine (**9**).—To a solution of **5** (3.23 g, 7.3 mmol) in MeOH (110 mL) was added Amberlite IR-120 (H^+) ion-exchange resin (30 g), which had been equilibrated five times in MeOH. The mixture was vigorously stirred and refluxed for 4 h, then allowed to cool to room temperature. TLC (G plate, 1:1 EtOAc – petroleum ether) showed that **5** was gone and a new spot had appeared. The resin was removed by filtration, and evaporation (30°C) of the MeOH gave a very viscous syrup (**6**), which was dissolved in dry pyridine (25 mL), chilled in an ice-bath, and benzoyl chloride (3.5 mL) was added, dropwise. After stirring at room temperature for 22 h, the mixture was again chilled, MeOH (2 mL) was slowly added, and the mixture was allowed to stir at room temperature for 3 h. It was then diluted with $CHCl_3$ (40 mL), and washed with satd $NaHCO_3$ (2 × 50 mL), and H_2O (50 mL). The $CHCl_3$ layer was evaporated (40°C) and the resulting syrup was dissolved in acetone (30 mL), H_2O (30 mL) was added and evaporated again to remove methyl benzoate as the H_2O azeotrope. This process was repeated three more times. The syrup was dissolved in $CHCl_3$, the solution was dried, filtered, evaporated (40°C), and stored in a vacuum desiccator for 5 days, yielding **7** as a glasslike substance, 4.06 g (91%). The product appeared homogeneous on TLC (GF); R_f 0.61, (1:1 EtOAc–petroleum ether); R_f 0.71 (4:1 benzene–MeOH). The IR spectrum (film from CH_2Cl_2) showed a strong C=O peak at 1728 cm^{-1}, but no peaks for hydroxyl or *O*-isopropylidene groups. The ^1H NMR spectrum also showed that there were no hydroxyl or *O*-isopropylidene groups, and that the methoxyl group was still present as a singlet at δ 3.45.

The glass (3.95 g) was dissolved in a mixture of Ac_2O (3 mL), and glacial AcOH (30 mL), chilled in an ice-bath, and concd H_2SO_4 (1.3 mL) was added, dropwise. The solution was stirred at room temperature for 21 h, and worked-up in the usual fashion [10,22]. A syrup was obtained that was stored in a vacuum desiccator for 4 days, yielding 4.06 g (98%) of **8**. The product appeared homogeneous on TLC

(GF); R_f 0.59 (1:1 EtOAc–petroleum ether), R_f 0.69 (4:1 benzene–MeOH). The ^{1}H NMR spectrum ($CDCl_3$) showed that the methoxyl group at δ 3.45 was gone and had been replaced by new peaks at δ 2.0–2.2, characteristic of the acetyl group as an anomeric mixture.

The 1-acetate **8** (3.91 g, 6.12 mmol) was dissolved in dry 1,2-dichloroethane (65 ml) and added to a reaction flask containing *N*-benzoyl-*N*,9-bis(trimethylsilyl) adenine (6.73 mmol, prepared from 1.61 g of *N*-benzoyladenine), followed by freshly distilled $SnCl_4$ (1.2 mL, 10.3 mmol) in 1,2-dichloroethane (10 mL), and the mixture was heated under reflux for 2 h. After the usual workup [14], a yellow foam (5.47 g) was obtained, which was dissolved in MeOH (115 mL) and N methanolic NaOMe (10 mL) was added. The solution was refluxed for 1 h, cooled to room temperature, neutralized with glacial AcOH, and allowed to stand. Within a few minutes the solution became turbid and crystals began to rapidly form. The crystals (0.944 g) were isolated by filtration, and a second crop (0.297 g) was obtained after concentration of the mother liquor. The pale-yellow crystals of **9** (1.243 g, 68% yield) had mp 234–235°C. The product was recrystallized from H_2O using a small amount of Darco G-60 to remove the yellow color. The nucleoside was obtained in three crops as needles, 1.07g (59%); mp 240–241°C; $[\alpha]_D^{25}$ − 32.4° (*c* 2.47, N HCl); UV_{max} (pH 1) 257 nm (ϵ 14130), (H_2O) 259 (ϵ 14410), (pH 13) 260 (ϵ 14930); UV_{min} (pH 1) 230 nm (ϵ 3260), (H_2O) 226 (ϵ 2,170), (pH 13) 230 (ϵ 3960); ^{1}H NMR (Me_2SO-d_6): δ 8.53, 8.26 (both s, 1 H each, H-2, H-8), 7.56 (s, 2 H, NH_2), 6.02 (d, 1 H, $J_{1',2'}$ 6.3 Hz, H-1'), 5.82 (d, 1 H, 5'OH), 5.58 (d, 1 H, 2' OH), 5.32 (d, 1 H, 3' OH), 4.81 (t, 1 H, 6' OH), 4.67 (q, 1 H, $J_{2',1'}$ 6.3 Hz, H-2'), 4.29 (br s, 1 H, H-3'), 4.26 (br s, 1 H, H-4'), 3.74 (m, 1 H, H-5'), 3.50 (m, 2 H, H-6'$_a$,6'$_b$); ^{13}C NMR (Me_2SO-d_6): δ 156.3 (C-6), 152.4 (C-2), 148.9 (C-4), 140.1 (C-8), 119.5 (C-5), 88.3 (C-1'), 84.9 (C-4'), 74.0 (C-2'), 71.7, 71.6 (C-3', C-5'), 62.4 (C-6'); R_{Adc} 0.39 (86:14 *n*-butanol–H_2O), R_{Adc} 1.54 (5% aq Na_2HPO_4). Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.47; H, 5.15; N, 23.49.

The D-form of the nucleoside had mp 242.5–243.5°C, $[\alpha]_D^{24}$ + 31.7° (*c* 3.44, N HCl) [17]. The IR spectrum of **9** had the same peaks as previously reported for the D-form [17].

9-(2,3-O-Isopropylidene-α-L-talofuranosyl)adenine (**10**).—A mixture containing **9** (272 mg), acetone (30 mL), 2,2-dimethoxypropane (3 mL), and *p*-toluenesulfonic acid monohydrate (0.64 g) was stirred at room temperature for 4 h. The solution was poured into a flask containing $NaHCO_3$ (1 g) and H_2O (10 mL), stirred for several minutes, filtered, and the filtrate evaporated (30°C). The residue was triturated with acetone (30 mL), filtered again, and the acetone evaporated to afford a gummy residue (388 mg). This was dissolved in a 7:3 AcOH–H_2O mixture (40 mL) and kept for 3 h at 50°C. The solvents were evaporated (30°C), and the residue was coevaporated with EtOH (3 × 10 mL), and then with 1:1 EtOH–toluene (3 × 10 mL). The glasslike residue was dissolved in H_2O (30 mL) and washed with $CHCl_3$ (3 × 10 mL). The aqueous layer was evaporated (40°C) and coevaporated with EtOH to form a white powder, which was crystallized in MeOH to give **10**, 100 mg (32% yield); mp 259–261°C (dec); ^{1}H NMR (Me_2SO-d_6):

δ 8.53, 8.26 (both s, 1 H each, H-2, H-8), 7.50 (s, 2 H, NH_2), 6.23 (d, 1 H, $J_{1',2'}$, 3.6 Hz, H-1'), 5.67 (d, 1 H, 5'OH), 5.27 (m, 1 H, H-2'), 5.12 (m, 1 H, H-3'), 4.81 (t, 1 H, 6'OH), 4.46 (m, 1 H, H-4'), 3.78 (br m, 1 H, H-5'), 3.40 (br m, 2 H, H-$6'_a$,$6'_b$), 1.68, 1.44 (both s, 3 H, each, gem-Me_2); ^{13}C NMR (Me_2SO-d_6): δ 156.2 (C-6), 152.6 (C-2), 148.9 (C-4), 139.9 (C-8), 119.0 (C-5), 113.1 (CMe_2), 89.7 (C-1'), 84.9 (C-4'), 83.5 (C-2'), 81.6 (C-3'), 71.6 (C-5'), 62.1 (C-6'), 27.3, 25.4 (CMe_2). Anal. Calcd for $C_{14}H_{19}N_5O_5$: C, 49.84; H, 5.68; N, 20.76. Found: C, 49.71; H, 6.02: N, 20.54.

Additional **10** (75 mg) was obtained in two crops from the mother liquors. These crystals were combined with the 13 mg isolated from the $CHCl_3$ extract (see below) and recrystallized to give 41 mg of **10**, mp 257–259°C (dec), for a total yield of 46%.

The $CHCl_3$ extract above was evaporated, and the residue was dissolved in MeOH and seeded with **10**. Crystals (13 mg) were obtained and combined with the 75 mg of **10** described above.

9-α-L-Talopyranosyladenine (**12**).—L-Talose (1.46 g, 8.1 mmol) was dissolved in warm, dry pyridine (16 mL), the solution was stirred and chilled in an ice-bath, and Ac_2O (8 mL) was added. The mixture was kept at room temperature for 22 h, then worked-up in the usual manner. The syrup (**11**) was stored under vacuum (30 Torr) over a mixture of P_2O_5, Drierite, and paraffin wax for 14 days, until a constant weight was achieved, 3.13 g (99%); $[\alpha]_D^{24}$ − 42.6° (*c* 4.62, $CHCl_3$).

A portion of the syrup (**11**) (2.71 g, 6.93 mmol) was coupled with *N*-benzoyl-*N*,9-bis(trimethysilyl)adenine (from 1.83 g of *N*-benzoyladenine, 7.62 mmol) as described for the preparation of **9**. The mixture was worked up in a similar manner to give a yellow foam (3.88 g). After removal of the blocking groups (methanolic NaOMe) and neutralization of the solution, **12** crystallized. Recrystallization from H_2O yielded three crops of crystals, 0.642 g (31%). Additional **12** was obtained by combining the MeOH and H_2O mother liquors, conversion to the picrate and regeneration of free **12** again with an ion-exchange resin (Bio-Rad AG1-X8, CO_3^{2-} form) [16,27]. Treatment with Darco G-60, followed by crystallization from a small volume of H_2O in the refrigerator, gave an additional 0.297 g of **12**, for a total yield of 46%. The crystals were in the form of small rodlike prisms, mp 250–251.5°C (dec); $[\alpha]_D^{25}$ − 92.9°C (*c* 2.22, N HCl); UV_{max} (pH 1) 257 nm (ϵ 14 600), (H_2O) 260 (ϵ 14 740), (pH 13) 260 (ϵ 14 970); UV_{min} (pH 1) 228 nm (ϵ 2 930), (H_2O) 225 (ϵ 2 090), (pH 13) 229 (ϵ 2 980); ^{1}H NMR (Me_2SO-d_6): δ 8.41, 8.27 (both s, 1 H each, H-2, H-8), 7.38 (s, 2 H, NH_2), 5.97 (d, 1 H, $J_{1',2'}$ 8.2 Hz, H-1'), 5.41 (d, 1 H, 3'-OH), 5.30 (d, 1 H, 2'-OH), 5.23 (d, 1 H, 4'-OH), 4.76 (t, 1 H, 6'-OH), 4.42 (m, 1 H, H-2'), 4.13 (br s, 1 H, H-3'), 4.04 (br s, 2 H, H-4', H-5'), 3.82 (q, 2 H, H-$6'_a$,$6'_b$); ^{13}C NMR (Me_2SO-d_6): δ 155.8 (C-6), 152.3 (C-2), 149.7 (C-4), 139.8 (C-8), 118.6 (C-5), 78.7 (C-1'), 77.1 (C-5'), 70.2, 68.3, 67.8 (C-3', C-2', C-4'), 57.9 (C-6'); R_{Adc} 0.18 (86 : 14 *n*-butanol–H_2O); R_{Adc} 1.55 (5% aq Na_2HPO_4). Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N 23.56. Found: C, 44.55; H, 5.21, N, 23.73.

The D form of the nucleoside was reported to have mp 251–252°C; $[\alpha]_D^{22}$ + 91.3° (*c* 3.00, N HCl) [16]. The IR spectrum of **12** had peaks corresponding to those reported for the D form [16].

Deamination with adenosine deaminase.—The enzyme (calf intestinal adenosine deaminase, type I) was purchased from Sigma Chemical Co. A solution (3 mL) of the nucleoside (5×10^{-5} M) in 0.05 M phosphate buffer (pH 7.6) was placed in a cuvette, and the reaction was started by addition of 0.1 mL (2.3 units) of the enzyme solution [22]. The reaction was followed with a Beckman 25 UV spectrophotometer at 265 nm at 25°C. Nucleoside **9** was completely deaminated in 30 min (UV_{max} 249 nm). Nucleside **12** was not a substrate, even after addition of 10 units of enzyme and a reaction time of several h.

Antileukemic assay.—Experimental details concerning the studies with L1210 cells were reported in previous papers [28,29]. The authors are grateful to Dr. Bertrum Sheid for providing these results.

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