# Preparation of 4'-Amino Hexopyranose Nucleosides from Keto Nucleosides. An Approach to Amino Nucleoside Antibiotics

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Amino hexopyranose nucleosides were prepared by treatment of the keto group with hydroxylamine hydrochloride followed by acetylation of the resulting oxime. Among other reagents, sodium borohydride–nickel chloride or sodium borohydride–molybdenum(vi) oxide were found to be excellent reductive systems for the facile synthesis of amino hexopyranose nucleosides.

The 4'-amino hexopyranose skeleton is found in several biologically active naturally occurring nucleosides including gougerotin and blasticidin[1,2] which are of great interest due to their pronounced antibiotic and antitumoral activities. Synthetic approaches to these nucleosides have been reported to occur either by condensation of amino sugars with heterocyclic bases[3,4] or by direct modification of a nucleoside.[5] In both cases the amino function was introduced *via* an azido group by a substitution-reduction sequence.

Blasticidin S

Gougerotin
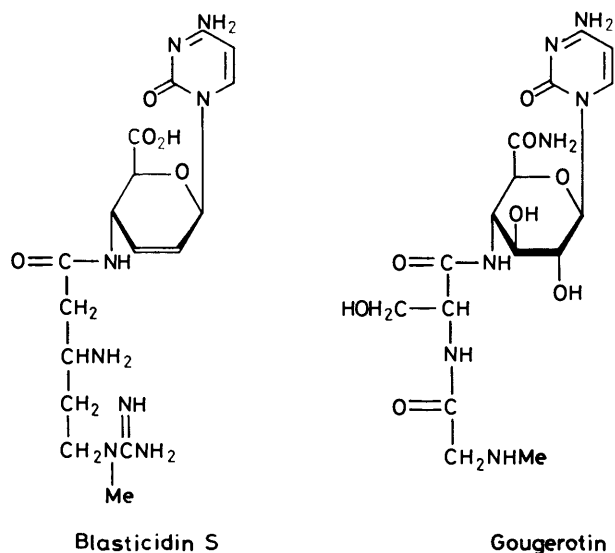
Considerably less attention has been given to biomimetic synthesis from keto nucleosides as has been hypothesized by Seto *et al.*[6] This strategy offers a straightforward approach avoiding side reactions which are often significant during azide group introduction.[7]

In connection with our continuing interest in keto hexopyranosyl nucleosides[8] we have recently shown that this class of biologically active compounds[9] are important building blocks for the preparation of a wide range of new nucleosidic structures such as fused lactone nucleosides[10] and spiro epoxy derivatives.[11] We have also demonstrated that hydride reduction of isopropylidene and unsaturated nucleosides proceeds with a high degree of stereo- and chemo-selectivity.[8] These results suggested that hydride addition to imino or hydroximino nucleosides prepared from keto nucleosides could lead to amino hexopyranose nucleosides in a straightforward and stereoselective manner.
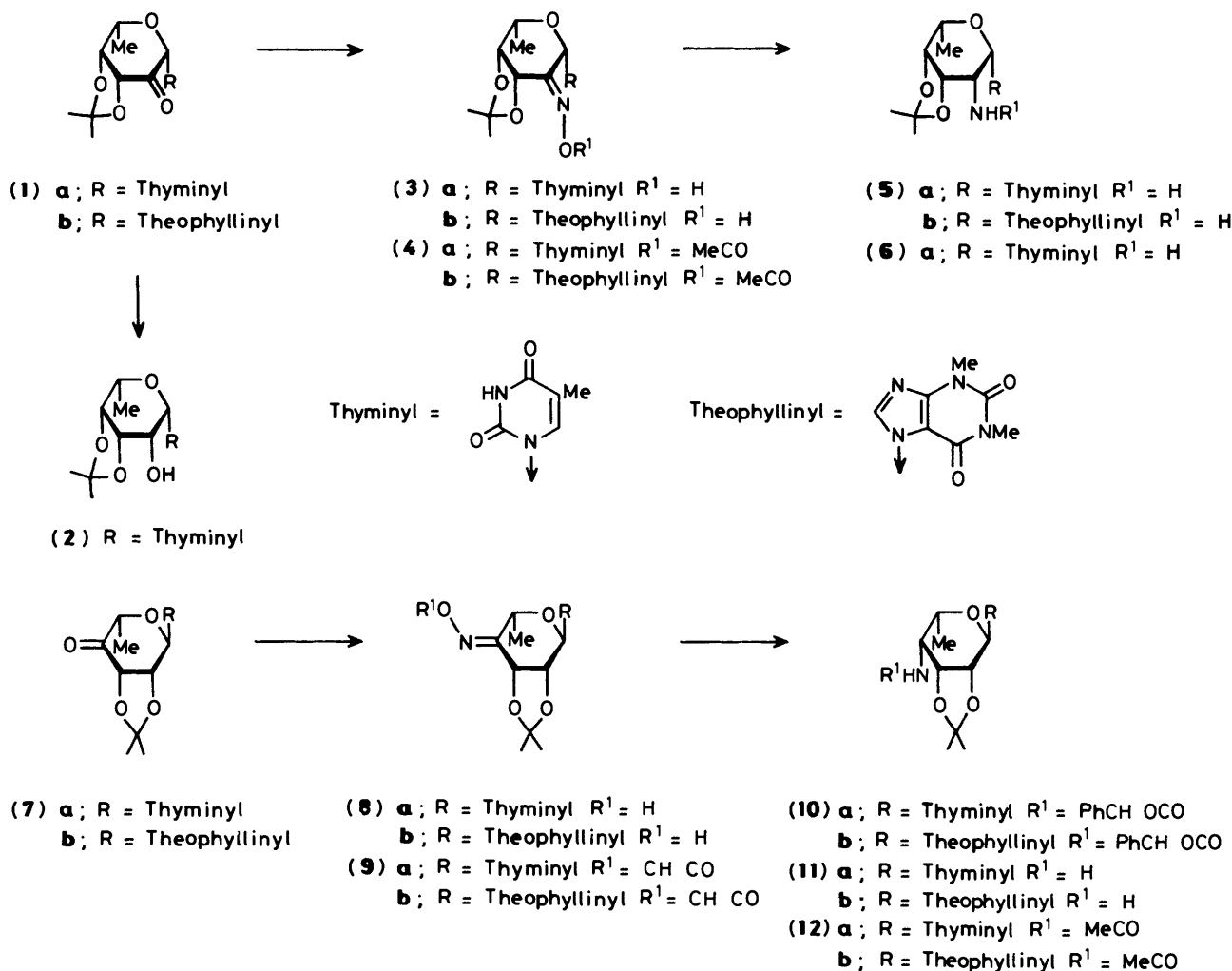
In this paper we describe the synthesis of 2'- and 4'-amino

nucleosides from readily accessible 6-deoxy-L-hexopyranosyl isopropylidene keto nucleosides and 6-deoxy-L-hexopyranosyl unsaturated keto nucleosides. The choice of these nucleosides as models originates from the idea that 6-deoxy-2- and -4-L-amino nucleosides may be expected to offer new antineoplastic properties since 6-deoxy-L-amino sugars constitute the carbohydrate part of a great number of naturally occurring biologically active glycosides.[12]

Results and Discussion

The approach employed initially was based on the reaction of keto nucleosides with sodium cyanoborohydride in the presence of ammonium acetate.[13] Reaction of 1-(6'-deoxy-3',4'-O-isopropylidene-β-L-*lyxo*-hexopyranosulosyl)thymine[10] (**1a**) with this system provided mainly the *talo*-nucleoside (**2**). A suitable strategy for amino nucleoside preparation[14,15] would involve conversion of the ketone into an oxime followed by reduction of the latter. Thus compound (**1a**) treated with hydroxylamine hydrochloride afforded the oxime nucleoside (**3a**). The product isolated in 70% yield consisted predominantly of the Z-isomer[9] (2:1) as established from ^{1}H n.m.r. spectroscopy {δ_H 6.7 [0.66 H, s, 1'-H (Z)], 6.5 [0.33 H, s, 1'-H (E)]}. Attempts to reduce the oxime with various standard reagents such as LiAlH$_4$ or BH$_3$ failed to provide the aminonucleoside. It was recognized that oxime O-acylation favoured reduction. Accordingly oxime (**3a**) was treated with acetic anhydride (Ac$_2$O–pyridine–DMAP) then submitted to catalytic hydrogenation (PtO$_2$).[16,17] Under these conditions, the nucleoside (**5a**), a polar compound giving a positive reaction with ninhydrin, was isolated in 20% yield. The presence of the amino group was indicated by the 60 MHz ^{1}H n.m.r. spectrum which had resonances at δ_H 3.3 (dd, J 3.6 and 5 Hz) and 5.9 (d, J 3.6 Hz) assigned respectively to 1'-H and 2'-H. These data indicated clearly that the addition of the hydride from the less hindered side led to the rare sugar L-*talo*-2'-amino nucleoside (**5a**). Although the catalytic reduction furnished the amino derivative, the low yield prompted us to examine sodium borohydride reduction of oxime in the presence of nickel chloride or molybdenum(vi) oxide.[18]

Reaction of the hydroximino nucleoside (**3a**) with NaBH$_4$ in methanol at −30 °C in the presence of nickel(ii) chloride by means of the Ipaktschi procedure[18] gave no conversion of the oxime group. In contrast treatment of the oxime-O-acetate (**4a**) afforded the 2'-amino nucleoside (**5a**) in 60% yield. Examination of the n.m.r. spectra at 60 MHz revealed the presence of two 2'-amino nucleosides with the same, $J_{1',2'}$ 3.6 Hz, coupling constants. Repeated purification showed only one product on t.l.c. and the compound homogeneity was ascertained by elemental analysis. Examination of the product at 300 MHz confirmed the presence of two L-*talo*-2'-amino derivatives. However reduction of compound (**4a**) followed by treatment of the reaction mixture

(1) a ; R = Thyminyl
   b ; R = Theophyllinyl

(3) a ; R = Thyminyl R^1 = H
(3) b ; R = Theophyllinyl R^1 = H
(4) a ; R = Thyminyl R^1 = MeCO
(4) b ; R = Theophyllinyl R^1 = MeCO

(5) a ; R = Thyminyl R^1 = H
(5) b ; R = Theophyllinyl R^1 = H
(6) a ; R = Thyminyl R^1 = H

(2) R = Thyminyl

Thyminyl =

Theophyllinyl =

(7) a ; R = Thyminyl
   b ; R = Theophyllinyl

(8) a ; R = Thyminyl R^1 = H
(8) b ; R = Theophyllinyl R^1 = H
(9) a ; R = Thyminyl R^1 = CH CO
(9) b ; R = Theophyllinyl R^1 = CH CO

(10) a ; R = Thyminyl R^1 = PhCH OCO
(10) b ; R = Theophyllinyl R^1 = PhCH OCO
(11) a ; R = Thyminyl R^1 = H
(11) b ; R = Theophyllinyl R^1 = H
(12) a ; R = Thyminyl R^1 = MeCO
(12) b ; R = Theophyllinyl R^1 = MeCO

with acetic anhydride yielded only the 2'-acetamido derivative (6a). Examination of the n.mr. spectrum revealed a single compound produced by the stereoselective addition of the hydride ion from the less hindered side. Finally acetylation of the crystalline compound (5a) with acetic anhydride in methanol gave compound (6a) quantitatively as a single product thus confirming the purity of the free amino nucleoside.*

The preparation of a 2'-amino purine derivative was carried out in a similar way. The theophylline nucleoside [19] (1b) was treated with hydroxylamine hydrochloride. After 2 h compound (3b) was isolated as a single Z-isomer as evidenced by the downfield shift of the 1'-H signal at δ_H 7.3. Acetylation of compound (3b) in the standard manner followed by boro-hydride reduction in the presence of NiCl$_2$ furnished the amino nucleoside (5b) in 20% yield only. MoO$_3$-Assisted reduction of (4b) at 0 °C gave better results and afforded the L-talo

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* Despite various experiments the nature of the interaction revealed by the n.m.r. spectrum could not be clearly established. The n.m.r. spectrum of compound (5a) exhibited a temperature and solvent dependency. In CDCl$_3$ variation of the temperature (25—55 °C) had a marked effect upon the equilibria affording exclusively the minor component of the mixture. In [^{2}H$_6$]acetone this transformation occurred in 5 min at 25 °C whereas in deuteriated dimethyl sulphoxide heating above 120 °C for several hours was required. Finally after cooling of the observed samples no formation of the major component of the mixture could be detected even after several days.

nucleoside (5b) in 60% yield. The ^{1}H n.m.r. spectrum of this compound closely resembled that of compound (5a). At 300 MHz the presence of the axial amino group at 2'-C was indicated by the characteristic resonance at δ_H 3.34 (1 H, dd, J 2.6 and 5 Hz) and by the 1'-H doublet at δ_H 6.10 (1 H, d, J 2.6 Hz).
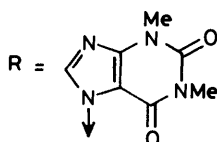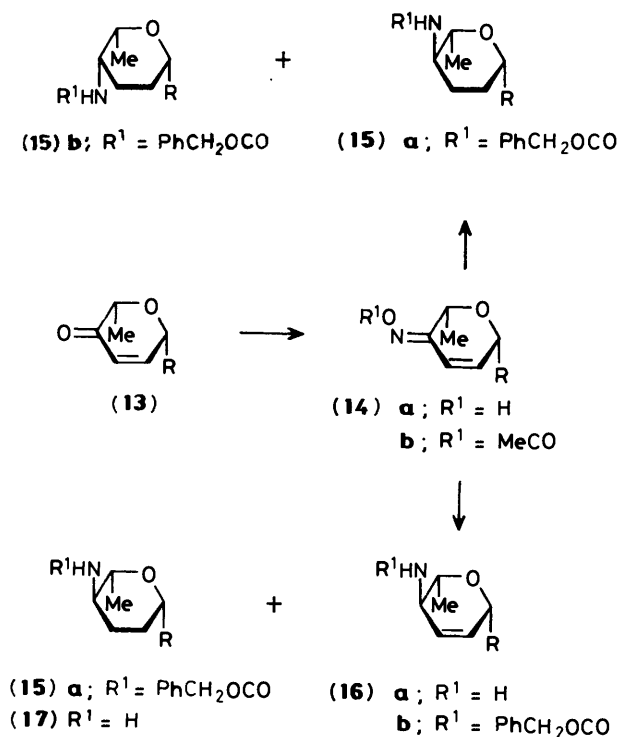
This success prompted further exploration and our attention was focussed on 4'-keto nucleosides. The keto nucleosides (7a)[20] and (7b)[21] were treated with hydroxylamine hydro-chloride affording oximes (8a) and (8b) as the E-isomers. The cis relationship between the oxime and the 5'-C carbon was clearly discernible by the upfield shift of the 5'-H resonance at δ_H 5.3 for (8a) and 5.04 for (8b).

Reduction of the acetylated oximes (9a) and (9b) in the presence of nickel chloride gave the 4'-amino nucleosides which were isolated as benzyl carbamates (10a) and (10b). Catalytic reduction of compounds (10a) and (10b) with Pd–C afforded the free amino nucleosides (11a) and (11b) but treatment with MoO$_3$–NaBH$_4$ gave the cleanest reaction allowing direct isolation of (11a) and (11b). The structures of the products were deduced from the ^{1}H n.m.r. spectra of the 4'-acetamido derivatives (12a) and (12b). The presence of the 4'-amido group was indicated by the 4'-H signals [(12a) δ_H 4.67 (1 H, ddd, J 4.4, 6.7, and 8.9 Hz), (12b) δ_H 4.75 (1 H, ddd, J 4.7, 6.4, and 8.9 Hz)]. Examination of the $J_{4',5'}$ coupling constants [(12a) 6.7 Hz, (12b) 6.4 Hz] suggested an axial equatorial relationship indicating addition of the hydride from the less hindered side. On the basis of molecular models it was expected that NOESY data would

ascertain the stereochemistry at 4'-C. Thus 2D proton-proton correlated spectra using CONOESY pulse sequence were recorded. For both the 4'-acetamido nucleosides (12a) and (12b) the 6'-H protons show a n.O.e. interaction with 1'-H and NH. Furthermore no correlation could be established between NH, 3'-H, and 5'-H. The $J_{NH,4'-H}$ value of 8.9 Hz suggesting a trans relationship,[22] these above observations demonstrated a *syn* relationship between the 6'-Me, 1'-H, and the 4'-acetamido group consistent with an L-*talo* configuration for compounds (12a) and (12b).

Reduction of α,β-unsaturated oximes[23] was also investigated in an attempt to prepare 2',3'-unsaturated 4'-amino nucleosides. Treatment of the keto nucleoside (13) with hydroxylamine

(15) b; R¹ = PhCH₂OCO   (15) a; R¹ = PhCH₂OCO

(13)   (14) a; R¹ = H
            b; R¹ = MeCO

(15) a; R¹ = PhCH₂OCO   (16) a; R¹ = H
(17) R¹ = H   b; R¹ = PhCH₂OCO

$$R = $$

hydrochloride resulted in the exclusive formation of the oxime (14a). The conjugated nature of (14a) was confirmed by the characteristic ¹H n.m.r. spectrum consisting of resonances at δ_H 4.8 (q, *J* 6.5 Hz, 5'-H), 6.5 (*J* 1.8 and 10 Hz, 3'-H), and 7.5 (*J* 1.8 and 10 Hz, 2'-H). Acetylation of the oxime (14a) yielded the oximinyl acetate (14b).

Reduction of compound (14b) with $NaBH_4–NiCl_2$ afforded a 1:1 mixture of two labile amines which could not be isolated. Treatment of the reaction mixture with benzyl chloroformate afforded the benzyl carbamates (15a) and (15b). As expected the presence of four methylene protons at δ_H 1.81, 2.15, and 2.25 p.p.m. for the less polar isomer (15a) and at δ_H 1.95 and δ_H 2.48 for (15b) indicated the reduction of the double bond. Furthermore examination of the 5'-H signal revealed a $J_{4',5'}$ 9.89 Hz coupling for the 7-(4'-*benzyloxycarbonylamino*-2',3',4',6'-*tetradeoxy*-β-L-erythro-*hexopyranosyl*)*theophylline* (15a) and a 1.6 Hz coupling constant for the 7-(4'-*benzyloxycarbonylamino*-

2',3',4',6'-*tetradeoxy*-β-L-threo-*hexopyranosyl*)*theophylline* (15b).

Molybdenum oxide assisted reduction of the oxime (14b) also afforded two products. Crystallization of the less polar isomer afforded the amino nucleoside (16a). The unsaturated nature of (16a) was deduced from the ¹H n.m.r. spectrum with the two olefinic multiplets occurring at δ_H 5.92 and 6.15 p.p.m. Examination of the 5'-H resonance at δ_H 3.71 (dq, *J* 6.1 and 8.36 Hz) indicated an axial addition of the hydride ion leading to the L-*erythro*-4'-amino nucleoside.

The 300 MHz high resolution n.m.r. spectrum of compound (17) was consistent with the 4'-amino tetrahydropyranosyl structure. The detailed assignments were supported by two dimensional chemical shift correlation. The high resolution COSY spectrum of compound (17) (Figure 1) clearly indicated that the 1'-H protons at δ_H 5.98 p.p.m. is coupled with the signal at δ_H 1.84 and 2.30 assigned respectively to 2'-H_a and 2'-H_e and that these two protons are coupled with each other. These two signals are correlated with the 3'-H resonances at δ_H 1.58 (3'-H_a) and δ_H 2.12 (3'-H_e) which in turn are coupled with each other and with the 4'-H signal at δ_H 2.58 Hz. Finally the overlapped resonance at δ_H 3.46 correlated to 4'-H and 6'-H was assigned to 5'-H. The 4'-H proton appeared as a multiplet (1 H, ddd, *J* 4.05, 9.25, and 11.17 Hz) with a large $J_{4',5'}$ 9.25 Hz coupling constant consistent with the L-*erythro* configuration for the labile amine (16a). Direct treatment of the reaction mixture with benzyl chloroformate furnished the 7-(4'-benzyloxycarbonylaminohex-2'-enopyranosyl)theophylline (16b) and a saturated carbamate which proved to be identical with the 7-(4'-*benzyloxycarbonylamino*-2',3',4',6'-*tetradeoxy*-β-L-erythro-*hexopyranosyl*)*theophylline* (15a) prepared by nickel chloride assisted reduction.

We have devised a new method for the preparation of amino hexopyranose nucleosides from keto nucleosides and found that these reactions are highly stereoselective and lead to amino nucleosides by hydride addition from the less hindered side. The formation of allylic amino nucleosides is also stereoselective and affords the equatorial amino group suggesting that this methodology could be applied to the synthesis of naturally occurring nucleosides.

Experimental

(E,Z)-1-(2'-*Acetoximino*-2',6'-*dideoxy*-3',4'-O-*isopropylidene*-β-L-talo-*hexopyranosyl*)*thymine* (4a).—Pyridine (0.492 g, 6.24 mmol), acetic acid anhydride (0.636 g, 6.24 mmol) and several crystals of 4-dimethylaminopyridine were added to a solution of (E,Z)-1-(2',6'-dideoxy-3',4'-O-isopropylidene-2'-hydroximino-
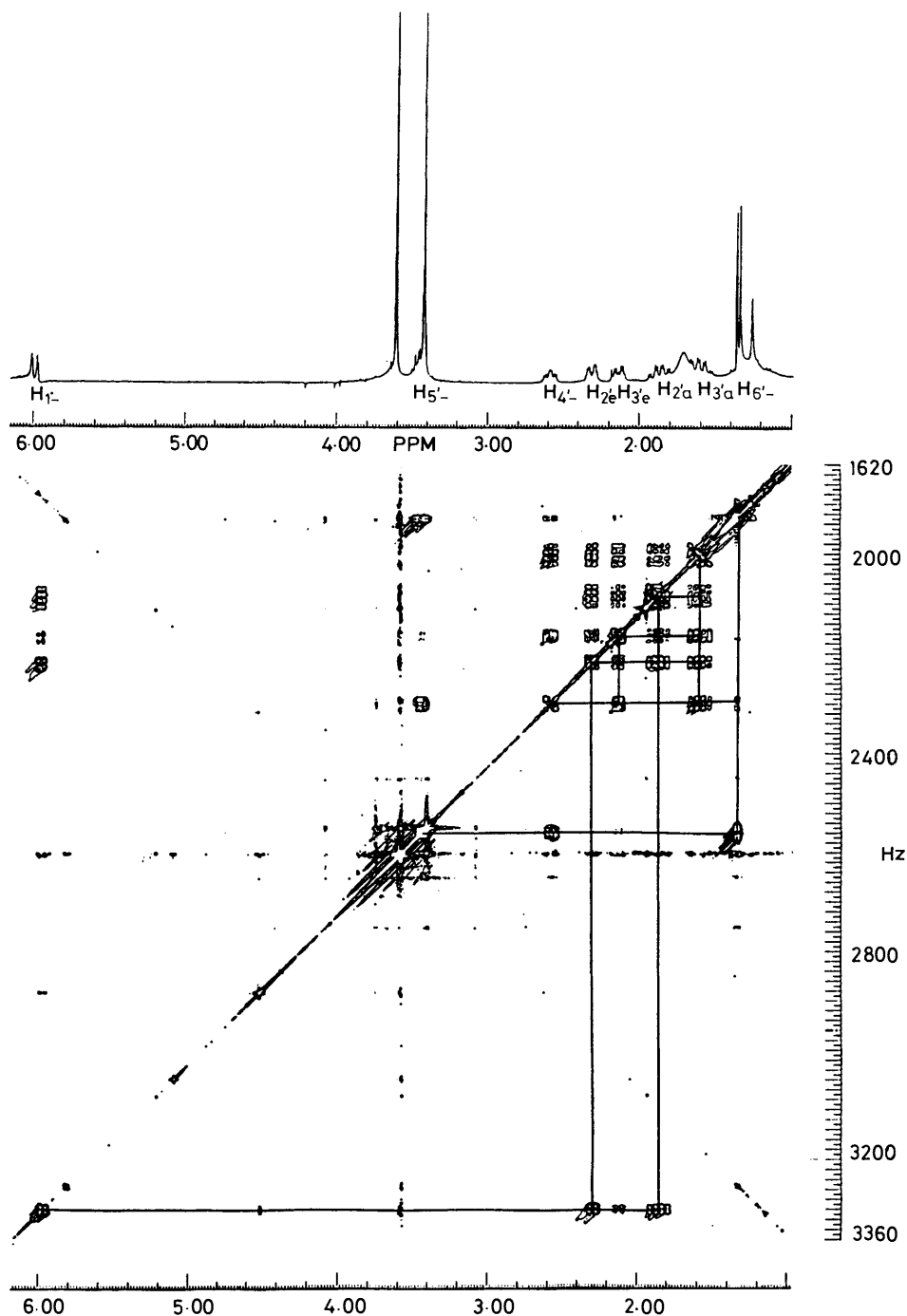
Figure 1. Contour plot of a high resolution COSY spectrum for (**17**). The 1D 300 MHz ¹H n.m.r. spectrum is shown above.

β-L-*lyxo*-hexopyranosyl)thymine (**3a**)* (1.688 g, 5.2 mmol) in dichloromethane (52 ml). After being stirred for 2 h the resulting mixture was concentrated under reduced pressure. Crystallisation yielded compound (**4a**) as a 2:1 mixture of (*E*) and (*Z*) isomers (1.465 g, 80%).

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* For (**3a**) δ_H(60 MHz, CDCl₃) 1.35 (3 H, d, *J* 6.5 Hz, 6'-H), 1.4 and 1.57 (2 × 3 H, 2 × s, Me₂C), 1.8 (3 H, s, 5-Me), 3.7 (1 H, dq, *J* 2 and 6.5 Hz, 5'-H), 4.3 (1 H, dd, *J* 2 and 7 Hz, 4'-H), 5 (0.66 H, d, *J* 7 Hz, 3'-H), 5.9 (0.33 H, d, *J* 7 Hz, 3'-H), 6.5 (0.33 H, s, 1'-H), 6.7 (0.66 H, s, 1'-H), 7.7 (0.33 H, s, 6-H), and 7.9 (0.66 H, s, 6-H).

Mixture: m.p. 177—180 °C (from EtOH); [α]_D^{20} −35° (*c* 0.1 in MeOH); λ_max.(MeOH) 262 nm (ε in dm³ mol⁻¹ cm⁻¹ 6 973); δ_H[60 MHz, (CD₃)₂CO] 1.30 (3 H, d, *J* 6 Hz, 6'-H), 1.45 and 1.60 (2 × 3 H, 2 × s, Me₂C), 1.80 (3 H, s, 6-Me), 2.10 (3 H, s, MeCO), 4 (1 H, dq, *J* 1.5 and 6 Hz, 5'-H), 4.20 (1 H, dd, *J* 1.5 and 7 Hz, 4'-H), 4.80 and 5.40 (0.33 H and 0.66 H, two d, *J* 7 Hz, 3'-H), 6.36 and 6.46 (0.66 H, and 0.33 H, 1'-H), and 7.50 and 7.80 (0.66 H and 0.33 H, 2 × s, 6-H).

'Flash' chromatography on silica gel with ethyl acetate–pentane (6:4) then crystallisation afforded the pure derivatives.

(*E*): m.p. 212 °C (from EtOH); [α]_D^{20} −60° (*c* 0.1 in MeOH)

(Found C, 52.2; H, 5.65; N, 11.45. $C_{16}H_{21}N_3O_7$ requires C, 52.32; H, 5.72; N, 11.34%); $\lambda_{max.}$(MeOH) 262 nm (ε 7 523).

(Z): m.p. 192 °C (from EtOH); $[\alpha]_D^{20}$ $-20°$ (c 0.1 in MeOH) (Found: C, 52.2; H, 5.7; N, 11.3); $\lambda_{max.}$(MeOH) 262 nm (ε 8 881).

1-(2'-Amino-2',6'-dideoxy-3',4'-O-isopropylidene-β-L-talo-hexopyranosyl)thymine (5a).—Nickel chloride (NiCl$_2$·6H$_2$O; 1.6 g, 6.75 mmol) was added to a solution of the (E,Z) nucleoside (4a) (1.04 g, 2.8 mmol) in methanol (30 ml) at -30 °C. To the resulting suspension sodium borohydride (1.06 g, 28 mmol) was added slowly. The reaction mixture was stirred for 1 h. It was then poured into brine (25 ml) and ethyl acetate (25 ml) and the aqueous phase was extracted with ethyl acetate (3 × 25 ml). The combined organic extracts were dried (Na$_2$SO$_4$) then evaporated under reduced pressure. Column chromatography on silica gel with ethyl acetate–methanol (8:2) gave the 2'-amino-talo-nucleoside (5a) (0.522 g, 60%), m.p. 130 °C (from acetone); $[\alpha]_D^{20}$ $-80°$ (c 0.1 in MeOH) (Found: C, 52.65; H, 6.5; N, 13.3. $C_{14}H_{21}N_3O_5$·0.5H$_2$O requires C, 52.5; H, 6.87; N, 13.2%); $\lambda_{max.}$(MeOH) 266 nm (ε 11 133); δ_H(300.13 MHz, CDCl$_3$) 1.39 (3 H, s, Me$_2$C), 1.52 (1.3 H, d, J 6.8 Hz, 6'-H), 1.6 (1.7 H, d, J 6.8 Hz, 6'-H), 1.63 and 1.67 (1.3 H and 1.7 H, 2 × s, Me$_2$C), 1.94 and 1.98 (1.3 H and 1.7 H, 2 × s, Me 5-C), 3.48 (0.43 H, dd, J 3.6 and 4.3 Hz, 2'-H), 4.06 (0.43 H, dd, J 2.6 and 6.8 Hz, 5'-H), 4.11—4.2 (m, 1.57 H, 4'-H and 5'-H), 4.24 (0.57 H, J 3.6 and 5.7 Hz, 2'-H), 4.49 (0.43 H, dd, J 4.3 and 5.7 Hz, 3'-H), 4.64 (0.57 H, dd, J 5.7 and 6.1 Hz, 3'-H), 6.15 (0.43 H, s, J 3.6 Hz, 1'-H), 6.31 (0.57 H, s, J 3.6 Hz, 1'-H), and 8.1 and 8.16 (0.43 H and 0.57 H, 2 × s, 6-H).

1-(2'-Acetamido-2',6'-dideoxy-3',4'-O-isopropylidene-β-L-talo-hexopyranosyl)thymine (6a).—(a) From the oxime acetate (4a). Nickel chloride (NiCl$_2$·6H$_2$O; 0.8 g, 3.36 mmol) was added to a solution of the nucleoside (4a) (0.52 g, 1.42 mmol) in methanol (15 ml) at -30 °C. To the resulting suspension sodium borohydride (0.53 g, 14 mmol) was added slowly. The reaction mixture was stirred for 1 h then acetic anhydride (0.33 g, 3.47 mmol) was added. The reaction mixture was then poured into brine (15 ml) and ethyl acetate (15 ml) and the aqueous phase was extracted with ethyl acetate (3 × 15 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated under reduced pressure to afford the 2'-acetamido-talo-nucleoside (6a) (0.247 g, 50%).

(b) From the amino nucleoside (5a). Acetic anhydride was added (0.121 g, 1.2 mmol) to a solution of the nucleoside (5a) (0.311 g, 1 mmol) in methanol (10 ml) at 25 °C. After 30 min the solvent was evaporated under reduced pressure to give the 2'-acetamido-talo-nucleoside (6a) (0.47 g, 95%), m.p. 145—148 °C (from diethyl ether–ethanol), $[\alpha]_D^{20}$ -85 °C (c 0.1 inMeOH) (Found: C, 51.25; H, 6.55; N, 10.9. $C_{16}H_{23}N_3O_6$·H$_2$O requires C, 51.75; H, 6.73; N, 11.32%); $\lambda_{max.}$(MeOH) 266 nm (ε 11 260); δ_H(60 MHz, C$_5$D$_5$N) 1.2—1.4 (9 H, m, J 6.5 Hz, 6'-H and Me$_2$C), 1.8 (3 H, s, MeCO), 2.1 (3 H, s, 5-Me), 3.8 (1 H, dq, J 2 and 6.5 Hz, 5'-H), 4.1 (1 H, dd, J 2 and 7 Hz, 4'-H), 4.6 (1 H, dd, J 5 and 7 Hz, 3'-H), 5.2 (1 H, ddd, J 5, 5, and 8.7 Hz, 2'-H), 6.4 (1 H, d, J 5 Hz, 1'-H), 7.9 (1 H, s, 6-H), and 8.4 (1 H, d, J 8.7 Hz, NH).

(Z)-7-(2',6'-Dideoxy-2'-hydroximino-3',4'-O-isopropylidene-β-L-lyxo-hexopyranosyl)theophylline (3b).—Hydroxylamine hydrochloride (1.4 g, 20 mmol) was added to a solution of 7-(6'-deoxy-3',4'-O-isopropylidene -β-L-lyxo-hexopyranosulosyl)theophylline (1b) (3.64 g, 10 mmol) in a 1:1 ethanol–pyridine mixture. The mixture was stirred at room temperature for 4 h then water was added and the aqueous mixture was extracted with dichloromethane (3 × 15 ml). The dichloromethane extracts were dried (Na$_2$SO$_4$) to leave, after the solvent was evaporated off, a crude product from which was isolated the oxime (3b) (3.03 g, 80%), m.p. 150 °C (from MeOH); $[\alpha]_D^{20}$

$-55°$ (c 0.1 in MeOH) (Found: C, 49.35; H, 5.5; N, 18.05. $C_{16}H_{21}N_5O_6$·0.5H$_2$O requires C, 49.48; H, 5.67; N, 18.08%); $\lambda_{max.}$(MeOH) 276 nm (ε 9 209); δ_H[60 MHz, (CD$_3$)$_2$CO] 1.3 (3 H, d, J 7 Hz, 6'-H), 1.5 and 1.6 (2 × 3 H, 2 × s, Me$_2$C), 3.4 and 3.6 (2 × 3 H, 2 × s, NMe), 3.8 (1 H, dq, J 7 and 2 Hz, 5'-H), 4.5 (1 H, dd, J 2 and 8 Hz, 4'-H), 5.1 (1 H, d, J 8 Hz, 3'-H), 7.3 (1 H, s, 1'-H), and 8.1 (1 H, s, 8-H).

7-(2'-Acetoximino-2',6'-dideoxy-3',4'-O-isopropylidene-β-L-hexopyranosyl)theophylline (4b).—The hydroximinyl nucleoside (3b) (1.875 g, 5 mmol) in pyridine (10 ml) was treated with acetic anhydride (0.61 g, 6 mmol) in the presence of a catalytic amount of 4-dimethylaminopyridine. The resulting solution was worked up as for (4a) to yield the title compound (4b); m.p. 205 °C (from EtOH); $[\alpha]_D^{20}$ $-125°$ (c 0.1 in MeOH) (Found: C, 51.45; H, 5.5; N, 16.45. $C_{18}H_{23}N_5O_7$ requires C, 51.30; H, 5.46; N, 16.62%); $\lambda_{max.}$(MeOH) 276 nm (ε 7 990); δ_H (60 MHz, CDCl$_3$) 1.3 (3 H, d, J 7 Hz, 6'-H), 1.5 and 1.6 (2 × 3 H, 2 × s, Me$_2$C), 2 (3 H, s, MeCO), 3.4 and 3.6 (2 × 3 H, 2 × s, NMe), 3.7 (1 H, m, 5'-H), 4.5 (1 H, dd, J 2 and 8 Hz, 4'-H), 5.1 (1 H, d, J 8 Hz, 3'-H), 7.3 (1 H, s, 1'-H), and 8.1 (1 H, s, 8-H).

7-(2'-Amino-2',6'-dideoxy-3',4'-O-isopropylidene-β-L-talo-hexopyranosyl)theophylline (5b).—Molybdenum oxide (0.36 g, 2.5 mmol) was added to a solution of the nucleoside (3b) (0.421 g, 1 mmol) in MeOH (10 ml) at 0 °C. Sodium borohydride (0.76 g, 20 mmol) was added portionwise for 1 h then the reaction mixture was poured into brine (10 ml) and ethyl acetate (10 ml) and the aqueous solution was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried (Na$_2$-SO$_4$) then evaporated under reduced pressure. Column chromatography on silica gel (ethyl acetate–MeOH, 9:1) gave the 2'-amino-talo-nucleoside (5b) (0.219 g, 60%), m.p. 195—197 °C (from diethyl ether–pentane); $[\alpha]_D^{20}$ $-95°$ (c 0.1 in MeOH) (Found: C, 52.6; H, 6.4; N, 19.9. $C_{16}H_{23}N_5O_5$ requires C, 52.60; H, 6.30; N, 19.17%); $\lambda_{max.}$(MeOH) 275 nm (ε 9 563); δ_H(300.13 MHz, CDCl$_3$) 1.44 (3 H, d, J 6.3 Hz, 6'-H), 1.41 and 1.60 (2 × 3 H, 2 × s, Me$_2$C), 3.34 (1 H, dd, J 2.6 and 5 Hz, 2'-H), 3.4 and 3.6 (2 × 3 H, 2 × s, NMe), 4.10—4.20 (2 H, m, 4'-H and 5'-H), 4.55 (1 H, dd, J 5 and 6.1 Hz, 3'-H), 6.10 (1 H, d, J 2.6 Hz, 1'-H), and 8.43 (1 H, s, 8-H).

(E)-1-(4',6'-Dideoxy-4'-hydroximino-2',3'-O-isopropylidene-α-L-lyxo-hexopyranosyl)thymine (8a).—Hydroxylamine hydrochloride (2.105 g, 30.3 mmol) was added to a solution of 1-(6'-deoxy-2',3'-O-isopropylidene-α-L-lyxo-hexopyranos-4'-ulosyl)-thymine (7a) (4.7 g, 15.15 mmol) in ethanol (15 ml) and pyridine (15 ml). After 2 h the solution was poured into brine (30 ml). The aqueous phase was extracted with ethyl acetate (3 × 30 ml) and the combined extracts were evaporated to yield (8a) (4.43 g, 90%), m.p. 303 °C (from EtOH); $[\alpha]_D^{20}$ $-40°$ (c 0.1 in MeOH) (Found: C, 51.8; H, 5.8; N, 13.1. $C_{14}H_{19}N_3O_6$ requires C, 51.68; H, 5.68; N, 12.91%); $\lambda_{max.}$(MeOH) 264 nm (ε 9 845); δ_H(60 MHz, CD$_3$CO$_2$D) 1.55 (3 H, d, J 7 Hz, 6'-H), 1.45 and 1.60 (2 × 3 H, 2 × s, Me$_2$C), 1.95 (3 H, s, 5-Me), 4.6 (1 H, dd, J 6 and 7 Hz, 2'-H), 5 (1 H, d, J 6 Hz, 3'-H), 5.3 (q, 1 H, J 7 Hz, 5'-H), 5.95 (1 H, J 7 Hz, 1'-H), and 7.5 (1 H, s, 6-H).

(E)-1-(4'-Acetoximino-4',6'-dideoxy-2',3'-isopropylidene-α-L-lyxo-hexopyranosyl)thymine (9a).—A 25 ml round bottom flask was charged successively with 4'-hydroximinyl nucleoside (8a) (8.44 g, 26 mmol), pyridine (2.46 g, 31.2 mmol), acetic anhydride (3.18 g, 31.2 mmol), dichloromethane (26 ml), and a catalytic amount of 4-dimethylaminopyridine. After being stirred for 2 h the solution was worked up as for (4a) to yield the title compound (9a) (8.58 g, 90%), m.p. 132—135 °C (from EtOH); $[\alpha]_D^{20}$ $-25°$ (c 0.1 in MeOH) (Found: C, 52.1; H, 5.9; N, 11.4. $C_{16}H_{21}N_3O_7$ requires C, 52.31; H, 5.72; N, 11.39%);

$\lambda_{max.}$(MeOH) 264 (ϵ 9 615); δ_H(300.13 MHz, CDCl$_3$) 1.39 and 1.60 (2 × 3 H, 2 × s, Me$_3$C), 1.62 (3 H, d, J 6.8 Hz, 6'-H), 1.92 (3 H, s, 5-Me), 2.22 (3 H, s, MeCO), 4.50 (1 H, dd, J 5.7 and 6.8 Hz, 2'-H), 5.03 (1 H, dd, J 5.7 Hz, 3'-H), 5.10 (q, 1 H, J 6.8 Hz, 5'-H), 5.86 (1 H, dd, J 6.8 Hz, 1'-H), and 7.07 (1 H, s, 6-H).

1-(4'-Benzyloxycarbonylamino-4',6'-dideoxy-2',3'-O-iso-propylidene-α-L-talo-hexopyranosyl)thymine (10a).—Nickel chloride (NiCl$_2$·6H$_2$O; 0.57 g, 2 mmol) was added to a solution of the nucleoside (9a) (0.367 g, 1 mmol) in methanol (10 ml) at −30 °C. To the resulting suspension sodium borohydride (0.38 g, 10 mmol) was added slowly. After being stirred for 0.5 h, the reaction mixture was cooled to −60 °C and benzyl chloro-formate (1.195 g, 7 mmol) was added. The reaction mixture was warmed to 0 °C and stirred for 1 h, then poured into brine (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residual oil washed with pentane to remove the benzyl derivative gave compound (10a) (0.266 g, 60%), m.p. 238 °C (from EtOH); $[\alpha]_D^{20}$ +5° (c 0.1 in MeOH) (Found: C, 59.45; H, 6.1; N, 9.5. C$_{22}$H$_{26}$N$_3$O$_7$ requires C, 59.45; H, 5.85; N, 9.45%); $\lambda_{max.}$(MeOH) 264 nm (ϵ 7 636); δ_H[300.13 MHz, (CD$_3$)$_2$CO] 1.41 (3 H, d, J 6.4 Hz, 6'-H), 1.33 and 1.54 (2 × 3 H, 2 × s, Me$_2$C), 1.92 (3 H, s, 5-Me), 4.32—4.41 (2 H, m, 4'-H and 5'-H), 4.5 (1 H, dd, J 4.7 and 7 Hz, 2'-H), 4.63 (1 H, dd, J 4.6 and 4.7 Hz, 3'-H), 5.17—5.21 (2 × 1 H, 2 × d, J 6 Hz, CH$_2$C$_6$H$_5$), 5.92 (1 H, d, J 7 Hz, 1'-H), and 7.45 (1 H, s, 6-H).

1-(4'-Amino-4',6'-dideoxy-2',3'-O-isopropylidene-α-L-lyxo-hexopyranosyl)thymine (11a).—(a) From benzyl carbamate (10a). A 125 ml high pressure reactor was charged with compound (10a) (0.444 g, 1 mmol), methanol (20 ml) and Pd–C catalyst (0.044 g). The reactor was pressurized with hydrogen at 3 atm. After 1 h the suspension was filtered off. The solvent was evaporated off and the aminonucleoside (11a) (0.248 g, 80%) was crystallized from ethanol.

(b) From oxime (9a). Molybdenum oxide (0.36 g, 2.5 mmol) was added to a solution of the nucleoside (9a) (0.367 g, 1 mmol) in MeOH (10 ml) at 0 °C. Sodium borohydride (0.76 g, 20 mmol) was added portionwise for 1 h then the reaction mixture was poured into brine (10 ml) and ethyl acetate (10 ml), and the aqueous solution was extracted with ethyl acetate (10 ml). The combined organic extracts were dried (Na$_2$SO$_4$), then evapor-ated under reduced pressure to give after crystallization the 4'-amino nucleoside (11a) (0.153 g, 50%), m.p. 182 °C (from EtOH); $[\alpha]_D^{20}$ −30° (c 0.1 in MeOH) (Found: C, 53.85; H, 7.35; N, 11.6. C$_{14}$H$_{20}$N$_3$O$_5$·C$_2$H$_5$OH requires C, 53.78; H, 7.56; N, 11.76%); $\lambda_{max.}$(MeOH) 264 nm (ϵ 11 594); δ_H(300.13 MHz, CDCl$_3$) 1.4 (3 H, d, J 6.8 Hz, 6'-H), 1.36 and 1.60 (2 × 3 H, 2 × s, Me$_2$C), 1.91 (3 H, s, 5-Me), 3.35 (1 H, dd, J 4.6 and 4.8 Hz, 4'-H), 4.17 (1 H, dq, J 4.6 and 6.8 Hz, 5'-H), 4.22 (1 H, dd, J 5.8 and 8 Hz, 2'-H), 4.48 (1 H, dd, J 4.8 and 5.8 Hz, 3'-H), 5.94 (1 H, d, J 8 Hz, 1'-H), and 7.5 (1 H, s, 6-H).

1-(4'-Acetamido-4',6'-dideoxy-2',3'-isopropylidene-α-L-talo-hexopyranosyl)thymine (12a).—NiCl$_2$·6H$_2$O (0.57 g, 2 mmol) and sodium borohydride (0.38 g, 10 mmol) were added suc-cessively to a solution of nucleoside (9a) (0.367 g, 1 mmol) in methanol (10 ml) at −30 °C. The black suspension was stirred for 1 h then acetic anhydride (1 ml) was added. The solution was partitioned between brine (10 ml) and ethyl acetate (10 ml). The two phases were separated and the aqueous layer was extracted twice with ethyl acetate (10 ml). The organic solution was dried (N$_2$SO$_4$) and concentrated under reduced pressure to yield the 4'-acetamido nucleoside (12a) (0.167 g, 53%), m.p. 286 °C (from dichloromethane–EtOH); $[\alpha]_D^{20}$ +5° (c 0.1 in MeOH) (Found: C, 54.2; H, 6.7; N, 11.7. C$_{16}$H$_{23}$N$_3$O$_6$ requires C, 54.38; H, 6.56;

N, 11.89%); $\lambda_{max.}$(MeOH) 264 nm (ϵ 13 590); δ_H(300.13 MHz, CDCl$_3$) 1.38 and 1.62 (2 × 3 H, 2 × s, Me$_2$C), 1.43 (1 H, dd, J 6.9 Hz, 6'-H), 1.94 (3 H, d, J 1.1 Hz, 5-Me), 2.07 (3 H, s, MeCO), 4.17 (1 H, dd, J 5 and 8 Hz, 2'-H), 4.39 (1 H, dd, 6.4 and 6.9 Hz, 5'-H), 4.67 (1 H, dd, J 4.7 and 5 Hz, 3'-H), 4.75 (1 H, ddd, J 4.7, 6.4 and 8.9 Hz, 4'-H), 5.97 (1 H, dd, J 8 Hz, 1'-H), 6.1 (1 H, dd, J 8.9 Hz, NH), and 7.11 (1 H, dd, J 1.1, 6-H).

(E)-7-(4',6'-Dideoxy-2',3'-O-isopropylidene-4'-hydroximino-α-L-lyxo-hexopyranosyl)theophylline (8b).—Hydroxylamine hydrochloride (1.4 g, 20 mmol) was added to a solution of the ketonucleoside (7b) (3.64 g, 10 mmol) in a mixture of ethanol and pyridine (1 : 1, 20 ml). After being stirred for 1 h, work-up as for compound (3b) afforded the oxime (8b) (2.9 g, 76%), m.p. 142 °C (from EtOH) $[\alpha]_D^{20}$ −95° (c 0.1 in MeOH) (Found: C, 48.65; H, 5.95; N, 17.55. C$_{16}$H$_{21}$N$_5$O$_6$·H$_2$O requires C, 48.36; 5.79; N, 17.63%); $\lambda_{max.}$(MeOH) 275 nm (ϵ 7 996); δ_H(300.13 MHz, CDCl$_3$) 1.42 (3 H, s, Me$_2$C), 1.61 and 1.63 (2 × 3 H, 2 × s, Me$_2$C and 6'-H), 3.42 and 3.60 (2 × 3 H, 2 × s, MeN), 4.72 (1 H, dd, J 6 and 6.1 Hz, 2'-H), 4.96 (1 H, d, J 6.1 Hz, 3'-H), 5.04 (1 H, q, J 7.1 Hz, 5'-H), 6.41 (1 H, d, J 6.1 Hz, 1'-H), and 7.42 (1 H, s, 8-H).

(E)-7-(4'-Acetoximino-4',6'-dideoxy-2',3'-isopropylidene-α-L-lyxo-hexopyranosyl)theophylline (9b).—Pyridine (0.35 g, 4.43 mmol), acetic anhydride (0.45 g, 4.43 mmol), and a catalytic amount of DMAP were added to a solution of compound (8b) (1.4 g, 3.69 mmol) in dichloromethane (18.5 ml). After being stirred for 5 min the reaction mixture concentrated under reduced pressure yielded the title compound (9b) (1.242 g, 80%), m.p. 132—135 °C (from benzene); $[\alpha]_D^{20}$ −87.5° (c 0.1 in MeOH); (Found: C, 48.6; H, 5.5; N, 16.15. C$_{18}$H$_{23}$N$_5$O$_7$·H$_2$O requires C, 49.20; H, 5.69; N, 15.94%); $\lambda_{max.}$(MeOH) 275 nm (ϵ 7 662); δ_H(300.13 MHz, CDCl$_3$) 1.41 and 1.64 (2 × 3 H, 2 × s, Me$_2$C), 1.68 (3 H, d, J 7 Hz, 6'-H), 2.21 (3 H, s, MeCO), 3.41 and 3.60 (2 × 3 H, 2 × s, NMe), 4.74 (1 H, dd, J 5.8 and 6.8 Hz, 2'-H), 5.05 (1 H, q, J 7 Hz, 5'-H), 5.11 (1 H, d, J 5.8 Hz, 3'-H), 6.46 (1 H, d, J 6.8 Hz, 1'-H), and 7.72 (1 H, s, 8-H).

7-(4'-Benzyloxycarbonylamino-4',6'-dideoxy-2',3'-O-iso-propylidene-α-L-talo-hexopyranosyl)theophylline (10b).—Nickel chloride (NiCl$_2$·6H$_2$O; 0.52 g, 2 mmol) was added to a solution of the nucleoside (9b) (0.42 g, 1 mmol) in methanol (10 ml) at −30 °C. To the resulting suspension sodium borohydride (0.38 g, 10 mmol) was added portionwise. The reaction mixture was stirred for 30 min, then cooled to −78 °C, benzyl chloroformate (1.195 g, 7 mmol) was added, and the cooled suspension was poured into brine (10 ml) and ethyl acetate (10 ml) immediately. The aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography using diethyl ether as eluant to give the carbamate (10b) (0.299 g, 60%), m.p. 96—100 °C (from diethyl ether and pentane); $[\alpha]_D^{20}$ −5° (c 0.1 in MeOH) (Found: C, 57.9; H, 5.85; N, 13.65. C$_{24}$H$_{29}$N$_5$O$_7$ requires C, 57.71; H, 5.81; N, 14.02%); $\lambda_{max.}$(MeOH) 275 nm (ϵ 10 528); δ_H[300.13 MHz, (CD$_3$)$_2$CO] 1.44 (3 H, d, J 6.7 Hz, 6'-H), 1.31 and 1.53 (2 × 3 H, 2 × s, Me$_2$C), 3.29 and 3.50 (2 × 3 H, 2 × s, NMe), 4.31 (1 H, dq, J 5 and 6.7 Hz, 5'-H), 4.36 (1 H, br dd, J 5 and 5.1 Hz, 4'-H), 4.40 (1 H, dd, J 5.1 and 5.4 Hz, 3'-H), 4.73 (1 H, dd, J 5.4 and 7.8 Hz, 2'-H), 5.11 (2 H, s, 1 H, CH$_2$C$_6$H$_5$), 6.21 (1 H, m, NH), 6.23 (1 H, d, J 7.8 Hz, 1'-H), 7.24—7.42 (5 H, m, C$_6$H$_5$), and 7.42 (1 H, s, 8-H).

7-(4'-Amino-4',6'-dideoxy-2',3'-O-isopropylidene-α-L-talo-hexopyranosyl)theophylline (11b).—(a) From benzyl carbamate (10b). A 125 ml high pressure reactor was charged with compound (10b) (0.499 g, 1 mmol), methanol (20 ml) and Pd–C

catalyst (0.05 g). The reactor was pressurized with hydrogen at 3.4 atm. After 1 h the suspension was filtered off. The solvent was evaporated off and the amino nucleoside (11b) (0.248 g, 80%) was crystallized.

(b) *From oxime* (9b). Molybdenum oxide (0.36 g, 2.5 mmol) was added to a solution of the nucleoside (9b) (0.42 g, 1 mmol) in MeOH (10 ml) at 0 °C. Sodium borohydride (0.76 g, 20 mmol) was added portionwise and the reaction mixture was stirred for 1 h. It was then poured into brine (10 ml) and ethyl acetate (10 ml) and the aqueous solution was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) then evaporated under reduced pressure. Column chromatography on silica gel with ethyl acetate–methanol (80:20) afforded the 4'-*amino nucleoside* (11b) (0.219 g, 60%), m.p. 95—98 °C (from pentane); $[\alpha]_D^{20}$ −30° (*c* 0.1 in MeOH) (Found: C, 51.3; H, 6.45; N, 18.2. $C_{16}H_{23}N_5O_5$·0.5H_2O requires C, 51.33; H, 6.41; N, 18.71%); $\lambda_{max.}$(MeOH) 275 nm (ε 8 650); δ_H(300.13 MHz, $CDCl_3$) 1.45 (3 H, d, *J* 6.7 Hz, 6'-H), 1.36 and 1.58 (2 × 3 H, 2 × s, Me_2C), 3.41 and 3.6 (3 H, 2 × s, MeN), 3.53 (1 H, dq, *J* 3.6 and 6.7 Hz, 5'-H), 4.32 (1 H, dd, *J* 3.6 and 5.3 Hz, 4'-H), 4.60 (1 H, dd, *J* 5.3 and 6.8 Hz, 3'-H), 4.76 (1 H, dd, *J* 6.8 and 8.1 Hz, 2'-H), 6.14 (1 H, d, *J* 8.1 Hz), and 7.79 (1 H, s, 8-H).

7-(4'-*Acetamido*-4',6'-*dideoxy*-2',3'-*isopropylidene*-α-L-*talo*-*hexopyranosyl*)*theophylline* (12b).—Nickel chloride ($NiCl_2$·6H_2O; 1.14 g, 4 mmol) and sodium borohydride (0.76 g, 20 mmol) were added successively to a solution of the nucleoside (9b) (0.842 g, 2 mmol) in methanol (20 ml) at −30 °C. The black suspension was stirred for 1 h then acetic anhydride (2 ml) was added. The solution was partitioned between brine (20 ml) and ethyl acetate (20 ml), the two phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 ml). The organic solution was dried (Na_2SO_4) and the solvent evaporated off under reduced pressure to give the 4'-*acetamido nucleoside* (12b) (0.56 g, 70%), m.p. 114—115 °C (from MeOH); $[\alpha]_D^{20}$ −10° (*c* 0.1 in MeOH) (Found: C, 51.7; H, 6.5; N, 15.9. $C_{18}H_{25}N_5O_6$·MeOH requires C, 52.04; H, 6.43; H, 15.97%); $\lambda_{max.}$(MeOH) 275 nm (ε 7 692); δ_H(300.13 MHz, $CDCl_3$) 1.38 and 1.56 (2 × 3 H, 2 × s, Me_2C), 1.52 (3 H, d, *J* 7 Hz, 6'-H), 2.08 (3 H, s, MeCO), 3.51 and 3.6 (2 × 3 H, 2 × s, NMe), 4.43 (1 H, dq, *J* 6.7 and 7 Hz, 5'-H), 4.53 (1 H, dd, *J* 5.2 and 7.5 Hz, 2'-H), 4.57 (1 H, dd, *J* 4.4 and 5.2 Hz, 3'-H), 4.67 (1 H, ddd, *J* 4.4, 6.7, and 8.9 Hz, 4'-H), 5.96 (1 H, d, *J* 8.9 Hz, NH), 6.24 (1 H, d, *J* 7.5 Hz, 1'-H), and 7.86 (1 H, s, 8-H).

(Z)-7-(2',3',4',6'-*Tetradeoxy*-4'-*hydroximino*-β-L-glycero-*hex*-2'-*enopyranosyl*)*theophylline* (14a).—The keto nucleoside (13) (1.9 g, 10 mmol) and hydroxylamine hydrochloride (2.8 g, 40 mmol) were stirred in a mixture of pyridine and ethanol (1:1, 20 ml) for 5 min. The reaction mixture was partitioned between water and brine, the aqueous phase was extracted with ethyl acetate (3 × 25 ml) and the organic extracts were dried (Na_2SO_4). Evaporation of the solvent yielded the *nucleoside* (14a) (2.44 g, 80%), m.p. 238—239 °C (from MeOH); $[\alpha]_D^{20}$ +100° (*c* 0.1 in CH_3COOH) (Found: C, 51.3; H, 6.45; N, 18.2. $C_{16}H_{23}N_5O_5$·0.5H_2O requires C, 51.33; H, 6.41; N, 18.71%); δ_H(60 MHz, $CDCl_3$) 1.6 (3 H, d, *J* 6.5 Hz, 6'-H), 3.45 and 3.6 (2 × 3 H, 2 × s, MeN), 4.8 (1 H, q, *J* 6.5 Hz, 5'-H), 6.5 (1 H, dd, *J* 1.5 and 10 Hz, 3'-H), 7.25 (1 H, br s, 1'-H), 7.5 (1 H, dd, *J* 1.8 and 10 Hz, 2'-H), and 8.2 (1 H, s, 8-H).

(Z)-7-(4'-*Acetoximino*-2',3',4',6'-*tetradeoxy*-β-L-glycero-*hex*-2'-*enopyranosyl*)*theophylline* (14b).—The nucleoside (14a) (1.4 g, 4.6 mmol) in dichloromethane (20 ml) was treated with acetic anhydride (2.04 g, 20 mmol) in the presence of pyridine (1.58 g, 20 mmol) and a catalytic amount of 4-dimethylaminopyridine to give after 1 h the *title compound* (14b) (1.276 g, 80%), m.p. 155—156 °C (from EtOH); $[\alpha]_D^{20}$ +112° (*c* 0.1 in MeOH)

(Found: C, 51.95; H, 4.95; N, 20.2. $C_{15}H_{17}N_5O_5$ requires C, 51.8; H, 4.89; N, 20.17%); $\lambda_{max.}$(MeOH) 273 nm (ε 10 965); δ_H(60 MHz, $CDCl_3$) 1.6 (3 H, d, *J* 6.5 Hz, 6'-H), 2.05 (3 H, s, MeCO), 3.45 and 3.6 (3 H, 2 × s, MeN), 4.7 (1 H, q, 6.5 Hz, 5'-H), 6.5 (1 H, dd, *J* 1.5 and 10 Hz, 3'-H), 7.05 (1 H, br s, 1'-H), 7.2 (1 H, dd, *J* 1.8 and 10 Hz, 2'-H), and 7.8 (1 H, s, 8-H).

7-(4'-*Benzyloxycarbonylamino*-2',3',4',6'-*tetradeoxy*-β-L-erythro-*hexopyranosyl*)*theophylline* (15a) *and* 7-(4'-*Benzyloxy*-*carbonylamino*-2',3',4',6'-*tetradeoxy*-β-L-threo-*hexopyranosyl*)-*theophylline* (15b).—Nickel chloride ($NiCl_2$·6H_2O; 1.04 g, 4 mmol) was added to a solution of the nucleoside (14b) (0.694 g, 2 mmol) in methanol (20 ml) at −15 °C followed by sodium borohydride (0.76 g, 20 mmol) portionwise. After being stirred for 30 min the reaction mixture was cooled to −78 °C, benzyl chloroformate (1.195 g, 7 mmol) was added, and the cooled suspension was poured into brine (10 ml) and ethyl acetate (10 ml) immediately. The aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and flash column chromatography using first diethyl ether then ethyl acetate afforded the *benzyloxycarbonylamino nucleosides* (15a) (0.213 g, 25%) and (15b) (0.213 g, 25%).

Compound (15a) had m.p. 205 °C (from EtOH); $[\alpha]_D^{20}$ −20° (*c* 0.1 in $CHCl_3$) (Found: C, 58.8; H, 5.95; N, 16.1. $C_{21}H_{25}N_5O_5$ requires C, 59.01; H, 5.85; N, 16.39%); $\lambda_{max.}$(MeOH) 277 nm (ε 12 126); δ_H(300.13 MHz, $CDCl_3$) 1.23 (3 H, d, *J* 6.1 Hz, 6'-H), 1.81 (1 H, dddd, *J* 5.11, 12.23, 12.26, and 12.52 Hz, 3'-H_a), 2.12—2.24 (m, 3 H, 2'-H_e, 2'-H_a, and 3'-H_e), 3.29 and 3.49 (2 × 3 H, 2 × s, MeN), 3.47 (1 H, m, 4'-H), 3.70 (1 H, dd, *J* 6.1 and 9.89 Hz, 5'-H), 5.09 (2 H, s, $CH_2C_6H_5$), 6.02 (1 H, dd, *J* 3.4 and 9.6 Hz, 1'-H), 6.44 (1 H, d, *J* 9 Hz, NH), 7.25—7.40 (5 H, m, C_6H_5), and 8.18 (1 H, s, 8-H).

Compound (15b) had m.p. 190 °C (from EtOH); $[\alpha]_D^{20}$ 0° (*c* 0.1 in $CHCl_3$) (Found: C, 58.85; H, 5.75; N, 16.35); $\lambda_{max.}$(MeOH) 277 nm (ε 11 827); δ_H(300.13 MHz, $CDCl_3$) 1.13 (3 H, d, *J* 6.4 Hz, 6'-H), 1.90—2.04 (3 H, m, 2'-H_e, 3'-H_a, and 3'-H_e), 2.48 (1 H, dddd, *J* 6.5, 11.2, 12.13, and 12.13 Hz, 2'-H_a), 3.33 and 3.5 (2 × 3 H, 2 × s, MeN), 3.81 (1 H, br d, *J* 8.7 Hz, 4'-H), 4.01 (1 H, dd, *J* 1.6 and 6.4 Hz, 5'-H), 5.13 (2 H, s, $CH_2C_6H_5$), 5.95 (1 H, dd, *J* 3 and 11.2 Hz, 1'-H), 7.09 (1 H, d, *J* 8.7 Hz, NH), 7.09—7.27 (5 H, m, C_6H_5), and 8.16 (1 H, s, 8-H).

Reduction of (Z)-7-(4'-*Acetoximino*-2',3',4',6'-*tetradeoxy*-β-L-glycero-*hex*-2'-*enopyranosyl*)*theophylline* (14b) *in the Presence of* MoO_3.—Molybdenum(VI) oxide (0.202 g, 1.4 mmol) was added to a solution of nucleoside (14b) (0.305 g, 1 mmol) in methanol (10 ml). After being cooled to 0 °C, the blue suspension was treated with sodium borohydride (0.76 g, 20 mmol). After 30 min the reaction mixture was treated in the following manner.

(*a*) The suspension was poured into brine (10 ml) and diethyl ether (10 ml) and the aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and the diethyl ether evaporated under reduced pressure. Column chromatography on silica gel with dichloro-methane–acetone (3:7) afforded the 4'-*amino nucleosides* (16a) (0.106 g, 25%) and (17) (0.106 g, 25%).

Compound (16a) had m.p. 182—183 °C (from acetone); $[\alpha]_D^{20}$ −170° (*c* 0.1 in MeOH); $\lambda_{max.}$(MeOH) 275 nm (ε 9 544); δ_H(300.13 MHz, $CDCl_3$) 1.39 (3 H, d, *J* 6.1 Hz, 6'-H), 3.34 (1 H, ddd, *J* 1.8, 2.1, and 8.36 Hz, 4'-H), 3.42 and 3.60 (2 × 3 H, 2 × s, Me-N), 3.71 (1 H, dq, *J* 6.1 and 8.36 Hz, 5'-H), 5.92 (1 H, ddd, *J* 1.8, 2.1, and 10 Hz, 3'-H), 6.15 (1 H, ddd, *J* 1.8, 2.1, and 10 Hz, 2'-H), 6.78 (1 H, dd, *J* 1.8 and 2.1 Hz, 1'-H), and 7.78 (1 H, s, 8-H).

Compound (17) had δ_H(300.13 MHz, $CDCl_3$) 1.34 (3 H, d, *J* 6.1 Hz, 6'-H), 1.58 (1 H, dddd, *J* 3.6, 11.17, 12.95, and 13 Hz, 3'-H_a), 1.84 (1 H, dddd, *J* 3.96, 10.8, 12.95, and 13.06 Hz, 2'-H_a),

2.12 (1 H, dddd, J 3.6, 3.96, 4.05, and 13 Hz, 3'-H$_e$), 2.30 (1 H, dddd, J 2.2, 3.6, 3.6, and 13.06 Hz, 2'-H$_e$), 2.58 (1 H, ddd, J 4.05, 9.25, and 11.17 Hz, 4'-H), 3.41 (3 H, s, NMe), 3.46 (1 H, overlapped, 5'-H), 3.6 (3 H, s, NMe), 5.98 (1 H, dd, J 2.2 and 10.8 Hz, 1'-H), and 7.86 (1 H, s, 8-H).

(b) The black suspension was stirred for 30 min then benzyl chloroformate was added. The solution was partitioned between a mixture of brine (10 ml) and ethyl acetate (10 ml). The aqueous phase was extracted with ethyl acetate (3 × 10 ml). The organic solution was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The resulting yellow syrup was chromatographed on silica gel (flash chromatography) with diethyl ether then ethyl acetate to give compounds (16b) (0.106 g, 25%) and (15a) (0.106 g, 25%).

Compound (16b) had m.p. 198 °C (from EtOH); $[\alpha]_D^{20}$ $-75°$ (c 0.1 in CDCl$_3$) (Found C, 58.4; H, 5.4; N, 15.9. C$_{21}$H$_{25}$N$_5$O$_5$·0.5H$_2$O requires C, 58.06; H, 5.52; N, 16.12%); $\lambda_{max.}$(MeOH) 276 nm (ε 9 223); δ_H(300.13 MHz, CDCl$_3$) 1.29 (3 H, d, J 6.2 Hz, 6'-H), 3.29 and 3.5 (2 × 3 H, 2 × s, MeN), 3.91 (1 H, dd, J 6.2 and 9.04 Hz, 5'-H), 4.23 (1 H, dddd, J 1.5, 1.7, 8.7, and 9.04 Hz, 4'-H), 5.12 (2 H, s, CH_2C$_6$H$_5$), 6.03 (1 H, ddd, J 1.5, 1.7, and 10.3 Hz, 3'-H), 6.11 (1 H, ddd, J 1.5, 2.3, and 10.3 Hz, 2'-H), 6.66 (1 H, d, J 8.7 Hz, NH), 6.76 (1 H, dd, J 1.5 and 2.3 Hz, 1'-H), 7.27—7.41 (5 H, m, C$_6$H$_5$), and 8.08 (1 H, s, 8-H).

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