Synthesis of Theophylline and 6-Thiotheophylline 7-Ribosyl Nucleosides

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Dedicated to the memory of Dr. Fidel Jorge López Herrera

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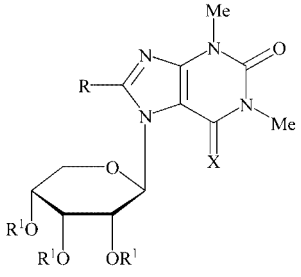
The syntheses of theophylline and thiotheophylline 7-ribopyranose and 7-ribofuranose nucleosides, both by direct coupling of the base and the sugar and by construction of the imidazole ring, are reported. The conformational *syn*/*anti* equilibrium of the peracetyl derivatives was studied by molecular mechanics and by the low-temperature line-shape/ ^{1}H NMR method.

Introduction

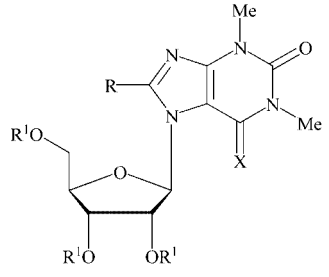
Cytotoxic nucleoside analogues and nucleobases were among the first chemotherapeutic agents to be introduced for the medical treatment of cancer.[1] This family of compounds has grown to include a variety of purine and pyrimidine nucleosides with activity both against solid tumours and against malignant disorders of the blood.[1,2] These agents behave as antimetabolites, compete with physiological nucleosides and interact with a large number of intracellular targets to induce cytotoxicity.[3] Progress has recently been made in the identification and characterisation of nucleoside transporters and the enzymes that metabolise them, in the optimisation of intracellular nucleoside accumulation and in the improvement of cancer cell selectivity. All this has provided a deeper understanding of the molecular mechanisms of anticancer nucleoside activity and opened up new prospects for potentiation of their antitumour effects.[4]

The search for new antiviral agents, particularly for the treatment of human immunodeficiency virus (HIV)[5] and, more recently, hepatitis B virus (HBV, especially as regards the chronic disease),[6] and of new adenosine A1, A2 and A3 receptor antagonists (ribose nucleosides),[7] has stimulated the study of thiopurine and thiopyrimidine derivatives of nucleosides, which are components of transfer ribonucleic acids.[8] Among these, 6-thiopurines and 6-thiopurine nucleosides exhibit significant antitumor activity.[9]

In addition, a number of alkylxanthines, such as those substituted at position 8 in theophylline, have aroused interest as adenosine receptor antagonists. 1,3-Dialkyl-7-ribosylxanthines, for example, have been found to be partial agonist adenosine receptors.[10] Unlike alkylxanthine bases, their nucleosides have scarcely been studied chemically and biologically.



	1	2	3	4	5	6	7	8
X	O	O	S	S	O	O	S	S
R	Me	Me	Me	Me	H	H	H	H
R^1	H	Ac	H	Ac	H	Ac	H	Ac



	9	10	11	12	13	14	15	16
X	O	O	S	S	O	O	S	S
R	H	H	H	H	Me	Me	H	Me
R^1	H	Ac	H	Ac	H	Ac	H	Ac

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Such important applications, which are continuously increasing, and the need to develop new building blocks with a view to devising useful combinatorial methodologies have fostered the application of modern synthetic methods to the synthesis of nucleoside analogues[11] (carbocyclic nucleosides included[12]) for the development of simple, flexible, efficient procedures for their production. Recent advances in the synthesis of modified purine nucleosides include the use of reactions such as Suzuki coupling,[13] Stille coupling,[14] Pd-mediated arylaminations,[15] organocuprate cross coupling[16] and, recently, the use of 6-bromopurine nucleosides as intermediates in the synthesis.[17] It is therefore of interest to design and prepare novel theophylline nucleosides. In this paper we report the synthesis of a series of new theophylline-ribopyranosyl and -ribofuranosyl nucleosides, as well as the corresponding 6-thio derivatives, all of which are of special interest on account of the ribose moiety, as present in nature. In addition, we examined some interesting conformational aspects of their peracetyl derivatives with a view to gaining better insight into their structure-activity relationship.

Results and Discussion

Traditionally, purine nucleosides and their analogues have been synthesised by one of three approaches: *i*) construction of the purine ring from a glycosylamino pyrimidine or a glycosyl imidazole, *ii*) direct coupling of the sugar with the base, or *iii*) derivation from a natural nucleoside.[18]

The synthesis of 7-(glycosyl)theophylline compounds through the construction of the imidazole ring requires the use of a 4-amino-5-(glycosylamino)pyrimidine as precursor (see Scheme 1). These can be synthesised in an almost quantitative yield by condensation of 4,5-diamino-1,3-dimethyluracil with a sugar, in an approach used in our laboratory for the synthesis of 7-substituted nucleoside derivatives.[19–21]

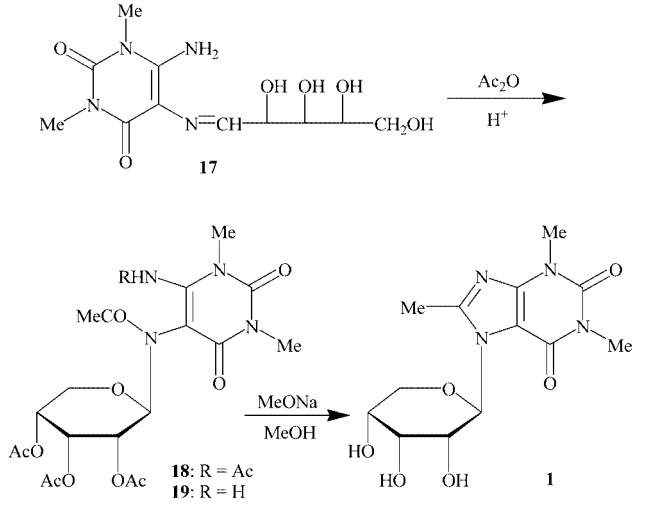
In this case, treatment of D-ribose with 4,5-diamino-1,3-dimethyluracil in methanol yields **17**.[19] Treatment of this D-ribosylidene imino derivative with acetic anhydride in an acid medium at 30 °C affords the 4-acetylamino derivative **18** in 63% yield, together with the amine **19** in 20% yield, but no ribofuranosyl derivative. The structure of **18** was established as a *N*-β-ribopyranoside from its ^{1}H NMR spectrum, which exhibits a signal at δ = 6.35 ppm as a doublet with J = 10.1 Hz (corresponding to the anomeric proton in a *trans*-diaxial arrangement with H-2′), and from its ^{13}C NMR spectrum, with a signal at δ = 68.0 ppm corresponding to C-4′ (CH correlated) typical of the pyranose ring.[22] Only **19** was obtained when the reaction was performed at 0 °C. Compounds **18** and **19** are the intermediates required for the cyclisation to the target purine nucleoside.

Heating of a solution of **18** at reflux in MeONa/MeOH gave the 8-methyl-substituted theophylline nucleoside **1** in 85% yield. The cyclisation involves the attack of the nitrogen atom of the 4-acetylamino group on the carbon atom of the 5-acetylamino group and the subsequent elimination of acetic acid. The reaction can also start from **19** (in this case the reaction involves the elimination of water) or even with a mixture of **18** and **19**, which affords **1** in a 80% overall yield.

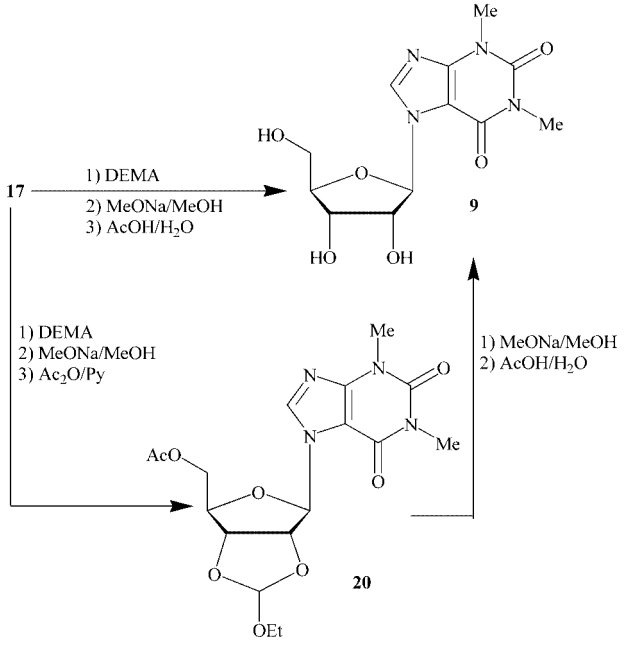
Compound **17** was treated with acetic-formic anhydride in order to prepare the corresponding theophylline ribopyranoside, but the reaction failed.

Diethoxymethyl acetate (DEMA) has been used as a reagent for the preparation of carbocyclic nucleosides from 5-amino-6-chloro-4-(cyclopentylamino)pyrimidine,[23] as well as of pyranosyl theophylline nucleosides in a one-pot reaction from 4-amino-1,3-dimethyl-5-*N*-(glycosylidene)iminouracil.[20]

Use of this formate equivalent with **17** at room temp. for 48 hours, followed by treatment with MeONa/MeOH and hydrolysis with aqueous acetic acid (Scheme 2), gave the ri-



Scheme 1



Scheme 2

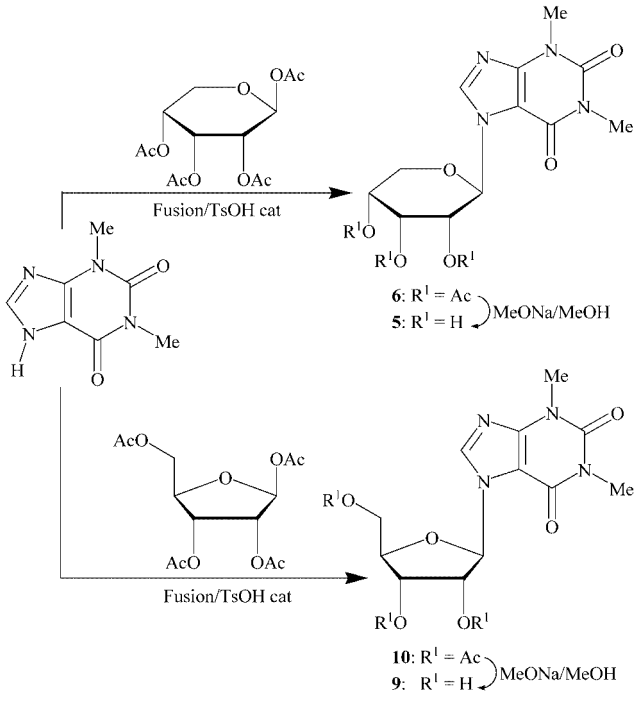
bofuranosyl theophylline nucleoside **9** in 35% yield, together with a small amount (less than 5%) of ribopyranosyl nucleoside. The NMR spectroscopic data confirmed the presence of the furanose ring in **9** (^{1}H NMR: δ = 6.31 ppm, d, J = 4.2 Hz, H-1′. ^{13}C NMR: δ = 79.8 ppm, C-4′).[22]

The formation of a ribofuranoside moiety as the major compound is unsurprising. In fact, various glycopyranosides have been found to rearrange to their furanose forms when the reaction involves acetonation or *ortho*-esterification.[24] Thus, acetylation of the reaction mixture upon treatment with MeONa yielded the orthoester **20**.

This is a straightforward synthetic approach to compounds **1** and **9** in only two steps from the readily available starting material **17**, but this pathway failed for the preparation of both theophylline derivatives (**5** and **13**). For this reason, we explored other nucleoside synthetic methods.

Direct glycosidation has been widely used,[25−27] one example being found in Sato's fusion method for the preparation of acetylated 7-β-D-(ribofuranosyl)theophylline **10**.[26] This reaction had never before been applied to the synthesis of a ribopyranose nucleoside. Under similar conditions, we extended the method to the synthesis of the ribopyranosyl-theophylline nucleoside **5** by melting theophylline and β-D-ribopyranose tetraacetate at 190 °C in vacuo, in the presence of *p*TsOH as catalyst (Scheme 3). The reaction afforded **6** in 35% yield after purification by column chromatography, and subsequent deacetylation yielded the desired nucleoside **5**, the melting point of which coincided with that reported in the literature (for the compound prepared from the mercury salt of theophylline).[27b]

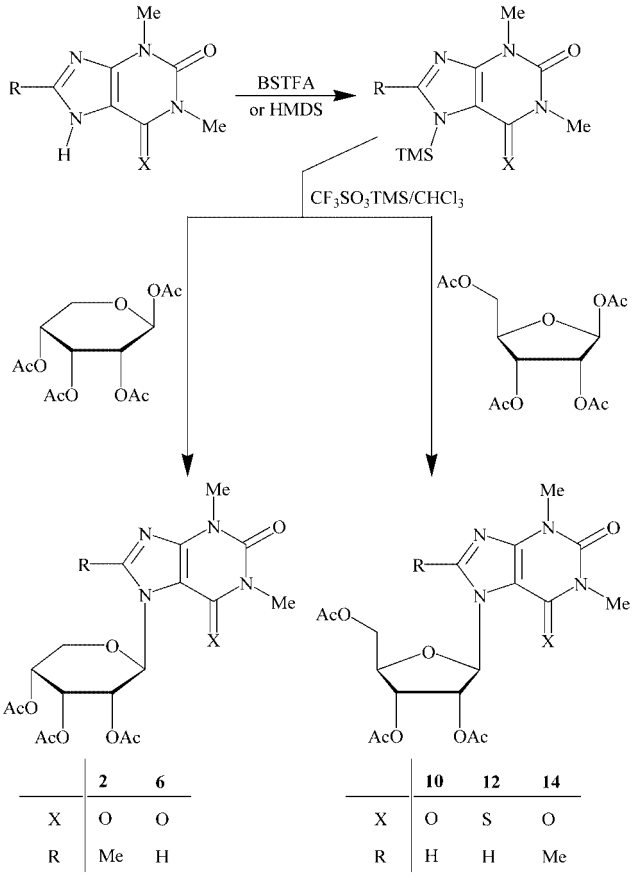
However, all attempts at preparing 8-methyl theophylline nucleosides **1** and **13** by the fusion method failed, owing to the increased melting point of the 8-(methyl)theophylline, and only charred material was obtained.



Scheme 3

We then focused on the silyl-Hilbert−Johnson glycosidation procedure developed by Vorbrüggen.[18,28] This method has been widely used for the preparation of many modified nucleosides, but to the best of our knowledge had never been applied to the synthesis of 8-alkyl base-substituted nucleosides.

The reaction between 8-methyl-7-(trimethylsilyl)theophylline and the corresponding β-D-ribose tetraacetate afforded the acetyl-protected nucleosides **2** and **14** in good yields (Scheme 4); these were in turn deacetylated to afford **1** and **13**. The reaction was extended to the preparation of acetylated nucleosides **6** and **10**, in almost quantitative yields. While 7-(trimethylsilyl)theophylline is usually prepared with hexamethyldisilazane, we found that 8-(methyl)theophylline required *N*,*O*-bis(trimethylsilyl)acetamide (BSTFA) as silylating agent.



	2	6
X	O	O
R	Me	H

	10	12	14
X	O	S	O
R	H	H	Me

Scheme 4

Compound **2** exhibits broadened signals in its room temp. ^{1}H NMR spectrum, and some protons in the ribopyranose moiety cannot be observed (see Figure 1, a, between δ = 5.2 and 6.6 ppm). On heating, though, the signals sharpen and all protons become apparent, the spectrum being consistent with the expectations for this compound at 363 K, with H-1′ as a doublet at δ = 6.41 ppm with J = 9.7 Hz (Figure 1, c). This can be ascribed to the presence of two rotational conformers and is further discussed in the conformational analysis section.

This reaction is carried out under very mild conditions that avoid the high temperatures used in the fusion method

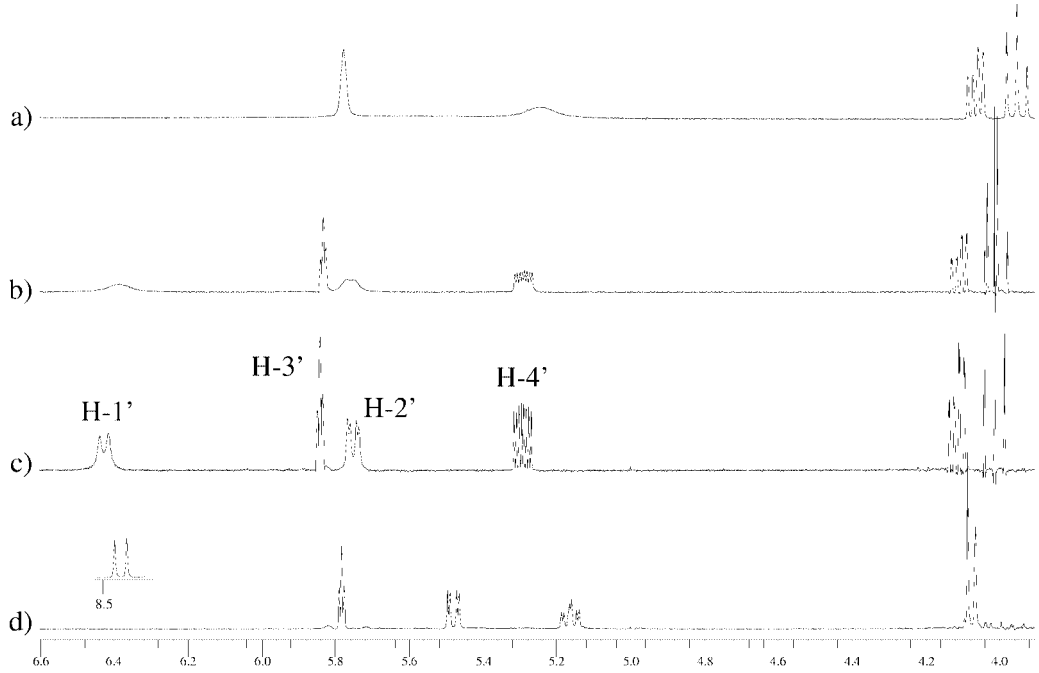
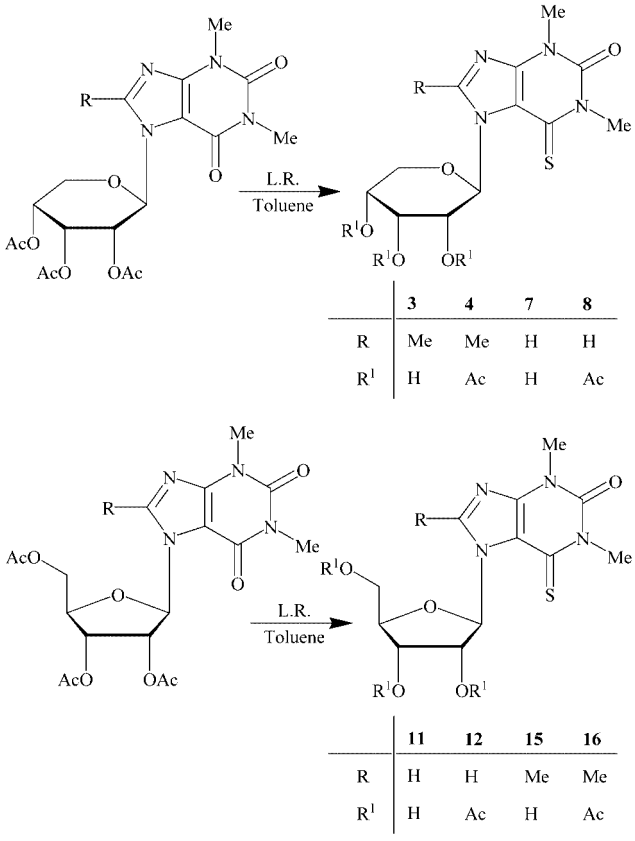


Figure 1. ^{1}H NMR ($CDCl_3$) spectra of compounds **2** (a, 298 K; b, 313 K; c, 363 K) and **4** (d, 298 K)



	3	4	7	8
R	Me	Me	H	H
R^1	H	Ac	H	Ac

	11	12	15	16
R	H	H	Me	Me
R^1	H	Ac	H	Ac

Scheme 5

and the acid conditions of the imidazole ring construction approach, which may cause rupture of the glycosidic bond. We modified the existing experimental procedure for the silylation reaction by using $CHCl_3$ as solvent (see Exp. Sect.), so this was a one-pot reaction requiring no isolation of the silyl derivative of the base and no removal of the solvent after upon silylation.[18]

6-Thiotheophylline Nucleosides

We found that Lawesson's reagent (LR)[29] could effectively replace the 6-oxo group of 7-glycosyl-8-(methyl)theophylline with a thioxo group, even when the oxo group was not enolisable. We exploited this finding to prepare 8-methyl-6-thiotheophylline nucleosides.[21]

Treatment of acetylated nucleoside **2** with LR in refluxing toluene afforded the corresponding 6-thiotheophylline derivative **4** in 58% yield. The ^{1}H NMR spectrum of this compound at room temp. exhibits sharp signals (see Figure 1, d), unlike the spectrum of **2** (Figure 1, a). The anomeric proton in **4** is now clearly observed at $\delta = 8.40$ ppm (J, 9.9 Hz) because of the anisotropic effect of the 6-thioxo group. The ^{13}C NMR spectrum exhibits the C-6 signal at $\delta = 175.6$ ppm, which confirms the regioselective substitution. Deprotection of the acetylated sugar moieties gives the thionucleoside **3**.

Thio-nucleosides **7**, **11** and **15** were similarly obtained from **6**, **10** and **14**, by way of the corresponding acetylated 6-thio derivatives **8**, **12** and **16**, respectively.

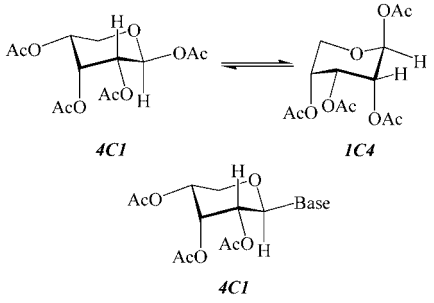
We extended the Vorbrüggen method to the direct synthesis of 6-thiotheophylline nucleoside derivative **12** by coupling 6-thiotheophylline and β-D-ribopyranose tetraacetate (Scheme 4). The yield (65%) was not as good as before, probably because the sulfur atom had undergone some reaction during the silylation process.

Conformational Analysis

One must consider two aspects in dealing with the conformations of the nucleosides in solution: one is the di-

hedral angles of the sugar moiety, and the other the relative orientation of the base and sugar around the glycoside bond.[21a,30] With acetylated ribose nucleosides, a third aspect, the *1C4* or *4C1* conformation of the ribopyranose tetraacetate ring, must also be taken into account.[31]

Horton showed that β-D-ribopyranose tetraacetate existed as a 11:9 mixture of the *4C1* and *1C4* conformers in rapid equilibrium in deuterated acetone at room temp. (Scheme 6).[32] The *1C4* conformer accounts for 45% of the mixture ($J_{1',2'}$ of 4.8 Hz) and has three acetoxy groups in an axial arrangement. This has been ascribed to the anomeric effect. The population of both forms was calculated by spin coupling averaging methods.[32]



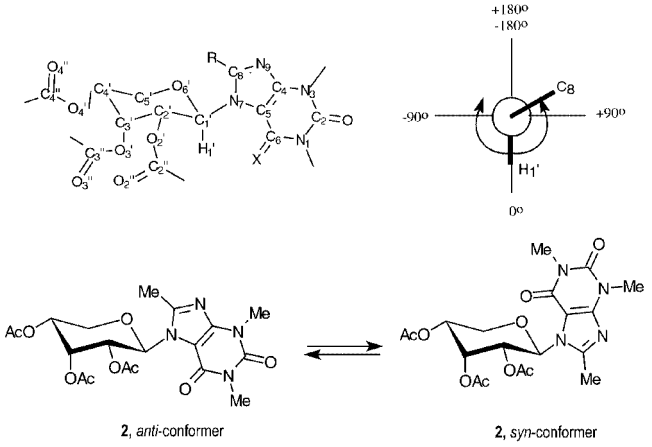
Scheme 6

The ^{1}H NMR spectra of compounds **2** (363 K, Figure 1, c), **6** and **18** are consistent with *4C1* conformations of the pyranose rings, as can be inferred from the coupling constants between H-1′ and H-2′ (J = 8.9, 9.7 and 10.1 Hz, respectively) and the other internal coupling constants (see Exp. Sect.), which correspond to antiperiplanar arrangements of these protons. The anomeric effects in the acetylamino ribopyranoside **18** and the theophylline ribonucleosides **2** and **6** are not large enough to compete with the steric effects of two acetoxy groups and the aglycon functions in equatorial arrangements.

The orientation of the base and sugar around the glycoside bond in compound **2** was studied by line-shape analysis and molecular mechanics calculations. The broadened signals for **2** can be ascribed to high molecular crowding, which hinders rotation about the glycoside bond. From the H1′−C1′−N7−C8 dihedral angle (see figure in Table 1), two conformers are possible: *syn* and *anti*.

The search for the minimum energy conformers for compound **2**, based on the rotation of the sugar moiety with respect to the base about the glycoside bond, gave two minima at χ = 133.3° (*anti* conformer) and χ = −11.1° (*syn* conformer). The population distribution for each minimum, calculated from the Boltzmann equation, was 61% for the *anti* conformer and 39% for the *syn* conformer ($\Delta G^*_{calcd.}$ 13.9 kcal/mol; this is the equilibrium rotational energy barrier obtained from a plot of E versus τ), consistently with the experimental data obtained by line-shape analysis of the ^{1}H NMR spectra of compound **2** at a variable temperature,

Table 1. Angle definition and principal geometric features of the minimum-energy conformers of ribose nucleosides **2**, **4**, **6** and **8** as obtained from MM calculations



Conf.	E kcal/mol	Gly[a] χ	Acetates[a] a	b	c	d	e	f
2/*anti*	37.7	133.3	30.2	34.4	−44.9	30.8	−58.2	46.9
2/*syn*	38.7	−11.1	20.8	41.5	−47.5	32.3	−54.2	51.5
4/*anti*	38.5	172.8	23.4	73.1	−34.1	54.0	−56.9	52.5
4/*syn*	41.0	−18.0	23.5	86.8	−35.7	52.4	−52.7	51.2
6/*anti*	26.1	151.1	27.8	54.1	−21.7	53.6	57.6	−48.2
6/*syn*	27.3	−15.3	32.8	24.7	−48.4	−152.7	42.5	0.9
8/*anti*	28.9	−132.8	26.7	46.7	−25.7	52.0	57.0	−45.5
8/*syn*	34.9	−46.9	30.9	98.7	2.9	51.4	57.4	−46.9

[a] Angles in °, χ =H1′−C1′−N7−C8. Acetates: a: H2′−C2′−O2′−C2″, b: C2′−O2′−C2″−O2″, c: H3′−C3′−O3′−C3″, d: C3′−O3′−C3″−O3″, e: H4′−C4′−O4′−C4″, f: C4′−O4′−C4″−O4″.

confirming the occurrence of the two postulated rotamers (Table 2 and 3).

It should be noted that the two conformers observed in the spectrum at 263 K have a J value of 9.9 Hz for both H-1′ protons (see Figure 2).

The experimentally ascertained equilibrium kinetic parameters were calculated by means of the Eyring equation for the absolute reaction rate theory, by least-squares linear regression analysis (r^2 = 0.997).[30,32] Because the signal corresponding to the methyl group at position 8 in theophylline was a singlet not involved in any coupling (2.59 and 2.66 ppm, Figure 2 and Table 2), it was good enough for obtaining accurate calculated values (Table 3).

The equilibrium $\Delta G^*_{exp.}$ obtained for this compound by this method was 13.7 kcal·mol^{-1}. The resulting rotational energy barrier is consistent with a *syn*/*anti* equilibrium at room temperature. An *anti*/*syn* ratio of 62%:38% for **2** was obtained from the integration of the low-temperature ^{1}H NMR spectra (263 K), consistently with the molecular mechanics value (see Figure 2).

The spectrum of the 6-thionucleoside analogue **4** exhibits sharp ^{1}H NMR signals (see Figure 1, d) as a result of the bulkiness of the sulfur atom at position 6, which precludes rotation around the glycoside bond, so only the *anti* conformer is observed.

Table 2. Results obtained by line-shape/^{1}H NMR (exp.) and molecular mechanics analysis (calcd.) for **2**

Compound	Conformer	$Pop_{calcd.}$ [%]	$Pop_{exp.}$ [%]	$\Delta G^*_{calcd.}$ [kcal/mol]	$\Delta G^*_{exp.}$ [kcal/mol]
2	*anti*	61	62	13.9	13.7
	syn	39	38		

Table 3. Line-shape analysis: corrected line width ($\delta\nu$), rate constants ($K\nu$),and activation parameters for **2**

T [K]	δν [Hz]	$K\nu$ [s^{-1}]	ΔH^* [kcal/mol]	ΔS^* [cal/mol K]	$\Delta G^*_{exp.}$ [kcal/mol]
233	1.19	3.74			
243	1.59	5.00			
253	2.18	6.85			
263	8.25	25.92			
268	15.10	47.44			
270	22.86	71.80			
272	23.25	73.04			
274	19.88	62.44			
276	17.49	54.95			
278	coalescence	temperature	10.7	−11.1	13.7
279	26.22	64.85			
283	15.49	109.78			
293	3.57	476.32			

The molecular mechanics study on compounds **4** and **8** was done on the assumption of an *anti*/*syn* ratio of 100:0. This confirms that rotation about the glycoside bond is now either completely restricted, by the considerably larger volume of the sulfur atom, or completely free, when no bulky group is at position 8 of the theophylline in **6**. This had previously been observed in other peracetylated theophylline nucleosides of glucose, xylose and arabinose.[21a,21c]

In conclusion, the synthesis of ribopyranose and ribofuranose theophylline and 8-(methyl)theophylline nucleosides in good yields can be accomplished by two different methods: either direct coupling between the sugar and base or from 4,5-diamino-1,3-dimethyluracil. We found direct coupling of silyl derivatives of the base with the tetracetylated ribose to be the more useful, with excellent yields in all cases, even with the more sterically hindered 8-(methyl)-theophylline or -thiotheophylline; this thus provides a straightforward synthetic pathway to the thio derivatives in only two steps. This also expands the arsenal of reactions and approaches available for the synthesis of purine nucleoside analogues as potential biochemical tools or new therapeutics, (particularly thiotheophylline derivatives). Finally, the joint use of ^{1}H NMR spectra and molecular mechanics analysis allows one to study *syn*/*anti* equilibria and molecular geometries, which can also help understanding of biological activity in these compounds.

Experimental Section

Melting points were determined with a Gallenkamp instrument and are given uncorrected. Optical rotations were measured with a Perkin−Elmer Model 241 polarimeter, and are given in 10^{-1} deg·cm^2·g^{-1} units. UV spectra were recorded with a Hewlett−Packard 8452A spectrophotometer, and IR spectra with Beckman Model Aculab IV and Perkin−Elmer 883 spectrophotometers. Mass spectrometry was carried out with a HP-MS 5988A instrument, with use of the direct injection and electron-impact (EI) modes. ^{1}H NMR and ^{13}C NMR spectra were recorded with 200 MHz AC 200 and 400 MHz ARX 400 Bruker spectrometers, with use of the residual solvent peak in $CDCl_3$ (δ = 7.24 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C), deuterium oxide (with CD_3OD as internal standard, δ = 4.8 ppm for ^{1}H and δ = 49.1 ppm for ^{13}C) or CD_3SOCD_3 (δ = 2.50 ppm for ^{1}H and δ = 39.5 ppm for ^{13}C). Chemical shifts are given in ppm. Variable temperature NMR spectra were obtained in sealed NMR tubes, with 0.2 M samples. The torsion angles for the most stable conformers were determined by molecular mechanics calculations performed with the aid of HyperChem™ V3.0 software, by use of MM+, similar to Allinger's MM2 force field. A root-mean-square gradient termination cut-off of 0.01 kcal·Å^{-1}·mol^{-1} was used for geometry optimisation with the Polak−Ribiere conjugate gradient algorithm. Molecular mech-

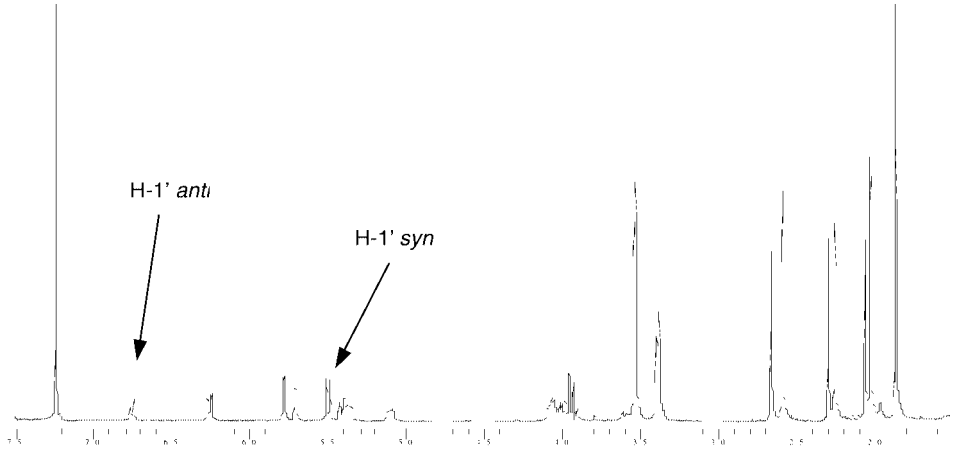


Figure 2. ^{1}H NMR ($CDCl_3$) for compound **2** (263 K)

anics results represent the gas-phase properties; minimisation with different permittivity values (5.6 for chloroform, or 11.2) did not improve on the prior calculations. TLC analyses were performed on silica gel 60 F 254 plates, and column chromatography was carried out on silica gel 60 (70−230 mesh). Thiotheophylline was prepared by treatment of theophylline with LR with MW irradiation.[29c]

Synthesis of Nucleosides by Imidazole Ring Construction

4-Acetylamino-5-(*N*-β-D-2′,3′,4′-tri-*O*-acetylribopyranosyl)acetylamino-1,3-dimethyluracil (18): Compound **17** (2.00 g, 6.90 mmol) was treated with acetic anhydride (70 mL) and sulfuric acid (0.18 mL) at 30 °C for 6 h. The solvent was removed in vacuo, and methanol (30 mL) was added to the residue. After 30 min, the solution was concentrated in vacuo to give a solid foam, which was dissolved in chloroform, washed with a 10% aqueous solution of $NaHCO_3$ and with water, and dried with anhydrous $MgSO_4$. The chloroform was removed, and the residue afforded a mixture of **18** and **19** (20%). Column chromatography afforded **18** (2.29 g, 63%) as a colourless solid. M.p. 156 °C. $[\alpha]_D^{22} = -106$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3250, 2960, 1750, 1710, 1250, 760 cm^{-1}. UV (MeOH): λ_{max} (ε) = 280 (14430), 206 (24770) nm. EI MS: *m*/*z* (%) = 512 (7) [M^+], 471 (7) [M^+ − Ac], 452 (10), 253 (30), 43 (100). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.87, 1.98, 2.00, 2.12, 2.17 (5 × s, 15 H, 5 × CH_3CO), 3.29 (s, 3 H, NCH_3), 3.38 (s, 3 H, NCH_3), 3.95 (m, 2 H, H-5 and H-5′), 4.60 (dd, J = 10.1, 3.8 Hz, 1 H, H-2′), 4.90 (dt, J = 8.3, 2.7 Hz, 1 H, H-4′), 5.60 (t, J = 3.8 Hz, 1 H, H-3′), 6.35 (d, J = 10.1 Hz, 1 H, H-1′), 9.05 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.5, 20.7 (2 C), 21.5, 23.6, 28.8, 33.4, 63.2, 65.5, 65.6, 68.0, 80.4, 104.0, 149.5, 150.3, 160.0, 169.3, 169.6, 169.9, 170.0, 173.1 ppm. $C_{21}H_{28}N_4O_{11}\cdot H_2O$ (530.2): calcd. C 47.53, H 5.70, N 10.56; found C 47.62, H 5.51, N 10.73.

4-Amino-5-[*N*-β-D-2′,3′,4′-tri-*O*-(acetyl)ribopyranosyl]acetylamino-1,3-dimethyluracil (19): Product **17** (270 mg, 0.93 mmol) was treated with acetic anhydride (5 mL) and sulfuric acid (24 μL) at 0 °C for 6 h. The reaction mixture was added to a 10% Na_2CO_3 aqueous solution and extracted with $CHCl_3$. The organic phase was washed with water, dried with anhydrous $MgSO_4$ and purified by preparative TLC to provide **19** (0.11 g, 25%) as a white solid. M.p. 165−166 °C. $[\alpha]_D^{20} = +55$ (c = 0.6, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3628, 2977, 1749, 1716, 1646 cm^{-1}. UV (MeOH): λ_{max} (ε) = 264 (25970), 208 (27260) nm. EI MS: *m*/*z* (%) = 470 (3) [M^+], 259 (49), 212 (93), 170 (78), 139 (100), 97 (53). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.97, 2.02, 2.18 (3 × s, 12 H, 4 × CH_3CO), 3.26 (s, 3 H, NCH_3), 3.48 (s, 3 H, NCH_3), 3.90 (m, 2 H, H-5 and H-5′), 4.78 (dd, J = 9.7, 3.0 Hz, 1 H, H-2′), 4.91 (ddd, J = 9.2, 6.6, 3.0 Hz, 1 H, H-4′), 5.54 (br. s, 2 H, NH_2), 5.58 (t, J = 3.0 Hz, 1 H, H-3′), 6.23 (d, J = 9.7 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.5, 20.7 (2 C), 21.6, 28.1, 29.8, 62.5, 65.6, 65.9, 68.1, 80.4, 90.3, 150.4, 153.5, 159.8, 169.6, 169.8, 170.0, 174.6 ppm. $C_{19}H_{26}N_4O_{10}\cdot H_2O$ (488.2): calcd. C 46.70, H 5.78, N 11.47; found C 46.87, H 5.77, N 11.35.

8-Methyl-7-β-D-(ribopyranosyl)theophylline (1): Compound **18** (0.51 g, 1.00 mmol) was treated with a solution of MeONa in methanol (20 mL, 0.2 m). The mixture was heated at reflux for 20 h and neutralised with Amberlyst IR-120 resin. After filtration, the solvent was removed in vacuo. The solid residue was recrystallised from ethanol to give **1** (0.28 g, 86%) as colourless crystals. M.p. 280 °C. $[\alpha]_D^{22} = -26$ (c = 1.0, H_2O). IR (KBr): $\tilde{\nu}$ = 3480, 2950, 1680, 1390, 1040, 750 cm^{-1}. UV (MeOH): λ_{max} (ε) = 276 (10010), 206 (24850) nm. EI MS: *m*/*z* (%) = 326 (6) [M^+], 194 (100), 109 (27). ^1H NMR (200 MHz, D_2O, 298 K): δ = 2.46 (s, 3 H, C-8−CH_3), 3.19 (s, 3 H, NCH_3), 3.36 (s, 3 H, NCH_3), 3.75 (m, 2 H, H-5, H-5′), 3.97 (m, 1 H, H-4′), 4.18 (t, J = 2.8 Hz, 1 H, H-3′), 4.35 (bd, J = 8.8 Hz, 1 H, H-2′), 5.56 (br. s, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, D_2O, reference [D_6]DMSO, 298 K): δ = 14.1, 28.7, 30.3, 64.9, 66.2, 68.8, 71.0, 82.4, 106.9, 149.3, 152.7, 154.6, 155.1 ppm. $C_{13}H_{18}N_4O_6$ (326.1): calcd. C 47.83, H 5.56, N 17.18; found C 47.81, H 5.46, N 16.90.

7-β-D-(Ribofuranosyl)theophylline (9): Compound **17** (1.00 g, 3.00 mmol) was dissolved in diethoxymethyl acetate (DEMA, 6 mL) at 20 °C. After 48 h, no starting material could be found by TLC. The reaction mixture was poured into water and the solvent was removed in vacuo. The residue was dissolved in MeONa/MeOH at room temp. overnight. The solution was neutralised with Amberlyst IR-120 resin, filtered and concentrated to dryness. Finally, the residue was treated with 50% aqueous AcOH (20 mL), and after 24 hours the solvent was removed in vacuo and the residue was recrystallised with methanol to afford **9** (0.33 g, 35%) as a white solid. M.p. 196 °C (ref.[27a] 190−191 °C). $[\alpha]_D^{31} = +28$ (c = 0.32, H_2O). IR (KBr): $\tilde{\nu}$ = 3600−3200, 1677, 1602 cm^{-1}. UV (MeOH): λ_{max} (ε) = 274 (17329) nm. EI MS: *m*/*z* (%) = 312 (2) [M^+], 180 (100). ^1H NMR (200 MHz, D_2O, 298 K): δ = 3.34 (s, 3 H, NCH_3), 3.53 (s, 3 H, NCH_3), 3.82 (dd, J = 12.7, 4.4 Hz, 1 H, H-5), 3.96 (dd, J = 12.7, 2.4 Hz, 1 H, H-5′), 4.21 (m, 1 H, H-4′), 4.31 (t, J = 5.6 Hz, 1 H, H-3′), 4.54 (dd, J = 5.6, 3.5 Hz, 1 H, H-2′), 6.21 (d, J = 3.5 Hz, 1 H, H-1′), 8.33 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, D_2O, reference CD_3OD, 298 K): δ = 29.2, 31.0, 61.7, 70.0, 75.9, 85.4, 91.3, 107.8, 142.1, 150.3, 153.6, 156.7 ppm. $C_{12}H_{16}N_4O_6$ (312.1): calcd. C 46.14, H 5.17, N 17.95; found C 45.89, H 4.95, N 17.63.

7-[5′-Acetyl-2′,3′-*O*-(ethoxymethylidene)-β-D-ribofuranosyl]theophylline (20): Compound **17** (1.00 g, 3.00 mmol) was dissolved in DEMA (6 mL) at 20 °C. After 48 h, the reaction mixture was concentrated to dryness. The residue was dissolved in MeONa/MeOH at room temp. overnight. The solution was neutralised with Amberlyst IR-120 resin, filtered, concentrated to dryness and finally acetylated, to provide **20** as a colourless solid. M.p. 180−181 °C. EI MS: *m*/*z* (%) = 410 (2) [M^+], 365 (11), 231 (100), 180 (11), 97 (20). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.26 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 2.06 (s, 3 H, CH_3CO), 3.36 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 3.66 (q, J = 7.0 Hz, 2 H, CH_3CH_2), 4.20−4.60 (m, 3 H, H-4′, H-5, H-5′), 5.00 (dd, J = 7.6, 4.5 Hz, 1 H, H-3′), 5.13 (dd, J = 7.6, 3.3 Hz, 1 H, H-2′), 6.03 (s, 1 H, HCOO), 6.07 (d, J = 3.3 Hz, 1 H, H-1′), 7.75 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 14.9, 20.7, 28.3, 29.9, 61.5, 64.4, 80.9, 84.3, 85.3, 93.1, 105.9, 118.8, 141.2, 150.3, 151.4, 154.5, 170.5 ppm.

Synthesis of Nucleosides by the Fusion Method: A mixture of the appropriate tetra-*O*-acetyl-β-D-ribose (1.60 g, 5.00 mmol), theophylline (0.60 g, 3.33 mmol) and *p*TsOH (20 mg, 0.10 mmol), in a round flask fitted with a vacuum adapter and a stirrer bar, was heated at 190 °C with continuous stirring in vacuo until an opaque solution was obtained and vigorous gas evolution ceased (ca. 20 min). The reaction mixture was then cooled to 20 °C and dissolved in $CHCl_3$, the solution being washed with a 10% aqueous solution of Na_2CO_3 and water. The organic layer was dried with $MgSO_4$ and the solvents were evaporated to dryness. The obtained syrup was column chromatographed (diethyl ether/acetone, 9:1) to provide compounds **6** and **10**, respectively.

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)theophylline (6): (0.51 g, 35%). Colourless solid. M.p. 101−103 °C. $[\alpha]_D^{21} = +12$ (c = 1.0,

$CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2954, 2895, 1732, 1684, 1210, 1065, 761 cm^{-1}. UV (MeOH): λ_{max} (ε) = 276 (6800), 206 (24111) nm. EI MS: *m/z* (%) = 438 (6) [M^+], 259 (100), 180 (44). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.86, 2.03, 2.23 (3 × s, 9 H, 3 × CH_3CO), 3.56 (s, 3 H, NCH_3), 3.41 (s, 3 H, NCH_3), 3.97 (t, *J* = 10.5 Hz, 1 H, H-5), 4.02 (dd, *J* = 10.5, 6.4 Hz, 1 H, H-5′), 5.20 (ddd, *J* = 10.5, 6.4, 2.6 Hz, 1 H, H-4′), 5.54 (dd, *J* = 9.7, 2.6 Hz, 1 H, H-2′), 5.78 (t, *J* = 2.6 Hz, 1 H, H-3′), 6.24 (bd, *J* = 9.7 Hz, 1 H, H-1′), 7.77 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.2, 20.4, 20.6, 28.1, 29.8, 63.5, 65.7, 68.1, 68.3, 80.3, 106.6, 139.9, 148.9, 151.3, 154.6, 168.8, 169.3, 169.9 ppm. $C_{18}H_{22}N_4O_9 \cdot H_2O$ (456.1): calcd. C 47.35, H 5.30, N 12.28; found C 47.58, H 5.52, N 12.15.

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribofuranosyl)theophylline (10): White solid (0.63 g, 43%). M.p. 106 °C (ref.[27a] 99−100 °C). $[\alpha]_D^{23}$ = +34 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2975, 1737, 1699, 1664, 1222, 1017 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε) = 274 (8060), 240 (2524) nm. EI MS: *m/z* (%) = 438 (6) [M^+], 259 (100), 180 (19), 139 (83), 97 (46). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 2.07, 2.09, 2.12 (3 × s, 9 H, 3 × CH_3CO), 3.36 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 4.39 (m, 3 H, H-4′, H-5, H-5′), 5.37 (t, *J* = 5.5 Hz, 1 H, H-3′), 5.65 (dd, *J* = 5.5, 4.2 Hz, 1 H, H-2′), 6.31 (d, *J* = 4.2 Hz, 1 H, H-1′), 7.90 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.3, 20.4, 20.7, 28.2, 29.9, 62.4, 69.3, 74.2, 79.8, 88.6, 106.4, 139.2, 149.4, 151.4, 154.7, 169.2, 169.4, 170.2 ppm. $C_{18}H_{22}N_4O_9$ (438.1): calcd. C 49.30, H 5.06, N 12.78; found C 49.37, H 5.04, N 12.78.

Deacetylation of Protected Nucleosides 6 and 10: A catalytic amount of Na (3 mg) was added to a solution of compound **6** or **10** (70 mg, 0.16 mmol) in methanol (5 mL). The reaction mixture was stirred overnight at 20 °C. Recrystallisation from methanol gave pure nucleosides **5** and **9**.

7-β-D-(Ribopyranosyl)theophylline (5): Colourless crystals (45 mg, 90%). M.p. 232 °C (ref.[27b] 235−236 °C). $[\alpha]_D^{30}$ = −33 (*c* = 0.8, H_2O). IR (KBr): $\tilde{\nu}$ = 3482, 2954, 1681, 1389, 1045, 752 cm^{-1}. UV (MeOH): λ_{max} (ε) = 276 (9453) nm. EI MS: *m/z* (%) = 312 (4) [M^+], 209 (6), 180 (100). ^1H NMR (200 MHz, D_2O + CD_3OD, 298 K): δ = 3.36 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 3.90 (m, 2 H, H-5 and H-5′), 4.05 (m, 1 H, H-4′), 4.38 (m, 2 H, H-3′ and H-2′), 5.89 (d, *J* = 9.0 Hz, 1 H, H-1′), 8.28 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, D_2O, reference CD_3OD, 298 K): δ = 29.3, 31.0, 65.8, 67.1, 69.9, 71.8, 83.7, 107.9, 143.7, 150.3, 153.4, 156.4 ppm. $C_{12}H_{16}N_4O_6$ (312.1): calcd. C 46.14, H 5.17, N 17.95; found C 46.20, H 5.10, N 17.85.

7-β-D-(Ribofuranosyl)theophylline (9): (47 mg, 95%).

Synthesis of Nucleosides by Silyl Coupling: A mixture of the base [theophylline, 8-(methyl)theophylline or thiotheophylline, 4.80 mmol] and BSTFA (1.4 mL, 5.80 mmol) in dry $CHCl_3$ (15 mL) was stirred under nitrogen for 40 min at 20 °C. A solution of tetra-acetyl ribose (4.00 mmol) and trimethylsilyl trifluoromethanesulfonate (0.1 mL, 5.80 mmol) in $CHCl_3$ (5 mL) was then added, and the reaction mixture was heated at reflux under nitrogen for 4 h. Saturated aqueous $NaHCO_3$ (120 mL) and dichloromethane were then added. After the system had been stirred for 15 min, two layers were separated, and the aqueous one was extracted with dichloromethane (3 × 120 mL). The combined organic layers and extracts were washed with brine, dried with anhydrous $MgSO_4$ and filtered, and the solvents were evaporated to dryness. The residue was crystallised from MeOH to provide **2**, **6**, **10**, **12** and **14**.

8-Methyl-7-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)theophylline (2): Colourless solid (1.44 g, 80%). M.p. 248 °C. $[\alpha]_D^{22}$ = +48 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2950, 2900, 1730, 1680, 1200, 1060, 760 cm^{-1}. UV (MeOH): λ_{max} (ε) = 276 (15360), 222 (13840) nm. EI MS: *m/z* (%) = 452 (10) [M^+], 259 (80), 194 (100). ^1H NMR (400 MHz, $CDCl_3$, 363 K): δ = 1.82, 2.04, 2.25 (3 × s, 9 H, 3 × CH_3CO), 2.60 (s, 3 H, C-8−CH_3), 3.56 (s, 3 H, NCH_3), 3.42 (s, 3 H, NCH_3), 3.99 (t, *J* = 10.8 Hz, 1 H, H-5), 4.10 (dd, *J* = 10.8, 5.7 Hz, 1 H, H-5′), 5.27 (ddd, *J* = 10.8, 5.7, 3.1 Hz, 1 H, H-4′), 5.74 (dd, *J* = 8.9, 3.1 Hz, 1 H, H-2′), 5.82 (t, *J* = 3.1 Hz, 1 H, H-3′), 6.40 (bd, *J* = 8.9 Hz, 1 H, H-1′) ppm. ^1H NMR (400 MHz, $CDCl_3$, 233 K, *anti* conformer): δ = 1.87, 2.03, 2.26 (3 × s, 9 H, 3 × CH_3CO), 2.59 (s, 3 H, C-8−CH_3), 3.40 (s, 3 H, NCH_3), 3.53 (s, 3 H, NCH_3), 3.93−4.08 (m, 2 H, H-5, H-5′), 5.10 (m, 1 H, H-4′), 5.42 (dd, *J* = 9.9, 2.6 Hz, 1 H, H-2′), 5.71 (m, 1 H, H-3′), 6.76 (d, *J* = 9.9 Hz, 1 H, H-1′) ppm. ^1H NMR (400 MHz, $CDCl_3$, 233 K, *syn* conformer): δ = 1.87, 2.06, 2.30 (3 × s, 9 H, 3 × CH_3CO), 2.66 (s, 3 H, C-8−CH_3), 3.39 (s, 3 H, NCH_3), 3.54 (s, 3 H, NCH_3), 3.93−4.08 (m, 2 H, H-5, H-5′), 5.35 (m, 1 H, H-4′), 6.26 (dd, *J* = 9.3, 2.9 Hz, 1 H, H-2′), 5.78 (m, 1 H, H-3′), 5.50 (d, *J* = 9.3 Hz, 1 H, H-1′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 15.4, 20.3, 20.5, 20.8, 23.3, 29.7, 63.7, 65.9, 67.4, 68.4, 80.2, 106.6, 148.3, 151.2, 151.6, 154.2, 168.7, 169.3, 169.8 ppm. $C_{19}H_{24}N_4O_9$ (452.2): calcd. C 50.43, H 5.35, N 12.39; found C 50.56, H 5.31, N 12.10.

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)theophylline (6): (1.64 g, 90%).

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribofuranosyl)theophylline (10): (1.73 g, 99%).

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-thiotheophylline (12): (1.18 g, 65%). Yellow crystals. M.p. 107 °C. $[\alpha]_D^{22}$ = +56 (*c* = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2934, 1762, 1741, 1687, 1598, 1222 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε) = 344 (15500) nm. EI MS: *m/z* (%) = 454 (17) [M^+], 259 (80), 331(21), 197 (49), 196 (37), 139 (100), 97 (70). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 2.01, 2.15 (2 × s, 9 H, 3 × CH_3CO), 3.60 (s, 3 H, NCH_3), 3.75 (s, 3 H, NCH_3), 4.39−4.49 (m, 3 H, H-4′, H-5, H-5′), 5.26 (dd, *J* = 8.4, 4.9 Hz, 1 H, H-3′), 5.58 (dd, *J* = 4.9, 1.7 Hz, 1 H, H-2′), 7.21 (d, *J* = 1.7 Hz, 1 H, H-1′), 8.22 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.3, 20.4, 20.8, 30.4, 34.4, 61.4, 67.5, 75.0, 78.7, 89.1, 117.3, 140.5, 145.5, 149.8, 169.0, 169.3, 170.1, 176.6 ppm. $C_{18}H_{22}N_4O_8S$ (454.1): calcd. C 47.56, H 4.88, N 12.33; found C 47.63, H 4.75, N 12.03.

8-Methyl-7-(2′,3′,4′-tri-*O*-acetyl-β-D-ribofuranosyl)theophylline (14): (1.60 g, 88%). Colourless crystals. M.p. 105 °C. $[\alpha]_D^{28}$ = +32 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2950, 2900, 1730, 1680, 1200, 1060, 760 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε) = 280 (12484) nm. EI MS: *m/z* (%) = 452 (2) [M^+], 259 (44), 194 (26), 139 (100), 97 (65). ^1H NMR (200 MHz, $CDCl_3$, 298 K): δ = 2.06, 2.09, 2.13 (3 × s, 9 H, 3 × CH_3CO), 2.55 (s, 3 H, C-8−CH_3), 3.38 (s, 3 H, NCH_3), 3.55 (s, 3 H, NCH_3), 4.26−4.41 (m, 2 H, H-4′, H-5), 4.55 (dd, *J* = 11.5, 3.3 Hz, 1 H, H-5′), 5.59 (dd, *J* = 7.3, 5.8 Hz, 1 H, H-2′), 5.77 (dd, *J* = 7.3, 5.8 Hz, 1 H, H-3′), 6.04 (d, *J* = 5.8 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 14.5, 20.3, 20.4, 20.8, 28.3, 29.8, 63.3, 69.8, 73.1, 79.9, 88.1, 106.5, 148.8, 151.4, 151.5, 154.1, 169.4 (2 C), 170.5 ppm. $C_{19}H_{24}N_4O_9$ (452.2): calcd. C 50.43, H 5.35, N 12.39; found C 50.39, H 5.28, N 12.25.

8-Methyl-7-β-D-(ribofuranosyl)theophylline (13): Compound **14** (0.20 g, 0.44 mmol) was dissolved in methanol (5 mL). Na (10 mg) was then added, and the reaction mixture was stirred at 20 °C overnight. Recrystallisation from methanol gave pure **13** (0.13 g, 91%). Colourless crystals. M.p. 209 °C. $[\alpha]_D^{29}$ = +160 (*c* = 0.4, H_2O). IR (KBr): $\tilde{\nu}$ = 3600−3200, 1677, 1600 cm^{-1}. UV (MeOH): λ_{max} (ε) = 278 (13516) nm. EI MS: *m/z* (%) = 326 (1) [M^+], 194 (100).

^{1}H NMR (200 MHz, D_2O, 298 K): δ = 2.58 (s, 3 H, C-8−CH_3), 3.27 (s, 3 H, NCH_3), 3.45 (s, 3 H, NCH_3), 3.86 (m, 2 H, H-5 and H-5′), 4.07 (m, 1 H, H-4′), 4.30 (m, 1 H, H-3′), 4.63 (t, *J* = 7.0 Hz, 1 H, H-2′), 5.95 (d, *J* = 7.0 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, D_2O, reference CD_3OD, 298 K): δ = 14.7, 29.4, 31.0, 62.6, 70.1, 74.0, 86.2, 89.9, 107.5, 150.0, 153.3, 155.4, 155.7 ppm. $C_{13}H_{18}N_4O_6$ (326.1): calcd. C 47.83, H 5.56, N 17.18; found C 47.83, H 5.48, N 16.95.

Treatment with Lawesson's Reagent (LR): Under nitrogen, compound **2**, **6**, **10** or **14** (0.68 mmol) was heated at reflux with LR (0.48 g, 1.20 mmol) in dry distilled toluene (40 mL). Excess LR (1.20 mmol) was added at 24 h to completely remove any starting material (TLC, 48 h). Toluene was then removed under reduced pressure. The residue was separated by column chromatography (eluent, 9:1 chloroform:acetone) to give **4**, **8**, **12** or **16**, respectively. The products were recrystallised from methanol/water.

8-Methyl-7-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)-6-thiotheophylline (4): (0.10 g, 31%). Yellow crystals. M.p. 110−112 °C. $[\alpha]_D^{22}$ = +169 (*c* = 1.1, $CHCl_3$). IR (KBr): ṽ = 2936, 1760, 1740, 1688, 1560, 1222 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε) = 354 (25100), 350 (24500) nm. EI MS: *m*/*z* (%) = 468 (29) [M$^+$], 259 (94), 210 (100), 139 (93), 97 (50). ^{1}H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.79, 2.05, 2.28 (3 × s, 9 H, 3 × CH_3CO), 2.69 (s, 3 H, C-8−CH_3), 3.59 (s, 3 H, NCH_3), 3.82 (s, 3 H, NCH_3), 4.02 (m, 2 H, H-5 and H-5′), 5.12 (dt, *J* = 8.5, 2.7 Hz, 1 H, H-4′), 5.43 (dd, *J* = 9.9, 2.7 Hz, 1 H, H-2′), 5.74 (t, *J* = 2.7 Hz, 1 H, H-3′), 8.40 (d, *J* = 9.9 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 16.9, 20.3, 20.6, 20.9, 30.4, 34.3, 64.0, 66.1, 67.5, 68.4, 78.5, 117.8, 144.6, 149.8, 155.5, 169.3, 169.6, 170.1, 175.6 (C-6) ppm. $C_{19}H_{24}N_4O_8S$ H_2O (486.1): calcd. C 46.90, H 5.39, N 11.52; found C 47.18, H 5.14, N 11.65.

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribopyranosyl)-6-thiotheophylline (8): (0.18 g, 58%). Yellow crystals. M.p. 200 °C. $[\alpha]_D^{23}$ = +87 (*c* = 1.0, $CHCl_3$). IR (KBr): ṽ = 2934, 1762, 1741, 1687, 1598, 1222 cm^{-1}. UV (MeOH): λ_{max} (ε) = 345 (15214) nm. EI MS: *m*/*z* (%) = 454 (15) [M$^+$], 259 (47), 197 (80), 139 (100), 97 (93). ^{1}H NMR (200 MHz, $CDCl_3$, 298 K): δ = 1.88, 2.05, 2.27 (3 × s, 9 H, 3 × CH_3CO), 3.64 (s, 3 H, NCH_3), 3.84 (s, 3 H, NCH_3), 4.00 (dd, *J* = 10.6, 10.0 Hz, 1 H, H-5), 4.05 (dd, *J* = 10.6, 6.4 Hz, 1 H, H-5′), 5.16 (ddd, *J* = 10.0, 6.4, 2.3 Hz, 1 H, H-4′), 5.34 (dd, *J* = 9.8, 2.3 Hz, 1 H, H-2′), 5.78 (t, *J* = 2.3 Hz, 1 H, H-3′), 7.72 (d, *J* = 9.8 Hz, 1 H, H-1′), 7.92 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 20.4, 20.6, 20.8, 30.5, 34.3, 63.6, 65.8, 68.3, 68.7, 78.3, 116.8, 141.5, 145.1, 149.8, 169.2, 169.4, 170.0, 176.7 ppm. $C_{18}H_{22}N_4O_8S$ (454.1): calcd. C 47.56, H 4.88, N 12.33; found C 47.24, H 4.68, N 12.01.

7-(2′,3′,4′-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-thiotheophylline (12): (0.12 g, 39%).

8-Methyl-7-(2′,3′,4′-tri-*O*-acetyl-β-D-ribofuranosyl)-6-thiotheophylline (16): (0.11 g, 35%). Yellow crystals. M.p. 106 °C. $[\alpha]_D^{28}$ = +163 (*c* = 0.8, $CHCl_3$). IR (KBr): ṽ = 2935, 1760, 1740, 1688, 1596, 1220 cm^{-1}. UV ($CHCl_3$): λ_{max} (ε) = 346 (12712) nm. EI MS: *m*/*z* (%) = 468 (5) [M$^+$], 259 (39), 210 (36), 139 (100), 97 (58). ^{1}H NMR (200 MHz, $CDCl_3$, 298 K): δ = 2.01, 2.07, 2.12 (3 × s, 9 H, 3 × CH_3CO), 2.62 (s, 3 H, C-8−CH_3), 3.57 (s, 3 H, NCH_3), 3.77 (s, 3 H, NCH_3), 4.26−4.44 (m, 3 H, H-4′, H-5, H-5′), 5.25 (t, *J* = 7.2 Hz, 1 H, H-3′), 5.57 (dd, *J* = 7.2, 6.0 Hz, 1 H, H-2′), 8.29 (d, *J* = 6.0 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 298 K): δ = 16.3, 20.3 (2 C), 20.6, 30.3, 34.3, 62.2, 68.8, 71.6, 78.2, 85.5, 117.7, 144.7, 149.7, 158.2, 169.6, 169.7, 170.2, 175.7 ppm. $C_{19}H_{24}N_4O_8S$ (468.1): calcd. C 48.70, H 5.17, N 11.97; found C 48.65, H 5.16, N 11.90.

Deacetylation of Thionucleosides

A solution of MeONa/MeOH (0.15 m, 0.5 mL) was added to a solution of compound **4**, **8**, **12** or **16** (0.46 mmol) in methanol (10 mL). The reaction mixture was stirred at 20 °C for 24 h, after which the formed precipitate was filtered. Recrystallisation from methanol gave the pure thionucleoside (**3**, **7**, **11** or **15**, respectively)

8-Methyl-7-(β-D-ribopyranosyl)-6-thiotheophylline (3): (0.14 g, 89%). Yellow crystals. M.p. 236 °C. $[\alpha]_D^{23}$ = +173 (*c* = 0.4, H_2O). IR (KBr): ṽ = 3600−3200, 1679, 1602 cm^{-1}. UV (MeOH): λ_{max} (ε) = 352 (14963) nm. EI MS: *m*/*z* (%) = 342 (8) [M$^+$], 279 (3), 210 (100). ^{1}H NMR (200 MHz, D_2O + CD_3OD, 298 K): δ = 2.64 (s, 3 H, C-8−CH_3), 3.55 (s, 3 H, NCH_3), 3.75 (s, 3 H, NCH_3), 3.81−4.21 (m, 5 H, H-2′, H-3′, H-4′, H-5, H-5′), 7.96 (d, *J* = 9.8 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO + CD_3OD, 298 K): δ = 17.4, 30.7, 34.6, 65.9, 67.0, 68.6, 71.8, 80.7, 118.7, 145.0, 150.1, 156.1, 175.3 ppm. $C_{13}H_{18}N_4O_5S$ (342.1): calcd. C 45.60, H 5.30, N 16.37; found C 45.35, H 5.29, N 16.10.

7-(β-D-Ribopyranosyl)-6-thiotheophylline (7): (0.14 g, 93%). Yellow solid. M.p. 255 °C. $[\alpha]_D^{25}$ = −40 (*c* = 1.0, DMSO). IR (KBr): ṽ = 3600−3200, 1678, 1600 cm^{-1}. UV (MeOH): λ_{max} = 338 (ε 16388) nm. EI MS: *m*/*z* (%) = 328 (3) [M$^+$], 197 (100), 196 (35). ^{1}H NMR (200 MHz, [D$_6$]DMSO, 298 K): δ = 3.48 (s, 3 H, NCH_3), 3.67 (s, 3 H, NCH_3), 3.60 (dd, *J* = 12.3, 2.8 Hz, 1 H, H-5), 3.77 (dd, *J* = 12.3, 2.8 Hz, 1 H, H-5′), 3.93 (dt, *J* = 6.7, 2.8 Hz, 1 H, H-4′), 4.09 (dd, *J* = 6.7, 4.4 Hz, 1 H, H-3′), 4.21 (dd, *J* = 9.2, 4.4 Hz, 1 H, H-2′), 6.94 (d, *J* = 9.2 Hz, 1 H, H-1′), 8.50 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 298 K): δ = 30.1, 33.8, 64.8, 66.6, 68.3, 71.2, 79.9, 116.7, 143.9, 145.1, 149.4, 175.6 ppm. $C_{12}H_{16}N_4O_5S$ (328.1): calcd. C 43.89, H 4.91, N 17.07; found C 43.86, H 4.81, N 16.86.

7-(β-D-Ribofuranosyl)-6-thiotheophylline (11): (0.12 g, 80%). Yellow crystals. M.p. 127−128 °C. $[\alpha]_D^{30}$ = +177 (*c* = 0.1, MeOH). IR (KBr): ṽ = 3600−3200, 1678, 1600 cm^{-1}. UV (EtOH): λ_{max} (ε) = 338 (16600) nm. EI MS: *m*/*z* (%) = 328 (9) [M$^+$], 236 (13), 197 (100), 196 (61). ^{1}H NMR (200 MHz, [D$_6$]DMSO, 298 K): δ = 3.50 (s, 3 H, NCH_3), 3.68 (s, 3 H, NCH_3), 3.85−4.25 (m, 5 H, H-2′, H-3′, H-4′, H-5, H-5′), 6.94 (d, *J* = 9.2 Hz, 1 H, H-1′), 8.50 (s, 1 H, H-8) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 298 K): δ = 30.1, 33.9, 59.6, 67.9, 75.3, 83.9, 89.6, 116.9, 143.0, 145.3, 149.3, 175.6 ppm. $C_{12}H_{16}N_4O_5S$ (328.1): calcd. C 43.89, H 4.91, N 17.07; found C 43.77, H 4.80, N 16.84.

8-Methyl-7-(β-D-ribofuranosyl)-6-thiotheophylline (15): (0.15 g, 95%). Yellow crystals. M.p. 153 °C. $[\alpha]_D^{29}$ = +165 (*c* = 1.7, CH_3OH). IR (KBr): ṽ = 3600−3200, 1676, 1603 cm^{-1}. UV (MeOH): λ_{max} (ε) = 348 (15120) nm. EI MS: *m*/*z* (%) = 342 (3) [M$^+$], 250 (14), 210 (100). ^{1}H NMR (200 MHz, CD_3OD, 298 K): δ = 2.66 (s, 3 H, C-8−CH_3), 3.57 (s, 3 H, NCH_3), 3.77 (s, 3 H, NCH_3), 3.81−3.93 (m, 3 H, H-4′, H-5, H-5′), 4.22 (dd, *J* = 6.5, 5.2 Hz, 1 H, H-3′), 4.46 (t, *J* = 6.5 Hz, 1 H, H-2′), 8.00 (d, *J* = 6.5 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, CD_3OD, 298 K): δ = 17.0, 30.8, 34.9, 62.5, 70.3, 74.6, 86.1, 89.4, 119.7, 145.8, 151.4, 156.8, 177.1 ppm. $C_{13}H_{18}N_4O_5S$ (342.1): calcd. C 45.60, H 5.30, N 16.37; found C 45.72, H 5.37, N 16.40.

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