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AN IMPROVED METHOD FOR THE PREPARATION OF 2′,3′-UNSATURATED NUCLEOSIDES: SYNTHESIS OF STEREOSPECIFICALLY LABELLED KETONUCLEOSIDES

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ABSTRACT

2′,3′-Unsaturated nucleosides have been prepared in excellent yields under mild conditions by the condensation of acetylated glycals with purine or pyrimidine derivatives in the presence of trityl perchlorate. The synthesis of (α- and β-hex-2-enopyranosyl-4-ulose)theophylline nucleosides labelled at position 3′ with deuterium is described.

INTRODUCTION

In our study of the biological properties of ketonucleosides[1,2], large amounts of 3′-deuterated 2′,3′-unsaturated ketonucleosides were needed. Retrosynthetic analysis suggested that such molecules[3,4] could be obtained by the condensation of a heterocycle with acetylated glycals stereospecifically deuterated at C-3. We now report an efficient approach to labelled glycals, which also furnished a route to labelled 2,3-unsaturated glycosides and *C*-glycosyl derivatives[5,6].

Numerous attempts have been made to condense glycal derivatives with nitrogen heterocycles. Thus, fusions of acetylated glycals with various purines in the presence of toluene-*p*-sulfonic acid and with trimethylsilylated purines or pyrimidines have been reported[7]. These reactions afforded hex-2′-enopyranosyl nucleosides in moderate to fair yields. A limitation of this approach is incomplete reaction or the formation of complex mixtures containing such by-products as 2′-deoxynucleosides. In addition, 2′,3′-unsaturated nucleosides are less stable than the corresponding glycals and often lead to hex-1′-enopyranosyl nucleosides.

Trityl perchlorate has been used in a facile synthesis of glycosides and *C*-glycosyl derivatives from 1-*O*-acyl sugars[8,9]. The use of this catalyst in the condensation of glycals with trimethylsilylated heterocycles was explored therefore as a route to 2′,3′-unsaturated nucleosides.

Reaction of 3,4-di-*O*-acetyl-L-rhamnal (**1**) with 7-*N*-trimethylsilyltheophylline (**3**) in dichloromethane for 4 h at room temperature, using 0.3 equiv. of trityl perchlorate, gave, after chromatography, 78% of a mixture of the hex-2′-enopyranosyl nucleosides **8a** and **8b**. The configurations of the products were

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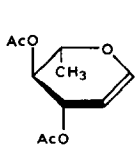
assigned from the 300-MHz n.m.r. spectra (Table II). Compound **8b** has been reported by Onodera and Yajimia[10], but inspection of the data indicated that the compound was probably a 1′,2′-unsaturated nucleoside. The $^5H_0$ conformation was identified by the $J_{4',5'}$ values (**8a**, 8.6 Hz; **8b**, 8.7 Hz). For **8a**, the $J_{1',2'}$ value of 3 Hz is characteristic of the relationship of vicinal equatorial and ethylenic protons[7c]; for **8b**, the $J_{1',2'}$ value of 1.3 Hz suggested H-1′ to be axial. These data were consistent with α and β configurations of **8a** and **8b**, respectively. Treatment of **8b** with sodium methoxide and then pyridinium dichromate/3 Å molecular sieve[11] gave, as expected, 7-(2,3,6-trideoxy-β-L-*erythro*-hex-2-enopyranosyl-4-ulose)theophylline[4] and thus confirmed the assigned structures.

TABLE I

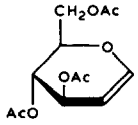
REACTION OF TRIMETHYLSILYLATED HETEROCYCLES WITH GLYCALS[a]

Entry	*Glycal*	*Base*	*Method*	*Products*[b]	*Yield (%)*[c] *(α/β) (purification)*
1	**1**	**3**	A	**8a, 8b**	78 (54/46) (Et_2O)[d]
2	**1**	**4**	A	**9a, 9b**	70 (54/46) (Hexane–EtOAc, 9:1)[d]
3	**1**	**5**	A	**10a, 10b**	61 (54/46) (EtOAc)[e]
4	**1**	**6**	B	**11a, 11b**	63 (45/55) (Hexane–EtOAc, 7:3)[d]
5	**1**	**7**	B	**12a, 12b**	81 (52/48) (EtOAc)[d]
6	**2**	**3**	A	**13a, 13b**	61 (49:51) (EtOAc)[d]
7	**2**	**4**	A	**14a, 14b**	76 (58/42) (Hexane–EtOAc, 4:1)[d]
8	**2**	**5**	A	**15a, 15b**	61 (50/50) (Hexane–EtOAc, 1:9)[e]
9	**2**	**6**	B	**16a, 16b**	63 (48:52) (Hexane–EtOAc, 2:3)[d]
10	**2**	**7**	B	**17**[f]	56 (56 β) (Hexane–EtOAc, 1:4)[d]

[a]Under nitrogen at room temperature. [b]All new compounds were fully characterised. [c]All yields refer to isolated compounds. [d]Flash chromatography. [e]Column chromatography. [f]T.l.c. indicated the presence of the α anomer (10–15%), but only **17** could be isolated.



1



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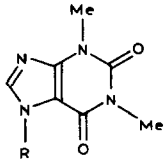

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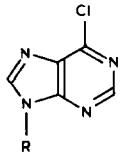

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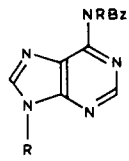

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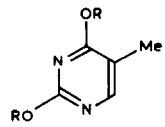

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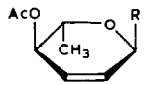
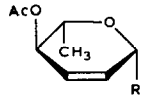
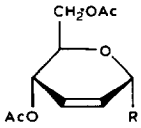
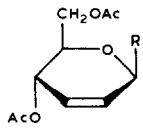




8a	8b	R = Theophyllin-7-yl
9a	9b	R = 6-Chloropurin-9-yl
10a	10b	R = *N*-Benzoyladenin-9-yl
11a	11b	R = Thymin-1-yl
12a	12b	R = *N*-Acetylcytosin-1-yl





13a	13b	R = Theophyllin-7-yl
14a	14b	R = 6-Chloropurin-9-yl
15a	15b	R = *N*-Benzoyladenin-9-yl
16a	16b	R = Thymin-1-yl
	17	R = *N*-Acetylcytosin-1-yl

Similarly, the trimethylsilylated derivatives of 6-chloropurine (**4**) and *N*-benzoyladenine (**5**) were condensed with **1** to give the corresponding hex-2′-enopyranosyl nucleosides in yields of 70 and 61%, respectively (Table I, entries 2 and 3).

Condensation of 3,4,6-tri-*O*-acetyl-D-glucal (**2**) with **3–5** occurred regioselectively at C-1 to produce 2,6-di-*O*-acetylhex-2-enopyranosyl nucleosides in yields of 60–75% (Table I, entries 6–8).

The reaction of the bis(trimethylsilyloxy)pyrimidine **6** with **1** or **2** under the above conditions gave mainly 1′,2′-unsaturated nucleosides. However, when the reaction was conducted under more basic conditions in the presence of 4 Å

TABLE II

^{1}H-N.M.R. DATA FOR **8–17** IN $CDCl_3$

Compound	*Chemical shifts (δ)*														
	H-1'	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-6'*	*H-2*	*H-5*	*H-6*	*H-8*	*AcO-4'*	*AcO-6'*	*AcN*	*BzN*	*MeN*	*Me-5*
8a	6.81	6.07	6.28	5.15	3.68	1.22				7.79	2.13				3.43	
															3.62	
8b	6.86	5.99	6.13	5.24	3.97	1.32				7.76	2.14				3.43	
															3.61	
9a	6.60	6.13	6.37	5.21	3.79	1.22	8.83			8.30	2.16					
9b	6.67	6.01	6.25	5.30	4.03	1.32	8.78			8.24	2.15					
10a	6.60	6.13	6.34	5.21	3.81	1.22	8.75			8.19	2.15			7.4–7.7		
														8.0–8.3		
10b	6.59	5.99	6.19	5.28	4.00	1.31	8.40			7.92	2.15			7.3–7.7		
														7.9–8.7		
11a	6.40	5.85	6.28	5.00	3.97	1.32			7.26		2.15					1.94
11b	6.49	5.73	6.14	5.18	3.88	1.30			7.27		2.13					1.89
12a	6.55	5.94	6.26	5.03	3.94	1.30		7.85	7.44		2.14		2.30			
12b	6.63	5.82	6.10	5.19	3.91	1.31		7.66	7.45		2.12		2.28			
13a	6.86	6.12	6.31	5.44	3.78	4.08				7.81	2.13	2.03			3.43	
						4.24									3.63	
13b	6.90	6.03	6.16	5.48	4.10	4.25				7.76	2.14	2.08			3.42	
															3.61	
14a	6.63	6.21	6.40	5.48	3.92	4.09	8.83			8.31	2.15	2.00				
						4.24										
14b	6.74	6.08	6.30	5.55			8.79			8.26	2.16	2.06				
15a	6.64	6.20	6.39	5.48	3.96	4.10	8.75			8.20	2.15	2.01		7.5–7.7		
						4.25								8.0–8.1		
15b	7.62	6.11	6.24	5.56			8.42			8.16	2.16	2.07		7.4–7.6		
														8.2–8.3		
16a	6.44	5.90	6.32	5.26	4.04	4.18			7.27		2.15	2.09				1.94
						4.29										
16b	6.57	5.78	6.17	5.40	4.03	4.24			6.99		2.13	2.10				1.93
17a	6.71	5.86	6.14	5.42	4.04	4.24		7.64	7.44		2.12	2.09	2.27			

	Coupling constants (Hz)									
	$J_{1',2'}$	$J_{1',3'}$	$J_{1',4'}$	$J_{2',3'}$	$J_{2',4'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'}$	$J_{6',6'}$	$J_{5,6}$
8a	3.0	1.6	1.9	10.2	1.9	2.0	8.6	6.2		
8b	1.3	2.0	2.7	10.3	2.0	1.5	8.7	6.1		
9a	3.0	1.7	1.9	10.2	1.9	2.0	8.5	6.2		
9b	0.4	2.1	2.5	10.2	2.1	1.7	8.7	6.1		
10a	3.0	1.7	1.9	10.2	2.0	2.0	8.5	6.2		
10b	1.5	2.2	2.6	10.2	2.1	1.8	8.7	6.2		
11a	2.5	1.9	2.1	10.2	1.3	3.2	6.3	6.5		
11b	1.4	2.3	2.7	10.2	2.1	1.7	8.8	6.2		
12a	2.6	1.8	2.0	10.2	1.2	3.3	5.8	6.5		7.5
12b	1.4	2.0	2.6	10.2	2.1	1.7	8.8	6.1		7.4
13a	3.0	1.6	1.9	10.2	1.9	2.0	9.0	4.8	12.3	
								2.8		
13b	1.5	2.1	2.3	10.3	2.0	1.8	9.0	3.9		
14a	3.0	1.7	1.9	10.1	1.9	2.0	9.0	5.2	12.3	
								2.6		
14b	1.6	2.2	2.4	10.3	2.1	1.8	8.7			
15a	3.1	1.7	1.8	10.2	1.9	2.1	9.1	5.2	12.3	
								2.6		
15b	1.4	2.1	2.6	10.3	2.0	1.8	8.8			
16a	2.7	1.9	2.1	10.2	1.6	2.8	6.8	5.6	12.2	
								3.5		
16b	1.5	2.2	2.7	10.2	2.1	1.8	9.2	4.2		
17a	1.3	2.1	2.4	10.2	2.1	1.8	9.1	4.0		7.5

TABLE III

HEX-2′-ENOPYRANOSYL-4′-ULOSE NUCLEOSIDES

Compound	*M.p. (degrees) (solvent for crystallisation)*	*Molecular formula*	*Analytical data (%)*			$[\alpha]_D^{20}$ [a] *(degrees)*	λ_{max} (ε)[b]
				Calc.	*Found*		
8a	179 (MeOH)	$C_{15}H_{18}N_4O_5$	C	53.89	53.93	−177.5	275 (7600)
			H	5.43	5.41		
			N	16.76	16.92		
8b	198 (MeOH)	$C_{15}H_{18}N_4O_5$	C	53.89	53.61	−65	275 (8180)
			H	5.43	5.33		
			N	16.76	16.83		
9a	oil	$C_{13}H_{13}ClN_4O_3$	C	50.58	51.24	−62.5	264 (8350)
			H	4.24	4.26		
			N	18.15	18.29		
			Cl	11.48	11.28		
9b	133 (MeOH)	$C_{13}H_{13}ClN_4O_3$	C	50.58	50.77	−95	264 (7170)
			H	4.24	4.35		
			N	18.15	18.30		
			Cl	11.48	11.58		
10a	s.c.	$C_{20}H_{19}N_5O_4 \cdot CH_3OH$	C	59.29	59.13	−52.5*	253 (11760)*
			H	5.45	5.05		
			N	16.46	16.35		
10b	161 (AcOEt)	$C_{20}H_{19}N_5O_4$	C	61.06	61.15	+90*	253 (10680)*
			H	4.87	5.05		
			N	17.80	17.31		
11a	87 (AcOEt)	$C_{13}H_{16}N_2O_5$	C	52.34	52.36	−82.5	264 (9250)
			H	6.08	6.14		
			N	9.39	9.36		
11b	205 (AcOEt)	$C_{13}H_{16}N_2O_5$	C	55.71	55.80	−115	264 (9900)
			H	5.75	5.70		
			N	9.99	9.96		
12a	224 (MeOH)	$C_{14}H_{17}N_3O_5$	C	53.16	53.30	−30*	250 (12480)*
			H	5.74	5.82		
			N	13.28	13.16		
12b	210 (AcOEt)	$C_{14}H_{17}N_3O_5$	C	54.71	54.28	−152.5*	250 (11610)*
			H	5.57	5.36		
			N	13.67	13.38		
13a	108 (MeOH)	$C_{17}H_{20}N_4O_7$	C	51.91	51.78	+137.5	275 (8400)
			H	5.38	5.20		
			N	14.24	14.15		
13b	142 (MeOH)	$C_{17}H_{20}N_4O_7$	C	51.91	51.96	+27.5	275 (7770)
			H	5.38	5.14		
			N	14.24	13.93		
14a	90 (AcOEt)–hexane) (lit.[7d] 85–86)	$C_{15}H_{15}ClN_4O_5$	C	49.12	48.99	+72.5*	265 (8310)*
			H	4.12	4.0		
			N	15.28	14.89		
			Cl	9.67	9.50		
14b	oil	$C_{15}H_{15}ClN_4O_5$	C	49.12	49.43	+100*	265 (10080)*
			H	4.12	4.35		
			N	15.28	14.73		
			Cl	9.67	9.50		
15a	104 (AcOEt) (lit.[7i] 108–111)	$C_{22}H_{21}N_5O_6$	C	57.39	57.00	+235*	253 (11460)*
			H	4.82	4.96		
			N	15.21	15.52		

TABLE III *(continued)*

Compound	*M.p. (degrees) (solvent for crystallisation)*	*Molecular formula*	*Analytical data (%)*			$[\alpha]_D^{20}$ [a] *(degrees)*	λ_{max} (ε)[b]
				Calc.	*Found*		
15b	95 (AcOEt–hexane)	$C_{22}H_{21}N_5O_6$	C	57.39	57.30	−77.5*	253 (16280)*
			H	4.82	5.01		
			N	15.21	14.89		
16a	131 (2-Propanol) [lit.[7i] 140 (EtOH)]	$C_{15}H_{18}N_2O_7 \cdot 0.5\,C_3H_8O$	C	52.26	52.55	+97	264 (16700)
			H	5.88	5.81		
			N	7.44	7.30		
16b	oil	$C_{15}H_{18}N_2O_7$	C	53.25	53.05	+105	264 (9060)
			H	5.36	5.67		
			N	8.28	7.78		
17	174 (AcOEt) (lit.[7i] 171–173)	$C_{16}H_{19}N_3O_7$	C	52.60	52.14	+140	250 (15010)
			H	5.24	5.27		
			N	11.50	11.74		

[a]In methanol (*c* 0.1); * signifies in dichloromethane (*c* 0.1). [b]In methanol; * signifies in dichloromethane.

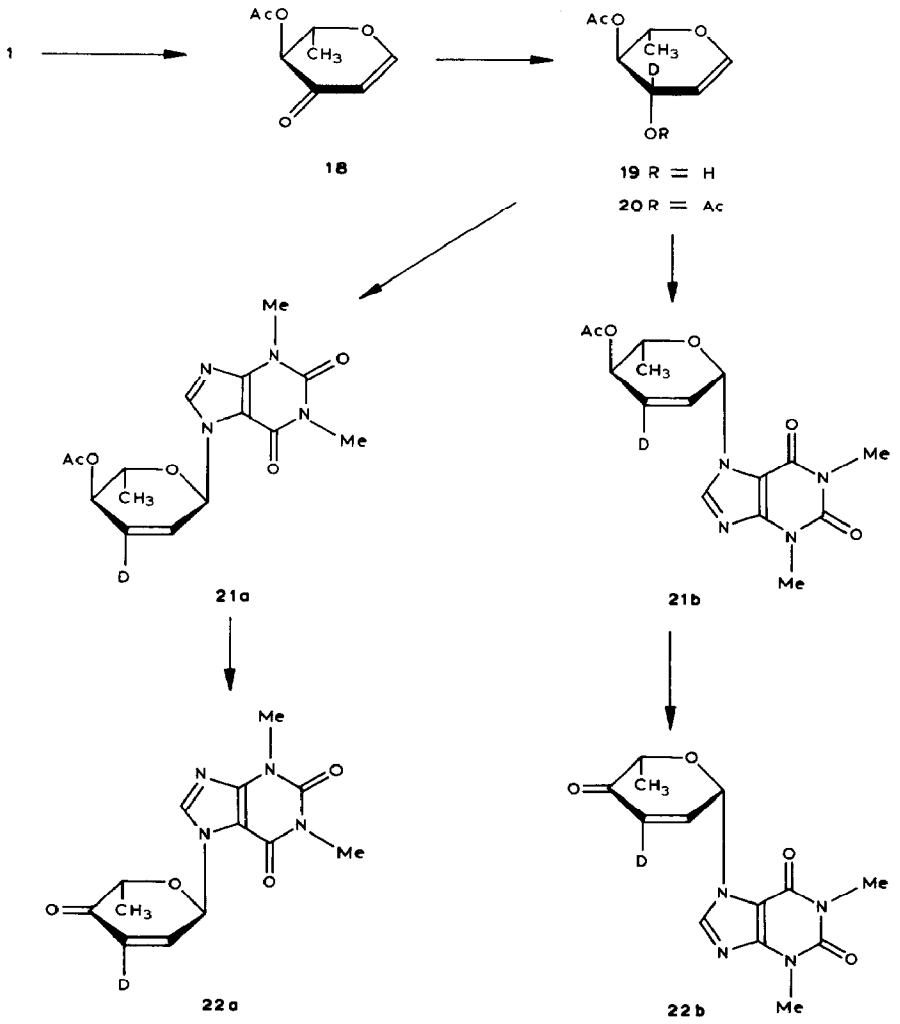
molecular sieves and lithium perchlorate, the hex-2-enopyranosylpyrimidine nucleosides were produced in good overall yields (Table I, entries 4 and 9).

Condensation of **1** with the bis(trimethylsilyloxy)cytosine **7** gave 81% of a 1:1 $\alpha\beta$-mixture of nucleosides (Table I, entry 5). Interestingly, preparation of *N*-acetyl-1-(2,6-di-*O*-acetyl-D-*erythro*-hex-2-enopyranosyl)cytosine, a molecule related to cytosinine the nucleoside part of the antibiotic blasticidin S, by the reaction of **2** with **7** gave the best selectivity, affording 56% of the β anomer (Table I, entry 10).

The structure of the 2′,3′-unsaturated nucleosides was also established from the $J_{1',2'}$[7c] and $J_{4',5'}$ values (Table II). For the more polar isomers, the recorded values ($J_{1',2'}$ 1.4–1.6, $J_{4',5'}$ 8.7–9.2 Hz) were consistent with a β configuration in the ^5H_O conformation for the L nucleosides and a $^OH_5$ conformation for the D derivatives. For the α isomers, the configuration was assigned from the $J_{1',2'}$ values (2.6–3.1 Hz). Examination of the H-5′ resonances indicated the same conformation for the α- and β-purine nucleosides ($J_{4',5'}$ 8.5–9 Hz). However, for the α derivatives in the pyrimidine series, the small values of $J_{4',5'}$ indicated an equilibrium between the $^OH_5$ and the ^5H_O conformations[12].

The method describe above was applied to the preparation of [3′-^{2}H]-labelled 2′,3′-unsaturated 4′-ketonucleosides. 3,4-Di-*O*-acetyl-L-[3-^{2}H]rhamnal (**20**) was synthesised from the dihydropyrone **18**[13]. Reduction[14] of **18** with sodium borodeuteride (−78°, $CeCl_3$) afforded **19**. The presence of deuterium at C-3 was indicated by the doublets for H-2 (δ 4.79) and H-4 (δ 4.74) in the ^{1}H-n.m.r. spectrum. Treatment of **19** with acetic anhydride and dimethylaminopyridine afforded **20**, the 300-MHz ^{1}H-n.m.r. spectrum of which closely resembled that of **1**.

Condensation of **20** with 7-trimethylsilyltheophylline (**3**) in the presence of trityl perchlorate afforded, after flash chromatography, α- (**21a**) and β-L-*glycero*-[3′-^{2}H]hex-2′-enopyranosyltheophylline nucleoside (**21b**). Deacetylation of **21a** and



21b and then oxidation, using pyridinium dichromate in the presence of 3 Å molecular sieves[11], gave the labelled ketonucleosides **22a** and **22b**, respectively, in yields of 85 and 59%, the 300-MHz ^{1}H-n.m.r. spectra of which closely resembled those of the corresponding 4′-ketonucleosides[11].

EXPERIMENTAL

All reactions were performed under dry nitrogen. Melting points were determined on a Reichert microstage block and are uncorrected. ^{1}H-N.m.r. spectra were recorded with a Bruker MSL 300 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). U.v. spectra were recorded with a Varian 635 spectrophotometer. Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS, Vernaison (France). T.l.c. was performed on Silica Gel F_{254} (Merck).

Column chromatography was performed on Silica Gel 60 (0.063–0.200 mm), and Silica gel 60 (0.04–0.063 mm) was used for flash chromatography[15]. Dichloromethane was distilled from calcium hydride. Solvents were evaporated at room temperature and ~12 mmHg. Trimethylsilylation was performed using saccharin as catalyst[16].

Synthesis of hex-2-enopyranosyl nucleosides. — Method A. To the trimethylsilylated heterocycle (5.5 mmol) was added, under nitrogen at room temperature, a solution of acetylated glycal (5 mmol in 7 mL of dichloroethane) and a solution of trityl perchlorate (0.32 mmol in 9 mL of dichloroethane). After 5 min, the solution was diluted with dichloromethane, washed sequentially with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), filtered, and concentrated. Chromatography using the solvent indicated (Table I) afforded the hex-2′-enopyranosyl nucleosides.

Method B. To a mixture of 4 Å molecular sieves (0.5 g/mmol of glycal) and lithium perchlorate (0.5 equiv.) was added, simultaneously under nitrogen at room temperature, a solution of the acetylated glycal (2 mmol in 2 mL of dichloroethane), a solution of trimethylsilylated heterocycle (1.1 equiv., 0.66M in dichloroethane), and a solution of trityl perchlorate (1 equiv., 0.33M in dichloroethane). The suspension was stirred for 3 h and then treated as in Method A.

4-O-Acetyl-1,5-anhydro-2,6-dideoxy-L-arabino-[*3-²H*]*hex-1-enitol* (**19**). — To 4-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose[13] (**18**; 0.34 g, 2 mmol) and $CeCl_3 \cdot 6H_2O$ (0.743 g, 2 mmol) in dry methanol (18.6 mL) at −78° was added a solution of sodium borodeuteride (92.4 mg, 2.2 mmol) in ethanol (4.7 mL) dropwise during 20 min. The solution was diluted with ethyl acetate (120 mL), washed successively with saturated aqueous sodium hydrogencarbonate (3 × 30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Crude **19** (0.34 g, 98%) was used without further purification. ^{1}H-N.m.r. data: δ 1.32 (d, 3 H, *J* 6.3 Hz, H-6), 2.14 (s, 3 H, Ac), 3.98 (dq, 1 H, *J* 6.3 and 9.4 Hz, H-5), 4.74 (d, 1 H, *J* 9.4 Hz, H-4), 4.79 (d, 1 H, *J* 6.1 Hz, H-2), 6.36 (d, 1 H, *J* 6.1 Hz, H-1).

3,4-Di-O-acetyl-1,5-anhydro-2,6-dideoxy-L-arabino-[*3-²H*]*hex-1-enitol* (**20**). — To a solution of **19** (0.34 g, 1.96 mmol) in dichloromethane (10 mL) at room temperature were added pyridine (0.5 mL), acetic anhydride (0.04 mL), and a crystal of dimethylaminopyridine. After 15 min, the solution was concentrated to dryness. Flash chromatography (hexane–ethyl acetate, 8:2) of the residue gave **20** (0.324 g, 77%), $[\alpha]_D^{20}$ −17.5° (*c* 0.1, chloroform). ^{1}H-N.m.r. data: δ 1.32 (d, 3 H, *J* 6.6 Hz, H-6), 2.05 and 2.14 (2 s, each 3 H, 2 Ac), 4.11 (dq, 1 H, *J* 6.6 and 8.2 Hz, H-4′), 4.77 (d, 1 H, *J* 6.1 Hz, H-2), 5.02 (d, 1 H, *J* 8.2 Hz, H-4), 6.43 (d, 1 H, *J* 6.1 Hz, H-1).

*7-(4-O-Acetyl-2,3,6-trideoxy-α-*L-erythro-[*3-²H*]*hex-2-enopyranosyl)theophylline* (**21a**) *and 7-(4-O-acetyl-2,3,6-trideoxy-β-*L-erythro-[*3-²H*]*hex-2-enopyranosyl)theophylline* (**21b**). — Compound **20** (0.34 g, 1.58 mmol) was treated with 7-tri-

methylsilyltheophylline (**3**), using method A. Flash column chromatography (hexane–ethyl acetate, 1:9) of the product gave **21a** (0.194 g, 36%) and **21b** (0.194 g, 36%).

Compound **21a** had m.p. 172° (from EtOH), $[\alpha]_D^{20}$ −205° (*c* 0.1, chloroform); $\lambda_{max}^{CHCl_3}$ 278 nm (ε 10,530). ^{1}H-N.m.r. data: δ 1.22 (d, 3 H, *J* 6.2 Hz, H-6′), 2.13 (s, 3 H, Ac), 3.43 and 3.62 (2 s, each 3 H, 2 NMe), 3.68 (dq, 1 H, *J* 6.2 and 8.6 Hz, H-5), 5.15 (ddd, 1 H, *J* 1.9, 1.9, and 8.6 Hz, H-4), 6.07 (dd, 1 H, *J* 1.9 and 3 Hz, H-2), 6.81 (dd, 1 H, *J* 1.9 and 3 Hz, H-1′), 7.79 (s, 1 H, H-8).

Compound **21b** had m.p. 189° (from EtOH), $[\alpha]_D^{20}$ −102° (*c* 0.1, chloroform); $\lambda_{max}^{CHCl_3}$ 278 nm (ε 12,830). ^{1}H-N.m.r. data: δ 1.32 (d, 3 H, *J* 6.1 Hz, H-6′), 2.14 (s, 3 H, Ac), 3.43 and 3.61 (2 s, each 3 H, 2 NMe), 3.97 (dq, 1 H, *J* 6.1 and 8.7 Hz, H-4′), 5.24 (ddd, 1 H, *J* 2, 2.6, and 8.7 Hz, H-4′), 5.99 (dd, 1 H, *J* 1.3 and 2 Hz, H-2′), 6.86 (dd, 1 H, *J* 1.3 and 2.6 Hz, H-1′), 7.76 (s, 1 H, H-8).

*7-(2,3,6-Trideoxy-α-*L-glycero-[*3-^{2}H*]*hex-2-enopyranosyl-4-ulose)theophylline* (**22a**). — To a solution of **21a** (0.1 g, 0.3 mmol) in methanol and dichloromethane (2 mL, 1:1) was added methanolic M sodium methoxide (0.75 mmol). After 10 min, the solution was dilued with dichloromethane, neutralised with Amberlite IR-120 (H^+) resin, and concentrated. The resulting foam was dissolved in dichloromethane (1.5 mL), molecular sieves (3 Å, 0.3 g) and pyridinium dichromate (0.169 g, 0.45 mmol) were added, and the suspension was stirred for 1.5 h. The mixture was then diluted with ethyl acetate (3 × 10 mL), filtered through Celite, and concentrated under reduced pressure. Flash column chromatography (hexane–ethyl acetate, 7:3) of the resulting oil and crystallisation from ethanol afforded **22a** (0.082 g, 85%), m.p. 152° (from EtOH), $[\alpha]_D^{20}$ −27° (*c* 0.1, chloroform); $\lambda_{max}^{CHCl_3}$ 279 nm (ε 9590). ^{1}H-N.m.r. data: δ 1.45 (d, 3 H, *J* 6.8 Hz, H-6′), 3.43 and 3.62 (2 s, each 3 H, 2 NMe), 4.26 (q, *J* 6.8 Hz, H-5′), 7.08–7.12 (m, 2 H, H-1′ and H-2′), 7.73 (s, 1 H, H-8).

Anal. Calc. for $C_{13}H_{13}DN_4O_4$: C, 53.61; H + D, 5.18; N, 19.24. Found: C, 53.97; H + D, 5.14; N, 18.89.

*7-(2,3,6-Trideoxy-β-*L-glycero-[*3-^{2}H*]*hex-2-enopyranosyl-4-ulose)theophylline* (**22b**). — Compound **21b** (0.1 g, 0.3 mmol) was treated as for **21a**, to give **22b** (0.052 g, 59%), m.p. 173° (from EtOH), $[\alpha]_D^{20}$ −13° (*c* 0.1, chloroform); $\lambda_{max}^{CHCl_3}$ 279 nm (ε 9380). ^{1}H-N.m.r. data: δ 1.47 (d, 3 H, *J* 6.6 Hz, H-6′), 3.44 and 3.63 (2 s, each 3 H, 2 NMe), 4.47 (dq, 1 H, *J* 1.7 and 6.6 Hz, H-5′), 7.08 (bs, 1 H, H-2′), 7.12 (bd, 1 H, *J* 1.7 Hz, H-1′), 7.73 (s, 1 H, H-8).

Anal. Calc. for $C_{13}H_{13}DN_4O_4$: C, 53.61; H + D, 5.18; N, 19.24. Found: C, 53.77; H + D, 4.93; N, 19.16.

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