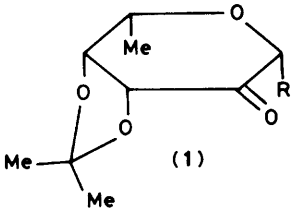
Synthesis of Spiroepoxynucleosides

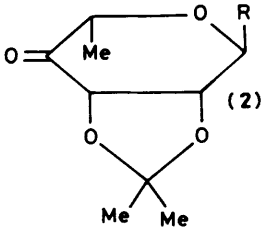
Jean Herscovici, Marie-José Egron and Kostas Antonakis
Institut de Recherches Scientifiques sur le Cancer, BP No. 8-94802, Villejuif, Cedex, France

The first syntheses of spiroepoxyhexopyranosyl-purines and -pyrimidines are reported. The spiro epoxy group was introduced at C-2′ by treatment of 2′-keto-β-L-nucleosides with dimethylsulphoxonium methylide. Addition of the sulphur ylide generated from Me_3SOCl and NaH afforded β-L-*talo*- and β-L-*galacto*-spironucleosides. Interestingly, when trimethylsulphoxonium chloride was activated with butyl-lithium, an inversion took place at C-1′ leading exclusively to an α-L-*galacto*-spironucleoside.

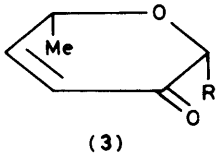
6-Deoxy-L-hexopyranosyl keto nucleosides have attracted considerable synthetic and biological attention.[1] As exemplified by 2- and 4-L-keto nucleosides (**1**) and (**2**) we have shown that these molecules inhibit the growth of KB cells *in vitro*[2] and exhibit significant activity against L1210 leukaemia *in vivo*,[3] whereas the parent compounds are inactive under the same experimental conditions.



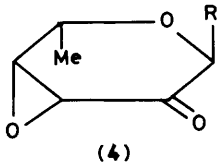
(1)



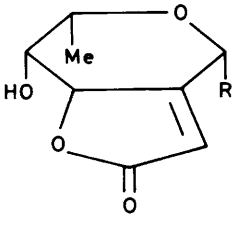
(2)



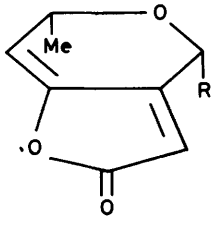
(3)



(4)

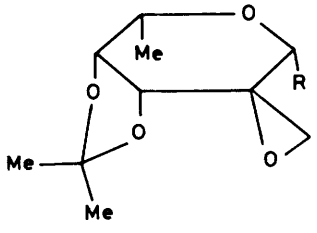


(5)



(6)

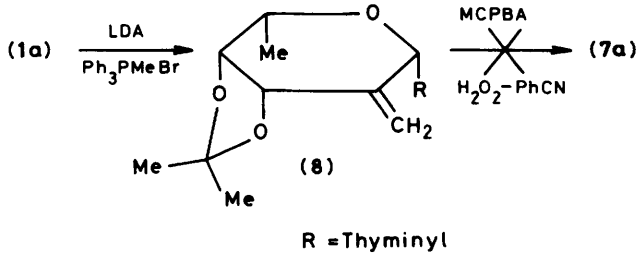
R = Purinyl or pyrimidinyl



(7)

During the last few years the synthesis of several analogues such as (**3**) and (**4**) having either unsaturation or an epoxy group conjugated to the carbonyl has been reported.[4,5] These molecules are potent antitumour agents and at low doses they preferentially impair DNA synthesis and strongly inhibit cell multiplication.[6] Our next effort in this area was mainly directed at a rational search for 6-deoxy-L-hexopyranosyl nucleosides with new functionalities which are known to be responsible for the biological activity of cytotoxic molecules, and recently we described the first synthesis of fused lactone nucleosides (**5**) and (**6**).[7]

Spiroepoxy nucleosides such as (**7**) may be expected to offer new antineoplastic properties since this group constitutes the critical moiety in the structure of important classes of anti-tumour compounds.[8] In the present publication we report the construction of the *exo*cyclic ring from keto nucleoside precursors. Initial attention was directed towards ketone olefination using the Buddrus procedure.[9] In contrast to our lactone nucleoside synthesis we were unable to prepare the 2′-*exo*methylene nucleoside when the keto nucleoside (**1a**)[7] was treated with triphenylphosphine and methyl iodide in the presence of ethylene or propylene oxide. Further investigation employing methyltriphenylphosphonium chloride and LDA in tetrahydrofuran at 0 °C gave the unsaturated nucleoside (**8**) in 70% yield (Scheme 1).

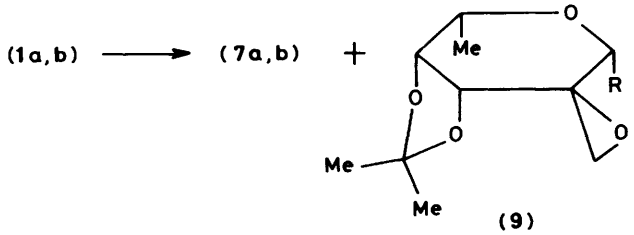


Scheme 1.

The presence of the *exo*cyclic double bond at C-2′ was deduced from ^1H n.m.r. spectroscopic data. The terminal methylene group was identified by one olefinic signal at δ 5.6 (2 H) and the position of the double bond was revealed by the multiplicity of the resonance at δ 4.6 (1 H, d, 3′-H) and 6.6 (1 H, s, 1′-H).

Attempted epoxidation using *m*-chloroperbenzoic acid or other oxidizing agents [TBHP(t-butyl hydroperoxide); PhCN–H_2O_2] was uniformly unsuccessful. In each case decomposition of the peroxy reagent was the only reaction observed.

Encouraged by the stability of the keto nucleoside (**1a**) towards carbanions, we explored the reaction of compounds (**1**) with a sulphur ylide (Scheme 2). Although the addition of



a; R = Thyminyl
b; R = Theophyllinyl

Scheme 2.

dimethylsulphoxonium methylide to cyclo-nucleosides has been described,[10] to our knowledge there is no example of reaction with sulphur ylides in the case of purine and pyrimidine nucleosides. Treatment of compound (**1a**) with dimethylsulphoxonium methylide generated from sodium hydride and trimethyl sulphoxonium iodide[9] afforded compound (**7a**) in 20% yield. At 60 MHz, the dioxaspiro[5.2]octane skeleton was clearly evidenced by the signals at δ 2.46 (1 H, d, *J* 5 Hz, oxirane CH), 2.79 (1 H, d, *J* 5 Hz, oxirane CH), 4.45 (1 H, d, *J* 5.5 Hz, 3′-H), and 6.03 (1 H, s, 1′-H).

In order to improve the yield, epoxidation of the keto nucleosides (**1**) was performed using the more stable dimethylsulphoxonium methylide.[11] Under these conditions (Me_3SOCl–NaH) the spiro epoxides (**7a**) and (**9a**) were isolated as 1:1 mixture with an overall yield of 80%. The 2′-branched nature of nucleoside (**9**) was deduced from the characteristic ^1H n.m.r. spectrum which showed a 1 H doublet at δ 3.94 (*J* 7.5 Hz, 3′-H), a 1 H singlet at δ 6.54 (1′-H) and a 2 H singlet at 2.96 assigned to the epoxidic protons. The success of this epoxidation prompted further exploration and our attention was focused on purine spironucleosides. Scheme 2 also outlines the synthesis of theophylline derivatives. The keto nucleoside (**1b**)[12] was treated with dimethylsulphoxonium methylide generated in the standard manner from sodium hydride and trimethylsulphoxonium chloride. After 2 h the nucleosides (**7b**) and (**9b**) were isolated as a 1:1 mixture (70% overall yield). The ^1H n.m.r. spectra of these compounds closely resembled those of compounds (**7a**) and (**9a**). At 250 MHz the presence of a spiro-epoxide was inferred for compound (**7b**) by the characteristic doublets at δ 2.43 and 2.8 and by a 2 H singlet (δ 2.93) for the spironucleoside (**9b**).

Variation in the length of reaction time had a marked effect upon the epoxidation of compound (**1b**). When the condensation was performed for five min, the spiro derivatives (**7b**) and (**9b**) were isolated in a 8:2 ratio. It is well known that dimethylsulphoxonium methylide gaves predominantly[11] the epoxide containing an equatorial carbon-carbon bond. Thus this observation suggested that the spiroepoxynucleoside (**7b**) had the β-L-*talo* configuration. Consequently we assigned the β-L-*galacto* configuration to the anhydro nucleoside (**9b**).

The structures proposed were confirmed by spectroscopic evidence. Examination of the 3′-H doublets [(**7a**) 4.43 p.p.m., (**9b**) 3.94 p.p.m.] revealed an unusual upfield shift for compound (**9b**). This difference would be explained by the anisotropy of the epoxide which exerts a shielding effect on the *syn* proton in 3′-H. Examination of the two epoxy nucleosides (**10**)[13] and (**11**)[14] recently synthesized in our laboratory allowed confirmation of the stereochemical assignment. Figure 1 displays the expected

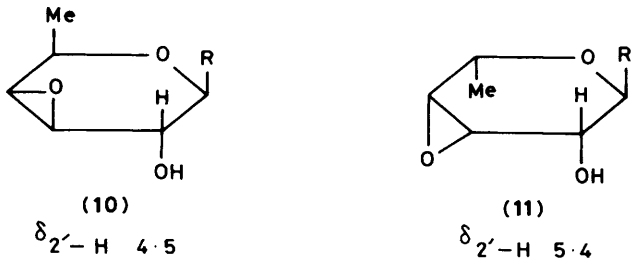


Figure 1.

chemical shift difference between the D-*altro* nucleoside (**10**) and the L-*allo* derivative (**11**) for the 2′-H signal.

N.O.e. experiments (Figure 2) provided complementary

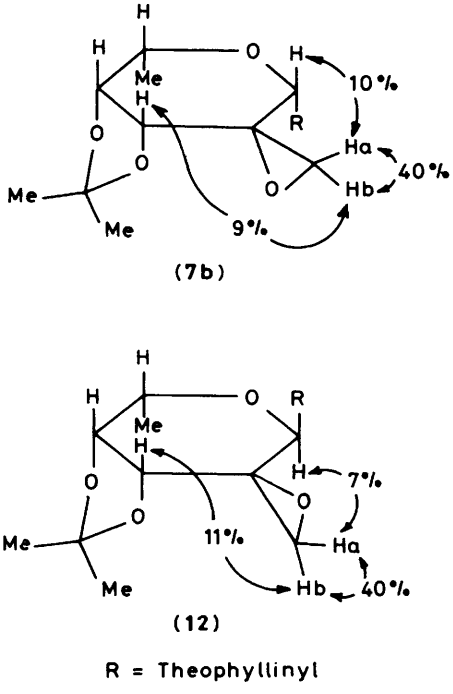
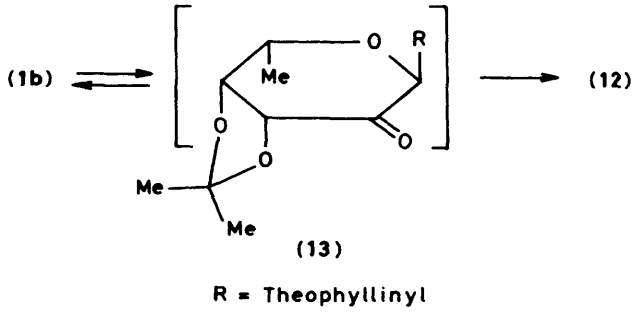


Figure 2. n.O.e. Effect (%).

information. For the nucleoside (**7b**) irradiation of the most shielded epoxy proton H_a at δ 2.4 produced a 10% enhancement of the 1′-H signals. In constrast, the epoxy protons appeared as a 2 H singlet at δ 2.93 for the L-*galacto* nucleoside (**9b**). This downfield shift was explained by the anisotropic effect of the heterocycle and was consistent with an *anti* relationship between the purine and the oxirane ring, so compound (**9b**) was assigned definitively as the 7-6′-deoxy-2′,2″-anhydro-6′-deoxy-2′-*C*-hydroxymethyl-3′,4′-*O*-isopropylidene-β-L-*galacto*-hexopyranosyl)theophylline. Furthermore, these data indicated the theophylline unit to be *syn* to the spiroepoxide compound (**7b**) and allowed final confirmation of the stereochemistry. Thus compound (**7b**) was established as the 7-(2,2″-anhydro-6′-deoxy-2′-*C*-hydroxymethyl-β-L-*talo*-hexopyranosyl)theophylline.

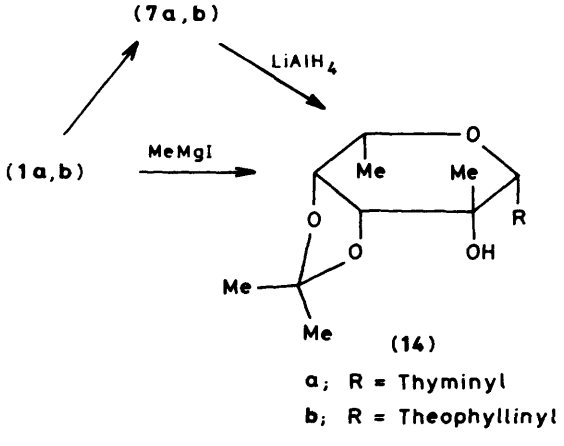
Variation of the base had a major effect on the course of the reaction (Scheme 3). Thus preparation of dimethylsulphoxonium methylide using butyl-lithium instead of sodium



Scheme 3.

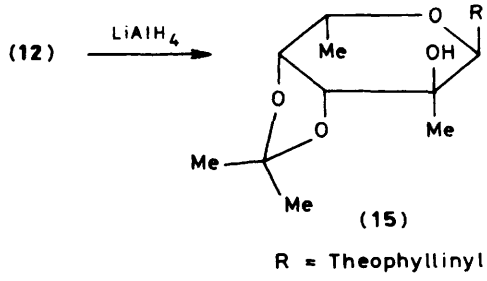
hydride afforded overnight a sole product (**12**) (70%). Again the presence of a spiroepoxide was evidenced by the resonances at δ 2.25 (1 H, d, *J* 3.8 Hz) and 2.84 (1 H, d, *J* 3.8 Hz). The *syn* relationship between 3′-H and the oxirane ring was clearly discernible by the upfield shift of the 3′-H resonance at δ 4 (1 H, d, *J* 7.6 Hz). Furthermore the multiplicity of this signal indicated that the addition of the sulphur ylide had occurred at C-2′ and suggested an unexpected stereochemical inversion at C-1′. Confirmation of the α-L-*galacto* stereochemistry was readily deduced from irradiation of the H_a doublet at δ 2.25 which produced a 7% n.O.e effect on the 1′-H signal. In the same manner as for the spironucleoside (**7b**) the downfield shift of this signal indicated that 1′-H was *anti* to the epoxy group and established the structure compound (**12**) as 7-(2′,2″-anhydro-6′-deoxy-2′-*C*-hydroxymethyl-3′,4′-*O*-isopropylidene-α-L-*galacto*-hexopyranosyl)theophylline.

The exclusive introduction of an equatorial C–C bond at C-2′ strongly suggested that the formation of compound (**12**) proceeded by sulphoxonium methylide addition to the α-keto nucleoside (**13a**). This observation implies a spontaneous inversion at the anomeric centre, a process which to our knowledge has not been described in nucleoside chemistry. The absence of β-spiroepoxy derivatives revealed the lack of reactivity of the β-keto nucleoside (**1b**) towards the BuLi–Me_3SOCl system which favoured the enolization at C-2′. Thus the mechanism of the reaction can be depicted as an equilibrium between keto nucleosides (**1b**) and (**13a**), shifted to the right by the addition of the sulphur ylide to the α-isomer (Scheme 3).



Scheme 4.

Finally the assigned structures were found to be fully consistent with the following experiments. It is well established that kinetic addition to 2′-keto nucleosides proceeds by an attack from the less hindered side.[1] Thus it could be anticipated that treatment of the keto nucleoside (**1**) (Scheme 4) with methylmagnesium iodide or with a metal hydride the β-L-*talo*-spiroepoxynucleoside (**7**) should lead in both cases to the same C-2′-methyl derivative (**14**). As expected Grignard addition of MeMgI to 1-(2′,6′-deoxy-3′,4′-*O*-isopropylidene-β-L-*lyxo*-hexopyranosyl)thymine (**a**) yielded the branched chain nucleoside (**14a**) as the sole product which was identical with a sample prepared by reduction of the anhydro nucleoside (**7a**) with $LiAlH_4$ identical fashion the theophylline derivative (**1b**) afforded the 7-(6′-deoxy-3′,4′-*O*-isopropylidene-2′-*C*-methyl-β-L-*talo*-hexopyranosyl)theophylline (**14b**). Treatment of the α-spironucleoside (**12**) with lithium aluminium hydride also provided the C-2′-methyl nucleoside (**15**) (Scheme 5) whereas



Scheme 5.

the sterically hindered β-L-*galacto*-nucleoside (**9b**) was inert towards reducing agents.

Biological and chemical properties of these new nucleosidic derivatives are now under investigation.

Experimental

All reactions requiring an inert atmosphere were run under a positive pressure of dry argon. M.p.s were determined on a Reichert microstage block and are uncorrected. ^1H n.m.r. spectra were recorded in the indicated solvent on a Varian T60 (60 MHz) or a Bruker WH250 (250 MHz). Chemical shifts are reported in δ units, p.p.m. downfield from tetramethylsilane. Coupling constant are reported in Hz. ^{13}C N.m.r. spectra were recorded on a Varian CFT20 (20 MHz). I.r. spectra were obtained on a Perkin Elmer 137 spectrophotometer. U.v. spectra were recorded on Varian 635 spectrophotometer. Microanalysis and mass spectra were performed by the Laboratoire Central de Microanalyse du CNRS Vernaison, France. T.l.c. was performed on E. Merck AG Darmstadt F254 silica gel precoated plastic sheets. The term flash chromatography is used for medium pressure liquid chromatography silica gel 60 (0.04—0.063 mm).

For reactions requiring dry solvents, tetrahydrofuran and diethyl ether were distilled from sodium diphenylketyl. Methanol, acetone (3 Å) and dichloromethane (4 Å) were dried on molecular sieves and used without further distillation. Diisopropylamine was distilled from calcium hydride. Sodium hydride was employed as a 50% dispersion in mineral oil and weights are recorded for the dispersion. Glassware for experiments requiring anhydrous conditions were flame dried under a stream of nitrogen. Evaporations were effected at room temperature using a rotary evaporator under a water-tap aspirator or a mechanical oil pump vacuum.

1-(2′,6′-*Dideoxy*-3′,4′-O-*isopropylidene*-2′-*C*-*methylene*-β-L-lyxo-*hexopyrano*)*thymine* (**8**).—Methyltriphenylphosphonium bromide (5.49 g, 5 mmol) was suspended in dry THF (30 ml)

and cooled to 0 °C. In a separate flask butyl-lithium (9.375 ml; 1.6M in hexane; 15 mmol) was slowly added to a solution of di-isopropylamine (2.1 ml, 15.75 mmol) in THF (30 ml) and stirred for 15 min. The resulting LDA solution was transferred by a cannula to the phosphonium salt suspension and the resulting slurry stirred at 0 °C for 90 min. The keto nucleoside (**1a**) (3.19 g, 10 mmol) in THF was then added in one portion. Immediately after the addition, the reaction was quenched with Na_2HPO_4 and the nucleoside extracted with dichloromethane (3 × 10 ml). The organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The *exo*-methylene nucleoside (**8**) was purified by flash chromatography [pentane ethyl acetate (1:1)] and isolated as a foam (2.22 g, 70%), $[\alpha]_D^{20}$ +15° (*c* 0.1, MeOH) (Found: C, 55.8; H, 6.5; N, 8.6. $C_{15}H_{20}N_2O_5 \cdot H_2O$ requires C, 55.2; H, 6.74; N, 8.58%); $\lambda_{max.}$ 264 nm (11 365 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ 1 692 (CO), 1 645 (conjugated CO) cm^{-1}; δ_H (60 MHz; CD_3CO_2H) 1.3 (3 H, d, *J* 6 Hz, 6′-H_3), 1.5 and 1.6 (6 H, 2 × s, Me_2C), 1.9 (3 H, s, 5-Me), 3.7 (1 H, dq, *J* 2 and 6 Hz, 5′-H), 4.3 (1 H, dd, *J* 2 and 7 Hz, 4′-H), 5 (1 H, d, *J* 7 Hz, 3′-H), 5.6 (2 H, s, 2′-CH_2), 6.6 (1 H, s, 1′-H), and 7.9 (1 H, s, 6-H).

1-(2′,2″-*Anhydro*-6′-*deoxy*-2′-C-*hydroxymethyl*-3′,4′-O-*isopropylidene*-β-L-talo-*hexopyranosyl*)*thymine* (**7b**) *and* 1-(2′,2″-*Anhydro*-6′-*deoxy*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranosyl*)*thymine* (**9a**).—THF (20 ml) was added to a slurry of pentane-washed sodium hydride (0.96 g, 20 mmol; 50% dispersion) then the suspension was cannulated to a 100 ml flask filled with trimethylsulphoxonium chloride (3.17 g, 20 mmol) and THF (10 ml). The mixture was heated at reflux for 2 h, cooled to room temperature then a 0.4M-solution of the keto nucleoside (**1a**) (3.1 g, 10 mmol) in THF was slowly added. After 1 h the stirred reaction was quenched with Na_2HPO_4 and extracted with dichloromethane (3 × 25 ml). The organic extracts were dried (Na_2SO_4), and the solvent evaporated. The residual oil was purified by flash chromatography (diethyl ether). Concentration under reduced pressure and crystallization yielded respectively the *talo*-nucleoside (**7a**) (1.29 g, 40%) and the *galacto*-nucleoside (**9a**) (1.29 g, 40%).

Compound (**7a**) had m.p. 125—127 °C (from MeOH), $[\alpha]_D^{20}$ −55° (*c* 0.1 in MeOH) (Found: C, 55.5; H, 6.9; N, 7.4. $C_{15}H_{20}N_2O_6 \cdot C_2H_5OH$ requires C, 55.13; H, 7.02; N, 7.56%); $\lambda_{max.}$(MeOH) 264 nm (ε 11 728 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H (60 MHz; $CDCl_3$); 1.42 (3 H, d, *J* 6.5 Hz, 6′-H_3), 1.3 and 1.6 (6 H, 2 × s, CMe_2), 1.9 (3 H, s, 5-Me), 2.5 (1 H, d, *J* 5 Hz, oxirane CH), 2.8 (1 H, d, *J* 5 Hz, oxirane CH), 4.03 (1 H, dq, *J* 1.5 and 6 Hz, 5′-H), 4.2 (H, dd, *J* 1.5 and 5 Hz, 4′-H), 4.45 (1 H, *J* 5 Hz, 3′-H), 6.0 (1 H, s, 1′-H), and 7.6 (1 H, s, 6-H).

Compound (**9a**) had m.p. 114 °C (from ethanol–pentane), $[\alpha]_D^{20}$ +20° (*c* 0.1 in MeOH) (Found: C, 55.55; H, 6.15; N, 8.65. $C_{15}H_{20}N_2O_6$ requires C, 54.9; H, 6.30; N, 8.35%); $\lambda_{max.}$(MeOH) 264 nm (ε 13 122 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H (60 MHz; $CDCl_3$) 1.3 (3 H, d, *J* 7 Hz, 6′-H_3), 1.4 and 1.6 (6 H, 2 × s, CMe_2), 1.9 (3 H, s, 5-Me), 2.96 (2 H, s, oxirane CH_2), 3.9 (1 H, d, *J* 7 Hz, 3′-H), 3.96 (1 H, m, overlapped, 5′-H), 4.3 (1 H, dd, *J* 2 and 7 Hz, 4′-H), 5.91 (1 H, s, 1′-H), and 8.06 (1 H, s, 6-H).

7-(2′,2″-*Anhydro*-6′-*deoxy*-2′-C-*hydroxymethyl*-3′,4′-O-*isopropylidene*-β-L-talo-*hexopyranosyl*)*theophylline* (**7b**) *and* 7-(2′,2″-*Anhydro*-6′-*deoxy*-2′-C-*hydroxymethyl*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranosyl*)*theophylline* (**9b**).—The keto nucleoside (**7b**) (3.64 g, 10 mmol) in THF (25 ml) was added during 5 min to a slurry of sodium dimethylsulphoxonium methylide prepared from pentane-washed sodium hydride (0.96 g, 20 mmol) and trimethylsulphoxonium chloride (3.17 g, 20 mmol) as described for compound (**7a**). The resulting yellow reaction mixture was worked up as above to yield the 2′,2″-anhydro-L-*talo*-nucleoside (**7b**) (2.11 g, 56%) and the L-*galacto*-spironucleoside (**9b**) (0.54 g, 14%). When the reaction was stopped after 2 h compound (**7b**) (1.51 g, 35%) and 35% of compound (**9b**) (1.51 g) were recovered.

The nucleoside (**7b**) had m.p. 180—182 °C (Et_2O), $[\alpha]_D^{20}$ −80° (*c* 0.1 MeOH) (Found: C, 54.2; H, 6.0; N, 14.75. $C_{17}H_{22}N_4O_6$ requires C, 53.96; H, 5.82; N, 14.81%); $\lambda_{max.}$(MeOH) 275 nm (ε 6.652 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$(KBr) 1 739 (CO), 1 647 cm^{-1} (conjugated CO); δ_H (250 MHz; $CDCl_3$) 1.39 and 1.62 (2 × 3 H, 2 × s, CMe_2), 1.44 (3 H, d, *J* 6.5 Hz, 6′-H_3), 2.43 (1 H, d, *J* 4.7 Hz, oxirane CH), 2.8 (1 H, d, *J* 4.7 Hz, oxirane CH), 3.39 and 3.96 (2 × 3 H, 2 × s, NMe), 4.13 (1 H, dq, *J* 2.2 and 6.5 Hz 5′-H), 4.25 (1 H, dd, *J* 2.2 and 5.9 Hz, 4′-H), 4.43 (1 H, d, *J* 5.9 Hz, 3′-H), 6.54 (1 H, s, 1′-H), and 8.16 (1 H, s, 8-H); δ_C (20 MHz; $CDCl_3$) 16.25 (q), 25.63 (q), 25.84 (q), 27.92 (q), 29.32 (q), 47.27 (t), 55.09 (s), 72.11 (d), 73.38 (d), 75.58 (d), 81.14 (d), 105.37 (s), 110.94 (s), 142.32 (d), 148.23 (s), 151.10 (s), and 155.27 (s).

The nucleoside (**9b**) had m.p. 168 °C (MeOH), $[\alpha]_D^{20}$ −25° (*c* 0.1 MeOH) (Found: C, 54.2; H, 6.0; N, 14.75. $C_{17}H_{22}N_4O_6$ requires C, 53.96; H, 5.82; N, 14.81%); $\lambda_{max.}$(MeOH) 275 nm (ε 14 779 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$(KBr) 1 709 (CO), 1 667 cm^{-1} (conjugated CO); δ_H (250 MHz; $CDCl_3$) 1.39 and 1.61 (2 × 3 H, 2 × s, CMe_2), 1.35 (3 H, d, *J* 6.6 Hz, 6′-H_3), 2.93 (2 H, s, oxirane CH_2), 3.4 and 3.6 (2 × 3 H, 2 × s, NMe), 3.94 (1 H, d, *J* 7.7 Hz, 3′-H), 4.07 (1 H, dd, *J* 1.9 and 6.6 Hz, 5′-H), 4.36 (1 H, dq, *J* 1.9 and 7.7 Hz, 4′-H), 6.26 (1 H, s, 1′-H), and 8.35 (1 H, s, 8-H); δ_C (20 MHz; $CDCl_3$) 15.5 (q), 24.43 (q), 25.91 (q), 27.99 (q), 29.78 (q), 48.38 (t), 54.41 (s), 70.45 (d), 75.42 (d), 76.91 (d), 85.10 (d), 106.30 (s), 110.94 (s), 142.39 (d), 147.33 (s), 151.46 (s), and 154.88 (s).

7-(2′,2″-*Anhydro*-6′-*deoxy*-2′-C-*hydroxymethyl*-3′,4′-O-*isopropylidene*-α-L-galacto-*hexopyransoyl*)*theophylline* (**12**).—Butyl-lithium (12.5 ml, 20 mmol; 1.6M-in hexane) was added to a slurry of trimethylsulphoxonium chloride (3.17 g, 20 mmol) in THF (20 ml) and the mixture was heated to reflux. After 2 h the suspension was cooled to room temperature then the keto nucleoside (**1b**) (364 g, 10 mmol) was added slowly and the reaction mixture was stirred overnight. Work-up as for compound (**7a**) followed by flash chromatography (Et_2O) gave the α-spironucleoside (**12**) (2.646 g, 70%), which showed m.p. 180 °C (MeOH), $[\alpha]_D^{20}$ −80° (*c* 0.1 MeOH) (Found: C, 53.9; H, 5.8; N, 14.6. $C_{17}H_{22}N_4O_6$ requires C, 53.96; H, 5.82; N, 14.81%); $\lambda_{max.}$(MeOH) 275 nm (ε 10.735 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$(KBr) 1 701 (CO), 1 653 cm^{-1} (conjugated CO); δ_H (250 MHz; $CDCl_3$) 1.38 (3 H, d, *J* 7.1 Hz, 6′-H_3), 1.39 and 1.67 (2 × 3 H, 2 × s, CMe_2), 2.25 (1 H, d, *J* 3.8 Hz, oxirane CH), 2.84 (1 H, d, *J* 3.8 Hz, oxirane CH), 3.40 and 3.59 (2 × 3 H, 2 × s, NMe), 4.0 (1 H, d, *J* 7.6 Hz, 3′-H), 4.4 (2 H, m, *J* 6.5 Hz, 4′-H and 5′-H), 7.23 (1 H, s, 1′-H), and 7.82 (1 H, s, 8-H); δ_C (20 MHz; $CDCl_3$) 16.72 (q), 24.56 (q), 26.28 (q), 27.95 (q), 29.73 (q), 47.39 (t), 55.36 (s), 69.90 (d), 76.2 (d), 76.75 (d), 77.72 (d), 106.29 (s), 111.41 (s) 141.46 (d), 148.16 (s), 151.47 (s), and 154.88 (s).

1-(6′-*Deoxy*-3′,4′-O-*isopropylidene*-2′-C-*methyl*-β-L-talo-*hexopyranosyl*)*thymine* (**14a**).—(*a*) *By Grignard reaction.* A 100 ml flask equipped with a Claisen adaptor and a condenser was charged with anhydrous diethyl ether (22.5 ml), magnesium chips (0.144 g, 6 mmol), methyl iodide (1.31 g, 9.27 mmol), and a crystal of iodine. When all the magnesium was dissolved a solution of the keto nucleoside (**7a**) (0.93 g, 3 mmol) in THF (7.5 ml) was added dropwise. After 20 min the reaction was quenched with saturated Na_2HPO_4 and extracted with dichloromethane (3 × 25 ml). The organic extracts were washed with sodium thiosulphate then dried (Na_2SO_4). Crystallization from ethanol yielded the 2′-C-methyl nucleoside (**14a**) (0.68 g, 70%).

(*b*) *By reduction with* $LiAlH_4$. A solution of the spiro-

nucleoside (**7a**) (0.972 g, 3 mmol) in dry THF (10 ml) was added dropwise to a solution of lithium aluminium hydride (0.157 g, 3.6 mmol) in diethyl ether at −20 °C. Ethyl acetate (2 ml) was then added and the resulting suspension was quenched with sodium hydrogensulphate. The aqueous solution was extracted with ethyl acetate (3 × 15 ml) and the organic extracts were dried (Na_2SO_4). Evaporation under reduced pressure followed by crystallisation afforded compound (**14a**) (0.489 g, 50%), which showed m.p. 140 °C (EtOH), $[\alpha]_D^{20}$ −110° (*c* 0.1 MeOH) (Found: 55.1; H, 6.9; N, 8.0. $C_{15}H_{22}N_2O_6$ requires C, 55.21; H, 6.74; N, 8.58%); $\lambda_{max.}$(MeOH) 265 nm (ε 11.931 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 1 739 (CO) and 1 647 cm^{-1} (conjugated CO); δ_H (60 MHz; $CDCl_3$) 1.08 (3 H, s, 2′-Me), 1.40 (6 H, m, CMe and 6′-H_3), 1.6 (3 H, s, CMe), 1.9 (3 H, s, 5-Me), 4.2 (3 H, m, 3′-H, 4′-H, 5′-H), 5.4 (1 H, s, 1′-H), and 8.2 (1 H, s, 6-H).

7-(6′-*Deoxy*-3′,4′-O-*isopropylidene*-2′-C-*methyl*-β-L-talo-*hexopyranosyl*)*theophylline* (**14b**).—(*a*) *By Grignard reaction.* Methylmagnesium iodide was treated with the keto nucleoside (**1b**) (1.092 g, 3 mmol) as for compound (**14a**) to yield the C-2′-methyl nucleoside (**14b**) (0.57 g, 50%).

(*b*) *By reduction with* $LiAlH_4$. Reduction of the spironucleoside (**7b**) (1.134 g, 3 mmol) was performed using $LiAlH_4$ to give, after work-up, the nucleoside (**4b**) (0.57 g, 50%), which showed, m.p. 220—223 °C (EtOH), $[\alpha]_D^{20}$ −100° (*c* 0.1, MeOH) (Found: C, 53.7; H, 6.05; N, 14.25. $C_{17}H_{24}N_4O_6$ requires C, 53.7; H, 6.31; N, 14.73%); $\lambda_{max.}$(MeOH) 275 nm (8 475 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 265 (OH), 1 739 (CO), and 1 647 cm^{-1} (conjugated CO); δ_H (60 MHz; $CDCl_3$) 0.8 (3 H, s, 2′-Me), 1.25 (6 H, m, CMe and 6′-H_3), 1.64 (3 H, s, CMe), 3.2 and 3.4 (2 × 3 H, s, NMe), 4.0 (3 H, m, 3′-H, 4′-H, 5′-H), 5.9 (1 H, s, 1′-H), and 8.2 (1 H, s, 8-H).

7-(6′-*Deoxy*-3′,4′-O-*isopropylidene*-2′-C-*methyl*-α-L-galacto-*hexopyransoyl*)*theophylline* (**15**).—Reduction of the spironucleoside (**12**) (1.134 g, 3 mmol) was performed using $LiAlH_4$ to give, after work-up, the nucleoside (**15**) (0.57 g, 50%), which showed m.p. 219—220 °C (EtOH), $[\alpha]_D^{20}$ −2.5° (*c* 0.1 MeOH) (Found: C, 53.95; H, 6.4; N, 14.45. $C_{17}H_{24}N_4O_6$ requires C, 53.63; H, 6.31; N, 14.73%); $\lambda_{max.}$(MeOH) 275 nm (ε 8 360 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 265 (OH), 1 739 (CO), and 1 647 cm^{-1} (conjugated CO); δ (60 MHz; $CDCl_3$) 0.8 (3 H, s, 2′-Me), 1.25 (6 H, m, CMe and 6′-H_3), 1.64 (3 H, s, CMe), 3.4 and 3.6 (2 × 3 H, each s, NMe), 4.6—5.0 (3 H, m, 3′-H, 4′-H, 5′-H), 6.4 (1 H, s, 1′-H), and 8.1 (1 H, s, 8-H).

References

1 K. Antonakis, *Adv. Carbohydr. Chem. Biochem.*, 1984, **42**, 217.
2 K. Antonakis and I. Chouroulinkov, *Biochem. Pharmacol.*, 1974, **23**, 2095.
3 I. Chouroulinkov and K. Antonakis, *C.R. Acad. Sci., Ser. D*, 1977, **285**, 1021.
4 J. Herscovici and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2682.
5 J. Herscovici, J. M. Argoullon, M. J. Egron, and K. Antonakis, *Carbohydr. Res.*, 1983, **112**, 301.
6 C. Aujard, Y. Moulé, E. Chany-Morel, and K. Antonakis, *Biochem. Pharmacol.*, 1978, **27**, 1037.
7 J. Herscovici, M. J. Egron, and K. Antonakis, *Carbohydr. Res.*, in press.
8 T. W. Doyle, and W. T. Bradner, in 'Anticancer drugs based on natural product models,' ed. J. M. Cassady and J. M. Douros, Academic Press, New York, 1980, p. 43.
9 J. Buddrus, *Chem. Ber.*, 1974, **107**, 2050.
10 A. Matsuda, K. Niizuma, and Ueda, *Chem. Pharm. Bull.*, 1980, **28**, 876; I. M. Sasson and B. Otter, *J. Org. Chem.*, 1981, **46**, 1114.
11 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
12 K. Antonakis, *Carbohydr. Res.*, 1972, **24**, 229.
13 M. Bessodes, J. M. Argoullon, and K. Antonakis, *Carbohydr. Res.*, 1982, **111**, 170.
14 R. Lakaf, Thèse de Doctorat, Université de Paris VII, 1985.

Received 9th October 1985; *Paper* 5/1748