Unexpected Outcome in the Titanium-catalysed Epoxidation of Branched Hydroxy-propene Nucleosides

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Asymmetric epoxidation of branched hydroxypropene nucleosides with either (+)- or (−)-di-isopropyl tartrate led surprisingly to only one diastereoisomer, whose stereochemistry was determined by comparison with the Darzens products.

Branched chain nucleosides have attracted a considerable amount of synthetic work, as they are constituents or intermediates of a variety of biologically active compounds. On the other hand, keto nucleosides have proved to be good intermediates in the synthesis of branched chain nucleosides such as spiroepoxides[1] or fused lactones.[2] Introduction of a chiral glycidyl function at the terminal position of glycosides[3] and nucleosides[4] has been recently described, showing that branched *C*-glycidyl nucleosides should be the synthons of choice for the synthesis of chiral branched chain sugar nucleosides. We now report the first synthesis of branched glycidyl nucleosides *via* the Sharpless epoxidation[5] of the corresponding branched hydroxypropenyl derivatives.

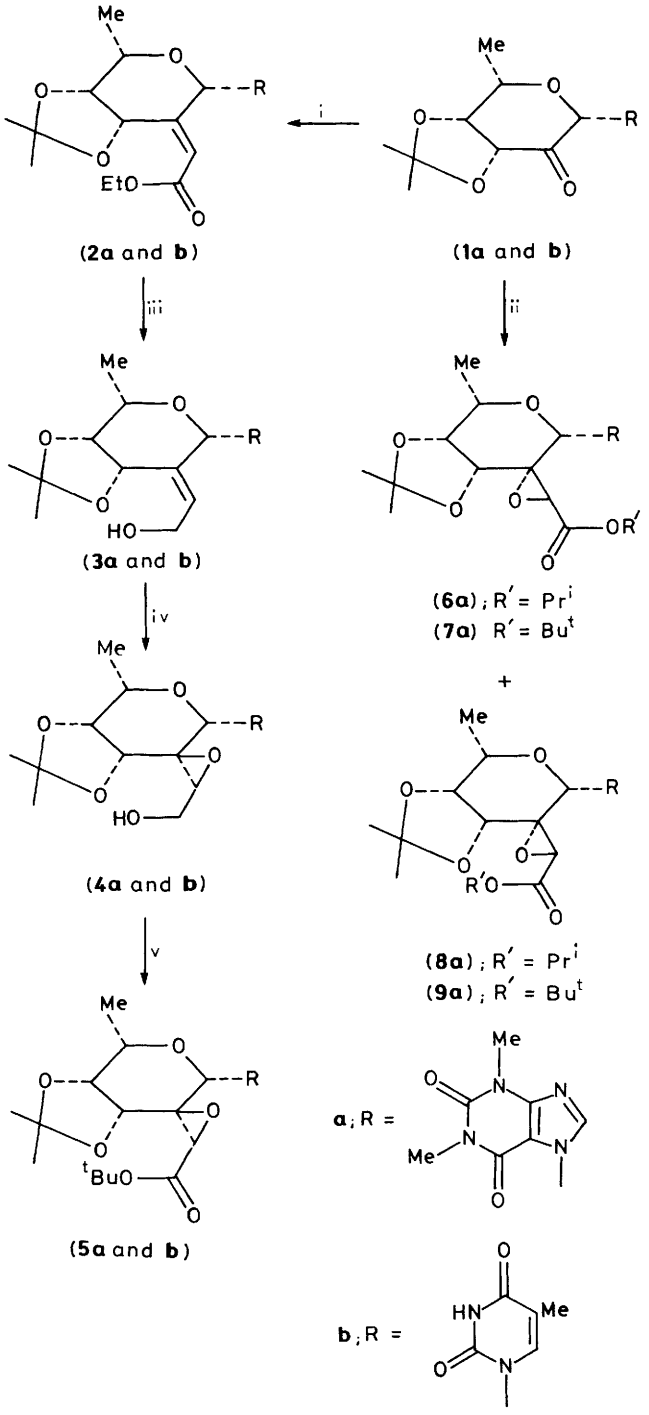
The Buddrus[6] reaction of ethyl bromoacetate with the 2′- and 4′-keto nucleosides of theophylline[7] afforded respectively the unsaturated esters (**2a**) and (**11a**) (Scheme 1). Examination of the n.m.r. signals corresponding to 3′-H[(**2a**), δ6.12] and 5′-H[(**11a**), δ5.70] showed a strong deshielding of these protons due to the proximity of the carbonyl group.[8] This result is in accord with properties of the known compounds (**2b**) and (**11b**),[2] obtained from the ketonucleosides (**1b**) and (**10b**).

Di-isobutylaluminium hydride (DIBAH) reduction of compounds (**2a**), (**2b**), (**11a**), and (**11b**) led quantitatively to the hydroxypropenyl derivatives (**3a**), (**3b**), (**12a**), and (**12b**), respectively. These compounds were then submitted to the chiral epoxidation procedure, giving the corresponding epoxides (**4a**), (**4b**), (**13a**), and (**13b**). Their structures were at first defined on the basis of the Sharpless model;[9] however, n.m.r. as well as other physical data showed that the supposed pairs of diastereoisomeric epoxides were actually identical compounds. Thus, epoxidation of (**3a**) with D- or L-tartrate gave the same product (**4a**). Similarly, (**3b**) gave only (**4b**), (**12a**) gave only (**13a**), and (**12b**) gave only (**13b**) when epoxidised with either D- or L-tartrate. These results were most surprising and to our knowledge this is the first example where the Sharpless epoxidation procedure is totally controlled by the olefinic substrate instead of the tartrate chiral template.

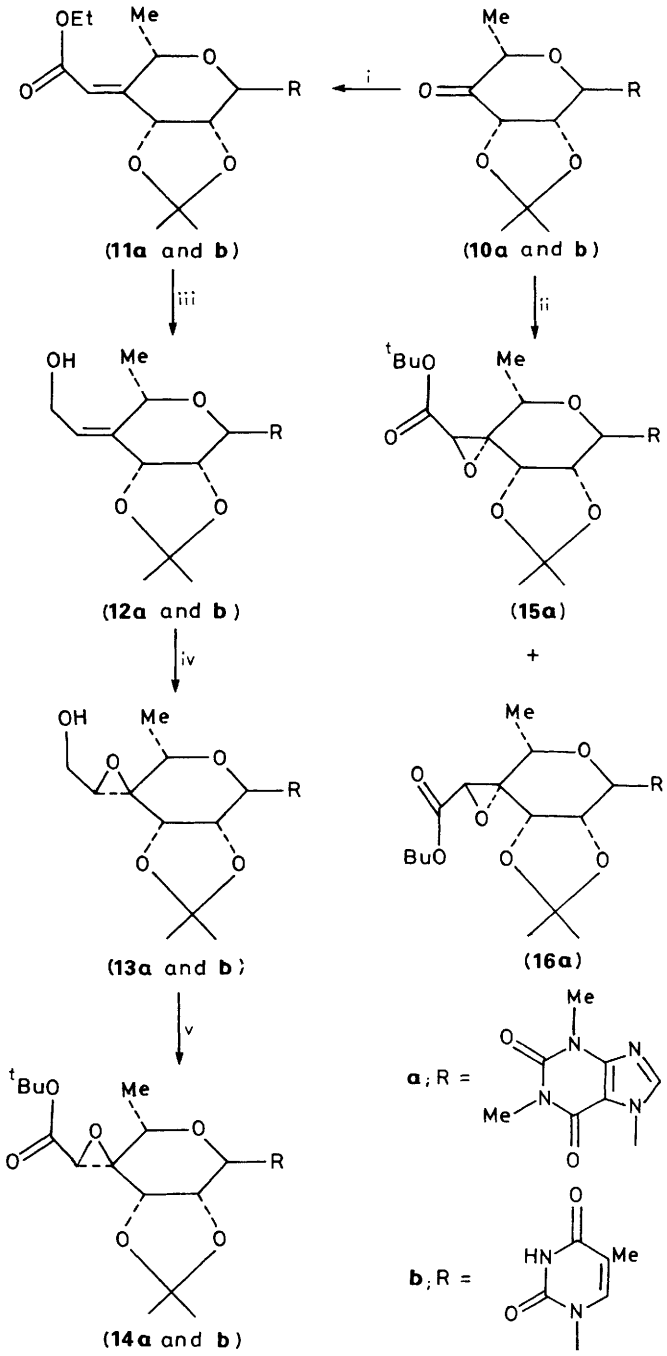
In order to confirm this result and to determine the configuration of the epoxides thus obtained, the Darzens glycidic ester condensation on the corresponding keto nucleosides was studied as a parallel route to the spiro glycidyl nucleosides, the stereochemical outcome of this reaction being well established.[10] When the keto nucleoside (**1a**) was treated by the isopropyl chloroacetate anion, generated by $LiNPr^{i}_{2}$ in tetrahydrofuran (THF) at −78 °C, a mixture of glycidic esters was obtained which could be partially resolved by flash chromatography in ether. N.m.r. study showed that the major isomer (**8a**) (65%) was the ester *trans* to the heterocycle as evidenced by the deshielding effect observed on 3′-H, whereas the minor ester (**6a**) (35%) was *cis* to the heterocycle as shown by the deshielded proton 1′-H.[8] In order to compare these epoxides with that obtained under Sharpless conditions, selective reduction of the ester function was attempted. Unfortunately, even the specific reducing agent DIBAH failed to give the glycidyl nucleoside, instead slowly migrating mixtures (t.l.c.) were obtained, suggesting that the epoxide function was destroyed in the process.

Therefore another route was considered to avoid this reduction step; the oxidation of the epoxy nucleosides (**4a**) and (**4b**) with chromium oxide–pyridine in the presence of t-butyl alcohol[11] led exclusively to the corresponding glycidic esters (**5a**) and (**5b**). The Darzens reaction was then performed on the 2′-keto nucleoside (**1a**) with t-butyl chloroacetate anion and gave as precedent a mixture of *cis* and *trans* glycidic esters (**7a**) and (**9a**); it is interesting to note that in spite of the bulkier ester group the same ratio of *cis* and *trans* esters was obtained, suggesting that in that case the aldol condensation step and not the ring-closure step was rate-limiting.[10] Comparison of the n.m.r. data of esters (**5a**), (**7a**), and (**9a**), finally showed that the epoxide obtained in the Sharpless reaction was different from those obtained from the Darzens condensation. Examination of the 3′-H doublets [(**5a**), δ 4.45; (**9a**), δ 4.83] and of the 1′-H singlets [(**5a**), δ 6.25; (**9a**), δ 6.45] revealed an upfield shift for (**5a**) which is the consequence of the shielding effect of the epoxide on the *syn* protons[1] 1′-H and 3′-H in compound (**5a**).

The same set of reactions was performed in the case of the 4′-substituted nucleoside (Scheme 2). Thus, reaction of keto nucleoside (**10a**) with t-butyl chloroacetate anion gave the corresponding glycidic ester. N.m.r. studies showed that, as in the case of the 2′-keto nucleoside, a mixture of *trans* (**15a**) and *cis* (**16a**) esters was obtained. From the integration of the two singlets at δ 4.32 and 4.41 corresponding to the epoxide protons a 1:1 ratio of isomers was determined. On the other hand Corey oxidation of the Sharpless products (**13a** and **b**) led to the glycidic esters (**14a** and **b**). Comparison of the n.m.r. data of esters (**14a**), (**15a**), and (**16a**) was undertaken. In particular the 3′-H doublet [(**14a**), δ 3.84; (**15a**), δ 4.87] revealed an important upfield shift for (**14a**) produced by the shielding effect of the epoxide on the *syn* proton 3′-H. The difference in shifting between the 2′- and 4′-branched nucleosides could be explained by the fact that, in the case of the 4′-branched compound, the shielding effect of the epoxide is not counteracted by the deshielding effects of the ester and the heterocycle. In this case the Darzens condensation gave the kinetic axial product as expected, since it also corresponds to attack on the least hindered face of the molecule. From these observations, it could be finally concluded that the epoxidation of olefins (**3a** and **b**) and (**12a** and **b**) with either tartrate, as well as the Darzens condensation on the keto nucleosides (**1a**) and (**10a**), proceeded through attack at the least hindered side of the carbonyl, thus giving access to axial or equatorial branched glycidic ester nucleosides.



Scheme 1. *Reagents and conditions:* i, Ph_3P, $BrCH_2CO_2Et$, propylene oxide, CH_2Cl_2, −20 °C; ii, $ClCH_2CO_2Bu^t$, LDA, THF, −78 °C; iii, DIBAH, THF, 0 °C; iv, Bu^tOOH, (−)- or (+)-DIPT, CH_2Cl_2, −20 °C; v, CrO_3, pyridine, Bu^tOH



Scheme 2. *Reagents and conditions:* i, Ph_3P, $BrCH_2CO_2Et$, propylene oxide, CH_2Cl_2, −20 °C; ii, $ClCH_2CO_2Bu^t$, LDA, THF, −78 °C; iii, DIBAH, THF, 0 °C; iv, Bu^tOOH, (−)- or (+)-DIPT, CH_2Cl_2, −20 °C; v, CrO_3, pyridine, Bu^tOH

Experimental

Reactions were monitored by t.l.c., using plates purchased from Merck Co. (plastic sheets, Silicagel 60 F254, 0.2 mm thickness), with ethyl acetate as eluant unless otherwise specified. The compounds were visualised by spraying a solution of 30% aqueous sulphuric acid, followed by charring with a heat gun. Purifications were obtained by flash chromatography on Chromagel (S.D.S., 60 Å, 200—400 mesh). Routine ^1H n.m.r. spectra were obtained with a Varian T-60 spectrometer. High-field ^1H n.m.r. spectra were obtained with a Bruker MSL-300 spectrometer, for deuteriated chloroform solutions with tetramethylsilane as internal standard. Complete identification of the signals was possible by using homonuclear spin decoupling. Specific rotations were measured at room temperature on a Roussel-Jouan Quick Polarimeter at the Na-D line. Microanalyses were performed by the Centre National de Microanalyses du CNRS, Vernaison, France.

7-(2′,6′-*Dideoxy*-2′-C-*ethoxycarbonylmethylene*-3′,4′-O-*isopropylidene*-β-L-lyxo-*hexopyranosyl*)*theophylline* (**2a**).—To a solution of compound (**1a**) (0.364 g, 1 mmol) in dry dichloromethane (5 ml) cooled at −20 °C, were added triphenyl-

phosphine (0.6 g, 2.3 mmol), ethyl bromoacetate (0.223 g, 1.34 mmol), and propylene oxide (1 ml). The mixture was then stored overnight at room temperature. After flash chromatography (ethyl acetate) and evaporation, *compound* (**2a**) was crystallised from ethanol (0.26 g, 60%), m.p. 158 °C; R_F 0.73; $[\alpha]_D$ − 170° (*c* 0.1 in MeOH) (Found: C, 55.5; H, 6.1; N, 12.8. $C_{20}H_{26}N_4O_7$ requires C, 55.29; H, 5.99; N, 12.90%); δ_H 9.92 (1 H, s, 8-H), 6.93 (1 H, s, C*H*CO_2Et), 6.30 (1 H, s, 1′-H), 6.12 (1 H, d, *J* 9.12 Hz, 3′-H), 4.20 (1 H, dd, *J* 2.42 and 9.26 Hz, 4′-H), 4.15 (2 H, m, OCH_2), 3.60 (1 H, dd, *J* 2.51 and 7.80 Hz, 5′-H), 3.57 and 3.39 (together 6 H, s, 2 × NMe), 1.6 (3 H, s, CMe), 1.46 (3 H, s, CMe), and 1.27 (6 H, m, 6′-H_3 and *Me*CH_2).

7-[2′,6′-*Dideoxy*-2′-C-(2-*hydroxyethylidene*)-3′,4′-O-*isopropylidene*-β-L-lyxo-*hexopyranosyl*]*theophylline* (**3a**).—A solution of compound (**2a**) (0.651 g, 1.5 mmol) in dry THF (5 ml) was cooled to 0 °C under nitrogen and DIBAH (1M in hexane; 3 ml, 3 mmol) was added *via* syringe. After 5 min, isopropyl alcohol (0.5 ml) was slowly added followed by HCl (6 ml; 2M) and the mixture was stirred at 0 °C for 2 h, the mixture was then diluted with dichloromethane (10 ml), decanted, and the aqueous phase was washed with dichloromethane (2 × 5 ml). The organic phase was dried on sodium sulphate, filtered, and concentrated. The residue was chromatographed with hexane–ethyl acetate (75:25) as eluant. Evaporation and crystallisation of the residue from ether gave the *title compound* (**3a**) (0.44 g, 75%), R_F 0.40; $[\alpha]_D$ − 20° (*c* 0.1 in MeOH) (Found: C, 53.1; H, 6.45; N, 14.05. $C_{18}H_{24}N_4O_6{\cdot}H_2O$ requires C, 52.68; H, 6.34; N, 13.67%); δ_H 8.24 (1 H, s, 8-H), 6.97 (1 H, s, 1′-H), 6.23 (1 H, t, *J* 6.64 Hz, CH=C), 5.29 (1 H, d, *J* 7.63 Hz, 3′-H), 4.37 (2 H, m, CH_2OH), 4.2 (1 H, m, *J* 7.5 Hz, 4′-H), 3.66 (1 H, m, 5′-H), 3.61 and 3.44 (together 6 H, s, 2 × NMe), 1.66 (1 H, br s, OH), 1.59 and 1.45 (together 6 H, s, 2 × CMe), and 1.31 (3 H, d, *J* 6.5 Hz, 6′-H_3).

7-(2′,6′-*Dideoxy*-3″-*hydroxymethyl*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**4a**).—Compound (**3a**) (0.392 g, 1 mmol) and L-di-isopropyl tartrate (DIPT) (0.304 g, 1.3 mmol) were dissolved in dry dichloromethane (10 ml) and the solution was cooled under nitrogen to −20 °C. Titanium(IV) isopropoxide (0.33 ml, 1.1 mmol) was added and the mixture was stirred for 15 min. t-Butyl hydroperoxide (3.2M in toluene; 0.4 ml, 1.28 mmol) was then added and the solution was left in a freezer (−25 °C) until disappearance of the starting material (t.l.c., 5 days). It was then allowed to warm to 0 °C and 10% aq. tartaric acid (4 ml) was added to the stirred mixture. After 30 min it was diluted with dichloromethane (20 ml) and washed with water (3 × 5 ml). Concentration* and column chromatography gave *compound* (**4a**), which was crystallised from ethanol (0.285 g, 70%), m.p. 161 °C; R_F 0.56; $[\alpha]_D$ − 17.5° (*c* 0.1 in MeOH) (Found: C, 53.0; H, 6.0; N, 13.7. $C_{18}H_{24}N_4O_7$ requires C, 52.94; H, 5.88; N, 13.72%); δ_H 8.31 (1 H, s, 8-H), 6.26 (1 H, s, 1′-H), 4.35 (1 H, dd, *J* 1.7 and 7.8 Hz, 4′-H), 4.28 (1 H, d, *J* 7.9 Hz, 3′-H), 4.01 (1 H, m, 5′-H), 3.85 (2 H, m, OCH_2), 3.60 and 3.40 (together 6 H, s, 2 × NMe), 3.23 (1 H, t, *J* 5.5 Hz, oxirane CH), 1.62 and 1.41 (together 6 H, s, 2 × CMe), and 1.34 (3 H, d, *J* 6.5 Hz, 6′-H). The same experiment using D-di-isopropyl tartrate gave a compound with identical physical data {$[\alpha]_D$ − 15° (*c* 0.1 in MeOH)}.

7-(3″-*t*-*Butoxycarbonyl*-2′,6′-*dideoxy*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**5a**).—To a solution of pyridine (0.065 ml, 0.8 mmol) in dichloromethane–dimethylformamide (DMF) (4:1; 1 ml) was added chromic acid (0.04 g, 0.4 mmol) and the mixture was stirred for 15 min. A solution of compound (**4a**) (0.04 g, 0.1 mmol) in dichloromethane–DMF (4:1; 0.2 ml), acetic anhydride (0.075 ml, 0.8 mmol), and t-butyl alcohol (0.19 ml, 2 mmol) were then added and the mixture was stirred overnight. The solution was diluted in ether (5 ml) and filtered through silica. Evaporation gave *compound* (**5a**) as a white powder (0.038 g, 80%), R_F 0.83; $[\alpha]_D$ − 36.3° (*c* 0.1 in $CHCl_3$) (Found: C, 54.5; H, 6.3; N, 11.3. $C_{22}H_{30}N_4O_8{\cdot}\frac{1}{2}H_2O$ requires C, 54.21; H, 6.37; N, 11.3%); δ_H 6.25 (1 H, s, 1′-H), 4.43 (1 H, d, *J* 7.9 Hz, 3′-H), 4.36 (1 H, dd, *J* 1.78 and 7.8 Hz, 4′-H), 3.99 (1 H, m, 5′-H), 3.62 and 3.40 (together 6 H, s, 2 × NMe), 3.46 (1 H, s, oxirane CH), 1.56 and 1.48 (together 15 H, 2 × s, 5 × CMe), and 1.32 (3 H, d, *J* 6.5 Hz, 6′-H).

1-[2′,6′-*Dideoxy*-2′-C-(2-*hydroxyethylidene*)-3′,4′-O-*isopropylidene*-β-L-lyxo-*hexopyranosyl*]*thymine* (**3b**).—Reduction of compound (**2b**) (0.465 g, 1.5 mmol) following the same procedure as for (**3a**) gave, after chromatography, a semi-crystalline *product* (**3b**) (0.430 g, 85%), R_F 0.4; $[\alpha]_D$ − 20° (*c* 0.1 in MeOH) (Found: C, 55.6; H, 6.7; N, 7.5. $C_{16}H_{22}N_2O_6{\cdot}\frac{1}{2}H_2O$ requires C, 55.33; H, 6.62; N, 8.06%); δ_H 9.0 (1 H, br s, NH), 7.75 (1 H, s, 6-H), 6.50 (1 H, s, 1′-H), 6.14 (1 H, t *J* 5.9 Hz, CH=C), 5.22 (1 H, d, *J* 7.7 Hz, 3′-H), 4.37 (2 H, m, OCH_2), 4.15 (1 H, dd, *J* 2 and 7.7 Hz, 4′-H), 3.61 (1 H, m, 5′-H), 2.17 (1 H, br s, OH), 1.88 (3 H, s, Me thymine), 1.59 and 1.44 (together 6 H, s, 2 × CMe), and 1.29 (3 H, d, *J* 6.4 Hz, 6′-H).

1-(2′,6′-*Dideoxy*-3″-*hydroxymethyl*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*thymine* (**4b**).—Compound (**3b**) (0.338 g, 1 mmol) was epoxidised according to the procedure used for (**4a**). After chromatography (hexane—ethyl acetate, 50:50) the product was crystallised from ether to give *compound* (**4b**) (0.265 g, 75%), m.p. 164 °C; R_F 0.62; $[\alpha]_D$ − 5° (*c* 0.1 in MeOH) (Found: C, 54.55; H, 6.4; N, 7.9. $C_{16}H_{22}N_2O_7$ requires C, 54.24; H, 6.21; N, 7.90%); δ_H 8.53 (1 H, br s, NH), 7.91 (1 H, s, 6-H), 5.84 (1 H, s, 1′-H), 4.33 (1 H, dd, *J* 2.0 and 8.0 Hz, 4′-H), 4.24 (1 H, d, *J* 8 Hz, 3′-H), 3.94—3.84 (3 H, m, OCH_2 and 5′-H), 3.30 (1 H, t, *J* 5.7 Hz, oxirane CH), 1.92 (3 H, s, Me thymine), 1.64 and 1.41 (6-H, s, CMe_2), and 1.32 (3 H, d, *J* 7.6 Hz, 6′-H). The same experiment using D-di-isopropyl tartrate gave a compound with identical physical data {$[\alpha]_D$ −2° (*c* 0.1 in MeOH)}.

1-(3″-*t*-*Butoxycarbonyl*-2′,6′-*di*-3′,4′-O-*isopropylidene*-β-L-galacto-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*thymine* (**5b**).—Oxidation of compound (**4b**) (0.354 g, 1 mmol) was performed as described for (**5a**). After purification, *title compound* (**5b**) was isolated as a semi-crystalline powder (0.32 g, 75%), R_F 0.85; $[\alpha]_D$ − 43.8° (*c* 0.1 in $CHCl_3$) (Found: C, 55.7; H, 6.9; N, 6.3. $C_{20}H_{28}N_2O_8{\cdot}\frac{1}{2}H_2O$ requires C, 55.43; H, 6.70; N, 6.47%); δ_H 8.03 (1 H, br s, NH), 7.98 (1 H, s, 6-H), 5.81 (1 H, s, 1′-H), 4.38 (1 H, d, *J* 7.7 Hz, 3′-H), 4.31 (1 H, dd, *J* 1.8 and 7.9 Hz, 4′-H), 3.87 (1 H, m, 5′-H), 3.41 (1 H, s, oxirane CH), 1.93 (3 H, s, Me thymine), 1.58 and 1.48 (together 12 H, s, 4 × CMe), and 1.32 (6 H, s, 6′-H_3 and CMe).

7-(2′,6′-*Dideoxy*-3″-*isopropoxycarbonyl*-3′,4′-O-*isopropylidene*-β-L-talo-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**6a**) and (**8a**).—To a solution of anhydrous di-isopropylamine (0.26 ml, 1.85 mmol) in THF (10 ml) cooled (−78 °C) under nitrogen was added butyl-lithium (1.84 ml; 1M in hexane). After 10 min, isopropyl chloroacetate (0.253 g, 1.85 mmol) was added and the mixture was stirred for 15 min. Then a solution of the keto nucleoside (**1a**) (0.7 g, 1.5 mmol) in dichloromethane (1 ml) was finally added. The reaction medium was stirred for 1 h at −78 °C, then poured into a cooled mixture (0 °C) of aqueous

* On a larger scale it is advisable to destroy chemically the excess of peroxide before concentrating (see for instance ref. 9).

sodium dihydrogen phosphate and ether. After 15 min, the ether was decanted and the aqueous phase was washed with ether (2 × 5 ml). The combined organic extracts were washed successively with water (5 ml) and brine (5 ml), dried and evaporated. The residue was purified on a column (hexane–ethyl acetate, 80:20) and evaporated to a *semi-crystalline powder* [mixture of (**6a**) + (**8a**); 40:60] (0.45 g, 65%); R_F 0.73; $[\alpha]_D$ − 27.5° (*c* 0.1 in $CHCl_3$) (Found: C, 52.1; H, 5.9; N, 11.6. $C_{21}H_{28}N_4O_8 \cdot H_2O$ requires C, 52.28; H, 6.22; N, 11.62%); δ_H (**6a**) 8.22 (1 H, s, 8-H), 6.55 (1 H, s, 1′-H), 5.14 (1 H, m, C*H*Me_2), 4.42 (1 H, d, *J* 6.6 Hz, 3′-H), 4.38 (1 H, dd *J* 2.0 and 7.0 Hz, 4′-H), 4.19 (1 H, s, oxirane CH), 4.05 (1 H, m, 5′-H), 3.60 and 3.38 (together 6 H, s, 2 × NMe), and 1.68—1.22 (15 H, unresolved, 6′-H_3 and 4 × CMe).

δ_H (**8a**) 8.36 (1 H, s, 8-H), 6.48 (1 H, s, 1′-H), 4.99 (1 H, m, C*H*Me_2), 4.42 (1 H, d, *J* 6.6 Hz, 3′-H), 4.38 (1 H, dd, *J* 2.0 and 7.0 Hz, 4′-H), 4.22 (1 H, s, oxirane CH), 3.86 (1 H, m, 5′-H), 3.61 and 3.38 (together 6 H, s, 2 × NMe), and 1.68—1.22 (15 H, unresolved, 6′-H_3 and 4 × CMe).

7-(3″-*t*-*Butoxycarbonyl*-2′,6′-*dideoxy*-3′,4′-O-*isopropylidene*-β-L-talo-*hexopyranose*-2′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**7a**) + (**9a**).—The keto nucleoside (**1a**) was treated with the anion of t-butyl chloroacetate under the conditions described above. The product was isolated as an amorphous powder composed of *diastereoisomers* (**7a**) and (**9a**) (0.48 g, 67%); R_F 0.8; $[\alpha]_D$ − 57.5° (*c* 0.1 in $CHCl_3$) (Found: C, 51.25; H, 5.8; N, 10.7. $C_{22}H_{30}N_4O_8 \cdot 2H_2O$ requires C, 51.36; H, 6.62; N, 10.89%); δ_H (**7a**) 8.5 (1 H, s, 8-H), 6.6 (1 H, s, 1′-H), 4.78 (1 H, d, *J* 5.9 Hz, 3′-H), 4.26—4.15 (2 H, m, 4′- and 5′-H), 3.94 (1 H, s, oxirane CH), 3.61 and 3.41 (together 6 H, s, 2 × NMe), and 1.65—1.42 (18 H, unresolved, 6′-H_3 and 5 × CMe).

δ_H (**9a**) 8.26 (1 H, s, 8-H), 6.46 (1 H, s, 1′-H), 4.83 (1 H, d, *J* 6.3 Hz, 3′-H), 4.26—4.15 (2 H, m, 4′- and 5′-H), 4.07 (1 H, s, oxirane CH), 3.61 and 3.40 (together 6 H, s, 2 × NMe), and 1.65—1.42 (18 H, unresolved, 6′-H_3 and 5 × CMe).

7-(4′,6′-*Dideoxy*-4′-C-*ethoxycarboxylmethylene*-2′,3′-O-*isopropylidene*-α-L-lyxo-*hexopyranosyl*)*theophylline* (**11a**).—Same procedure as described for (**2a**) from (**10a**). After purification *compound* (**11a**) was obtained as an oil (0.29 g, 50%); R_F 0.77; $[\alpha]_D$ − 60° (*c* 0.1 in MeOH) (Found: C, 55.5; H, 6.3; N, 12.75. $C_{20}H_{26}N_4O_7 \cdot H_2O$ requires C, 55.29; H, 5.99; N, 12.90%); δ_H 7.78 (1 H, s, 8-H), 6.42 (1 H, d, *J* 7.7 Hz, 1′-H), 6.06 (1 H, s, CH=C), 5.7 (1 H, dd, *J* 6.6 Hz, 5′-H), 4.78 (1 H, d, *J* 5.4 Hz, 3′-H), 4.63 (1 H, dd, *J* 5.4 and 7.7 Hz, 2′-H), 4.20 (2 H, m, OCH_2), 3.61 and 3.43 (together 6 H, s, 2 × NMe), 1.73 (3 H, d, *J* 6.9 Hz, 6′-H_3), 1.65 and 1.4 (together 6 H, s, 2 × CMe), and 1.3 (3 H, t, *J* 7.2 Hz, *Me*CH_2).

7-[4′,6′-*Dideoxy*-4′-C-(2-*hydroxyethylidene*)-2′,3′-O-*isopropylidene*-α-L-lyxo-*hexopyranosyl*]*theophylline* (**12a**).—Compound (**11a**) (0.65 g, 1.5 mmol) was reduced according to the procedure described for (**3a**). The *product* (**12a**) was obtained as a semi-crystalline solid (0.44 g, 75%); R_F 0.35; $[\alpha]_D$ − 60° (*c* 0.1 in MeOH) (Found: C, 54.0; H, 6.14; N, 13.5. $C_{18}H_{24}N_4O_6 \cdot \frac{1}{2}H_2O$ requires C, 53.86; H, 6.23; N, 13.96%); δ_H 7.79 (1 H, s, 8-H), 6.37 (1 H, d, *J* 7.26 Hz, 1′-H), 5.96 (1 H, t *J* 5.1 Hz, CH=C), 4.85 (1 H, m, 5′-H), 4.79 (1 H, d, *J* 5.5 Hz, 3′-H), 4.54 (1 H, dd, *J* 5.7 and 7 Hz, 2′-H), 4.29 and 4.17 (together 2 H, ABq, *J* 4.9 and 13.8 Hz, OCH_2), 3.59 and 3.41 (together 6 H, s, 2 × NMe), 1.8 (1 H, br s, OH), 1.62 (6 H, s, 6′-H_3 and CMe), and 1.4 (3 H, s, CMe).

7-(4′,6′-*Dideoxy*-3″-*hydroxymethyl*-2′,3′-O-*isopropylidene*-α-L-manno-*hexopyranose*-4′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**13a**).—Epoxidation of compound (**12a**) followed the same procedure as for (**4a**). The *product* (**13a**) was crystallised from pentane (0.2 g, 50%), m.p. 110 °C; R_F 0.69; $[\alpha]_D$ − 50° (*c* 0.1 in MeOH) (Found: C, 51.8; H, 6.0; N, 13.0. $C_{18}H_{24}N_4O_7$ requires C, 51.79; H, 5.99; N, 13.42%); δ_H 7.99 (1 H, s, 8-H), 6.46 (1 H, d, *J* 8.6 Hz, 1′-H), 4.64 (1 H, dd, *J* 5.5 and 8.5 Hz, 2′-H), 4.22 (1 H, m, 5′-H), 4.03 (1 H, dd, *J* 3.5 and 12.6 Hz, OCH*H*), 3.86 (1 H, d, *J* 5 Hz, 3′-H), 3.79 (1 H, dd, *J* 5.8 and 12.5 Hz, OC*H*H), 3.61 and 3.43 (together 6 H, s, 2 × NMe), 3.35 (1 H, dd, *J* 3.6 and 5.8 Hz, oxirane CH), 1.7 (6 H, s, 6′-H_3 and CMe), and 1.35 (3 H, s, CMe). The same experiment using D-di-isopropyl tartrate gave a compound with identical physical data {$[\alpha]_D$ − 60° (*c* 0.1 in MeOH)}.

7-(3″-*t*-*Butoxycarbonyl*-4′,6′-*dideoxy*-2′,3′-O-*isopropylidene*-α-L-manno-*hexopyranose*-4′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**14a**).—Same procedure as for (**5a**) from (**13a**). *Compound* (**14a**) was isolated, after chromatography, in semi-crystalline form (0.04 g, 85%); R_F 0.7; $[\alpha]_D$ − 48.8° (*c* 0.1 in $CHCl_3$) (Found: C, 54.4; H, 6.3; N, 11.2. $C_{22}H_{30}N_4O_8 \cdot \frac{1}{2}H_2O$ requires C, 54.21; H, 6.37; N, 11.50%); δ_H 7.96 (1 H, s, 8-H), 6.5 (1 H, d, *J* 8.8 Hz, 1′-H), 4.62 (1 H, dd, *J* 5.3 and 8.7 Hz, 2′-H), 4.45 (1 H, dd, *J* 7.2 Hz, 5′-H), 3.84 (1 H, d, *J* 5.9 Hz, 3′-H), 3.61 and 3.42 (together 6 H, s, 2 × NMe), 3.59 (1 H, s, oxirane CH), 1.68, 1.53, and 1.35 (together 15 H, s, 5 × CMe), and 1.57 (3 H, d, *J* 7.3 Hz, 6′-H_3).

1-[4′,6′-*Dideoxy*-4′-C-(2-*hydroxyethylidene*)-2′,3′-O-*isopropylidene*-α-L-lyxo-*hexopyranosyl*]*thymine* (**12b**).—The ester (**11b**)[12] (0.38 g, 1 mmol) was treated with DIBAH under the conditions described for (**3a**) and the *product* (**12b**) was isolated after column chromatography as a semi-crystalline solid (0.25 g, 74%); R_F 0.5; $[\alpha]_D$ − 30° (*c* 0.1 in MeOH) (Found: C, 56.7; H, 6.35; N, 8.1. $C_{16}H_{22}N_2O_6$ requires C, 56.80; H, 6.50; N, 8.28%); δ_H 8.38 (1 H, br s, NH), 7.35 (1 H, s, 6-H), 6.07 (1 H, d, *J* 8.6 Hz, 1′-H), 5.93 (1 H, t, *J* 6.8 Hz, CH=C), 4.95 (1 H, dd, *J* 6.1 Hz, 5′-H), 4.7 (1 H, d, *J* 4.9 Hz, 3′-H), 4.38—4.25 (1 H, m, 2′-H), 4.21—4.08 (2 H, m, OCH_2), 1.97 (3 H, s, Me thymine), 1.7 and 1.45 (together 6 H, s, 2 × CMe), and 1.6 (3 H, d, *J* 7.0 Hz, 6′-H_3).

1-(4′,6′-*Dideoxy*-3″-*hydroxymethyl*-2′,3′-O-*isopropylidene*-α-L-manno-*hexopyranose*-4′-*spiro*-2″-*oxiran*-1′-*yl*)*thymine* (**13b**).—Same procedure as for (**4a**) from (**12b**). The *product* (**13b**) was crystallised from ethyl acetate (0.26 g, 73%), m.p. 137 °C; R_F 0.6; $[\alpha]_D$ − 62.5° (*c* 0.1 in MeOH) (Found: C, 54.25; H, 6.4; N, 7.6. $C_{16}H_{22}N_2O_7$ requires C, 54.24; H, 6.21; N, 7.90%); δ_H 8.58 (1 H, br s, NH), 7.26 (1 H, s, 6-H), 6.09 (1 H, d, *J* 8.9 Hz, 1′-H), 4.31 (1 H, dd, *J* 5.3 and 9.0 Hz, 2′-H), 4.20 (1 H, dd, *J* 7 Hz, 5′-H), 4.04—3.97 (1 H, m, OCH*H*), 3.82—3.76 (2 H, m, 3′-H and OC*H*), 3.32 (1 H, dd, *J* 3.6 and 5.7 Hz, oxirane CH), 6.09 (1 H, t, *J* 6.1 Hz, OH), 1.95 (3 H, s, Me thymine), 1.64 and 1.34 (together 6 H, s, 2 × CMe), and 1.59 (3 H, d, *J* 7.2 Hz, 6′-H). The same experiment using D-di-isopropyl tartrate gave a compound with identical physical data {$[\alpha]_D$ − 67.5° (*c* 0.1 in MeOH)}.

1-(3″-*t*-*Butoxycarbonyl*-4′,6′-*dideoxy*-2′,3′-O-*isopropylidene*-α-L-manno-*hexopyranose*-4′-*spiro*-2″-*oxiran*-1′-*yl*)*thymine* (**14b**).—Chromium(VI) oxidation of compound (**13b**) (0.338 g, 1 mmol) according to the procedure described for (**5a**) gave the *title compound* (**14b**), isolated as a semi-crystalline powder (0.37 g, 87%); R_F 0.78; $[\alpha]_D$ − 86.3° (*c* 0.1 in $CHCl_3$) (Found: C, 55.55; H, 6.7; N, 6.3. $C_{20}H_{28}N_2O_8 \cdot \frac{1}{2}H_2O$ requires C, 55.43; H, 6.70; N, 6.47%); δ_H 7.9 (1 H, br s, NH), 7.2 (1 H, s, 6-H), 6.11 (1 H, d, *J* 8.9 Hz, 1′-H), 4.40 (1 H, dd, *J* 7.8 Hz, 5′-H), 4.29 (1 H, dd, *J* 5.0 and 8.5 Hz, 2′-H), 3.76 (1 H, d, *J* 5.0 Hz, 3′-H), 3.56 (1 H, s, oxirane CH), 1.95 (3 H, s, Me thymine), 1.66, 1.53, and 1.35 (together 15 H, s, 5 × CMe), and 1.49 (3 H, d, *J* 7.3 Hz, 6′-H).

7-(3″-*t*-*Butoxycarbonyl*-4′,6′-*dideoxy*-2′,3′-O-*isopropylidene*-α-L-talo-*hexopyranose*-4′-*spiro*-2″-*oxiran*-1′-*yl*)*theophylline* (**15a**).—Same procedure as for (**6a**) from (**10a**). After purifi-

cation the *product* (**15a**) was crystallised from ether and its isomer (**16a**) was recovered from the mother liquor and isolated as an amorphous powder (0.36 g, 75%) (**15a**), m.p. 183 °C; R_F 0.67; $[\alpha]_D$ − 56.3° (*c* 0.1 in $CHCl_3$) (Found: C, 51.5; H, 6.2; N, 10.8. $C_{22}H_{30}N_4O_8 \cdot 2H_2O$ requires C, 51.36; H, 6.62; N, 10.89%); δ_H (**15a**) 7.72 (1 H, s, 8-H), 5.84 (1 H, d, *J* 8.6 Hz, 1′-H), 5.05 (1 H, t, *J* 7.8 Hz, 2′-H), 4.87 (1 H, d, *J* 7.7 Hz, 3′-H), 4.55 (1 H, dd, *J* 4.5 Hz, 5′-H), 4.32 (1 H, s, oxirane CH), 3.60 and 3.43 (together 6 H, s, 2 × NMe), and 1.54, 1.50, 1.37, and 1.34 (together 18 H, unresolved, 5 × CMe and 6′-H).

δ_H (**16a**) 7.74 (1 H, s, 8-H), 5.86 (1 H, d, *J* 6.0 Hz, 1′-H), 5.08—4.98 (2 H, m, 2′- and 3′-H), 4.48 (1 H, m, 5′-H), 4.41 (1 H, s, oxirane CH), 3.60 and 3.41 (together 6 H, s, 2 × NMe), and 1.57—1.34 (18 H, unresolved, 5 × CMe and 6′-H_3).

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