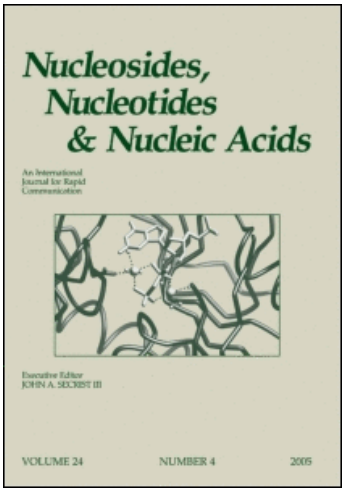

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REACTIONS OF SOME 2,3-ANHYDRO PYRIMIDINE NUCLEOSIDES WITH DILITHIUM TETRAHALOCUPRATES

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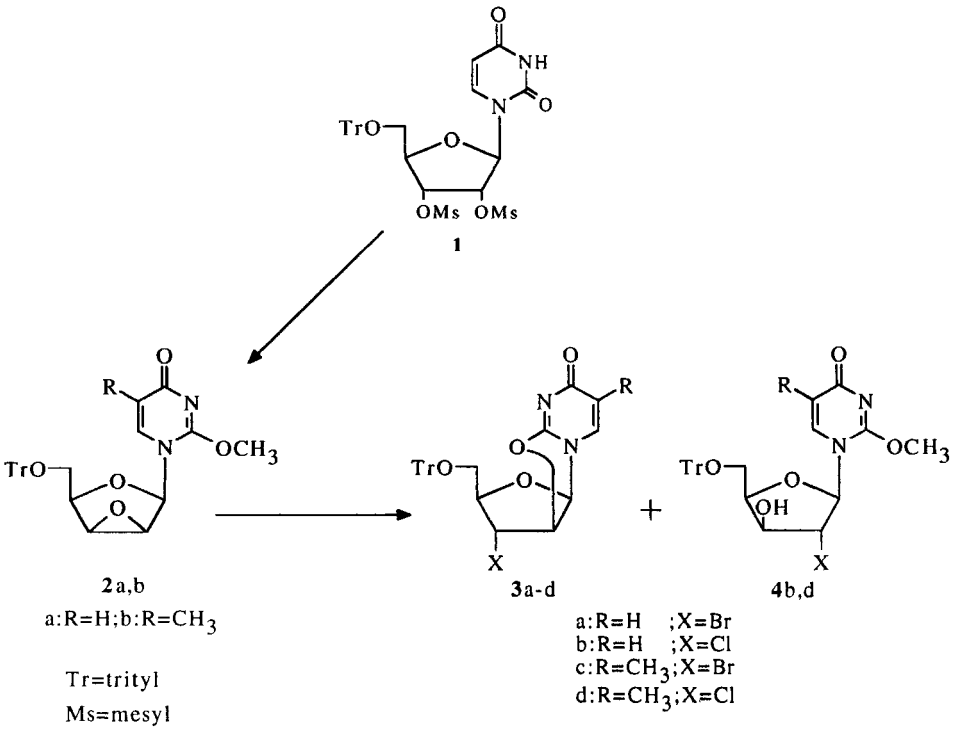
Abstract: The reaction of 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-methyluracil (**2**a) and its thymine analogue (**2**b) with dilithium tetrahalocuprates (Li_2CuX_4) revealed an excellent to perfect regioselectivity, yielding 2,2'-anhydro-3'-halonucleosides (**3**a-d), while the same reactions with 2,3-anhdro uracil and thymine nucleosides (**5**a,b) gave arabinosyl (**6**a-d) and xylosyl halohydrins (**7**a-d) with respective product ratios of 7:3 to 8:2 which were estimated after mesylation to **8**a-d and **9**a-d.

Since in 1962 the synthesis of (2,3-anhydro-ß-D-lyxofuranosyl)uracil derivatives was reported by Fox and co-workers,[1] the epoxy cleavage of 2,3-anhydro nucleosides with nucleophiles has long been one of the standard methods for the sugar modification of nucleosides,[2] and it is recognized that a certain degree of electronic and steric influences by the base moiety direct such reactions usually in favor of arabinosyl products, although the product ratio of arabinosyl and xylosyl isomers is widely changeable according to the reaction conditions, substrate species and nucleophilic reagents.[2e,h,k] Although as for halogenation *via* the lyxo epoxy route, only arabinosyl isomers were isolated in yields below 70% in many cases,[2a-c,e] the formation of small amounts of the corresponding xylosyl isomers cannot be precluded. It is well known that the separation of both isomers is not always easy. Hence, regioselectivity in the ring opening of 2,3-anhydro nucleosides is often a matter of concern even now. We report herein the results of halogenation of some 2,3-anhydro pyrimidine nucleosides with the use of dilithium tetrahalocuprates (Li_2CuX_4, X=Br, Cl), which are claimed to have cleaved the epoxy ring of a variety of functionalized oxiranes regio and chemoselectively under mild conditions.

In view of the fact that the normal nucleoside molecules contain multiple heteroatoms open to possible metal coordination, we chose to use 2,3-anhydro pyrimidine nucleosides having a O^2-methylated aglycon besides the normal uracil and thymine analogues as substrates to compare possible coordination patterns. For this purpose, 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-methyluracil (**2a**) was synthesized from 2',3'-di-*O*-methanesulfonyl-5'-*O*-trityluridine (**1**).[5] The structure of **2a** is consistent with the spectral data described in the experimental section: in the ^{1}H NMR spectrum the chemical shifts of H_2 and H_3 signals (4.18 and 4.13 ppm, respectively) and $J_{2,3}$ (3.2 Hz) are in accord with those described for other analogues.[2f] 1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-methcedures for the preparation of Li_2CuX_4 and their reactions with **2a,b** were standardized as described in the experimental section. The reaction of **2a** with Li_2CuBr_4 gave exclusively 2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)uracil (**3a**) (Scheme 1, TABLE 1), whose structure followed from the hypsochromic shift of the UV absorption compared with that of thymidine and the ^{1}H NMR data lacking a N^3- H signal. The notable downfield shift of the $H_{2'}$-signal (5.69 ppm) as well as the large $J_{1',2'}$ (5.6 Hz) is in accord with the arabinosyl structure. Similarly, compound **2b** with the same reagent gave 2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)thymine (**3c**)[6] in 94% yield in a similar reaction time. On the other hand, the reaction of **2a** with Li_2CuCl_4 was rather sluggish and gave 1-(2-chloro-2-deoxy-5-*O*-trityl-ß-D-xylofranosyl)-2-*O*-methyluracil (**4b**) as a side-product besides the major 2,2'-anhydro-1-(3'-chloro-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)uracil (**3b**). Similarly, compound **2b** with the same reagent gave 2,2'-anhydro-1-(3'-chloro-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)thymine (**3d**) and 1-(2-chloro-2-deoxy-5-*O*-trityl-ß-D-xylofuranosyl)-2-*O*-methylthymine (**4d**) with a similar product ratio (TABLE 1). The structures of **4b,d** are consistent with the general spectroscopic data: the singlet signal of H_1 substantiates the *trans* H_1-H_2 geometry.

The reaction of 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)uracil(**5a**)[7] with Li_2CuBr_4 (Scheme 2) gave a mixture of two products, the major of which was slightly more polar in terms of TLC. Similar product distribution was also observed in the reaction of **5b**[2f] with the same reagent. The major products in these reactions were suggested to be the arabinosyl counterparts (**6a,c**) on the basis of our previous observation[2f] that a series of 5'-*O*-tritylated arabino isomers were more polar than the corresponding xylosyl counterparts. However, these mixtures proved to partially regenerate **5a** or **5b** during the workup procedures including chromatography. Hence, the crude mixtures were mesylated after rapid workup. However, in neither case was the chromatographical separation of the mesylated isomers realized and accordingly the product ratio was estimated from the intensities of the ^{1}H NMR resonances of the mesyl groups of each mixture (TABLE 2,3). Thus, the reactions of **5a,b** with Li_2CuX_4 and the workup were standardized as described in

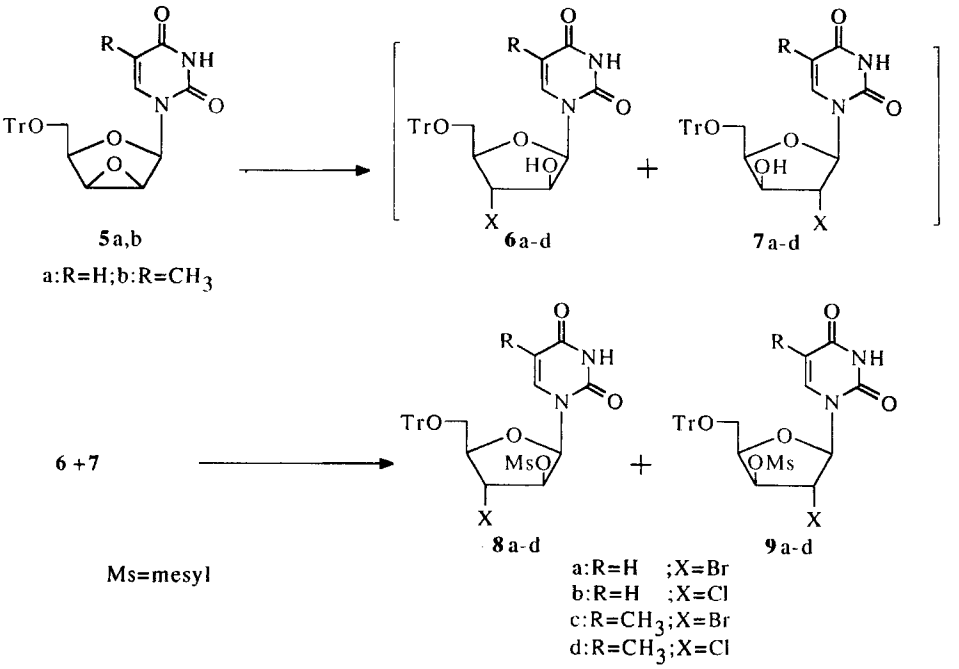


Scheme 1

TABLE 1. Total Yields, Product Ratios of **3** and **4** and Reaction Times.

	R	X	Reaction Time(h)	Yield(%) (3:4)
a	H	Br	45	92 (100: 0)
b	H	Cl	70	69 (84: 16)
c	CH_3	Br	43	94 (100: 0)
d	CH_3	Cl	72.5	72 (72: 28)

the experimental section and the synthetic procedure for **8a** and **9a** is given there as an example. Although the assignments of the signals of the major sugar protons were abandoned because of complexity due to extensive overlapping, the anomeric proton signals were well resolved (TABLE 3) and easily assignable: it is generally known that the arabinosyl isomer shows a $J_{1,2}$ value larger than that of the xylosyl counterparts.[2f,g,2j] The assignments of the two mesyl signals followed from the comparison of their intensity order



Scheme 2

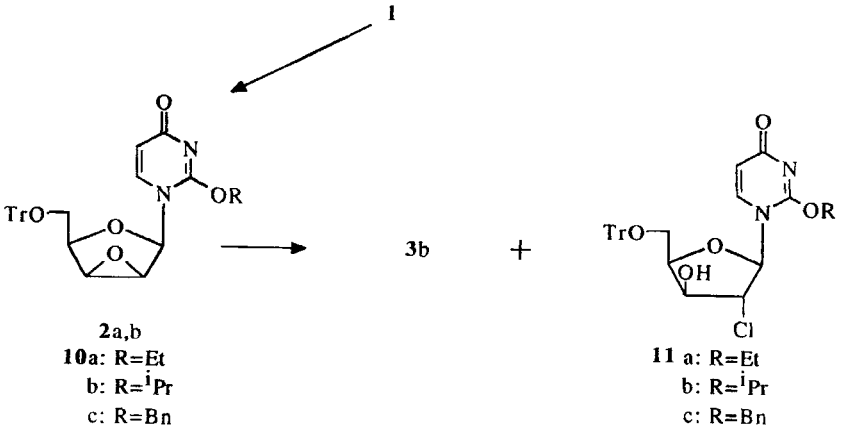
TABLE 2. Combined Yields, Product Ratios of **8** and **9** and Reaction Times.

	R	X	Reaction Time (h)	Combined Yield (**8**+**9**)(%)	Product Ratio **8** : **9**
a	H	Br	74	68	71 : 29
b	H	Cl	80	53	79 : 21
c	CH_3	Br	75	61	75 : 25
d	CH_3	Cl	75	81	77 : 23

TABLE 3. ^{1}H NMR Resonances of **8** and **9** in $CDCl_3$.[a,b]

	2-OMs [**8**]	3-OMs [**9**]	H_1 ($J_{1,2}$) [**8**]	H_1 ($J_{1,2}$) [**9**]
a	3.06 (s)	2.85 (s)	6.31 (d, 5.2)	6.22 (d, 2.0)
b	3.04 (s)	2.86 (s)	6.34 (d, 5.8)	6.11 (d, 2.2)
c	3.02 (s)	2.84 (s)	6.34 (d, 5.6)	6.32 (d, 3.4)
d	3.03 (s)	2.83 (s)	6.33 (d, 5.6)	6.20 (d, 3.6)

[a] s=singlet, d=doublet. [b] Chemical shifts are given in parts per million and J values in hertz.



2a,b
10a: R=Et
b: R=^{i}Pr
c: R=Bn

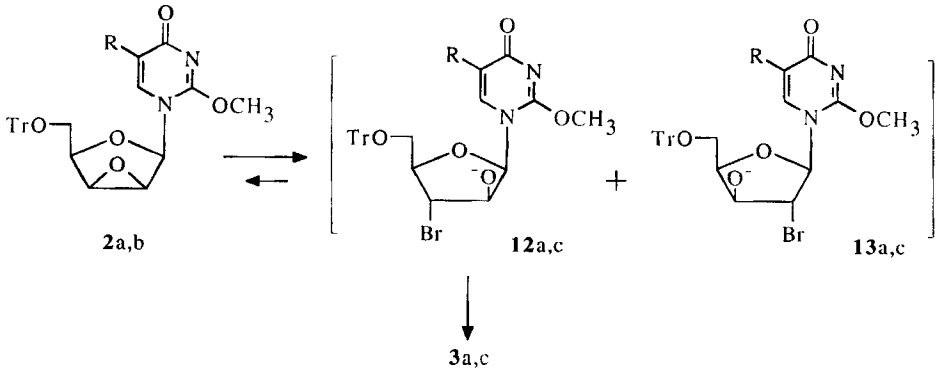
11 a: R=Et
b: R=^{i}Pr
c: R=Bn

Scheme 3

with that of the H_1-signals in each case. Furthermore, the UV-measurement of each mixture confirmed that the base moiety was intact.[8]

As seen from TABLE 2, the reactions of Li_2CuX_4 with **5**a,b were less selective than with **2**a,b and more or less similar to that of pyridinium chloride with **5**b[2f] or those of ammonium halides with some 2,3-epoxy pyrimidine nucleosides.[2e]

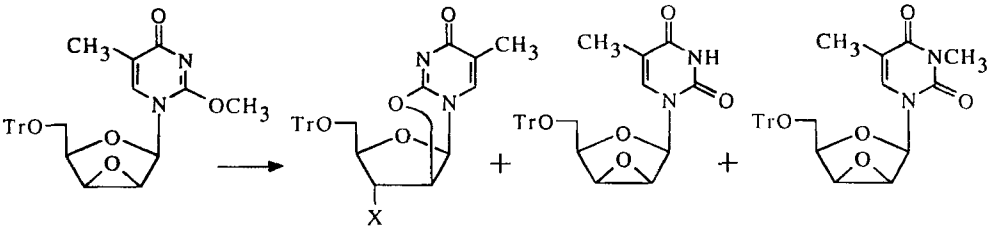
With a view to gaining an insight into the origin of the high to perfect regioselectivity in the reaction of **2**a,b, 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-ethyluracil (**10**a), its 2-*O*-isopropyl (**10**b) and 2-*O*-benzyl analogues (**10**c) were further synthesized and subjected to some control experiments using Li_2CuCl_4 (Scheme 3) to give 1-(2-chloro-2-deoxy-5-*O*-trityl-ß-D-xylofuranosyl)-2-*O*-ethyluracil (**11**a), its 2-*O*-isopropyl (**11**b) and 2-*O*-benzyl analogues (**11**c) in 21, 33 and 31% yield, respectively, together with the 2,2'-anhydro compound **3**b. The formation of the xylosyl compounds **11**a-c in a rather increased yields as compared to the reaction of **2**a was unexpected and suggested that steric hindrance to the 2-position of the sugar by the 2-*O*-alkyl group is improbable. Instead, on the basis of the above stated observation that the mixture of **6**a and **7**a or of **6**c and **7**c tended to regenerate **5**a or **5**b, the selective formations of **3**a,c may be explicable in the following way (Scheme 4): after the copper chelation-assisted epoxy cleavage, the resulting mixtures of anions (**12** and **13**) and the starting material **2**a or **2**b are in equilibrium in favor of the anions, from which **12** are easily extruded from the system as the anhydro nucleosides **3**. In fact, TLC-monitoring at the early stages of the reactions of **2**a,b with Li_2CuBr_4 indicated two very thin spots (probably corresponding to **12** and **13**), which disappeared with elongation of the reaction time. The retardation of the reactions and generation of **4**b,d when Li_2CuCl_4 was used reflect the weaker nucleophilicity and leaving ability



Scheme 4

of chlorine. For comparative evaluation of these reagents, the reaction of **2b** with LiBr was carried out under similar mild conditions to affored 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-N^3-metylthymine (**14**) as a major product together with low yields of **3c** and **5b** (Scheme 5). The structure of **14** is in agreement with the general spectroscopic data.[9] Similar reaction of **2b** with LiCl was quite sluggish but gave compound **3d** as a major product together with **5b** from a rather complex mixture. In this reaction, the TLC spot corresponding to **14** was negligible. Further tiny scale experiments by us have shown that the 2-alkoxy group cannot survive the use of ammonium halides[2e] or pyridinium chloride[2f] in DMF under heating, a complex mixture having been obtained in each case.

Thus, although the exact pattern of metal coordination is unclear at present, Li_2CuX_4 proved to be at least chemoselective for **2a,b** and quite useful as far as the synthesis of **3** is concerned.[10] Although in the case of **10**a-c the regioselectivity of the epoxy cleavage was moderate, the total yields of **3b** and **11** were good to excellent. The 2,2'-anhydro nucleosides **3** are generally quite polar and easily separable from the corresponding xylosyl derivatives (**4, 11**). Appropriate acidic treatment of **3** may directly give the corresponding pyrimidine arabinosides. In our recent publication,[6] a high yield two step conversion of 5'-*O*-tritylthymidinene into **3c** with the use of hypobromous acid has been reported. However, no appropriate chloride electrophiles for obtaining a good yield of **3d** from the 2',3'-thymidinene derivative have been found as yet. Unexpectedly, the present synthesis of **3d** is a rather good 3 step version starting from 5'-*O*-trityl-2',3'-thymidinene. An obvious merit of these reagents resides in that they can be used as a solution under mild, nearly neutral conditions compatible with sensitive functionalities[3,4] involving even the 2-alkoxy group of the pyrimidine bases.



Scheme 5

EXPERIMENTAL SECTION

Mps were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were measured on a JASCO V-550 UV/VIS spectrophotometer. The ^1H NMR spectra were recorded on a GEMINI-200 FT NMR spectrometer and the elemental analyses were conducted using a Perkin-Elmer 240B elemental analyzer. For preparative scale thick-layer chromatograpy, glass plates coated with a 2-mm thickness of Wakogel B-5F silica gel were used after activation at 100°C for 10-12 h. All evaporations were carried out under reduced pressere at or below 40°C.

General Procedures for the Preparation and Reaction of Li_2CuX_4.

In the case of X=Br, a mixture of LiBr (278 mg, 3.20 mmol) and $CuBr_2$(358 mg, 1.60 mmol) in anhydrous tetrahydrofuran (THF) (3.0 ml) was stirred under ice cooling to give a dark green solution, which was immediately warmed to room temperature. To this solution was added each substrate (1 mmol) and the mixture stirred at room temperature until the starting material disappeared. After each reaction time, the mixture was poured into stirred acetate buffer solution (pH 4.1, 0.02 M) (6 ml). After 10 min of stirring, the mixture was subjected to EtOAc-extraction and preparative TLC. Similarly, a deep-red solution of Li_2CuCl_4 was obtained by dissolving LiCl (136 mg, 3.21 mmol) and $CuCl_2$ (216 mg, 1.61 mmol) in THF (3.0 ml) to treat 1 mmol of each substrate.

1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-methyluracil (2a). To a solution of 2',3'-di-*O*-methanesulfonyl-5'-*O*-trityluridine[5] (2.5 g, 3.9 mmol) in a mixture of acetone (8.3 ml) and MeOH (8.3 ml) was added MeONa (695 mg, 12.87 mmol), and the mixture stirred at room temperature for 20 h. After addition of more MeONa (47 mg, 0.87 mmol), stirring was continued for additional 4 h. The mixture was neutralized with 1 N AcOH/EtOH and poured into stirred ice-water (200 ml) to give a precipitate, which was collected by suction, washed with water, air-dried and recrystallized from acetone to give 1.44 g (3.07 mmol, 78.7%) of **2a**, mp 224-225°C: λmax (MeOH) nm (ε) 224 (18700, infl),

253(10700, infl); ^{1}H NMR (Me_2SO-d_6) δ 3.93 (3H, s, 2-*O*Me), 3.25 (2H, m, 5-CH_2), 4.13 (1H, d, $J_{3,2}$ = 3.2, H_3), 4.18 (1H, d, $J_{2,3}$ = 3.2, H_2), 4.31 (1H, t, $J_{4,5}$ = 5.6, H_4), 5.83 (1H, d, $J_{5,6}$ = 8.0, H_5 of the base), 6.09 (1H, s, H_1), 7.58 (1H, d, $J_{6,5}$ = 8.0, H_6), 7.29-7.42 (15H, m, Ar-H).

Anal. ($C_{29}H_{26}N_2O_5$) Calcd: C, 72.18; H, 5.43; N, 5.81. Found: C, 71.94; H, 5.68; N, 5.64.

2,2'-Anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)uracil (3a). A solution of compound **2a** (200 mg, 0.41 mmol) in a THF solution of Li_2CuBr_4 prepared as above was stirred at room temperature for 45 h, during which time the starting material disappeared and a single, more polar product formed as judged by TLC. The mixture was poured into acetate buffer solution (0.02 M, pH 4.1) (4 ml). After stirring for 10 min, the mixture was extracted with EtOAc (10 ml) and the EtOAc-extract purified on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1). The product was eluted with a mixture of acetone and MeOH (1:1) and recrystallized from MeOH to give 202 mg (92%) of **3a** as a mono-methanolate, mp 109-112°C: λmax (MeOH) nm (ε) 223 (21300, infl), 248 (8700, infl); ^{1}H NMR (Me_2SO-d_6) δ 2.85 (1H, dd, J_{gem} = 10.3, $J_{5'a,4'}$ = 7.2, $H_{5'a}$), 3.13 (1H, dd, J_{gem} = 10.3, $J_{5'b,4'}$ = 4.0, $H_{5'b}$), 4.60 (1H, ddd, $J_{4',3'}$ = 3.2, $J_{4',5'a}$ = 7.2, $J_{4',5'b}$ = 4.0, $H_{4'}$), 4.78 (1H, dd, $J_{3',2'}$ = 2.4, $J_{3',4'}$ = 3.2, $H_{3'}$), 5.69 (1H, dd, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 2.4, $H_{2'}$), 5.93 (1H, d, $J_{5,6}$ = 8.0, H_5), 6.45 (1H, d, $J_{1',2'}$ = 5.6, $H_{1'}$), 7.24-7.33 (15H, m, Ar-H), 7.95 (1H, d, $J_{6,5}$ = 8.0, H_6).

Anal. ($C_{28}H_{23}N_2O_4Br{\cdot}CH_3OH$) Calcd: C, 61.82; H, 4.83; N, 4.97. Found: C, 61.80; H, 4.87; N, 5.06.

2,2'-Anhydro-1-(3'-chloro-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)uracil (3b) and 1-(2-Chloro-2-deoxy-5-*O*-trityl-ß-D-xylofuranosyl)-2-*O*-methyluracil (4b). A mixture of **2a** (483 mg, 1.0 mmol) and the above prepared solution of Li_2CuCl_4 in THF was stirred at room temperature for 70 h. TLC-monitoring (silica, $CHCl_3$/MeOH, 9:1) at this stage showed formation of two major, more polar products. The mixture was worked up as above and the finally obtained EtOAc-extract subjected to preparative TLC (silica, 20 × 20 cm, $CHCl_3$/MeOH, 9:1, twice developed) to give from the polar fraction 302 mg (58.2%) of **3b** as a mono-methanolate after recrystallization from MeOH, mp 107-111°C; λmax (MeOH) nm (ε) 220 (12600, infl), 256 (4350, infl); ^{1}H NMR ($CDCl_3$) δ 2.91 (1H, dd, J_{gem} = 10.2, $J_{5'a,4'}$ = 7.2, $H_{5'a}$), 3.10 (1H, dd, J_{gem} = 10.2, $J_{5'b,4'}$ = 6.2, $H_{5'b}$), 4.52-4.55 (2H, m, $H_{3'}$ and $H_{4'}$), 5.35 (1H, dd, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 1.0, $H_{2'}$), 5.96 (1H, d, $J_{5,6}$ = 7.6, H_5), 6.19 (1H, d, $J_{1',2'}$ = 5.6, $H_{1'}$), 7.22-7.30 (16H, m, Ar-H and H_6).

Anal. ($C_{28}H_{23}N_2O_4Cl{\cdot}CH_3OH$) Calcd: C, 67.11; H, 5.24; N, 5.40. Found: C, 67.17; H, 5.05; N, 5.50.

The less polar fraction gave 56 mg (9.7%) of **4b** as a mono-acetone solvate, mp 139-143°C (acetone): λmax (MeOH) nm (ε) 222 (13800, infl), 256 (6100, infl); ^{1}H NMR ($CDCl_3$) δ 3.43 (1H, dd, J_{gem} = 10.6, $J_{5a,4}$ = 3.0, H_{5a}), 3.71 (1H, dd, J_{gem} = 10.6, $J_{5b,4}$ = 7.8, H_{5b}), 3.98 (3H, s, 2-*O*Me), 4.25 (1H, dd, $J_{3,4}$ = 2.8, H_3), 4.68-4.76 (1H, m, H_4), 4.76 (1H, s,

H_2), 5.52 (1H, d, $J_{5,6}$=7.6, H_5 of the base), 5.88 (1H, br s, 3-OH), 5.97 (1H, s, H_1), 7.24-7.52 (15H, m, Ar-H), 7.57 (1H, d, $J_{6,5}$ = 7.6, H_6, base).

Anal. ($C_{29}H_{27}N_2Cl{\cdot}CH_3COCH_3$) C, 66.61; H, 5.76; N, 4.85. Found: C, 66.59 ; H, 5.79; N, 4.87.

2,2'-Anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)thymine (3c). Compound 2b[2f] (249 mg, 0.50 mmol) was similarly treated with Li_2CuBr_4/THF for 43 h to give a single product. Similar workup and preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 9:1) gave 258 mg (94.3%) of 3c as a form, which was recrystallized from EtOAc to give 233 mg (85%) of crystals of 3c, mp 210-212°C: λmax (MeOH) nm (ε) 225 (16200, infl), 253 (7600, infl); ^{1}H NMR (Me_2SO-d_6) δ 1.78 (3H, s, 5-Me), 2.81 (1H, dd, J_{gem} = 11.0, $J_{5'a,4'}$ = 8.0, $H_{5'a}$), 3.10 (1H, dd, J_{gem} = 11.0, $J_{5'b,4'}$ = 4.0, $H_{5'b}$), 4.61(1H, m, $H_{4'}$), 4.82 (1H, dd, $J_{3',2'}$ = 1.6, $J_{3',4'}$ = 3.5, $H_{3'}$), 5.64 (1H, dd, $J_{2',1'}$ = 5.5, $J_{2',3'}$ = 1.5, $H_{2'}$), 6.43 (1H, d, $J_{1',2'}$ = 5.5, $H_{1'}$), 7.23-7.33 (15H, m, Ar-H), 7.85 (1H, s, H_6).

Anal. ($C_{29}H_{25}N_2O_4Br$) Calcd: C, 63.86; H, 4.62; N, 5.14. Found: C, 63.87; H, 4.51; N, 5.23. This compound was spectroscopically identified with an authentic sample.[6]

2,2'-Anhydro-1-(3'-chloro-3'-deoxy-5'-*O*-trityl-ß-D-arabinofuranosyl)thymine (3d) and 1-(2-Chloro-2-deoxy-5-*O*-trityl-ß-D-xylofuranosyl)-2-*O*-methylthymine (4d). Compound 2b (497 mg, 1.0 mmol) was treated with Li_2CuCl_4/THF as above for 72.5 h, during which time 2b was completely consumed and two major products formed. The mixture was similarly worked up and the finally obtained pasty mixture fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1) to afford, from the more polar fraction, 282 mg (56.2%) of crystals of 3d (EtOAc), mp 219-221°C: λmax (MeOH) nm (ε) 225 (8200, infl), 253 (3600, infl); ^{1}H NMR ($CDCl_3$) δ 1.91 (3H, d, J = 1.4, 5-Me), 2.91 (1H, dd, J_{gem} = 10.2, $J_{5'a,4'}$ = 7.2,$H_{5'a}$), 3.12 (1H, dd, J_{gem} = 10.2, $J_{5'b,4'}$ = 6.4, $H_{5'b}$), 4.47-4.57 (2H, m, $H_{3'}$ and $H_{4'}$), 5.33 (1H, dd, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 0.6, $H_{2'}$), 6.18 (1H, d, $J_{1',2'}$ = 5.6, $H_{1'}$), 7.14 (1H, d, J = 1.4, H_6), 7.26-7.34 (15H, m, Ar-H).

Anal. ($C_{29}H_{25}N_2O_4Cl$) Calcd: C, 69.53; H, 5.03; N, 5.59. Found: C, 69.58; H, 4.99; N, 5.58.

The less polar fraction gave 83 mg (15.6%) of 4d as crystals of mp 210-214°C after recrystallization from acetone: λmax (MeOH) nm (ε) 228 (22700, infl), 251 (15600, sh); ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, s, 5-Me), 3.52 (1H, dd, J_{gem} = 10.8, $J_{5a,4}$ = 3.6, H_{5a}), 3.73 (1H, dd, J_{gem} = 10.8, $J_{5b,4}$ = 7.0, H_{5b}), 4.06 (3H, s, 2-*O*Me), 4.31 (1H, d, $J_{3,4}$ = 2.4, H_3), 4.63-4.70 (1H, m, H_4), 4.80 (1H, s ,H_2), 5.36 (1H, br s, 3-OH, D_2O-Exchangeable, 3-OH), 6.04 (1H, s ,H_1), 7.27-7.53 (16H, m, Ar-H ans H_6).

Anal. ($C_{30}H_{29}N_2O_5Cl$) Calcd: C, 67.60; H 5.48; N, 5.26. Found: C, 67.79; H, 5.31; N, 5.25.

Reactions of 5a,b with Li_2CuX_4. In all cases, 1 mmol of 5 was treated with the above stated standard solution of Li_2CuX_4 in anhydrous THF and worked up as in the case of 2a,b. Mesylation of the crude mixture of 6 and 7, purification of the product mixturre (8 and 9)

and ^{1}H NMR measurements were conducted precisely in the same way with the following example of **8a** and **9a** except the difference of the reaction time.

1-(3-Bromo-3-deoxy-2-*O*-methanesulfonyl-5-*O*-trityl-ß-D-arabinofuranosyl)uracil (8a) and 1-(2-Bromo-2-deoxy-3-*O*-methanesulfonyl-5-*O*-trityl-ß-D-xylofuranosyl)-uracil (9a). Compound **5a** (469 mg, 1 mmol) in a THF solution of Li_2CuBr_4 was stirred at room temperature for 74 h. TLC-monitoring confirmed a trace amount of the starting material and two products. The mixture was poured into a stirred acetate buffer solution (6 ml). After 10 min, the mixture was extracted with EtOAc (20 ml). The separated organic layer was dried over Na_2SO_4 and evaporated to give a form, which was dissolved in pyridine (8 ml) and treated with methanesulfonyl chloride (0.15 ml, 1.95 mmol) under ice-cooling. The total was allowed to warm up to room temperature and stirring continued overnight. The mixture was treated with MeOH (1 ml) at room temperature for 30 min, concentrated to the half volume and poured into stirred ice-water (50 ml). The precipitate was collected by suction, thoroughly washed with water, air-dried and subjected to preparative TLC (silica, 20 × 20 cm; $CHCl_3$/EtOAc, 3:1). The major band gave 402 mg (68.0%) of the mixture of **8a** and **9a** as a foam: λmax (MeOH) nm (ε) 261 (7000).

1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-ethyluracil (10a). To a solution of 2',3'-di-*O*-methanesulfonyl-5'-*O*-trityluridine (3.21 g, 5.0 mmol) in a mixture of EtOH (12 ml) and acetone (10 ml) was added EtONa (375 mg, 5.51 mmol) and the mixture stirred at room temperature. After 20 h, further EtONa (375 mg, 5.51 mmol) was added and the mixture stirred for additional 15 h. After neutralization with 1 N AcOH/EtOH and evaporation, the residue was partitioned between EtOAc (50 ml) and H_2O (15 ml). The separated organic layer was dried, evaporated and the residue fractionated on silica plates (20 × 20 cm, 3 sheets; $CHCl_3$/EtOAc, 3:1) to give from the major fraction 1.82 g (3.77 mmol, 75.5%) of **10a** as crystals, mp 180-182°C (EtOAc): λmax (MeOH) nm (ε) 226 (22100, infl), 253 (10700, infl); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.2, 2-*O*-$CH_2\mathbf{CH_3}$), 3.34 (1H, dd, J_{gem} = 10.0, $J_{5a,4}$ = 5.4, H_{5a}), 3.48 (1H, dd, J_{gem} = 10.0, $J_{5b,4}$ = 6.2, H_{5b}), 3.87 (1H, dd, $J_{3,4}$ = 0.8, $J_{3,2}$ = 3.0, H_3), 3.89 (1H, dd, $J_{2,3}$ = 3.0, $J_{2,1}$ =0.6, H_2), 4.19 (1H, t-like dd, H_4), 4.51 (2H, J = 7.2, 2-*O*-$\mathbf{CH_2}CH_3$), 5.93 (1H, d, $J_{5,6}$ = 7.8, H_5 of the base), 6.04 (1H, s, H_1), 7.50 (1H, d, $J_{6,5}$=7.8, H_6), 7.24-7.46 (15H, m, Ar-H).

Anal. ($C_{30}H_{28}N_2O_5$) Calcd: C, 74.98; H, 5.87; N, 5.83. Found: C, 74.91; H, 5.91; N, 5.85.

1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-isopropyluracil (10b). A mixture of 2',3'-di-*O*-methanesulfonyl-5'-*O*-trityluridine (1.29 g, 2.0 mmol) and K_2CO_3 (608 mg, 4.40 mmol) in a mixture of isopropanol (4.0 ml) and acetone (4.0 ml) was heated to reflux for 3 h. After addition of further K_2CO_3 (100 mg, 0.72 mmol), the mixture was refluxed for 6 h. The mixture was neutralized with 1 N AcOH, evaporated and the residue partitioned between EtOAc (30 ml)/H_2O (10 ml). The EtOAc extract was fractionated on silica plates (20

× 20 cm, 2 sheets; $CHCl_3$/EtOAc, 1:1) to give 378 mg (38.2%) of **10b**, mp 189-191°C (EtOAC): λmax (MeOH) nm (ε) 224 (17500, infl), 349 (8900,infl); ^1H NMR ($CDCl_3$) δ 1.39 (6H, J = 6.2, 2-*O*-^{i}Pr), 3.37 (1H, dd, J_{gem} = 9.8, $H_{5a,4}$ = 5.4, H_{5a}), 3.51 (1H, dd J_{gem} = 9.8, $J_{5b,4}$ = 6.3, H_{5b}), 3.89 (2H, m, H_2 and H_3), 4.22 (1H, t-like dd, J = 6.0 and 5.8, H_4), 5.54 (1H, sept, J = 6.2, 2-*O*-^{i}Pr), 5.95 (1H, d, $J_{5,6}$ = 8.0, H_5 of the base), 6.05 (1H, s, H_1), 7.51 (1H, d, $J_{6,5}$ = 8.0, H_6), 7.27-7.45 (15H, m, Ar-H).

Anal. ($C_{31}H_{30}N_2O_4$) Calcd: C, 75.29; H, 6.11; N, 5.66. Found: C, 75.26; H, 6.21; N, 5.58.

1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-benzyluracil (10c). A mixture of 2',3'-di-*O*-methanesulfonyl-5'-*O*-trityluridine (1.29 g, 2.0 mmol), K_2CO_3 (608 mg, 4.40 mmol), benzyl alcohol (0.8 ml, 7.8 mmol), in acetone (7.2 ml) was heated to reflux for 3 h. After cooling, further K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture heated to reflux for additional 11 h. The workup followed as in the cases of **10a,b** and the finally obtained paste was fractionated on a silica plates (20 × 20 cm, 2 sheets, $CHCl_3$/ EtOAc, 1:1, developed 3 times) to give 568 mg (51%) of **10c**, mp 156-158°C (EtOAc): λmax (MeOH) nm (ε) 227 (24000, infl), 248 (14200, infl); ^1H NMR ($CDCl_3$) δ 3.38 (1H, dd, J_{gem} = 9.8, $J_{5a,4}$ = 5.2, H_{5a}), 3.49 (1H, dd, J_{gem} = 9.8, $J_{5b,4}$ = 6.4, H_{5b}), 3.85 (2H, m, H_2 and H_3), 4.18 (1H, t-like dd, J = 6.0 and 5.8, H_4), 5.48 (2H, dd, J_{gem} = 12.0, 2-*O*-CH_2-), 5.99 (1H, d, $J_{5,6}$ = 7.8, H_5 of the base), 6.04 (1H, s, H_1), 7.55 (1H, d, $J_{6,5}$ = 7.8, H_6, base), 7.25-7.48 (20H, m, Ar-H).

Anal. ($C_{35}H_{30}N_2O_5$) Calcd: C, 75.25; H, 5.41; N, 5.01. Found: C,75.25; H, 5.40; N,5.02.

Reaction of 1-(2,3-anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-ethyluracil (10a) with Li_2CuCl_4. A solution of **10a** (496.5 mg, 1 mmol) in a THF solution of Li_2CuCl_4 was stirred at room temperature for 3 days to give two major products as judged by TLC. The mixture was worked up as above and finally obtained pasty mixture was fractionated on two sheets of silica plates (20 × 20 cm; $CHCl_3$/MeOH, 9:1) to afford 304 mg (59%) of **3b** (methanolate), identical with the above obtained specimen in terms of general spectroscopy and mixed fusion.

The less polar fraction gave 117 mg (21%) of **11a** as crystals of mp 207-209°C (acetone): λmax (MeOH) nm (ε) 224 (22400, infl), 249 (11000, sh); ^1H NMR ($CDCl_3$) δ 1.46 (3H, t, 2-*O*-CH_2CH_3), 3.47 (1H, dd, J_{gem} = 10.6, $J_{4,5a}$ = 3.2, H_{5a}), 3.72 (1H, dd, J_{gem} = 10.6, $J_{4,5b}$ = 7.3, H_{5b}), 4.26 (1H, dd, $J_{3,4}$ = 2.6, $J_{3,2}$ = 0.6, H_3), 4.50 (2H, q, J = 7.2, 2-*O*-CH_2CH_3), 4.68 (1H, br s, H_2), 4.68-4.76 (1H, m, H_4), 5.52 (1H, d, $J_{5,6}$ = 7.8, H_5 of the base), 5.99 (1H, s, H_1), 7.25-7.59 (16H, m, Ar-H and H_6).

Anal. ($C_{30}H_{29}N_2O_5Cl$) Calcd: C, 67.60; H, 5.48; N, 5.26. Found: C, 67.61; H, 5.52; N, 5.22.

Reaction of 1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-isopropyluracil (10b) with Li_2CuCl_4. A solution of **10b** (255.3 mg, 0.5 mmol) in a THF solution of Li_2CuCl_4 was stirred at room temperature for 52 h, during which time **10b** was consumed and two products formed. After the similar workup and preparative TLC (silica, 20 × 20 cm; $CHCl_3$/

MeOIH, 9:1, twice developed), 122 mg (47%) of **3b** (methanolate) was obtained from the polar fraction (identical with an authentic sample in every respect).

The less polar fraction gave 92 mg (33%) of **11b** as needles of mp 149-152°C (MeOH): λmax (MeOH) nm (ε) 223 (23500, infl), 250 (11100, sh); ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, d, J = 6.2, Me of iPr), 1.48 (3H, d, J = 6.2, Me of i Pr), 3.50 (1H, dd, J_{gem} = 10.6, $J_{4,5a}$ = 3.6, H_{5a}), 3.73 (1H, dd, J_{gem} = 10.6, $J_{4,5b}$ = 7.2, H_{5b}), 4.27 (1H, m, H_3), 4.51 (1H, br s, H_2), 4.71 (1H, m, $J_{3,4}$ = 2.6, H_4), 5.41 (1H, q, J = 6.2, -C**H**Me_2), 5.51 (1H, d, $J_{5,6}$ = 7.8, H_5 of the base), 5.95 (1H, s, H_1), 7.25-7.56 (16H, m, Ar-H and H_6).

Anal. ($C_{32}H_{33}N_2O_5Cl$) Calcd: C, 68.50; H, 5.93; N, 4.99. Found: C, 68.54; H, 5.76; N, 5.12.

Reaction of 1-(2,3-Anhydro-5-*O*-trityl-ß-D-lyxofuranosyl)-2-*O*-benzyluracil (10c) with Li_2CuCl_4. A mixture of **10c** (279.3 mg, 0.5 mmol) and a solution of Li_2CuCl_4 in THF was stirred at room temperature for 72 h. The similar workup and preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 9:1, developed 3 times) gave 159 mg (61%) of **3b** (methanolate) and 93 mg (31.2%) of **11c** as crystals of mp 229-231°C (acetone): λmax (MeOH) nm (ε) 227 (20000, infl), 249 (10500, sh); ^{1}H NMR (Me_2SO-d_6) δ 3.35 (1H, dd, J_{gem} = 11.0, $J_{4,5}$ = 2.7, H_{5a}), 3.49 (1H, dd, J_{gem} = 11.0, $J_{4,5b}$ = 8.0, H_{5b}), 4.19 (1H, dd, $J_{2,3}$ = 1.0, H_3), 4.41 (1H, br s, H_2), 4.57 (1H, m, $J_{3,4}$ = 3.2, H_4), 5.41 (2H, dd, J_{gem} = 12.0, 2-*O*-CH_2-), 5.75 (1H, d, $J_{5,6}$ = 7.8, H_5 of the base), 6.04 (1H, s, H_1), 7.29-7.55 (21H, m, Ar-H and H).

Anal. ($C_{35}H_{31}N_2O_5Cl$) Calcd: C, 70.64; H, 5.25; N, 4.71. Found: C, 70.74; H, 5.26; N, 4.60.

Reaction of 2b with LiBr. A mixture of LiBr (50 mg, 0.58 mmol) and **2b** (250 mg, 0.50 mmol) in anhydrous THF (1.5 ml) was stirred at room temperature for 115 h, during which time the starting material disappeared and three major products formed (one product was more polar and the other two were less polar than **2b**). The mixture was neutralized with 1 N AcOH/EtOH, evaporated and partitioned between EtOAc (7ml)/H_2O (2ml). The separated organic layer was dried over sodium sulfate, evaporated and fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1) to afford, from the most polar fraction, 44 mg (16.1%) of **3c** and, from the intermediate fraction, 36 mg (12.6%) of **5b**. These were spectroscopically identified with the authentic samples. The most mobile band gave 88 mg (35.4%) of **14,** mp 139-142°C (MeOH): λmax (MeOH) nm (ε) 265.0 (3250); ^{1}H NMR ($CDCl_3$) δ 1.85 (3H, d, J = 1.2, 5-Me), 3.36 (3H, s, 3-*N*Me), 3.37 (1H, dd, J_{gem} = 9.8, $J_{5a,4}$ = 5.4, H_{5a}), 3.45 (1H, dd, J_{gem} = 9.8, $J_{5b,4}$ = 6.0 H_{5b}), 3.86 (1H, dd, $J_{3,2}$ = 3.0, $J_{3,4}$ = 0.8, H_3), 3.91 (1H, dd, $J_{2,1}$ = 0.6, $J_{2,3}$ = 3.0, H_2), 4.17 (1H, m, H_4), 6.24 (1H, d, $J_{1,2}$ = 0.6, H_1), 7.25-7.50 (16H, m, Ar-H and H_6).

Anal. ($C_{30}H_{28}N_2O_5$) Calcd: C, 72.56; H,5.68; N, 5.64. Found: C, 72.51; H, 5.69; N,5.58.

Reaction of 2b with LiCl. A mixture of LiCl (24.6 mg, 0.58 mM) and **2b** (250 mg, 0.5 mM) in THF (1.5 ml) was stirred at room temperature for 2 weeks, during which time the starting material was nearly completely consumed and two major products formed with

slight amounts of several by-products. The mixture was neutralized with 1 N AcOH/EtOH, evaporated and fractionated on a silica plate (20 × 20 cm; $CHCl_3$/EtOAc, 3:1, developed 4 times) to give, from the most polar fraction, 124 mg (50%) of **3d** and, from the less polar fraction, 67.4 mg (24%) of **5b** (EtOAc-solvate). These were spectroscopically identified with the corresponding authentic samples. The TLC spot corresponding to **14** was negligible.

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8. λmax (MeOH) nm (ε) **8a** + **9a**, 261 (7000); **8b** + **9b**, 260 (8200); **8c** + **9c**, 263 (9900); **8d** + **9d**, 263 (9450).
9. Similar reaction of **2b** with $CuBr_2$ gave a very complex mixture, in which compounds **3c**, **5c**, **14**, **6c** and **7c** were discerned by TLC.

10. The possibility that, at least in part, intramolecular double coordination of copper between the oxirane and 2-alkoxy oxygen contributes to the regiochemistry cannot be ruled out.[11]
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