Structure and Reactivity of D-Ribofuranosylpyrimidine homo-*C*-Nucleosides Halogenated on the Bridge C-atom

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The reactions of the ylide (**2a**) with the D-ribose derivative (**1**) led to protected 4-chloro-6-[chloro(β-D-ribofuranosyl)methyl]pyrimidine homo-*C*-nucleosides (**3**). Configuration at the bridge C-α of compounds (**3**) was established by comparison with the resulting products of the iodine-induced cyclisation of the unsaturated derivatives (*E,Z*)-(**4c**), *i.e.* compounds (α,β)-(**6**), as well as by spectroscopic methods (^{1}H and ^{13}C n.m.r., N.o.e.-difference NOESY) and by chemical transformation to the *C*-nucleosides (**12**) and (**13**).

In recent years, synthetic interest in, and the biological activity of, several homo-*C*-nucleosides have led to several syntheses of these compounds.[1–12] In previous papers,[13–16] we have reported the synthesis of some *C*-nucleosides as well as several related *C*-glycosides, besides the synthesis of some homo-*C*-nucleosides.[17] In this paper we report the synthesis and configurational analysis of some homo-*C*-nucleosides related to those previously reported by Katagiri,[10] which interest us as possible intermediates in the synthesis of *C*-nucleoside antibiotics.

The reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranose (**1**) with ylides (**2a**—**d**) has been previously reported[10] to lead to mixtures of the α and β anomers of the *C*-glycosides (**3a**—**d**) with the unsaturated derivatives (**4a**—**d**). The structure of compound β-(**3b**) was confirmed by *X*-ray crystallography, while the other compounds were characterised by ^{1}H n.m.r. spectroscopy.[10] We are interested in these compounds as intermediates in the synthesis of *C*-nucleosides, but our experience in similar reactions suggest that the reported configurational assignments are partly erroneous. A simple examination of the reported ^{13}C n.m.r. data (Table 1), shows that the chemical shifts of C(Ip) and of the 'endo' Me(Ip), are very similar for all the isomers α,β-(**3a** and **b**) and clearly different for the α and β anomers of (**3c** and **d**). These last compounds show typical Me(Ip) values[15,18] for the α (24.9 + 0.3 and 26.3 + 0.3) and β (25.5 + 0.2 and 27.5 + 0.2) anomers[18] while compounds (**3a** and **b**) show typical values of β-anomers only.

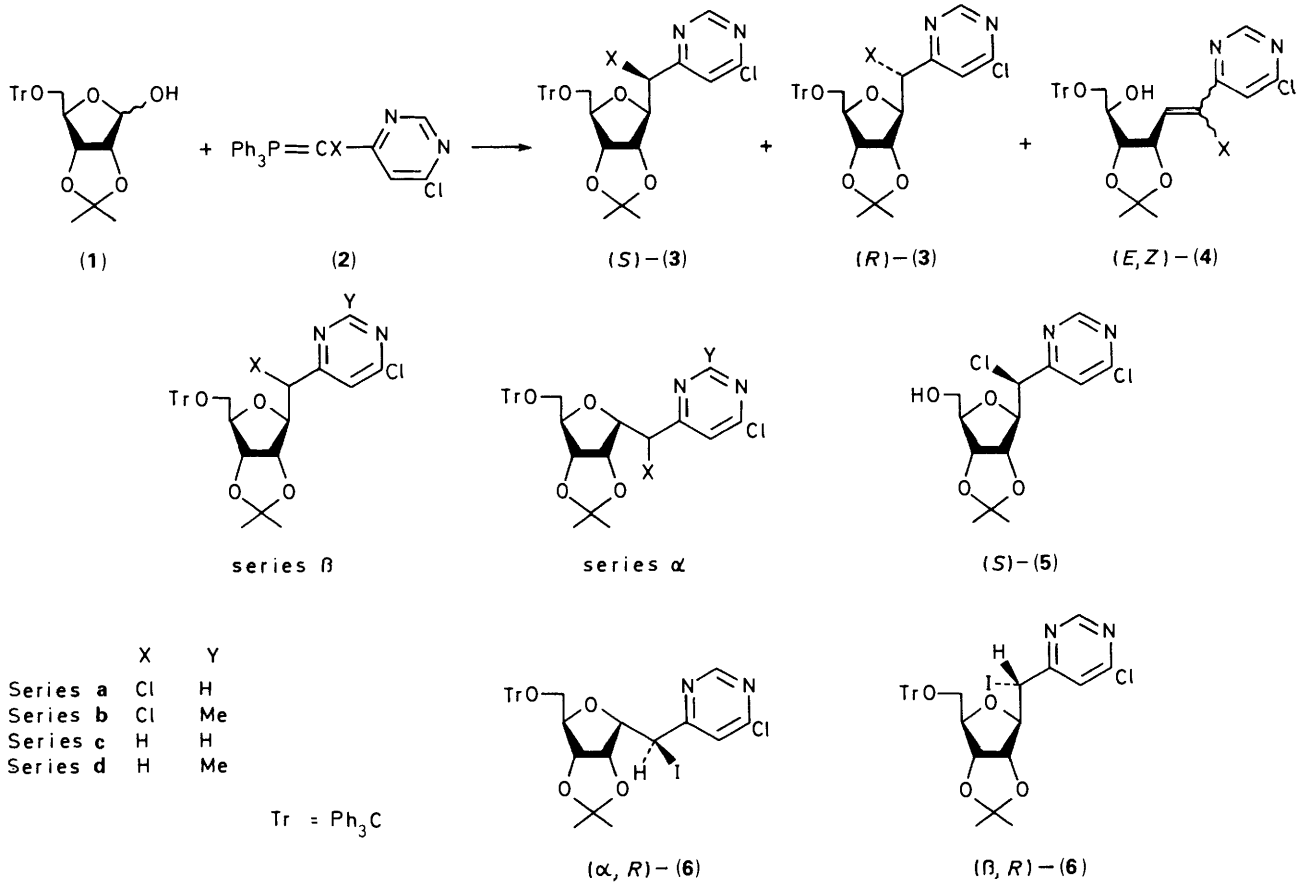
Surprisingly, these data were not interpreted, and neither were the incomplete ^{1}H n.m.r. (100 MHz) data. Thus, we have repeated the reaction between compounds (**1**) and (**2a**), obtaining a mixture of the same four compounds previously reported, for which we propose the (*R*)-(**3a**) and (*S*)-(**3a**) structures to replace those previously reported as α and β anomers, and the correct ones (*E*)-(**4a**) and (*Z*)-(**4a**) respectively, all on the basis of the previous ^{13}C n.m.r. and new ^{1}H n.m.r. data (Table 2). Thus, $J_{3',4'}$ values of 4 and 3 Hz respectively for (*R*)-(**3a**) and (*S*)-(**3a**) (Table 3) are indicative of a β configuration for both products. (The 2,3-*O*-isopropylidene-α-D-ribofuranosyl-*C*-glycosides show $J_{3',4'}$ values of 0—1 Hz, while β-anomers show values of 1.5—4.5 Hz.[15]) The absolute configuration assignment at the CHCl group was made first from the $J_{CHCl,1'}$ values of 8 and 3.8 Hz for which Karplus equation suggests dihedral angles of 10 or 159° and 50 or 127°, respectively. Studies of molecular models and of dipolar interactions suggested to us a conformation with an angle of 159° for the first product (*R*)-(**3**) and of 127° for the second one (*S*)-(**3**).

Both assignments were confirmed later by chemical transformations or by comparison with similar compounds. Thus we have studied the reaction of substrate (**1**) with the phosphorane (**2c**) in methylene dichloride, obtaining as major products the unsaturated products (*Z*)-(**4c**) and (*E*)-(**4c**)[10] which could be separated by thick layer chromatography. Electrophile-induced cyclisation of (*E*)-(**4c**) and (*Z*)-(**4c**) individually with iodine leads to the stereospecific formation of (α,*R*)-(**6**) and (β,*R*)-(**6**) respectively. These results are in agreement with similar ones previously reported[19,20] and support mechanistically our total configuration assignments made for (α,*R*)-(**6**) and (β,*R*)-(**6**) as well as those for (*R*)-(**3a**) and (*S*)-(**3a**). Thus, compound (β,*R*)-(**6**) has a ^{1}H n.m.r. spectrum completely analogous to that of (*R*)-(**3a**). Conversely, the (α,*R*)-(**6**) isomer shows a spectrum clearly different from that of (*S*)-(**3a**), showing the typical values of an α-D-ribo anomer ($J_{3',4'} < 1$ Hz).

Trifluoroacetic acid (TFA) hydrolysis of the mixture of (*R,S*)-(**3**) gave a mixture of (*R,S*)-(**5**), from which we could isolate compound (*S*)-(**5**) in pure state. The anomalous low value of $J_{3',4'}$ (1 Hz) led to some confusion for the anomeric configuration of (*S*)-(**5**). Thus we decided to obtain the ^{13}C n.m.r. spectrum of (*S*)-(**5**) (Table 1), from which we concluded that it has a β-anomeric configuration owing to the great difference of the chemical shifts of the two Me(Ip) (27.13 − 25.39 = 1.74 p.p.m.) and the higher value of that of C(Ip) (δ_C 113.88). Moreover, we have studied the n.O.e.-difference spectra of this isomer. Thus, the saturation of one methyl of the isopropylidene group, the one at higher field, produces a n.O.e.-effect of 2.74% on the signal of protons 2′-H and 3′-H. Saturation of the 'endo' methyl group yielded an n.O.e. effect of 8.47% on 1′-H, and another of 2.88% on 4′-H. These results clearly established the *cis* configuration of the 'exo' methyl group and protons at C-2′ and -3′, as well as the *cis* relationship between the 'endo' methyl group and protons at C-1′, and -4′, in favour of the β-anomeric configuration. Saturation of the CHCl proton leads to an n.O.e. effect (12%, with simultaneous SPT) of proton 1′-H and a second n.O.e. effect (4%) on 2′-H. These n.O.e. effects, principally that on 2′-H, can be justified only for a β-configuration.

We then studied the reactivity of the CHCl group of the compounds (*R,S*)-(**3a**) with several nucleophiles. Thus, we treated the mixture of these epimers with methanolic ammonia at high temperature in a sealed tube obtaining a mixture of the methoxypyrimidines (*R,S*)-(**7**) and the aminopyrimidines (*R,S*)-(**8**). Short reaction times led to higher proportions of methoxy derivatives while longer times produced more amino derivatives. Substrates (*R,S*)-(**7**) were separated from amines (*R,S*)-(**8**) by column chromatography, but we could not separate the two epimeric pairs. Nevertheless, the 2:3 (*R*:*S*) composition of both mixtures led to a clear assignment of its ^{1}H n.m.r. spectra.

These results prompted us to study the reactivity of (*R,S*)-(**8**)



	X	Y
Series **a**	Cl	H
Series **b**	Cl	Me
Series **c**	H	H
Series **d**	H	Me

with more reactive nucleophiles, such as hydrazine and sodium azide. Compound (*R,S*)-(**8**) reacts with 30% hydrazine in ethanol at 85 °C to give the reduced compound (β)-(**9**)[17] as the major product. This result can be interpreted as being due to a substitution Cl ⟶ $NHNH_2$, followed by oxidation to hydrazone and a posterior Wolf–Kishner reduction type of the intermediate product to compound (**9**).

Reaction of (*R,S*)-(**8**) with sodium azide in dimethylformanide (DMF) at 90 °C led finally to a normal substitution product (*R,S*)-(**10**). Reduction of the mixture (*R,S*)-(**10**) with lithium aluminium hydride in anhydrous diethyl ether gave the diamino derivatives (*R,S*)-(**11**).

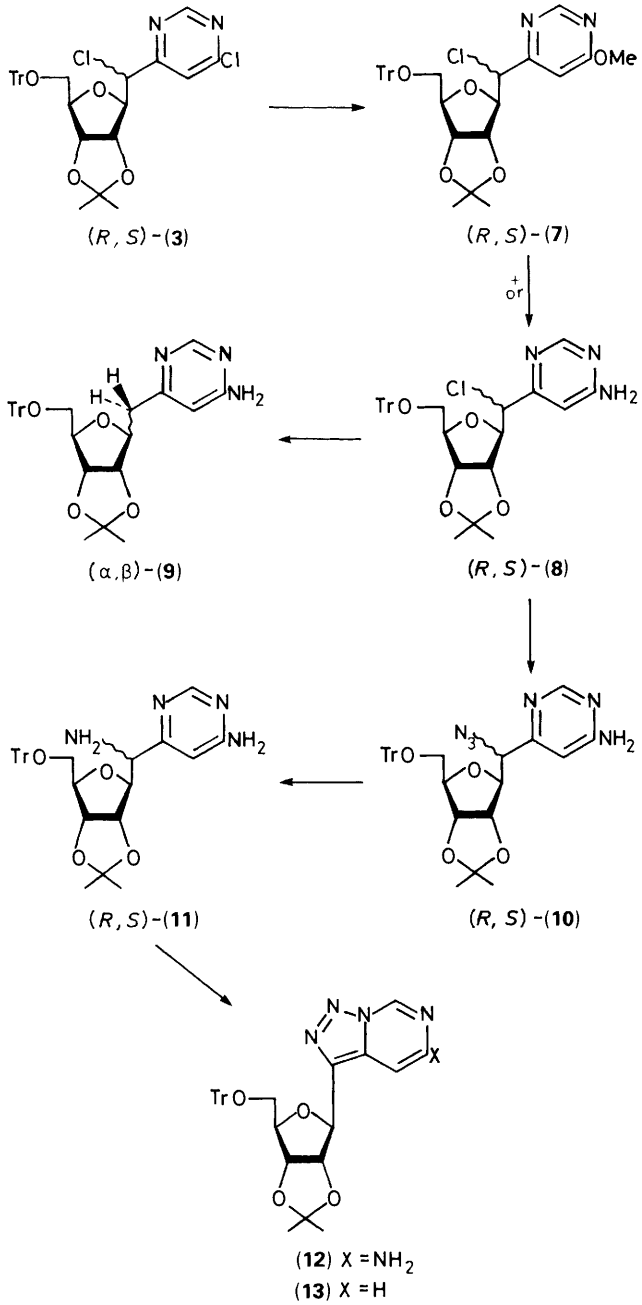
As a final proof of the β-anomeric configuration of these compounds we obtained a sole product (**12**), from the diazotisation of the mixture (*R,S*)-(**11**), for which ^{1}H n.m.r. data ($J_{3',4'}$ 3.5 Hz) enabled us to assign a β-anomeric configuration. Thus, if compound (**11**) exists as an α,β-anomeric mixture, the last reaction would give an α,β-anomeric mixture of triazolopyrimidines analogous to (**12**). Our results can only be interpreted as being caused by the disappearance of the chirality on the aminated carbon in the diazotisation process followed by cyclisation to the triazolopyrimidine (**12**). If the reaction time and proportion of sodium nitrite are increased, we obtained, besides the product (**12**), a second compound (**13**). Compound (**13**) resulted from a consecutive reductive deamination of the 4-amino group.[21,22]

Experimental

M.p.s were measured on a Büchi (Dr. Tottoli) apparatus and are uncorrected. I.r. spectra were recorded with a Beckman Aculab IV spectrophotometer. ^{1}H and ^{13}C N.m.r. spectra were recorded with a Perkin-Elmer Hitachi R-24 or with a Bruker WP 200 SY spectrometer ($CDCl_3$ was used as solvent and internal reference). Mass spectra were obtained with a Hewlett Packard 5988A, or with a Kratos MS25RFA. Elemental analyses were carried out in the Microanalysis Service of the University of Malaga, in a Perkin-Elmer 240. High-performance liquid chromatography (h.p.l.c.) was carried out on a Hewlett Packard 1084 B, using a 254 nm u.v. detector.

[*Chloro*-(6-*chloropyrimidin*-4-*yl*)*methylene*]*triphenylphosphorane* (**2a**).—This product was prepared as described previously.[10] Nevertheless, it was very difficult to obtain it free from trace quantities of [6-chloropyrimidin-4-yl)methylene]triphenylphosphorane (**2c**). This by-product results from the partial hydrolysis of the title compound by traces of water followed by reaction of the resulting 4-chloro-6-chloromethylpyrimidine with the triphenylphosphine of the reaction medium. Thus, it is necessary to use anhydrous reactives and benzene. Compound (**2a**) could be purified by reflux in ether in which the by-product is more soluble. Compound (**2c**) could be obtained practically quantitatively by the same procedure, using benzene saturated with water. DTA-TG (Differential Thermal and Thermogravimetric Analysis) of recrystallised (**2c**) showed that it crystallises as a dihydrate, and that it is possible to obtain it anhydrous by heating for 24 h at 100–120 °C.

Reaction of the Phosphorane (**2a**) *with* 2,3-O-*Isopropylidene*-5-O-*trityl*-β-D-*ribofuranose* (**1**).—Compound (**1**) (4 g, 9.3 mmol), the phosphorane (**2a**) (4.4 g, 10.4 mmol), and a catalytic amount of benzoic acid were refluxed in anhydrous benzene for 30 h, after which t.l.c. (hexane–ethyl acetate 6:2.5) showed the disappearance of reactant (**1**), and the presence of several new products. The solvent was evaporated off under reduced pressure (< 30 °C) and the residue was submitted to flash



column chromatography (silica gel Merck 9385, 20 × 3 cm) with hexane–ethyl acetate (19:1), to produce a 1:3 mixture of 4-chloro-6-[(1*R*,*S*)-chloro-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)methyl]pyrimidines (*R*,*S*)-(**3a**) as a white foam. (4.3 g, 80%). Finally, elution with hexane–ethyl acetate (9:1) gave 4-chloro-6-(1-chloro-1,2-dideoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-*ribo*-hex-1-enitol-1-yl)pyrimidine (*E*,*Z*)-(**4a**) (140 mg, 2.6%). Analytical data of those products were similar to those reported.[10] ^{1}H and ^{13}C n.m.r. data were completely resolved as shown in the Tables.

Hydrolysis of the Mixture (R,S)-(**3a**).—Compound (*R*,S)-(**3a**) (58 mg, 0.1 mmol) was dissolved in chloroform (1 ml), and of water (0.5 ml) and TFA (three drops) were added. The mixture was stirred for 10 min at room temperature, when t.l.c. (hexane–ethyl acetate 3:1) showed the disappearance of the starting products (R_F 0.77) and the presence of a new and more polar product. Then the stirred mixture was neutralised with $NaHCO_3$ and the organic layer was separated and concentrated to give a white solid, which was purified by flash column chromatography (silica gel Merck 9385; hexane–ethyl acetate (3:1) to give 4-chloro-6-[(1*R*,*S*)-chloro-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)methyl]pyrimidine (*R*,*S*)-(**5**) (30 mg, 90%). The principal epimer (*S*)—(**5**) was partially separated by thick layer chromatography, R_F 0.59 (hexane–ethyl acetate 1:1); $\lambda_{max.}$(MeOH) 251 nm (ε 3 920) and 212 nm (3 760); high-resolution mass spectra *m*/*z* 323.0200 (M^+ + 4), $C_{12}H_{13}{}^{37}Cl_2N_2O_4$, 321.0223, ($M^+$ + 2) $C_{12}H_{13}{}^{37}Cl^{35}ClN_2O_4$, 319 ($M^+$ interfered with a reference peak, and no mass measurement was possible on this ion).

Cyclisation of (E)-(**4a**) *Induced by Iodine to give* (α,R)-(**6**).—A solution of (*E*)-(**4a**) (50 mg, 0.09 mmol) in tetrahydrofuran (2 ml) was treated with solution of iodine (117 mg, 0.46 mmol) in di-ethyl ether (6.5 ml), and the mixture was shaken with saturated aqueous of $NaHCO_3$ (77.5 mg, 0.92 mmol). The reaction was monitored by t.l.c. and, after four days, a solution of sodium thiosulphate was added to decolorise the ether layer. The aqueous solution was washed several times with diethyl ether, and the combined ether solutions were concentrated to yield a syrup, which was purified by thick layer chromatography (hexane–ethyl acetate 10:1), to give 4-*chloro*-6-[(1R)-*iodo*-2,3-O-*isopropylidene*-5-O-*trityl*-α-D-*ribofuranosyl*)*methyl*]-*pyrimidine* (α,R)-(**6**) (52.3 mg, 85%), R_F 0.79 (hexane–ethyl acetate (6:2.5); $\lambda_{max.}$($CHCl_3$) 261 nm (4 910) and 242 nm (4 605); $\nu_{max.}$ 3 060, 2 940, 1 565, 1 535, 1 450, 1 385, 1 375, 1 215, 1 110, 1 080, 710, and 223 cm^{-1}; *m*/*z* 591 (M^+ − Ph), 541 (M^+ − I), 425 (M^+ − Tr), and 243 (Tr, 100%) (Found: C, 54.8; H, 4.5; N, 3.7. $C_{32}H_{30}ClIN_2O_4{\cdot}2H_2O$ requires C, 54.51; H, 4.86; N, 3.97%).

Cyclisation of (Z)-(**4a**) *Induced by Iodine to give* (β,R)-(**6**). Compound (*Z*)-(**4a**) (100 mg, 0.18 mmol) was treated with a solution of iodine (235 mg, 0.92 mmol) in diethyl ether (13 ml), and shaken with saturated aqueous of $NaHCO_3$ (160 mg, 1.9 mmol). After 1 h, and work-up as above, 4-*chloro*-6-[(1R)-*iodo*-(2,3-O-*isopropylidene*-5-O-*trityl*-β-D-*ribofuranosyl*)*methyl*]-*pyrimidine* (β,R)-(**6**) was isolated (110.7 mg, 90%), R_F 0.75 (hexane–ethyl acetate 6:2.5); *m*/*z* 591 (M^+ − Ph), 541 (M^+ − I), 425 (M^+ − Tr), and 243 (Tr, 100%) (Found: C, 54.5; H, 4.6; N, 3.65. $C_{32}H_{30}ClIN_2O_4{\cdot}H_2O$ requires C, 54.51; H, 4.86; N, 3.97%).

Reaction of the Mixture (R,S)-(**3a**) *with Methanolic Ammonia*.—Compound (R,S)-(**3a**) (0.965 g, 1.67 mmol) was dissolved in methanol (50 ml) saturated with ammonia, and the solution was introduced into a sealed tube and heated to 90 °C for 20 h. After this time t.l.c. showed the absence of substrate (**3a**) and the presence of at least two products. The solvent was evaporated off under reduced pressure, the residue was dissolved in a little ethyl acetate, and the solution was filtered and concentrated to give a syrup (0.820 g), which was resolved by column chromatography (silica gel Merck 7734). Elution with hexane–ethyl acetate (3:1) gave 6-[(1R,S)-*chloro*-(2,3-O-*isopropylidene*-5-O-*trityl*-β-D-*ribofuranosyl*)*methyl*]-4-*methoxypyrimidine* (R,S)-(**7**) (0.141 g, 15%). Further elution with hexane–ethyl acetate (1:8) gave 4-*amino*-6-[(1R,S)-*chloro*-(2,3,O-*isopropylidene*-5-O-*trityl*-β-D-*ribofuranosyl*)-*methyl*]*pyrimidine* (R,S)-(**8**) as a white foam (0.430 g, 46%).

(*R*,*S*)-(**7**): R_F 0.65 (hexane–ethyl acetate 3:1); $\lambda_{max.}$(MeOH) 232 (3 070) and 253 nm (1 890); *m*/*z* 572 (M^+), 557 (M^+ − Me), 542 (M^+ − 2Me), 537 (M^+ − Cl), 495 (M^+ − Ph), 479 (M^+ − Me_2CO − Cl), and 243 (100) (Found: C, 69.3; H, 6.1; N, 4.7. $C_{33}H_{33}ClN_2O_5$ requires C, 69.16; H, 5.80; N, 4.89%).

(*R*,*S*) (**8**): R_F 0.34 (hexane–ethyl acetate 1:1), 0.72 (ethyl

Table 1. ^{13}C N.m.r. chemical shifts (δ) for compounds (**3a**—**d**)[10] to (**10**) [δ (50 MHz)][a]

	(*R*)-(**3a**)	(*S*)-(**3a**)	α-(**3b**)	β-(**3b**)	α-(**3c**)	β-(**3c**)	α-(**3d**)	β-(**3d**)	(*S*)-(**5**)	α-(**6**)	β-(**6**)	(*R*)-(**7**)	(*S*)-(**7**)	(*R*)-(**8**)	(*S*)-(**8**)	(*R*)-(**10**) *b*	(*S*)-(**10**) *b*	(*R*)-(**11**) *b*	(*S*)-(**11**) *b*
CHCl	61.88	59.94	62.12	60.24	37.93	41.57	38.04	41.74	60.06	23.69	24.30	62.25	60.87	61.29	60.32	66.74	66.14	58.01	58.17
C-1′	81.72	82.26	81.61	82.13	80.26	82.19	80.55	82.19	81.78	82.23	82.69	86.38	85.61	86.20	85.71	81.75	81.29	86.70	86.95
C-2′	82.13	83.28	82.25	83.19	82.02	82.78	82.19	82.84	84.31	83.05	83.49	84.34	83.16	84.37	84.04	85.91	86.69	82.33	82.27
C-3′	84.07	84.55	84.07	84.43	83.37	83.49	83.49	83.49	87.46	84.31	85.77	84.04	82.31	83.08	82.36	81.85	83.92	81.36	81.53
C-4′	85.48	86.63	85.42	86.48	—	84.36	—	84.48	87.98	85.19	86.89	82.31	81.69	81.89	81.68	83.97	85.09	83.92	83.63
C-5′	63.64	64.13	63.58	64.11	64.70	64.05	64.88	64.05	62.60	64.96	63.91	63.75	64.13	62.56	64.06	63.88	63.98	63.90	63.84
C-2	158.22	158.67	161.74	161.51	158.40	158.52	160.87	160.80	157.75	158.86		158.33	157.87	158.63	158.24	158.46	158.54	158.23	158.49
C-5	120.88	120.85	117.42	117.30	121.65	121.70	118.30	118.24	120.39	120.73		107.32	107.32	104.00	103.86	103.19	103.35	102.43	103.03
C-4	162.15	161.93	167.44	167.03	160.98	161.16	169.67	168.62	162.86	170.30		165.76	165.36	163.28	163.92	163.50			
C-6	167.56	167.19	168.62	169.14	169.76	168.79	—	—	167.60	161.48		170.32	170.16	164.28	165.98	163.50			
Me(Ip)	25.66	25.58	25.66	25.54	25.01	25.66	25.13	25.66	25.39	25.07		25.63	25.63	25.64	25.64	25.56	25.56	25.62	25.62
Me(Ip)	27.48	27.44	27.48	27.36	26.30	27.53	26.36	27.48	27.13	26.38		27.45	27.45	27.45	27.45	27.37	27.37	27.51	27.51
C(Ip)	114.49	114.03	114.27	113.95	112.37	114.31	112.43	114.25	113.88	112.65		114.26	114.02	114.18	114.02	113.97	114.19	113.87	114.03

[a] Carbons C-1′, C-2′, C-3′, C-4′, C-4, and C-6 are not correctly assigned except for products marked *b*. Chemical shifts of these compounds are assigned by C–H correlation. Isomers were characterized by their relative intensities of the signals. Ip = isopropylidene.

Table 2. ^{1}H N.m.r. chemical shifts of products (**3**)—(**13**) [δ (200 MHz)]

Compound-(X)	CHX	1′-H	2′-H	3′-H	4′-H	5′-H_a	5′-H_b	Me_2C		2-H	5-H	Tr	CH_2a	CH_2b	Others
(*R*)-(**3a**)-Cl	5.16 d	4.52 dd	4.87 d	4.70 dd	4.14 ddd	3.17 dd	3.36 dd	1.53 s	1.34 s	8.99 d	7.71 d	7.20—7.50 m			
(*S*)-(**3a**)-Cl	4.94 d	4.64 dd	5.00 dd	4.77 dd	4.24 ddd	3.22 dd	3.25 dd	1.57 s	1.40 s	9.03 d	7.20—7.50 m				
(*R*)-(**5**)-Cl	5.17 d	4.54 dd	4.81 dd	4.75 dd	4.10 bc	3.86 dd	3.69 dd	1.56 s	1.37 s	8.95 d	7.71 d				2.7 br s (OH
(*S*)-(**5**)-Cl	4.88 d	4.42 dd	4.89 dd	4.83 d	4.15 dd	3.73 dd	3.61 dd	1.52 s	1.38 s	8.89 d	7.66 d				2.7 br s (OH)
(α,*R*)-(**6**)-I	5.09 d	5.31 dd	5.11 dd	4.74 dd	4.16 br t	3.27 dd	3.00 dd	1.50 s	1.38 s	8.98 d	7.15—7.50 m				
(β,*R*)-(**6**)-I	5.30 d	4.05 dd	4.60 dd	4.73 dd	4.28 br	3.36 dd	3.27 dd	1.50 s	1.31 s	8.90 d	7.15—7.60 m				
(*R*)-(**7**)-Cl	5.07 d	4.54 t	4.86 dd	4.64 dd	4.12 q	3.30 dd	3.14 dd	1.50 s	1.30 s	8.73 d	7.06 d	7.20—7.50 m			3.97 s (MeO)
(*S*)-(**7**)-Cl	4.84 d	4.63 dd	4.92 dd	4.67 dd	4.18 q	3.23 dd	3.16 dd	1.55 s	1.35 s	8.79 d	6.70 d	7.20—7.50 m			3.94 s (MeO)
(*R*)-(**8**)-Cl	4.97 d	4.58 dd	4.85 dd	4.62 dd	4.14 q	3.29 dd	3.16 dd	1.50 s	1.30 s	8.51 d	6.66 d	7.20—7.50 m			5.13 s (NH_2)
(*S*)-(**8**)-Cl	4.81 d	4.66 dd	4.92 dd	4.66 dd	4.19 ddd	3.28 dd	3.17 dd	1.53 s	134 s	8.56 d	6.31 d	7.20—7.50 m			5.08 s (NH_2)
(α)-(**9**)-H		4.60 m	4.74 dd	4.70 br d	4.20 br t	3.18 dd	3.07 dd	1.51 s	1.33 s	8.49 d	6.43 d	7.15—7.45 m	—2.97 m—		5.00 br s (NH_2)
(β)-(**9**)-H		4.35 m	—4.55—4.65 m—		4.13 m	3.27 dd	3.12 dd	1.50 s	1.30 s	8.49 d	6.33 d	7.15—7.45 m	3.95 dd	3.85 dd	4.92 br s (NH_2)
(*R*)-(**10**)-N_3	4.57 d	4.35 dd	4.84 dd	4.59 dd	4.19 ddd	3.32 dd	3.20 dd	1.50 s	1.31 s	8.59 d	6.53 d	7.15—7.50 m			
(*S*)-(**10**)-N_3	4.53 d	4.50 dd	4.75 dd		4.16 dd	3.30 dd	3.22 dd	1.50 s	1.31 s	8.61 d	6.44 d	7.15—7.50 m			
(*R*)-(**11**)-NH_2	3.88 d	4.35 dd	4.85 dd	4.61 dd	4.08 bc	3.30 dd	3.18 dd	1.50 s	1.30 s	8.50 d	6.50 d	7.15—7.50 m			5 and 2.4 br s (NH_2)
(*S*)-(**11**)-NH_2	3.91 d	4.22 dd	4.80 dd	4.65 dd	4.08 bc	3.35 dd	3.18 dd	1.50 s	1.30 s	8.52 d	6.35 d	7.15—7.50 m			5 and 2.4 br s (NH_2)
(**12**)		5.32 dd	5.17 dd	4.84 dd	4.32 bc	3.31 dd	3.14 dd	1.62 s	1.38 s	9.12 d	6.64 d	7.15—7.50 m			4.0 br s (NH_2)
(**13**)		5.42 dd	5.38 dd	4.70 dd	4.40 bc	3.20 dd	3.10 dd	1.62 s	1.38 s	9.48 d	7.75 dd	7.15—7.50 m			7.70 d (4-H)

Table 3. ^{1}H N.m.r. coupling constants of products (**3**)—(**13**)

	J/Hz										
Compound-(X)	CHX, 1′	1′, 2′	2′, 3′	3′, 4′	4′, 5′a	4′, 5′b	5′a, 5′b	1, 4	CH_2a, CH_2b	CH_2a, 1′	CH_2b, 1′
(*R*)-(**3**)-Cl	3.8	4.2	6.2	4	4.2	3	10	1.5			
(*S*)-(**3**)-Cl	8	3.8	6	3	4	3	10	1.5			
(*R*)-(**5**)-Cl	3	4.2	6.8	3.6	3.6	3.4	12	1.5			
(*S*)-(**5**)-Cl	9.5	1		1	2.6	3	12	1.5			
(α,*R*)-(**6**)-I	9	4	6	<1	4	4	10	1			
(β,*R*)-(**6**)-I	5.5	4.3	6.7	3.8	3.3	4.6	10.3	1			
(*R*)-(**7**)-Cl	4	4	6.2	4	3.4	4.3	10	1.5			
(*S*)-(**7**)-Cl	7.5	3.8	6.6	3.4	3.8	4.2	10	1.5			
(*R*)-(**8**)-Cl	4.4	4	6.5	4	3	5	10	1.5			
(*S*)-(**8**)-Cl	7.4	3.5	6.5	3.8	3	3.8	10	1.5			
(α)-(**9**)-H		3.5	6	0.6	4.5	4.5	10	1.5			
(β)-(**9**)-H		3.2	6	5	5	7.5	14	1.5	10	3.8	4.6
(*R*)-(**10**)-N_3	5.5	4	6.5	3.5	4	5	10	1.5			
(*S*)-(**10**)-N_3	5.5	3.7	6.5	4.5	4	5	10				
(*R*)-(**11**)-NH_2	4.5	3.2	6.5	4.5	3.5	5	10.5	1.5			
(*S*)-(**11**)-NH_2	6.5	4	6.5	6	4	5	10	1.5			
(**12**)		4.4	6.6	3.5	3.7	4.9	10.2	1.5			
(**13**)		4.2	6.4	3.5	3.5	5.0	10	<1	$J_{2,3}$ = 6 Hz		

acetate); $\lambda_{max.}$(MeOH) 232 nm (3 220); *m/z* 542 (M^+ − Me), 522 (M^+ − Cl), 314 (M^+ − Tr), and 298 (M^+ − TrO) (Found: C, 67.7; H, 7.3; N, 5.9. $C_{32}H_{32}ClN_3O_4 \cdot \frac{1}{2}H_2O$ requires C, 67.77; H, 7.41; N, 5.87%).

Reaction of the Mixture (R,S)-(**8**) *with Hydrazine.*—Compound (*R,S*)-(**8**) (50 mg) was refluxed in ethanol (0.3 ml) containing 10% of hydrazine. After 20 h no reaction was detected by t.l.c. (hexane–ethyl acetate 2:1). Thus we employed other conditions; 30% hydrazine in ethanol and 18 h at 85 °C in a sealed tube. The solution was concentrated under reduced pressure and the residue was purified by thick-layer chromatography (ethyl acetate) to give 4-amino-6-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosylmethyl)pyrimidine (**9**) (13 mg), which was identical to a sample prepared from 4-chloro-6-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosylmethyl)-pyrimidine.[17]

Reaction of Compound (R,S)-(**8**) *with Sodium Azide. Synthesis of Compound* (R,S)-(**10**).—Compound (*R,S*)-(**8**) (1.557 g) and sodium azide (623 mg) were heated gently (60—65 °C) in DMF (150 ml) for 48 h. Solvent was removed at reduced pressure, and the residue was extracted with chloroform (3 × 100 ml). The extracts were concentrated (<35 °C) and the residue was chromatographed by flash chromatography on silica gel (hexane–ethyl acetate 1:1) to yield *compound* (R,S)-(**10**) (1.4 g), R_F 0.31 (hexane–ethyl acetate 1:1), 0.75 (methylene dichloride–methanol 8:1); $\lambda_{max.}$(MeOH) 232 nm (34 000); *m/z* 536 (M^+ − N_2), 321 (M^+ − Tr), 293 (M^+ − Tr − N_2), and 243 (100%) (Found: C, 64.1; H, 5.8; N, 13.7. $C_{32}H_{32}N_6O_4 \cdot 2H_2O$ requires C, 63.98; H, 6.04; N, 13.99%).

Reaction of Compound (R,S)-(**10**) *with Lithium Aluminium Hydride. Synthesis of Compound* (R,S)-(**11**).—Compound (*R,S*)-(**10**) (1.4 g) was dissolved in anhydrous diethyl ether (80 ml). Small portions of LAH (100 mg) were consecutively added until t.l.c. (ethyl acetate) showed the complete disappearance of (*R,S*)-(**10**). Excess of LAH was destroyed by the addition of ethyl acetate (1 ml) and then water (10 ml). The solutions were filtered and the organic layers were separated, dried, and concentrated to give a residue (1.6 g), which was purified by flash column chromatography (methylene dichloride–methanol 20:1) to yield *compound* (R,S)-(**11**) (1.1 g), R_F 0.10 (ethyl acetate), 0.45 (methylene dichloride–methanol (8:1); $\lambda_{max.}$(MeOH) 231 (10 500); *m/z* 538 (M^+), 523 (M^+ − Me), 444 (M^+ − pyrimidine), 418 (M^+ − Ph − Me_2CO), and 243 (100%) (Found: C, 66.5; H, 5.9; N, 9.6. $C_{32}H_{33}N_4O_4$·HCl requires C, 66.87; H, 6.13; N, 9.74%).

Reaction of Compound (R,S)-(**11**) *with Nitrous Acid. Synthesis of the* [1,2,3]*Triazolo*[1,5-c]*pyrimidine Nucleoside Derivatives* (**12**) *and* (**13**).—To a stirred solution of (*R,S*)-(**11**) (190 mg) in $CHCl_3$ (5 ml) placed in an ice-bath were added $NaNO_2$ (40 mg) and NaOAc (95 mg) dissolved in water. When the mixture was cooled, aqueous HCl (2.5%) was added dropwise for 30 min (*ca.* 3 ml) in such a way that the pH was always >5. T.l.c. (CH_2Cl_2–MeOH 8:1) showed the presence of two new products, which were separated by thick-layer chromatography, to yield the nucleoside derivatives (**12**) (170 mg, 90%) and (**13**) (10 mg, 5%).

(**12**): R_F 0.75 (methylene dichloride–methanol 8:1); $\lambda_{max.}$(MeOH) 292 (9 760) and 242 nm (11 690); *m/z* 549.2990 (M^+) ($C_{32}H_{31}N_5O_4$) and 243 (100%).

(**13**) R_F 0.60 (methylene dichloride–methanol 8:1); $\lambda_{max.}$(MeOH) 278 (9 300); *m/z* 534.2268 (M^+) ($C_{32}H_{30}N_4O_4$), 519 (M^+ − 15), and 243 (100%).

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