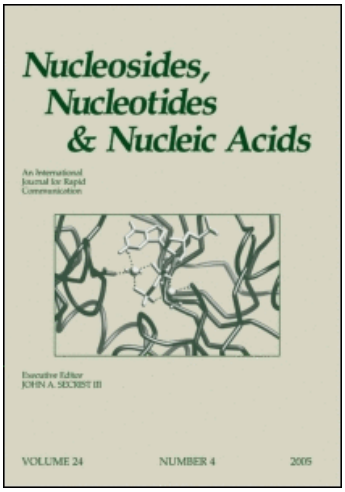

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SYNTHESES OF TRIAZOLE AND PYRIMIDINE HOMO-C-NUCLEOSIDES

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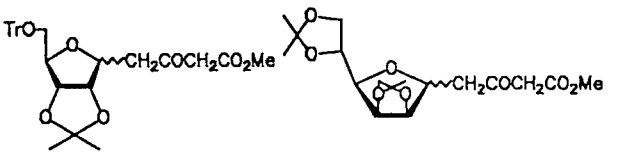
Abstract: The preparation of 2,3:5,6-di-O-isopropylidene-α,β-D-mannofuranosyl-pyrimidine and 2,3-O-isopropylidene-5-O-trityl-α,β-D-ribofuranosyl-pyrimidine and triazole homo-C-nucleosides **3**, **4**, **6**, **10-17** by different synthetic approaches is discussed and their anomeric configurational assigments are made based upon ^{1}H- and ^{13}C-NMR data.

Since Holy[1] reported the interesting biological activity of homonucleotides, several syntheses of homo-C-nucleosides have been reported. Thus, Gensler[2,3] reported several syntheses of triazole homo-C-nucleosides, and Just[4] the syntheses of 6-azauracil and pyrazole homo-C-nucleosides. Secrist[5] has prepared some 6-substituted 4- pyrimidinones, and Sato some pyrimidine homo-C-nucleosides[6], homoshowdomycin, homopyrazomycin[7], and pyrazole homo-C-nucleosides[8,9]. Cupps[10] and Katagiri[11] have prepared some pyrimidine homo-C-nucleosides, some of them as intermediate products in the synthesis of a pyrrolo [3,2-d]pyrimidine nucleoside[12].

As a part of our work on the synthesis of antibiotic C-nucleosides and analogs[13,14,15], we show in this paper the synthesis of some homo-C-nucleosides and the transformation of several different types of C-glycosides into homo-C-nucleosides potentially interesting for the preparation of C-nucleosides.



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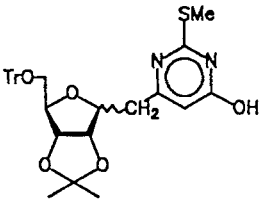

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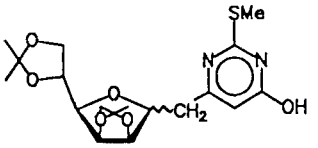

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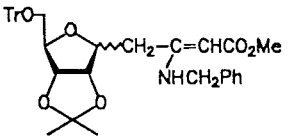

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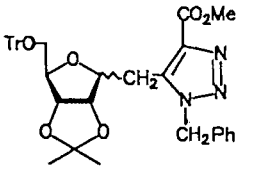


(6)

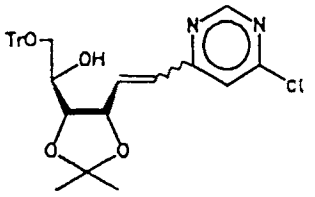
In a first approach we employed the α,β-mixture of methyl 4-D-ribo- or 4-D-manno-furanosyl-2-oxo-butanoate derivatives (**1**$\alpha\beta$ and **2**$\alpha\beta$ respectively), two products previously reported by us[13], and with a synthetically interesting β-ketoester group. Thus, the reaction of **1**$\alpha\beta$, **2**α and **2**β separately with S-methyl thiourea hydroiodide in methanol /water and in the presence of K_2CO_3 gave the corresponding 4-hydroxy-2-methylthio-6-(D-ribo or D-manno-furanosylmethyl) pyrimidine derivatives (**3**$\alpha\beta$, **4**α and **4**β). The mixture **3**$\alpha\beta$ was partially resolved by thick layer chromatography. The anomeric configuration of these products was determined by ^{1}H- and ^{13}C-NMR spectroscopy. Thus, the $J_{3',4'}$ values found for **3**α (<1 Hz) and for **3**β (4 Hz) are in agreement with the previously reported data[13a] for α-D-ribofuranosyl- and β-D-ribofuranosyl-C-glycosides and C-nucleosides, respectively. Similarly the $J_{1',2'}$ values found for **4**α (<1 Hz) and **4**β (3.6 Hz), are also in agreement with the assigned configuration of α-D-mannofuranosyl- and β-D-mannofuranosyl-C-glycosides respectively[13a]. These assignments were confirmed by the ^{13}C chemical shifts of 2',3'-O-isopropylidene groups. Thus, the "exo" anomer or β-D-ribofuranosyl derivative **3**β, shows a

larger chemical shift difference between the two methyls of the 2',3'-O-isopropylidene group (1.85 ppm), a higher chemical shift for the corresponding quaternary carbon CMe_2 (114.07) and methylene group (41.97), than the "endo" or α-anomer **3α** (1.22 ppm, 112.38 ppm and 38.09, respectively)[16]. Similarly, the "exo" or α-D-mannofuranosyl derivative **4α** shows higher chemical shift values for the methylene group (38.77 ppm) than the "endo" or β-anomer **4β** (36.44 ppm).

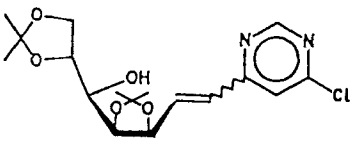
Alternatively, the reaction of **1αβ** with benzylamine in benzene, with azeotropic elimination of water, yielded the corresponding enamines **5αβ** in good yield which were easily converted into the triazole homo-C-nucleosides **6αβ**, also in good yield, by reaction with p-toluenesulfonyl azide in acetonitrile and in the presence of ethylamine. Both isomers were separated by column chromatography and characterized by analytical data. Thus, ^{1}H-NMR shows a $J_{3',4'}$ <1 Hz for **6α** and 4.1 Hz for **6β**, and ^{13}C-NMR shows a minor chemical shift difference between the two isopropylidene methyls for the "endo" or α-anomer **6α** (1.58 ppm) than for the "exo" or β-anomer **6β** (1.89 ppm).

Finally, the Wittig reaction between the partially protected sugars 2,3-O-isopropylidene-D-ribofuranose (**7**) and 2,3:5,6-di-O-isopropylidene-D-mannofuranose (**8**) with (6-chloropyrimidin-4-yl)methylenetriphenylphosphorane (**9**), gave the D-ribofuranosyl or D-mannofuranosyl-methylpyrimidine-homo-C-nucleosides (**10αβ**)[10] and (**14αβ**), respectively, besides minor quantities of the unsaturated products **10EZ**[10] and **14EZ**. The α- and β-anomers **14α** and **14β** were separated by column chromatography.

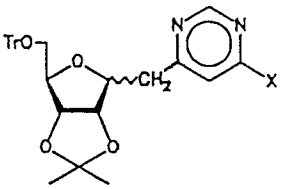
In connection with our studies on the transformation of these and similar C-glycosides into C- and homo-C-nucleosides, we are interested in studying the reactivity of compounds (**10αβ**) and (**14αβ**) with different nucleophiles, (we have substituted the 4-chloro by OMe, OH and NH_2) to modify the reactivity at C-5 against electrophiles. Thus, the



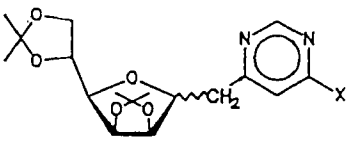
(10 EZ)



(14 EZ)



(10αβ) X = Cl
(11αβ) X = OMe
(12αβ) X = NH_2
(13αβ) X = OH



(14αβ) X = Cl
(15αβ) X = OMe
(16αβ) X = NH_2
(17αβ) X = OH

reaction of 10α,β separately with methanolic ammonia give the 4-methoxy derivatives **11α,β** besides the 4-amino analogues **12α,β**. Reaction of **10** with aqueous potassium hydroxide, led to the corresponding α,β mixture **13αβ** which could be separated by thick layer chromatography. The same product was obtained from Ni-Raney reduction of **3αβ**. Similarly, treatment of **14** with methanolic ammonia gave **15αβ** and **16αβ**, while with aqueous potassium hydroxide or reduction of **4β** with Ni-Raney led to **17β**.

The annomeric configurational assignments of all these compounds were determined by ^{1}H- and ^{13}C-NMR spectroscopy 13a,16. Thus, as above, all α-D-ribo-derivatives showed smaller $J_{3',4'}$ <1 Hz, chemical shift differences between the isopropylidene methyls (1.19 to 1.22 ppm), and chemical shifts for quaternary carbon of isopropylidene group (112.32 to 112.38 ppm) and CH_2 (37.75 to 38.09 ppm), than β-D-ribo-anomers (3.0 to 4.0 Hz, 1.74 to 1.85, 114.07 to

114.26 and 41.53 to 41.97 ppm, respectively), (Tables I to VI). Reactivity study of these products with different nucleophiles is in progress. In all cases, the basic medium causes anomerization, yielding a greather proportion of the "endo" anomer, showing that these anomers are the thermodinamically more stable ones, in agreement with previously reported analogous observations[13,16].

EXPERIMENTAL RESULTS

Melting points are uncorrected. Infrared spectra were recorded with a Beckman Aculab IV spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded 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 UV detector. Preparative thick layer chromatography was performed with silica gel 60 PF_{254} (Merck 7747), thin layer chromatography with silica gel 60 F_{254} (Merck 5719), column chromatography with silica gel 60 (Merck 7734).

Synthesis of 6-(2,3-O-isopropylidene-5-O-trityl-α- and β-D-ribofuranosyl)methyl-4-hydroxy-2-methylthiopyrimidine (3αβ). To a solution of 4.46 g (8.41 mmol) of **1αβ**[13b] in 15 mL of ethanol were added 3.55 g (17.23 mmol) of S-methyl thiourea hydroiodide dissolved in 6.35 mL of water and 5.97 g of K_2CO_3 in 4.3 mL of water. The reaction was left at r.t. for 95 hrs, and then heated at reflux for one additional hour. The solution was neutralized with diluted hydrochloric acid, leading to a gummy precipitate which was purified by column chromatography on silica gel (hexane: ethyl acetate 3:1) to yield 0.98 g of unaltered **1αβ**, and 2.48 g of a mixture of

TABLE I

^{13}C-NMR chemical shifts (δ) of D-ribo compounds 3, 6[a], 11 and 12 (δ, 50 MHz).

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-2	C-4	C-6	C-5	------	CMe_2	------	Trityl	Others
3α	--83.59-83.44-82.29-80.28--				65.38	165.88-165.24-161.29			109.18	26.40	25.18	112.38	87.28-143.60-128.62-127.87-127.13	38.09 (CH_2) 12.89 (SMe)
3β	--84.65-83.47-82.55-82.33--				64.23	164.90-161.21-143.59			109.24	27.50	25.65	114.07	87.00-143.83-128.72-127.83-127.06	41.97 (CH_2) 13.23 (SMe)
11α	-----83.45-82.18-80.47-----				64.51	170.00-167.32-157.97			107.58	26.36	25.17	112.38	87.30-143.64-128.66-127.81-127.02	37.78 (CH_2) 53.58 (OMe)
11β	--84.41-83.43-82.94-82.63--				64.17	169.92-168.52-157.97			107.70	27.52	25.68	114.26	87.10-143.82-128.66-127.81-127.03	41.60 (CH_2) 53.58 (OMe)
12α	-----83.32-82.18-80.41-----				64.22	166.32-162.97-158.28			104.38	26.34	25.12	112.32	87.06-143.57-128.57-127.82-127.05	37.75 (CH_2)
12β	--84.25-83.44-82.84-82.01--				64.17	165.19-162.88-158.23			104.61	27.47	25.63	114.16	86.60-143.79-128.70-127.62-127.06	41.53 (CH_2)

[a] For compounds 6α and 6β see the experimental part.

TABLE II

^{1}H-NMR chemical shifts of D-ribo products 3, 11, 12 and 13[a] (δ, 200 MHz)

Compound	H-1'	H-2'	H-3'	H-4'	H-5'a	H-5'b	---Me_2C -----	Tr	H-2	H-5	--- CH_2 -----	Others
3α	---- 5.00-4.70 m ----			4.18 t	3.35 dd	3.08 dd	1.55 s	1.32 s	7.5-7.2 m	----	6.22 s	2.90 d 2.95 d	2.18 s (SMe)
3β	4.35 m	4.55 dd	4.65 dd	4.12 c	3.25 dd	3.15 dd	1.54 s	1.30 s	7.5-7.2 m	----	6.10 s	-- 2.80 d --	2.52 s (SMe)
11α	4.60 m	4.77 dd	4.72 dd	4.19 t	3.20 dd	3.06 dd	1.52 s	1.31 s	7.5-7.2 m	8.72 d	6.76 d	-- 3.07 d --	3.96 s (OMe)
11β	4.34 dd	4.57 dd	4.61 dd	4.12 dd	3.26 dd	3.13 dd	1.51 s	1.31 s	7.5-7.2 m	8.72 d	6.68 d	3.11 dd 2.94 dd	3.92 s (OMe)
12α	4.60 m	4.74 dd	4.70 bd	4.20 bt	3.18 dd	3.07 dd	1.51 s	1.33 s	7.5-7.2 m	8.49 d	6.43 d	-- 2.97 m --	5.00 bs (NH2)
12β	4.35 m	--4.55-4.65 m--		4.13 m	3.27 dd	3.12 dd	1.50 s	1.30 s	7.5-7.2 m	8.49 d	6.33 d	3.95 dd 3.85 dd	4.92 bs (NH2)
13α	---- 4.80-4.60 m ----			4.20 t	3.24 dd	3.10 dd	1.52 s	1.32 s	7.4-7.1 m	8.10 s	6.50 s	-- 2.96 d --	
13β	4.30 m	4.53 dd	4.63 dd	4.13 dd	3.27 dd	3.13 dd	1.52 s	1.31 s	7.5-7.2 m	8.03 s	6.40 s	2.95 dd 2.82 dd	

[a] For compounds 5α, 5β, 6α and 6β see the experimental part.

TABLE III

^{1}H-NMR coupling constants of D-ribo products 3, 11, 12 and 13[a].

Compound	CH2a-H1'	CH2b-H1'	CH2a-CH2b	H1'-H2'	H2'-H3'	H3'-H4'	H4'-H5'a	H4'-H5'b	H5'a-H5'b	H2-H5
3α	---	---	---	---	6.0	<1	5.0	5.0	12	-
3β	2	1	---	5.0	6.0	4.0	5.0	5.0	10	-
11α	---	---	---	3.5	6.0	1	4.5	---	9.5	1.0
11β	5.0	8.0	14	4.0	6.5	3.0	4.0	4.5	10	1.0
12α	---	---	---	3.2	6.0	<1	4.5	4.5	10	1.5
12β	---	---	---	---	---	---	3.5	4.5	10	1.0
13α	---	---	---	3.6	5.9	0.5	4.1	4.5	10	1.0
13β	5.5	8	14	4.5	6.5	3.5	4.0	4.1	10	1.0

[a] For compounds 5α, 5β, 6α and 6β see the experimental part.

TABLE IV

^{13}C-NMR chemical shifts of D-manno compounds 4, 14, 15, 16 and 17 (δ, 50 MHz).

Compound	CH_2	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-2	C-4	C-6	C-5	------ $\underline{C}Me_2$ ------	$\underline{C}Me_2$	Others
4α	38.77	-----82.81-82.81-80.86-----				73.37	67.03	164.43-164.23-161.55			109.22	24.78-25.20-26.16-26.94	112.87	14.50 (SMe)
4β	36.44	--81.63-81.21-80.73-79.59--				73.09	66.84	165.32-165.17-161.17			109.00	24.61-25.24-25.74-26.85	112.47	13.16 (SMe)
14β	36.48	--81.67-81.16-80.71-79.70--				73.06	66.67	158.57	169.20-161.09		121.73	26.77-25.68-25.24-24.52	112.60-108.99	
15β	36.24	--81.75-81.35-80.82-80.13--				73.15	66.89	157.61	---167.06----		107.75	26.85-25.79-25.32-24.67	112.54-109.03	53.78 (OMe)
16β	36.24	--81.48-81.22-80.62-80.06--				73.03	66.69	158.07	165.43-162.98		104.46	26.74-25.68-25.15-24.52	112.31-108.91	
17β	36.54	--81.75-81.32-80.79-79.54--				73.08	66.89	147.95	166.42-164.20		112.61	26.88-25.77-25.28-24.66	114.35-109.06	

TABLE V

^{1}H-NMR chemical shifts of D-manno products 4, 14, 15, 16 and 17 (δ, 200 MHz)

Compound	CH_2a	CH_2b	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'a	H-6'b	----- Me_2C ------	H-5	Others
4α	--- 2.63 m ---		4.50 t	4.69 d	4.82 dd	3.81 dd	4.37 ddd	4.07 dd	3.97 dd	1.49, 1.45, 1.37, 1.33 4s	6.08 s	2.50 s (SMe) 13 bs (OH)
4β	2.97 dd	2.84 dd	3.95 m	4.65 dd	4.76 dd	3.50 dd	4.39 ddd	4.06 d	4.05 d	1.50, 1.43, 1.37, 1.33 4s	6.17 s	2.56 s (SMe)
14α	2.88 dd	2.96 dd	4.50 bt	4.70 dd	4.84 dd	3.89 dd	4.41 ddd	4.07 dd	3.96 dd	1.51, 1.46, 1.39, 1.34 4s	7.30 d	8.92 d
14β	--- 3.14 d ---		3.95 m	4.67 dd	4.75 dd	3.53 dd	4.38 ddd	- 3.95-4.15 m -		1.51, 1.42, 1.37, 1.34 4s	7.36 d	8.90 d
15α	2.85 dd	2.76 dd	4.45 bt	4.69 bd	4.80 dd	3.80 dd	4.37 ddd	4.03 dd	3.94 dd	1.44, 1.40, 1.33, 1.30 4s	6.60 d	8.68 d 3.94 s (OMe)
15β	3.01 dd	2.93 dd	3.90 m	4.57 dd-	4.65 dd	3.40 dd	4.30 m	3.95 dd	3.91 dd	1.41, 1.32, 1.27, 1.24 4s	6.59 d	8.59 d 3.86 s (OMe)
16α	2.76 dd	2.67 dd ---		4.71 d	4.80 dd	3.81 dd ---		---	---	1.48, 1.43, 1.34, 1.31 4s	6.31 d	8.47 d 4.90 bs (NH_2)
16β	2.99 dd	2.90 dd	3.95 m	4.65 dd-	4.75 dd	3.47 dd	4.37 ddd	4.05 dd	3.99 dd	1.48, 1.40, 1.34, 1.31 4s	6.38 d	8.47 d 4.90 bs (NH_2)
17α	--- 2.67 m ---		---	4.66 dd	4.80 dd	3.78 dd ---		---	---	1.46, 1.42, 1.33, 1.30 4s	6.32 s	8.08 s (H-2)
17β	--- 2.91 m ---		3.91 dt	4.63 dd	4.73 dd	3.46 dd	4.36 ddd	4.04 dd	3.98 dd	1.47, 1.39, 1.33, 1.30 4s	6.40 s	8.08 s (H-2)

TABLE VI

^{1}H-NMR coupling constants of D-manno products 4, 14, 15, 16 and 17

Compound	CH_2a-H1'	CH_2b-H1'	CH_2a-CH_2b	H1'-H2'	H2'-H3'	H3'-H4'	H4'-H5'	H5'-H6'a	H5'-H6'b	H6'a-H6'b	H2-H5
4α	7.5	7.5	---	<1	6.0	3.6	7.7	6.3	4.4	8.7	---
4β	6.4	6.4	16	3.6	6.0	3.6	7.4	5.7	5.0	---	---
14α	9	8	14	0.5	6.0	4.0	7.2	6.0	4.0	8.0	1.5
14β	6.6	6.6	---	3.5	6.1	3.5	7.2	8.7	5.0	9.0	1.5
15α	7.5	7.5	14.5	<0.5	6.0	3.5	7.5	6.0	4.5	8.0	1.5
15β	7	6.2	14.5	3.5	6.0	3.5	7.5	6.0	4.0	8.0	1.5
16α	7.5	7.5	13	<1	6.0	3.5	7.0	---	---	---	1.0
16β	6	7.2	14	3.5	6.0	3.5	7.0	6.0	5.0	8.5	1.0
17α	---	---	---	0.7	6.0	3.5	7.5	---	---	---	1.5
17β	---	---	---	3.6	6.0	3.5	7.6	5.9	3.8	8.8	1.5

epimers **3αβ** (66.48% yield), which could be partially separated by thick layer chromatography (hexane:ethyl acetate 5:1). Rf: 0.85 (**3α**) and 0.90 (**3β**) (hexane:ethyl acetate 1:3); UV λ_{max} (MeOH): 285 nm (ϵ 7.8x10^3) and 227 nm (ϵ 1.6x10^4); IR ν_{max} (KBr): 3500-3300, 3100-3000, 2980, 2930, 2860, 1650, 1575, 1530, 1445, 1380, 1210, 1155, 1100, 1070, 860, 760, 740, 700 cm^{-1}.

Anal. Calc. for $C_{33}H_{34}N_2O_5S$: C, 69.45; H, 6.00; N, 4.90. Found: C, 69.51; H, 6.12; N, 5.02.

Synthesis of 6-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl)methyl-4-hydroxy-2-methylthiopyrimidine (4α). To a solution of 0.75 g (2.09 mmol) of methyl 4-(2,3:5,6-di-O-isopropylidene-D-mannofuranosyl)-3-oxobutanoate (**2α**)13a in 4 mL of ethanol were added 0.88 g (2.45 mmol) of S-methyl thiourea hydroiodide and 1.5 g of K_2CO_3 dissolved in 4 mL of water. The reaction was left at r.t. for 36 hrs and then heated at reflux for 1 h. The solution was neutralized with diluted acetic acid, concentrated and purified by column chromatography on silica gel (hexane:ethyl acetate 3:2) to yield 0.525 g (63 %) of **4α**. Rf 0.14 (hexane:ethyl acetate 1:1); $[\alpha]_D^{20}$ +27° (c 0.1, MeOH); m.p. 124°C; UV λ_{max} (MeOH): 288 nm (ϵ 1.1x10^4) and 238 nm (ϵ 0.99x10^4); IR ν_{max} (KBr): 3600-3300, 2980, 2940, 2880, 1660, 1580, 1545, 1465, 1385, 1215, 1170, 1120, 1070, 850 cm^{-1}.

Anal. Calc. for $C_{18}H_{26}N_2O_6S$: C, 54.25; H, 6.57, N, 7.03. Found: C, 54.28; H, 6.62; N, 7.11.

Synthesis of 6-(2,3:5,6-di-O-isopropylidene-β-D-mannofuranosyl)methyl-4-hydroxy-2-methylthiopyrimidine(4β). A solution of 0.56 g (1.56 mmol) of **2β**13a in 1 mL of ethanol, was mixed with a solution of 0.66 g (3.20 mmol) of S-methyl thiourea hydroiodide and 1.13 g of K_2CO_3 in 3.5 mL of water. Working as above, were obtained 0.419 g (67 %) of **4β**. Rf 0.36 (hexane: ethyl acetate 1:2); $[\alpha]_D^{20}$ -8.3° (c 0.79, MeOH); m.p. 68°C; UV λ_{max} (MeOH): 282 nm (ϵ 1.35x10^4) and

232 nm (ε 1.45 x104); IR νmax (KBr): 3600-3300, 2980, 2930, 2860, 1660, 1580, 1530, 1455, 1375, 1210, 1160, 1120, 1060, 840 cm-1.

Anal. Calc. for $C_{18}H_{26}N_2O_6S$: C, 54.25; H, 6.57, N, 7.03. Found: C, 54.31; H, 6.59; N, 7.11.

Synthesis of methyl 4-(2,3-O-isopropylidene-5-O-trityl-α and β-D-ribofuranosyl)3-benzylamino-2-butenoate (5αβ). A mixture of 2.02 g (3.80 mmol) of **1αβ**13b and 0.41 g (3.83 mmol) of benzylamine in 15 mL of dry benzene were heated at reflux for 1h. Water was removed azeotropically by distillation and the rest of the solvent was eliminated under vacuo. The residue was chromatographed on silica gel (hexane-ethyl acetate 5:1) yielding 1.63 g (69.43 %) of a mixture of epimers **5αβ**. Rf 0.49 (hexane-ethyl acetate 3:1); $[\alpha]_D^{20}$ -6.9° (c 1, $CHCl_3$); UV λ_{max} 268 nm (ε 3.84x104) and 256 nm (ε 3.16x104); IR νmax (KBr): 3600-3200, 3100-3000, 2990-2940, 1690, 1660, 1610, 1450, 1380, 860, 760, 740 and 700 cm-1. 1H-N.M.R. (δ): 9.1-8.9 (m, 2H, NH), 7.4-7.1 (m, 2 OH aromatics), 4.8-4.3 (m, 5H, H-1', H-2', H-3' of β, and H-2', H-3' of α-epimer), 4.71 (s, 1H, =CH β), 4.69 (s, 1H, =CH α), 4.48 (m, 2H, $-CH_2$-Ph of β), 4.42 (m, 2H, $-CH_2$-Ph of α), 4.25-4.00 (m, 3H, H-1', H-4' of α and H-4' of β), 3.64 (s, 3H, MeO), 3.30 (dd, 1H, 4.4 and 10.1 Hz, H-5'a of α), 3.28 (dd, 1H, 4.3 and 9.9 Hz, H-5'a of β), 3.15 (dd, 1H, 4.4 and 10.1, H-5'b of α), 3.10 (dd, 1H, 4.3 and 9.9, H-5'b of β), 2.64 (d, 2H, 7.2 Hz, H-4a and H-4b of β), 2.55 (d, 2H, 6.3 Hz, H-4a and H-4b of α), 1.49, 1.43 and 1.31 (3s, 2x3H and 6H, Me_2C).

Anal. Calc. for $C_{39}H_{41}NO_6$: C, 75.58, H, 6.66, N, 2.26. Found: C, 75.72; H, 6.80; N, 2.32.

Synthesis of 1-benzyl-4-methoxy-carbonyl-5-(2,3-O-isopropylidene-5-O-trityl-α and β-D-ribofuranosyl)-1,2,3-triazole (6αβ). To a solution of 1.45 g (2.34 mmol) of **5αβ** and 0.24 g (2.37 mmol) of triethylamine in 3.7 mL of acetonitrile cooled at 0°C was added 0.48 g (2.43 mmol) of tosyl

azide. The reaction was left to rise to room temperature and after 48 h the solvent was evaporated under vacuo. The residue was dissolved in 30 mL of ethyl ether, washed with 0.18 g of NaOH in 20 mL of water, then with 0,1 g of NaOH in 10 mL of water and finally with water (2x10 mL), dried over Na_2SO_4 and chromatographed on silica gel (hexane-ethyl acetate 7:2), to yield the separated anomers **6α** and **6β** (0.59 and 0.40 g, 39% and 26.7% respectively).

6α: Rf: 0.24 (hexane-ethyl acetate 7:2); m.p. 52 °C; $[\alpha]_D^{20}$ +19.1° (c 1.01, $CHCl_3$); UV λ_{max} ($CHCl_3$): 290 nm (ε 545), 260 nm (ε 1540) and 241 nm (ε 6720); IR ν_{max} (KBr): 3090-3030, 2980-2870, 1745, 1720, 1570, 1450, 1375, 1250, 1210, 1075, 860, 760, 740 and 700 cm-1. ^{1}H-N.M.R. (δ): 7.5-7.0 (m, 2 OH, Ph and Tr); 5.82 and 5.67 (2d, 2x1H , 15.4 Hz, CH_2-Ph), 4.9-4.6 (m, 3H, H-1', H-2', H-3'), 4.18-4.08 (bt, 3.3 Hz, 1H, H-4'), 3.67 (s, 3H, MeO), 3.37 (dd, 1H, 3.5 and 14.2 Hz, CH_{2a}C=), 3.22 (dd, 1H, 3.2 and 10.1 Hz, H-5'a), 3.09 (dd, 1H, 9.3 and 14.2 Hz, CH_{2b}C=), 2.99 (dd, 1H, 3.44 and 10.1 Hz, H-5'b), 1.54 and 1.33 (2s, 6H, Me_2C). ^{13}C-N.M.R. (δ): 161.89 (C=O), 143.49-127.07 (Ph and Tr), 112 (Me_2C), 83.66, 83.63, 82.03 and 81.14 (C-4', C-3', C-2' and C-1'), 65.32 (C-5'), 52.15 (CH_2-C=), 51.51 (MeO), 26.52 and 24.94 (Me_2C), 24.16 (CH_2-Ph).

Anal. Calc. for $C_{39}H_{39}N_3O_6$: C, 72.53; H, 6.08; N, 6.50. Found: C, 72.42; H, 5.83; N, 6.47.

6β: Rf: 0.15 (hexane-ethyl acetate 7:2); m.p. 80 °C; $[\alpha]_D^{20}$ -22.1° (c 1.06, $CHCl_3$); UV λ_{max} ($CHCl_3$): 290 nm (ε 272), 260 nm (ε 1450) and 241 nm (ε 6810); IR ν_{max} (KBr): 3080-3020, 2980-2860, 1740, 1720, 1570, 1450, 1370, 1250, 1215, 1075, 860, 760, 740 and 700 cm-1. ^{1}H-N.M.R. (δ): 7.5-7.1 (m, 2 OH, Ph and Tr), 5.7 and 5.53 (2d, 2x1H, 15.6 Hz, CH_2-Ph), 4.48 (dd, 1H, 4.1 and 6.8 Hz, H-3'), 4.35 (dd, 1H, 5.8 and 6.8 Hz, H-2'), 4.15-4.0 (m, 2H, H-1' and H-4'), 3.93 (s, 3H, MeO), 3.41 (dd, 1H, 3.9 and 14.3 Hz, CH_{2a}-C=), 3.35 (dd, 1H, 3.5 and 10.4 Hz, H-5'a), 3.17 (dd, 1H, 5 and 10.4 Hz, H-5'b), 3.0 (dd, 1H, 7.7 and 14.3 Hz, CH_{2b}-C=), 1.49 and 1.28 (2s, 6H, Me_2C). ^{13}C-N.M.R. (δ): 161.9 (C=O),

143.7-126.81 (Ph and Tr), 114 (Me_2C), 83.5, 83.26, 82.74 and 81.88 (C-1', C-2', C-3' and C-4'), 63.68 (C-5'), 52.32 (MeO), 51.71 (CH_2-C=), 27.48 and 25.59 (Me_2C),26.84 (CH_2-Ph).

Anal. Calc. for $C_{39}H_{39}N_3O_6$: C, 72.53; H, 6.08; N, 6.50. Found: C, 72.51; H, 6.00; N, 6.43.

Synthesis of 4-methoxy-6-(2,3-O-isopropylidene-5-O-trityl-α and β-D-ribofuranosyl) methylpyrimidine (11αβ) and 4-amino-6-(2,3-O-isopropylidene-5-O-trityl-α and β-D-ribofuranosyl)methylpyrimidine (12αβ). A solution of 0.145 g (0.267 mmol) of **10αβ** in 30 mL of methanol saturated with ammonia was heated in a sealed tube for 23 h at 90°C. After this time TLC showed the absence of **10αβ** and the presence of at least two new products. The solvent was evaporated under vacuo and the residue dissolved in a little of ethyl acetate. Filtration and reconcentration of the solution gave a syrup (0.110 g) which was resolved by column chromatography. Elution with hexane-ethyl acetate (2.5:1) gave 0.030 g (21%) of **11αβ**, (α/β, 5:1). Elution with hexane-ethyl acetate (1:10) and then pure ethyl acetate, gave 0.060 g (43%) of **12αβ**, (α/β, 5:1).

11αβ: Rf 0.49 hexane-ethyl acetate (2:1); UV λ_{max} 230 nm; MS m/z 523 (M^+ -15), 295 (M^+ -Tr), 243 (Tr^+).

Anal. Calc. for $C_{33}H_{34}N_2O_5$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.72; H, 6.54; N, 5.02.

12αβ: Rf 0.54 ethyl acetate; UV λ_{max} (MeOH) 244 nm (ϵ 6.27x10^3) and 260 nm (ϵ 3.89x10^3); MS m/z 281 (M^+ -Tr), 265 (M^+ -TrO), 243 (Tr^+).

Anal. Calc. for $C_{32}H_{33}N_3O_4x1.5\ H_2O$: C, 69.80; H, 6.59; N, 7.63. Found: C, 69.71; H, 6.79; N, 7.26.

Synthesis of 6-(2,3-O-isopropylidene-5-O-trityl-α and β-D-ribofuranosyl)methyl-4-hydroxypyrimidine (13αβ). Method A.- To a solution of 230 mg (0.40 mmol) of **3αβ** in 25 mL of ethanol, an excess of Ni-Raney in 5 mL of ethanol was added, besides a few drops of ammonia. The reaction was heated at

reflux for one day, was filtered and the products were separated by column chromatography on silica gel (hexane-ethyl acetate 2:3) to yield 79 mg of **13α** and 49 mg of **13β** (overall yield 60.7%). UV of the mixture, λ_{max} (MeOH): 233 nm (ϵ 3220); IR ν_{max} (KBr): 3700-2300, 3110, 3090, 3050, 3000, 2975, 2950, 2900, 2000-1750, 1675, 1615, 1550, 1500, 1450, 1420, 1380, 1340, 1270, 1220, 1170, 1150-960, 875, 810, 770, 710 and 630 cm^{-1}; MS m/z: 509 (M^+ -15), 494 (M^+ -30), 447 (M^+ -Ph), 281 (M^+ -Tr), 243 (100%). Rf 0.39 (**13α**), 0.33 (**13β**) (hexane-ethyl acetate 1:3); $[\alpha]_D^{20}$ +1.54° (c 0.5, methanol) (**13 α**), +0.66° (c 1.0, methanol) (**13β**).

The same procedure was applied to separated epimers **3α** and **3β**, obtaining the corresponding reduced products **13α** and **13β**, respectively, without any observed epimerization.

Anal. Calc. for $C_{32}H_{32}N_2O_5.2H_2O$: C, 68.55; H, 6.47; N, 5.00. Found: C, 69.09; H, 6.67; N, 5.00.

Method B.- A solution of 112 mg (0.206 mmol) of **10αβ** in 7 mL of 10% ethanolic KOH was heated at reflux for 15 h. The disappearance of **10αβ** was followed with TLC (hexane-ethyl acetate 2:1). After this time, TLC showed the presence of only one new product. The solution was neutralized with concentrated hydrochloric acid, extracted several times with chloroform and the organic layers concentrated giving 99 mg (90%) of **13αβ** as a yellow product, (α/β, 2:1). The mixture has the same spectra as previously reported 10.

Synthesis of 4-chloro-6-(2,3:5,6-di-O-isopropylidene-α and β-D-mannofuranosyl)methylpyrimidine (14αβ), and of Z- and E-4-chloro-6-[5-hydroxy-3,4:6,7-bis(isopropylidenedioxy)-1--hepten-1-yl]pyrimidine (14EZ). A solution of 1 g (3.86 mmol) of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (**8**) and 1.8 g (4.6 mmol) of 4-chloropyrimidin-6-yl-methylenetriphenyl-phosphorane (**9**) in 6 mL of methylene chloride was heated at reflux for 36 h. The solvent was eliminated and the residue was dissolved in methanol, filtered , and then purified by column chromatography (hexane-ethyl acetate 83:17), yield-

ing 1.07 g (75%) of a mixture of **14E**, **14Z** and **14β** (in a 1:4:16 ratio) as a transparent pale violet oil and 143 mg (10%) of **14α** as a yellow syrup. The h irradiation of the mixture results in a rapid stereoselective cyclization of the open chain isomer **14EZ** to the cyclic **14β**.

14αβ: UV max (MeOH): λ248 nm (ϵ 3560) and 210 nm (ϵ 3000); IR νmax (KBr): 3000, 2960, 2910, 2875, 1575, 1540, 1470, 1380, 1325, 1275, 1215, 1175, 1130, 1110, 1100, 1070, 1000, 980, 930, 900, 870, 850 and 750 cm^{-1}; MS m/z: 373 and 371 (M^+ +1), 357 and 355 (M^+ -Me), 314 and 312 (M^+ -Me_2CO), 299 and 297 (M^+ -Me_2CO -Me). Rf: 0.40 (**14α**), 0.48 (**14β**) (hexane-ethyl acetate 2:1); $[\alpha]_D^{20}$ = +54° (**14α**), -17.5° (**14β**) (c 1, MeOH).

14E: ^{1}H-NMR (from the mixture) (δ): 8.95 (d, 1H, 1 Hz, H-2), 7.32 (d, 1H, 1 Hz, H-5), 6.67 (d, 1H, 18 Hz, H-1'), 7.25 (dd, 1H, 18 and 8 Hz, H-2'), 4.95 (m, 1H, H-3').

14Z: ^{1}H-NMR (from the mixture) (δ): 9.1 (s, 1H, H-2), 7.6 (s, 1H, H-5), 6.4 (m, 2H, H-1' and 2'), 5.8 (dd, 1H, 6 and 8 Hz, H-3').

14αβ + 14EZ mixture: Anal. Calc. for $C_{17}H_{23}ClN_2O_5$: C, 55.06; H, 6.25; N, 7.56. Found: C, 54.69; H, 6.21; N, 7.54.

Synthesis of 4-methoxy-6-(2,3:5,6-di-O-isopropylidene-α and β-D-mannofuranosyl)methylpyrimidine (15αβ) and 4-amino-6-(2,3:5,6-di-O-isopropylidene-α and β-D-mannofuranosyl)methylpyrimidine (16αβ). A solution of 0.418 g (1.127 mmol) of **14αβ** in 20 mL of methanol saturated with ammonia was heated in a sealed tube for 23 h at 90°C. After this time TLC (AcOEt) showed the absence of **14αβ** (Rf 0.79) and the presence of at least two new products (Rf 0.68 and 0.15). The solvent was evaporated under vacuo and the residue dissolved in a little of ethyl acetate. Filtration and reconcentration of the solution gave a syrup (0.400 g) which was resolved by column chromatography. Elution with hexane-ethyl acetate (1:10) gave 0.120 g (29%) of **15αβ**, (α/β, 1:9) as a colorless oil. Elution with methanol-ethyl acetate

(1:5) gave 0.250 g (63.2%) of **16αβ**, (α/β, 1:6). Epimers **15α** and **15β** were separated by thick layer chromatography (ethyl acetate:hexane 2:1).

15αβ: Rf 0.68 ethyl acetate; UV λ_{max} (MeOH) 233 nm (ε 1.05x10^3); IR νmax (film): 3000, 2950, 2890, 1600, 1550, 1475, 1375, 1260, 1210, 1160, 1125, 1070, 1040, 990, 870, 850, 810; MS m/z: 366 (M^+), 351 (M^+ -Me), 308 (M^+ -Me_2CO), 293 (M^+ -Me_2CO -Me), 250 (M^+ -2Me_2CO).

Anal. Calc. for $C_{18}H_{26}N_2O_6.2H_2O$: C, 56.23; H, 7.34; N, 7.29. Found: C, 56.51; H, 6.90; N, 7.07.

16αβ: Rf 0.73 ethyl acetate; UV λ_{max} (MeOH) 267 nm (ε 3.33x10^3), 232 nm (ε 6.27x10^3) and 208 nm (ε 3.33x10^3); IR νmax(film): 3360, 3200, 3000, 2950, 2910, 2875, 1660, 1610, 1540, 1500, 1450, 1385, 1350, 1275, 1220, 1170, 1075, 1000, 925, 900, 850 cm^{-1}; MS m/z 351 (M^+), 336 (M^+ -Me), 293 (M^+ -Me_2CO), 278 (M^+ - Me_2CO -Me).

Anal. Calc. for $C_{17}H_{25}N_3O_5.1.5\ H_2O$: C, 53.95; H, 7.46; N, 11.11. Found: C, 53.99; H, 7.59; N, 10.71.

Synthesis of 6-(2,3:5,6-di-O-isopropylidene-β-D-manno-furanosyl)methyl-4-hydroxypyrimidine (17). Method A.- To a solution of 130 mg (0.32mmol) of **4β** in 25 mL of ethanol, a two fold excess of Ni-Raney in 5 mL of ethanol was added, besides a few drops of ammonia. After being heated at reflux for one day, the mixture was filtered and the solvent evaporated under vacuo. The residue was purified by column cromatography (ethyl acetate) to yield 97.5 mg of **17β** (84.5%) UV of the mixture, λ_{max} (MeOH): 232 nm (ε 3220) and 254 nm (ε 1930), IR νmax (KBr): 3450, 3300-2750, 3200, 3150, 31000, 3000, 2950, 2920, 1670, 1600, 1540, 1470, 1420, 1390, 1275, 1215, 1175, 1075, 1100, 995, 950, 860, 825 and 810 cm^{-1}. M.S. m/z: 352(M^+), 337(M^+ -15), 294 (M^+ -Me_2CO), 279 (M^+ -Me_2CO -Me) or (M^+ -Me -HOCN), 252 (M^+ -Me_2CO -Me -CNH).

Anal. Calc. for $C_{17}H_{24}N_2O_6x0.5\ H_2O$: C, 56.50; H, 6.97. Found: C, 56.97; H, 6.80.

Method B.- A solution of 147 mg (0.40 mmol) of **14αβ** in 7 mL of 10% of ethanolic KOH was heated at reflux for 14 h. The disappearance of **14αβ** was followed with TLC (hexane-ethyl acetate 2:1). After this time, TLC showed the presence of only one new product. The solution was neutralized with concentrated hydrochloric acid, extracted several times with chloroform and the organic layers concentrated giving 125 mg (90%) of **17αβ** as a yellow product, (α/β, 2:1). The mixture has the same spectra as the ones reported above. Rf: 0.15 (**17α**) and 0.25 (**17β**).

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