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Synthesis of D-Psico- and D-Fructofuranosyl Nucleosides

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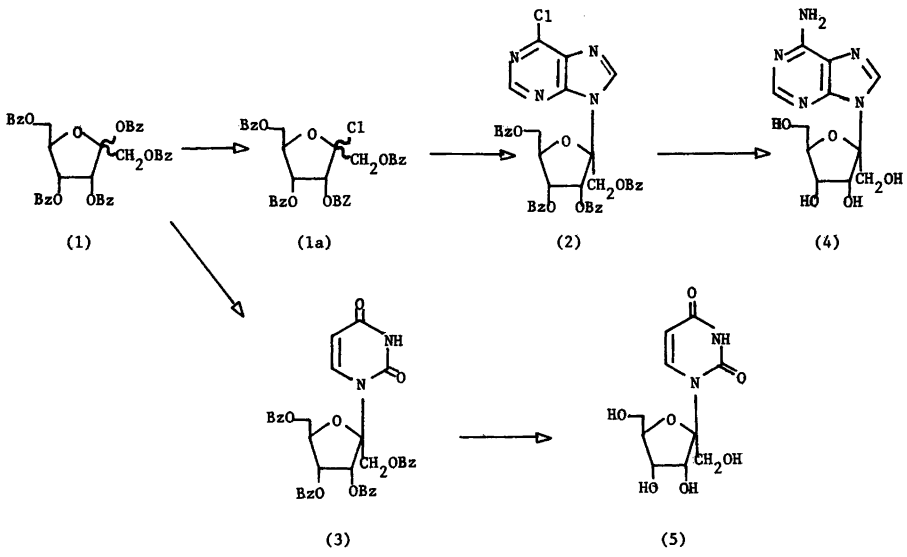
The condensation of 6-chloropurine with peracylated psicofuranosyl and fructofuranosyl chlorides, using Yamaoka's procedure, afforded respectively the β and α anomers of the corresponding purine nucleosides. A similar result was obtained when silylated uracil was reacted with peracylated ketose. The first chemical synthesis of 1-β-D-fructofuranosyluracil has also been accomplished from 1-β-D-psicofuranosyluracil *via* the 2,3'-anhydro derivative.

As part of a program on the preparation of nucleosides with biological activities, we have reinvestigated the synthesis of ketohexose nucleosides derived from psicose and fructose.

The natural nucleoside antibiotic psicofuranine (6-amino-9-β-D-psicofuranosylpurine) (*4*) was previously synthesized by two groups: Farkas *et al.*[1] prepared it by the reaction of the mercury salt of 6-benzamidopurine with per-*O*-benzoyl-D-psicofuranosyl bromide affording the blocked nucleoside in 4.6 % yield. Recently Lichtenthaler *et al.*[2] also obtained the mixture of both α and β anomers of benzoyl-psicofuranine in a 1:2 ratio in 64 % yield through the condensation of bis(trimethylsilyl)-6-*N*-benzoyladenine with per-*O*-benzoyl-D-psicofuranose in the presence of tin tetrachloride. The synthesis of α-anomer of fructofuranosyl adenine (*9*) has also been reported by Baker and his co-workers[3] with the help of mercury salts. It should be added that the latter group did not observe the formation of any



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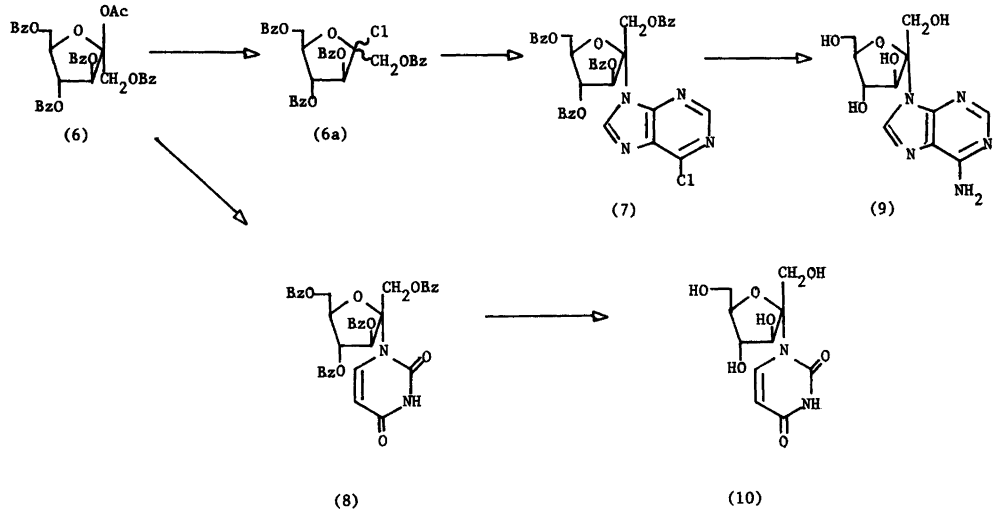
β-isomer in their reactions. Farkas *et.al.*[4] synthesized 1-β-D-psicofuranosyluracil (*5*) and 1-β-D-psicofuranosylcytosine by the reaction of per-*O*-toluyl-D-psicofuranosyl bromide with the corresponding silylated bases. The fully protected ketohexose nucleosides were thus obtained respectively in 20 and 15.5 % yields. In a similar manner, Moffatt and his co-workers[5] obtained 1-(per-*O*-benzoyl-β-D-psicofuranosyl)cytosine in 33 % yield using mercuric cyanide instead of mercuric acetate as catalyst.

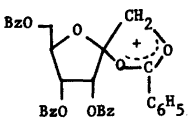
In this paper we report our procedure on a high yielding stereoselective synthesis of 9-β-D-psicofuranosyladenine (*4*) along with the preparation of 1-β-D-psicofuranosyluracil (*5*) and its conversion to the 1-β-D-fructofuranosyluracil (*15*). The first chemical synthesis of *15* is particularly interesting in view of the biological properties that are associated with the "*arabino* configuration" especially in well known anticancer and antitumor agents like 1-β-D-arabinofuranosyl-5-fluorocytosine and 9-β-D-arabinofuranosyladenine.

The condensation of 1,3,4,6-tetra-*O*-benzoyl-D-psicofuranosyl chloride (*1a*), generated by the reaction of (*1*)[5] with dry HCl gas in dry CH_2Cl_2 at −10 °C, with 6-chloropurine in nitromethane using $Hg(CN)_2$ as a catalyst, according to a procedure first devised by Yamaoka and his co-workers,[6] gave 6-chloro-9-(1,3,4,6-tetra-*O*-benzoyl-β-D-psicofuranosyl)purine (*2*) in 61 % yield. It should be emphasized that only traces of the α-anomer were obtained (>5 %) under the latter reaction condition. The conversion of 6-chloropurine nucleoside (*2*) to 6-amino derivative (*4*) was carried out by the treatment with methanolic ammonia in a sealed stainless steel container at 30 °C for 30 h in 52 % yield. In the same manner, the reaction of 6-chloropurine with 1,3,4,6-tetra-*O*- benzoyl-D-fructofuranosyl chloride (*6a*) afforded exclusively the α-anomer of 6-chloro-9-(1,3,4,6-tetra-*O*-benzoyl-D-fructofuranosyl)-purine (*7*) in 88 % yield which was converted to 9-α-fructofuranosyladenine (*9*) by ammonolysis in 55 % yield.

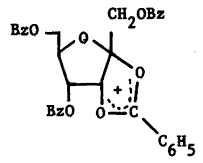
In the pyrimidine nucleoside series, 1-(1,3,4,6-tetra-*O*-benzoyl-β-D-psicofuranosyl)uracil (*3*) was obtained in 81 % yield, according to the method of Niedballa and Vorbrüggen,[7] by the reaction of 1,2,3,4,6-penta-*O*-benzoyl-D-psicofuranose[5] (*1*) with 2,4-bis(trimethylsilyl)uracil in acetonitrile in the presence of tin tetrachloride at room temperature. The ammonolysis of (*3*) afforded 1-β-D-psicofuranosyluracil (*5*) in 75 % yield showing identical physico-chemical characteristics with those previously reported.[4] When 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzoyl-β-D-fructofuranose[8] (*6*) was submitted to the same condensation procedure, 1-α-D-fructofuranosyluracil (*8*) was obtained exclusively which was converted to the free nucleoside (*10*) by usual ammonolysis procedure.

The stereochemistry of these condensation reactions is apparently controlled by the structure of the intermediary carboxonium ions that are presumably involved in such reactions.[3] In the





(A)



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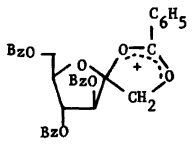

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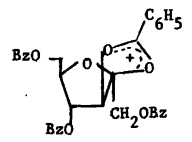
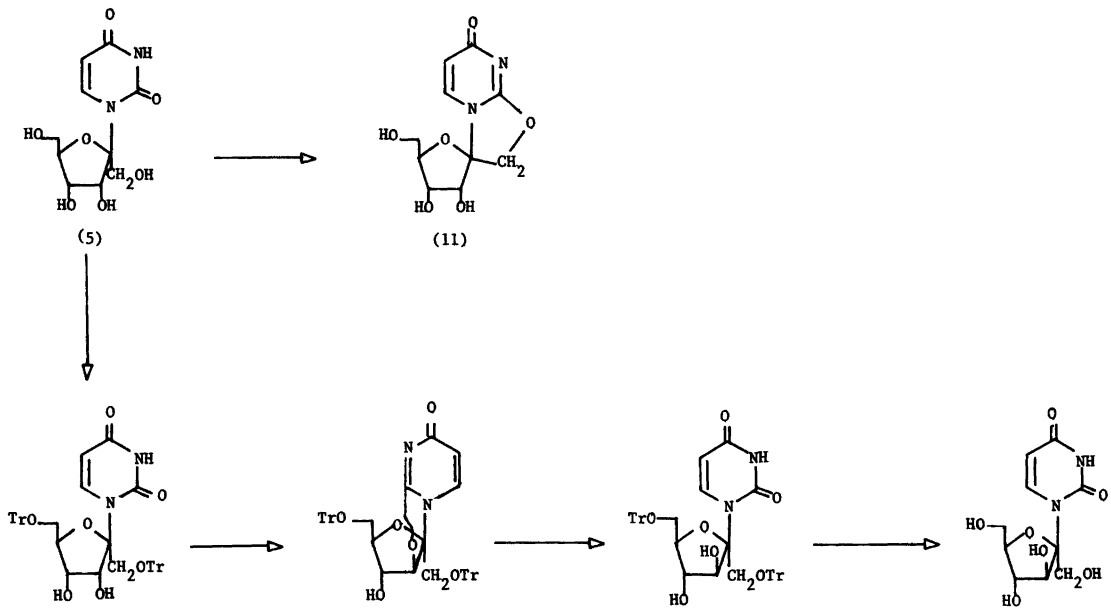


(D)

simple case of the aldose sugars, a C_1,C_2-*trans* configuration is generally obtained.[14] With the ketose sugars, it is perhaps more complex because of the possibility of participation of different isomeric carboxonium ions.[3] Thus one can clearly conceive of the formation of two alternative carboxonium ion intermediates from the peracylated psicofuranose (structures: A and B) and a similar possibility exists also for the peracylated fructofuranose (structures: C and D). It is also conceivable that the formation of the carboxonium ion intermediates like A and C, respectively from peracylated psico- and fructofuranosyl derivatives, would promote a non-stereoselective attack by the base while the participation of the intermediates like B and D should encourage the attack of the base from the relatively unhindered side giving rise to 2′,3′-*trans* products. Thus, in view of the high stereoselectivities of glycosylation reactions that are obtained by us during the preparations of both psico- and fructo-furanosyl nucleosides, it is possible that the carboxonium intermediates like B and D might have been actually involved. It is also apparent that the nature of metal ion at least partially controls the stabilities and interconversions of these carboxonium ions as well as the nature of the base. Thus tin chloride promoted glycosylation reactions by Lichtenthaler and his co-workers[2] gave a 2:1 ratio of β and α anomers respectively of psicofuranosyladenine while a reaction, in presence of $Hg(CN)_2$, gave us essentially pure 9-β-D-psicofuranosyladenine with less than 5 % of the α-anomer. It should be added that the effect of the nature of the base is remarkable in the former reaction in view of the fact that we obtained exclusively β-isomer when we used Lichtenthaler's condition with uracil.

In view of the interesting antiviral properties that are generally exhibited by β-pyrimidine nucleosides with the *arabino* configuration,[9] we then decided to undertake preparation of new 1-β-D- fructofuranosyluracil. One successful way that is reported for the synthesis of a uracil nucleoside with *arabino* configuration deals with the opening of a versatile intermediate, 2,2′-*O*-anhydrouridine, which is still nowadays well studied.[10] Among the methods[14] that are developed for the formation of the anhydro bridge, Hampton and Nichol reported that 2,2′-*O*-anhydro-1-β-D-arabinofuranosyluracil was formed in high yield when uridine was treated with diphenyl carbonate and $NaHCO_3$ in hot *N*,*N*-dimethylformamide[12]. Thus we reacted 1-β-D-psicofuranosyluracil (*5*) for 1 h with an equimolar amount of diphenyl carbonate and an excess of $NaHCO_3$ (2.5 equiv.) in dry dimethylformamide in an oil bath (80 °C) for 1 h. After an usual work up and purification on a preparative TLC plate we isolated the major compound in 42 % yield. This was later characterized by UV and ^{1}H–NMR spectroscopy as to be 1′,2-*O*-anhydro-1-β-D-psicofuranosyluracil (*11*). A further evidence for the structure (*11*) was also



obtained by the reaction of (*11*) in methanolic solution with 1M aq. NaOH at room temperature for 10 min followed by neutralization with Dowex H^+ which regenerated the starting material: 1-β-D-psicofuranosyluracil (*5*). Thus the above futile attempt to synthesize 2,3′-*O*-anhydro-1-β-D-fructofuranosyluracil led us to protect both 1′-and 6′-hydroxyl functions in the form of a ditrityl derivative to give (*12*) in 40 % yield. We then subjected (*12*) to the same treatment with diphenyl carbonate and $NaHCO_3$, under the above condition to give the desired compound (*13*). Its alkali promoted 2,3′-anhydro bridge opening into (*14*) followed by the detritylation with formic acid–water (9.1 v/v) at room temperature led to 1-β-D-fructofuranosyluracil (*15*) in 74 % yield constituting its first chemical synthesis.

The present work thus offers a variety of synthetic procedures for and β ketose nucleosides with either fructo- or psico-configuration. The availability of these isomers now offers the possibilities of their comparison in terms of their physico-chemical and biological properties with respect to ribofuranosyl- and arabinofuranosyl nucleosides.

EXPERIMENTALS

Melting points were determined with an Electrothermal melting point apparatus (IA 6304) and are uncorrected. ^1H NMR spectra were recorded with a Bruker WP-80 and a Jeol FX 90Q spectrometers and are reported relative to the tetramethylsilane signal. IR spectra were recorded with a Beckman Acculab-4 spectrophotometer, and UV spectra with a Beckman DU-8 and a Cecil CE 545 spectrophotometers. Optical rotations were determined with a Perkin Elmer 241 polarimeter. Short column chromatography was performed on Silica Gel 60 G (Merck) and TLC on Silica Gel 60 F_{254} plastic sheets (Merck).

9-(1,3,4,6-tetra-O-benzoyl-β-D-psicofuranosyl)-6-chloropurine (2). A solution of (*1*) (9 g, 12.8 mmol) in dichloromethane (45 ml) was added at −10 °C to dichloromethane (200 ml) presaturated with anhydrous hydrogen chloride at 0 °C. A further excess of HCl gas was bubbled through this cold solution for 2 h. The mixture was then kept in a stoppered flask for 20 h at room temperature and evaporated to dryness under vacuum. The residue was dissolved in toluene. Evaporation of the solution to dryness gave pale-yellow crystals which were immediately dissolved in nitromethane (135 ml, distilled in the

presence of phosphorus pentoxide). To this solution were added 6-chloropurine (4 g, 25.8 mmol), mercuric cyanide (4 g, 15.8 mmol) and molecular sieve 3Å (5 g) and the mixture was heated for 5 h at 110 °C. The reaction mixture was filtered hot, and the residue was washed with hot nitromethane. After evaporation of the combined filtrates under an aspiration vacuum, the remaining solid was washed with chloroform (3×300 ml) and the suspension filtered. The filtrate was washed with 50 % potassium iodide in half-saturated sodium chloride solution (80 ml), followed by saturated sodium chloride solution (2×80 ml) and then dried. The volatile matters were evaporated using a rotavapor to obtain a crystalline residue which was purified by silica gel column chromatography with 1:2 (v/v) ethyl acetate–hexane as eluent to afford (*2*) (5.7 g, 61%): m.p. 71 °C; R_f 0.77 ($CHCl_3$–5 % MeOH v/v); $[\alpha]_D^{25}$ −48.5° (c 0.072, $CHCl_3$); UV (95 % EtOH): λ_{max} 266nm (ε 12 555), 230 (50 220), 202 (56 117): IR (KBr): ν_{max} 1720, 1600, 1590, 1560, 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.52, 8.50 (s, 2H), H-2 and H-8; 8.25–7.3 (m, 20 H), benzoyl protons; 7.05 (d, $J_{3',4'}$=5.4 Hz, 1H), H-3′; 6.05 (dd, $J_{4',5'}$=3.9 Hz, 1H), H-4′; 5.50–4.9 (m, 4H), H-1′ and H-6′; 4.60 (m,1H), H-5′; (Found: C, 47.3; H, 3.8; N, 6.4; $C_{39}H_{29}N_4O_9Cl$ requires: C, 47.53; H, 3.96; N, 6.33 %).

*9-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-6-chloropurine* (*7*). To a solution of *6*[8] (6 g, 9.4 mmoles) in anhydrous ether (100 ml) were added molecular sieve 3 Å (3 g) and acetyl chloride (3 ml, 37 mmol). Through this solution, cooled to −10 °C, was bubbled dry hydrogen chloride until the gas escaped from the drying tube. The mixture was then kept for 1 h at 0 °C and stored for 10 h at room temperature. After evaporation of the mixture to dryness, per-*O*-benzoylated fructofuranosyl chloride was converted into nucleoside (*7*) as descibed previously for *2* (6.3 g, 88 %): m.p. 72 °C; R_f 0.84 ($CHCl_3$–5 % MeOH v/v); $[\alpha]_D^{25}$ −4.1° (c. 0.076, $CHCl_3$); UV (95 % EtOH): λ_{max} 266 nm (ε 13 698), 231 (53 333), 202 (56 183); IR (KBr): ν_{max} 1725, 1600, 1590, 1560, 1265 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.70, 8.62 (s, 2 H), H-2 and H-8; 8.25–7.1 (m, 20 H), benzoyl protons; 5.70 (s, 1 H), 5.1 (s, 2 H), 4.85 (s, 3 H), 4.70 (m, 1 H), H-5′; (Found: C, 47.6, H, 4.1; N, 6.25 $C_{39}H_{29}N_4O_9Cl$ requires: C. 47.53; H. 3.96; N, 6.33 %).

6-amino-9-β-D-psicofuranosyl purine (*4*) and *6-amino-9-α-D-fructofuranosyl purine* (*9*). A suspension of blocked nucleoside (9.6 mmol) in methanolic ammonia (liq. NH_3–MeOH; 1:1 v/v, 200 ml at 0 °C) was kept in a sealed stainless-steel container at 30 °C for 30 h. After the excess ammonia was allowed to escape, the reaction mixture was concentrated under vacuum and the residue was co-evaporated with ethanol leaving a jelly which was purified by silica gel column chromatography with 1:2 (v/v) ethyl acetate–ethanol as eluent. Crystallization from 95 % ethanol afforded 1.5 g (52 %) of (*4*) from (*2*) and 1.6 g (55 %) of (*9*) from (*7*).

Compound *4*: m.p. 183 °C (lit. 211 °C); R_f 0.27 ($CHCl_3$–30 % MeOH v/v); $[\alpha]_D^{25}$ −39.2° (c 0.165, H_2O); UV (H_2O, pH 7.3): λ_{max} 260 nm (ε 10 731), 200 (17 651); IR (KBr): ν_{max} 3380, 3340, 3200, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 8.30, 8.15 (s, 2 H), H-2 and H-8; 7.20 (s, 2 H), NH_2; 4.90 (d, $J_{3',4'}$=3.6 Hz, 1 H), H-3′; 4.45–3.37 (m, 6 H), H-1′, H-4′, H-5′ and H-6′; (Found: C, 44.6; H, 5.2; N, 23.7; $C_{11}H_{15}N_4O_5$ requires C, 44.44; H, 5.05; N, 23.57 %).

Compound *9*: m.p. 230 °C (lit. 234); R_f 0.35 ($CHCl_3$–30 % MeOH v/v); $[\alpha]_D^{25}$ +48.0° (c 0.186, H_2O); UV (H_2O, pH 7.3): λ_{max} 260 nm (ε 16 662), 203 (25 426); IR (KBr): ν_{max} 3420, 3360, 3220, 1650 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 8.15, 8.02 (s, 2 H), H-2 and H-8; 7.15 (s, 2 H), NH_2; 4.80 (d, $J_{3',4'}$=3Hz; 1H), H-3′; 4.4–3.5 (m, 6 H), H-1′, H-4′, H-5′ and H-6′; (Found: C, 44.3; H, 4.8; N, 23.4; $C_{11}H_{15}N_5O_5$ requires: C, 44.44; H, 5.05; N, 23.57 %).

*1-(1,3,4,6-tetra-*O*-benzoyl-β-D-psicofuranosyl)uracil* (*3*) and *1-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)uracil* (*8*). To a solution of peracylated sugar (21 mmol) in acetonitrile (130 ml) a solution of 2,4-bis(trimethylsiloxy)pyrimidine[13] (15 ml, 11 g, 43 mmol) in acetonitrile (20 ml) was added. After cooling the mixture in an ice bath, stannic chloride (6 ml, 51 mmol) was added dropwise with vigorous stirring. The yellow homogeneous solution was stirred for 1 h at room temperature when TLC (5 % MeOH–$CHCl_3$ mixture), indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was dissolved in methylene chloride and the solution was shaken with saturated aqueous sodium bicarbonate. The resulting emulsion was filtered over a layer of celite. The organic phase was separated and evaporated under a reduced pressure. The crystalline residue was then purified through a short column of silica gel ($CHCl_3$, then 5 % EtOH–$CHCl_3$): (*3*) was obtained from (*1*) in 81 % yield and (*8*) was obtained from (*6*)[8] in 88 % yield.

Compound *3*: m.p. 99 °C; R_f 0.54 ($CHCl_3$–5 % MeOH v/v) and 0.80 ($CHCl_3$–10 % MeOH v/v); $[\alpha]_D^{25}$ −37.5° (c. 0.081, $CHCl_3$); UV (95 % EtOH): λ_{max} 265 nm (ε 16 863), 230 (58 084), 202 (54 268); IR (KBr): ν_{max} 1720, 1690, 1600, 1265 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25–7.2 (m, 21 H),

H-6 and benzoyl protons: 6.65 (d, $J_{3',4'}$=5.7 Hz, 1 H), H-3'; 6.00 (dd, $J_{4',5'}$=3.9 Hz, 1 H), H-4'; 5.55 (d, $J_{5,6}$=8.4 Hz, 1 H), H-5; 5.35–4.75 (m, 4 H), H-1' and H-6'; 4.45 (m, 1 H), H-5'; Found: C, 66.2; H, 4.5; N, 4.2; $C_{38}H_{30}N_2O_{11}$ requires: C, 66.09; H, 4.35; N, 4.06.

Compound *8*: m.p. 104 °C; R_f 0.58 ($CHCl_3$–5 % MeOH v/v) and 0.82 ($CHCl_3$–10 % MeOH v/v); $[\alpha]_D^{25}$+13.2° (c 0.080, $CHCl_3$); UV (95 % EtOH): λ_{max} 265 nm (ε 10 215), 231 (39 930), 202 (42 545); IR (KBr): ν_{max} 1720, 1690, 1600, 1265 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20–7.25 (m, 21 H)), H-6 and benzoyl protons; 5.80 (d, $J_{5,6}$=8.4 Hz, 1 H), H-5; 5.70 (m, 1 H); 5.10 (d, 2 H); 5.0–4.5 (m, 4 H); (Found: C, 66.2; H, 4.3; N, 3.8; $C_{38}H_{30}N_2O_{11}$ requires: C. 66.9; H, 4.35; N, 4.06 %).

1-β-D-psicofuranosyluracil (*5*) and *1-α-D-fructofuranosyl-uracil* (*10*). A suspension of blocked nucleoside (10 mmol) in a mixture of methanol (70 ml) and concentrated ammonium hydroxide (106 ml) was stirred at room temperature for 20 h. The homogeneous solution was evaporated and the residue was taken up in water. The insoluble material was filtered and the aqueous filtrate was evaporated to dryness *in vacuo* leaving the crude product which was purified by column chromatography (30 % MeOH–$CHCl_3$): (*5*) was obtained from (*3*) in 75 % yield and (*10*) was obtained from (*8*) in 69 % yield after recristallization from EtOH.

Compound *5*: m.p. 62 °C; R_f 0.33 ($CHCl_3$–30 % MeOH v/v); $[\alpha]_D^{25}$+0.99 (c 0.181, H_2O); UV (H_2O, pH 7.3) λ_{max} 263 nm (ε 8088), 194.5 (26 652); IR (KBr): ν_{max} 3350, 3200, 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6): 8.05, 5.55 (d, $J_{5,6}$=8.4 Hz, 2 H), H-6 and H-5; 4.65 (d, $J_{3',4'}$=5Hz, 1 H), H-3'; 4.25–3.25 (m, 6 H); Found: C, 43.9; H, 5.04; N, 10.1; $C_{10}H_{14}N_2O_7$ requires: C, 43.79; H, 5.11; N, 10.22 %).

Compound *10* m.p. 192 °C; R_f 0.40 ($CHCl_3$–30 % MeOH v/v); $[\alpha]_D^{25}$+24° (c 0.190, H_2O); UV (H_2O, pH 7.3): λ_{max} 263 nm (ε 16 648), 194 (20 559); IR (KBr): ν_{max} 3350, 3200, 3050, 1720, 1680, 1470 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 7.70, 5.55 (d, $J_{5,6}$=8.4 Hz, 2H), H-6 and H-5; 4.60 (s, 1 H); 4.25–3.40 (m, 6 H); Found: C, 43.6; H, 5.3; N, 10.4; $C_{10}H_{14}N_2O_7$ requires: C, 43.79; H, 5.11; N, 10.22 %).

1',2-anhydro-1-β-D-psicofuranosyluracil (*11*). (*5*) (274 mg, 1 mmol) and diphenylcarbonate (184 mg, 0.86 mmole) were dissolved in dimethyl formamide (1.5 ml). Sodium bicarbonate (200 mg, 2.4 mmol) was added and the mixture was heated at 80 °C for 1h. After cooling to room temperature, ether was added. A precipitate formed which was collected by centrifugation and dissolved in methanol. The solution was separated from a small amount of insoluble material and applied to one thick layer plate which was developed in chloroform–methanol (7:3). A band appeared at R_f 0.30 and was eluted to yield 108 mg (42 %) of (*11*): m.p. 227 (decomp.); R_f 0.39 ($CHCl_3$–30 % MeOH v/v); UV (H_2O, pH 7.3): λ_{max} 262 nm (ε 6001), 194 (28 831); IR (KBr): ν_{max} 3420, 1690 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 7.77, 5.59 (d, $J_{5,6}$=8.3 Hz, 2 H), H-6 and H-5; 5.72 (d, $J_{3',4'}$=7.33 Hz, 1 H), H-3' 5.28 (d, $J_{4',5'}$=0.5 Hz, 1 H), H-4'; 4.68 (m, 1 H), H-5'; 3.40–3.2 (m, 4H), H-1' and H-6'; Found: C, 46.7; H, 4.5; N, 11.1; $C_{10}H_{12}N_2O_6$ requires: C, 46.87; H, 4.69; N, 10.94 %).

1',6'-di-O-trityl-1-β-D-psicofuranosyluracil (*12*). (*5*) (1.1 g, 4 mmol) dried by co-evaporation with dry pyridine (7 ml) was stirred with triphenylmethyl chloride (3 g, 10.8 mmol) in dry pyridine (13 ml) for 18 h at room temperature. The solution was then heated at 100 °C during 2 h and poured, after cooling, into a mixture of ice and water (80 ml). The supernatant was decanted from the gummy precipitate and was centrifuged. The pellet was combined with the gummy material, well washed with water and then dissolved in acetone. The solution was evaporated to dryness under the vacuum of a water pump leaving a reddish syrup that was made free of residual pyridine by co-evaporation with toluene. The crude product was dissolved in acetone and the solution was decolorized with charcoal and centrifuged. The supernatant was evaporated to a foam which was purified by passage through a short column on silica gel ($CHCl_3$) yielding 1.2 g of pure (*12*) (40.5 %): m.p. 82 °C; R_f 0.47 ($CHCl_3$–5 % MeOH v/v); UV (95 % EtOH): λ_{max} 263 nm (ε 8315), 205 (83 388); IR (KBr): ν_{max} 3410, 1690, 770, 705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00, 5.70 (d, $J_{5,6}$=8.4 Hz, 2 H), H-6 and H-5; 7.30 (s, 30 H), trityl protons; 4.70 (d, $J_{3',4'}$=5.1 Hz, 1 H), H-3'; 4.45 (m, $J_{4',5'}$=3.5 Hz, 1 H), H-4'; 4.25 (m, 1 H), H-5'; 3.65, 3.30 (m, 4 H), H-1' and H-6'; (Found: C, 75.8; H, 5.7; N, 3.5; $C_{48}H_{42}N_2O_7$ requires: C, 75.99; H, 5.54; N. 3.69 %).

1',6'-di-O-trityl-2,3'-anhydro-1-β-D-fructofuranosyluracil (*13*). A solution of (*12*) (670 mg, 0.9 mmole) and diphenylcarbonate (502 mg, 2.35 mmol) in dimethyl formamide (4 ml) was heated with sodium bicarbonate (558 mg, 6.64 mmol) at 80 °C for 1 h. After cooling to room temperature ether was added. The solution was separated from insoluble material by centrifugation and evaporated. DMF was eliminated by evaporation with an oil pump. The brown residue, thus obtained, was purified by column chromatography ($CHCl_3$) leaving (*13*) as an oil which was sufficiently pure for direct use in the next step.

1',6'-di-O-trityl-1-β-D-fructofuranosyluracil (*14*). Sodium hydroxide (1.0 N, 5 ml) was added dropwise to a solution of (*13*) in 20 ml of methanol and the mixture was stirred for 2 h at room temperature. Precipitation of a granular solid began whereupon the reaction solution was neutralized with Dowex H^+ to pH 6. After filtration and washing of the resin with acetone, the filtrate and the washing solution were evaporated together giving white crystals of pure *14*: 420 mg, 63 % yield calculated from (*12*): m.p. 137 °C; R_f 0.43 ($CHCl_3$ −5 % MeOH v/v); UV (95 % EtOH): λ_{max} 258 nm (ε 11 544), 253 (11 688), 206 (85 480); IR (KBr): ν_{max} 3320, 1650, 1540, 765, 705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25 (s, 30 H, trityl protons; 6.90, 5.95 (d, $J_{5,6}$=7.5 Hz, 2 H; 5.45 (d, $J_{3',4'}$=1.8 Hz, 1H), H-3'; 4.45 (m, 1H), H-4'; 4.30 (m, 1 H), H-5'; 3.60 (s, 2 H), H-1'; 3.05 (m, 2 H, H-6').

1-β-D-fructofuranosyluracil (*15*). *14* (300 mg, 0.4 mmol) was dissolved in formic acid/water (9:1 v/v; 2.5 ml). The solution was stirred for 30 min at room temperature whereupon triphenylmethanol precipitated. The products were concentrated under reduced pressure and the residue was co-evaporated with ethanol. The resulting gum thus obtained was purified by passage through a short column of silica gel ($CHCl_3$−30 % MeOH v/v) yielding 80 mg of pure *15* as a glass (74 %): R_f 0.32 ($CHCl_3$−30 % MeOH v/v); $[\alpha]_D^{25}$ −9.69° (c 0.233, H_2O); UV (H_2O, pH 7.3): λ_{max} 250 nm (ε 117 27), 222 (123 11), 194 (18 470); IR (KBr): ν_{max} 3350, 3200, 3000, 1650, 1470 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 7.95 (d, $J_{5,6}$=8 Hz, 1H), H-6; 7.30 (s, 1 H), −NH−; 5.95 (d, 1 H), H-5; 5.10 (s, 1 H), H-3'; 4.45 (m, $J_{4',5'}$=0.5 Hz, 1 H), H-4'; 4.15 (m, 1 H), H-5'; 3.60−3.15 (m, 4H), H-1' and H-6'; Found: C, 43.7; H, 4.9; N, 10.4; $C_{10}H_{14}N_2O_7$ requires: C, 43.8; H, 5.11; N, 10.22 %).

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