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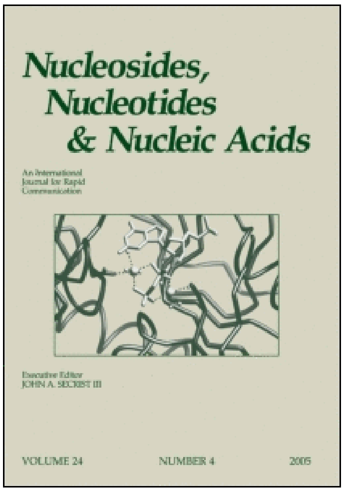

Nucleosides, Nucleotides and Nucleic Acids

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SYNTHESIS OF D-FRUCTOFURANOSYLPURINE NUCLEOSIDES

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Abstract: The Mitsunobu reaction has been applied to the formation of purine nucleosides of D-fructofuranose. The use of O-benzyl protection results in a predominance of the β-configuration in these novel compounds and both α- and β-D-fructofuranosyladenine are obtained in stereochemically pure form.

In spite of the widespread occurrence of fructose and its biochemical importance very little attention has been paid to the investigation of the structure and chemotherapeutic potential of fructose purine nucleosides. Indeed the synthesis of ketose nucleosides generally has not been extensively explored, although there are some notable examples of such as psicofuranine and decoyinine which exhibit antibacterial and antitumour activities and inhibit xanthosine 5'-phosphate aminase.[1] The potential of this area is even more interesting when it is considered that fructose can be regarded as a 1-substituted arabinose and several types of arabinose nucleoside have been found to exhibit useful chemotherapeutic activity. These include the antitumour agent, β-arabinocytosine,[2] the potent established antiviral agent, BVaraU, an arabinouracil,[3] and new expressions of antiviral activity in β-arabino 6-methoxypurine[4] and β-arabino 6-dimethylaminopurine.[5] Although some fructose pyrimidine nucleosides are known,[6,7] and α-fructofuranosyl adenine has been obtained by stereoselective routes by several groups,[7,8] to our knowledge the synthesis of the archetypal purine nucleoside, β-fructose adenine, has not been reported.

Routes to fructose nucleosides which have been described previously, have involved O-acyl protection of the D-fructofuranosyl precursor, and direct condensation with a

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Dedicated to the memory of Dr. Roland K. Robins.

heterocyclic base, promoted by a metal salt. In all cases this resulted in a high stereoselectivity for the α-configuration. We have recently demonstrated[9] the usefulness of the Mitsunobu reaction for elaboration of the tertiary anomeric site in O-benzoyl protected fructofuranose. The Mitsunobu intermediate is formed preferentially from the α-anomer of *O*-benzoyl protected fructose due to steric effects and the reaction with primary alcohols proceeds without inversion due to participation of the neighbouring 3-*O*-benzoyl group in the stabilisation of the putative carbocationic intermediate. The combined effect of these two factors is a very high selectivity for the α-configuration during the formation of fructosides.[9]

Application of our Mitsunobu methodology to the formation of nucleosides served only to confirm the established stereoselectivity; the reaction of 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose (1) with 6-chloropurine in presence of diisopropyl azodicarboxylate and triphenylphosphine (Mitsunobu conditions) gave the corresponding α-nucleoside (2) in stereochemically pure form. Compound (2) was identical to that obtained by a classical direct condensation route.[7] Evidently the Mitsunobu reaction shows the same selectivity for the formation of the α-anomer in reactions leading to fructosides *or* fructose nucleosides, when the *O*-protecting group is benzoyl. In order to change the observed stereoselectivity, from the α-configuration toward the β-configuration we reasoned that a different, non-participating, protecting group was required. Thus if the Mitsunobu intermediate is formed preferentially as the α-anomer and then reacts with inversion at the substitution site then a preponderance of the β-nucleoside should result. We report the successful use of an O-benzyl protection protocol in the formation of β-fructofuranose adenine.

Benzylation of a mixture of methyl D-fructosides by the method of Ness[10] gave methyl 1,3,4,6-tetra-*O*-benzyl-D-fructofuranoside (3), α,β ratio 1:3. Glycosidic hydrolysis of this anomeric mixture gave 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (4), with a similar α,β ratio. The anomeric composition has not been established previously and the predominance of the β-configuration is notable since the corresponding compound with benzoyl as the O-protecting group is predominantly in the α-configuration.[9] Compound 4 was further characterised by formation of the 2-*O*-acetyl and 2-*O*-(4-nitrobenzoyl) derivatives (5 and 6 respectively). Compound 5 was predominantly in the β-form but, due presumably to the bulk of the aroyl substituent, 6 was isolated as the stereochemically pure α-anomer. The anomeric configuration of these simple fructose derivatives was established using ^{1}H and ^{13}C NMR data. The presence of four benzylic groups means that most of the fructose ring protons are obscured and analysis is difficult in most cases. The coupling $J_{3,4}$ is in the range 1.7 - 2.5 Hz in the α-form and in the range 5.2 - 7.1 Hz in the β-form, in keeping with the values observed for a larger range of derivatives of tetra-*O*-benzoyl-D-fructofuranose.[9] The pattern of the ^{13}C spectra is also useful since C-2 is 3 - 4 ppm to higher frequency in the α-anomers and C-4 is similarly shifted by about 2 ppm. The separation between C-3 and C-5 is about 3 ppm in the α-anomers and about 1 ppm in the β-anomers.

Reaction of the protected D-fructose (4) with 6-chloropurine in presence of diisopropyl azodicarboxylate and triphenylphosphine (Mitsunobu conditions) gave the corresponding nucleoside, 9-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)-6-chloropurine (7) (α,β ratio 1:3) in admixture with the usual byproduct, diisopropyl hydrazinedicarboxylate (DIHD). The impurity could be removed by chromatography at this stage or after amination (see below). Separation of the anomers in this mixture by further chromatography was difficult but could be achieved by slow elution from a long column to give the pure β-anomer (the high running spot on TLC) and the α-anomer (low running spot). In practice anomeric separation was achieved more efficiently at a later stage. The mixture of the anomers of 7 was aminated with methanolic ammonia for 48 hours at 30 °C. These conditions minimised methanolysis of the glycosidic bond but always gave rise to some methanolysis of the 6-chloro group. The use of liquid ammonia as aminating reagent was less successful. Severe degradation was observed probably due to the lability of the glycosidic bond.

Thus the reaction product was a mixture of 6-amino-9-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)purine (8) and 9-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)-6-methoxypurine (9). The ratio of these two nucleosides was *ca* 1:1. Chromatographic fractionation of this mixture resulted in the isolation of each of the anomers of the 6-methoxypurine nucleoside (9), but the 6-aminopurine nucleoside could only be obtained as an anomeric mixture, α,β ratio 1:3.

Each of the separated anomers of the 6-chloropurine (7) was also aminated under these conditions giving in each case a mixture of the corresponding anomer of 8 and 9. These compounds were easily separated by chromatography. There was no evidence of anomerisation during the amination and hence each anomer of 8 and each anomer of 9 is accessible in stereochemically pure form.

Anomeric configuration in these *O*-protected nucleosides was established by the magnitude of $J_{3,4}$ (< 1 Hz in α-anomer and > 3Hz in the β-anomer). Proton H-3' is significantly deshielded in the α-anomer but is not readily accessible for the β-anomer in every case and a more obvious diagnostic is the presence of two sets of shielded aromatic ortho protons in the α-form compared to only one set in the β-form. This shielding arises from an interaction with the heterocyclic ring and the O-3' benzylic group is affected only in the α-form, whereas the O-1' benzylic group is affected in both anomers. This criterion is unequivocal for all the purine nucleosides.

Removal of the protecting benzyl groups from 8 was achieved efficiently by catalytic hydrogenation with palladium on charcoal using hydrazine hydrate as the hydrogen source. Thus 6-amino-9-α,β-D-fructofuranosylpurine (10) ('fructose adenine') was obtained in excellent yield (93%), α,β ratio 1:3. This anomeric mixture could be separated easily by HPLC and the α- and β-anomers of fructose adenine were obtained in stereochemically pure form. These compounds were identical (TLC, spectra and optical rotation) to the species obtained by aminating and deprotecting the separate anomers of the 6-chloropurine nucleoside.

We have shown that the Mitsunobu reaction can be applied to the formation of fructose nucleosides and furthermore the combination of selectivity for the α-intermediate with normal inversion at the reacting site, results in a significant preference for the β-configuration. The methodology described in this paper should allow easy access to a variety of β-D-fructofuranosyl nucleosides involving different heterocyclic bases. Since D-fructose is relatively inexpensive, modifications to the sugar moiety could provide an economic route to other β-ketose nucleosides, presently only accessible from expensive precursors such as D-psicose.

EXPERIMENTAL

General Procedures. NMR spectra were recorded with a JEOL GX270 spectrometer using standard conditions with a data point resolution of ca. 0.1 Hz. ^1H chemical shifts were measured relative to Me_4Si and ^{13}C chemical shifts relative to $CDCl_3$ (77.05 p.p.m.) or $(CD_3)_2SO$ (39.5 p.p.m.). Assignments of the ^1H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. For benzylic derivatives the data for the benzylic groups is not given. For anomeric mixtures the α,β ratio was determined from the integration of suitable peaks. Column chromatography was performed on silica gel (230 – 400 mesh; Aldrich) and TLC on silica gel 60, F_{254} (Merck) with detection by UV absorbance or ethanolic sulphuric acid. HPLC separations were carried out using a Dynmax semi-preparative column. Optical rotations were obtained using an ETL-NPL automatic polarimeter. In the case of some compounds obtained as syrups satisfactory elemental analysis data were not obtained but these compounds were fully characterised by spectroscopic data.

9-(1,3,4,6-Tetra-*O*-benzoyl-α-D-fructofuranosyl)-6-chloropurine (2). A mixture of 6-chloropurine (0.13 g, 0.8 mmol) and triphenylphosphine (0.58 g, 2.2 mmol) in dry tetrahydrofuran (20 mL) was refluxed for 20 min, then cooled to r.t. Diisopropyl azodicarboxylate (0.44 g, 2.2 mmol) was added dropwise followed by 1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranose[9] (1) (0.5 g, 0.8 mmol) in tetrahydrofuran (2 mL) and the mixture refluxed for 2 h. The solution was concentrated under reduced pressure, diluted with a small amount of ether and filtered. The filtrate was concentrated to a solid mass which was recrystallised (EtOH) to give 9-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-6-chloropurine (**9**) (0.19 g, 32%), mp 71-72 °C (Lit.[7] 72 °C); $[\alpha]_D^{22}$ −3.0° (*c* 0.87, $CHCl_3$),[Lit.[7] $[\alpha]_D^{25}$ −4.1° (*c* 0.08, $CHCl_3$)].

Methyl 1,3,4,6-tetra-*O*-benzyl-α,β-D-fructofuranoside (3). Using the method of Ness[9] D–fructose (45 g) was converted to the methyl fructoside and then benzylated to afford **3** (124 g). A small amount was purified by column chromatography for spectroscopic analysis: α,β ratio 1:3; ^1H NMR ($CDCl_3$), *α-anomer* (**3α**), δ 3.65 (m, 2 H, H-1, H-1'), 4.05 (d, 1 H, $J_{3,4}$ = 2.3 Hz, H-3), 3.82 (m, 1 H, $J_{4,5}$ = 5.9 Hz, H-4), 3.55 (m, H-6, H-6'), 3.308 (s, 3 H, OMe); *β-anomer* (**3b**), δ 3.57 (s, 2 H, H-1, H-1'), 4.327 (d, 1 H, $J_{3,4}$ = 6.9 Hz, H-3), 4.160 (t, 1 H, $J_{4,5}$ = 6.7 Hz, H4), 4.09 (m, H-5), 3.55 (m, H-6, H-6'), 3.310 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$), **3α**, δ 70.3 (C-1), 108.3 (C-2), 84.6 (C-3), 80.8 (C-4), 87.4 (C-5), 65.8 (C-6), 48.6 (OMe); **3β**, δ 70.1 (C-1), 104.3 (C-2), 83.9 (C-3), 79.2 (C-4), 84.6 (C-5), 71.3 (C-6), 49.7 (OMe).

1,3,4,6-Tetra-*O*-benzyl-α,β-D-fructofuranose (4). The methyl fructoside **3** (124 g) in acetic acid (500 mL) and water (120 mL) was heated on a steam bath for 2 h. After cooling the mixture was diluted with water (1 L) and extracted with dichloromethane (4 × 150 mL). The extract was washed successively with sodium bicarbonate solution and water, then dried (magnesium sulphate) and concetrated to a thick syrup (125 g): α,β ratio 1:4; ^1H NMR ($CDCl_3$), *α-anomer* (**4α**), δ 3.65 (d, 1 H, $J_{1,1'}$ = 10.1 Hz, H-1), 3.73 (d, 1 H, H-1'), 4.025 (d, 1 H, $J_{3,4}$ = 1.9 Hz, H-3), 3.93 (dd, 1 H, $J_{4,5}$ = 3.8 Hz, H-4), 4.4 (m, H-5), 3.5 (m, H-6, H6'); *β-anomer* (**4β**), δ 3.56 (s, 2 H, H-1, H-1'), 4.22 (d, 1 H, $J_{3,4}$ = 5.2 Hz, H-3), 4.17 (t, 1 H, $J_{4,5}$ 4.9 Hz, H-4), 4.09 (m, H-5), 3.50 (m, 1 H, $J_{5,6}$ = 3 9, $J_{6,6'}$ = 10.0 Hz, H-6), 3.58 (m, 1 H, $J_{5,6'}$ = 4.4 Hz, H-6'); ^{13}C NMR ($CDCl_3$), **4α**, δ 70.1 (C-1), 105.4 (C-2), 82.7 (C-3), 81.8 (C-4), 86.3 (C-5), 71.0 (C-6); **4β**, δ 70.6 (C-1), 102,5 (C-2), 83.4 (C-3), 80.0 (C-4), 83.7 (C-5), 70.6 (C-6).

2-*O*-Acetyl-1,3,4,6-tetra-*O*-benzyl-α,β-D-fructofuranose (5). A solution of **2** (2.0 g, 3.7 mmol) in a mixture of acetic anhydride (2.5 mL) and dry pyridine (10 mL) was heated at 100 °C and monitored (TLC, toluene–ethyl acetate 10:1) until the reaction was complete (3 h). Excess acetic anhydride was destroyed with water (5 mL) and the mixture diluted with dichloromethane (50 mL), washed successively with sulphuric acid (0.5M, 20 mL), sodium bicarbonate solution (20 mL) and water (2 × 20 mL), then dried (magnesium sulphate) and purified by column chromatography to give **5** as a colourless syrup (0.83 g, 38%): α,β ratio 1:2, $[\alpha]_D^{22}$ +19° (*c* 4.6, $CHCl_3$); ^1H NMR ($CDCl_3$), *α-anomer* (**5α**), δ 4.00 (d, 1 H, $J_{1,1'}$ = 10.2 Hz, H-1), 4.11 (d, 1 H, H-1'), 4.46 (d, 1 H, $J_{3,4}$ = 2.5 Hz, H-3), 4.00 (m, 1 H, $J_{4,5}$ = 5.2 Hz, H-4), 3.64 (m, 1 H, $J_{5,6}$ = 4.8, $J_{6,6'}$ = 10.4 Hz, H-6), 3.58 (m, 1 H, $J_{5,6'}$ = 5.4 Hz, H-6'), 1.88 (s, 3 H, CH_3CO); *β-anomer* (**5β**), δ 3.80 (d, 1 H, $J_{1,1'}$ = 10.7 Hz, H-1), 4.06 (d, 1 H, H-1'), 4.43 (m, H-3), 4.35 (m, H-4), 4.14 (m, H-5), 3.59 (d, 2 H, $J_{5,6}$ = $J_{5,6'}$ = 4.2 Hz, H-6, H-6'), 2.04 (s, 3 H, CH_3CO); ^{13}C NMR ($CDCl_3$), **5α**, δ 68.2 (C-1), 110.9 (C-2), 83.5 (C-3), 82.8

(C-4), 86.5 (C-5), 69.6 (C-6), 23.1 (CH$_3$), 171.0 (CO); 5β, δ 70.4 (C-1), 107.0 (C-2), 82.7 (C-3), 80.7 (C-4), 84.2(C-5), 70.8 (C-6), 22.2 (CH$_3$), 169.2 (CO).

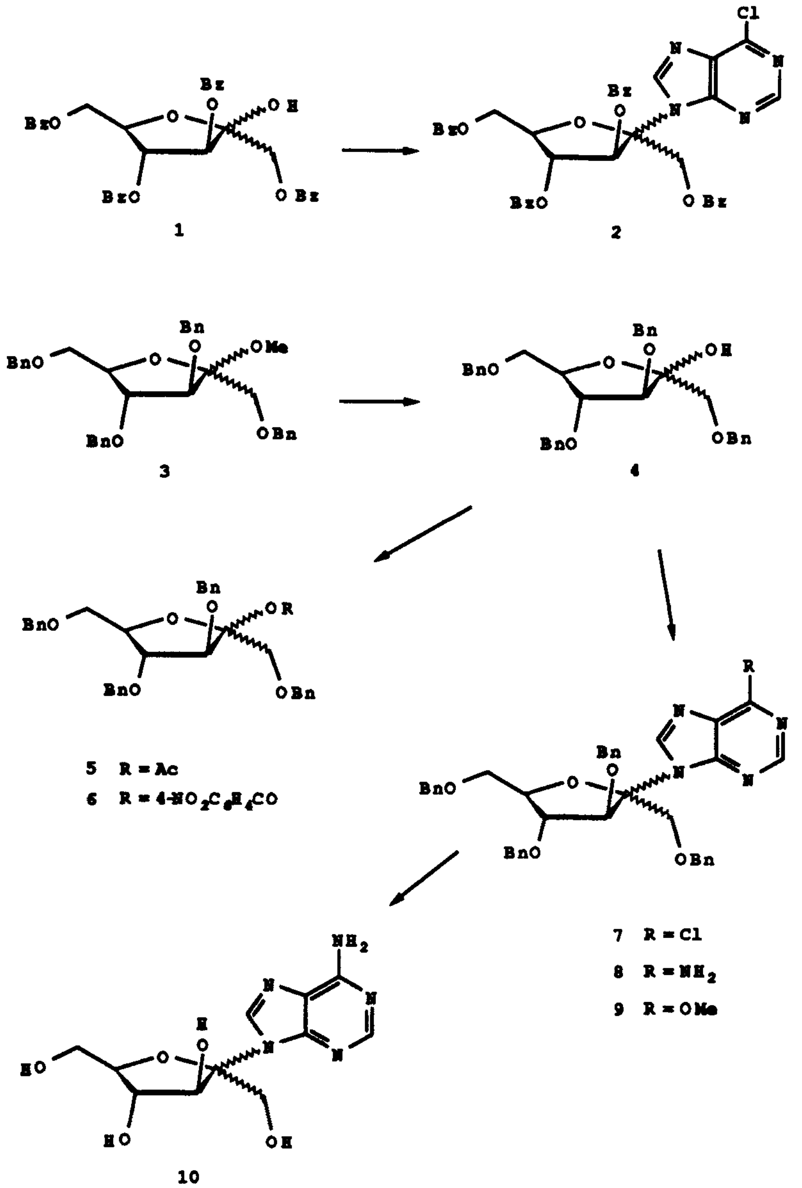
1,3,4,6-Tetra-*O*-benzyl-2-*O*-(4-nitrobenzoyl)-α-D-fructofuranose (6). Compound 4 (10.0 g, 18 mmol) was added portionwise to a stirred solution of 4-nitrobenzoyl chloride (6.8 g, 36 mmol) in pyridine (60 mL) at –5 °C. Stirring was continued for 15 h at 4 °C and a further 6 h at 20 °C until the reaction was complete (TLC, toluene-ethyl acetate 10:1). Water (10 mL) was added, the mixture stirred for 30 min then diluted with dichloromethane (150 mL), washed succesively with water (2 × 80 mL), ice cold hydrochloric acid (1M, 2 × 80 mL), and sodium bicarbonate solution (2 × 80 mL), then dried (magnesium sulphate) and concentrated to a syrup which crystallised from acetone/methanol to give 6 (5.9 g, 48%). After recrystallisation from the same solvent the product had mp 66-67 °C; $[\alpha]_D^{26}$ +37° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$), *α-anomer* (6α), δ 4.19 (d, 1 H, $J_{1,1'}$ = 10.5 Hz, H-1), 4.32 (d, 1 H, H-1'), 4.515 (d, 1 H, $J_{3,4}$ = 1.7 Hz, H-3), 4.045 (m, 1 H, $J_{4,5}$ = 4.0 Hz, H-4), 4.6 (m, 1 H, H-5), 3.68 (m, 1 H, $J_{5,6}$ = 5.2, $J_{6,6'}$ = 10.5 Hz, H 6), 3.585 (m, 1 H, $J_{5,6'}$ = 6.2 Hz, H-6'); ^{13}C NMR (CDCl$_3$), 6α, δ 67.6 (C-1), 112.6 (C-2), 84.4 (C-3), 83.5 (C-4), 85.8 (C-5), 69.7 (C-6). Anal. Calc for $C_{41}H_{39}NO_9$: C, 71.40; H, 5.7; N, 2.03. Found: C,71.08; H, 5.64; N, 2.00.

9-(1,3,4,6-Tetra-*O*-benzyl-α,β-D-fructofuranosyl)-6-chloropurine (7). A mixture of 6-chloropurine (1.44 g, 9.3 mmol) and triphenylphosphine (3.4 g, 13 mmol) in dry THF (60 mL) was refluxed for 60 min, then cooled to 21 °C. Diisopropyl azodicarboxylate (2.6 g, 13 mmol) was added dropwise followed by 4 (5.0 g, 9.3 mmol) in THF and the mixture refluxed for 6 h and then concentrated to a gum. This residue was diluted with a little ether and filtered. The filtrate was concentrated and chromatographed (toluene-ethyl acetate 5:1) to give 7 as two syrup fractions: α-anomer (0.77 g, 12%), $[\alpha]_D^{22}$ +25.6° (*c* 5.8, MeOH), β-anomer (2.3 g, 37%) $[\alpha]_D^{22}$ +13.3° (*c* 2.2, MeOH); ^{1}H NMR (CDCl$_3$), *α-anomer* (7α), δ 3.99 (d, 1 H, $J_{1',1''}$ = 10.8 Hz, H-1'), 4.2 (m, H-1''), 5.299 (d, 1 H, $J_{3',4'}$ = 0.8 Hz, H-3'), 4.004 (m, 1 H, H-4'), 4.49 (m, 1 H, H-5'), 3.75 (m, 1 H, $J_{5',6'}$ = 5.9 Hz, $J_{6',6''}$ = 10.0 Hz, H-6'), 3.60 (m, 1 H, $J_{5',6''}$ = 7.4 Hz, H-6''), 8.45 (s, 1 H, H-2), 8.37 (s, 1 H, H-8), 6.68 (m, 2 H, H-ortho), 6.85 (m, 2 H, H-ortho); *β-anomer* (7β), δ 3.64 (m, 1 H, H-6'), 3.68 (m, 1 H, H-6''), 8.45 (s, 1 H, H-2), 8.72 (s, 1 H, H-8), 6.72 (m, 2 H, H-ortho); ^{13}C NMR (CDCl$_3$), 7α, δ 69.4 (C-1'), 99.7 (C-2'), 85.3 (C-3'), 83.1 (C-4'), 85.3 (C-5'), 69.8 (C-6'), 150.9 (C-2), 150.8 (C-4), 132.8 (C-5), 150.5 (C-6), 144.7 (C-8); 7β, δ 68.3 (C-1'), 97.2 (C-2'), 81.8 (C-3'), 80.9 (C4'), 84.1 (C-5'), 69.9 (C-6'), 150.9 (C-2), 151.1 (C-4), 132.4 (C-5), 150.6 (C-6), 145.2 (C-8).

6-Amino-9-(1,3,4,6-tetra-*O*-benzyl-α,β-D-fructofuranosyl)purine (8) and 9-(1,3,4,6-Tetra-*O*-benzyl-α,β-D-fructofuranosyl)-6-methoxypurine (9). Compound 7 1.0 g, 1.4 mmol) and methanol, saturated with dry NH$_3$, (15 mL) were heated in a sealed reaction vessel at 35 °C for 48 h. Removal of the solvent in vacuo gave a gum which was chromatographed (toluene-ethyl acetate 5:1). The first component eluted was the β-anomer of **9** (0.2 g, 20%), $[\alpha]_D^{22}$ +35.2° (*c* 2.0, MeOH) and the second component was the α-anomer of **9** (0.1 g, 10%), $[\alpha]_D^{22}$ +24.3° (*c* 0.4, MeOH); ^1H NMR ($CDCl_3$), *α-anomer* (**9**α), δ 3.99 (d, 1 H, $J_{1',1''}$ = 10.8 Hz, H-1'), 4.20 (d, 1 H, H-1"), 5.38 (d, 1 H, $J_{3',4'}$ = 0.8 Hz, H-3'), 4.01 (m, 1 H, $J_{4',5'}$ = 2.8 Hz, H-4'), 4.46 (m, H-5'), 3.75 (m, 1 H, $J_{5',6'}$ = 5.7, $J_{6',6''}$ = 10.1 Hz, H-6'), 3.61 (m, 1 H, $J_{5',6''}$ = 7.0 Hz, H-6"), 8.34 (s, 1 H, H-2), 8.20 (s, 1 H, H-8), 6.77 (m,2 H, H-ortho), 6.91 (m, 2 H, H-ortho), 4.19 (s, 3 H, OMe); *β-anomer* (**9**β), δ 4.32 (d, 1 H, $J_{1',1''}$ = 10.8 Hz, H-1'), 4.44 (d, 1 H, H-1"), 4.45 (d, 1 H, $J_{3',4'}$ = 4.0 Hz, H-3'), 4.20 (m, 1 H, $J_{4',5'}$ = 5.2 Hz, H-4'), 4.32 (m, H-5'), 3.67 (d, 2 H, $J_{5',6'}$ = $J_{5',6''}$ = 4.8 Hz, H-6',H-6"), 8.33 (s, 1 H, H-2), 8.50 (s, 1 H, H-8), 6.77 (m, 2 H, H-ortho), 4.17 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$), **9**α, δ 70.2 (C-1'), 99.2 (C-2'), 84.8 (C-3'), 83.6 (C-4'), 84.9 (C-5'), 70.3 (C-6'), 151.2 (C-2), 122.5 (C-5), 141.7 (C-8), 54.1 (OMe); **9**β, δ 68.6 (C-1'), 96.9 (C-2'), 81.6 (C-3'), 81.3 (C-4'), 84.2 (C-5'), 69.9 (C-6'), 151.1 (C-2), 122.0 (C-5), 161.0 (C-6), 142.1 (C-8), 54.1 (OMe).

Further elution of the column (ethyl acetate-ethanol 9:1) gave **8** as an anomeric mixture (0.32 g, 32%), α,β ratio 1:2, $[\alpha]_D^{22}$ +3.0° (*c* 3.4, MeOH); ^1H NMR ($CDCl_3$), *α-anomer* (**8**α), δ 4.01 (d, 1 H, $J_{1',1''}$ = 10.8 Hz, H-1'), 5.40 (d, 1 H, $J_{3',4'}$ = 1.0 Hz, H-3'), 4.00 (m, 1 H, $J_{4',5'}$ = 2.6 Hz, H-4'), 3.75 (m, 1 H, $J_{5',6'}$ = 5.7 Hz, $J_{6',6''}$ = 10.1 Hz, H-6'), 3.61 (m, 1 H, $J_{5',6''}$ = 7.0 Hz, H-6"), 8.19 (s, 1 H, H-2), 8.10 (s, 1 H, H-8), 6.77 (m, 2 H, H-ortho), 6.93 (m, 2 H, H-ortho); *β-anomer* (**8**β), δ 4.33 (d, 1 H, $J_{1',1''}$ = 10.8 Hz, H-1'), 4.20 (q, 1 H, $J_{3',4'}$ = 4.0 Hz, $J_{4',5'}$ = 5.0 Hz, H-4), 3.68 (m, 2 H, $J_{5',6'}$ = $J_{5',6''}$ = 4.9 Hz, H-6', H-6"), 8.19 (s, 1 H, H-2), 8.39 (s, 1 H, H-8), 6.80 (m, 2 H, H-ortho); ^{13}C NMR ($CDCl_3$), **8**α, δ 69.9 (C-1'), 99.0 (C-2'), 84.8 (C-3'), 83.6 (C-4'), 84.6 (C-5'), 69.9 (C-6'), 150.1 (C-2), 149.3 (C-4), 120.8 (C-5), 155.25 (C-6), 140.1 (C-8); **8**β, δ 68.6 (C-1'), 96.7 (C-2'), 81.3 (C-3'), 81.3 (C4'), 84.1 (C-5'), 70.2 (C-6'), 152.1 (C-2), 148.9 (C-4), 120.3 (C-5), 155.3 (C-6), 140.5 (C-8).

6-Amino-9-(α,β-D-fructofuranosyl)purine (10). A mixture of the O-protected nucleoside **9** (1.0 g, 1.5 mmol), in methanol (30 mL), 10% palladium on carbon (2.4 g) and hydrazine hydrate (80% grade, 1.5 mL) was refluxed until the reaction was complete (TLC), about 20 min. The catalyst was removed by filtration and the filtrate concentrated and chromatographed to afford a white foam (0.41 g, 93%), α,β ratio 1:3; ^1H NMR (DMSO-d_6), *α-anomer* (**10**α), δ 4.84 (d, 1 H, $J_{3',4'}$ = 3.5 Hz, H-3'), 3.99 (m, 1 H, H-4'), 3.59 (m, 1 H, $J_{5',6'}$ = 4.6 Hz, $J_{6',6''}$ = 12.0 Hz, H-6'), 8.115 (s, 1 H, H-2), 7.97 (s, 1 H, H-8); *β-anomer* (**10**β), δ 4.04 (d, 1 H, $J_{1',1''}$ = 12.0 Hz, H-1'), 4.22 (d, 1 H, H-1"), 4.26 (d, 1 H, $J_{3',4'}$ = 6.5 Hz, H-3'), 4.03 (m, 1 H, $J_{4',5'}$ = 7.0 Hz, H-4'), 3.81 (m, 1 H, H-5') 3.66 (m, 1 H, $J_{5',6'}$ = 4.1, $J_{6',6''}$ = 12.0 Hz, H-6'), 3.73 (m, 1 H, $J_{5',6''}$ = 3.0 Hz, H-6"), 8.06 (s, 1 H, H-2), 8.38 (s, 1 H, H-8), 6.90 (br s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6), **10**α, δ 61.3 (C-1'), 98.0 (C-2'), 80.6 (C-3'), 76.8 (C-4'), 86.0 (C-5'), 62.4 (C-6'), 151.5 (C-2), 149.1 (C-4), 119.5 (C-5), 155.8 (C-6), 139.3 (C-8); **10**β, δ 59.7 (C-1'), 96.5 (C-2'), 77.5 (C-3'), 73.7 (C4'), 82.7 (C-5'), 63.5 (C-6'), 151.3 (C-2), 149.1 (C-4), 119.5 (C-5), 156.0 (C-6), 140.1 (C-8).



HPLC of this anomeric mixture on a semi-preparative column (MeOH/H_2O gradient) gave clean separation of the two components, capacity factors 26.8 min, 29.5 min. The first component was the α-anomer of **10**, $[\alpha]_D^{22}$ +85° (*c* 3.2, MeOH), λ_{max} 260 nm (water), and the second component was the β-anomer of **10**, $[\alpha]_D^{22}$ −7.4° (*c* 0.97, MeOH), λ_{max} 259 nm (water).

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