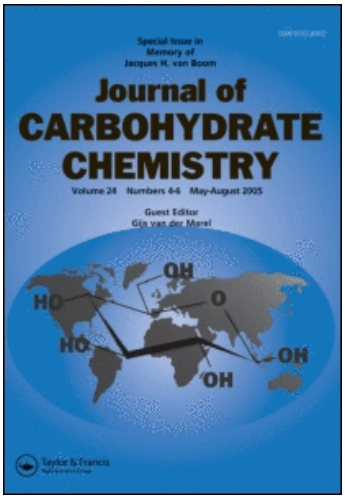

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Derivatisation of 1,3,4,6-Tetra-*O*-Benzoyl-α-D-Fructofuranose at the Anomeric Site : *O*-Alkylation, *O*-Acylation, *O*-Arylation, Amination and Selenation Reactions

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DERIVATISATION OF 1,3,4,6-TETRA-*O*-BENZOYL-α-D-FRUCTOFURANOSE AT THE ANOMERIC SITE : *O*-ALKYLATION, *O*-ACYLATION, *O*-ARYLATION, AMINATION AND SELENATION REACTIONS.

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Dedicated to Professor Henri Pacheco on the occasion of his 65th birthday

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ABSTRACT

Treatment of D-fructose with benzoyl chloride gave either 1,2,3,4,6-penta-*O*-benzoyl-α-D-fructofuranose or 1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranose (1α) which with methanol, 2-nitrophenol, or 4-nitrophenol in the presence of the Mitsunobu reagents, diisopropyl azodicarboxylate and triphenylphosphine, gave the corresponding fructofuranosides in good yield; an analogous reaction with 4-methoxybenzylamine gave the corresponding D-fructofuranosylamine. Alkylation with isopropyl alcohol or t-butyl alcohol was complicated by competition from transesterification and fructose disaccharide formation. There was little or no inversion in these reactions. The 2-*O*-acetyl derivative of 1 reacted with selenophenol and diethyl ether-boron trifluoride to give phenyl 1-deoxy-3,4,6-tri-*O*-benzoyl-2-seleno-α,β-D-fructofuranose as a minor product and phenyl 1,3,4,6-tetra-*O*-benzoyl-2-seleno-α,β-D-fructofuranose which with tris(trimethylsilyl)silane and AIBN gave 1,3,4,6-tetra-*O*-benzoyl-2,5-anhydro-D-mannitol and 1,3,4,6-tetra-*O*-benzoyl-2,5-anhydro-D-glucitol. Treatment of the acetyl derivative of 1 with Me_3SiN_3 gave 1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranosyl azide which was hydrogenated to afford the corresponding fructofuranosylamine. This compound rearranged to give *N*-benzoyl-1,4,6-tri-*O*-benzoyl-β-D-fructofuranosylamine.

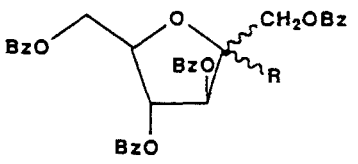
INTRODUCTION

In spite of the widespread occurrence of D-fructose in natural saccharides there has been very little study of the anomeric reactivity of this important ketose, and the variety of substituents which can be obtained at the anomeric centre (C-2) of D-fructofuranose is relatively limited. Acid catalysed methylation of selected 1- and 6-substituted fructose derivatives and of 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose (1) gives the corresponding methyl fructosides[1] but partial removal of the blocking groups can be a complication. Other standard methods of glycosidation are ineffective[1] although 4-hydroxyphenyl β-D-fructofuranoside has been reported as a very minor species obtained from sucrose.[2]

We have been particularly interested in the application of the Mitsunobu reaction[3] to the anomeric derivatisation of fructose. This reaction has been widely applied to the activation of alcohols by treatment with triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD) (or the analogous ethyl ester, DEAD). Subsequent reaction with a second alcohol affords the corresponding ether, usually with stereochemical inversion. Thus methyl α- and β-D-fructofuranosides are readily converted[4] to the corresponding 3,4-anhydro-D-tagatofuranosides, an example of intramolecular S_N2 substitution. However substitution at the tertiary anomeric site is more difficult. Guthrie *et al.*[1] reported that there was no reaction between **1** and methanol in presence of TPP and DEAD although an analogous reaction with 4-nitrophenol did give a low yield of a product which was probably the corresponding aryl fructoside. We have reinvestigated this reaction and report the successful formation of methyl and aryl fructosides in good yield. The formation of amino and seleno derivatives of **1** is also investigated.

RESULTS AND DISCUSSION

The protected fructofuranose **1** was synthesised in good yield (70%) by the treatment of D-fructose with benzoyl chloride in pyridine and dichloromethane according to the method of Brigl and Schinle.[5] Recrystallisation of the anomeric mixture (α,β ratio, 4.5:1) from ethanol gave the pure α-anomer (1α) in 62% yield. This stereochemically homogeneous material, which has not been isolated previously, was used in all subsequent Mitsunobu reactions. A similar reaction but with a smaller amount of solvent gave only 1,2,3,4,6-penta-*O*-benzoyl-α-D-fructofuranose (2α). It is evident from these results that the α-configuration

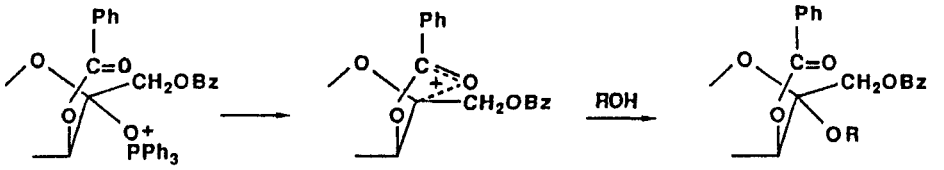


	R
1	OH
2	$OCOC_6H_5$
3	OMe
4	OC_6H_4-2-NO_2
5	OC_6H_4-4-NO_2
6	NHC_6H_4-4-OMe
7	$OCHMe_2$
8	$OCMe_3$
9	OAc
10	N_3
11	NH_2
13	SePh

of the tetra-*O*-protected fructose species is formed preferentially. Presumably this form can adopt a conformation of lower energy than that available to the corresponding β-anomer.

The configuration of 1 and 2 and all other compounds discussed below was established by inspection of the ^1H and ^{13}C NMR spectra. We find that the chemical shift of H-4 is consistently upfield of H-3 in the α-anomer whereas these two proton chemical shifts are nearly the same in most of the β-anomers. Thus the shift pattern for H-2 and H-3 is usually diagnostic of the anomeric configuration. Confirmation is found in the coupling constant $J_{3,4}$ which varies with the nature of the anomeric substituent but the range for the α-anomers is narrow (1.2 – 2.9 Hz) and does not overlap with the somewhat larger range (5.6 – 7.8 Hz) for the β-anomers. Carbon chemical shifts mostly follow the usual pattern for methyl D-fructofuranosides[1] with C-1 upfield of C-6 in both anomers and C-2 downfield in the α-anomer relative to the β-anomer. However the overall range of shifts for C-2 is too large for this shift to be of real diagnostic value. The pattern of shifts for C-3, C-4, and C-5 is also quite characteristic of the anomeric configuration.

In contrast to an earlier report,[1] 1α reacted smoothly with methanol in the presence of the Mitsunobu reagents, TPP and DIAD, to give the methyl D-fructofuranoside (3) (α,β ratio, 1:1). The analogous reactions with both 2-nitrophenol and 4-nitrophenol were also found to proceed smoothly in the presence of TPP and DIAD to give the corresponding aryl fructofuranosides (4) (α,β ratio, 4:1), and (5) (α only), respectively, in about 70% yield. The Mitsunobu reaction was extended to the amination of 1. Thus *N*-(4-methoxybenzyl)-1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranosylamine (6), (α,β ratio, 1:1) was obtained by the condensation of 4-methoxybenzylamine with 1. It is notable that in this application of the



SCHEME 1

Mitsunobu reaction to the tertiary hydroxyl (anomeric) site in fructose substitution occurs mainly with retention of configuration since the α-anomer was usually the major or even the sole product. Evidently, substitution at C-2 in D-fructose is less stereospecific than is normally associated with the Mitsunobu reaction for which inversion is usually expected. This implies a change of mechanism which may be attributed to neighbouring group participation resulting in an acyloxonium intermediate, formed *via* intramolecular cyclisation of the 3-*O*-benzoyl group (Scheme 1). This stabilises the putative carbocation in a *quasi* α-configuration and prevents inversion.

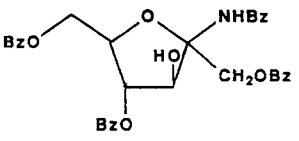
The effectiveness of the Mitsunobu method for glycosidation of **1** with a primary alcohol is evident from the reactions discussed above. This raises the interesting possibility of using this methodology to obtain disaccharides which incorporate a fructose residue. Glycosylation of **1** with suitable monosaccharides containing a free primary hydroxyl group is under investigation. In contrast to the results with primary alcohols, reaction of **1** with a secondary alcohol proved to be much less satisfactory. Treatment of **1** with isopropyl alcohol in presence of TPP and DIAD gave a mixture of several products. Examination of the NMR spectra of the mixture indicated that the main component was the pentabenzoyl derivative **2α**, ca. 50%, identified by a doublet at δ 6.456 (H-3), a quartet at 5.755 (H-4) and five carbon lines at 62.40, 63.61, 79.87, 83.05 and 109.61. This product is presumably formed by an intermolecular transesterification.

The isopropyl 1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranoside (**7**) is formed to a smaller extent, (ca. 30% of the mixture) as indicated by peaks for the α-anomer (H-3 doublet at δ 5.892, H-4 quartet at 5.550) and the β-anomer (H-3,H-4 multiplet at 6.0), with an α,β ratio of 2:1. Several other peaks in the ^{1}H NMR spectrum were attributed to species derived from coupling of two fructose moieties. This was confirmed by reacting **1** with TPP and DIAD in the absence of any other alcohol. A solid material was isolated which had the same spectral features noted above (with evidence for the formation of **2α**). Presumably disaccharide formation is implicated in these reactions but the structures were not investigated further.

An attempt to alkylate **1** at the anomeric site *via* a Mitsunobu reaction with t-butyl alcohol also gave a solid product which was a mixture of **2**, 'fructose disaccharides' and the t-butyl fructofuranoside (**8**), a 10% component identified as the α-anomer by a doublet at δ 5.87 (H-3) and a quartet at 5.48 (H-4).

Since the protected fructose **1** was available in stereochemically pure form we have investigated other reactions at the anomeric site in this system, in particular the introduction of amino and seleno functionalities to give potential precursors of novel D-fructofuranosides.

Acetylation of **1** (α,β ratio 4.5:1) with acetic anhydride gave the 2-*O*-acetyl derivative (**9**, α,β ratio 5:1) which was converted to the azide (**10**, α,β ratio, 2:1) with Me_3SiN_3 in dichloromethane. Hydrogenation of **10** over 5% palladium on charcoal afforded the corresponding D-fructofuranosylamine (**11**) which rearranged *via* an O → N migration to *N*-benzoyl-1,4,6-tri-*O*-benzoyl-β-D-fructofuranosylamine (**12**β). No evidence was found for the alternative migration involving the 1-*O*-benzoyl group.



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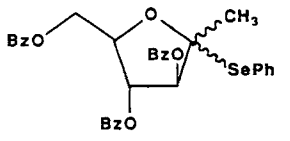

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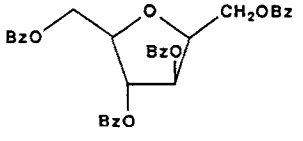

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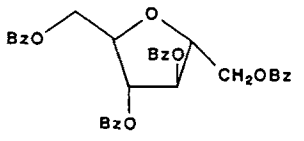

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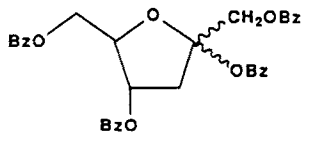

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The phenyl 2-seleno-D-fructofuranoside (**13**, α,β ratio 1:1) was obtained from **9** by treatment with selenophenol and diethyl ether-boron trifluoride. Notably, a minor byproduct obtained from this reaction was the analogous 1-deoxy-2-seleno-fructofuranoside (**14**). However, attempts to effect a reductive elimination of selenophenol[6] from **13** with

tris(trimethylsilyl)silane and azobisisobutyronitrile (AIBN) to give the 3-deoxy derivative (**17**) yielded only a mixture of the starting material and the two 2,5-anhydrohexitols (**15** and **16**). The formation of compounds **15** and **16** indicates that the glycosyl radical is produced, as expected, but that this radical is stable with respect to rearrangement. Evidently the tertiary fructosyl radical is considerably more stable than the analogous secondary ribosyl radical which readily rearranges by transfer of the adjacent benzoyloxy group to afford an analogous 2-deoxyribose derivative.[6]

EXPERIMENTAL

General Procedures. Evaporations were carried out with a Büchi rotary evaporator and a Cryocool trap, under oil pump vacuum at < 40 °C, unless otherwise specified. 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 $CDCl_3$ (77.1 p.p.m.) or Me_2SO (39.5 p.p.m.). 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. 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.

1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranose (1). Benzoyl chloride (19.0 mL, 164 mmol) was added dropwise, with vigorous stirring, to D-fructose (6.0 g, 33 mmol) in a mixture of pyridine (10 mL) and dichloromethane (70 mL). The stirring was continued at room temperature for 2.5 h. The solution was poured into ice-water (25 mL) and the organic layer separated, washed ($NaHCO_3$ soln, water) and dried ($MgSO_4$). Evaporation of the solvents gave a pasty product which was recrystallised (EtOH) to afford white crystals of **1**, (13.7 g, 70%); mp 125-126 °C; ^1H NMR data ($CDCl_3$), α-*anomer* (1α), δ 4.80 (d, 1 H, $J_{1,1'}$ = –12.0 Hz, H-1), 4.55 (d, 1 H, H-1'), 5.866 (d, 1 H, $J_{3,4}$ = 1.7 Hz, H-3), 5.592 (q, 1 H, $J_{4,5}$ = 4.7 Hz, H-4), 4.76 (m, 1 H, H-5), 4.81 (m, 1 H, H-6), 4.68 (m, 1 H, H-6'); β-*anomer* (1β), δ 4.61 (d, 1 H, H-1), 4.583 (d, 1 H, H-1'), 5.980 (d, 1 H, $J_{3,4}$ = 5.6 Hz, H-3), 5.868 (q, 1 H, $J_{4,5}$ = 4.7 Hz, H-4), 4.564 (m, 1 H, H-5), 4.98 (m, 1 H, $J_{5,6}$ = 7.3, $J_{6,6'}$ = –11.7 Hz, H-6), 4.705 (m, 1 H, $J_{5,6'}$ = 4.1 Hz, H-6'); ^{13}C NMR ($CDCl_3$), 1α, δ 65.01 (C-1), 104.59 (C-2), 81.31 (C-3), 78.59 (C-4), 81.09 (C-5), 63.79 (C-6); 1β, δ 66.70 (C-1), 102.01 (C-2), 77.60 (C-3), 77.95 (C-4), 79.74 (C-5), 65.52 (C-6). Further recrystallisation (EtOH) gave the pure α-*anomer*; mp 128 °C; $[\alpha]_D^{22}$ –11° (*c* 1.3, chloroform).

Anal. Calcd for $C_{34}H_{28}O_{10}$: C, 68.46; H, 4.70. Found: C, 68.39; H, 4.65.

1,2,3,4,6-Penta-*O*-benzoyl-α-D-fructofuranose (2α). The procedure described for **1** was used but with less dichloromethane (10 mL) and with a reaction time of 2 h. The crude product was recrystallised (EtOH) to give **2α** as white crystals (16.5 g, 80%); mp 114 °C; $[\alpha]_D^{22}$ +8° (*c* 1.3, chloroform); ^{1}H NMR ($CDCl_3$) δ 5.303 (d, 1 H, $J_{1,1'}$ = −12.1 Hz, H-1), 5.020 (d, 1 H, H-1'), 6.453 (d, 1 H, $J_{3,4}$ = 2.2 Hz, H-3), 5.754 (q, 1 H, $J_{4,5}$ = 4.7 Hz, H-4), 4.921 (m, 1 H, H-5), 4.818 (m, 1 H, $J_{5,6}$ = 3.3, $J_{6,6'}$ = −12.2 Hz, H-6), 4.730 (m, 1 H, $J_{5,6'}$ = 4.9 Hz, H-6'); ^{13}C NMR ($CDCl_3$) δ 62.42 (C-1), 109.62 (C-2), 79.89 (C-3), 77.51 (C-4), 83.07 (C-5), 63.62 (C-6).

Anal. Calcd for $C_{41}H_{32}O_{11}$: C, 70.28; H, 4.57. Found: C, 70.21; H, 4.53.

Methyl 1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranoside (3). A solution of TPP (0.29 g, 1.1 mmol) in dry methanol (6 mL) was refluxed for 40 min, cooled to room temperature and DIAD (0.22 g, 1.1 mmol) added dropwise followed by **1** (0.5 g, 0.8mmol). This mixture was refluxed (6 h) until the reaction was complete (TLC) and then the methanol was evaporated to leave a crude syrup. This crude material was applied to a column of silica gel and eluted with ethyl acetate-toluene (1:9) to afford **3** (0.3 g, 72%) as a colourless syrup; $[\alpha]_D^{22}$ −12° (*c* 1.9, chloroform); ^{1}H NMR ($CDCl_3$), α-*anomer* (3α), δ 4.975 (d, 1 H, $J_{1,1'}$ = −12.4 Hz, H-1), 4.388 (d, 1 H, H-1'), 5.878 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-3), 5.563 (q, 1 H, $J_{4,5}$ = 5.0 Hz, H-4), 4.6 (m, 1 H, H-5), 4.78 (m, 1 H, H-6), 4.7 (m, 1 H, H-6'), 3.45 (s, 3 H, OMe); β-*anomer* (3β), δ 4.66 (d, 1 H, $J_{1,1'}$ = −12.1 Hz, H-1), 4.62 (d, 1 H, H-1'), 6.108 (d, 1 H, $J_{3,4}$ = 6.9 Hz, H-3), 5.992 (d, 1 H, $J_{4,5}$ = 5.6 Hz, H-4), 4.52 (m, 1 H, H-5), 4.85 (m, 1 H, H-6), 4.72 (m, 1 H, H-6'), 3.46 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$), 3α, δ 58.92 (C-1), 107.38 (C-2), 81.05 (C-3), 78.97 (C-4), 81.45 (C-5), 63.66 (C-6), 48.98 (OMe); 3β, δ 63.14 (C-1), 103.41 (C-2), 78.00 (C-3), 77.20 (C-4), 78.83 (C-5), 65.13 (C-6), 49.97 (OMe).

2-Nitrophenyl 1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranoside (4). A mixture of 2-nitrophenol (0.25 g, 1.8 mmol) and TPP (0.29 g, 1.1 mmol) in dry THF was refluxed for 20 min, then cooled to room temperature. DIAD (0.22 g, 1.1 mmol) was added dropwise followed by **1α** (0.5g, 0.8 mmol) in THF (1.0 mL) and the mixture refluxed for 50 min. The solvent was evaporated and the resulting crude syrup applied to a column of silica gel and eluted with ethyl acetate-toluene (1:9). Crystallisation (EtOH) gave **4** (0.46 g, 77%); mp 56 °C; $[\alpha]_D^{27}$ −3° (*c* 6.7, chloroform); ^{1}H NMR ($CDCl_3$), α-*anomer* (4α), δ 4.880 (d, 1 H, $J_{1,1'}$ = −12.6 Hz, H-1), 4.735 (d, 1 H, H-1'), 6.212 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-3), 5.656 (q, 1 H, $J_{4,5}$ = 4.4 Hz, H-4), 4.77 (m, 1 H, H-5), 4.90 (m, 1 H, H-6), 4.75 (m, 1 H, H-6'); β-*anomer* (4β), δ 4.855 (d, 1 H, $J_{1,1'}$ = −12.4 Hz, H-1), 4.694 (d, 1 H, H-1'), 6.355 (d, 1 H, $J_{3,4}$ = 7.8 Hz, H-3), 6.182 (q, 1 H, $J_{4,5}$ = 6.3 Hz, H-4), 4.722 (m, 1 H, H-5), 4.955 (m, 1 H, $J_{5,6}$ = 3.1, $J_{6,6'}$ = −12.2 Hz, H-6), 4.595 (m, 1 H, $J_{5,6'}$ = 5.2 Hz, H-6'); ^{13}C NMR ($CDCl_3$), 4α, δ 60.66 (C-1), 111.12 0 (C-2), 81.61 (C-3), 77.78 (C-4), 83.44 (C-5), 63.44 (C-6); phenyl 146.32 (C-1), 143.19 (C-2), 125.46 (C-3), 123.60 (C-4), 133.78 (C-5), 121.27 (C-6); 4β, δ 61.99 (C-1), 106.19 (C-2), 76.21

(C-3), 75.72 (C-4), 80.39 (C-5), 64.07 (C-6); phenyl 146.56 (C-1), 142.78 (C-2), 125.01 (C-3), 123.32 (C-4), 133.18 (C-5), 121.21 (C-6).

Anal. Calcd for $C_{40}H_{31}NO_{12}$: C, 66.94; H, 4.35; N, 1.95. Found: C, 66.87; H, 4.40; N, 1.86.

4-Nitrophenyl 1,3,4,6-Tetra-*O*-benzoyl-α-D-fructofuranoside (5α). The procedure was identical to that described for the preparation of **4**. The product was crystallised (EtOH) to give **5α** (0.4 g, 68%); mp 66 °C; $[\alpha]_D^{27}$ −12° (*c* 1.5, chloroform); ^{1}H NMR ($CDCl_3$) δ 4.917 (d, 1 H, $J_{1,1'}$ = −12.3 Hz, H-1), 4.680 (d, 1 H, H-1'), 6.229 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-3), 5.647 (q, 1 H, $J_{4,5}$ = 4.2 Hz, H-4), 4.89 (m, 1 H, H-5), 4.790 (m, 1 H, H-6), 4.75 (m, 1 H, H-6'); ^{13}C NMR ($CDCl_3$) δ 60.12 (C-1), 110.43 (C-2), 81.45 (C-3), 78.12 (C-4), 82.98 (C-5), 63.35 (C-6); phenyl 158.82 (C-1), 120.37 (C-2), 125.71 (C-3), 143.62 (C-4).

Anal. Calcd for $C_{40}H_{31}NO_{12}$: C, 66.94; H, 4.35; N, 1.95. Found : C, 66.82; H, 4.39; N, 1.93.

***N*-(4-Methoxybenzyl)-1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranosylamine (6).** A solution of 4-methoxybenzylamine (0.2 g, 1.4 mmol), TPP (0.3 g, 1.1 mmol), DIAD (0.22 g, 1.1 mmol) and **1α** (0.5 g, 0.8 mmol) in tetrahydrofuran (6 mL) was stirred at room temperature under anhydrous conditions for 18 h. The solution was concentrated under reduced pressure, diluted with a small quantity of ether and filtered. The filtrate, after concentration, was applied to a column of silica gel and eluted with toluene-ethyl acetate (5:1) to give **6** as a syrup (0.23 g, 40%); $[\alpha]_D^{27}$ −9° (*c* 2.2, chloroform); ^{1}H NMR ($CDCl_3$), α-*anomer* (**6α**), δ 6.45 (d, 1 H, $J_{3,4}$ = 2.4 Hz, H-3), 5.75 (q, 1 H, $J_{4,5}$ = 4.8 Hz, H-4), 3.75 (s, 3 H, OMe); β-*anomer* (**6β**), δ 6.32 (m, 2 H, H-3, H-4), 3.80 (s, 3 H, OMe).

Isopropyl 1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranoside (7). The procedure used was analogous to that described for the formation of **4** except that 3 mol equivalents of isopropyl alcohol (0.2 mL, 2.6 mmol) was used and the reaction mixture set aside overnight. The material obtained after elution from a column of silica gel was a mixture of at least five components, including the α-anomer (**7α**) and β-anomer (**7β**) of the expected isopropyl D-fructofuranoside, the pentabenzoyl derivative **2α**, and two other compounds, probably fructose disaccharides; ^{1}H NMR ($CDCl_3$), **2α**, δ 6.456 (d, 1 H, $J_{3,4}$ = 2.4 Hz, H-3), 5.755 (q, 1 H, $J_{4,5}$ = 4.5 Hz, H-4); **7α**, δ 5.892 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-3), 5.500 (q, 1 H, $J_{4,5}$ = 4.5 Hz, H-4); **7β**, δ 6.0 (m, 2 H, H-3, H-4); ^{13}C NMR ($CDCl_3$), **7α**, δ 60.84 (C-1), 107.83 (C-2), 81.75 (C-3), 78.93 (C-4), 81.48 (C-5), 63.39 (C-6), 24.5, 24.2 (two Me).

t-Butyl 1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranoside (8). The procedure was the same as that described for **7** but using t-butyl alcohol (1 mL, 10.4 mmol). After purification on a column of silica gel the product was a mixture of **2α**, fructose disaccharides and **8α** as a minor component; ^{1}H NMR ($CDCl_3$), δ 5.87 (d, 1 H, $J_{3,4}$ 1.5 Hz, H-3), 5.48 (q, 1 H, $J_{4,5}$ = 4.5 Hz, H-4).

2-*O*-Acetyl-1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranose (9). Compound **1** (45.0 g, 70 mmol) was dissolved in acetic anhydride (10 mL) at 80 °C and sodium acetate (10 g, 117 mmol) was added. After heating and stirring for 10 h, the reaction mixture was cooled, poured on to crushed ice (250 mL), stirred for 5 h and then extracted with dichloromethane (200 mL). The extract was washed ($NaHCO_3$ soln, water), dried ($MgSO_4$), and concentrated to a crude syrup which was applied to a column of silica gel. Elution with hexane-ethyl acetate (3:1) gave a clear syrup (25 g, 52%); $[\alpha]_D^{20}$ –20° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$), α-*anomer* (**9α**), δ 5.06 (d, 1 H, H-1), 4.83 (d, 1 H, H-1'), 6.349 (d, 1 H, $J_{3,4}$ = 2.9 Hz, H-3), 5.728 (q, 1 H, $J_{4,5}$ = 5.5 Hz, H-4), 4.81 (m, 1 H, H-5), 4.77 (m, 1 H, H-6), 4.68 (m, 1 H, H-6'), 2.16 (Me); β-*anomer* (**9β**), δ 6.22 (d, 1 H, H-1), 6.19 (d, 1-H, H-1'), 6.220 (d, 1 H, $J_{3,4}$ = 5.6 Hz, H-3), 6.195 (q, 1 H, $J_{4,5}$ = 5.4 Hz, H-4), 2.02 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$), **9α**, δ 62.42 (C-1), 108.71 (C-2), 79.67 (C-3), 77.32 (C-4), 82.10 (C-5), 63.62 (C-6); **9β**, δ 64.70 (C-1), 105.01 (C-2), 77.59 (C-3), 77.23 (C-4), 80.32 (C-5), 65.38 (C-6).

Anal. Calcd for $C_{36}H_{30}O_{11}$: C, 67.71; H, 4.70. Found: C, 67.60; H, 4.75.

1,3,4,6-Tetra-*O*-benzoyl-α,β-D-fructofuranosyl azide (10). Azidotrimethylsilane (0.31 mL, 2.3 mmol) was added to a solution of **9** (1.2 g, 1.9 mmol) in dichloromethane (2 mL) followed by dropwise addition of a solution of titanium tetrachloride (0.25 mL) in dichloromethane. This mixture was stirred for 2.5 h, then diluted with dichloromethane (3 mL), and the organic layer washed (water, $NaHCO_3$ soln, water) and dried ($MgSO_4$). After evaporation of the solvent, the resulting crude syrup was applied to a column of silica gel and eluted using ethyl acetate-hexane (1:2) to give **10** (0.75 g, 63%) as a syrup; $[\alpha]_D^{20}$ 0° (*c* 1.0, chloroform), +2° (*c* 1.0, dimethylformamide); ^1H NMR ($CDCl_3$), α-*anomer* (**10α**), δ 4.89 (d, 1 H, $J_{1,1'}$ = –12 Hz, H-1), 4.66 (d, 1 H, H-1'), 5.783 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-3), 5.629 (q, 1 H, $J_{4,5}$ = 4.2 Hz, H-4), 4.7-4.8 (m, H-5, H-6, H-6'); β-*anomer* (**10β**), δ 6.02 (d, 1 H, $J_{3,4}$ = 5.7 Hz, H-3), 6.00 (t, 1 H, $J_{4,5}$ = 5.5, H-4), 4.7-4.8 (m, H-5, H-6, H-6'); ^{13}C NMR ($CDCl_3$), **10α**, δ 63.35 (C-1), 98.54 (C-2), 80.55 (C-3), 78.54 (C-4), 83.35 (C-5), 63.89 (C-6); **10β**, δ 63.93 (C-1), 95.93 (C-2), 77.73 (C-3), 76.60 (C-4), 78.87 (C-5), 65.92 (C-6).

The azide **10** (3.0 g, 4.8 mmol) in DMF (40 mL) was hydrogenated quantitatively over palladium (5%) on charcoal (0.312 g) at atmospheric pressure and room temperature for 20 h (or alternatively at 140 bar for 10 h). The catalyst was removed by filtration and the filtrate evaporated to give **1,3,4,6-tetra-*O*-benzoyl-α,β-D-fructofuranosylamine (11)** as a colourless syrup; $[\alpha]_D^{20}$ –113° (*c* 0.22, dimethylformamide); ^1H NMR ($CDCl_3$) δ 5.7 – 5.9 (m, 2 H, H-3, H-4), 4.4-5.0 (m, 5 H, H-1, H-1', H-5, H-6, H-6'), 2.3 (s, 2 H, NH_2). If this syrup is taken up in THF then spontaneous rearrangement occurs after 12-24 h to afford ***N*-benzoyl-1,4,6-tri-*O*-benzoyl-β-D-fructofuranosylamine** (**12β**). This rearrangement also occurs in EtOH at 95 °C in 2 h or on a column of silica gel when eluted with hexane-ethyl acetate (1:1). Thus **12β** was obtained in quantitative yield as colourless crystals mp 207-208 °C; $[\alpha]_D^{20}$ –11° (*c* 1.0, dimethylformamide); ^1H NMR (DMSO) δ 8.15 (s, 1 H, NH), 6.47 (d, 1 H,

$J_{3,OH}$ = 5.6 Hz, OH-3), 5.82 (t, 1 H, $J_{3,4}$ = 5.6, $J_{4,5}$ = 5.6 Hz, H-4), 4.96 (d, 1 H, $J_{1,1'}$ 11.9 Hz, H-1), 4.93 (d, 1 H, H-1'), 4.78 (t, 1 H, H-3), 4.58 (m, 2 H, H-6, H-6'), 4.5 (m, 1 H, H-5).

Anal. Calcd for $C_{34}H_{29}NO_9$: C, 68.57; H, 4.87; N, 2.35. Found : C, 68.77; H, 4.83; N, 2.42.

Phenyl 1,3,4,6-Tetra-*O*-benzoyl-2-seleno-α,β-D-fructofuranoside (13) and **Phenyl 1-Deoxy-3,4,6-tri-*O*-benzoyl-2-seleno-α,β-D-fructofuranoside (14).** Boron trifluoride etherate (0.327 mL) was added at 0 °C under N_2 to a solution of **9** (1.8 g, 2.8 mmol) and selenophenol (0.44 mL, 4.2 mmol) in chloroform (29 mL). After 2 h the reaction mixture was washed ($NaHCO_3$ soln, water), dried ($MgSO_4$), the solvent removed and the residue applied to a column of silica gel and eluted with ethyl acetate-hexane (1:3) to give **13** (1.45 g, 70%) as a syrup; ^1H NMR ($CDCl_3$), α-*anomer*, (13α) δ 6.058 (d, 1 H, $J_{3,4}$ = 2.6, $J_{3,Se}$ = 9.9 Hz, H-3), 5.720 (q, 1 H, $J_{4,5}$ = 6.2 Hz, H-4); β-*anomer*, (13β) δ 6.355 (d, 1 H, $J_{3,4}$ = 2.6, $J_{3,Se}$ = 4.2 Hz, H-3), 6.18 (t, 1 H, $J_{4,5}$ = 6.0 Hz, H-4); ^{13}C NMR ($CDCl_3$), **13α**, δ 62.33 (C-1), 93.04 (C-2), 63.35 (C-6); **13β**, δ 64.11 (C-1), 92.57 (C-2), 66.86 (C-6).

Anal. Calcd for $C_{40}H_{32}O_9Se$: C, 65.31; H, 4.35. Found: C, 65.41; H, 4.80.

A second eluted component (14) was obtained as a syrup (0.08 g); ^1H NMR ($CDCl_3$), α-*anomer* (**14α**), δ 5.770 (d, 1 H, $J_{3,4}$ = 1.7, $J_{3,Se}$ = 9.0 Hz, H-3), 5.552 (q, 1 H, $J_{4,5}$ = 5.6 Hz, H-4), 4.81 (m, 1 H, H-5), 4.77 (m, 1 H, H-6), 4.66 (m, 1 H, H-6'), 1.68 (s, 3 H, Me); β-*anomer* (14β), δ 5.833 (d, 1 H, $J_{3,4}$ = 6.0 Hz, H-3), 5.978 (t, 1 H, $J_{4,5}$ = 5.0 Hz, H-4), 4.66 (m, 1 H, H-5), 4.92 (m, 1 H, H-6), 4.84 (m, 1 H, H-6'), 1.76 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$), **14α**, δ 24.09 (C-1), 92.91 (C-2), 80.93 (C-3), 79.38 (C-4), 83.77 (C-5), 63.59 (C-6); **14β**, δ 29.60 (C-1), 92.90 (C-2), 80.05 (C-3), 78.41 (C-4), 82.72 (C-5), 64.50 (C-6).

1,3,4,6-Tetra-*O*-benzoyl-2,5-anhydro-D-mannitol (15) and **1,3,4,6-Tetra-*O*-benzoyl-2,5-anhydro-D-glucitol (16).** Tris(trimethylsilyl)silane (0.042 g, 0.168 mmol) and AIBN (4.6 mg, 0.028 mmol) were added to a solution of **13** (0.1 g, 0.14 mmol) in toluene (2.8 mL) and the resulting mixture was heated under N_2 for 2 h at 80 °C. After evaporation, the residue was applied to a column of silica gel and eluted with ethyl acetate-hexane (1:3). A mixture was obtained (32 mg) consisting of unreacted **13** and the epimeric pair of 2,5-anhydro-D-hexitols, **15** and **16** (3:2, by ^1H NMR); ^1H NMR ($CDCl_3$), **13**, δ 5.880 (q, 1 H, $J_{2,3}$ = 4.0, $J_{3,4}$ = 1.2 Hz, H-3), 5.614 (q, 1 H, $J_{4,5}$ = 3.6 Hz, H-4), 4.46 (m, 1 H, H-2); **14**, δ 5.77 (m, 2 H, H-2, H-3).

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