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Synthesis of 4-deoxy and 4-deoxy-4-halogeno derivatives of L-fucose as potential enzyme inhibitors

Thisbe K. Lindhorst and Joachim Thiem*
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Orléans-Ring 23, D-4400 Münster (F.R.G.)

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ABSTRACT

Methyl 2,3-di-*O*-benzoyl-6-deoxy-α-L-galactopyranoside (**2**) was converted into the 4-deoxy-4-iodo-α-L-*gluco* derivative **4** by triflate-mediated inversion. Catalytic reduction of **4** gave methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-α-L-*xylo*-hexopyranoside (**6**) and subsequent *O*-debenzoylation gave methyl 4,6-dideoxy-α-L-*xylo*-hexopyranoside (**7**). Selective benzoylation of L-fucose gave 1,2,3-tri-*O*-benzoyl-α-L-fucopyranose (**14**). An analogous sequence of reactions, based on the inversion of configuration at C-4, yielded 4,6-dideoxy-4-iodo-L-glucopyranose (**17**) and 4,6-dideoxy-L-*xylo*-hexopyranose (**19**). Reaction of the 4-trifluoromethanesulfonate (**15**) of **14** with sodium fluoride in *N*,*N*-dimethylformamide gave 1,2,3-tri-*O*-benzoyl-6-deoxy-4-*O*-formyl-α-L-glucopyranose (**12**) and 1,2,3-tri-*O*-benzoyl-4,6-dideoxy-α-L-*threo*-hex-4-enopyranose (**13**). Treatment of **14** with diethylaminosulfur trifluoride and then *O*-debenzoylation gave 4,6-dideoxy-4-fluoro-L-glucopyranose (**11**). Reaction of **15** with sodium iodide in *N*,*N*-dimethylformamide gave 1,2,3-tri-*O*-benzoyl-4,6-dideoxy-4-iodo-α-L-glucopyranose (**16**). The α-glycosyl bromide (**20**) derived from **16** reacted stereoselectively with dibenzyl phosphate to give the β- (**21**) or α-glycosyl dibenzyl phosphate (**22**).

INTRODUCTION

The considerable biological interest in glycoconjugates is based on their important role in, for example, cell–cell recognition, cell specification, and control of cell growth[1]. L-Fucose, which is a component of many glycolipids and glycoproteins, is frequently found at the non-reducing ends of oligosaccharide chains, or bound to other strategic sites such as the protein-linked GlcNAc residue[2].

The presumption that, because of its antennal position in glycoconjugates, L-fucose is of particular importance in cell biochemistry is supported by the fact that, in cancer tissue, enhanced concentrations of L-fucose are observed and higher activities of fucosyltransferase have been demonstrated[3].

Transferases attach L-fucose from GDP-fucose to a growing oligosaccharide chain, and GDP-fucose is synthesised[4] by phosphorylation of L-fucose and reaction of the resulting L-fucosyl phosphate with GTP.

In order to elucidate the biochemical significance of L-fucose, derivatives are needed which serve as inhibitors or modulators of fucosyltransferases. It has been

* Author for correspondence. Present address: Insitut für Organische Chemie der Universität Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, F.R.G.

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demonstrated that methyl α-L-fucopyranoside is an inhibitor of fucokinase and fucose 1-phosphate pyrophosphorylase[5].

We now report on the syntheis of 4-deoxy and 4-deoxy-4-halogeno derivatives of L-fucose as potential enzyme inhibitors, since fucose-specific enzymes may use the axial HO-4 in L-fucose as a recognition site.

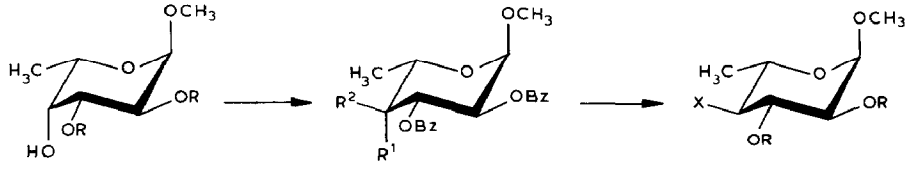
RESULTS AND DISCUSSION

The axial HO-4 of L-fucose is the least reactive towards benzoylation, a fact which led to the synthesis[6] of methyl 2,3-di-*O*-benzoyl-6-deoxy-α-L-galactopyranoside (**2**) from the methyl glycoside **1**. By using a slightly modified procedure, the yield could be raised from 80% to 95%.

Several methods for the 4-deoxygenation of **2** were attempted. Following the Barton–McCombie procedure[7], the 4-xanthate **5** was prepared from **2**, using sodium hydroxide–dimethyl sulfoxide[8], but was isolated in pure form only once. Reduction of **5** with tributyltin hydride gave the 4-deoxy derivative **6** that was detected by t.l.c. but not isolated in pure form.

Application to **2** of a modified Mitsunobu reaction with the ZnI_2–PPh_3–diethyl azodicarboxylate (DEAD) system[9] gave the 4-deoxy-4-iodo-L-*gluco* compound **4** (~30%). Reaction of the 4-triflate (**3**) of **2** with sodium iodide gave **4** in excellent yield, whereas the corresponding 3-mesylate[6] did not react under similar conditions. The labile 4-triflate **3** was usually reacted immediately to give other products, but could be isolated for analysis by n.m.r. spectroscopy. As expected, H-4 was deshielded. The ^{1}H-n.m.r. spectrum of **4** showed typical *gluco* couplings and the dd systems of H-3 and H-4 were simplified to triplets. Due to the +M effect of I-4, the resonance of H-4 was shifted to higher field (δ 3.87).

Zemplén *O*-deacetylation of **4** gave **8**, and catalytic reduction gave **6**, which was deprotected to give methyl 4,6-dideoxy-α-L-*xylo*-hexopyranoside (**7**). The site of deoxygenation was assigned on the basis of the ^{1}H-n.m.r. spectrum. The signal for H-4*eq* appeared as a ddd [δ 2.35 (**6**) and 1.64 (**7**)], whereas that for H-4*ax* was a quartet at higher field [δ 1.67 (**6**) and 1.16 (**7**)]. As a result of the 4-deoxygenation, the signals for H-3 and H-5 were complex multiplets.



1 R = H
2 R = Bz

3 R^1 = OSO_2CF_3, R^2 = H
4 R^1 = H, R^2 = I
5 R^1 = OC(S)SCH_3, R^2 = H

6 R = Bz, X = H
7 R = H, X = H
8 R = H, X = I

Formation of the pyranose derivatives **17** and **19** from the methyl pyranosides **8** and **7**, respectively, required rather forcing conditions. Therefore, it was desirable to start from a precursor other than **2**. Selectively esterified carbohydrates are useful precursors for specific functionalisation, and selective benzoylations have been performed with pyranosides and pyranoses[10–13]. Treatment of L-fucose with benzoyl chloride–pyridine at −40° for 12 min gave 65% of 1,2,3-tri-*O*-benzoyl-α-L-fucopyranose (**14**) with only a small proportion of the tetrabenzoate. Due to the lack of a primary hydroxyl group, this is a straightforward reaction. The order of reactivity towards benzoylation was shown[14] to be HO-3 > HO-2 > HO-4.

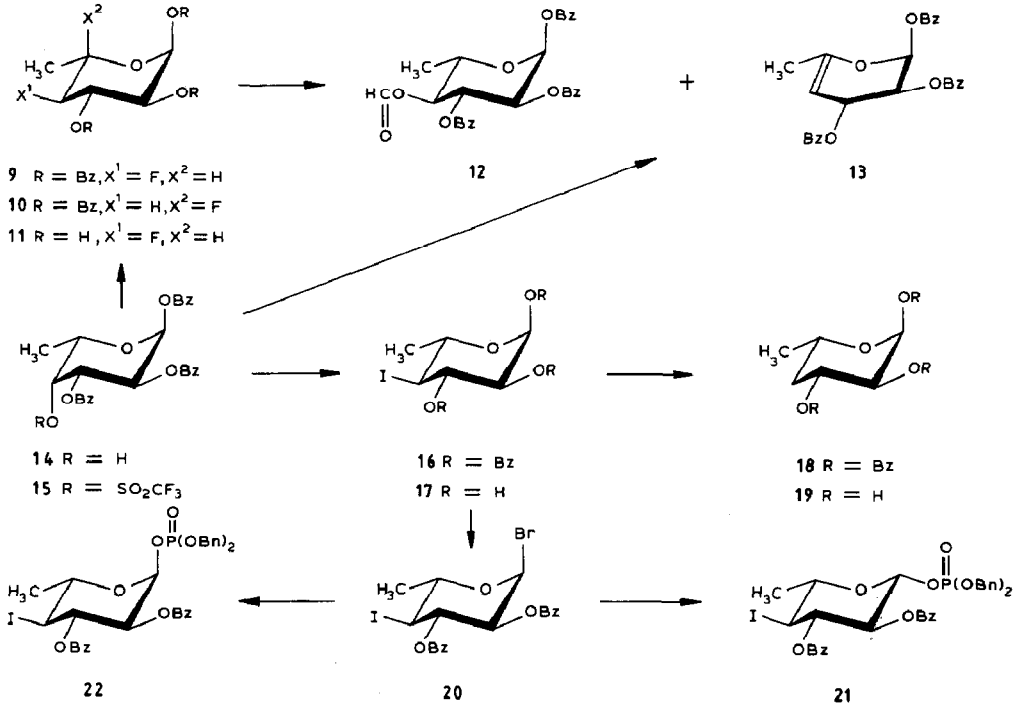
Treatment of **14** with triflic anhydride gave the 4-triflate **15**, which was converted into the 4-deoxy-4-iodo-L-*gluco* derivative **16** and thence into 4,6-dideoxy-4-iodo-α,β-L-glucopyranose (**17**). Hydrogenation of **16** gave the 4,6-dideoxy derivative **18**, Zemplén *O*-deacylation of which gave 4,6-dideoxy-α,β-L-*xylo*-hexopyranose (**19**). The n.m.r. spectra of the α,β-mixtures **17** and **19** were complex, but could be interpreted fully.

The 4-deoxy-4-fluoro-L-*gluco* compound **9** could not be synthesised by a route analogous to that for the iodide **16**. Reaction of the 4-triflate **15** with sodium or tetrabutylammonium fluoride in *N*,*N*-dimethylformamide gave 43% of the 4-*O*-formyl-L-*gluco* derivative **12** together with 4% of the labile elimination product **13**. Due to the low nucleophilicity of the fluoride anion, **12** was formed by an S_N2 attack of the carbonyl oxygen of *N*,*N*-dimethylformamide at C-4 of **15** and hydrolysis of the resulting iminium cation $RCOCH\overset{+}{N}Me_2$. A similar species has been suggested[15] for the chlorination of primary hydroxyl groups by methanesulfonyl chloride in *N*,*N*-dimethylformamide. There was evidence for the 4-*O*-formyl group in the ^{1}H-n.m.r. spectrum of **12**, which contained a signal at δ 7.99 (s) that was correlated with the ^{13}C signal at δ 164.4. Accordingly, the signal for H-4 appeared at lower field (t, δ 5.24). Compound **13** can be regarded as a *C*-glycal, and its structure was confirmed by irradiation experiments and a COSY spectrum. Because of long-range coupling ($J_{4,6}$ 1.0 Hz), the signal for H-6,6,6 appeared as a doublet.

After treatment of the 4-triflate **15** under reflux with sodium fluoride in benzene and h.p.l.c., 9% of the 4-deoxy-4-fluoro-α-L-*gluco* derivative **9** was isolated. When benzene was replaced by the non-toxic dipolar aprotic solvents 5,6-tetrahydro-2(1*H*)-pyrimidone or 1,3-dimethyl-2-imidazolidinone, no **9** was obtained. However, reaction of the 4-hydroxy compound **14** with diethylaminosulfur trifluoride in dichloromethane gave 60% of **9**. H.p.l.c. was necessary in order to separate **9** from the 5-fluoro derivative **10** (characterised by n.m.r. spectroscopy).

Compound **10** is assumed to have been formed by an elimination reaction of the diethylaminosulfur difluoride-activated derivative of **14** to give **13**. Attack of fluoride ion at C-5 in **13** and protonation led to the 4-deoxy function in **10**. The ^{1}H-n.m.r. spectrum of **10** contained signals for H-4,4 at δ 2.92 (m, H-4*eq*) and 2.15 (m, H-4*ax*) with $J_{4,F}$ values of 5.0 and 34.8 Hz, respectively. The signal for Me-5 appeared at lower field (δ 1.64, d, $J_{6,F}$ 17.6 Hz). The ^{13}C-n.m.r spectrum showed C–F couplings for C-4,5,6.

Zemplén *O*-deactylation of **9** gave **11**. As expected[16], all of the protons in positions 1–6 in **11** were coupled to F-4. The comparatively large value (3.4 Hz) of $J_{1,F}$ may reflect



the fact that there are two planar-W routes from H-1 to F-4, namely, along the carbon chain and through the ring oxygen. The ^{13}C-n.m.r. spectrum showed C–F couplings for C-2,3,4,5. These results accord with other data for fluorinated sugars[17].

Reaction of the 4-deoxy-4-iodo derivative **16** with hydrogen bromide–acetic acid gave the glycosyl bromide **20** as a potential donor for the synthesis of 4-deoxyglycosides. Reductive cleavage of the iodo substitutent may be desirable at a later stage, since reaction of the 4-deoxy compound **18** with hydrogen bromide–acetic acid gave only a poor yield of the glycosyl bromide. Treatment of **20** with dibenzyl phosphate and silver carbonate gave 88% of the β-glycosyl dibenzyl phosphate **21**. Glycosylation was accompanied by anomerisation when the soluble silver trifluoromethanesulfonate was used as the catalyst, to yield the crystalline, more stable α-glycosyl dibenzyl phosphate **22**. The structures of **21** and **22** were confirmed by the $J_{H,P}$ and $J_{C,P}$ values. It is remarkable that the α anomer **22** shows a $^4J_{H,P}$ coupling (to H-2). The $^3J_{C,P}$ values are larger than the $^2J_{C,P}$ values for both **21** and **22**.

EXPERIMENTAL

General methods. — Reactions were monitored by t.l.c. on Silica Gel 60 GF_{254} (Merck) with detection by u.v. light or charring with sulfuric acid. Flash chromatography was performed on Silica Gel 60 (230–400 mesh) and h.p.l.c. on a Knauer-Nucleosil 100 column (diam. 32 mm). Melting points were determined with a Reichert melting-point microscope and are uncorrected. Optical rotations (1-dm path length) were

measured with a Perkin–Elmer 241 polarimeter. N.m.r. spectra (^{1}H 300, 360, and 400 MHz; ^{13}C 75.43, 90.52, and 100.57 MHz) were recorded with Bruker WM-300 and AM-360 spectrometers. For additional information, 2D ^{1}H-COSY and 2D ^{1}H–^{13}C-CORR spectra were obtained. Microanalyses were performed by the Microanalytical Laboratory of the Organisch-Chemisches Insitut, Universität Münster. Mass spectra were obtained with Varian MAT CH7 (e.i.) and Finnigan MAT 8230 (d.c.i.) spectrometers.

*Methyl 2,3-di-*O*-benzoyl-6-deoxy-α-*L*-galactopyranoside* (**2**). — A solution of L-fucose (**1**; 2.80 g, 15.7 mmol) in dry pyridine (30 mL) was treated dropwise with a mixture of benzoyl chloride (3.6 mL, 31.1 mmol) and dry pyridine (10 mL) at −40°. The mixture was stirred at −40° for 20 min, then poured into water and extracted with dichloromethane, and the extract was concentrated with toluene. Flash chromatography (light petroleum–ethyl acetate, 2:1) yielded amorphous **3** (5.80 g, 95%), $[\alpha]_D^{20}$ −150° (*c* 9, chloroform); lit.[6] $[\alpha]_D$ −187° (chloroform). ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 8.03–7.32 (m, 10 H, 2 Ph), 5.70 (dd, H-3), 5.61 (dd, H-2), 5.12 (d, H-1), 4.20 (bq, H-5), 4.14 (m, H-4), 3.42 (s, 3 H, OMe), 2.46 (d, HO-4), 1.36 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.6, $J_{3,4}$ 2.9, $J_{4,HO\text{-}4}$ 4.4, $J_{4,5}$ < 1, $J_{5,6}$ 6.6 Hz.

*Methyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-trifluoromethanesulfonyl-α-*L*-galactopyranoside* (**3**). — Compound **3** was synthesised as described in (*b*) below for **4**. The resulting mixture was poured into water and extracted with dichloromethane, and the extract was concentrated to give **3**. ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 8.01–7.27 (m, 10 H, 2 Ph), 5.82 (dd, H-3), 5.47 (dd, H-2), 5.21 (bd, H-4), 5.11 (d, H-1), 4.30 (bq, H-5), 3.36 (s, 3 H, OMe), 1.32 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.8, $J_{3,4}$ 3.0, $J_{4,5}$ 1.0, $J_{5,6}$ 6.6 Hz.

*Methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4-iodo-α-*L*-glucopyranoside* (**4**). — (*a*) A solution of **2** (80 mg, 0.20 mmol) and triphenylphosphine (200 mg, 0.76 mmol) in dry toluene (4 mL) was treated with dry zinc iodide (100 mg, 0.30 mmol) and, after a few min, with diethyl azodicarboxylate (DEAD; 0.12 mL, 0.77 mmol). The mixture was stirred for 24 h at room temperature, then concentrated. Flash chromatography (toluene–ethyl acetate, 4:1) of the residue gave **4** (40 mg, 40%). However, lower yields (~20%) were obtained often.

(*b*) To a solution of **2** (5.8 g, 15.0 mmol) in dry dichloromethane (75 mL) and dry pyridine (10 mL) at −20°, with the exclusion of moisture, was added dropwise a solution of trifluoromethanesulfonic anhydride (6.1 mL, 36.2 mmol) in dry dichloromethane (10 mL). The mixture was stirred for 30 min at −20°, then concentrated, and diluted with dry *N*,*N*-dimethylformamide (75 mL). Sodium iodide (6.1 g, 40.69 mmol) was added, and the mixture was stirred at room temperature until the reaction was complete (t.l.c.; hexane–ethyl acetate, 4:1). Addition of water, extraction with dichloromethane, concentration of the extract, and flash chromatography (hexane–ethyl acetate, 4:1) of the residue yielded syrupy **4** (7.1 g, 95%), $[\alpha]_D^{20}$ −90.5° (*c* 0.4, chloroform). ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 7.99–7.25 (m, 10 H, 2 Ph), 5.98 (dd ~ t, H-3), 5.08 (d, H-1), 5.01 (dd, H-2), 4.19 (dq, H-5), 3.87 (dd ~ t, H-4), 3.48 (s, 3 H, OMe), 1.51 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.0, $J_{3,4}$ 10.6, $J_{4,5}$ 10.6, $J_{5,6}$ 6.2 Hz.

Anal. Calc. for $C_{21}H_{21}IO_6$ (496.3): C, 50.82; H, 4.26. Found: C, 51.12; H, 4.34.

Methyl 2,3-di-O-benzoyl-6-deoxy-4-[(methylthio)thiocarbonyl]-α-L-galactopyranoside (**5**). — To a solution of **2** (50 mg, 0.14 mmol) in dry dichloromethane (5 mL) and methyl sulfoxide (0.17 mL) was added carbon disulfide (0.3 mL, 4.9 mmol). The mixture was cooled to −40° and stirred with 2 drops of 3M sodium hydroxide for 15 min, methyl iodide (0.14 mL, 2.2 mmol) was added, and the temperature was allowed to rise to 10° during 2 h (t.l.c.; toluene–ethyl acetate, 4:1). The mixture was then stirred with water and extracted with hexane, and the extract was dried and concentrated. The resulting yellow syrup crystallised on storage to yield **5** (40 mg, 62%), m.p. 156°, $[\alpha]_D^{20}$ −49° (*c* 0.3, chloroform). ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 8.08–7.32 (m, 10 H, 2 Ph), 6.29 (dd, H-2), 5.86 (dd, H-3), 5.68 (dd, H-4), 5.17 (d, H-1), 4.31 (bq, H-5), 3.42 (s, 3 H, OMe), 2.40 (s, 3 H, SMe), 1.20 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.8, $J_{3,4}$ 3.4, $J_{4,5}$ 1.2, $J_{5,6}$ 6.6 Hz.

Anal. Calc. for $C_{23}H_{24}O_7S_2$ (476.6): C, 57.96; H, 5.07. Found: C, 57.72; H, 5.17.

Methyl 2,3-di-O-benzoyl-4,6-dideoxy-α-L-xylo-hexopyranoside (**6**). — A solution of **4** (6.8 g, 13.7 mmol) in ethyl acetate (30 mL), hexane (20 mL), methanol (10 mL), and triethylamine (2 mL) was stirred under hydrogen in the presence of 10% Pd–C (700 mg) for 48 h, then filtered, and concentrated. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue yielded **6** as a colourless syrup (4.1 g, 81%), $[\alpha]_D^{20}$ −161° (*c* 0.13, chloroform). ^{1}H-N.m.r. data (300 MHz, $CDCl_3$): δ 8.06–7.30 (m, 10 H, 2 Ph), 5.68 (dd, H-3), 5.23 (dd, H-2), 5.06 (d, H-1), 4.11 (m, H-5), 3.39 (s, 3 H, OMe), 2.35 (ddd, H-4*eq*), 1.67 (ddd ~ q, H-4*ax*), 1.26 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.2, $J_{3,4ax}$ 11.4, $J_{3,4eq}$ 5.2, $J_{4ax,4eq}$ 12.6, $J_{4ax,5}$ 11.6, $J_{4eq,5}$ 2.2, $J_{5,6}$ 6.2 Hz.

Anal. Calc. for $C_{21}H_{22}O_6$ (370.4): C, 68.09; H, 5.98. Found: C, 67.95; H, 6.08.

Methyl 4,6-dideoxy-α-L-xylo-hexopyranoside (**7**). — A solution of **6** (400 mg, 1.08 mmol) in dry methanol (50 mL) was stirred with a small amount of solid sodium methoxide at room temperature until the reaction was complete (t.l.c.; methanol–chloroform, 1:5). The mixture was neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Flash chromatography of the residue gave **7** (160 mg, 91%), m.p. 107°, $[\alpha]_D^{20}$ −163° (*c* 1.1, methanol). N.m.r. data: ^{1}H (360 MHz, CD_3OD), δ 4.53 (d, H-1), 3.79 (ddq ~ m, H-5), 3.68 (ddd, H-3), 3.26 (s, 3 H, OMe), 3.19 (dd, H-2), 1.64 (ddd, H-4*eq*), 1.16 (ddd ~ q, H-4*ax*), 1.06 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.7, $J_{2,3}$ 9.5, $J_{3,4ax}$ 11.4, $J_{3,4eq}$ 5.0, $J_{4eq,4ax}$ 12.8, $J_{4ax,5}$ 12.4, $J_{4eq,5}$ 2.1, $J_{5,6}$ 6.2 Hz; ^{13}C (90 MHz, CD_3OD), δ 101.64 (C-1), 75.31 (C-2), 68.75 (C-3), 64.96 (C-5), 55.41 (OCH_3), 42.14 (C-4), 21.25 (C-6).

Anal. Calc. for $C_7H_{14}O_4$ (162.2): C, 51.83; H, 8.70. Found: C, 51.54; H, 8.61.

Methyl 4,6-dideoxy-4-iodo-α-L-glucopyranoside (**8**). — A solution of **4** (350 mg, 0.70 mmol) in dry methanol (10 mL) was stirred with a small amount of solid sodium methoxide at room temperature for 30 min, then neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Flash chromatography (methanol–chloroform), 1:5) of the residue yielded **8** (195 mg, 96%), m.p. 75°, $[\alpha]_D^{20}$ −75° (*c* 1, dichloromethane). ^{1}H-N.m.r. data (300 MHz, CD_3OD): δ 4.67 (d, H-1), 4.01 (dq ~ m, H-5), 3.76 (dd ~ t, H-3), 3.58 (dd ~ t, H-4), 3.38 (s, 3 H, OMe), 3.37 (dd, H-2), 1.43 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.7, $J_{2,3}$ 9.3, $J_{3,4}$ 10.4, $J_{4,5}$ 10.8, $J_{5,6}$ 6.2 Hz.

Anal. Calc. for $C_7H_{13}IO_4$ (288.1): C, 29.18; H, 4.54. Found: C, 29.04; H, 4.46.

1,2,3-Tri-O-benzoyl-4,6-dideoxy-4-fluoro-α-L-glucopyranose (**9**) *and 1,2,3-tri-O-*

benzoyl-4,6-dideoxy-5(R)*-fluoro-β-*D-threo*-hexopyranose* (**10**). To a solution of **14** (1.30 g, 2.72 mmol) in dry dichloromethane (50 mL) at 0° was added diethylaminosulfur trifluoride (DAST; 1.0 mL, 7.5 mmol). The mixture was stirred at room temperature for 1 h, then diluted with methanol, and concentrated. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue yielded a mixture of two products, which was fractionated by h.p.l.c. (hexane–ethyl acetate 7:1 plus 5% of methanol) to yield crystalline **9** (800 mg, 61%) and syrupy **10** (200 mg, 15%).

N.m.r. data for **10**: ^{1}H (400 MHz, $CDCl_3$), δ 8.18–7.25 (m, 15 H, 3 Ph), 6.80 (d, H-1), 6.15 (ddd ~ m, H-3), 5.66 (dd, H-2), 2.93 (ddd ~ m, H-4*eq*), 2.15 (ddd, H-4*ax*), 1.64 (d, 3 H, H-6,6,6); $J_{1,2}$ 4.0, $J_{2,3}$ 10.4, $J_{3,4eq}$ 5.1, $J_{3,4ax}$ 11.5, $J_{4ax,4eq}$ 13.6, $J_{4ax,F}$ 34.8, $J_{4eq,F}$ 5.0, $J_{6,F}$ 17.8 Hz; ^{13}C (100 MHz, $CDCl_3$), δ 165.6, 165.5, and 164.9 (3 C=O), 133.7–128.3 (m, aryl C), 112.8 (d, C-5), 90.1 (C-1), 70.3 (C-2), 65.3 (C-3), 39.5 (d, C-4), 26.5 (d, C-6); $J_{4,F}$ 30.5, $J_{5,F}$ 225.6, $J_{6,F}$ 25.7 Hz.

Compound **9** had m.p. 144°, $[\alpha]_D^{20}$ −203° (*c* 1.5, dichloromethane). N.m.r. data ($CDCl_3$): ^{1}H (360 MHz), 8.06–7.20 (m, 15 H, 3 Ph), 6.61 (dd ~ t, H-1), 6.10 (ddd, H-3), 5.44 (ddd, H-2), 4.41 (ddd ~ m, H-4), 4.21 (ddq ~ m, H-5), 1.38 (dd, 3 H, H-6,6,6); $J_{1,2}$ 4.0, $J_{2,3}$ 10.4, $J_{3,4}$ 9.3, $J_{4,5}$ 10.0, $J_{5,6}$ 6.1, $J_{1,F}$ 3.4, $J_{2,F}$ 0.9, $J_{3,F}$ 13.0, $J_{4,F}$ 50.0, $J_{5,F}$ 4.0, $J_{6,F}$ 1.0 Hz; ^{13}C (90 MHz), δ 165.74, 165.38, and 164.46 (3 C=O), 133.87–128.40 (aryl C), 91.81 (d, C-4), 89.64 (C-1), 70.45 (d, C-3), 70.14 (d, C-2), 67.87 (d, C-5), 17.29 (C-6); $J_{2,F}$ 7.7, $J_{3,F}$ 19.8, $J_{4,F}$ 188.3, $J_{5,F}$ 23.7 Hz.

Anal. Calc. for $C_{27}H_{23}FO_7$ (478.5): C, 67.77; H, 4.84. Found: C, 67.67; H, 4.97.

*4,6-Dideoxy-4-fluoro-α- and -β-*L*-glucopyranose* (**11**). — To a solution of **9** (200 mg, 0.42 mmol) in dry methanol (20 mL) was added a small amount of solid sodium methoxide, and the mixture was stirred for 30 min at room temperature, then neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Flash chromatography (chloroform–methanol, 5:1) of the residue yielded **11** (60 mg, 86%), m.p. 115°. ^{1}H-N.m.r. data (300 MHz, CD_3OD): δ 5.01 (ddd ~ t, H-1α), 4.48 (d, H-1β), 3.36 (m, H-2α), 3.15 (dd, H-2β), 1.28 and 1.23 (2 dd, each 3 H, H-6α,6α,6α,6β,6β,6β); $J_{1\alpha,2\alpha}$ 3.6, $J_{1\beta,2\beta}$ 8.0, $J_{2\beta,3\beta}$ 9.0, $J_{5\alpha,6\alpha}$ 6.2, $J_{5\beta,6\beta}$ 6.2, $J_{1\alpha,F}$ 3.4 Hz.

Anal. Calc. for $C_6H_{11}FO_4$ (166.1): C, 43.37; H, 6.67. Found: C, 43.29; H, 6.69.

*1,2,3-Tri-*O*-benzoyl-6-deoxy-4-*O*-formyl-α-*L*-glucopyranose* (**12**) *and 1,2,3-tri-*O*-benzoyl-4,6-dideoxy-α-*L*-threo-hex-4-enopyranose* (**13**). — Compound **14** (500 mg, 1.0 mmol) was treated, as described above for **2**, with trifluoromethanesulfonic anhydride to give the crude triflate **15**, a solution of which in dry *N,N*-dimethylformamide (40 mL) was stirred with sodium fluoride (100 mg, 2.38 mmol) at room temperature for 24 h. The mixture was then poured into water and extracted with dichloromethane, and the extract was washed with water and concentrated. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue gave the labile compound **13** (20 mg, 4%), **15** (100 mg, 17%), and **12** (220 mg, 43%).

N.m.r. data ($CDCl_3$) for **13**: ^{1}H (360 MHz), δ 8.09–7.08 (m, 15 H, 3 Ph), 6.65 (d, H-1), 5.87 (m, H-3), 5.71 (dd, H-2), 4.93 (bd, H-4), 1.62 (bs, 3 H, H-6,6,6); $J_{1,2}$ 2.5, $J_{2,3}$ 6.8, $J_{3,4}$ 3.0, $J_{4,6}$ 1.0 Hz; ^{13}C (90 MHz), δ 165.93, 165.41, and 164.75 (3 C=O), 152.09 (C-5), 135.81–128.17 (aryl C), 95.46 (C-4), 89.39 (C-1), 68.42 and 67.48 (C-2,3), 19.29 (C-6).

Compound **12** had $[\alpha]_D^{20}$ −205° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^1H (300 MHz), δ 8.09–7.06 (m, 3 Ph and OCHO), 7.99 (s, OCHO), 6.64 (d, H-1), 6.05 (t, H-3), 5.48 (dd, H-2), 5.24 (t, H-4), 4.22 (dq, H-5), 1.24 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.2, $J_{3,4}$ 10.1, $J_{4,5}$ 10.0, $J_{5,6}$ 6.2 Hz; ^{13}C (90 MHz), δ 165.73, 165.26, and 164.40 (3 C=O), 159.35 (OCHO), 133.78–128.33 (aryl C), 89.74 (C-1), 72.32 (C-3), 70.61 (C-2), 70.04 (C-4), 68.01 (C-5), 17.30 (C-6).

Anal. Calc. for $C_{28}H_{24}O_9$ (504.5): C, 66.66; H, 4.79. Found: C, 66.44; H, 4.78.

1,2,3-Tri-O-benzoyl-6-deoxy-α-L-galactopyranose (**14**). — A solution of L-fucose (1.0 g, 6.1 mmol) in dry pyridine (10 mL) at −40° was treated with benzoyl chloride (2.3 mL, 19.8 mmol) in dry pyridine (10 mL). The mixture was stirred for 12 min at −40°, then diluted with water, and extracted with dichloromethane, and the extract was concentrated with toluene. Flash chromatography (toluene–ethyl acetate, 4:1) of the residue yielded **14** (1.9 g, 65%) as a white foam, $[\alpha]_D^{20}$ −160° (*c* 3.15, chloroform). ^1H-N.m.r. data (300 MHz, $CDCl_3$): δ 8.15–7.15 (m, 3 Ph, $CHCl_3$), 6.71 (d, H-1), 5.97 (dd, H-2), 5.80 (dd, H-3), 4.40 (bq, H-5), 4.24 (m, H-4), 2.47 (d, HO-4), 1.34 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.8, $J_{2,3}$ 10.8, $J_{3,4}$ 3.0, $J_{4,5}$ <1, $J_{4,HO-4}$ 4.4, $J_{5,6}$ 6.6 Hz.

Anal. Calc. for $C_{27}H_{24}O_8$ (476.5): C, 68.06; H, 5.07. Found: C, 68.70; H, 5.73.

A better elemental analysis could not be obtained.

1,2,3-Tri-O-benzoyl-6-deoxy-4-O-trifluoromethanesulfonyl-α-L-galactopyranose (**15**). — Compound **15** was synthesised from **14**, as described for **16**, and worked-up as for the triflate **3**. N.m.r. data ($CDCl_3$): ^1H (300 MHz), δ 8.05–7.05 (m, 3 Ph and $CHCl_3$), 6.72 (d, H-1), 5.92 (dd, H-3), 5.83 (dd, H-2), 5.33 (bd, H-4), 4.54 (bq, H-5), 1.34 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.9, $J_{3,4}$ 2.8, $J_{4,5}$ <1, $J_{5,6}$ 6.6 Hz; ^{13}C (90 MHz), δ 165.7, 165.1, and 164.3 (3 C=O), 133.9–128.1 (aryl C), 118.5 (q, CF_3), 90.1 (C-1), 85.6 (C-4), 68.0, 66.9, and 66.3 (C-2,3,5), 21.3 (C-6); $J_{C,F}$ 319.1 Hz.

1,2,3-Tri-O-benzoyl-4,6-dideoxy-4-iodo-α-L-glucopyranose (**16**). — To a solution of **14** (4.66 g, 9.78 mmol) in dry dichloromethane (50 mL) and pyridine (6.5 mL) at −20°, with exclusion of moisture, was added dropwise a solution of trifluoromethanesulfonic anhydride (4.0 mL, 23.77 mmol) in dry dichloromethane (7 mL). The mixture was stirred until the reaction was complete (t.l.c.; toluene–ethyl acetate, 4:1), then concentrated, and the residue was dissolved in dry *N,N*-dimethylformamide (50 mL). Sodium iodide (4 g, 26.68 mmol) was added, and the mixture was stirred at room temperature until the reaction was complete (t.l.c.; hexane–ethyl acetate, 4:1), then poured into water, and extracted with dichloromethane. The extract was washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue yielded **16** (5.0 g, 87%), m.p. 140.5° (from dichloromethane–methanol), $[\alpha]_D^{20}$ −123° (*c* 0.29, dichloromethane). N.m.r. data ($CDCl_3$); ^1H (300 MHz), δ 8.14–7.26 (m, 15 H, 3 Ph), 6.76 (d, H-1), 6.20 (t, H-3), 5.42 (dd, H-2), 4.47 (dq, H-5), 4.09 (t, H-4), 1.62 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.2, $J_{3,4}$ 11.0, $J_{4,5}$ 11.0, $J_{5,6}$ 6.2 Hz; ^{13}C (90 MHz), δ 165.17, 165.14, and 164.42 (3 C=O), 133.63–128.22 (aryl C), 90.14 (C-1), 72.60, 71.85, and 70.96 (C-2,3,5), 30.68 (C-4), 20.74 (C-6).

Anal. Calc. for $C_{27}H_{23}IO_7$ (586.4): C, 55.30; H, 3.95. Found: C, 55.04; H, 3.98.

4,6-Dideoxy-4-iodo-α,β-L-glucopyranose (**17**). — To a solution of **16** (410 mg, 0.70

mmol) in dry methanol (50 mL) was added a small amount of solid sodium methoxide. The mixture was stirred for 30 min at room temperature, neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Flash chromatography (hexane–ethyl acetate, 1:3) of the residue gave **17** (180 mg, 94%), m.p. 98° and 140°. N.m.r. data (CD_3OD): ^1H (360 MHz), δ 5.10 (d, H-1α), 4.48 (d, H-1β), 4.27 (dq ~ m, H-5α), 3.83 (dd, H-3α), 3.76 (dq ~ m, H-5β), 3.60 (t, H-4β), 3.58 (t, H-4α), 3.54 (dd, H-3β), 3.35 (dd, H-2α), 3.11 (t, H-2β), 1.48 (d, 3 H, H-6β,6β,6β), 1.40 (d, 3 H, H-6α,6α,6α); $J_{1\alpha,2\alpha}$ 3.6, $J_{1\beta,2\beta}$ 8.0, $J_{2\alpha,3\alpha}$ 9.4, $J_{2\beta,3\beta}$ 8.5, $J_{3\alpha,4\alpha}$ 10.2, $J_{3\beta,4\beta}$ 10.4, $J_{4\alpha,5\alpha}$ 10.6, $J_{4\beta,5\beta}$ 10.2, $J_{5\alpha,6\alpha}$ 6.2, $J_{5\beta,6\beta}$ 6.1 Hz; ^{13}C (90 MHz), δ 97.8 (C-1β), 94.6 (C-1α), 79.4 (C-3β), 77.3 (C-2β), 75.5 (C-3α), 74.5 (C-2α,5β), 69.7 (C-5α), 41.4 (C-4α), 40.4 (C-4β), 21.5 (C-6α,6β). E.i.-mass spectrum (70 eV): *m/z* 274 (M^+, 1.6%).

Anal. Calc. for $C_6H_1IO_4$ (274.1): C, 26.30; H, 4.05. Found: C, 26.40; H, 4.14.

*1,2,3-Tri-*O*-benzoyl-4,6-dideoxy-*α*-*L*-xylo-hexopyranose* (**18**). — A mixture of **16** (1.8 g, 3.07 mmol), 10% Pd–C (0.2 g), dry methanol (50 mL), dichloromethane (10 mL), and triethylamine (1 mL, 7.2 mmol) was hydrogenated for 30 h at room temperature, then filtered, washed with aqueous 10% sodium thiosulfate, and concentrated. Flash chromatography (hexane–ethyl acetate, 4:1) of the residue yielded **18** (1.2 g, 85%) as a white foam, $[\alpha]_D^{20}$ −223° (*c* 1, dichloromethane). N.m.r. data ($CDCl_3$): ^1H (360 MHz), δ 8.02–7.25 (m, 15 H, 3 Ph), 6.65 (d, H-1), 5.75 (dd, H-3), 5.51 (dd, H-2), 4.27 (ddq ~ m, H-5), 2.40 (ddd, H-4*eq*), 1.72 (ddd ~ q, H-4*ax*), 1.20 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.6, $J_{2,3}$ 10.4, $J_{3,4ax}$ 11.6, $J_{3,4eq}$ 5.0, $J_{4eq,4ax}$ 12.9, $J_{4ax,5}$ 11.6, $J_{4eq,5}$ 2.1, $J_{5,6}$ 6.2 Hz; ^{13}C (90 MHz), δ 165.9, 165.5, and 164.7 (3 C=O), 133.5–128.2 (aryl C), 91.1 (C-1), 71.0 (C-2), 68.6 (C-3), 66.4 (C-5), 37.8 (C-4), 20.6 (C-6).

Anal. Calc. for $C_{27}H_{27}O_7$ (460.5): C, 70.42; H, 5.25. Found: C, 70.53; H, 5.34.

*4,6-Dideoxy-α,β-*L*-xylo-hexopyranose* (**19**). — A solution of **18** (1.0 g, 2.17 mmol) and a small amount of solid methoxide in dry methanol (50 mL) was stirred for 30 min at room temperature, then neutralised with Amberlite IR-120 (H^+) resin, and concentrated. Flash chromatography (hexane–ethyl acetate, 1:3) of the residue yielded **19** (300 mg, 93%), m.p. 125° and 141°. ^1H-N.m.r. data (360 MHz, CD_3OD): δ 5.08 (d, H-1α), 4.39 (d, H-1β), 4.12 (ddq ~ m, H-5α), 3.83 (ddd, H-3α), 3.61 (ddq ~ m. H-5β), 3.54 (ddd, H-3β), 3.25 (dd, H-2α), 3.01 (dd t, H-2β), 1.91 (m, 2 H, H-4*eq*α,4*eq*β), 1.28 (m, 2 H, H-4*ax*α,4*ax*β), 1.20 (d, 3 H, H-6β,6β,6β), 1.13 (d, 3 H, H-6α,6α,6α); $J_{1\alpha,2\alpha}$ 3.6, $J_{1\beta,2\beta}$ 7.8, $J_{2\alpha,3\alpha}$ 9.4, $J_{2\beta,3\beta}$ 9.0, $J_{3\alpha,4ax\alpha}$ 11.4, $J_{3\beta,4ax\beta}$ 11.5, $J_{3\alpha,4eq\alpha}$ 5.0, $J_{3\beta,4eq\beta}$ 5.0, $J_{4ax\alpha,5\alpha}$ 12.4, $J_{4ax\beta,5\beta}$ 12.6, $J_{4eq\alpha,5\alpha}$ 2.0, $J_{4eq\beta,5\beta}$ 2.0, $J_{5\alpha,6\alpha}$ 6.2, $J_{5\beta,6\beta}$ 6.2 Hz.

Anal. Calc. for $C_6H_{12}O_4$ (148.2): C, 48.64; H, 8.16. Found: C, 48.31; H, 8.55.

*2,3-Di-*O*-benzoyl-4,6-dideoxy-4-iodo-*α*-*L*-glucopyranosyl bromide* (**20**). — A solution of **16** (1.0 g, 1.7 mmol) in dry dichloromethane (10 mL) and acetic acid (10 mL) at 0° was treated with 30% hydrogen bromide in acetic acid (4 mL). The solution was allowed to warm to room temperature, stirred for 5 h, poured into saturated aqueous $NaHCO_3$, and extracted with dichloromethane, and the extract was concentrated. Flash chromatography (ethyl acetate–light petroleum, 1:1) of the residue yielded **20** (950 mg, 91%), m.p. 127–128°, $[\alpha]_D^{20}$ −150° (*c* 2, dichloromethane). N.m.r. data ($CDCl_3$): ^1H (300 MHz), δ 7.99–7.34 (m, 10 H, 2 Ph), 6.81 (d, H-1), 6.15 (dd ~ t, H-3), 5.10 (dd, H-2), 4.56 (dq,

H-5), 4.05 (dd ~ t, H-4), 1.64 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.9, $J_{2,3}$ 9.7, $J_{3,4}$ 10.7, $J_{4,5}$ 11.0, $J_{5,6}$ 6.2 Hz; ^{13}C (75 MHz), δ 165.2 and 164.9 (2 C=O), 133.7–128.3 (aryl C), 87.3 (C-1), 74.3, 72.8, and 71.8 (C-2,3,5), 29.5 (C-4), 20.4 (C-6).

Owing to the low stability of **20**, a correct elemental analysis could not be obtained.

*Dibenzyl (2,3-di-*O*-benzoyl-4,6-dideoxy-4-iodo-β-*L*-glucopyranosyl) phosphate* (**21**). — A solution of **20** (170 mg, 0.31 mmol) in dry dichloromethane, ether, and acetonitrile (5 mL each) was stirred with freshly activated powdered molecular sieves (1.0 g, 3 Å) and, in the dark, dibenzyl phosphate (300 mg, 1.07 mmol) and silver carbonate (200 mg, 0.72 mmol) were added. The mixture was stirred overnight, then filtered, and concentrated. Flash chromatography (toluene–ethyl acetate, 3:1) of the residue yielded **21** (210 mg, 91%), $[\alpha]_D^{20}$ −7.8° (*c* 2.7, dichloromethane). N.m.r. data ($CDCl_3$): ^1H (300 MHz), δ 7.98–6.96 (m, 20 H, 4 Ph), 5.75 (dd ~ t, H-3), 5.57 (dd, H-1), 5.41 (dd, H-2), 5.06, 5.02, 4.81, and 4.71 (2 dd, each 2 H, 2 PhCH_2), 4.04 (dq ~ m, H-5), 3.97 (dd t, H-4), 1.62 (d, 3 H, H-6,6,6); $J_{1,2}$ 8.1, $J_{2,3}$ 9.5, $J_{3,4}$ 10.0, $J_{4,5}$ 10.2, $J_{5,6}$ 5.7, $J_{PhCH,P}$ 7.2 and 6.8, $J_{PhCH'}$ 7.6 and 7.2, $J_{1,P}$ 7.3 Hz; ^{13}C (75 MHz), δ 165.1 and 165.0 (2 C=O), 135.5–127.4 (aryl C), 96.6 (d, C-1), 75.5 and 74.7 (C-3,5), 72.8 (d, C-2), 70.0 (d, PhCH_2), 69.8 (d, PhCH'_2), 30.1 (C-4), 20.7 (C-6); $J_{1,P}$ 5.1, $J_{2,P}$ 9.3, $J_{PhCH,P}$ 5.7, $J_{PhCH',P}$ 5.5 Hz.

Anal. Calc. For $C_{34}H_{32}IO_9P$ (742.5): C, 54.99; H, 4.34. Found: C, 55.45; H, 4.29.

*Dibenzyl (2,3-di-*O*-benzoyl-4,6-dideoxy-4-iodo-α-*L*-glucopyranosyl) phosphate* (**22**). — A solution of **20** (300 mg, 0.55 mmol) in dry ether, dichloromethane, and acetonitrile (10 mL each) was stirred with freshly activated molecular sieves (1.0 g, 3 Å) for 15 min, and, in the dark, dibenzyl phosphate (0.6 g, 2.15 mmol) and silver trifluoromethanesulfonate (0.6 g, 2.33 mmol) were added. The mixture was stirred overnight at room temperature, filtered, and concentrated. Flash chromatography (toluene–ethyl acetate, 4:1) of the residue yielded **22** (270 mg, 66%), m.p. 123°, $[\alpha]_D^{20}$ −83.5° (*c* 2.2, dichloromethane). N.m.r. data ($CDCl_3$): ^1H (360 MHz), δ 7.92–7.06 (m, 4 Ph and $CHCl_3$), 6.06 (dd, H-1), 5.96 (dd ~ t, H-3), 5.13 (ddd, H-2), 4.91 (m, 4 H, 2 PhCH_2), 4.28 (dq ~ m, H-5), 3.89 (dd ~ t, H-4), 1.40 (d, 3 H, H-6,6,6); $J_{1,2}$ 3.3, $J_{2,3}$ 10.1, $J_{3,4}$ 10.8, $J_{4,5}$ 11.0, $J_{5,6}$ 6.1, $J_{1,P}$ 7.7, $J_{2,P}$ 3.0 Hz; ^{13}C (90 MHz), δ 165.4 and 165.1 (2 C=O), 133.4–127.7 (aryl C), 95.1 (d, C-1), 72.0 (d, C-2), 71.9 and 71.3 (C-3,5), 70.0 and 69.9 (2 d, 2 PhCH_2), 30.4 (C-4), 20.6 (C-6); $J_{1,P}$ 5.4, $J_{2,P}$ 7.4, $J_{PhCH_2,P}$ 3.0, $J_{PhCH'_2,P}$ 2.9 Hz.

Anal. Calc. for $C_{34}H_{32}IO_9P$ (742.5): C, 54.99; H, 4.34. Found: C, 55.01; H, 4.65.

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