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Preparation of new acylated derivatives of L-arabinofuranose and 2-deoxy-L-*erythro*-pentofuranose as precursors for the synthesis of L-pentofuranosyl nucleosides*

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ABSTRACT

1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-L-arabinofuranose and 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-L-*erythro*-pentofuranose have been synthesised from L-arabinose for use in the preparation of L-pentofuranosyl nucleosides.

INTRODUCTION

Sugar-modified mucleoside analogues have attracted considerable interest, mainly as potential antiviral or antitumor agents[1,2], but also as units of synthetic oligonucleotides[3] designed as antisense inhibitors of gene expression. We have reported the synthesis and biological evaluation of α,β-D-xylofuranosyl[4] and α,β-D-lyxofuranosyl[5] nucleosides, and have investigated unusual oligonucleotides that consist of 2′-deoxy-α-D-*erythro*-pentofuranonucleoside[6] and α-D-ribofuranonucleoside[7] units. We are in the process of extending these studies to α-L-arabinofuranosyl nucleosides and to their 2′-deoxy derivatives, compounds which have received little attention.

It was anticipated that these compounds could be synthesised by condensation of the purine or pyrimidine bases with a suitably protected L-pentofuranose, such as 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-arabinofuranose (**9**) and 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-L-*erythro*-pentofuranose (**12**). Indeed, **9** should enable preferential or exclusive formation of *trans*-1′,2′ α-L-arabinofuranonucleosides in accord with Baker's rule[8], and permit selective 2′-modification of these compounds as reported in the D-xylose series[4,5,9–11]. Moreover, **12** fulfills the structural requirements for the synthesis of 2′-deoxy-L-*erythro*-pentofuranosyl nucleosides by an improved procedure that involves phase-transfer conditions[12].

We now describe the synthesis of **9** and **12** from L-arabinose.

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* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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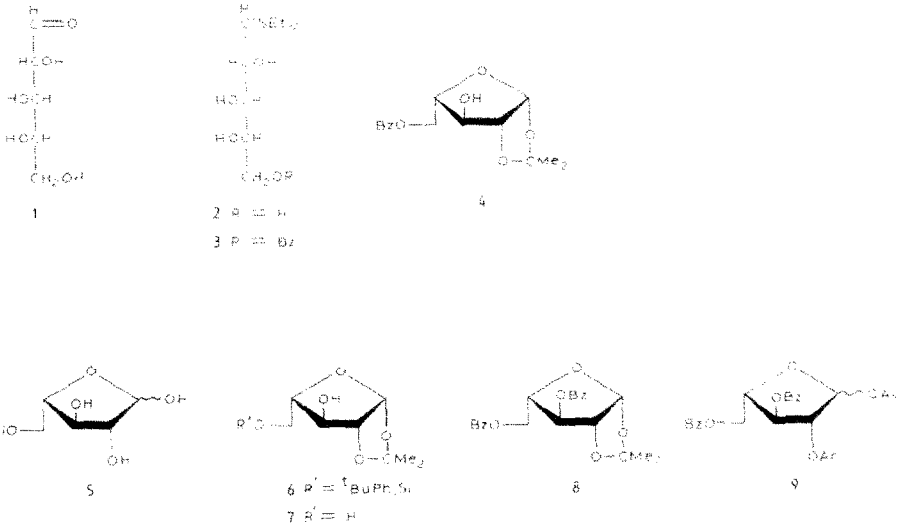
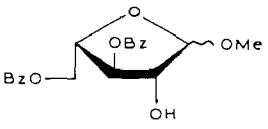
RESULTS AND DISCUSSION

The key precursor of **9** was 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-*β*-L-arabinofuranose (**8**) (only its D enantiomer has been reported[13]), which was prepared by two routes. L-Arabinose diethyl dithioacetal[14] (**2**) was 5-benzoylated, then treated with mercury(II) chloride in anhydrous acetone to give **4**. Benzoylation of **4** afforded **8** (15% from L-arabinose). Alternatively, 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-*β*-L-arabinofuranose[15] (**6**) was converted into **8** (24% from L-arabinose) by fluoride-ion-mediated desilylation followed by 3,5-benzoylation.

Attempted acetolysis[16] (acetic acid–acetic anhydride–sulfuric acid) of **8**, to give **9**, also yielded a hexa-*O*-acyl-*aldehydo*-L-arabinose aldehydrol as a by-product that was difficult to remove from the non-crystalline **8** (data not shown). However, **8** could be deacetonated in aqueous 85% acetic acid with sulfuric acid, and the resulting 3,5-di-*O*-benzoyl-L-arabinofuranose intermediate was not isolated, but acetylated (acetic anhydride) to afford 81% of *α,β*-**9**.



The strategy followed for the preparation of **12** was based on a Barton-type[17] selective 2-deoxygenation of a suitably protected methyl L-arabinofuranoside, followed by hydrolysis and acetylation at the anomeric position. Thus, **8** was transformed into **10** by an acetal-cleavage reaction with concomitant conversion into a methyl glycoside by treatment with a boiling dilute solution of iodine in methanol[18]. Reaction of **10** with phenyl chlorothionocarbonate[19] and 4-(dimethylamino)pyridine in dichloromethane gave the corresponding 2-*O*-(phenoxythiocarbonyl) derivative, which was treated with tributyltin hydride and *α,α'*-azobis(isobutyronitrile) in toluene to afford, after column chromatography, methyl 3,5-di-*O*-benzoyl-2-deoxy-*α,β*-L-*erythro*-pentofuranoside (**11**). Hydrolysis of **11** with aqueous 50% acetic acid followed by acetylation and column chromatography afforded *α,β*-**12** (28% from **8**), from which the *β* anomer could be isolated pure by crystallisation from methanol.



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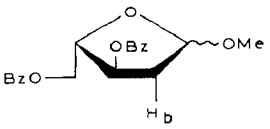

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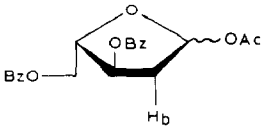

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Structural assignments for the compounds reported were based on elemental analysis and physical constants. Unless otherwise noted, the data accorded with those in the literature for compounds described previously or for their D enantiomers.

The use of **9** and **12** for the synthesis of L-pentofuranosyl nucleosides and α-L-oligonucleotides is being studied. Preliminary reports on the synthesis and properties of several α-L-pentofuranonucleosides of thymine and of an oligo (α-L-d**T**)$_8$ have been published[20].

EXPERIMENTAL

General methods. — Solvents were removed with a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010M apparatus and are uncorrected. ^{1}H-N.m.r. spectra were recorded at ambient temperatures for solutions in Me_2SO-d_6 or $CDCl_3$ with a Bruker WM 360 WB spectrometer. Chemical shifts are expressed relative to those of Me_2SO-d_5 (2.49 p.p.m.) or $CHCl_3$ (7.26 p.p.m.). Deuterium exchange and decoupling experiments were performed in order to confirm proton assignments. F.a.b.-mass spectra were recorded in the positive-ion mode with a JEOL DX 300 mass spectrometer and a JMA-DA 5000 mass data system. Xe atoms were used at 3 keV with a total discharge current of 20 mA. Optical rotations were measured in a 1-cm cell on a Perkin–Elmer Model 241 spectropolarimeter. Elemental analyses were determined by the Service de Microanalyses du CNRS, Division de Vernaison (France). T.l.c. was performed on Silica Gel 60 F_{254} (Merck, 5554) with detection by u.v. absorbance (for benzoates) and by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 9385) at atmospheric pressure.

L-*Arabinose diethyl dithioacetal* (**2**). — Compound **2** was prepared as described[21] for D-lyxose. Recrystallisation from 2-butanol gave **2** (75%), m.p. 125–127°, $[\alpha]_D^{20}$ −22° (*c* ~1, methyl sulfoxide), +10° (*c* ~1, methanol); lit.[14] m.p. 125–126°, $[\alpha]_D^{13}$ ~0° (pyridine); lit.[22] −11° (methanol) for the D enantiomer. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.20 (t, 6 H, *J* 7.5 Hz, 2 C*H*$_3$CH$_2$S), 2.69 (q, 4 H, 2 CH$_3$C*H*$_2$S), 3.3–4.6 (m, 10 H).

5-O-*Benzoyl*-L-*arabinose diethyl dithioacetal* (**3**). — Compound **3** was prepared by a route analogous to that[23] employed for 5-*O*-benzoyl-D-ribose diethyl dithioacetal. Recrystallisation from toluene gave **3** (53%), m.p. 117–120°, $[\alpha]_D^{20}$ −26° (*c* ~1, methyl sulfoxide), +44° (chloroform); lit.[13] m.p. 117–118°, $[\alpha]_D^{17}$ −52.8° (chloroform) for the D enantiomer; lit.[24] $[\alpha]_D^{22}$ +49.5° (chloroform). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.18 (t, 6 H, *J* 7.0 Hz, 2 C*H*$_3$CH$_2$S), 2.65 (q, 4 H, 2 CH$_3$C*H*$_2$S), 3.6–5.2 (m, 9 H), 7.3–8.1 (m, 5 H, Ph).

5-O-*Benzoyl*-1,2-O-*isopropylidene*-β-L-*arabinofuranose* (**4**). — Compound **3** was

treated[13] with mercury(II) chloride in the presence of excess of acetone, as for the D enantiomer. After the usual work-up, the residue was subjected to column chromatography, using a stepwise gradient of acetone (0–5%) in dichloromethane. Crystallisation of the product in the appropriate fractions from toluene afforded **4** (42%), m.p. 146–148°, $[\alpha]_D^{20}$ −25° (*c* ~ 1, methyl sulfoxide); lit.[13] m.p. 148–149°, $[\alpha]_D$ −24° (chloroform), for the D enantiomer. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.25 and 1.44 (2 s, each 3 H, CMe_2), 4.2 (m, 2 H, H-3,4), 4.40 (d, 2 H, *J* 6.3 Hz, H-5a,5b), 4.49 (d, 1 H, *J* 3.9 Hz, H-2), 5.60 (d, 1 H, *J* 4.1 Hz, HO-3), 5.87 (d, 1 H, *J* 3.9 Hz, H-1), 7.5–8.0 (m, 5 H, Ph).

Anal. Calc. for $C_{15}H_{18}O_5$: C, 61.22; H, 6.16. Found: C, 61.30; H, 6.17.

5-O-tert-Butyldiphenylsilyl-α,β-L-arabinofuranose (**5**). — L-arabinose (**1**) was treated with *tert*-butylchlorodiphenylsilane and imidazole in *N,N*-dimethylformamide as described[15]. Column chromatography of the product with a stepwise gradient of methanol (0–7%) in dichloromethane afforded **5** (49%), as an oil. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.0 (m, 9 H, ^{t}Bu), 3.6–3.9 (m, 5 H, H-2,3,4,5a,5b), 4.95 and 5.04 [2 d after D_2O exchange, 1 H total sum, H-1α (*J* 2.9 Hz) and H-1β (*J* 4.3 Hz), α,β-ratio ~ 10:3], 5.1, 5.2, and 6.2 (3 bs, each 1 H, HO-1,2,3), 7.3–7.7 (m, 10 H, 2 Ph); ($CDCl_3$): δ 5.28 and 5.40 [d and s, 1 H, H-1β (*J* 3.9 Hz) and H-1α] (lit.[15] δ 5.27 (d, 1 H, *J* 3.9 Hz, H-1α), 5.43 (d, 1 H, *J* 4.4 Hz, H-1β).

5-O-tert-Butyldiphenylsilyl-1,2-O-isopropylidene-β-L-arabinofuranose (**6**). — Compound **5** was treated[15] with anhydrous copper(II) sulfate and sulfuric acid in anhydrous acetone. Column chromatography of the product, using a stepwise gradient of acetone (0–2%) in dichloromethane, gave **6** (67%), as an oil. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.01 (s, 9 H, ^{t}Bu), 1.21 (s, 6 H, CMe_2), 3.6–3.9 (m, 2 H, H-5a,5b), 4.0 (m, 1 H, H-4), 4.2 (bs, 1 H, H-3), 4.45 (d, 1 H, *J* 4.0 Hz, H-2), 5.52 (d, 1 H, *J* 4.2 Hz, HO-3), 5.83 (d, 1 H, *J* 4.0 Hz, H-1), 7.4–7.7 (m, 10 H, 2 Ph).

1,2-O-Isopropylidene-β-L-arabinofuranose (**7**). — Compound **6** was treated with tetrabutylammonium fluoride in tetrahydrofuran as described[25] for the D enantiomer. Column chromatography of the product, using a stepwise gradient of methanol (0–3%) in dichloromethane, gave **7** (89%), m.p. 118–120° (from dichloromethane), $[\alpha]_D^{20}$ −15° (*c* 1, methyl sulfoxide); lit.[26] m.p. 117–118°, $[\alpha]_D$ −29° (water) for the D enantiomer. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.22 and 1.40 (2 s, each 3 H, CMe_2), 3.3–3.6 (m, 2 H, H-5a,5b), 3.8 (m, 1 H, H-4), 4.0 (bs, 1 H, H-3), 4.40 (d, 1 H, *J* 3.9 Hz, H-2), 4.75 (t, 1 H, *J* 5.6 Hz, HO-5), 5.34 (d, 1 H, *J* 4.3 Hz, HO-3), 5.78 (d, 1 H, *J* 3.9 Hz, H-1).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.74; H, 7.72.

3,5-Di-O-benzoyl-1,2-O-isopropylidene-β-L-arabinofuranose (**8**). — To a cooled (ice-bath) solution of **4** (0.59 g, 2.0 mmol) or **7** (0.19 g, 1.0 mmol) in anhydrous pyridine (8 mL for **4** and 4 mL for **7**) was added a solution of benzoyl chloride (0.30 mL, 2.6 mmol) in pyridine (3 mL) dropwise with stirring. Each mixture was stirred at room temperature for 3 h with the exclusion of moisture. Water (1 mL) was added, stirring was continued for 2 h, and the mixture was concentrated to a small volume, diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), filtered, and concentrated to dryness, and toluene was evaporated three times from residue. Crystallisation from methanol then afforded **8** (0.72 g, 90%

from **4**; 0.33 g, 82% from **7**), m.p. 80–81°, $[\alpha]_D^{20}$ −15° (*c* ~ 1, methyl sulfoxide); lit.[13] m.p. 81–82°, $[\alpha]_D^{26}$ +20.4° (chloroform) for the D enantiomer. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.37 and 1.63 (2 s, each 3 H, CMe_2), 4.6–4.7 (m, 3 H, H-3,5a,5b), 4.79 (d, 1 H, *J* 3.8 Hz, H-2), 5.48 (d, 1 H, *J* 1.7 Hz, H-4), 6.05 (d, 1 H, *J* 3.8 Hz, H-1), 7.4–8.1 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.19, H, 5.55.

*1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-α,β-*L*-arabinofuranose* (**9**). — A solution of **8** (7.0 g, 17.6 mmol) and sulfuric acid (0.18 mL, 3.4 mmol) in aqueous 85% acetic acid (17.8 mL) was stirred and heated for 1.5 h at 50°. The mixture was concentrated *in vacuo* to ~ 10 mL, then diluted with pyridine (3.6 mL). Acetic anhydride (22.3 mL, 236 mmol) was added dropwise with stirring at 50°, and stirring was continued for 1.5 h at 50°. After cooling to room temperature, the mixture was concentrated *in vacuo*, diluted with dichloromethane, washed with aqueous 5% sodium hydrogen carbonate and water, dried (Na_2SO_4), filtered, and concentrated to dryness, and toluene was evaporated three times from the residue followed by chloroform to afford **9** (6.3 g, 81%), as an oil. ^{1}H-N.m.r. data ($CDCl_3$): δ 2.00, 2.08, 2.09, and 2.14 (4 s, 6 H, 2 Ac; 2.00 and 2.09, Ac for the β anomer), 4.5–4.8 (m, 3 H, H-4,5a,5b; 4.50, m, H-4β), 5.41 and 5.60 [d and dd, 1 H, H-2α ($J_{2,3}$ 1.2 Hz) and H-2β ($J_{1,2}$ 4.7 Hz, $J_{2,3}$ 7.0 Hz)], 5.46 and 5.79 [m and dd, 1 H, H-3α and H-3β ($J_{2,3}$ 7.0 Hz, $J_{3,4}$ 5.6 Hz], 6.31 and 6.48 [s and d, 1 H, H-1α and H-1β (*J* 4.7 Hz), α,β-ratio ~ 3:4)], 7.4–8.1 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{22}O_9 \cdot 0.1CHCl_3$: C, 61.06; H, 4.90. Found: C, 61.30; H, 5.05.

*Methyl 3,5-di-*O*-benzoyl-α,β-*L*-arabinofuranoside* (**10**). — A solution of **8** (3.0 g, 7.53 mmol) in methanolic 0.5% iodine (191 mL) was stirred and boiled under reflux overnight, then cooled to room temperature. The iodine was reduced by dropwise addition of saturated aqueous sodium thiosulfate. The mixture was then concentrated *in vacuo*, diluted with dichloromethane, twice washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness. Column chromatography of the residue, using a stepwise gradient of ethyl acetate (0–40%) in dichloromethane, gave **10** (2.5 g, 89%), as an oil. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 3.28 and 3.30 (2 s, 3 H, MeO-1β and MeO-1α, respectively), 4.1–4.6 [m, 4 H, H-2,4,5a,5b (4.17, m, H-2α; 4.28, m, H-4β)], 4.84 and 4.90 [d and s, 1 H, H-1β (*J* 4.3 Hz) and H-1α, respectively, α,β-ratio ~ 5:3], 5.16 and 5.41 (2 m, 1 H, H-3α and H-3β, respectively), 5.49 and 5.80 [2 d, 1 H, HO-2β (*J* 7.0 Hz) and HO-2α (*J* 4.1 Hz), respectively], 7.4–8.1 (m, 10 H, 2 Ph). F.a.b.-mass spectrum (matrix, glycerol–thioglycerol 50:50): *m/z* 373 $(M + H)^+$, 105 $(PhC \equiv O)^+$.

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.89; H, 5.67.

*Methyl 3,5-di-*O*-benzoyl-2-deoxy-α,β-*L*-erythro-pentofuranoside* (**11**). — To a solution of **10** (2.38 g, 6.39 mmol) in anhydrous dichloromethane (66 mL) were added phenyl chlorothionocarbonate (1.88 mL, 13.67 mmol) and 4-(dimethylamino)pyridine (2.38 g, 19.43 mmol). The solution was stirred for 0.5 h at room temperature and then diluted with dichloromethane, water was added, and the organic layer was washed successively with ice-cold 0.1M hydrochloric acid and water, dried (Na_2SO_4), filtered, and concentrated to dryness. A solution of the residue in dry toluene was concentrated *in vacuo*, and this process was repeated three times. The residue was dissolved in dry toluene (137 mL) and treated with tributyltin hydride (4.5 mL, 16.76 mmol) and

α,α'-azobis(isobutyronitrile) (176.4 mg, 1.07 mmol) at 80° for 3 h. The mixture was cooled to room temperature, concentrated *in vacuo*, diluted with dichloromethane, twice washed with water, dried (Na_2SO_4), filtered, and concentrated to dryness. Column chromatography of the residue, using a stepwise gradient of dichloromethane (60–100%) in cyclohexane, afforded **11**, slightly contaminated by phenol. Further column chromatography, using a stepwise gradient of dichloromethane (70–100%) in cyclohexane followed by a stepwise gradient of ethyl acetate (0–15%) in dichloromethane, gave **11** (1.2 g, 53%), as an oil that was sufficiently pure to be used in the next step. A pure sample of each anomer was isolated by column chromatography, using a stepwise gradient of ethyl acetate (0–8%) in cyclohexane. ^{1}H-N.m.r. data (Me_2SO-d_6): **11**β (high R_F), δ 2.32–2.44 (m, 2 H, H-2a,2b), 3.25 (s, 3 H, MeO), 4.34–4.40 (m, 1 H, H-5a or H-5b), 4.5 (m, 2 H, H-4 and H-5a or H-5b), 5.22 (dd, 1 H, *J* 2.5 and 5.2 Hz, H-1), 5.5 (m, 1 H, H-3), 7.5–8.1 (m, 10 H, 2 Ph); **11**α (low R_F), δ 2.05 (d, 1 H, $J_{2a,2b}$ 14.6 Hz, H-2b), 2.49–2.57 (m, H-2a partially obscured by Me_2SO-d_5), 3.29 (s, 3 H, MeO), 4.43–4.53 (m, 3 H, H-4,5a,5b), 5.16 (d, 1 H, $J_{1,2a}$ 5.2 Hz, H-1), 5.4 (m, 1 H, H-3), 7.5–8.1 (m, 10 H, 2 Ph).

*1-O-Acetyl-3,5-di-O-benzoyl-2-deoxy-α,β-*L*-erythro-pentofuranose* (**12**). — A solution of **11** (0.79 g, 2.22 mmol) in aqueous 50% acetic acid (11 mL) was stirred at 100° for 3 h, then cooled to room temperature, and concentrated to dryness. Toluene–ethanol (4:1) was evaporated twice from the residue followed by toluene. A solution of the residue in pyridine (2.3 mL) was stirred with acetic anhydride (1.12 mL, 11.8 mmol) for 0.5 h at 100°, then diluted with dichloromethane, washed with water, saturated aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), filtered, and concentrated to dryness. Column chromatography of the residue, using a stepwise gradient of ethyl acetate (10–20%) in cyclohexane, afforded **12** (0.50 g, 59%), as a pale-yellow oil. α,β-ratio ~1:1 [^{1}H-N.m.r. data ($CDCl_3$) accorded with those reported[27] for the α,β-D-enantiomers of **12**]. Crystallisation from methanol afforded **12**β, m.p. 86–88°, $[\alpha]_D^{20}$ +21° (*c* 1.15, methyl sulfoxide); lit.[28] m.p. 86.5–87.5°, $[\alpha]_D^{25}$ −23.7° (chloroform) for the D enantiomer. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.87 (s, 3 H, Ac), 2.56–2.60 (m, 2 H, H-2a,2b), 4.41–4.60 (m, 3 H, H-4,5a,5b), 5.6 (m, 1 H, H-3), 6.36 (dd, 1 H, H-1), 7.5–8.1 (m, 10 H, 2 Ph). The assignment of the β-anomeric configuration to this crystalline isomer accords[29] with the narrow band-width (0.04 p.p.m.) of the H-2a,2b resonances, as compared with those for the α anomer (δ 2.26, d, *J* 15 Hz for H-2a; and δ 2.62–2.71, m, H-2b, $\Delta\delta$ ~0.5 p.p.m.).

Anal. Calc. for $C_{21}H_{20}O_7$: C, 65.62; H, 5.25. Found: C, 65.40; H, 5.30.

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