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Regioselective phthalation and succinylation of D-glucose and D-galactose using protecting groups: Conversion of the products to organotin derivatives

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1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was acylated at the free 0-3 position with phthalic and succinic anhydrides. Removal of the protecting groups gave the 3-*O*-acylglucopyranose compounds which were converted to their acetyl and organostannyl derivatives. A similar sequence of reactions was carried out with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

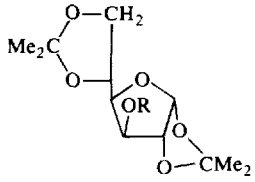
Keywords: Phthalation, succinylation, D-glucose, D-galactose, organotin, stannylation

INTRODUCTION

Direct reaction of sugars, particularly disaccharides, with phthalic and succinic anhydrides gives mixtures of partially acylated sugars, some of which have been characterized.[1,2] Treatment of these crude sugar hydrogen phthalate and succinate mixtures with organotin oxides or hydroxides gave organotin sugar phthalates and succinates with useful biocidal properties.[3] As an aid to understanding of the relationship between structure and biological activity of these derivatives it was decided to prepare some specific sugar phthalates and succinates by unambiguous routes. This paper describes the preparation and characterization of 3-*O*-phthalyl-D-glucopyranose and 6-*O*-phthalyl-D-galactopyranose, the corresponding succinyl compounds and their conversion to organotin derivatives.

RESULTS AND DISCUSSION

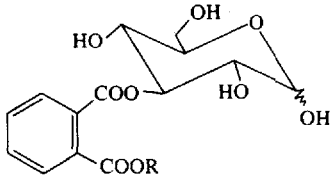
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**)



1 R = H
2 R = *o*-OCC_6H_4COOH
3 R = $OCCH_2CH_2COOH$

reacted at room temperature with phthalic anhydride in DMF in the presence of triethylamine to give the 3-*O*-phthalyl derivative (**2**). The structure of this product was confirmed from the ^1H NMR spectrum (see Experimental) and from the mass spectrum which was as expected, showing major ions at *m/z* 393 (31.6%) due to loss of a methyl group from the molecular ion and *m/z* 149 (53.1%) due to $[o\text{-}HOOCC_6H_4C{\equiv}O]^+$.

When **2** was treated with trifluoroacetic acid, 3-*O*-phthalyl-D-glucose (**4**) was obtained as a mixture of anomers following ring expansion. The ^1H NMR spectrum was entirely consistent with the assigned structure, the two low field doublets



4 R = H
5 R = $SnBu_3$
6 R = $SnPh_3$

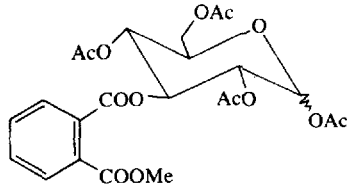


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Table 1 Values of ^{13}C NMR chemical shifts (D_2O)[a]

	C-1	C-2	C-3	C-4	C-5	C-6
α-D-Glucose[b]	92.9	72.5	73.8	70.6	72.3	61.6
β-D-Glucose	96.7	75.1	76.7	70.6	76.8	61.7
	92.73	76.16	69.10	71.41	71.03	61.76
4	96.82	77.77	73.39	70.88	79.95	61.86
	92.56	76.36	68.27	68.34	71.71	61.12
8	96.31	78.22	74.76	70.29	76.17	61.34
α-D-Galactose[b]	93.2	69.4	70.2	70.3	71.4	62.2
β-D-Galactose[b]	97.3	72.9	73.8	69.7	76.0	62.0
	92.93	68.34	69.31	69.55	69.83	65.70
13	97.02	72.37	72.75	68.81	73.21	65.46
	93.32	68.27	69.32	69.67	69.95	64.42
16	97.80	70.37	73.01	69.97	73.97	64.10

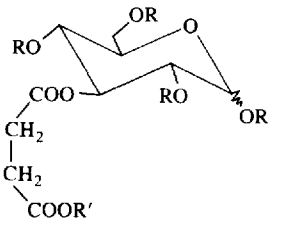
[a]Except for C-1 and C-6, these assignments are tentative.
[b]Values taken from ref. 4.

at δ4.88 and δ5.34 being assigned, respectively, to the α($J_{1,2}$ = 4.0 Hz) and β($J_{1,2}$ = 8.0 Hz) forms. Only the H-3 proton signals were markedly downfield compared with the free sugar, confirming the position of substitution and absence of acyl migration. This was confirmed by the ^{13}C NMR spectrum (see Table 1).

Compound **4** was further characterized by conversion to its methyl ester with diazomethane followed by acetylation to give 1,2,4,6-tetra-*O*-acetyl-3-*O*-(*o*-methoxycarbonylbenzoyl)-D-glucopyranose (**7**). As before, the ^{1}H NMR spectrum was in agreement with the assigned structure (see Table 2). Although the molecular ion was not seen in the mass spectrum of **7**, an ($M-51$) peak was observed at *m/z* 451 indicating loss of an acetoxy group. Loss of two and three molecules of acetic acid from this ion gave signals at *m/z* 331 and 271 respectively; the base peak occurred at *m/z* 163 due to $[o\text{-MeOOCC}_6H_4C{\equiv}O]^+$.

Heating **4** with tributyltin oxide in benzene with azeotropic removal of water gave the tributyltin ester (**5**). The corresponding triphenyltin compound (**6**) was obtained from a similar reaction with triphenyltin hydroxide. The infrared spectra of both **5** and **6** showed the two characteristic carbonyl bands $\nu(C{=}O)_{COOC}$ 1720 cm^{-1} and $\nu(C{=}O)_{COOSn}$ 1660–1670 cm^{-1}.

By using succinic anhydride instead of phthalic anhydride, **1** was convereted to the 3-*O*-succinyl ester **3**. Removal of the isopropylidene groups as before gave 3-*O*-succinyl-D-glucose (**8**). Compound **8** on successive methylation and acetylation gave **9** and, as in the previous examples, ^{1}H or ^{13}C NMR confirmed that the acyl group was



8 R = R′ = H
9 R = Ac; R′ = Me

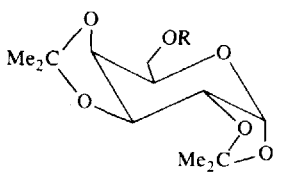
Table 2 Values of ^{1}H NMR chemical shifts[a] and coupling constants ($CDCl_3$) at 250 MHz for the gluose derivatives **7** and **9**

	7	**9**
H-1α	6.29 (dd)	6.32 (d)
H-1β	5.71 (d)	5.72 (d)
H-2α	5.20 (dd)	5.12 (dd)
H-2β	5.16 (dd)	5.14 (dd)
H-3α	5.71 (t)	5.52 (t)
H-3β	5.50 (t)	5.34 (t)
H-4α, H-4β	*ca* 5.22 and 5.20 (t) overlapping H-2α and H-2β	*ca* 5.20–5.10 (t) overlapping H-2α and H-2β
H-5α, H-5β, H-6aα, H-6aβ, H-6bα, H-6bβ	*ca* 4.30–4.00 overlapped	*ca* 4.34–3.80 overlapped
$J_{1,2}(\alpha)$	4.0	4.0
$J_{1,2}(\beta)$	8.0	8.2
$J_{2,3}$	10.0	10.0
$J_{3,4}$	10.0	10.0
$J_{4,5}$	10.0	10.0

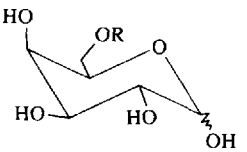
[a]d = doublet, t = triplet, dd = double doublet.

attached to O-3 in **8** and **9** (Tables 1 and 2). The mass spectrum of **9** was also in agreement with the assigned structure.

The protected D-galactopyranose derivative **10** was phthalylated in a similar manner to give 1,2:3,4-di-*O*-isopropylidene-6-*O*-phthalyl-α-D-galactopyranose (**11**). The ^{13}C and ^{1}H NMR spectra of **11** were as expected with the H-6a and H-6b protons giving low field quartets at, respectively, δ4.54 ($J_{5,6a}$=3.0; $J_{6a,6b}$=12 Hz) and δ4.35 ($J_{5,6b}$=8.0 Hz). In the mass spectrum, loss of a methyl group gave rise to the ($M-15$) ion at *m/z* 393 and the [*o*-$HOOCC_6H_4C{\equiv}O]^+$ ion was seen at *m/z* 149. Removal of the isopropylidene groups with trifluoroacetic acid gave a mixture of the anomeric forms of 6-*O*-phthalyl-D-galactopyranose (**13**). The absence of the isopropylidene group was confirmed by the ^{1}H NMR spectrum but second-order effects made full interpretation difficult. However the ^{13}C NMR spectrum (Table 1) showed that the biggest change in chemical shift (3.5 ppm upfield) compared with the free sugar is at C-6. For secondary sugar hydroxyls, acylation normally causes a downfield shift but this is sometimes reversed when acylation occurs at the O-6 position of aldohexopyranosides.[4] Compound **13** reacted with tributyltin oxide and with triphenyltin hydroxide to give, respectively, the esters **14** and **15** which were both obtained as mixtures of anomers.



10 R = H
12 R = $OCCH_2CH_2COOH$
11 R = *o*-OCC_6H_4COOH



13 R = *o*-OCC_6H_4COOH
14 R = *o*-$OCC_6H_4COOSnBu_3$
15 R = *o*-$OCC_6H_4COOSnPh_3$
16 R = $OCCH_2CH_2COOH$

In a similar manner, the protected galactose **10** was treated with succinic anhydride to give 1,2:3,4-di-*O*-isopropylidene-6-*O*-succinyl-α-D-galactopyranose (**12**). The ^{1}H NMR spectrum of **12** was similar to that of the corresponding phthalyl derivative **11** except for the absence of the aromatic proton signal at δ 7.6 but the presence of the methylene protons was revealed by the signal at δ 2.69. Further evidence for the assigned structure of **12** was obtained from the ^{13}C NMR spectrum and the mass spectrum. The latter showed an ($M-15$) peak at *m/z* 345 due to loss of a methyl group (characteristic of *O*-isopropylidene derivatives) and a signal at *m/z* 101 due to $[OCCH_2CH_2COOH]^+$. The isopropylidene groups were removed as before to give the mixed anomers of 6-*O*-succinyl-D-galactose (**16**); the ^{13}C NMR spectrum (Table 1) is similar to that of the corresponding phthalyl derivative (**13**).

Biological evaluation of the organotin compounds is incomplete but **5** and **14** show enhanced pesticidal activity. Biological effects will be discussed in a forthcoming publication.

EXPERIMENTAL

General

Nuclear magnetic resonance spectra were measured on the ULIRS instruments at Queen Mary College (Bruker WH 400) and King's College (Bruker WM 250), University of London. ^{13}C chemical shift values refer to tetramethylsilane. Mass spectra measurements were made on a Kratos MS25 instrument at 70 eV. Optical rotations were determined using a Perkin-Elmer 141 polarimeter.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-phthalyl-α-D-glucofuranose (2)

Phthalic anhydride (1.48 g, 10 mmol), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2.6 g, 10 mmol), triethylamine (5.57 cm^3, 4 mmol) and DMF (50 cm^3) were stirred at room temperature for 4 h; TLC (dichloromethane/acetic acid, 20:1), showed completion of reaction. The mixture was evaporated to a thick syrup which was dissolved in dichloromethane and then extracted with water to remove traces of DMF. The dried organic layer was evaporated to give a solid which was recrystallized from dichloromethane/light petroleum (b.p. 40–60°C) to give the product **2** as colourless needles (3.5 g, 85%), m.p. 166°C, [α] −74.17° (*c* 1.0, chloroform). ^{1}H NMR data (250 MHz, $CDCl_3$); δ 7.60–7.91 (4H, m, aromatic), 5.92 (d, $J_{1,2}$ 3.68 Hz H-1), 4.82 (d, H-2), 5.44 (s, H-3), 4.29 (m, H-4, H-5 over-

lapped), 4.0–4.1 (m, H-6a, H-6b overlapped), 1.34–1.55 (12H, isopropylidene), 10.18 (br, carboxylic). Found: C, 58.40; H, 5.88. Calc. for $C_{20}H_{24}O_9$: C, 58.82; H, 5.88%.)

3-*O*-Phthalyl-D-glucose (4)

The preceding isopropylidene derivative (**2**) (0.5 g, 1.23 mmol) was shaken with 90% trifluoroacetic acid (5 cm^3) until TLC (acetic acid/toluene/ethanol, 2:2:1) indicated that no starting material remained. Volatile material was evaporated to give a white solid which was dried *in vacuo* giving compound **4** (0.4 g, 80%), $[\alpha]_D + 19.91° \rightarrow +49.29°$ (*c* 1.0, water). ^{13}C NMR data are given in Table 1.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-(o-methoxycarbonylbenzoyl)-D-glucopyranose (7)

Diazomethane in ether was added, in portions, to a solution of glucose phthalate (**4**) (200 mg, 0.6 mmol) in methanol (3 cm^3). When the colour persisted, excess diazomethane was decomposed by addition of acetic acid and the solvent removed under reduced pressure. The residue was dissolved in dry pyridine (2 cm^3), acetic anhydride (1 cm^3) added and the mixture allowed to stand overnight. The reaction mixture was evaporated to a thick syrup which was dissolved in chloroform and the solution washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and water. The dried (magnesium sulphate) chloroform solution was evaporated to give **7** as a white solid (0.20 g, 66%), m.p. 40°C, $[\alpha] + 22.56° \rightarrow +31.79°$ (*c* 1.0, chloroform). ^1H NMR data are given in Table 2. (Found: C, 54.21; H, 4.62. Calc. for $C_{23}H_{26}O_{13}$:C, 54.11; H, 5.13%.)

3-*O*-(o-Tributylstannyloxycarbonylphenyl)-D-glucose (5)

3-*O*-Phthalylglucose (**4**) (0.49 g, 1.5 mmol) was added to a solution of bis(tributyl)tin oxide (0.25 cm^3, 0.5 mmol) in dry benzene (25 cm^3) and the mixture boiled under reflux for 2 h. The cooled mixture was centrifuged, the centrifugate evaporated and the residue dried *in vacuo* over potassium hydroxide to give **5** (0.41 g, 67%) as a white solid; the infrared spectrum showed carbonyl bands $\nu(C{=}O)_{COOC}$ 1720 cm^{-1} and $\nu(C{=}O)_{COOSn}$ 1670 cm^{-1}

In a similar manner, 3-*O*-(*o*-triphenylstannyloxycarbonylphenyl)-D-glucose (**6**) was prepared from triphenyltin hydroxide in 66% yield. The infrared spectrum of the white solid product showed carbonyl bands $\nu(C{=}O)_{COOC}$ 1720 cm^{-1} and $\nu(C{=}O)_{COOSn}$ 1660 cm^{-1}.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-succinyl-α-D-glucofuranose (3)

A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (7.81 g, 30 mmol), succinic anhydride (3.02 g, 30 mmol) and triethylamine (12.12 g, 60 mmol) in DMF (150 cm^3) was stirred for 4 h at room temperature until TLC (dichloromethane/acetic acid, 20:1) indicated completion of reaction. The solvent was evaporated under reduced pressure and the residue dissolved in the minimum volume of dichloromethane. The product (**3**) was precipitated with light petroleum (b.p. 40–60°C) and obtained as a thick syrup, shown by TLC to be homogeneous (8.1 g, 75%). ^1H NMR data (250 MHz, $CDCl_3$) revealed a resonance at δ 2.70 (4 H, m, CH_2CH_2); otherwise the spectrum was similar to that of **2** except for the absence of aromatic proton signals. (Found: C, 53.21; H, 6.59. Calc. for $C_{16}H_{24}O_9$: C, 53.33; H, 6.66%.)

3-*O*-Succinyl-D-glucose (8)

The succinyl derivative (**3**) (1.00 g, 2.78 mmol) was treated with 90% trifluoroacetic acid (10 cm^3) for 30 min. TLC (acetic acid/toluene/ethanol, 2:2:1) then showed the absence of starting material and the formation of a single product. The mixture was evaporated and the solid residue dried over potassium hydroxide *in vacuo* to give **8** as a white solid (0.71 g, 91%), $[\alpha] + 2.54° \rightarrow +35.67°$ (*c* 1.0, water). Details of the ^{13}C NMR spectrum are given in Table 1.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-(3′-methoxycarbonylpropionyl)-D-glucopyranose (9)

Compound **8** (200 mg) in methanol (3 cm^3) was methylated by portion wise addition of an excess of diazomethane in ether. The solvent was removed and the residue dissolved in pyridine (3 cm^3), acetic anhydride (1.5 cm^3) added and the mixture left overnight at room temperature. After addition of methanol, the mixture was evaporated and the residue dissolved in chloro-

form. The solution was washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and water, dried with magnesium sulphate and evaporated to give the syrupy product (**9**) (100 mg). Details of the ^{1}H NMR spectrum are given in Table 2. (Found: C, 48.95; H, 5.31. Calc. for $C_{19}H_{26}O_{13}$:C, 49.35; H, 5.63%.)

1,2:3,4-Di-*O*-isopropylidene-6-*O*-phthalyl-α-D-galactopyranose (11)

A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2.6 g, 10 mmol), phthalic anhydride (1.48 g, 10 mmol), triethylamine (5.56 cm^3, 40 mmol) and DMF (850 cm^3) was stirred at room temperature for 2 h; TLC (chloroform–acetic acid, 20:1) then indicated completion of reaction. The mixture was concentrated to a syrup, which was dissolved in chloroform. After extracting with water and drying with magnesium sulphate, this solution was evaporated to give **11** as a solid (3.5 g, 86%) which was homogeneous (TLC), $[\alpha]_D - 11.7°$ (*c* 1, chloroform). ^{1}H NMR data (250 MHz, $CDCl_3$):δ 5.58 (d, $J_{2,3}$ 2.0 Hz, H-1), 4.58 (q, $J_{3,4}$ 8.0 Hz, H-3), 4.24 (m, $J_{4,5}$ 1.5 Hz, H-4), 4.06 (m, H-5), 4.54 (q, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.35 (q, $J_{5,6b}$ 8.0 Hz, H-6b). The downfield shift of the H-6a and H-6b protons compared with their positions in **10** confirmed the location of phthalate at O-6. (Found: C, 58.72; H, 5.88. Calc. for $C_{20}H_{24}O_9$: C, 58.82, H, 5.98%.)

The isopropylidene groups were removed by treatment with trifluoroacetic acid exactly as for the glucose derivative to give **13** as a white solid (90%), $[\alpha]_D + 1.52 \rightarrow +20.25°$ (*c*1, water). The ^{1}H NMR spectrum (250 MHz, $CDCl_3$) showed absence of signals from methyl protons of isopropylidene groups in the δ 2.5–3.0 region and presence of a four proton signal at δ7.6–7.7 from the aromatic residue. The H-1α and H-1β signals occurred at δ 5.33 ($J_{1,2(\alpha)}$ 3.5 Hz) and 4.65 ($J_{1,2(\beta)}$ 8.0 Hz) respectively. ^{13}C NMR chemical shifts are shown in Table 1. Treatment of **13** with bis(tributyltin) oxide under the same conditions used to prepare **5** gave the tributyltin derivative **14**, (71%); the IR spectrum showed ν(C=O)$_{COOC}$ 1720 cm^{-1} and ν(C=O)$_{COOSn}$ 1660 cm^{-1}. The triphenyltin compound **15** was made similarly (76%); ν(C=O)$_{COOC}$ 1720 and ν(C=O)$_{COOSn}$ 1650 cm^{-1}.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-succinyl-α-D-galactopyranose (12)

A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2.6 g, 10 mmol), succinic anhydride (1.0 g, 10 mmol), triethylamine (5.6 cm^3, 40 mmol) and DMF (50 cm^3) was stirred at room temperature for 2 h. The mixture was concentrated, the residue dissolved in dichloromethane (25 cm^3) and the solution washed with water and dried over magnesium sulphate. Evaporation gave the crude product which was crystallized from dichloromethane–petroleum ether to give **12** as colourless crystals (2.0 g, 56%), m.p. 110°C, $[\alpha]_D - 43.71°$ (*c* 1.0, water). The ^{1}H NMR spectrum (250 Mz, $CDCl_3$) was similar to that of **11** except for the absence of aromatic proton signals at δ 7.6–7.77; instead δ 2.69 (s, CH_2CH_2) was observed. (Found: C, 53.35; H, 6.68. Calc. for $C_{16}H_{24}O_9$:C, 53.33; H, 6.66%.) The isopropylidene groups were removed as before by treatment with trifluoroacetic acid to give 6-*O*-succinylgalactose (**16**) as a white solid (64%), $[\alpha]_D + 10.2 \rightarrow +33.4°$ (*c* 1.0, water). The structure was confirmed by the ^{13}C NMR spectrum (Table 1).

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REFERENCES

1. Parkin, A and Poller, R C *Carbohydr. Res.*, 1978, 62: 83
2. Patel, A and Poller, R C *Main Group Metal Chemistry*, in press
3. Parkin, A and Poller, R C *International Pest Control*, 1977, 19: 5
4. Block, K and Pedersen, C *Adv. Carbohydr. Chem. Biochem.*, 1983, 41: 27