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Note

"Standardized intermediates" for oligosaccharide synthesis: convenient preparation of 2-amino-2-deoxy-D-glucose derivatives and their conversion into the D-galactose analogues

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The chemical synthesis of oligosaccharides composed of more than one type of sugar unit and having more than one type of intersugar linkage typically involves the coupling of an activated sugar carrying transient protecting groups to an acceptor sugar. We now report the synthesis of a series of derivatives of 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-galactose which may be regarded as glycosyl donors and acceptors.

The starting point for the synthesis was 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose[1–3] (**1**), which was prepared by the method of Baker *et al.*[1].

Compounds **3** and **4** were prepared from 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranose (**2**). Several methods[4–8] have been described for the preparation of **2**, but treatment of **1** with hydrazine acetate[6] proved to be the method of choice.

Treatment of **2** with diethylaminosulfur trifluoride gave the fluoride **3**, and with trichloroacetonitrile in the presence of sodium hydride gave the trichloroacetimidate **4**.

The starting compounds for the synthesis of the glycosyl acceptors were allyl[9,10] (**5**) and benzyl[10] 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**6**) prepared by reacting **1** with allyl alcohol, benzyl alcohol, or ethanethiol in the presence of anhydrous ferric chloride. Treatment of these glycosides severally with methanolic sodium methoxide gave the respective 3,4,6-triols **7**, **8** (ref. 11) and **9** (ref. 12).

Selective benzoylation of **7**–**9**, using 2.2 equiv. of benzoyl chloride in pyridine at −45°, furnished chiefly the corresponding 3,6-dibenzoates **10**–**12** suitable for 4-coupling. Treatment of **7** and **9** with benzaldehyde and anhydrous zinc chloride[13] gave the corresponding 4,6-*O*-benzylidene derivatives **13** and **14** as acceptors suitable for 3-coupling.

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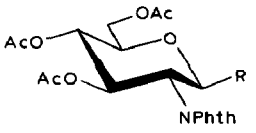
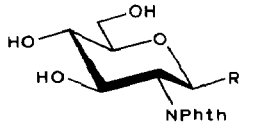
The most convenient route to the *galacto* isomers (**18–20**), suitable for 4-coupling, involved the reaction of **10–12** severally with triflic anhydride in dichloromethane at −15°, to give the corresponding intermediate triflates **15–17** which were treated, without purification, with sodium nitrite in *N,N*-dimethylformamide at ambient temperature to give **18–20**.

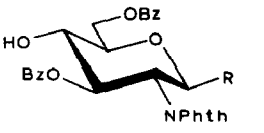
The ^{1}H-n.m.r. spectra of the above compounds accorded with the structures assigned (see Experimental).



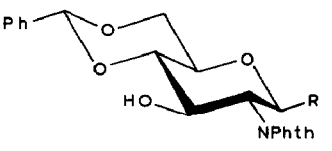
1 R = Ac
2 R = OH
3 R = F
4 R = OC(=NH)CCl$_3$
5 R = OCH$_2$CH=CH$_2$
6 R = SEt



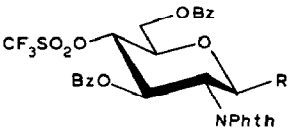
7 R = OCH$_2$CH=CH$_2$
8 R = OBn
9 R = SEt



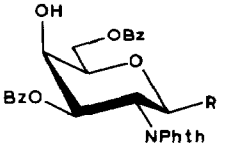
10 R = OCH$_2$CH=CH$_2$
11 R = OBn
12 R = SEt



13 R = OCH$_2$CH=CH$_2$
14 R = SEt



15 R = OCH$_2$CH=CH$_2$
16 R = OBn
17 R = SEt



18 R = OCH$_2$CH=CH$_2$
19 R = OBn
20 R = SEt

EXPERIMENTAL

General. — Melting points were determined on a Buchi 510 instrument and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 241 or 243 Polarimeter in a 10-cm cell at 589 nm. The ^{1}H- and ^{13}C-n.m.r. spectra (internal Me_4Si) were recorded with a Bruker WM-270 or WM-400 spectrometer. Elemental analyses were performed at the University of Hamburg. T.l.c. was performed on Silica Gel GF_{254} (Merck). For column chromatography, Silica Gel 60 (70–230 mesh, ASTM, Merck) was used.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl fluoride (**3**). — To a stirred solution of **2** (3 g, 6.9 mmol) in tetrahydrofuran (25 mL) at −30°, under nitrogen, diethylaminosulfur trifluoride (1 mL, 1.2 equiv.) was added rapidly. The cooling bath was removed immediately and the mixture was left for 20 min at room temperature. Methanol (5 mL) was added, the mixture was concentrated, and a solution of the residue in chloroform was washed with water, dried, and concentrated. The residue was crystallized from ethyl acetate–hexane to give **3** (2.38 g, 79%), m.p. 115°, $[\alpha]_D$ +7.7° (*c* 1.1, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 6.23–6.00 (dd, 1 H, $J_{1,F}$ 52.7, $J_{1,2}$ 10.1 Hz, H-1), 4.52–4.40 (4 d, 1 H, H-2).

Anal. Calc. for $C_{20}H_{20}FNO_9$ (437.38): C, 54.90; H, 4.60; F, 4.30; N, 3.20. Found: C, 55.10; H, 4.60; F, 4.20; N, 3.10.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate (**4**). — To a stirred solution of **2** (4.5 g, 10.34 mmol) in dichloromethane (80 mL) containing molecular sieves 4 Å (1.5 g) was added trichloroacetonitrile (6 mL, 59.82 mmol) followed by sodium hydride (200 mg, 8.7 mmol) portionwise. After 10 min, the mixture was filtered through Celite and concentrated under diminished pressure. Column chromatography (20:1 dichloromethane–acetone) of the residue and recrystallization from ether gave **4** (4.4 g, 73%), m.p. 146°, $[\alpha]_D$ +76° (*c* 1, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 8.67 (s, 1 H, D_2O-exchangeable, NH), 7.90–7.70 (2 m, 4 H, C_6H_4), 6.63 (d, 1 H, $J_{1,2}$ 8.8 Hz, H-1), 5.92 (t, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 5.29 (t, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 4.64 (dd, 1 H, $J_{1,2}$ 8.8, $J_{2,3}$ 10.6 Hz, H-2), 4.40–4.20 (dq, 2 H, H-6,6'), 4.08 (m, 1 H, H-5), 2.13, 2.06, 1.90 (3 s, 9 H, 3 Ac).

Anal. Calc. for $C_{22}H_{21}Cl_3N_2O_{10}$ (579.78): C, 45.58; H, 3.65; N, 4.83. Found: C, 45.61; H, 3.80; N, 4.74.

Ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**6**). — A solution of **1** (25 g, 52.14 mmol) in dichloromethane (150 mL) was treated with ferric chloride (12.5 g), and the solution was stirred for 10 min, then cooled to 0°. Ethanethiol (8 mL, 2 mol. equiv.) was added, and the reaction mixture was stirred for 15 min, then poured into water (200 mL), and extracted with dichloromethane. The extract was washed, dried, and concentrated. The residue **6** (19.3 g, 77%) had m.p. 118° (from ethyl acetate–hexane), $[\alpha]_D$ +44° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.76–2.58 (m, 2 H, CH_2CH_3) and 1.19 (t, 3 H, CH_3CH_2).

Anal. Calc. for $C_{22}H_{25}NO_9S$ (479.50): C, 55.10; H, 5.25; N, 2.92; S, 6.67. Found: C, 55.08; H, 5.09;N, 3.15; S, 6.83.

Allyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (**7**). — Methanolic 0.3M sodium methoxide (25 mL) was added to a stirred solution of **5** (10 g) in dichloromethane–methanol (125 mL, 3:2) at room temperature. After 2 h, the solution was neutralized using an ion-exchange resin, filtered, and concentrated. The residue was crystallized from ethyl acetate–hexane to give **7** (5.4 g, 76%), m.p. 190°, $[\alpha]_D$ +19° (*c* 0.8, chloroform). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 5.41 (d, 1 H, $J_{3,OH}$ 4.7 Hz, D_2O-exchangeable, HO-3), 5.18 (d, 1 H, $J_{4,OH}$ 5.1 Hz, D_2O-exchangeable, HO-4), 4.63 (t, 1 H, *J* 6.5 Hz, D_2O-exchangeable, HO-6).

Anal. Calc. for $C_{17}H_{19}NO_7$ (349.34): C, 58.45; H, 5.48; N, 4.01. Found: C, 58.21; H, 5.91; N, 3.79.

Allyl 3,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**10**). — To a solution of **7** (1 mol) in dry pyridine at −45° was added benzoyl chloride (2.2 mol. equiv.) during 20 min. Stirring was continued for a further 2 h, the solution was then allowed to attain room temperature gradually, methanol (10 mL) was added, and the solution was concentrated to dryness to give **10** (95.8%), m.p. 138°, $[\alpha]_D$ +93° (*c* 0.7, chloroform). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 8.11–7.27 (m, 14 H, C_6H_4, and 2 Ph), 5.99 (dd, 1 H, $J_{3,4}$ 11.4 Hz, H-3), 5.81–5.70 (m, 1 H, –CH=), 5.56 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 5.17–5.03 (dq, 2 H, $=CH_2$), 4.78–4.73 (m, 2 H, H-6,6'), 4.51 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 10.8 Hz, H-4), 4.35–4.08 (dq, 2 H, $-OCH_2-CH=$), 4.03–3.90 (m, 2 H, H-2,5), 3.80–3.70 (bs, 1 H, D_2O-exchangeable, HO-4).

Anal. Calc. for $C_{13}H_{27}NO_9$ (557.56): C, 66.78; H, 4.88; N, 2.51. Found: C, 66.58; H, 4.87; N, 2.53.

Benzyl 3,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**11**). —Prepared from **8**, as described for **10** and with column chromatography (dichloromethane–acetone, 20:1), amorphous **11** (69%) had m.p. 118°, $[\alpha]_D$ +41° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 8.16–7.03 (m, 19 H, C_6H_4, 3 Ph), 5.94 (dd, 1 H, $J_{3,4}$ 8.3, $J_{2,3}$ 11.1 Hz, H-3), 5.47 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 5.87, 4.57 (ABq, 2 H, J_{AB} 12.5 Hz, PhCH_2), 4.84–4.68 (m, 2 H, H-6,6'), 4.53 (dd, 1 H, $J_{3,4}$ 8.3, $J_{4,5}$ 10.9 Hz, H-4), 3.97–3.87 (m, 2 H, H-2,5), 3.62–3.42 (bs, 1 H, D_2O-exchangeable, HO).

Anal. Calc. for $C_{35}H_{29}NO_9$ (607.62): C, 69.19; H, 4.81; N, 2.31. Found: C, 69.01; H, 4.91; N, 2.31.

Ethyl 3,6-di-O-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**12**). —Prepared from **9**, as described for **10** and with column chromatography (dichloromethane–acetone, 20:1), amorphous **12** (75%) had $[\alpha]_D$ +100° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 8.14–7.28 (m, 14 H, C_6H_4 and 2 Ph), 6.35 (t, 1 H, *J* 9.1 Hz, H-3), 5.68 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.76 (m, 2 H, H-6,6'), 4.57 (t, 1 H, *J* 9.1 Hz, H-4), 4.10–3.88 (m, 2 H, H-2,5), 3.71 (s, 1 H, HO-4).

Anal. Calc. for $C_{30}H_{27}NO_8S$ (561.62): C, 64.15; H, 4.84;N, 2.49; S, 5.70. Found: C, 64.24; H, 4.83; N, 2.59; S, 5.53.

Allyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**13**). — Fused zinc chloride (5 g) was stirred quickly with benzaldehyde (25 mL) for 30 min, and **7** (5 g) was added. Stirring was continued for 3 h, and the syrupy mass was then poured into ice–water (50 mL) and light petroleum (50 mL). After vigorous shaking, the product was collected and crystallized from ethanol–hexane to give **13** (82%), m.p. 150°, $[\alpha]_D$ −39° (*c* 1, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 7.87–7.26 (m, 9 H, Ph and C_6H_4), 5.77–5.62 (m, 1 H, –CH=), 5.57 (s, 1 H, PhC*H*), 5.30 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 5.18–5.01 (m, 2 H, $=CH_2$), 4.63 (dd, 1 H, $J_{2,3}$ 9.1, $J_{3,4}$ 10.4 Hz, H-3), 4.42–4.18 (m, 4 H, H-6,6', OCH_2–CH=), 3.87–3.78 (t, 1 H, $J_{3,4}$ 10.4 Hz, H-4), 3.67–3.56 (m, 2 H, H-2,5).

Anal. Calc. for $C_{24}H_{24}NO_7$ (428.46): C, 65.90; H, 5.30; N, 3.20. Found: C, 66.14; H, 5.34; N, 3.23.

Ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**14**). — Prepared from **9**, as described for **13** and after recrystallization from ethanol–hexane, **14** (69%) had m.p. 157°, $[\alpha]_D$ +14° (*c* 0.6, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 7.84–7.32 (m, 9 H, C_6H_4 and *Ph*CH), 5.53 (s, 1 H, PhC*H*), 5.35 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.60 (t, 1 H, *J* 9.0, H-3), 4.38–3.51 (m, 5 H, H-2,4,5,6,6'), 3.13 (bs, 1 H, HO-3), 2.72–2.56 (m, 2 H, CH_2CH_3), 1.18 (t, 3 H, *J* 8.1 Hz, CH_2CH_3).

Anal. Calc. for $C_{23}H_{23}NO_6S$ (441.51): C, 62.57; H, 5.25; N, 3.17; S, 7.26. Found: C, 62.58; H, 5.33; N, 3.21; S, 7.24.

Allyl 3,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (**18**). — To a stirred solution of trifluoromethanesulfonic anhydride (3 mL, 18.2 mmol) in dichloromethane (60 mL) at −15° was added dropwise pyridine (3 mL, 36.5 mmol) diluted with dichloromethane (1 mL) followed by a solution of **10** (16.5 mmol) in dichloromethane (80 mL). After 30 min at −15°, the solution was diluted with chloroform, washed with

aqueous 10% hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, and then concentrated. To a solution of the resulting 4-triflate **15** in the minimum volume of *N,N*-dimethylformamide was added sodium nitrite (7.9 mol. equiv.). The mixture was stirred at room temperature until the reaction was complete (t.l.c.; dichloromethane–acetone, 20:1), then diluted with chloroform, washed with water, and concentrated. The residue was recrystallized from ethyl acetate–hexane to give **18** (86%), m.p. 128°, $[\alpha]_D$ +56° (*c* 0.8, chloroform). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 8.08–7.28 (m, 14 H, aromatic), 5.90 (dd, 1 H, $J_{3,4}$ 3.3, $J_{2,3}$ 11.7 Hz, H-3), 5.79–5.68 (m, 1 H, –CH=), 5.48 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 5.16–5.03 (m, 2 H, CH_2=), 4.88 (dd, 1 H, $J_{2,3}$ 11.4, $J_{1,2}$ 8.7 Hz, H-2), 4.73–4.62 (m, 2 H, H-6,6'), 4.42 (d, 1 H, $J_{3,4}$ 3.3, $J_{4,5}$ < 1 Hz, H-4), 4.34–4.08 (m, 3 H, –OCH_2–CH=, and H-5), 2.85 (bs, 1 H, HO-4).

Anal. Calc. for $C_{31}H_{27}NO_9$ (557.56): C, 66.78; H, 4.88; N, 2.51. Found: C, 66.90; H, 5.00; N, 2.58.

*Benzyl 3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-*D*-galactopyranoside* (**19**). — Prepared from **11**, as described for **18** and after recrystallization from ethyl acetate–hexane, **19** (80%) had m.p. 160°, $[\alpha]_D$ +18° (*c* 0.6, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 8.10–7.03 (m, 19 H, C_6H_4, 3 Ph), 5.89 (dd, 1 H, $J_{3,4}$ 3.2, $J_{2,3}$ 11.7 Hz, H-3), 5.42 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1), 4.88 (t, 1 H, $J_{1,2}$ 8.5 Hz, H-2), 4.87, 4.58 (ABq, 2 H, J_{AB} 11.9 Hz, PhCH_2), 4.76–4.63 (m, 3 H, H-6,6', HO-4), 4.40 (bd, 1 H, $J_{3,4}$ 3.5, $J_{4,5}$ < 1 Hz, H-4), 4.16 (bt, 1 H, $J_{5,6}$ 6.7, $J_{4,5}$ < 1 Hz, H-5).

Anal. Calc. for $C_{35}H_{29}NO_9$ (607.62): C, 69.19; H, 4.81; N, 2.31. Found: C, 69.24; H, 4.91; N, 2.29.

*Ethyl 3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-1-thio-β-*D*-galactopyranoside* (**20**). — Prepared from **12**, as described for **18** and after recrystallization from ethyl acetate–hexane, **20** (74%) had m.p. 155°, $[\alpha]_D$ +77° (*c* 1, chloroform). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 8.07–7.28 (m, 14 H, C_6H_4 and 2 Ph), 5.98 (dd, 1 H, $J_{3,4}$ 3.2, $J_{2,3}$ 10.7 Hz, H-3), 5.58 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 4.95 (t, 1 H, $J_{2,3}$ 10.7 Hz, H-2), 4.74–4.57 (m, 2 H, H-6,6'), 4.43 (bd, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ < 1 Hz, H-4), 4.21 (t, 1 H, $J_{5,6}$ 6.9, $J_{4,5}$ < 1 Hz, H-5), 2.83–2.62 (m, 3 H, HO-4, CH_3CH_2), 1.23 (t, 3 H, *J* 8.1 Hz, CH_3CH_2).

Anal. Calc. for $C_{30}H_{27}NO_8S$ (561.62): C, 64.14; H, 4.84; N, 2.49; S, 5.70. Found: C, 64.04; H, 4.97; N, 2.53; S, 5.55.

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