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Preliminary communication

New synthesis of a benzylated chitobiose derivative, employing 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl chloride*

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Partially protected derivatives of chitobiose [2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucopyranose] are needed for the synthesis of oligosaccharides corresponding to the "core" region of the sugar chains of the *N*-glycoproteins[1]. Suitable compounds, such as allyl 2-acetamido-4-*O*-(2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**11**) have been synthesized[2] by the "oxazoline procedure", but good yields were difficult to obtain because of unavoidable side-reactions. The alternative procedure, in which a glycosyl halide (usually per-*O*-acetylated) having an *N*-phthalimido group is the glycosyl donor in a silver triflate-promoted, coupling reaction, gives good yields, and has been successfully applied to the synthesis of β-D-(1→4) linkages[3]. Recently, the advantage of including molecular sieves in the reaction mixture has been demonstrated[4,5], and, in this communication, we extend this synthetic method to a glycosyl donor having benzyl substituents, to give allyl 2-acetamido-4-*O*-(2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**12**).

Allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside[6] (**1**) was selected as precursor of the glycosyl chloride **9**, because of the ease of preparation by selective benzylation *via* stannylated intermediates[7]. After conversion into the 1-propenyl glycoside **2**, treatment with strong alkali gave, in high yield, the amorphous 2-amino-2-deoxy compound **3**, $[\alpha]_D^{25}$ +81° (*c* 1, chloroform), which was treated with phthalic anhydride[8] to yield the 2-(2-carboxybenzamido) derivative **4** (100%), $[\alpha]_D^{25}$ +67.5° (*c* 1, chloroform).

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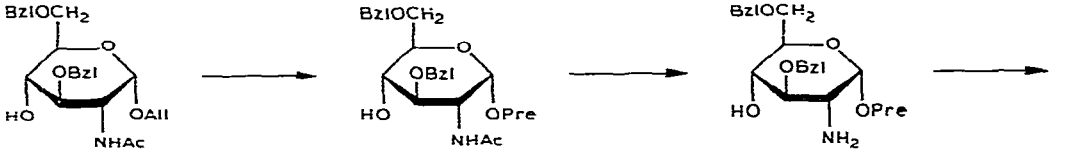
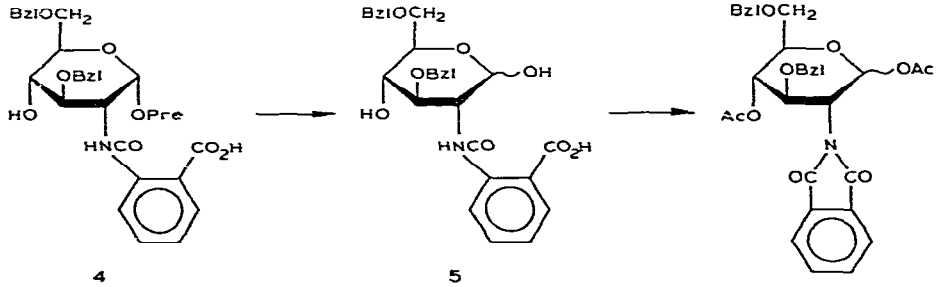
In the first attempt to prepare a glycosyl chloride from **4**, the 1-propenyl group was hydrolyzed with mercuric chloride in aqueous acetone[9], to yield the diol **5** (100%), which crystallized from methanol, m.p. 158.9–159°, $[\alpha]_D^{25}$ +69 → +58° (24 h; *c* 1, chloroform). This was treated with acetic anhydride–pyridine, to give the 1,4-di-*O*-acetyl-*N*,*N*-phthaloyl derivative **6**, which crystallized from methanol, m.p. 121.2–122.8°, $[\alpha]_D^{25}$ +112° (*c* 1, chloroform); *m/z* 530 ($M^+ - COCH_3$). However, all attempts to convert **6** into a glycosyl halide (under the usual conditions, employing hydrogen bromide, hydrogen chloride, stannic chloride, or acetyl chloride) failed, owing to stability of the 1-*O*-acetyl group, or lability of the benzyl groups.



1 2 3

Bzl = $PhCH_2$ Pre = $MeCH{=}CH$

All = $H_2C{=}CHCH_2$

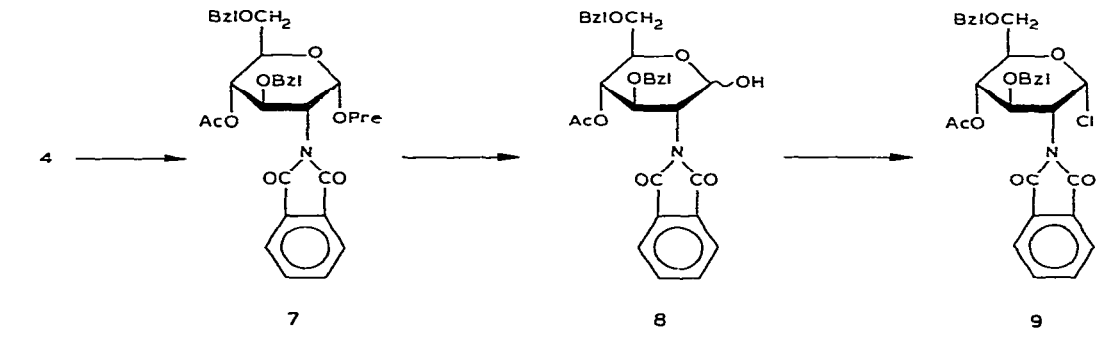


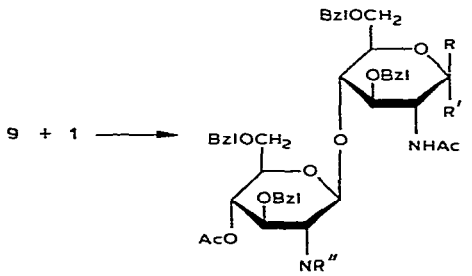
4 5 6

Therefore, **4** was converted into the syrupy 2-phthalimido derivative **7**, $[\alpha]_D^{25}$ +32.5° (*c* 1, chloroform), which, on treatment with mercuric chloride, gave the OH-1 compound **8** in quantitative yield, $[\alpha]_D^{25}$ +12° (*c* 1, chloroform, no mutarotation); t.l.c.: R_F 0.33 in 1:1 (v/v) ethyl acetate–hexane. When **8** was treated with freshly prepared chloro-*N*,*N*-dimethylformamidium chloride[10], it was efficiently converted into the glycosyl chloride **9**; t.l.c. R_F 0.56 (a double spot, showing a mixture of the anomers) which was directly treated with **1**.

A stirred mixture of **1** (1.7 mmol), silver triflate (2.7 mmol), collidine (2.9 mmol), and molecular sieve 4A (200 mg) in dichloromethane (1 mL) was treated at room temperature[4] with a solution of the glycosyl chloride **9** (2.4 mmol) in dichloromethane (1 mL). After being stirred for 48 h in the dark, the solution showed, in t.l.c.,

the formation of the desired disaccharide **10**, R_F 0.68, in 20:1 (v/v) chloroform–methanol, together with some unchanged **1**, and a small proportion of the OH-1 compound **8** arising from hydrolysis of **9**. After purification by p.l.c., the yield of amorphous **10** (based on the amount of **9** used in the reaction) was 62.5%, $[\alpha]_D^{25}$ +44° (*c* 1, chloroform). The structure of **10** was confirmed by elemental analysis, i.r. and ^{1}H-n.m.r. spectroscopy, and mass spectrometry.





10 R = H, R' = OAll, R'' = $C_6H_4(CO)_2$
11 R = OAll, R' = H, R'' = HAc
12 R = H, R' = OAll, R'' = HAc

When the coupling of **9** and **1** was performed under the "classical", triflate-promoted conditions[3] (with cooling to –30° and without molecular sieve), the yield of **10** was much lower (10%), and a major by-product having much higher mobility in t.l.c. was isolated (22% yield, based on **9**). I.r. and n.m.r. spectra, the desorptive chemical-ionization mass spectrum, and elemental analysis indicated that it was 1,4-di-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-D-glucopyranose (**6**), probably arising from the intermolecular transacetylation of the hydrolysis product **8**.

Removal of the *N,N*-phthaloyl group from **10**, followed by *N*-acetylation, gave the desired compound **12** (80%), m.p. 232.4–232.6°, $[\alpha]_D^{25}$ +53° (*c* 0.6, chloroform). The identity of the synthetic intermediates **3**, **4**, **7**, **8**, and of compounds **5** and **6**, was confirmed by elemental analysis, and i.r. and ^{1}H-n.m.r. spectroscopy.

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