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Preliminary communication

The synthesis of disaccharides by the ferric chloride-catalyzed coupling of 2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates to protected sugar acceptors

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As outlined in the immediately preceding communication[1], we have found that such tri-*O*-acetyl-2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates as **1a** react with simple alcohols, in the presence of ferric chloride in dichloromethane solution, to give excellent yields of alkyl β-glycosides. The present communication describes the application of this "direct" glycosylation reaction to the synthesis of β-linked disaccharides of 2-amino-2-deoxy-D-glucopyranose.

Three of the glycosyl donors used in our disaccharide syntheses, namely **1a**, **1c**, and **1d**, were drawn from the group of β-1-acetates used in experiments with simple alcohols[1]. In addition, we prepared[2], from the corresponding allyl β-glycosides, the two *O*-benzylated donors 2-acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranose (**1b**, allyl glycoside[3]) and 2-acetamido-1,4-di-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranose[2] (**1e**). As acceptors, we employed 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**), propyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside[4] (**3**), allyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside[5] (**4**), and benzyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside[4] (**8**).

The glycosylation procedure was a slight modification of that used with simple alcohols[1]. With respect to the glycosyl donor, mixtures contained 1.5-molar proportions of anhydrous ferric chloride and 0.5–2.0 molar proportions of acceptor. One molar proportion of *N,N,N′,N′*-tetramethylurea was routinely included, as it was found that this weak base[6] prevented the decomposition of **2** and other acid-labile components. The mixtures, protected from atmospheric moisture, were stirred overnight, or for a period of 2–3 days, at room temperature or at 35°. All reactions were monitored periodically by t.l.c. Extractive processing[1] after completion of the reaction gave, in each instance, a residue containing unreacted acceptor, disaccharide, and decomposition products. The disaccharides were isolated from these residues by chromatography and (in most cases) rechromatography on columns of silica gel. Mixtures of chloroform and acetone or methanol (chloroform being the major component) were employed as eluants.

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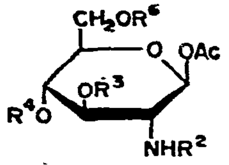
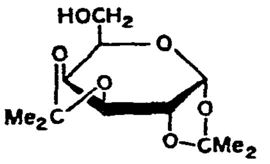


1a $R^{2\text{-}6}$ = Ac
1b R^2 = Ac, $R^{3\text{-}6}$ = Bn
1c R^2 = Bz, $R^{3\text{-}6}$ = Ac
1d R^2 = $ClCH_2CO$, $R^{3\text{-}6}$ = Ac
1e $R^{2,4}$ = Ac, $R^{3,6}$ = Bn



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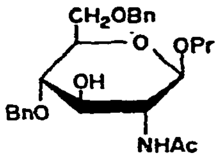

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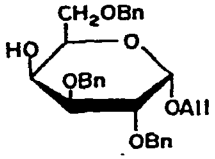

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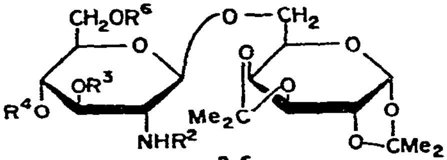
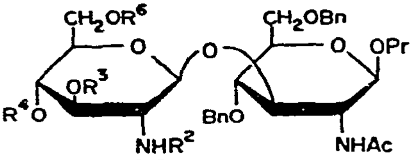
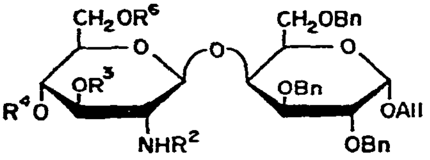


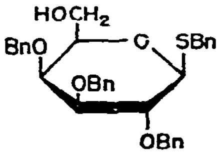
5a $R^{2\text{-}6}$ = Ac
5b R^2 = Ac, $R^{3\text{-}6}$ = Bn
5c R^2 = Bz, $R^{3\text{-}6}$ = Ac
5d R^2 = $ClCH_2CO$, $R^{3\text{-}6}$ = Ac



6a $R^{2\text{-}6}$ = Ac
6b R^2 = Ac, $R^{3\text{-}6}$ = Bn
6c R^2 = Bz, $R^{3\text{-}6}$ = Ac
6d R^2 = $ClCH_2CO$, $R^{3\text{-}6}$ = Ac



7a $R^{2\text{-}6}$ = Ac
7b R^2 = Ac, $R^{3\text{-}6}$ = Bn
7c R^2 = Bz, $R^{3\text{-}6}$ = Ac



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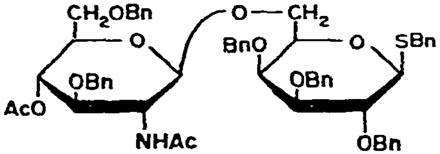

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All = allyl Bn = benzyl Pr = *n*-propyl

The results, given in Table I, may be summarized as follows. The β-1-acetates **1a–d** all gave good yields of (1→6)-linked (**5a–d**) and (1→3)-linked (**6a–d**), substituted disaccharides when coupled to **2** and **3**, respectively. The low reactivity of OH-4 frequently noted in partially protected hexoses was encountered in coupling to **4**, which furnished only modest yields of disaccharide products (**7a–c**). Higher rates of coupling were observed with compounds **1b**, **1c**, and **1d** as glycosyl donors than with **1a**, but the use of the more active donors did not lead to improved yields of disaccharides. Probably, the limiting factor in most of the syntheses was the difficult chromatographic purification of the final products. In the preparation of disaccharide derivatives **5c** and **9**, not only the β-1-acetates **1c** and **1e**, respectively, but also the corresponding preformed oxazolines were employed successfully as glycosyl donors.

The disaccharide products were characterized by comparison of their physical constants with literature values or by elemental analysis, by examination of the ^{1}H-n.m.r. spectra taken at 270 MHz, and in some instances by interconversion or by deprotection to give known, free disaccharides. All were shown to have the β-anomeric configuration at the intersugar linkage. All new compounds had elemental compositions in satisfactory accord with theory.

These findings establish ferric chloride-catalyzed glycosylation by 2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates or the corresponding oxazolines as a practical method for the incorporation of 2-acylamido-2-deoxy-β-D-glucopyranosyl groups into oligo-

TABLE I

DISACCHARIDES SYNTHESIZED

Formula	*Donor: acceptor ratio*	*Yield*[a] *(isolated) (%)*	*M.p. (°C)*	$[\alpha]^{25}_{D}$ (°)[b]	$[\alpha]^{25}_{436}$ (°)[b]
5a[c]	1:1.2	67	105–107	–66.6	–134
6a	2:1[d]	61	amorph.	–30.8	–64.6
7a	2:1[d]	42	142–143	+41.2	+76.6
5b[c]	1:2	80	amorph.	–28.8	–58
6b	1:1.5	62	173–175	–1	–6
7b	2:1[d]	45	syrup	+42	+80.8
5c	1:1.2	70	198–199	–44	–89.4
6c	2:1[d]	60	amorph.	–18.4	–39.2
7c	2:1[d]	30	amorph.	+46.4	+94.6
5d	1:1.2	80	amorph.	–42	–83
6d	1:1	60	176–177	–25.4	–52
9	1:1.2	80	178–179	–20.8	–42.2

[a] Based on limiting reactant. [b] Specific rotations determined in chloroform, $c = 0.5$. [c] Lit., ref. 2 and, for **5a**, further references cited there. [d] Donor, ferric chloride, and tetramethylurea added in portions, at intervals during the reaction period. Ratio based on total amount of donor used.

saccharides. The method may in some cases have advantages over the currently used procedures, which employ oxazolines with catalysis by protonic acids[2,3,7], or 2-phthalimido-2-deoxy-β-D-glucopyranosyl halides[8,9], as glycosylating agents.

ACKNOWLEDGMENTS

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