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1,3,4,6-Tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose as a glycosyl donor in syntheses of oligosaccharides*

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ABSTRACT

1,3,4,6-Tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose was tested as a glycosyl donor for oligosaccharide synthesis *via* a ferric chloride-catalyzed coupling reaction. Glycosyl acceptors tried (6 in all) were *O*-benzyl-protected D-galactosides having free OH groups at positions 3 and 4, respectively, and similarly protected glycosides of D-glucose and 2-acetamido-2-deoxy-D-glucose unsubstituted on O-4. Existing syntheses of all the acceptors were improved, in four instances by exploitation of Garegg and Hultberg's cyanoborohydride procedure for the conversion 4,6-*O*-benzylidene →6-*O*-benzyl [*Carbohydr. Res.*, 93 (1981) c10–c11; 108 (1982) 97–101]. Good to excellent yields of β-linked disaccharides were obtained from the galactoside and glucoside acceptors, but with allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside, stereoselectivity was lost (α:β-ratio 1:2). Allyl and benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosides gave, respectively, the allyl and benzyl β-glycosides of the donor as major products. A mechanism is proposed for this transglycosidation reaction. The *N*-chloroacetyl groups in the disaccharide products were readily converted into *N*-acetyl by reduction with zinc–acetic acid.

INTRODUCTION

Previous work in this laboratory showed that 3,4,6-tri-*O*-substituted 2-acylamino-2-deoxy-β-D-glucopyranose 1-acetates form β-glycosides by reaction with alcohols in the presence of anhydrous ferric chloride[1,2]. When the *N*-acyl group was acetyl, the reactivities of the compounds seemed to parallel those of the corresponding oxazolines, which are probably intermediates in the reaction. Satisfactory yields of glycosylated products were obtained only with acceptors having relatively unhindered OH groups. However, it appeared that the reactivities of the β-1-acetates could be modulated by varying the *N*-acyl group, and the *N*-chloroacetyl derivative **1**, in particular, showed promise of improved performance[2]. We now report on the qualities of **1** as a glycosylating agent.

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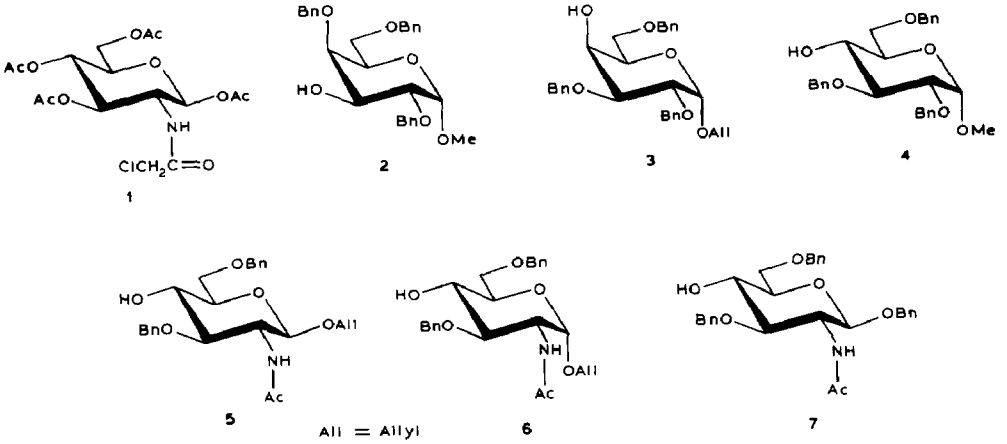
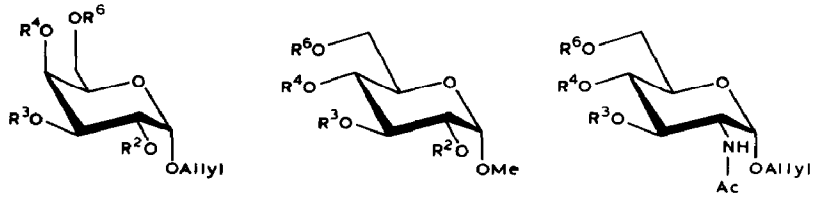


RESULTS

In order to test the efficacy of **1** as a donor, we required a series of coreactants typical of the glycosyl acceptors encountered in syntheses of oligosaccharides. The initial choices were the hexosides **2–4** and the glucosaminide **5**, designed for coupling at position 3, which is normally fairly reactive, or position 4, usually the least reactive in hexopyranosides. Coupling proceeded efficiently with **2–4**, but, from the reaction with **5**, the allyl β-glycoside of the *donor* was obtained, and no disaccharide product. Therefore, the study was extended to include the α anomer (**6**) and the benzyl congener (**7**) of the β-glycoside **5**.

Preparation of the acceptors. — Compounds **2–7** were all known substances that, in the past, were made by roundabout routes or nonspecific methods. However, improved syntheses could be based on recently developed procedures. Thus, ready access to methyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside[3] (**2**) was achieved by the dibutyltin oxide-mediated direct 3-crotylation[4] of methyl α-D-galactopyranoside, followed by benzylation, then *O*-decrotylation. The overall method was essentially that employed in our laboratory for the preparation of 1-propenyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside[5]. Kohata *et al.*[6] made β-**2** by a minor variation of this sequence.

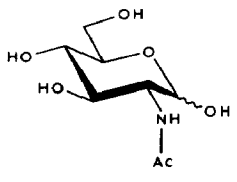
A short synthesis of *O*-benzyl-protected glycopyranosides having position 4 open was made possible by the availability of the cyanoborohydride procedure[7,8] for the reductive conversion of 4,6-benzylidene acetals into 6-benzyl ethers. The complete synthesis comprises the preparation of the 4,6-*O*-benzylidene derivative from the parent glycoside, benzylation of the product at O-2 and O-3 for hexosides, or at O-3 only for *N*-acylhexosaminides, and reductive cleavage. We followed this route in making the D-galactoside **3**, the D-glucoside **4**, and the *N*-acetyl-α-D-glucosaminide **6**, with excellent results. The details are given in the Experimental, along with improved procedures for the preparation of the known intermediates **10**, **13**, and **15**. The method has been used by Matta and collaborators[9] for the synthesis of the methyl glycoside corresponding to **6**, and perhaps by others.



	R^6	R^4	R^3	R^2
8	H	H	H	H
9	>CHPh		H	H
10	>CHPh		Bn	Bn

	R^6	R^4	R^3	R^2
11	H	H	H	H
12	>CHPh		H	H
13	>CHPh		Bn	Bn

	R^6	R^4	R^3
14	H	H	H
15	>CHPh		H
16	>CHPh		Bn



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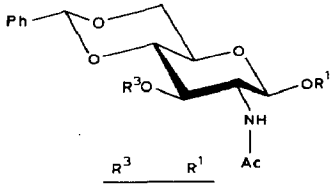
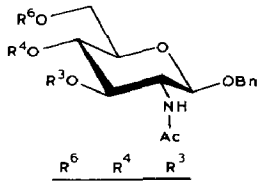


	R^3	R^1
18	H	H
19	Ac	Ac
20	Ac	Allyl
21	H	Allyl
22	Bn	Allyl



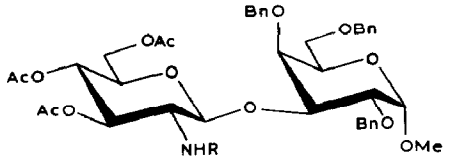
	R^6	R^4	R^3
23	H	H	H
24	>CMe_2		H
25	>CMe_2		Bn
26	H	H	Bn

Presumably the allyl *N*-acetyl-β-D-glucosaminide **5** could also be made by the above scheme, but the difficulties associated with the preparation of the parent glycoside[10] led us to explore an alternative route beginning with the 4,6-*O*-benzylidene derivative (**18**) of the free *N*-acetyl sugar **17**. The acetylation of **18** has in the past given *aβ*-mixtures[11], but, by conducting the reaction in dichloromethane, we were able to obtain the β-diacetate **19** as the primary product. This compound underwent facile glycosidation without loss of its cyclic acetal protecting group when treated in 1,2-dichloroethane with an alcohol and trimethylsilyl triflate. With allyl alcohol, **19** gave **20**, which could be *O*-deacetylated (→**21**) then converted into the 3,6-di-*O*-benzyl derivative (**5**) as described for **15**, *etc.* Thus, the route from **17** yields **5** considerably more efficiently than our previously reported synthesis[10] of this important oligosaccharide building block.

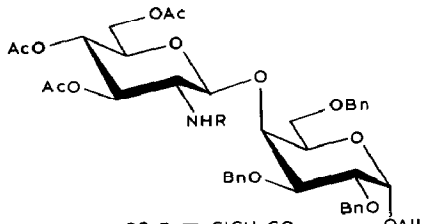
The preparation of **7** by the general method just discussed was reported by Rana *et al.*[12], but, in our hands, the reductive cleavage failed because of difficulty in dissolving the proposed precursor, benzyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside, in oxolane. Accordingly, we made **7** by an alternative route, in which positions 4 and 6 of the parent glycoside (**23**) were protected temporarily by an isopropylidene group (→**24**). After the benzylation of O-3 (→**25**), the protecting group was removed and the product (**26**) was benzylated selectively at O-6 with the aid of dibutyltin oxide[4].

Coupling. — Reaction mixtures for glycosylation usually consisted of acceptor, the glycosyl donor **1**, molecular sieves, and ferric chloride, added last, in dichloromethane. The mixtures were stirred at room temperature, with a mid-course supplement of **1** if needed, until the reaction was complete. Under these conditions, the acceptor galactosides **2** and **3** gave the disaccharide derivatives **27** and **29**, respectively, in yields of 80% after chromatography. The yield of the disaccharide derivative **31** from the glucoside **4** was considerably lower (60%), but it rose to 70% when the procedure was modified so that the acceptor was added last.

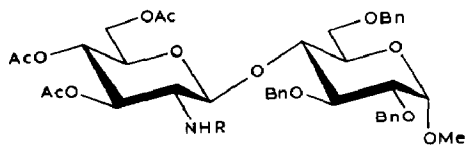
The coupling products **27**, **29**, and **31** were purified easily and characterized by their ^{1}H- and ^{13}C-n.m.r. spectra (see Table I, and Experimental). The spectra showed signals characteristic of both the donor and acceptor moieties, and clearly showed the added glycosyl unit to be β. No α-linked products were detected.



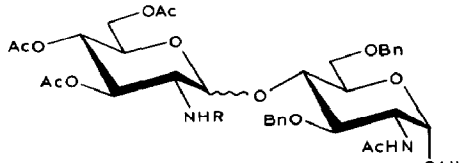
27 R = $ClCH_2CO$
28 R = CH_3CO



29 R = $ClCH_2CO$
30 R = CH_3CO



31 R = $ClCH_2CO$
32 R = CH_3CO



33 R = $ClCH_2CO$
34 R = CH_3CO

The major product (67%) of the reaction of **1** with the allyl *N*-acetyl-β-glucosaminide **5** was shown to be allyl 3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranoside (**38**), obviously formed by a transglycosidation process. Fractionation of the mixture of products obtained at reflux temperature gave **38**, its α anomer **40**, and the anomers (**41** and **42**) of the 1-*O*-deacetylated donor. Products derived from the glycosyl portion of **5** were not detected, perhaps owing to ferric chloride-catalyzed decomposition after loss of the aglycon (see below). In the reaction of **1** with **6**, the α anomer of **5**, the primary outcome was coupling, but with nearly complete loss of stereoselectivity. The coupling product (**33**, 76%) was a 1.5:1 mixture of β- and α-linked disaccharide derivatives. In addition, 5% of the transglycosidation product **38** was isolated. With **7**, like **5** a β-glycoside, but having a benzyl instead of an allyl group as aglycon, only the product of transglycosidation (**39**, 63%) was observed.

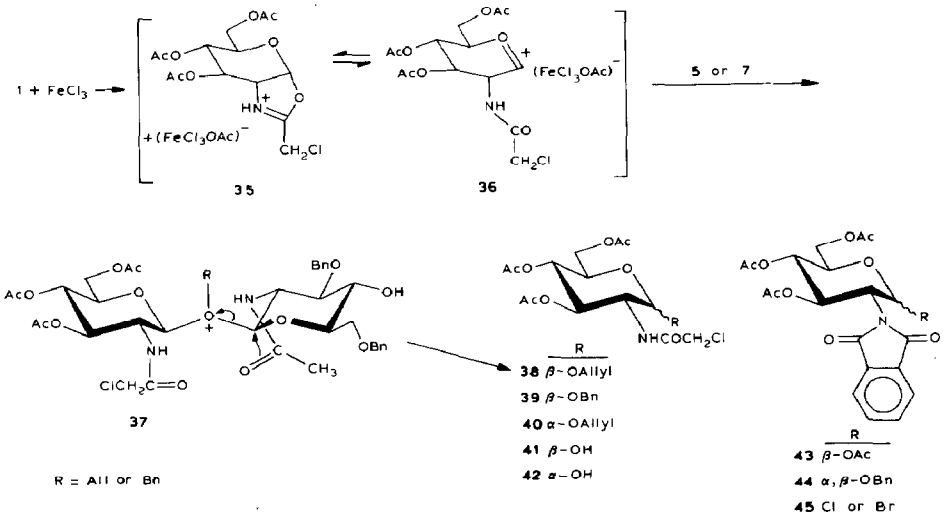
Several variations of the above reaction conditions were investigated with a view to finding improvements. Heating the reaction mixture under reflux shortened the time

TABLE I

^{1}H-N.m.r. data for the disaccharide products (C*H* and CH_2 of the sugar residues)

Compound	*Chemical shifts in p.p.m. (coupling constants in Hz)*[a]														
	H-6'a ($J_{6'a,6'b}$)	*H-6'b* ($J_{5',6'a}$)	*H-5'* ($J_{4',5'}$)	*H-4'* ($J_{3',4'}$)	*H-3'* ($J_{2',3'}$)	*H-2'* ($J_{1',2'}$)	*H-1'*	*H-6a*	*H-6b* ($J_{5,6}$)	*H-5*	*H-4*	*H-3* ($J_{2,3}$)	*H-2* ($J_{1,2}$)	*H-1*	
27	4.27dd (12.3)	4.16~ (5)	3.76m (9.2)	5.12t (9.2)	5.22t (~9.5)	4.16~ (8.3)	4.96d			3.88bt (5.76)	3.99bd	4.16~ (~10)	3.94dd (3.5)	4.51d	
28	*4.25*	*4.10* (5.7)	3.67m (9.3)	5.13t (9.3)	5.0t (9.5)	*4.25* (8.4)	4.8d	3.46m	3.46m	3.9bt (6.3)	*3.98*	*4.10*	*3.98* (3.6)	4.63d	
29	*4.13*	4.01dd	3.49m	5.05t	5.05t	*3.92* (6)	4.77d	3.64dd	3.53dd	*3.92*	*3.92*	*3.92*	3.77dd (2.7)	4.88d	
30	*4.2*		(9.6)	5.08t (9.6)	4.75t (9.3)	*3.9* (9)	4.67d	*3.5*	*3.5*	*3.9*	*3.9*	*3.9*	*3.8* (3.5)	4.92d	
31	4.11dd (12.3)	*3.83* (4.1)	3.34m (9.3)	4.98t (9.3)	4.89t (9.3)	*3.83* (7.9)	4.4d	*3.62*	*3.62*	*3.83*	*3.62*	*3.83* (9.2)	3.46dd (3.9)	4.56d	
32	4.13dd (12)	*3.86* (4.5)	*3.52* (9.3)	5.03t (9.3)	4.93t (9.5)	*3.86* (8.4)	4.45d	*3.65*	*3.52*	*3.86*	*3.65*	*3.86*	*3.52* (3.9)	4.7d	
33*a*	4.25dd	*4.04*	3.42m	5.1t	*4.91*	*4.04*	*4.91*	*3.63*	*3.63*	*3.63*	*4.04*	*3.63*	4.2m	*4.91*	
33*β*	*4.12*	*3.78*	3.45m (9.6)	5.17t (9.6)	5.27t (9.5)	*3.78* (8.4)	4.95d	*3.78*	*3.78*	4.39m	*4.12*	*3.96*	4.46m (4.5)	5.33d	
34*β*	*4.1*	*3.8*	3.4	5.1m	5.1m	*3.8* (8.6)	4.84d	*3.8*	*3.8*	4.4	*4.1*	*4.0*	4.5 (5.3)	5.2d	

[a] Chemical shift values in italics are for signals that were overlapped, so that their form and spacings could not be accurately determined.



to completion but did not improve the yield, and the use of > 2 mol of ferric chloride per mol of donor caused excessive degradation. The alternative catalyst trimethylsilyl trifluoromethanesulfonate ("triflate"), which effectively promotes glycosylation by various glycose 1-acetates[13,14], and by the oxazoline from β-D-GlcNAc tetra-acetate[13], caused no detectable change in a mixture of **1** and galactoside **3**. Boron trifluoride etherate was more active, in that it catalyzed slow reactions of **1** with **6** and **7** (t.l.c.), but in both cases multiple products were formed.

The *N*-chloroacetyl groups of the initial coupling products **27**, **29**, **31**, and **33** were reduced easily to *N*-acetyl by treatment with zinc and acetic acid in refluxing oxolane. The resonances for $COCH_2Cl$ in the ^1H- and ^{13}C-spectra were replaced by signals characteristic of $NHCOCH_3$. Thus, the products of reduction were the *N*-acetylated protected disaccharide glycosides **28**, **30**, **32**, and **34**. We previously used tributyltin hydride for the chloroacetyl→acetyl conversion[2], but now found Zn–HOAc to be more reliable.

Kiso and Anderson[2] earlier demonstrated the facile ferric chloride-catalyzed glycosylation of allyl alcohol by the *N*,*N*-phthaloylglucosamine β-1-acetate **43**. We now treated the benzyl glucosaminide **7** with **43** in the presence of $FeCl_3$ and, as in the reaction of **1** with **7**, observed the apparent formation of the benzyl glycoside (**44**, both anomers) of the "donor" reagent (details not presented).

DISCUSSION

The present results show that 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose (**1**) is an effective reagent for incorporating 2-acetamido-2-deoxy-β-D-glucose units into oligosaccharides. As judged by its behavior with the relatively hindered acceptors **2**–**4**, **1** is much more reactive than its *N*-acetyl congener[2], or the oxazoline derived therefrom[15,16]. Indeed, for the glycosylation of partially benzylated

hexosides, **1** compares favorably with the *O*-acetylated 2-deoxy-2-phthalimido-D-glucopyranosyl halides (**45**) that are currently the standard donors of β-GlcNAc residues*. Two advantages of **1** are (*a*) the required catalyst, ferric chloride, is less expensive and more convenient to handle than the silver salts used with the phthalimido halides, and (*b*) the conversion *N*-chloroacetyl→*N*-acetyl in the products can be achieved in a single step, without affecting most of the protecting groups employed in syntheses of oligosaccharides. A limitation in the use of **1** is its tendency, with some acceptors, to undergo transglycosidation, or to couple with reduced stereoselectivity.

The transglycosidation reaction. — Transglycosidation was favored over coupling in the reactions of **1** with two β-glycosides of 2-acetamido-2-deoxy-D-glucose in which the available hydroxyl group is unreactive[15,17]. Regarding the possible mechanism, it seems reasonable to suggest that transglycosidation and coupling involve the same reactive intermediate, primarily the 2-(chloromethyl)oxazolinium ion (**35**) formed from **1** by the anchimerically assisted loss of ferric chloride-complexed AcO from C-1. If the ion **35** attacks the glycosidic oxygen of the coreactant (**5** or **7**) instead of its free OH, the result could be an alkyl diglycosyloxonium ion (**37**) from which the product glycoside (**38** or **39**) is cleaved with the participation of the *N*-acetyl group in the benzylated glucosamine moiety. The fact that the α-glycoside **6** undergoes coupling rather than transglycosidation may reflect steric hindrance to the formation of the postulated diglycosyloxonium intermediate, or the inability of the intermediate to decompose by cleavage of the pre-existing glycoside bond. Failure of this cleavage, which would allow the ion to revert to its precursors, would be expected when the neighboring *N*-acetyl group is *cis* and thus not able to participate.

The formation of some α-glycoside (**40**) in the reaction of **1** with **5**, and of some α-linked coupling product in its reaction with **6**, is evidence that the oxazolinium ion **35** is in equilibrium with its ring-opened form **36**, in which the α-face is accessible for bonding.

The finding that the transglycosidation path is followed in the reaction of the *N,N*-phthaloyl analog (**43**) of **1** with **7** is not surprising at first sight. However, this behavior contrasts with that of the *N,N*-phthaloyl-glycosyl chloride **45**-Cl in its silver ion-promoted reaction with a close congener (*N,N*-phthaloyl) of **7**, where the primary outcome was coupling[18]. As previously suggested[2], it may be supposed that the same active species arises from **43** on removal of OAc^- by $FeCl_3$ as from **45** on removal of Cl^- by Ag^+ ion, so that the two donor-catalyst systems should give parallel results with similar coreactants. The apparently more complex behavior of the β-1-acetate–$FeCl_3$ system may reflect the involvement of ferric chloride at more than one point in the reaction.

* In experiments on the coupling of the *N,N*-phthaloyl-glycosyl bromide **45**-Br to **4** (silver triflate as the catalyst; details not presented), the yields of disaccharide derivative were 60–70%, about the same as could be obtained from **1** and **4**.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus, and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter, on solutions in chloroform unless otherwise stated. The recording of ^{1}H- and ^{13}C-n.m.r. spectra was accomplished with a Bruker WH-270 and a Nicolet NT-200 spectrometer, respectively, on solutions in $CDCl_3$ (internal Me_4Si). Decoupling was done as required in order to identify ^{1}H signals that could not be assigned unambiguously by inspection. The positions of the free OH groups in **2–7** were verified by ^{1}H-n.m.r. spectroscopy after acetylation. The δ_H and $^3J_{H,H}$ values for skeletal CH and CH_2 of the disaccharide products are recorded in Table I, and the remaining n.m.r. data are included in the descriptions of the individual compounds. Elemental analyses were performed by the Galbraith Laboratories, Knoxville, TN.

T.l.c. was performed on glass plates coated with Silica Gel 60 G (Merck) with detection by charring with sulfuric acid (10% in EtOH). Silica Gel 60 (Merck, 0.063–0.200 mm, usually 50–60 g/g of mixture) was used for column chromatography. Columns were packed dry under suction, then the sample was applied. Most elutions were accomplished by the successive application of two solvent mixtures, first a limited amount (one to two thirds of the bed volume) of the more polar one, then as much as required of the less polar.

Preparative procedures. — All reactions were carried out under nitrogen. Benzylations were accomplished with benzyl bromide in *N,N*-dimethylformamide in the presence of sodium hydride[19] for glucose and galactose derivatives, or barium hydroxide–barium oxide[20] for derivatives of *N*-acetylglucosamine. The latter reaction mixtures were worked up by dilution with a little methanol, filtration, concentration to dryness, and crystallization or chromatography of the residue. The conversion of 4,6-*O*-benzylidene into 6-*O*-benzyl groups by cyanoborohydride reduction was done as described by Garegg *et al.*[7,8].

For coupling, the acceptor and *N*-chloroacetyl tetra-acetate **1** (1–2 mol with respect to acceptor) were weighed into a flask and vacuum dried for 2–3 h on a liquid nitrogen-filled trap[21]. Dichloromethane (0.5–1 mL/100 mg of reactants) and molecular sieves 3A were added, and the slurry was stirred for 1 h at room temperature. Then anhydrous $FeCl_3$ (weighed in a stoppered vial, 1–2 mol with respect to **1**) was added quickly and stirring was continued. If the reaction was not substantially complete after 3–5 h (t.l.c.), more **1** was added, and more $FeCl_3$ if that was limiting, and stirring was continued for a few more hours. For workup, reaction mixtures were filtered through Celite, and the flask and filter cake were rinsed with the appropriate solvent. The combined filtrate was washed with aqueous sodium hydrogencarbonate and water. Iron salts suspended in the organic layer were removed by filtration through a bed of NaCl layered on Celite. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure at $<40°$. All coupling products were purified by column chromatography.

For the conversion *N*-chloroacetyl→*N*-acetyl, the protected disaccharide was

dissolved in peroxide-free oxolane, glacial acetic acid and activated[22] zinc powder were added, and the slurry was heated under reflux with vigorous stirring for up to 15 h, with further additions of zinc at 5 h and 10 h if required.

*1,3,4,6-Tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-*D*-glucopyranoside* (**1**). — 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride[23] (17 g, 44.3 mmol) was dispersed in dichloromethane (200 mL) containing triethylamine (13.6 mL, 98 mmol), and chloroacetyl chloride (5.3 mL, 65 mmol) was added at 5–10°. Stirring afforded a clear solution which, on extractive workup and evaporation of the organic layer, gave a brown solid. After recrystallization from ethanol, the yield of pure **1** was 13.5 g (72%), m.p. 170–171°, $[\alpha]_D^{25}$ +14° (*c* 8.4); lit.[23] m.p. 165–166°; lit.[2] m.p. 171–172°, $[\alpha]_D^{25}$ +12°. ^{1}H-N.m.r. data: δ 7.0 (d, 1 H, *J* 9.4 Hz, N*H*), 5.85 (d, 1 H, *J* 8.7 Hz, H-1), 5.39 (t, 1 H, H-3), 5.14 (t, 1 H, H-4), and 4.0 (s, 2 H, COCH_2Cl).

Anal. Calc. for $C_{16}H_{22}ClNO_{10}$ (423.80): C, 45.35; H, 5.23; N, 3.31. Found: C, 45.50; H, 5.29; N, 3.31.

*Methyl 2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**2**). — The synthesis (kindly carried out by Dr. J. L. Navia) was accomplished as outlined in the Results section, except that *O*-decrotylation with potassium *tert*-butoxide (the last step) was done in the usual way, in toluene, rather than in Me_2NCHO as described in the reference cited. Compound **2** had $[\alpha]_D^{25}$ +46°; lit.[3] $[\alpha]_D^{25}$ +46.6° (chloroform).

*Allyl 2,3,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**3**). — Allyl α-D-galactopyranoside[24] (**8**) was converted into the 4,6-*O*-benzylidene derivative[25] (**9**), which was benzylated (see *Preparative procedures*, above) to give **10** (6.2 g, 60%; ref. 25). Reductive ring opening (*Preparative procedures*) of **10** gave a syrup containing **3** as the major product (R_F 0.6 in 5:1 toluene–acetone). Column chromatography [silica gel (300 g), 15:1 (300 mL) then 30:1 toluene–acetone] afforded **3**, isolated as a syrup (5 g, 81%), $[\alpha]_D^{25}$ +42° (*c* 2.4), $[\alpha]_{436}^{25}$ +81° (*c* 3.1); lit.[26] $[\alpha]_D^{25}$ +52.8°, $[\alpha]_{436}^{25}$ +99.7°. ^{1}H-N.m.r. data: δ 7.4–7.1 (m, 15 H, Ph-H), 5.9 (m, 1 H, C*H*=CH_2), 5.24 (m, 2 H, CH=CH_2), 4.87 (d, 1 H, *J* 2.7 Hz, H-1), 4.1 (d, 1 H, *J* < 1 Hz, H-4), 3.96 (t, 1 H, H-5), 3.88 (~t, 2 H, *J* ~2 Hz, H-2,3), 3.7 (AB of ABX, 2 H, H-6a,6b), and 2.6 (s, 1 H, O*H*).

Anal. Calc. for $C_{30}H_{34}O_6$ (490.60): C, 73.45; H, 6.99. Found: C, 73.11; H, 7.0.

*Methyl 2,3,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (**4**). — Benzylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[27] (**12**; 2.1 g) gave the 2,3-dibenzyl ether[28,29] **13** (3.37 g of purified material). Reductive ring opening of a portion (1.2 g) and column chromatography [silica gel (150 g), 12:2:1 hexane–ethyl acetate–acetone] of the product afforded **4** (1.1 g, 91%), isolated as a syrup, $[\alpha]_D^{25}$ +17° (*c* 3.4); Garegg *et al.* recorded $[\alpha]_D$ +11° (chloroform) for **4** made by the partial benzylation of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[30], and $[\alpha]_D$ +13° for that made[7] by reductive cleavage of **13**.

*2-Acetamido-1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranose* (**19**). — A dispersion of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose[31] (**18**; 5.4 g) in dichloromethane (160 mL) plus 2:1 pyridine–acetic anhydride (40 mL) was stirred for 15 h at room temperature, then washed with water, aqueous $NaHCO_3$, and water, dried, and concentrated. Pyridine and acetic acid were removed from the residue by successive additions and evaporations of toluene therefrom. Crystallization of the crude

product from ethanol afforded **19** (5.2 g, 76%), m.p. 253–255°, $[\alpha]_D^{25}$ −44° (*c* 0.9); lit.[11] m.p. 260°, $[\alpha]_D^{25}$ −17.1° (*N,N*-dimethylformamide). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 7.94 (d, 1 H, *J* 10 Hz, N*H*), 7.37 (s, 5 H, Ph-H), 5.78 (d, 1 H, *J* 8 Hz, H-1), 5.65 (s, 1 H, PhC*H*), 5.24 (t, 1 H, *J* ~ 10 Hz, H-3), 4.25 (dd, 1 H, *J* 4.6, 11.5 Hz, H-6*e*), 3.98 (q, 1 H, H-2), 3.83 (t, 1 H, H-5), 3.78 (t, 1 H, H-4), 3.63 (m, 1 H, H-6*a*), 2.0, 1.98, and 1.78 (3 s, 9 H, COCH_3).

Anal. Calc. for $C_{19}H_{23}NO_8$ (393.39): C, 58.01; H, 5.89; N, 3.56. Found: C, 57.84; H, 5.83; N, 3.48.

Workup of the mother liquor yielded a little of the *α* isomer, m.p. 203–205°, $[\alpha]_D^{25}$ +61° (*c* 2.3). ^{1}H-N.m.r. data: δ 7.5–7.3 (m, 5 H, Ph-H), 6.13 (d, 1 H, *J* 3.8 Hz, H-1), 6.06 (d, 1 H, *J* 9.1 Hz, N*H*), 5.54 (s, 1 H, PhC*H*), 5.35 (t, 1 H, *J* 10 Hz, H-3), 4.5 (m, 1 H, H-2), 4.3 (dd, 1 H, H-6*e*), 3.95 (m, 1 H, H-6*a*), 3.78 (apparent q of 2 overlapping t's, 2 H, H-4,5), 2.1 (s, 6 H, 2 OCOCH_3), and 1.97 (s, 3 H, NHCOCH_3).

*Allyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranoside* (**20**). — To a mixture of **19** (20 g, 51 mmol), molecular sieves 3A (~4 g), allyl alcohol (25 mL), and tetramethylurea (7.4 mL) in dichloroethane (130 mL), stirred at 0°, was added trimethylsilyl triflate (9.5 mL). The mixture was then heated for 10 h under reflux, cooled, and filtered into cold aqueous $NaHCO_3$. Standard workup gave crude **20** (20 g, quant.), which, on recrystallization from ethanol, furnished the pure product, m.p. 280–285° (dec.), $[\alpha]_D^{25}$ −87° (*c* 2.6). ^{1}H-N.m.r. data: δ 7.55–7.37 (m, 5 H, Ph-H), 6.06 (d, 1 H, *J* 9.6 Hz, N*H*), 5.85 (m, 1 H, C*H*=CH_2), 5.52 (s, 1 H, PhC*H*), 5.3 (t, 1 H, *J* 10 Hz, H-3), 5.26–5.13 (m, 2 H, CH=CH_2), 4.48 (d, 1 H, *J* 8.15 Hz, H-1), 4.35 (dd, 1 H, $J_{5,6}$ 5, $J_{6a,6e}$ 10 Hz, H-6*e*), 4.31–4.14 (m, 2 H, H-2, one of OCH_2CH=), 3.95–3.78 (m, 1 H, one of OCH_2CH=), 3.78, 3.71 (2 t, overlapping, 2 H, $J_{5,6} = J_{6a,6e} = 10$, $J_{3,4}$ ~9.5 Hz, H-4, H-6*a*), 3.58 (m, 1 H, H-5), 2.16, and 2.04 (2 s, 6 H, COCH_3).

Anal. Calc. for $C_{20}H_{25}NO_7$ (391.42): C, 61.37; H, 6.44; N, 3.58. Found: C, 61.14; H, 6.36; N, 3.66.

*Allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**5**). — Compound **20** (19 g) was treated with methanolic sodium methoxide until *O*-deacetylation was complete (t.l.c.). The solution was then neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Crystallization of the residue from methanol afforded allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (**21**; 15.8 g, 93%), m.p. 164–165°*, $[\alpha]_D^{25}$ −87.5° (*c* 1.5, 3:1 chloroform–methanol); lit.[32] m.p.* 279–281° (dec.), $[\alpha]_D^{22}$ −86° (pyridine); lit.[33] m.p.* 262–264°, $[\alpha]_D$ −90° (pyridine).

Benzylation of a portion (3.7 g) of **21** gave allyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (**22**; 4.4 g, 95%), m.p. 259–261°, $[\alpha]_D^{25}$ −56° (*c* 2.1, pyridine); lit.[32] m.p. 263–265°, $[\alpha]_D^{25}$ −54° (pyridine); lit.[33] m.p. 261–262°, $[\alpha]_D$ −59° (*N,N*-dimethylformamide).

The reductive ring opening of **22** (5.1 g, 11.6 mmol) with $NaBH_3CN$ (4.21 g, 67 mmol) was carried out in *N,N*-dimethylformamide (80 mL). After acidification (HCl–Et_2O), chloroform (120 mL) was added, and the reaction was continued at 0° until

* The much lower m.p. indicates a second crystalline form. The identity of **21** is well established by the characterization of its precursor and subsequent products.

effervescence ceased. The crude product, obtained by standard extractive workup, was charged to a column of dry silica gel (300 g), and eluted first with 20:6:1 toluene–acetone–methanol (400 mL) and then 10:3 toluene–acetone to give pure **5** (2.5 g, 49%), m.p. 143–145°, $[\alpha]_D^{25}$ −10° (*c* 1); lit.[34] m.p. 145–146°, $[\alpha]_D^{22}$ −10° (chloroform).

Allyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside (**6**). — Allyl 2-acetamido-2-deoxy-α-D-glucopyranoside[24] (**14**; 3.1 g, 11.9 mmol) was treated with α,α-dimethoxytoluene (3.6 mL, 24 mmol) in the presence of *p*-toluenesulfonic acid[35] (15 mg), to give the 4,6-*O*-benzylidene derivative **15**, m.p. 233–236° (from ethanol), $[\alpha]_D^{25}$ +88° (*c* 0.7, methanol); lit.[17] m.p. 234–237°, $[\alpha]_D^{20}$ +99° (*N,N*-dimethylformamide).

Benzylation of **15** (2.2 g) gave **16**, m.p. 232–235° (from dichloromethane–hexane), $[\alpha]_D^{25}$ +74° (*c* 0.6, acetone); lit.[17] m.p. 224–228°, $[\alpha]_D^{20}$ +88° (chloroform).

Finally, the reductive ring opening of **16** (1.4 g, 3.2 mmol) gave **6** (1.25 g, 89%), m.p. 93–94° (from ether–hexane), $[\alpha]_D^{25}$ +95° (*c* 2.2); lit.[17] m.p. 97–98°, $[\alpha]_D^{20}$ +90° (chloroform).

Anal. Calc. for $C_{25}H_{31}NO_6$ (441.52): C, 68.01; H, 7.08; N, 3.17. Found: C, 68.09; H, 7.21; N, 3.17.

Benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**7**). — Suspensions of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride[23] were stirred with pyridine (2 mol) and acetic anhydride (1.5 mol) until clear, when t.l.c. showed complete conversion into product. After standard extractive workup (aq. $NaHCO_3$ then water), the organic layer was evaporated, and the residue was subjected to several additions and evaporations of toluene. A portion of the resulting penta-acetate[23] (4.6 g), on treatment with $BF_3{\cdot}Et_2O$ (1.7 mL) in dichloromethane (70 mL) at room temperature, afforded the corresponding oxazoline (n.m.r.)[10]. The mixture was washed with aqueous $NaHCO_3$, then water, and concentrated, and a solution of the residue in 1,2-dichloroethane (~35 mL) was treated with benzyl alcohol (2 mL) and trimethylsilyl trifluoromethanesulfonate (100 μL). After standard extractive workup, column chromatography [silica gel (250 g), 30:5:1 (200 mL) then 40:5:1 toluene–acetone–methanol] of the residue gave the fully protected benzyl glycoside[1] (3.76 g). *O*-Deacetylation with methanolic NaOMe, followed by neutralization with Amberlyst 15 (H^+) resin, filtration, and concentration, furnished benzyl 2-acetamido-2-deoxy-β-D-glucopyranoside[36] (**23**).

A suspension of well dried **23** (3.14 g, 10.1 mmol) in acetone (80 mL) and 2,2-dimethoxypropane (30 mL) was stirred for ~2 h with molecular sieves 3A (5 g). *p*-Toluenesulfonic acid (120 mg) was added, and the mixture was heated under reflux until t.l.c. indicated complete reaction (1 h), cooled, treated with solid $NaHCO_3$ then $MgSO_4$, with stirring for ~1 h after each addition, filtered, and concentrated. A solution of the residue in chloroform (70 mL) was washed (aqueous $NaHCO_3$ then water), dried, and concentrated to afford benzyl 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside (**24**; 3 g), m.p. 194–196° (from ethanol), $[\alpha]_D^{25}$ −101° (*c* 1.4); lit.[37] m.p. 173.5–175.5°, $[\alpha]_D^{20}$ −60° (chloroform); lit.[38] m.p. 186–187°, $[\alpha]_D$ −110° (chloroform).

Benzylation of **24** (2.79 g) gave benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-4,6-*O*-

isopropylidene-β-D-glucopyranoside (**25**), m.p. 157–158° (from ethanol–hexane), $[\alpha]_D^{25}$ −20° (*c* 1.6); lit.[37] m.p. 152–153°, $[\alpha]_D^{20}$ −21° (chloroform). The bulk of this intermediate, without purification, was dissolved in 99:1 methanol–water (50 mL), and the solution was stirred with Amberlyst 15 (H^+) resin for 6 h at room temperature, then diluted with a little chloroform, filtered, and concentrated. Crystallization of the residue from ethanol–hexane afforded benzyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**26**; 1.89 g), m.p. 178–180°, $[\alpha]_D^{25}$ −19.5° (*c* 1.08, methanol); lit.[39] m.p. 183–184°, $[\alpha]_D^{25}$ −19° (methanol); lit.[40] m.p. 180°, $[\alpha]_D^{26}$ −21° (methanol). Additional **26** was isolated from the mother liquor.

For regioselective benzylation, **26** (1.89 g) was treated[4] with dibutyltin oxide (2.9 g), tetrabutylammonium iodide (1.93 g), and benzyl bromide (0.62 mL) in benzene (24 h at reflux). Column chromatography [silica gel (250 g), 16:2:1 (180 mL) then 20:2:1 toluene–acetone–methanol] afforded pure **7** (1.6 g, 69% from **26**), m.p. 180–181° (ethanol), $[\alpha]_D^{25}$ −37° (*c* 1.2); lit.[39] m.p. 181°, $[\alpha]_D^{22}$ −37° (chloroform). Some unreacted **26** was recovered.

Anal. Calc. for $C_{29}H_{33}NO_6$ (491.58): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.79; H, 6.91; N, 2.84.

Methyl O-*(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-*D*-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**27**). — The reaction mixture for coupling (see *Preparative procedures*) consisted of **1** (0.42 g, 0.99 mmol), **2** (0.29 g, 0.62 mmol), ferric chloride (0.25 g, 1.5 mmol), and molecular sieves 3A (1.2 g) in dichloromethane (8 mL). T.l.c. (12:3:1 toluene–acetone–methanol) after 5 h showed a major product (R_F 0.53) along with a little unreacted **2** (R_F 0.67) and some degradation products. Column chromatography [silica gel (40 g), 80:10:1 (30 mL) and then 100:10:1 toluene–acetone–methanol] of the mixture of products gave pure **27** (~0.5 g, >95%); m.p. 117–119° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ −9.8° (*c* 4.8). N.m.r. data: ^1H, δ 7.45–7.20 (15 H, Ph-H), 6.54 (d, 1 H, *J* 9.35 Hz, N*H*), 3.82 (s, 2 H, $COCH_2Cl$), 3.29 (s, 3 H, OCH_3), and 2.09–1.95 (3 s, 9 H, 3 $COCH_3$); ^{13}C, δ 170.64, 170.5, 169.35 (3 *C*=O), 165.98 (*C*OCH_2Cl), 138.7, 138.3, 137.9 (C-1 of 3 $PhCH_2$), 101.79 (C-1′), 98.26 (C-1), 55.2 (OCH_3), 54.88 (C-2′), 42.3 ($COCH_2Cl$), 20.6 (3 $COCH_3$), 78.5, 76.9, 76.3, 74.8, 79.4, 79.1, 72.4, 71.7, 69.2, 69.1, 68.5, and 62.0.

Anal. Calc. for $C_{42}H_{50}ClNO_{14}$ (828.31): C, 60.90; H, 6.08. Found: C, 60.66; H, 6.11.

Methyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**28**). — A solution of **27** (0.56 g, 0.68 mmol) in oxolane was stirred for 14 h with zinc (2.2 g) and acetic acid (0.23 mL) (see *Preparative procedures*). Column chromatography [silica gel (75 g), 4:1 (60 mL) then 6:1 toluene–acetone] afforded **28** (0.414 g, 77%), m.p. 166–167° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ −6.8° (*c* 1.33). N.m.r. data: ^1H, δ 7.45–7.2 (15 H, Ph-H), 5.16 (d, 1 H, *J* 9 Hz, N*H*), 3.36 (s, 3 H, OCH_3), 2.05, 2.02, and 1.7 (3 s, 12 H, 4 $COCH_3$); ^{13}C, δ: 170.96, 170.5, 169.7, 169.32 (4 *C*=O), 102.4 (C-1′), 98.11 (C-1), 62.07 (C-6′), 55.31 (C-2′), 23.07 ($NHCOCH_3$), and 20.64 (3 $OCOCH_3$).

Anal. Calc. for $C_{42}H_{51}NO_{14}$ (793.86): C, 63.55; H, 6.48; N, 1.76. Found: C, 63.61; H, 6.70; N, 1.73.

Allyl O-*(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-*D*-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**29**). — Compound **3** (0.53 g, 1.1 mmol), the donor **1** (0.41 g, 0.97 mmol), molecular sieves 3A (1 g), ferric chloride (0.31 g, 1.9 mmol), and dichloromethane (5 mL) were used for the coupling reaction. After 3 hours' stirring, more **1** (0.12 g, 0.28 mmol) was added, and the reaction was continued (3 h) until t.l.c. (4:1 toluene–acetone) showed one major product (R_F 0.41). Column chromatography [silica gel (70 g), 5:1 (100 mL) then 7:1 toluene–acetone] of the crude product afforded pure **29**, isolated as a syrup (0.72 g, 78%), $[\alpha]_D^{25}$ +34° (*c* 2.4). ^{1}H-N.m.r. data: δ 7.1–7.5 (15 H, Ph-H), 6.62 (d, 1 H, *J* 8.6 Hz, N*H*), 5.88 (m, 1 H, -C*H*=), 4.13 (m, overlapped, 1 H of OCH_2CH=), 3.97–3.87 (m, overlapped, 1 H of OCH_2CH=), 3.67 (s, 2 H, COCH_2Cl), 2.03, and 2.00 (2 s, 9 H, 3 COCH_3).

Anal. Calc. for $C_{44}H_{52}ClNO_{14}$ (854.35): C, 61.86; H, 6.14. Found: C, 61.69; H, 6.11.

Allyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**30**). — A solution of **29** (76 mg, 0.089 mmol) in oxolane (2 mL) was reduced by treatment with acetic acid (0.2 mL) and zinc powder (80 mg). Heating was continued, with the addition of fresh zinc (80 mg) at 5 h and 10 h, for a total of 15 h, when t.l.c. (4:1 toluene–acetone) showed conversion into a single product (R_F 0.26). Column chromatography [silica gel (70 g), 4:1 (40 mL) then 6:1 toluene–acetone] of the crude product gave pure **30**, isolated as a syrup (60 mg, 82%), $[\alpha]_D^{25}$ +35° (*c* 3.7); lit.[2] for the crystalline solid, $[\alpha]_D^{25}$ +41° (chloroform). N.m.r. data: ^{1}H, δ 7.2–7.5 (15 H, Ph-H), 5.93 (d, 1 H, *J* 8.5 Hz, N*H*), 2.05, 1.96, and 1.54 (3 s, 12 H, 4 COCH_3); ^{13}C, δ 170.5 (2 C), 169.9, 169.2 (*C*=O), 138.4, 138.1, 137.7 (C-1 of 3 PhCH_2), 133.4 (*C*H=CH_2), 118.2 (CH=*C*H_2), 102.58 (C-1′), 95.4 (C-1), 53.9 (C-2′), 22.8 (NHCO*C*H_3), 20.7 (3 OCO*C*H_3), 77.1, 76.5, 74.7, 74.0, 73.3, 72.9, 72.2, 69.4, 69.0, 68.3, and 68.2.

Anal. Calc. for $C_{44}H_{53}NO_{14}$ (819.90): C, 64.46; H, 6.52. Found: C, 64.22; H, 6.58.

Methyl O-*(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-*D*-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (**31**). — Coupling was conducted with **4** (0.51 g, 1.1 mmol), **1** (0.93 g, 2.2 mmol), molecular sieves 3A (1 g), and ferric chloride (0.51 g, 3.1 mmol) in dichloromethane (8 mL). Column chromatography [silica gel (100 g), 8:1 (100 mL) then 10:1 toluene–acetone] of the product afforded **31** (0.61 g, 67%), m.p. 184–185° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ −14°, $[\alpha]_{436}^{25}$ −35° (*c* 1.45). N.m.r. data: ^{1}H, δ 7.5–7.2 (15 H, Ph-H), 5.97 (d, 1 H, *J* 9.1 Hz, N*H*), 3.9–3.76 (m, overlapped, COCH_2Cl), 3.37 (s, 3 H, OCH_3), 2.05, 2.01, and 1.95 (3 s, 9 H, 3 COCH_3); ^{13}C, δ 170.63, 170.55, 169.32 (*C*=O), 166.02 (*C*OCH$_2$Cl), 139.5, 138.2, 137.7 (C-1 of 3 PhCH_2), 99.62 (C-1′), 98.37 (C-1), 61.8 (C-6′), 55.4 (C-2′), 55.14 (O*C*H$_3$), 42.4 (CO*C*H$_2$Cl), and 20.6 (3 CO*C*H$_3$).

Anal. Calc. for $C_{42}H_{50}ClNO_{14}$ (828.31): C, 60.90; H, 6.08; N, 1.69. Found: C, 60.45; H, 5.98; N, 1.63.

Methyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-*

*(1→4)-2,3,6-tri-*O*-benzyl-α-*D*-glucopyranoside* (**32**). — Compound **31** (0.28 g, 0.34 mmol) was stirred with acetic acid (0.15 mL) and zinc (1 g) in oxolane (8 mL) heated under reflux for 15 h. Column chromatography [silica gel (30 g), 4:1 (40 mL) then 6:1 toluene–acetone] of the product gave **32** (0.25 g, 93%), m.p. 202–204° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ −18° (*c* 2.7). N.m.r. data: ^{1}H, δ 7.7–7.38 (15 H, Ph-H), 4.54 (d, 1 H, *J* 9.5 Hz, N*H*), 3.36 (s, 3 H, OCH_3), 2.13, 2.1, 2.03, and 1.83 (4 s, 12 H, 4 COCH_3); ^{13}C, δ 170.5 (2 C), 169.5, 169.1 (*C*=O), 100.3 (C-1'), 98.2 (C-1), 61.7 (C-6'), 55.1 (O*C*H$_3$), 54.4 (C-2'), 22.98 (NHCO*C*H$_3$), and 20.4 (3 OCO*C*H$_3$).

Anal. Calc. for $C_{42}H_{51}NO_{14}$ (793.86): C, 63.55; H, 6.48; N, 1.76. Found: C, 63.2; H, 6.49; N, 1.68.

Reaction between the donor **1** *and the acceptor* **6**. — *(a) At room temperature.* A mixture of **1** (0.64 g, 1.5 mmol), **6** (0.44 g, 1 mmol), molecular sieves 3A (1 g), and ferric chloride (0.26 g, 1.6 mmol) in dichloromethane (8 mL) was prepared (*Preparative procedures*) and stirred at room temperature. After 5 h, more **1** (0.18 g, 0.42 mmol) and ferric chloride (0.11 g, 0.68 mmol) were added. T.l.c. (double elution, 78:16:6 then 85:11:4 toluene–acetone–methanol) after 24 h indicated two probable condensation products (R_F 0.34 and 0.29), along with some **1** (R_F 0.46), **6** (R_F 0.38), and a little of a faster moving component (R_F 0.52). More ferric chloride (44 mg, 0.27 mmol) was added, and the reaction was continued for another 24 h.

(b) Under reflux. The reaction was carried out as in (*a*) using **1** (0.14 g, 0.33 mmol), **6** (0.12 g, 0.27 mmol), molecular sieves 3A (0.5 g), and ferric chloride (95 mg, 0.58 mmol) in dichloromethane (3.5 mL), but heating under reflux. Fresh ferric chloride (50 mg, 0.30 mmol) was added after 19 h and 25 h, and heating was continued for a total of 30 h.

Flash chromatography (1:1 hexane–ethyl acetate) of the combined residues from reaction mixtures (*a*) and (*b*) separated the minor product and a mixture (0.61 g, 76%) of the coupling products from slower-moving impurities. The minor product (23 mg, 5.5%) was allyl 3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranoside (**38**), m.p. 165–167° (from ethanol), $[\alpha]_D^{25}$ −8.9° (*c* 1); lit.[1] m.p. 166–167°, $[\alpha]_D^{25}$ −9° (chloroform).

Column chromatography [silica gel (100 g), 40:4:1 (50 mL) then 50:4:1 toluene–acetone–methanol] of the mixture of coupling products first gave allyl *O*-(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**33β**; 0.35 g, 44%), m.p. 206–207° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ +4.7° (*c* 3.9). N.m.r. data: ^{1}H, δ 7.6–7.35 (10 H, Ph-H), 6.6 (d, 1 H, *J* 9 Hz, N*H*COCH$_2$Cl), 6.25 (d, 1 H, *J* 7.5 Hz, N*H*Ac), 5.89 (m, 1 H, C*H*=CH$_2$), 5.33 (m, overlapping, CH=C*H*$_2$), 4.95 (m, overlapping, C*H*$_2$Ph), 3.96 (m, overlapping, OC*H*$_2$CH=), 3.92–3.63 (m, overlapping, COC*H*$_2$Cl), and 2.13–2.0 (3 s, 9 H, 3 COC*H*$_3$); ^{13}C, δ 170.6 (2 C), 169.7, 169.3 (*C*=O), 166.35 (*C*OCH$_2$Cl), 138.5, 138.1 (C-1 of 2 PhCH$_2$), 133.7 (*C*H=CH$_2$), 117.7 (CH=*C*H$_2$), 99.87 (C-1'), 99.3 (C-1), 61.5 (C-6'), 57.6 (C-2'), 55.1 (C-2), 42.4 (CO*C*H$_2$Cl), 23.4 (NHCO*C*H$_3$), and 20.6 (3 OCO*C*H$_3$).

Allyl O-*(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-α-D-glucopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside* (**33α**). — Continued

elution of the column just described gave **33***α* (0.23 g, 29%), m.p. 209–211° (from ethyl acetate–hexane), $[\alpha]_D^{25}$ +49° (*c* 2.2). N.m.r. data: ^{1}H, *δ* 7.6–7.3 (10 H, Ph-H), 6.1 (d, 1 H, *J* 9.3 Hz, N*H*COCH$_2$Cl), 5.9 (m, 1 H, C*H*=CH$_2$), 5.22 (d, *J* 9 Hz, N*H*Ac), 4.97–4.85 (m, overlapped, C*H*$_2$Ph), 4.1–3.98 (m, overlapped, COC*H*$_2$Cl, 1 H of OC*H*$_2$CH=), 2.09, 2.06, 2.00, and 1.83 (4 s, 12 H, 4 COC*H*$_3$); ^{13}C, *δ* 170.6 (2 C), 169.8, 169.3 (*C*=O), 166.1 (*C*OCH$_2$Cl), 139.1, 137.7 (C-1 of 2 PhCH$_2$), 133.5 (*C*H=CH$_2$), 117.7 (CH=*C*H$_2$), 99.9, 96.5 (C-1,1′), 61.7 (C-6′), 54.8, 52.1 (C-2,2′), 42.4 (CO*C*H$_2$Cl), 23.3 (NHCO*C*H$_3$), and 20.6 (3 OCO*C*H$_3$).

Anal. Calc. for $C_{39}H_{49}ClN_2O_{14}$ (805.27): C, 58.17; H, 6.13; N, 3.48. Found: C, 58.12; H, 6.29; N, 3.2.

Allyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside* (**34***β*). — Compound **33***β* (0.174 g) was treated with zinc (0.65 g) and acetic acid (0.15 mL) in oxolane (5 mL) for 3 h under reflux. T.l.c. (20:4:1 toluene–acetone–methanol) revealed a major product (R_F 0.22) and a minute quantity of unchanged **33***β* (R_F 0.52). Column chromatography [silica gel (25 g), 20:4:1 (25 mL) then 40:4:1 toluene–acetone–methanol] afforded pure **34***β* (0.14 g, 84%), m.p. 197–198° (from ethyl acetate), $[\alpha]_D^{25}$ +2.8° (*c* 3.2). N.m.r. data: same as **33***β* except ^{1}H, *δ* 5.6 (d, 1 H, *J* 9 Hz, new N*H*) and 1.7 (s, 3 H, new NHCOC*H*$_3$); ^{13}C, *δ* 170.7, 170.6, 170.3, 169.7, 169.3 (5 *C*=O), 138.5, 137.9 (C-1 of 2 PhCH$_2$), 133.7 (*C*H=CH$_2$), 117.7 (CH=*C*H$_2$), 100.58 (C-1′), 99.33 (C-1), 61.6 (C-6′), 57.5 (C-2′), 54.6 (C-2), 23.4, 23.1 (2 NHCO*C*H$_3$), 20.65, and 20.6 (3 OCO*C*H$_3$).

Anal. Calc. for $C_{39}H_{50}N_2O_{14}$ (770.83): C, 60.77; H, 6.54; N, 3.63. Found: C, 60.73; H, 6.62; N, 3.51.

Reaction between the donor **1** *and the acceptor* **5**. — Compounds **5** (0.16 g, 0.36 mmol) and **1** (0.24 g, 0.57 mmol) were reacted in dichloromethane (3.5 mL) at room temperature in the presence of ferric chloride (0.11 g, 0.68 mmol) and molecular sieves 3A (1 g). After 4 h, fresh ferric chloride (0.13 g, 0.80 mmol) was added and reaction was continued for 4 h. Column chromatography [silica gel (60 g), 6:1 toluene–acetone] of the product obtained after the usual workup afforded **38** (81 mg, 54%), corresponding in m.p. (167–168°) and $[\alpha]_D^{25}$ (−8.7°) to the sample obtained from the reaction of **1** and **6**.

A similar reaction mixture was also heated for 6 h under reflux. T.l.c. of the organic layer obtained on workup revealed two products and a trace of **5**, but no **1**. Column chromatography of this fraction gave first **38**, then the *α* anomer **40** (δ_H 4.92, d, 1 H, *J* 3.7 Hz, H-1). The solid residue from the reaction, on thorough extraction with methanol, yielded additional material (R_F 0.33 and 0.22; t.l.c., 3:1 then 4:1 toluene–acetone) that could be resolved on a column of silica gel. Eluted first was 3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-*β*-D-glucopyranose (**41**), m.p. 174–176°. *I* H-N.m.r. data: *δ* 4.78 (d, 1 H, *J* 8.6 Hz, H-1) and 2.98 (br.s, 1 H, D$_2$O exchangeable, *H*O-1). Eluted next was the *α* anomer **42**. ^{1}H-N.m.r. data: *δ* 5.21 (d, 1 H, *J* 3.5 Hz, H-1) and 3.0 (br.s, D$_2$O exchangeable, *H*O-1).

Reaction between the donor **1** *and the acceptor* **7**. — Compounds **7** (0.31 g, 0.63 mmol) and **1** (0.23 g, 0.54 mmol), molecular sieves 3A (1 g), and ferric chloride (0.24 g, 1.5 mmol) were stirred in 1,2-dichloroethane (7 mL) at 30–40°. After ~4 h, a product

(R_F 0.33) was detected by t.l.c. (4:1 toluene–acetone), along with some unreacted **1** (R_F 0.27), **7** (R_F 0.20), and two minor constituents. More **1** (54 mg, 0.13 mmol) was added, followed by ferric chloride (25 mg, 0.15 mmol), and the reaction was allowed to continue for another 14 h. Column chromatography [silica gel (70 g), 4:1 (30 mL), 6:1 (60 mL), and 7:1 toluene–acetone] of the crude product (0.56 g) obtained by standard workup afforded benzyl 3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranoside (**39**; 0.19 g, 63%), m.p. 192–193° (from ethanol), $[\alpha]_D^{25}$ −38° (*c* 2.3, 2:3 chloroform–methanol).

The ^{1}H-n.m.r. spectrum matched that of an authentic sample prepared by treating a solution of **1** (0.3 g, 0.71 mmol) and benzyl alcohol (0.3 mL, 2.9 mmol) in dichloromethane (3 mL) with anhydrous ferric chloride (0.21 g, 1.3 mmol) and stirring the mixture at room temperature for 10 h. Column chromatography [silica gel (60 g), 4:1 (40 mL) then 6:1 toluene–acetone] of the product obtained by the usual workup gave **39** (0.28 g, 85%), m.p. 194–195° (from ethanol), $[\alpha]_D^{25}$ −44° (*c* 3.4, 2:3 chloroform–methanol). ^{1}H-N.m.r. data: δ 7.4–7.2 (5 H, Ph-H), 6.55 (d, 1 H, *J* 9.1 Hz, N*H*), 5.3 (t, 1 H, *J* ~9.5 Hz, H-3), 5.1 (t, 1 H, *J* ~9.5 Hz, H-4), 4.9 (d, 1 H of PhCH_2), 4.7 (d, 1 H, *J* 8.8 Hz, H-1), 4.6 (d, 1 H of PhCH_2), 4.3 (dd, 1 H, *J* 4.5 and 12.2 Hz, H-6a), 4.17 (dd, 1 H, *J* 2.5 and 12.2 Hz, H-6b), 4.0–3.9 (m, 3 H, H-2, COCH_2Cl), 3.7 (m, 1 H, H-5), 2.13, and 2.03 (2 s, 9 H, 3 COCH_3).

Anal. Calc. for $C_{21}H_{26}ClNO_9$ (471.89): C, 53.45; H, 5.55; N, 2.97. Found: C, 53.53; H, 5.39; N, 2.87.

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