Simple and efficient strategy for making β-(1→6)-linked galactooligosaccharides using 'naked' galactopyranosides as acceptors [1]

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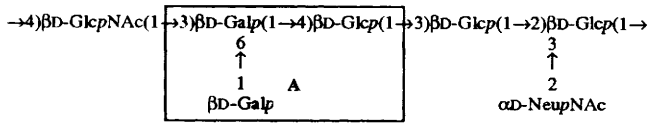
Unprotected (naked) galactopyranosides were used for the first time in the direct regio- and stereo-selective synthesis of β-(1→6)-linked oligosaccharides in 75–90% yield by coupling them with acetobromosugars in the presence of silver carbonate in dichloromethane. β-(1→4)-Linked oligosaccharides (yield 5–10%) were the by-products.

Introduction

Regioselective silylation, tritylation and tosylation of unprotected glycosides leading to their corresponding primary hydroxy-substituted ethers and esters are well known in carbohydrate chemistry.[2,3] However, the possibility of regioselective glycosylations in sugars is not well explored. Ricketts[4] and Foster and Horton[5] reported acid-catalysed polymerizations of D-glucose and 2-acetamido-2-deoxy-D-glucose, which gave preponderantly and in low yields mixtures of their respective α- and β-(1→6)-linked oligosaccharides. Later, Defaye *et al.*[6] observed that in anhydrous hydrogen fluoride, D-glucose formed, also in low yield, β-(1→6)-linked oligosaccharides ranging from di- to hexa-saccharides.

Earlier we had tried to use dibutyltin oxide-mediated regioselective etherification[7] for preparing oligosaccharides regioselectively. However, treatment of the stannylene acetal derivative (acceptor) with acetobromohexoses (donor) resulted in the exclusive formation of the corresponding orthoesters.[8] However, when acetochlorosialic acid methyl ester, in which the formation of orthoester is impossible, was used as the donor in the above reaction together with the 3,4-*O*-stannylene acetal of 2-(trimethylsilyl)ethyl β-D-galactoside as the acceptor, glycosides were formed.[9] Interestingly however, for steric reasons, instead of the expected (2→3)-linked glycoside an α,β mixture of the (2→6)-linked disaccharides was obtained.

In addition, during the course of our work on the synthesis of oligosaccharides (fragment **A**) related to the capsular polysaccharide antigen **1** of type II group B *Streptococcus*, we



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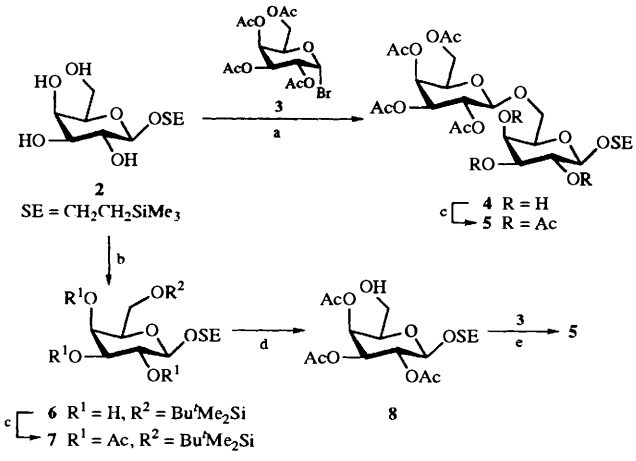
also observed a remarkable regioselectivity in a glycosylation using 2-(trimethylsilyl)ethyl 3′-*O*-benzyl-β-D-lactoside, bearing six free hydroxy groups (two primary and four secondary) as the acceptor, and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **3** as the donor.[10] A trisaccharide product with a newly formed glycosidic linkage in the β configuration at O-6′ of the lactoside was obtained in more than 65% yield. All the above observations prompted us to explore further the use of naked glycosides as acceptors for making β-(1→6)-linked oligosaccharides.

Results and discussion

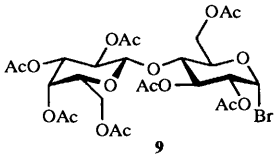
We now report that even when using an unprotected aldohexopyranoside as an acceptor, glycosidic linkages can be generated in a regio- and stereo-selective manner under extremely mild conditions, essentially by the Koenigs–Knorr reaction. Thus, when 2-(trimethylsilyl)ethyl β-D-galactoside **2** in dry dichloromethane was treated with acetobromogalactose **3** in the presence of silver carbonate and powdered molecular sieves for 20 h at 22 °C, the 6-*O*-glycosylated product **4** with β-configuration was obtained in ~90% isolated yield (Scheme 1).



Scheme 1 *Reagents and conditions:* **a**; Ag_2CO_3, CH_2Cl_2, 22–25 °C, 20 h; **b**; Bu^tMe_2SiCl, pyridine, 0–4 °C, 12 h; **c**; pyridine, Ac_2O, 15–20 °C, 16 h; **d**; 80% aq. HOAc, 20–25 °C, 20 h; **e**; Ag_2CO_3, $AgClO_4$, CH_2Cl_2, 22–25 °C, 16 h

The β-configuration of the new glycosidic linkage in the product was revealed by the appearance of a new anomeric proton (δ 4.59, d) in its ^1H NMR spectrum with a coupling constant ($J_{1',2'}$ 8.1 Hz) which is in accord with that of a 1,2-*trans* configuration. The structure of compound **4** was further confirmed by the conversion into its peracetate which was homogeneous with the heptaacetate **5** synthesized by a more conventional procedure (see Scheme 1). A minor disaccharide by-product was detected (TLC) which had a slightly higher mobility than compound **4** obtained in the above glycosylation. This compound could easily be collected separately in the chromatographic isolation of the major product and was, following peracetylation, identified by ^1H NMR spectroscopy as the β-(1→4)-linked disaccharide (see Experimental section).

When the above reaction was carried out with acetobromolactose **9** as the donor, trisaccharide **10** was obtained in more than 85% yield, and with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide **12** as the donor the partially protected disaccharide product **13** was obtained in 75% yield.



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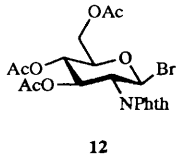

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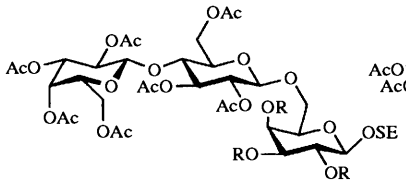
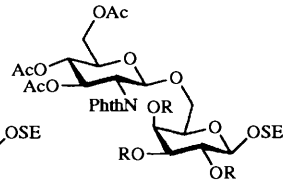


10 R = H
11 R = Ac

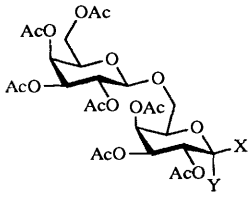


13 R = H
14 R = Ac

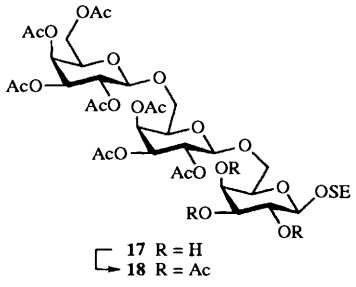
In order to optimize yields of compound **4**, further manipulation of the reaction conditions was attempted. When unprotected glycoside **2** was treated with compound **3**, in the absence of molecular sieves, the disappearance of compound **2** was slightly faster (12 h at room temp.) but the yield was found to be reduced by a few percentage points (85%). When the reaction was performed in toluene instead of dichloromethane it was found that it proceeded at a much reduced rate (approximately 2 days at room temperature). Using a more polar solvent such as acetonitrile was also not of any advantage. In fact, in acetonitrile it was not only seen that the glycosylation was slower as compared with that in dichloromethane, but also that selectivity was poor, which resulted in the formation of other disaccharides. Substituting silver carbonate in the reaction by hindered bases such as collidine or 2,6-di-*tert*-butylpyridine, *etc.*, did not yield any disaccharide product. In addition, the incorporation of silver perchlorate, one molar equivalent based on the donor, was of no advantage in terms of minimizing the reaction time and, in fact, resulted in reduced yields of the expected product **4**.

By taking advantage of having the 2-(trimethylsilyl)ethyl group as the temporary protective group at the C-1 position, compound **5** was converted into acetobromogalactobiose **16** *via* galactobiose octaacetate **15** (see Experimental section) in nearly quantitative yield [11] and was used as the donor for the synthesis of the trisaccharide **17**, thus demonstrating the usefulness of the current methodology for the simple synthesis of (1→6)-linked oligosaccharides. In this routine synthesis, acetylation of the three free hydroxy groups in compound **4**, to produce heptaacetate **5** *in situ*, and the subsequent acetolysis to give the octaacetate could be achieved in a single step making the process more simple (see Experimental section).

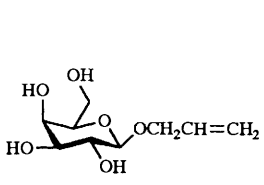
Initially we thought that the unusual hydrophilic–lipophilic balance in compound **2**, due to the presence of several free hydroxy groups in combination with the hydrophobic 2-(trimethylsilyl)ethyl (SE) group, was responsible for this unique reactivity. However, further experiments using allyl β-D-galactopyranoside **19** instead of compound **2** (see Scheme 1)



15 X/Y = OAc/H
16 X = H, Y = Br



17 R = H
18 R = Ac



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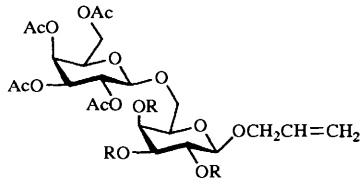

20 R = H
21 R = Ac

showed that this was not the whole explanation. However, the fact that the reaction proceeded at a much slower rate in the latter case demonstrates the distinct advantage of using the SE group as a temporary protective group for the hemiacetal function. One possible explanation for the increased reactivity of compound **2** is its greater solubility in dichloromethane compared with the more poorly soluble compound **19**. Success achieved in the foregoing regioselective glycosylations has application in other synthetic strategies, and these form part of investigations currently under progress in our laboratories.

Experimental

TLC was performed with 0.2 mm Merck pre-coated silica gel 60 aluminium sheets. Compounds were detected by spraying with 5% sulfuric acid in ethanol and heating. Merck silica gel G-60 (70–230 mesh) or Wakogel BW-127 (100–200 mesh) and solvents (Aldrich/Wako) purchased were used as such for column chromatography. Hexane refers to *n*-hexane. Mps were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Specific rotations were determined with the help of a Union MP-201 polarimeter at 22 °C for solutions in dichloromethane, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a JASCO IR-1 spectrophotometer. ^{1}H NMR spectra were recorded at 270 MHz on a JEOL JNM-GX270 spectrometer in deuteriochloroform and the chemical shifts are expressed relative to internal $SiMe_4$. Assignments of resonances are based on published data and in most of the cases only relevant data are listed. Solvents used for reactions were dried by standard procedures. MSP refers to powdered molecular sieves (4 Å).

Compounds **4**, **10**, **13**, **17** and **20** showed strong hydroxy-group absorption (ν_{max} 3450 cm^{-1}) characteristic of compounds with free hydroxy groups, in addition to other absorption bands diagnostic of the substituents present in the respective compounds. The hydroxy-group absorption bands disappeared on acetylation of these compounds to give the fully acetylated compounds **5**, **11**, **14**, **18** and **21** respectively. They all gave satisfactory elemental analyses.

General procedure for the synthesis of β-(1→6)-linked galacto-oligosaccharides

To a stirred mixture of the acceptor (**2** or **19**, 1 mmol), silver carbonate (414 mg, 1.5 mmol) and MSP in dry dichloromethane (10 cm^3) at room temperature (22–24 °C) was added the donor (**3**, **9**, **12** or **16**, 1.2–1.5 mmol) and stirring was continued until TLC [irrigant: dichloromethane–methanol (95:5)] showed complete disappearance of the acceptor. The solids were separated by filtration through a bed of Celite and washed successively with dichloromethane and methanol. The combined filtrate was concentrated under reduced pressure and was chromatographed on a column of silica gel with ethyl acetate–

hexane (50:50) and dichloromethane–methanol (100:2) as successive eluents. The former removed constituents of lower polarity, such as any unchanged (excess of) donor and any of its degradation products. The latter eluent gave in order the (1→4)-linked (in 5–10% yield) and the (1→6)-linked (in 75–90% yield) glycosides as glasses. On lyophilization from 1,4-dioxane they were obtained as solids.

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→6)-β-D-galactopyranoside 4

The product mixture from the coupling reaction of acceptor **2** (280.4 mg, 1 mmol) and donor **3** (617 mg, 1.5 mmol) as described in the general procedure above gave, on column chromatography, first a minor fraction (48.9 mg, 8%) followed by compound **4** (550.5 mg, 90%) as a glassy foam. Lyophilization gave powdery compound **4**: $[\alpha]_D$ −24.9 (*c*, 0.7); δ_H 5.40 (1 H, d, 4-H), 5.20 (1 H, dd, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.5, 2'-H), 5.00 (1 H, dd, $J_{3',4'}$ 3.4, 3'-H), 4.59 (1 H, d, 1'-H), 4.22 (1 H, d, $J_{1,2}$ 7.1, 1-H), 4.16 (2 H, d, 6'-H_2), 1.98, 2.05, 2.06 and 2.11 (12 H, 4 s, 4 × MeCO) and 1.00 (2 H, m, CH_2SiMe$_3$).

The minor, faster moving fraction was identified as 2-(trimethylsilyl)ethyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-β-D-galactopyranoside and had $[\alpha]_D$ +6.0 (*c*, 0.5); δ_H 5.38 (1 H, d, $J_{3',4'}$ 3.3, 4'-H), 5.29 (1 H, dd, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.4, 2'-H), 5.06 (1 H, dd, 3'-H), 4.80 (1 H, d, 1'-H), 4.21 (1 H, d, $J_{1,2}$ 7.5, 1-H), 4.16 (2 H, d, 6'-H_2), 1.98, 2.08 and 2.14 (12 H, 3 s, 4 × MeCO) and 1.0 (2 H, m, CH_2SiMe$_3$).

A portion of this compound when treated with acetic anhydride in pyridine gave 2-(trimethylsilyl)ethyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-galactopyranoside in quantitative yield, $[\alpha]_D$ +3.2 (*c*, 0.6); δ_H 5.37 (1 H, d, $J_{3',4'}$ 3.1, 4'-H), 5.26 (1 H, dd, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.4, 2'-H), 5.08 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 10.3, 2-H), 5.00 (1 H, dd, 3'-H), 4.89 (1 H, dd, 3-H), 4.45 and 4.43 (2 d, 1- and 1'-H), 4.30 (m) and 4.10 (d) (together 4 H, d, 6- and 6'-H_2), 3.95 and 3.55 (2 m, CH_2CH$_2$SiMe$_3$), 2.17, 2.15, 2.10, 2.07, 2.05, 2.03 and 1.99 (21 H, 7 s, 7 × MeCO) and 0.95 (2 H, m, CH_2SiMe$_3$).

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-acetyl-β-D-galactopyranoside 5

Compound **4** (200 mg) was dissolved in pyridine (2 cm^3) and after the addition of acetic anhydride (1 cm^3) was left at 22 °C for 20 h. Extractive isolation gave title compound **5** quantitatively, $[\alpha]_D$ −9.6 (*c*, 0.7); δ_H 5.35 and 5.34 (each 1 H, 2 d, *J* 3.5 and 3.3, 4- and 4'-H), 5.17 and 5.16 (1 H each, 2 dd, *J* 8.1, 10.4 and 7.9, 10.4 respectively, 2- and 2'-H), 4.98 and 4.96 (1 H each, 2 dd, 3- and 3'-H), 4.52 and 4.45 (1 H each, 2 d, 1- and 1'-H), 2.12, 2.03, 1.95 and 1.94 (21 H, 4 s, 7 × MeCO) and 0.95 (2 H, m, CH_2SiMe$_3$). The structure of compound **5** was further confirmed by synthesis (see below).

A mixture of compound **8** (203 mg, 0.5 mmol) obtained as described below, silver carbonate (207 mg), silver perchlorate (104 mg) and MSP (0.5 g) in dichloromethane (6 cm^3) was stirred for several hours at 22 °C before donor **3** (308 mg) was added and stirring was continued for 12 h. The product obtained was isolated in the same manner as described in the general procedure except that the eluent used for column chromatography was ethyl acetate–hexane (2:3). The product was homogeneous with compound **5** obtained above as determined by its identical ^{1}H NMR spectrum.

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranoside 8

Butyldimethylsilyl (TBDMS) chloride (1.5 mol equiv.) was added to a solution of acceptor **2** (280.4 mg, 1 mmol) in pyridine (6 cm^3) at 0 °C and the mixture was gently stirred for 4.5 h during which time the temperature of the bath was allowed to rise to 15 °C. By this time, acceptor **2** had been completely consumed [TLC; irrigant: dichloromethane–methanol (95:5)]. The reaction mixture was again cooled in an ice-bath and acetic anhydride (1.5 cm^3) was added. The temperature was slowly allowed to rise to ~20 °C and after storage of the mixture for 16 h, compound **7** was isolated by extraction with dichloromethane. A portion of the product was purified by chromatography on a silica gel column [eluent: ethyl acetate–hexane (1:8 and 1:3)] and was obtained as crystals, mp 98–100 °C; $[\alpha]_D$ −16.7 (*c*, 0.9); δ_H 5.46 (1 H, d, $J_{3,4}$ 2.7, 4-H), 5.17 (1 H, dd, $J_{1,2}$ 7.8, $J_{2,3}$ 10.4, 2-H), 5.02 (1 H, dd, $J_{3,4}$ 3.5, $J_{2,3}$ 10.4, 3-H), 4.46 (1 H, d, 1-H), 4.00 and 3.52 (2 H, 2 m, CH_2CH$_2$SiMe$_3$), 3.75–3.60 (3 H, m, 5-H and 6-H_2), 2.13, 2.06 and 1.98 (9 H, 3 s, 3 × MeCO) and 0.90 (11 H, m, CH_2SiMe$_3$ and Me$_3$C). The remaining material was treated with aq. acetic acid (80% v/v; 7 cm^3) at 22 °C for 20 h, and following removal of acetic acid and water by coevaporation with toluene, was purified by chromatography on a silica gel column [eluent: ethyl acetate–hexane (2:3)] to yield title compound **8** as a clear syrup in 90% yield, $[\alpha]_D$ +3.7 (*c*, 0.8%); δ_H 5.36 (1 H, d, $J_{3,4}$ 3.3, 4-H), 5.22 (1 H, dd, $J_{1,2}$ 8.0, $J_{2,3}$ 10.6, 2-H), 5.04 (1 H, dd, $J_{2,3}$ 10.3, 3-H), 4.50 (1 H, d, 1-H), 4.00 (1 H, m, one H of CH_2CH$_2$SiMe$_3$), 3.80–3.48 (4 H, m, 1 H of CH_2CH$_2$SiMe$_3$, 5-H and 6-H_2), 2.17, 2.05 and 2.00 (9 H, 3 s, 3 × MeCO) and 0.91 (2 H, m, CH_2SiMe$_3$).

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→6)-β-D-galactopyranoside 10

Coupling of compounds **2** (280.4 mg) and **9** (1.05 g) was carried out as described in the general procedure to give trisaccharide **10** (774 mg, 86%) as a powder, $[\alpha]_D$ −18.1 (*c*, 0.7); δ_H 5.35 (1 H, d, $J_{3'',4''}$ 3.4, 4''-H), 5.17 (1 H, t, 3'-H), 5.09 (1 H, dd, 2''-H), 4.98 (1 H, dd, $J_{2'',3''}$ 10.4, $J_{3'',4''}$ 3.4, 3''-H), 4.88 (1 H, dd, $J_{2',3'}$ 9.5, 2'-H), 4.51 and 4.58 (1 H each, 2 d, $J_{1',2'}$ = $J_{1'',2''}$ = 7.9, 1'- and 1''-H), 4.21 (1 H, d, $J_{1,2}$ 7.2, 1-H), 2.15, 2.13, 2.06, 2.05, 2.04, 2.03 and 1.97 (21 H, 7 s, 7 × MeCO) and 1.00 (2 H, m, CH_2SiMe$_3$).

Compound **10** on treatment with acetic anhydride in pyridine gave decaacetate **11**, $[\alpha]_D$ −13.1 (*c*, 0.6); δ_H 5.40 and 5.35 (1 H each, 2 d, *J* 3.4 and 3.3, 4- and 4''-H), 5.17 (1 H, dd, 2-H), 5.15 (1 H, t, 3'-H), 5.10 (1 H, dd, $J_{2'',3''}$ 10.6, 2''-H), 4.99 (1 H, dd, $J_{2'',3''}$ 10.9, $J_{3'',4''}$ 3.3, 3''-H), 4.95 (1 H, dd, $J_{2,3}$ 10.7, $J_{3,4}$ 3.4, 3-H), 4.85 (1 H, dd, $J_{2',3'}$ 9.4, 2'-H), 4.52 and 4.48 (1 H each, 2 d, $J_{1',2'}$ = $J_{1'',2''}$ = 7.9, 1'- and 1''-H), 4.45 (1 H, d, $J_{1,2}$ 8.0, 1-H), 2.14, 2.12, 2.06, 2.04, 2.03 and 1.96 (30 H, 6 s, 10 × MeCO) and 0.95 (2 H, m, CH_2SiMe$_3$).

2-(Trimethylsilyl)ethyl *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→6)-β-D-galactopyranoside 13

Coupling of reagents **2** and **12** was carried out as described in the general procedure to give title compound **13**, which after column chromatography was obtained in 75.5% yield as a powder, $[\alpha]_D$ +13.6 (*c*, 0.7); δ_H 7.87 and 7.77 (4 H, 2 m, ArH), 5.77 (1 H, dd, $J_{2',3'}$ 10.8, $J_{3',4'}$ 9.2, 3'-H), 5.50 (1 H, d, $J_{1',2'}$ 8.6, 1'-H), 5.14 (1 H, t, $J_{4',5'}$ 10.1, 4'-H), 4.31 (1 H, dd, 2'-H), 4.26 (2 H, d, 6'-H_2), 4.14 (1 H, d, $J_{1,2}$ 7.3, 1-H), 2.13, 2.04 and 1.86 (9 H, 3 s, 3 × MeCO) and 0.93 (2 H, m, CH_2SiMe$_3$).

A portion of compound **13**, on acetylation with acetic anhydride in pyridine, gave the hexaacetate 2-(trimethylsilyl)-ethyl *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-acetyl-β-D-galactopyranoside **14**, $[\alpha]_D$ +12.9 (*c*, 0.7); δ_H 7.86 and 7.75 (4 H, 2 m, ArH), 5.72 (1 H, dd, $J_{2',3'}$ 10.6, $J_{3',4'}$ 9.2, 3'-H), 5.47 (1 H, d, $J_{1',2'}$ 8.6, 1'-H), 5.26 (1 H, d, $J_{3,4}$ 3.5, 4-H), 5.17 (1 H, t, $J_{4',5'}$ 9.9, 4'-H), 5.11 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 10.3, 2-H), 4.93 (1 H, dd, 3-H), 4.40 (1 H, d, 1-H), 4.29 (1 H, dd, 2'-H), 4.25 (2 H, m, 6'-H_2), 2.13, 2.09, 2.03, 2.01, 1.91 and 1.85 (18 H, 6 s, 6 × MeCO) and 0.85 (2 H, m, CH_2SiMe$_3$).

O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-acetyl-α-D-galactopyranosyl bromide 16 from compound 5

Compound **5** (310 mg) dissolved in dry toluene (2.5 cm^3) was treated with acetic anhydride (15 mol equiv.) and boron trifluoride–diethyl ether (0.8 mol equiv.) for 4 h at room temperature,[11] and the product, galactobiose octaacetate, **15** was isolated and converted into title compound **16** by treatment with hydrogen bromide in glacial acetic acid (for details see below).

From compound 4. To a stirred solution of compound **4** (3.05 g, 10 mmol) in dry toluene (25 cm^3) at 0 °C was added acetic anhydride (20 mol equiv.) followed by boron trifluoride–diethyl ether (0.85 mol equiv.). After a few minutes, when reactant **4** had been completely transformed into compound **5** (TLC), the cooling bath was removed and the reaction was allowed to continue at room temperature for 4 h. The reaction mixture was then diluted with dichloromethane (100 cm^3), and was washed successively with aq. sodium carbonate and water. It was then dried (sodium sulfate), concentrated, and lyophilized from dioxane to give the octaacetate **15** as powder in nearly quantitative yield. This was dissolved in dry dichloromethane (100 cm^3) and was treated with hydrogen bromide (HBr–HOAc 25% w/v; 12 cm^3) at 0 °C. Extractive isolation of the product, as described above for octoacetate **15**, gave title compound **16** as a powder (3.2 g, 92%), $[\alpha]_D$ +115.8 (*c*, 1.3); δ_H 6.70 (1 H, d, $J_{1,2}$ 3.8, 1-H), 5.48 and 5.38 (2 H, 2 d, 4- and 4′-H), 5.40 (1 H, dd, 2-H), 5.18 (1 H, dd, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.4, 2′-H), 5.03 (2 H, m, 3- and 3′-H), 4.52 (1 H, d, $J_{1,2}$ 8.1, 1′-H) and 2.15, 2.12, 2.09, 2.06, 2.01 and 1.98 (21 H, 6 s, 7 × MeCO).

2-(Trimethylsilyl)ethyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1→6)-O-(2,3,4-tri-O-acetyl-β-D-galactopyranosyl)-(1→6)-β-D-galactopyranoside 17

Coupling of acceptor **2** (280.4 mg) and donor **16** (1.05 g) as described in the general procedure gave title trisaccharide **17** (630 mg, 70%) as a solid, $[\alpha]_D$ −8.8 (*c*, 1.0); δ_H 5.38 and 5.33 (1 H each, 2 d, *J* 3.1 and 3.3, 4′- and 4″-H), 5.26 and 5.18 (1 H each, 2 dd, *J* 8.1, 10.4 and 8.6, 10.6 respectively, 2′- and 2″-H), 4.99 (2 H, ddd, 3′- and 3″-H), 4.55 (2 H, d, 1′- and 1″-H), 4.22 (1 H, d, $J_{1,2}$ 7.5, 1-H), 2.17, 2.15, 2.08, 2.07, 2.06, 1.98 and 1.97 (21 H, 7 s, 7 × MeCO) and 1.00 (2 H, m, CH_2SiMe_3).

2-(Trimethylsilyl)ethyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1→6)-O-(2,3,4-tri-O-acetyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-acetyl-β-D-galactopyranoside 18

Acetylation of triol **17** (250 mg) with acetic anhydride (1.2 cm^3) in pyridine (3 cm^3) gave peracetate **18** (285 mg, quantitative), $[\alpha]_D$ −15.3 (*c*, 1.0); δ_H 5.37 (3 H, m, 4-, 4′- and 4″-H), 5.16 (3 H, m, 2-, 2′- and 2″-H), 4.97 (3 H, m, 3-, 3′- and 3″-H), 4.49 (3 H, ddd, 1-, 1′- and 1″-H), 4.15 (2 H, dd, 6″-H_2), 4.05 and 3.55 (1 H each, 2 m, $CH_2CH_2SiMe_3$), 2.16, 2.14, 2.06, 2.05, 1.98, 1.97 and 1.96 (30 H, 7 s, 10 × MeCO) and 0.95 (2 H, m, CH_2SiMe_3).

Allyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1→6)-β-D-galactopyranoside 20

Reaction of donor compound **3** (617 mg) with acceptor **19** (220 mg, 1 mmol) in dichloromethane (15 cm^3) for 2 days at 22 °C followed by the same work-up as described for the preparation of compound **4** yielded, first, a minor compound (50 mg, 9.1%), followed by title compound **20** (385.5 mg, 70%) obtained as a solid after lyophilization. Compound **20**: $[\alpha]_D$ −14.7 (*c*, 0.8); δ_H 5.94 (1 H, m, CH=CH_2), 5.39 (1 H, d, $J_{3',4'}$ 3.3, 4′-H), 5.26 (2 H, m, CH=CH_2), 5.19 (1 H, dd, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.8, 2′-H), 5.03 (1 H, dd, 3′-H), 4.59 (1 H, d, 1′-H), 4.38 and 4.10 (1 H each, 2 m, CH_2CH), 4.27 (1 H, d, $J_{1,2}$ 7.3, 1-H), 4.15 (2 H, d, 6′-H_2) and 2.16, 2.06, 2.05 and 1.98 (12 H, 4 s, 4 × MeCO).

The faster moving, minor product having $[\alpha]_D$ +1.3 (*c*, 0.8) was characterized as allyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-β-D-galactopyranoside, δ_H 5.92 (1 *H*, m, CH=CH_2), 5.34 (1 H, d, $J_{3',4'}$ 3.5, 4′-H), 5.29 (1 H, dd, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.4, 2′-H), 5.26 (2 H, m, CH=CH_2), 5.05 (1 H, dd, 3′-H), 4.80 (1 H, d, 1′-H), 4.36 and 4.10 (1 H each, 2 m, CH_2CH), 4.25 (1 H, d, $J_{1,2}$ 7.7, 1-H), 4.22 (1 H, 2 d, 6′-H[a]) and 2.15, 2.08 and 1.98 (12 H, 3 s, 4 × MeCO).

The product of its acetylation using acetic anhydride in pyridine had $[\alpha]_D$ +2.8 (*c*, 0.7) and was characterized as the heptaacetate, allyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-galactopyranoside by ^1H NMR spectroscopy: δ_H 5.86 (1 H, m, CH=CH_2), 5.37 (1 H, d, $J_{3',4'}$ 3.3, 4′-H), 5.24 and 5.12 (1 H each, 2 dd, 2- and 2′-H), 5.02 and 4.90 (1 H each, 2 dd, 3- and 3′-H), 4.46 (2 H, t, 1- and 1′-H), 4.40–4.05 (7 H, m, CH_2CH, 6- and 6′-H_2, and 4-H), 3.85 and 3.70 (1 H each, 2 t, 5- and 5′-H) and 2.17, 2.15, 2.11, 2.07, 2.05, 2.04 and 1.99 (21 H, 7 s, 7 × MeCO).

Allyl O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-O-acetyl-β-D-galactopyranoside 21

Compound **20** (100 mg) was dissolved in pyridine (1 cm^3) and, after the addition of acetic anhydride (0.5 cm^3), the solution was left at 22 °C for 20 h. Extractive isolation gave title compound **21** in quantitative yield, $[\alpha]_D$ −9.9 (*c*, 0.7); δ_H 5.92 (1 H, m, CH=CH_2), 5.37 (2 H, t, 4- and 4′-H), 5.30 (2 H, m, CH_2=CH), 5.24 and 5.18 (1 H each, 2 dd, 2- and 2′-H), 5.00 and 4.97 (1 H each, 2 dd, 3- and 3′-H), 4.53 and 4.51 (1 H each, 2 d, 1- and 1′-H), 4.37 and 4.12 (1 H each, 2 m, CH_2CH), 4.15 and 4.13 (2 H, 2 d, 6′-H_2) and 2.16, 2.15, 2.07, 2.06, 2.05, 1.99 and 1.98 (21 H, 7 s, 7 × MeCO).

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