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Selectively protected galactose derivatives for the synthesis of branched oligosaccharides

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Abstract—Synthesis and characterization of several new anomerically pure galactose derivatives, based on simple and effective protective group manipulations of benzyl β-D-galactopyranoside, are reported. The monosaccharides described contain selectively protected/deprotected hydroxyl functionalities at their 1,2,3,4- and 6-positions rendering them useful as building blocks for construction of branched oligosaccharides.

1. Introduction

Carbohydrates and glycoconjugates play a central role in various biological recognition processes.[1] Recent years have seen a rapid extension of the field of glycobiology with carbohydrate-derived therapeutics now entering clinical trials.[2] The limited availability of pure and structurally defined specific oligosaccharides nevertheless remains a major impediment to the study of carbohydrates in biological applications. Besides the traditional chemical synthesis techniques, enzymatic[3] and automated solid-phase synthetic[4] methods have been successfully applied for constructing stereo- and regiospecific glycosidic linkages in complex oligosaccharide structures. However, both of these methods suffer from limitations in scale-up. An additional concern is the inability of fermentation techniques to produce unnatural branched oligosaccharides. Thus, in many cases, conventional organochemical synthesis remains the method of choice for the preparation of multigram amounts of chemically defined oligosaccharides and the improvement and development of efficient protective group strategies and purification methods remains an important and actively investigated area of carbohydrate chemistry.[5] Of particular significance is the preparation of partially protected carbohydrate building blocks, where the protecting groups can be manipulated such that each can be selectively removed during the course of the synthetic route. In this regard, galactose is a particularly interesting monosaccharide due to its occurrence as a building block in various biological structures. In plants it is one of the main constituents of galactoglucomannans[6] and arabinogalactans.[7] In humans, it is one of the main constituents of human milk oligosaccharides[8] and polylactosamines.[9] The latter structures consisting of *N*-acetyllactosamine units [β-D-galactopyranosyl-(1→4)-*N*-acetyl-D-glucosamine] with galactose residues at their non-reducing ends have been extensively studied as anti-inflammatory agents. Furthermore, the axial 4-OH group of galactose renders it an optimal starting material for exploitation of various protective group strategies. Here, we report the preparation of some new anomerically pure galactose derivatives, obtained by simple and efficient protective group manipulations of benzyl β-D-galactopyranoside (**1**). The present paper continues our recently initiated studies on the synthesis and conformational behavior[10] of galactose-containing mono- and oligosaccharides. The galactose derived monosaccharides described here contain selectively protected hydroxyl functionalities in their 1,2,3,4- and/or 6-positions, thus potentially serving as useful building blocks for the construction of branched oligosaccharide libraries.

2. Results and discussion

Benzyl β-D-galactopyranoside (**1**) was prepared from β-D-galactose pentaacetate in 66% overall yield following a slightly modified literature procedure.[11] Protecting group manipulations of **1** are summarized in Scheme 1. The following strategy was designed in order to create selectively deprotected hydroxyl functionalities on the 1,2,3,4- and 6-positions of a fully protected galactose

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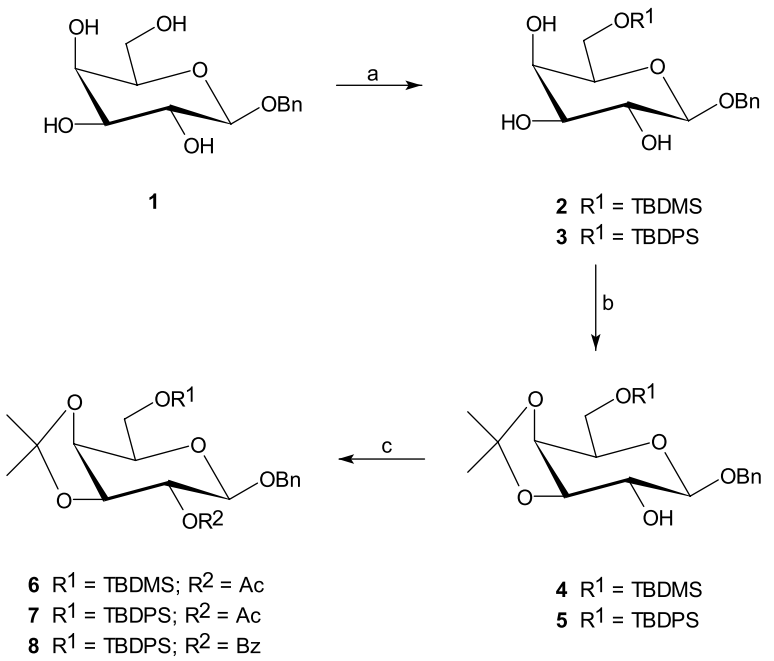
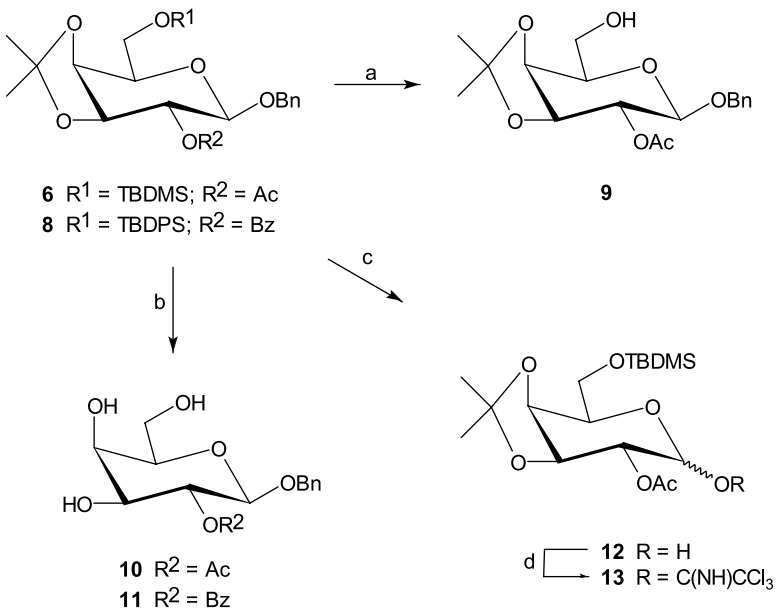


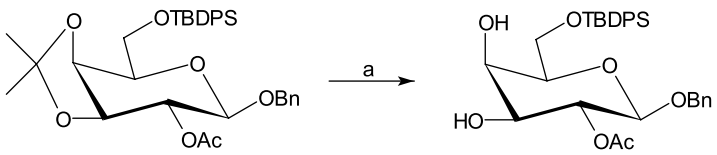
Scheme 1. (a) TBDMSCl, DBU, CH_2Cl_2, 0 °C then rt, 48 h, 98% (**2**); or TBDPSCl, imidazole, DMF, 0 °C then rt, 24 h, 60% (**3**); (b) 2,2-dimethoxypropane, TsOH, rt, 2–3 h, 93% (**4**) or 71% (**5**); (c) acetic anhydride, Et_3N or pyridine, CH_2Cl_2, rt, 12–48 h, 74% (**6**) or 93% (**7**); or BzCl, pyridine, rt, 6 h, 99%.

backbone: in the first step, the 6-*O*-position of **1** was protected as silyl ethers of varying acid lability (TBDMS or TBDPS). Next, the 3- and 4-hydroxyls were protected using the conventional isopropylidene ketal formation. Finally, the 2-hydroxyl group was protected as the base labile acetate or benzoate.

Thus, reaction of **1** with TBDMSCl and DBU in dichloromethane gave the 6-*O*-protected silyl ether, benzyl 6-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranoside (**2**) in 98% isolated yield after purification by flash chromatography. The corresponding β-D-glucopyranoside has been described previously.[12,13] The previously reported 6-*O*-TBDPS analogue, benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (**3**)[14,15] was prepared as described in the literature and isolated in 60% yield after purification by flash chromatography. Acid catalyzed reactions of **2** and **3** with 2,2-dimethoxypropane gave the corresponding isopropylidene ketals **4** and **5** in 93 and 71% yields, respectively, after purification by flash chromatography. Compound **5** has been prepared and characterized previously by Redlich and co-workers.[14a] Both compounds **4** and **5** were converted into the corresponding benzyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside 2-*O*-acetates **6** and **7** according to standard procedures. Compound **5** was additionally converted



Scheme 2. (a) $Bu_4NF{\cdot}3H_2O$, THF, 0 °C then rt, 1.5 h, 84%; (b) As (a) then Dowex DR-2030, MeOH, 22 h, 65% (**10**) or 55% (**11**); (c) 10% Pd/C, cyclohexene, EtOH, reflux, 72 h, 93%; (d) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 2 h, 78%.



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Scheme 3. (a) 98% CF_3COOH, CH_2Cl_2, 0 °C then rt, 30 min, 76%.

into the corresponding 2-*O*-benzoate **8**. The 6-*O*-TBDMS derivative **6** was isolated as a transparent oil in 74% yield after purification by flash chromatography, while its 6-*O*-TBDPS analogue was conveniently purified by crystallization from pentane to afford **7** as a bright white solid in 93% isolated yield. The benzoate **8** was obtained as a white solid and in quantitative yield after standard work-up procedures. Remaining trace impurities were removed by column chromatography.

Selective deprotection sequences for the new compounds **6**-**8** are summarized in Schemes 2 and 3. In order to obtain a 1,2,3,4-protected galactose derivative with a free hydroxyl group in the 6-position, the TBDMS group of **6** was cleaved with Bu_4NF in THF under standard conditions to yield benzyl 2-*O*-acetyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (**9**) in 84% yield after purification by flash chromatography.[16] The 3,4,6-deprotected derivatives benzyl 2-*O*-acetyl-*β*-D-galactopyranoside (**10**) and benzyl 2-*O*-benzoyl-*β*-D-galactopyranoside (**11**)[17] were prepared in 65 and 55% yields, respectively, by treating compounds **6** and **8** first with Bu_4NF in THF to obtain the crude desilylated products, which then were stirred overnight with Dowex DR-2030 acidic ion-exchange resin in order to cleave the 3,4-*O*-isopropylidene protection. Analytically pure **10** and **11** were then conveniently obtained after filtration of the acid catalyst, evaporation of the solvent and crystallization from $CHCl_3$ or pentane/EtOAc. In a simplified approach, both 6-TBDMS and 3,4-*O*-isopropylidene protective groups of **6** were successfully and simultaneously cleaved by stirring **6** with Dowex DR-2030 in MeOH overnight. Monitoring by TLC indicated the formation of one major product after 17 h. Filtration of the catalyst and evaporation of the solvent left an off-white solid that was shown to consist of fairly pure **10** by ^1H NMR analysis. This batch was not purified further. The 2,3,4,6-protected compound 2-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranose (**12**), containing a free hydroxyl group only in the anomeric position, was prepared from **6** in 93% yield under standard debenzylation conditions using Pd/C and cyclohexene followed by subsequent purification by flash chromatography. Compound **12** was converted to the corresponding trichloroacetimidate **13** in 78% yield following standard procedures.

The TBDPS silyl ether group is considerably (≈100 times) more stable than the TBDMS group toward acid hydrolysis.[18] Thus, the 3,4-*O*-isopropylidene protection of **7** was successfully and selectively cleaved with CF_3COOH in CH_2Cl_2 leaving the protective groups in 1,2- and 6-positions intact (Scheme 3). The desired benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-*β*-D-galactopyranoside (**14**) containing free hydroxyl groups in the 3,4-positions only was conveniently purified by precipitation from pentane to obtain analytically pure product in 76% isolated yield.

In summary, we have prepared several new anomerically pure *β*-D-galactopyranoside derivatives containing selectively protected hydroxyl groups in the 1,2,3,4- and 6 positions of the galactose framework. All new compounds have been fully characterized by elemental analysis, mass spectrometry, polarimetry, as well as by ^1H and ^{13}C NMR spectroscopy. A specific objective of this study was to design a versatile and orthogonal protective group strategy in a simple and efficient manner. First, the anomeric position of galactose was protected as a conventional benzyl ether. This protective group may later be easily removed by hydrogenation under neutral conditions. The free 1-OH can then potentially be further activated using various strategies leaving the protected 2,3,4- and 6-positions intact. For example, imidate,[19] fluoride[20] and thiophenyl[21] activations can be used for further glycosidations.

Next, the 6-OH position was protected as a silyl ether, removable in high yields by tetrabutylammonium fluoride. The acid lability of the silyl ether may be tuned by choosing properly substituted silyl chlorides as silylation reagents. The 3,4-*O*-isopropylidine protection installed in the subsequent step may then be removed in nearly quantitative yields with concomitant removal or retention of the 6-*O*-silyl ether protection. Galactose precursors containing free 3- and 4-hydroxyl groups may be selectively glycosidated in the 3-*O*-position using activated imidate[22] or halogenide[23] donors. Likewise, selective 4-*O*-glycosidations in the presence of free 3-OH groups have been reported.[24,25]

In the final step of the strategy described herein, the 2-OH position is protected as an acetyl or benzoyl ester. Thus, both 2-*O*- and 6-*O*-glycosidations should be accessible with the selectively removable 2-*O*-ester and 6-*O*-silyl ether protection strategies.[26] Compound **10**, described in the present work, containing only 2-*O*-acetyl protection in addition to the 1-*O*-benzyl ether group, is in turn a suitable candidate for either 3,6-*O*-[27] or 4,6-*O*-diglycosidations and, with its free 3,4,6-hydroxyl groups, a particularly interesting model compound for intramolecular acetyl group migration studies.[28] This topic is currently under investigation in the authors' laboratories.

3. Experimental

3.1. General remarks

All operations with air or moisture sensitive reagents and materials were carried out under an argon atmosphere using

standard Schlenk and vacuum techniques. Solvents were dried and distilled under argon prior to use when applicable or purchased from commercial sources NMR spectra were recorded on a JEOL JNM A 500 NMR spectrometer, unless otherwise indicated, and referenced against tetramethylsilane or the solvent signal. The sample temperature was maintained at 30 °C by a Jeol variable temperature unit. The ^{1}H and ^{13}C NMR spectra were recorded at 500.16 and 125.78 MHz, respectively, using a broadband 5 mm probe. All 2D experiments were performed with an inverse 5 mm probe with pulsed field gradient capability. For the complete assignment of the ^{1}H and ^{13}C NMR spectra of compounds **1**-**14**, a combination of two-dimensional COSY, TOCSY, HMBC and HMQC experiments were carried out. Inverse detected $^{1}H-^{13}C$ 2D chemical shift correlation spectra were acquired using the pulsed field gradient versions of HMBC and HMQC. In the cases of severe signal overlapping, the 500.16 MHz ^{1}H NMR spectra were finally analyzed by PERCH software[29] to perform complete spectral analyses. Electron impact high resolution mass spectra (EIMS) were obtained with Fisons ZabSpec mass spectrometer at 70 eV. Polarimetric measurements were carried out using a Perkin Elmer 241 Polarimeter with a cell volume of 1 mL and a cell length of 10 cm. TLC analyses were performed using silica gel F254 precoated aluminum sheets or glass plates and visualized by charring with 25% H_2SO_4 in methanol or methanol/orcinol and/or UV. Column chromatography was performed using silica gel 60 optionally enriched with 0.1% Ca to minimize hydrolysis of acid-labile protecting groups. Microanalyses were conducted at the Department of Microanalytics, University of Groningen, the Netherlands.

3.2. Synthesis and characterization of the monosaccharides

3.2.1. Benzyl β-D-galactopyranoside (1). To a solution of β-D-galactose pentaacetate (29.87 g, 76.52 mmol) in CH_2Cl_2 (300 mL) was added molecular sieves 4 Å (30 g) and benzyl alcohol (10.34 mL, 99.48 mmol). The reaction mixture was cooled on an ice-bath and $BF_3{\cdot}Et_2O$ (19.39 mL, 153.04 mmol) was added dropwise during a period of 15 min. The reaction mixture was slowly warmed up to ambient temperature and stirred for 20 h. The mixture was cooled to 0 °C, neutralized with triethylamine, extracted with CH_2Cl_2 and washed with water (3×200 mL). The organic layer was filtered through paper, the solvents were evaporated and the crude product was dried in vacuo. The obtained benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (42.05 g) was used in the subsequent step without further purification. This product was dissolved in a mixture of MeOH (1000 mL) and 1,4-dioxane (160 mL) and treated with sodium methoxide (4.0 g, 74 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC indicating completion of the reaction after 22 h ($MeOH/CH_2Cl_2$ 1:5, R_f=0.33 for the product). The reaction mixture was neutralized with Dowex 50 W (H^+ form), filtered and concentrated in a rotary evaporator. Solvents were co-evaporated with toluene and the product obtained was dried in vacuo. Column chromatography (silica gel, $MeOH/CH_2Cl_2$, gradient elution) gave pure **1** (13.53 g, overall yield 66% based on β-D-galactose pentaacetate) as a white solid: $[\alpha]_{22}^{D}=-31.4$ (c=0.14 in MeOH); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.44–7.30 (5H, m, Ph), 4.86, 4.68 (2H, d, J=11.6 Hz, CH_2Ph), 4.38 (1H, d, J=7.7 Hz, H-1), 3.84 (1H, dd, J=0.8, 3.4 Hz, H-4), 3.73 (1H, dd, J=4.5, 11.7 Hz, H_b-6), 3.67 (1H, dd, J=7.8, 11.7 Hz, H_a-6), 3.59 (1H, ddd, J=0.8, 4.5, 7.8 Hz, H-5), 3.53 (1H, dd, J=3.4, 9.9 Hz, H-3), 3.47 (1H, dd, J=9.9, 7.7 Hz, H-2); δ_C (125.78 MHz, $CDCl_3$, 303 K); 139.3, 129.6, 129.6, 129.3 (Ph), 102.7 (C-1), 76.1 (C-3), 73.8 (C-2), 72.3 (C-5), 71.7 (CH_2Ph), 69.6 (C-4), 61.9 (C-6); EIMS calcd for $C_{13}H_{19}O_6$ $[M+H]^+$ 271.1181. Found 271.1200. Anal. Calcd for $C_{13}H_{18}O_6$ (270.3): C, 57.77; H, 6.71. Found C, 56.76; H, 6.81.

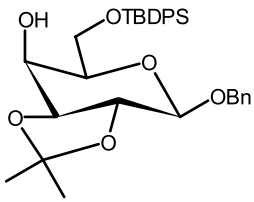
3.2.2. Benzyl 6-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranoside (2). To a solution of **1** (2.30 g, 8.52 mmol) in CH_2Cl_2 (60 mL) was added *tert*-butyldimethylchlorosilane (1.41 g, 9.35 mmol). The reaction mixture was stirred for 30 min at ambient temperature and cooled to 0 °C. A solution of DBU (1.40 mL, 9.37 mmol) in CH_2Cl_2 (10 mL) was added during a period of 30 min and the reaction mixture was stirred for 48 h at ambient temperature. Silica gel was added to the reaction mixture and the solvents were removed in vacuo. Flash column chromatography (silica gel containing 0.1% Ca, CH_2Cl_2/MeOH, gradient elution) gave pure **2** (3.22 g, 98%) as a white solid: $[\alpha]_{22}^{D}=-38.6$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.28–7.14 (5H, m, Ph), 4.80, 4.50 (2H, d, J=11.6 Hz, CH_2Ph), 4.18 (1H, d, J=7.8 Hz, H-1), 3.85 (1H, ddd, J=1.1, 3.3, 4.0 Hz, H-4), 3.80 (1H, dd, J=5.4, 10.5 Hz, H_b-6), 3.76 (1H, dd, J=6.9, 10.5 Hz, H_a-6), 3.61 (1H, ddd, J=2.7, 7.8, 9.5 Hz, H-2), 3.40 (1H, ddd, J=3.3, 5.9, 9.5 Hz, H-3), 3.32 (1H, ddd, J=1.1, 5.4, 6.9 Hz, H-5), 3.25 (1H, d, J=5.9 Hz, OH-3), 3.06 (1H, d, J=2.7 Hz, OH-2), 2.99 (1H, d, J=4.0 Hz, OH-4), 0.81 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.3, 128.6, 128.5, 128.2 (Ph), 102.1 (C-1), 75.2 (C-5), 73.9 (C-3), 71.7 (C-2), 70.9 (CH_2Ph), 69.1 (C-4), 62.7 (C-6), 26.0 (CMe_3), 18.5 (CMe_3), −5.2, −5.5 ($SiMe_2$); EIMS calcd for $C_{15}H_{23}O_6Si$ $[M-C(CH_3)_3]^+$ 327.1263. Found 327.1240. Anal. Calcd for $C_{19}H_{32}O_6Si$ (384.5): C, 59.34; H, 8.39. Found C, 59.18; H, 8.42.

3.2.3. Benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (3). To an ice-cooled solution of **1** (5.10 g, 18.87 mmol) and imidazole (2.57 g, 37.74 mmol) in DMF (50 mL) was added dropwise a solution of *tert*-butyldiphenylchlorosilane (5.19 g, 18.88 mmol) in DMF (25 mL). The reaction mixture was stirred overnight at ambient temperature. Monitoring by TLC indicated the disappearance of nearly all starting material after 23 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and extracted with Et_2O (3×80 mL). The combined organics were washed with H_2O (100 mL) and dried over sodium sulphate. Evaporation of the solvents left a yellowish oily foam (7.87 g) that was analyzed by ^{1}H NMR (250 MHz) in $CDCl_3$ indicating the presence of the desired product and *tert*-butyldiphenylsilanol in a 1:1 mixture. Flash column chromatography (silica gel, dichloromethane/methanol, gradient elution) gave pure **3** (5.75 g, 60%) as confirmed by ^{1}H and ^{13}C NMR analysis. δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.65–7.14 (15H, m, Ph), 4.78, 4.47 (2H, d, J=11.6 Hz, CH_2Ph), 4.18 (1H, d, J=7.8 Hz, H-1), 3.83, (1H, dd, J=0.8, 3.4 Hz, H-4), 3.82, (1H, dd, J=5.7, 10.6 Hz, H_b-6), 3.80 (1H, dd, J=6.0, 10.6 Hz, H_a-6), 3.61 (1H, dd,

J=7.8, 9.5 Hz, H-2), 3.40 (1H, dd, J=3.4, 9.5 Hz, H-3), 3.38 (1H, ddd, J=0.8, 5.7, 6.0 Hz, H-5), 0.99 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.2–127.9 (Ph), 101.9 (C-1), 74.9 (C-5), 73.8 (C-3), 72.1 (C-2), 70.9 (CH_2Ph), 69.2 (C-4), 63.4 (C-6), 27.0 (CMe_3), 19.4 (CMe_3). The 500.16 MHz NMR spectral data for **3** are consistent with those reported previously for this compound.[14]

3.2.4. Benzyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (4). To a solution of compound **2** (5.20 g, 13.54 mmol) in 2,2-dimethoxypropane (100 ml) was added in one portion *p*-TsOH·H_2O (50 mg, 0.26 mmol). The reaction mixture was stirred at ambient temperature under argon. The reaction was quenched after 3 h by neutralizing the solution with a mixture of Et_3N and dichloromethane (1:1). The solvents were evaporated and the remaining transparent oil was dried in vacuo. Flash column chromatography (silica gel containing 0.1% Ca, EtOAc/toluene 5:100) gave pure **4** (5.34 g, 93%) as a white solid: $[\alpha]_{23}^{D}$=−17.9 (c=0.12 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.34–7.15 (5H, m, Ph), 4.80, 4.49 (2H, d, J=11.6 Hz, CH_2Ph), 4.11 (1H, d, J=8.3 Hz, H-1), 4.05 (1H, dd, J=2.2, 5.4 Hz, H-4), 3.91 (1H, dd, J=5.4, 7.3 Hz, H-3), 3.82 (1H, dd, J=7.2, 9.9 Hz, H_b-6), 3.79 (1H, dd, J=5.8, 9.9 Hz, H_a-6), 3.66 (1H, ddd, J=2.2, 5.8, 7.2 Hz, H-5), 3.49 (1H, dd, J=7.3, 8.3 Hz, H-2), 1.40, 1.21 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.0, 128.6, 128.4, 128.0 (Ph), 110.0 (CMe_2), 101.1 (C-1), 78.9 (C-3), 73.9 (C-5), 73.8 (C-2), 73.3 (C-4), 70.6 (CH_2Ph), 62.2 (C-6), 28.3, 26.4 (CMe_2), 26.0 (CMe_3), 18.3 (CMe_3), −5.2, −5.5 ($SiMe_2$); EIMS calcd for $C_{21}H_{33}O_6Si$ $[M-CH_3]^+$ 409.2046. Found 409.2049.

3.2.5. Benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (5). To a solution of **3** (5.65 g, 11.1 mmol) in 2,2-dimethoxypropane (100 mL) was added *p*-TsOH·H_2O (50 mg). The reaction mixture was stirred at ambient temperature. Monitoring by TLC indicated the formation of three products. The reaction was quenched after 2 h by neutralizing with Et_3N in CH_2Cl_2 and evaporated to dryness. The remaining off-white/yellow foamy solid (7.61 g) was flash chromatographed (silica gel, toluene/ethyl acetate, gradient elution) to afford the desired product as a highly viscous colorless oil (4.55 g) in a mixture with toluene, as confirmed by NMR. The residual toluene was removed by co-evaporation with EtOH to leave, after drying in vacuo, pure **5** (4.34 g, 71%) as an off-white solid: $[\alpha]_{24}^{D}$=−12.9 (c=0.14 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.68–7.21 (15H, m, Ph), 4.83, 4.52 (2H, d, J=11.6 Hz, CH_2Ph,), 4.18 (1H, dd, J=2.2, 5.4 Hz, H-4), 4.15 (1H, d, J=8.3 Hz, H-1), 3.97 (1H, dd, J=5.4, 7.4 Hz, H-3), 3.95 (1H, dd, J=5.2, 10.0 Hz, H_b-6), 3.85 (1H, dd, J=6.4, 10.0 Hz, H_a-6), 3.79 (1H, ddd, J=2.2, 5.2, 6.4 Hz, H-5), 3.54 (1H, ddd, J=1.9, 7.4, 8.3 Hz, H-2), 2.25 (1H, d, J=1.9 Hz, OH-2), 1.44, 1.27 (6H, s, CMe_2), 1.00 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.08–127.8 (Ph), 110.3 (CMe_2), 101.1 (C-1), 78.9 (C-3), 74.1 (C-2), 74.0 (C-5), 73.5 (C-4), 70.9 (CH_2Ph), 63.0 (C-6), 27.0 (CMe_3), 28.4, 26.5 (CMe_2), 19.5 (CMe_3). The NMR spectral data for **5** are consistent with those reported previously for this compound.[14a] EIMS calcd for $C_{31}H_{37}O_6Si$ $[M-CH_3]^+$ 533.2359. Found 533.2359. Anal. Calcd for $C_{32}H_{40}O_6Si$ (548.7): C, 70.04; H, 7.35. Found C, 70.11; H, 7.26. Residual fractions from the flash chromatography were combined, evaporated to dryness and dried in vacuo to leave a viscous off-yellow oil (1.43 g) consisting of three major components as shown by TLC. Refluxing of this mixture for 24 h in MeOH/H_2O (50:5 mL) and monitoring by TLC indicated the conversion of one unidentified compound to **5**. The solvents were evaporated and the residual transparent oil (1.26 g) purified by flash chromatography according to the procedure described for the initial crude product (vide supra) to afford an additional crop of **5** (0.98 g, 16%) containing trace impurities, as confirmed by NMR, and an off-yellow oil (165 mg, 3%) identified as benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-β-D-galactopyranoside by ^1H and ^{13}C NMR analyses: δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.73–7.26 (15H, m, Ph), 4.90, 4.66 (2H, d, J=11.7 Hz, CH_2Ph), 4.67 (1H, d, J=7.9 Hz, H-1), 4.42 (1H, ddd, J=1.2, 2.6, 3.3 Hz, H-4), 3.99 (1H, dd, J=5.4, 10.5 Hz, H_b-6), 3.96 (1H, dd, J=6.5, 10.5 Hz, H_a-6), 3.94 (1H, dd, J=7.9, 9.5 Hz, H-2), 3.56 (1H, ddd, J=1.2, 5.4, 6.5 Hz, H-5), 3.52 (1H, dd, J=2.6, 9.5 Hz, H-3), 2.41 (1H, d, J=3.3 Hz, OH-4), 1.48, 1.46 (6H, s, CMe_2), 1.08 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.08–127.8 (Ph), 110.3 (CMe_2), 101.1 (C-1), 79.2 (C-3), 76.0 (C-5), 73.1 (C-2), 69.9 (CH_2Ph), 67.2 (C-4), 62.9 (C-6), 26.8 (CMe_3), 26.8, 26.5 (CMe_2), 19.2 (CMe_3).



3.2.6. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (6). To a solution of **4** (1.14 g, 2.69 mmol) in CH_2Cl_2 (50 mL) was added acetic anhydride (10 mL, 0.11 mol) and Et_3N (3 mL, 21.6 mmol). The reaction mixture was stirred for 48 h at ambient temperature, cooled to 0 °C and treated with MeOH (100 mL). The solvents were evaporated and the remaining oil was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2×50 mL) and water (50 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated to dryness. Flash column chromatography (silica gel containing 0.1% Ca, ethyl acetate/toluene, gradient elution) gave pure **6** (0.92 g, 74%) as a transparent oil: $[\alpha]_{23}^{D}$=−16.3 (c=0.12 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.25–7.16 (5H, m, Ph), 4.95 (1H, dd, J=7.6, 8.3 Hz, H-2), 4.77, 4.50 (2H, d, J=12.4 Hz, CH_2Ph), 4.23 (1H, d, J=8.3 Hz, H-1), 4.09 (1H, dd, J=2.1, 5.4 Hz, H-4), 4.01 (1H, dd, J=5.4, 7.6 Hz, H-3), 3.83 (1H, dd, J=7.0, 10.0 Hz, H_b-6), 3.81 (1H, dd, J=6.1, 10.0 Hz, H_a-6), 3.68 (1H, ddd, J=2.1, 6.1, 7.0 Hz, H-5), 1.97 (3H, s, Me), 1.47, 1.22 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.5, 128.6, 128.0, 127.9 (Ph), 110.6 (CMe_2), 99.1 (C-1), 77.3 (C-3), 73.9 (C-5), 73.6 (C-4), 73.5 (C-2), 70.1 (CH_2Ph), 62.3 (C-6), 28.0, 26.6 (CMe_2), 26.0 (CMe_3), 21.2 (Me), 18.5 (CMe_3), −5.1, −5.2 ($SiMe_2$); EIMS calcd for $C_{23}H_{35}O_7Si$ $[M-CH_3]^+$ 451.2152. Found 451.2147.

3.2.7. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (7). To a solution of **5** (3.41 g, 6.21 mmol) in pyridine (40 mL) was added acetic anhydride (20 mL) and the reaction mixture was stirred overnight at ambient temperature. Monitoring by TLC indicated the formation of one major product after 2 h. The reaction mixture was cooled using an ice-bath and quenched by addition of MeOH (100 mL). The solvents were evaporated and the remaining oil extracted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL) and evaporated to dryness. The residual pyridine was co-evaporated with toluene after which the remaining toluene traces were co-evaporated with EtOH. The resulting oil (3.73 g) was dried in vacuo and crystallized from pentane at −20 °C to afford pure **7** (3.42 g, 93%) as a bright white solid: $[\alpha]_{24}^{D}=-14.5$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.72–7.22 (15H, m, Ph), 5.02 (1H, dd, J=8.0, 8.3 Hz, H-2), 4.83, 4.57 (2H, d, J=12.5 Hz, CH_2Ph), 4.32 (1H, d, J=8.3 Hz, H-1), 4.25 (1H, dd, J=2.1, 5.4 Hz, H-4), 4.11 (1H, dd, J=5.4, 8.0 Hz, H-3), 3.99 (1H, dd, J=7.0, 10.1 Hz, H_b-6), 3.95 (1H, dd, J=6.2, 10.1 Hz, H_a-6), 3.83 (1H, ddd, J=2.1, 6.2, 7.0 Hz, H-5), 2.05 (3H, s, Me), 1.54, 1.32 (6H, s, CMe_2), 1.05 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.5–127.9 (Ph), 110.6 (*C*Me_2), 99.1 (C-1), 77.0 (C-3), 73.8 (C-4), 73.7 (C-2), 73.5 (C-5), 70.2 (*C*H_2Ph), 63.0 (C-6), 28.0, 26.8 (C*Me*$_2$), 27.0 (C*Me*$_3$), 21.2 (Me), 19.5 (*C*Me_3); EIMS calcd for $C_{33}H_{39}O_7Si$ $[M-CH_3]^+$ 575.2465. Found 575.2463. Anal. Calcd for $C_{34}H_{42}O_7Si$ (590.8): C, 69.12; H, 7.17. Found C, 69.58; H, 7.19.

3.2.8. Benzyl 2-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (8). To a solution of **5** (0.58 g, 1.06 mmol) in pyridine (10 mL) was added benzoyl chloride (0.18 mL, 1.58 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC. Quantitative conversion of the starting material to a single product was observed after 6 h. The mixture was cooled using an ice-bath, quenched by addition of MeOH (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic phase was washed with H_2O (100 mL), dried over sodium sulphate and evaporated to dryness. The residual pyridine was co-evaporated with toluene after which the remaining toluene traces were co-evaporated with EtOH. Drying in vacuo afforded **8** as a white solid containing trace impurities as confirmed by ^{1}H NMR. Flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:100) gave after subsequent evaporation and drying 700 mg (99%) of pure **8** as a white solid: $[\alpha]_{24}^{D}=-11.4$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 8.04–7.14 (20H, m, Ph), 5.23 (1H, dd, J=7.3, 8.3 Hz, H-2), 4.76, 4.55 (2H, d, J=12.7 Hz, CH_2Ph), 4.39 (1H, d, J=8.3 Hz, H-1), 4.23 (1H, dd, J=5.4, 2.1 Hz, H-4), 4.20 (1H, dd, J=7.3, 5.4, Hz, H-3), 3.97 (1H, dd, J=6.7, 10.1 Hz, H_b-6), 3.94 (1H, dd, J=6.5, 10.1 Hz, H_a-6), 3.83 (1H, ddd, J=2.1, 6.5, 6.7 Hz, H-5), 1.51, 1.34 (6H, s, CMe_2), 1.10 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 165.6 (C=O), 137.3–127.9 (Ph), 110.7 (*C*Me_2), 98.9 (C-1), 77.5 (C-3), 74.0 (C-2), 73.9 (C-5), 73.7 (C-4), 69.9 (*C*H_2Ph), 63.0 (C-6), 27.0 (C*Me*$_3$), 28.0, 26.5 (C*Me*$_2$), 19.5 (*C*Me_3); EIMS calcd for $C_{38}H_{41}O_7Si$ $[M-CH_3]^+$ 637.2622. Found 637.2617. Anal. Calcd for $C_{39}H_{44}O_7Si$ (652.8): C, 71.75; H, 6.79. Found C, 71.61; H, 6.77.

3.2.9. Benzyl 2-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (9). To an ice-cooled solution of **6** (681 mg, 1.46 mmol) in THF (15 mL) was added in one portion a solution of $Bu_4NF{\cdot}3H_2O$ (920 mg, 2.92 mmol) in THF (10 mL). The ice-bath was removed after 15 min and the reaction mixture was stirred at ambient temperature. Monitoring by TLC indicated the formation of one major product. The reaction was quenched after 1 h by the addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with an additional portion of CH_2Cl_2 (20 mL) and the combined organics washed with brine (2×50 mL) and dried over sodium sulphate. The solvents were evaporated and the remaining off-yellow oil was dried in vacuo to leave 636 mg of fairly pure **9** as an off-white solid (identified by ^{1}H and ^{13}C NMR spectroscopy). Flash column chromatography (silica gel, toluene/ethyl acetate, gradient elution) gave pure **9** (433 mg, 84%): $[\alpha]_{24}^{D}=-0.83$ (c=0.06 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.38–7.05 (5H, m, Ph), 5.05 (1H, dd, J=7.2, 8.2 Hz, H-2), 4.86, 4.66 (2H, d, J=12.5 Hz, CH_2Ph), 4.41 (1H, d, J=8.2 Hz, H-1), 4.17 (1H, dd, J=5.4, 7.2 Hz, H-3), 4.15 (1H, dd, J=2.2, 5.4 Hz, H-4), 3.99 (1H, dd, J=4.3, 11.9 Hz, H_b-6), 3.84 (1H, dd, J=7.4, 11.9 Hz, H_a-6), 3.84 (1H, ddd, J=2.2, 4.3, 7.4 Hz, H-5), 2.07 (3H, s, Me), 1.55, 1.32 (6H, s, CMe_2); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.4, 128.6, 128.1, 127.9 (Ph), 111.1 (*C*Me_2), 99.5 (C-1), 77.5 (C-3), 74.2 (C-4), 73.6 (C-5), 73.1 (C-2), 70.9 (*C*H_2Ph), 62.6 (C-6), 27.8, 26.6 (CMe_2), 21.2 (Me). The ^{1}H and ^{13}C NMR data of **9** reported here in $CDCl_3$ solution deviate from those given previously in CD_3CN/D_2O.[16] EIMS calcd for $C_{18}H_{24}O_7$ 352.1522. Found 352.1489. Anal. Calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86. Found C, 61.11; H, 6.91.

3.2.10. Benzyl 2-*O*-acetyl-β-D-galactopyranoside (10). To an ice-cooled solution of **6** containing a trace of the α-anomer (171 mg, 0.37 mmol) in THF (10 mL) was added in one portion a solution of $Bu_4NF{\cdot}3H_2O$ (230 mg, 0.74 mmol) in THF (10 mL). An immediate color change to light yellow was observed. TLC analysis after 90 min indicated the formation of one major product in accordance with the earlier observations during the synthesis of **9** (vide supra). The reaction was quenched by the addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with additional portions of CH_2Cl_2 (2×20 mL) and the combined organics washed with brine (50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left a yellowish oily solid (183 mg) that was dissolved in MeOH (30 mL) and stirred at ambient temperature overnight with Dowex DR-2030 (0.5 g, Fluka, H^+-form). The reaction was monitored by TLC showing the disappearance of all starting material after 21 h. The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-white/yellowish solid (113 mg). The residue was purified by repeated washing and cooling cycles with $CHCl_3$ to yield pure **10** (75 mg, 65%) as a bright white crystalline solid: $[\alpha]_{23}^{D}=-10.4$ (c=0.02 in MeOH); δ_H (500.16 MHz, CD_3OD, 303 K); 7.34–7.24 (5H, m, Ph), 5.07 (1H, dd, J=8.1, 10.0 Hz, H-2), 4.86, 4.62 (2H, d, J=12.2 Hz, CH_2Ph), 4.46 (1H, d, J=8.1 Hz, H-1), 3.87 (1H, dd, J=0.8, 3.4 Hz, H-4), 3.81 (1H, dd, J=6.9, 11.4 Hz, H_b-6), 3.75 (1H, dd, J=5.2, 11.4 Hz, H_a-6), 3.62 (1H, dd,

J=3.4, 10.0 Hz, H-3), 3.54 (1H, ddd, J=0.8, 5.2, 6.9 Hz, H-5), 2.01 (3H, s, Me); δ_C (125.78 MHz, CD_3OD, 303 K); 172.3 (C=O), 139.3, 129.5, 129.0, 128.9 (Ph), 101.8 (C-1), 77.1 (C-5), 74.1 (C-2), 73.4 (C-3), 71.7 (CH_2Ph), 70.6 (C-4), 62.6 (C-6), 21.2 (Me); EIMS calcd for $C_{14}H_{15}O_5$ $\{[M-H_2O]-CH_2OH\}^+$ 263.0919. Found 263.0913. Anal. Calcd for $C_{15}H_{20}O_7$ (312.3): C, 57.69; H, 6.45. Found C, 57.34; H, 6.22. Alternatively, a solution of **6** (75 mg, 0.16 mmol) in MeOH (15 mL) was stirred at ambient temperature overnight with Dowex DR-2030 (0.31 g). TLC showed the formation of one major product after 17 h. The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-white solid (50 mg). The crude product was analyzed by ^{1}H NMR (250 MHz) in MeOD showing nearly quantitative cleavage of both isopropylidene and TBDMS protective groups and the high yield formation of **10** evidenced by comparison of the ^{1}H NMR spectrum with that of the pure compound (vide supra). Further purification was not performed.

3.2.11. Benzyl 2-*O*-benzoyl-β-D-galactopyranoside (11). To an ice-cooled solution of **8** (332 mg, 0.51 mmol) in THF (10 mL) was added in one portion a solution of $Bu_4NF\cdot 3H_2O$ (320 mg, 1.0 mmol) in THF (10 mL). TLC analysis after 2 h was consistent with complete conversion of the starting material. The reaction was quenched by addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The organic phase was washed with H_2O (2×50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left a viscous yellow oil that was dissolved in MeOH (30 mL) and stirred at ambient temperature overnight with Dowex DR-2030 (0.5 g, Fluka, H^+-form). The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-yellow/brown solid (300 mg). Washing with pentane and subsequent crystallization from ethyl acetate afforded **11** (105 mg, 55%) as an off white powder: $[\alpha]_{23}^{D}$=−34.0 (c=0.02 in MeOH); δ_H (500.16 MHz, CD_3OD, 303 K); 8.00–7.05 (10H, m, Ph), 5.33 (1H, dd, J=8.0, 9.9 Hz, H-2), 4.83, 4.64 (2H, d, J=12.4 Hz, CH_2Ph), 4.60 (1H, d, J=8.0 Hz, H-1), 3.92 (1H, dd, J=1.1, 3.4 Hz, H-4), 3.85 (1H, dd, J=7.1, 11.4 Hz, H_b-6), 3.79 (1H, dd, J=5.0, 11.4 Hz, H_a-6), 3.79 (1H, dd, J=3.4, 9.9 Hz, H-3), 3.61 (1H, ddd, J=1.1, 5.0, 7.1 Hz, H-5); δ_C (125.78 MHz, CD_3OD, 303 K); 167.6 (C=O), 138.8–128.6 (Ph), 101.6 (C-1), 77.0 (C-5), 74.5 (C-2), 73.2 (C-3), 71.4 (CH_2Ph), 70.7 (C-4), 62.5 (C-6). In the EIMS analysis of the parent compound **11** ($C_{20}H_{22}O_7$) only peaks corresponding to decomposition products were observed. A satisfactory analysis was, however, obtained from the fully silylated 3,4,6-trimethylsiloxy derivative of **11**, benzyl 2-*O*-benzoyl-tris-3,4,6-*O*-(trimethylsilyl)-β-D-galactopyranoside for which EIMS calcd for $C_{28}H_{43}O_7Si_3$ 575.2317 gave the observed 575.2313.

3.2.12. 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranose (12). To a solution of **6** (1.45 g, 3.11 mmol) in EtOH (100 mL) was added activated 10% Pd/C (250 mg) and cyclohexene (5 mL). The reaction mixture was refluxed for 72 h. The solids were separated by filtration through Celite and subsequent washing with CH_2Cl_2. Evaporation of the solvents and drying in vacuo afforded a dark oil (1.45 g). Analysis of the crude product by ^{1}H NMR (250 MHz) indicated the formation of the desired product as a mixture of the α- and β-anomers. Flash column chromatography (silica gel, toluene/ethyl acetate, gradient elution) gave pure **12** (1.04 g, 93%): (α-form) δ_H (500.16 MHz, $CDCl_3$, 303 K); 5.25 (1H, dd, J=3.5, 4.1 Hz, H-1), 4.83 (1H, ddd, J=1.3, 3.5, 7.7 Hz, H-2), 4.28 (1H, dd, J=5.7, 7.7 Hz, H-3), 4.21 (1H, ddd, J=2.4, 2.6, 6.1 Hz, H-5), 4.20 (1H, dd, J=2.4, 5.7 Hz, H-4), 3.80 (1H, dd, J=6.1, 10.0 Hz, H_b-6), 3.71 (1H, dd, J=2.6, 10.0 Hz, H_a-6), 2.90 (1H, dd, J=1.3, 4.1 Hz, OH-1), 2.02 (3H, s, Me), 1.38, 1.21 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 170.8 (C=O), 109.8 (CMe_2), 90.6 (C-1), 73.2 (C-3), 73.1 (C-5), 72.3 (C-2), 68.3 (C-4), 62.5 (C-6), 28.1, 26.4 (CMe_2), 26.1 (CMe_3), 21.3 (Me), 18.6 (CMe_3), −5.1, −5.2 ($SiMe_2$); (β-form) δ_H (500.16 MHz, $CDCl_3$, 303 K); 4.74 (1H, dd, J=7.3, 7.8 Hz, H-2), 4.46 (1H, dd, J=9.8, 7.8 Hz, H-1), 4.20 (1H, ddd, J=2.0, 4.6, 5.4 Hz, H-5), 4.13 (1H, dd, J=5.4, 7.3 Hz, H-3), 3.79 (1H, dd, J=5.4, 10.3 Hz, H_b-6), 3.77 (1H, dd, J=2.0, 10.3 Hz, H_a-6), 3.77 (1H, dd, J=4.6, 5.4 Hz, H-4), 3.40 (1H, d, J=9.8 Hz, OH-1), 2.02 (3H, s, Me), 1.53, 1.45 (6H, s, CMe_2), 0.81 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 170.8 (C=O), 109.9 (CMe_2), 95.6 (C-1), 76.1 (C-3), 75.8 (C-2), 73.6 (C-4), 73.2 (C-5), 61.9 (C-6), 28.0, 26.2 (CMe_2), 26.0 (CMe_3), 21.3 (Me), 18.5 (CMe_3), −5.2, −5.2 ($SiMe_2$); EIMS calcd for $C_{16}H_{29}O_7Si$ $[M-CH_3]^+$ 361.1683. Found 361.1691.

3.2.13. 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranosyl trichloroacetimidate (13). To an ice-cooled solution of **12** (1.04 g, 2.88 mmol) in CH_2Cl_2 (50 mL) was subsequently added trichloroacetonitrile (4.16 g, 2.9 mL, 28.8 mmol) and DBU (0.52 mL, 3.46 mmol). The reaction mixture was monitored by TLC showing consumption of all starting material after 2 h. The solvents were evaporated to leave a thick brown oil that was dissolved in a small amount of a solvent mixture containing toluene, ethyl acetate and CH_2Cl_2. Flash column chromatography (silica gel, with toluene/ethyl acetate/Et_3N, gradient elution) gave **13** in two fractions (1.07+0.1 g, total yield 78%) as a thick yellow oil. ^{1}H NMR (600 MHz) analysis revealed the first fraction to consist of fairly pure **13** enriched in single anomer, whereas the second fraction consisted of the anomeric mixture. (α-form) δ_H (600.13 MHz, $CDCl_3$, 298 K); 8.55 (s, 1H, NH), 6.36 (1H, d, J=3.6 Hz, H-1), 5.09 (1H, dd, J=3.6, 7.6 Hz, H-2), 4.41 (1H, dd, J=5.5, 7.6 Hz, H-3), 4.35 (1H, dd, J=2.3, 5.5 Hz, H-4), 4.22 (1H, ddd, J=2.3, 6.1, 7.3 Hz, H-5), 3.87 (1H, dd, J=7.3, 10.0 Hz, H_b-6), 3.79 (1H, dd, J=6.1, 10.0 Hz, H_a-6), 2.04 (3H, s, Me), 1.51, 1.31 (6H, s, CMe_2), 0.85 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (150.90 MHz, $CDCl_3$, 298 K); 170.5 (C=O), 161.0 (C=NH), 110.1 (CMe_2), 93.8 (C-1), 91.2 (CCl_3), 73.0 (C-3), 72.7 (C-4), 70.9 (C-5), 70.6 (C-2), 62.0 (C-6), 28.0, 26.4 (CMe_2), 26.0 (CMe_3), 21.0 (Me), 18.5 (CMe_3), −5.1, −5.2 ($SiMe_2$); EIMS calcd for $C_{18}H_{29}Cl_3NO_7Si$ $[M-CH_3]^+$ 504.0779. Found 504.0792.

3.2.14. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (14). To an ice-cooled solution of **7** (105 mg, 0.18 mmol) in freshly distilled CH_2Cl_2 (15 mL) was added via syringe CF_3COOH (1 mL) containing 2%

deionized H_2O. The reaction mixture was stirred for 10 min at 0 °C followed by 20 min at ambient temperature. Next, the reaction mixture was cooled on an ice-bath followed by addition of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Ice-cold saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture extracted with CH_2Cl_2 (2×50 mL). The combined organics were washed with $NaHCO_3$ (30 mL), H_2O (50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left an off-yellow solid (122 mg) that was analyzed by ^1H NMR (250 MHz) in $CDCl_3$. The spectral data indicated nearly quantitative conversion of the starting material to the desired product. Precipitation from pentane gave an isolated yield of 75 mg (76%) of pure **14** as a white solid: $[\alpha]_{24}^{D}=-27.9$ (c=0.02 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.74–7.24 (15H, m, Ph), 5.07 (1H, dd, J=7.9, 9.7 Hz, H-2), 4.89, 4.62 (2H, d, J=12.4 Hz, CH_2Ph), 4.43 (1H, d, J=7.9 Hz, H-1), 4.09 (1H, ddd, J=1.1, 3.3, 4.4 Hz, H-4), 4.00 (1H, dd, J=5.9, 10.6 Hz, H_b-6), 3.97 (1H, dd, J=5.0, 10.6 Hz, H_a-6), 3.60 (1H, ddd, J=3.3, 8.5, 9.7 Hz, H-3), 3.51 (1H, ddd, J=1.1, 5.0, 5.9 Hz, H-5), 2.92 (1H, d, J=8.5 Hz, OH-3), 2.88 (1H, d, J=4.4 Hz, OH-4), 2.11 (3H, s, Me), 1.10 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 171.5 (C=O), 137.4–127.8 (Ph), 99.7 (C-1), 74.3 (C-5), 73.7 (C-2), 73.2 (C-3), 70.3 (*C*H_2Ph), 69.7 (C-4), 63.6 (C-6), 27.0 (C*Me*$_3$), 21.2 (Me), 19.4 (*C*Me_3). Anal. Calcd for $C_{31}H_{38}O_7Si$ (550.7): C, 67.61; H, 6.95. Found C, 67.72; H, 6.86.

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References and notes

1. (a) Varki, A.; Cummings, R.; Esko, J.; Freeze, H.; Hart, G.; Marth, J. *Essentials of glycobiology*; Cold Spring Harbor Laboratory: Cold Spring Harbor, NY, 1999. (b) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, 637–674. (c) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
2. (a) Hakomori, S.; Zhang, Y. *Chem. Biol.* **1997**, *4*, 97–104. (b) Alper, J. *Science* **2001**, *291*, 2338–2343. (c) Dove, A. *Nature Biotechnol.* **2001**, *19*, 913–917. (d) In *Glycobiology (thematic issue). Chem. Rev.*, Dwek, R. A., Butters, T. D., Eds.;, 2002; 102, pp 283–602.
3. Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465–4493.
4. (a) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349–4393. (b) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523–1527. (c) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344–2350.
5. Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3215–3237.
6. Willför, S.; Sjöholm, R.; Laine, C.; Roslund, M.; Hemming, J.; Holmbom, B. *Carbohydr. Polym.* **2003**, *52*, 175–187.
7. (a) Du, Y.; Pan, Q.; Kong, F. *Carbohydr. Res.* **2000**, *323*, 28–35. (b) Pan, Q.; Du, Y.; Kong, F.; Pan, J.; Lü, M. *J. Carbohydr. Chem.* **2001**, *20*, 297–306.
8. (a) Knuhr, P.; Castro-Palomino, J.; Grathwohl, M.; Schmidt, R. R. *Eur. J. Org. Chem.* **2001**, 4239–4246. Galactose structures also serve as branching points in human blood group antigens, see for example: (b) Martín, M. J.; Feizi, T.; Lateux, C.; Pavlovic, D.; Piskarev, V. E.; Chai, W. *Glycobiology* **2002**, *12*, 829–835.
9. (a) Renkonen, O. *Cell. Mol. Life Sci.* **2000**, *57*, 1423–1439. (b) Miller-Podraza, H. *Chem. Rev.* **2000**, *100*, 4663–4681. (c) Biet, T.; Peters, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4189–4192.
10. Roslund, M. U.; Klika, K. D.; Lehtilä, R. L.; Tähtinen, P.; Sillanpää, R.; Leino, R. *J. Org. Chem.* **2004**, *69*, 18–25.
11. Clausen, M. H.; Jørgensen, M. R.; Thorsen, J.; Madsen, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 543–551.
12. Francisco, C. G.; González Martín, C.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099–2109.
13. Francisco, C. G.; León, E. I.; Martín, A.; Moreno, P.; Rodríguez, M. S.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 6967–6976.
14. (a) Redlich, H.; Sudau, W.; Szardenings, A. K.; Vollerthun, R. *Carbohydr. Res.* **1992**, *226*, 57–78. (b) Lin, C.-C.; Shimzaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzèn, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826–6840.
15. For the β-D-glucopyranoside analogue of **3**, see, for example: Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498–4508.
16. Compound **9** has been prepared previously by a combination of chemical synthesis and enzymatic methods, see: Barili, P. L.; Catelani, G.; D'Andrea, F.; Mastrorilli, E. *J. Carbohydr. Chem.* **1997**, *16*, 1001–1010.
17. Compound **11** has been described previously, see: Levy, A.; Flowers, H. M.; Sharon, N. *Carbohydr. Res.* **1967**, *4*, 305–311.
18. Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 3rd ed.; Wiley: New York, 1999; pp 141–144.
19. (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235. (b) Du, Y.; Zhang, M.; Kong, F. *Org. Lett.* **2000**, *2*, 3797–3800. (c) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559–4564. (d) Chen, L.; Kong, F. *Tetrahedron Lett.* **2003**, *44*, 3691–3695.
20. (a) Defaye, J.; Gadelle, A.; Pedersen, C. *Carbohydr. Res.* **1989**, *186*, 177–188. (b) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15–26.
21. (a) Lictenhaler, F. W.; Oberthür, M.; Peters, S. *Eur. J. Org. Chem.* **2001**, 3849–3869. (b) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142–8148.
22. Verduyn, R.; Douwes, M.; van der Klein, P. A. M.; Mösinger, E. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1993**, *49*, 7301–7316.
23. (a) Beith-Halahmi, D.; Flowers, H. M.; Shapiro, D. *Carbohydr. Res.* **1967**, *5*, 25–30. (b) Acher, A. J.; Rabinsohn, Y.; Rachaman, E. S.; Shapiro, D. *J. Org. Chem.* **1970**, *35*, 2346–2347. (c) Kaji, E.; Shibayama, K.; In, K. *Tetrahedron Lett.* **2003**, *44*, 4881–4885.
24. Paulsen, H.; Paal, M.; Hadamczyk, D.; Steiger, K.-M. *Carbohydr. Res.* **1984**, *131*, C1–C5.
25. Kitov, P. I.; Railton, C.; Bundle, D. R. *Carbohydr. Res.* **1998**, *307*, 361–370.
26. 2-*O*-glycosidations of galactopyranosides: (a) Kumagai, D.; Miyazaki, M.; Nishimura, S.-I. *Tetrahedron Lett.* **2001**, *42*, 1953–1956. (b) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Fan, H.-F.; Pai, C.-L.; Yang, W.-C.; Lu, L.-D.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362. 6-*O*-glycosidations: (c) Konradsson, P.; Fraser-Reid, B. *J. Chem. Soc., Chem.*

Commun. **1989**, 1124–1125. (d) Garegg, P. J.; Maloisel, J.-L.; Oscarson, S. *Synthesis* **1995**, 409–414. (e) Borbás, A.; Jánossy, L.; Lipták, A. *Carbohydr. Res.* **1999**, *318*, 98–109. (f) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554. (g) Wittman, V.; Lennartz, D. *Eur. J. Org. Chem.* **2002**, 1363–1367.

27. Du, Y.; Zhang, M.; Yang, F.; Ga, G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3122–3127.
28. (a) Peters, T.; Weimar, T. *Liebigs Ann. Chem.* **1991**, 237–242. (b) Chiu-Machado, I.; Castro-Palomino, J. C.; Madrazo-Alonso, O.; Lopetegui-Palacios, C.; Verez-Bencomo, V. *J. Carbohydr. Chem.* **1995**, *14*, 551–561. (c) Horrobin, T.; Tran, C. H.; Crout, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1069–1080. (d) Kurahashi, T.; Mizutani, T.; Yoshida, J. *J. Chem. Soc., Perkin Trans.* **1999**, 465–473.
29. Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson., Ser. A* **1996**, *120*, 1–10.