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<td>Author(s)</td>
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Regiospecific Anomerisation of Acylated Glycosyl azides and Benzoylated Disaccharides Using TiCl₄

Mark Farrell, Jian Zhou, and Paul V. Murphy*[

Abstract: Chelation induced anomerisation is promoted when Lewis acids, such as TiCl₄ or SnCl₄, coordinate to the pyranose ring oxygen atom and another site, giving rise to endocyclic cleavage and isomerisation to the more stable anomer. In this research regiospecific site-directed anomerisation is demonstrated. TiCl₄ (2.5 equiv) was employed to induce anomerisation of 15 glycosyl azide and disaccharide substrates. The methyl ester of low reactivity, and high yields (>75%) and stereoselectivities (α/β > 9:1) were achieved. The examples included glucopyranuronate, galactopyranuronate and mannopyranuronate as well as N-acetylated glucopyranosyl azide and galactopyranuronate derivatives. A disaccharide with the α1→4 linkage found in polygalacturonan was included. The use of benzoylated saccharides was found to be important in disaccharide anomerisation as attempts to isomerise related acetyl protected and 2,3-carbonate protected derivatives were not successful.

Keywords: anomerisation · glycuronic acid · Lewis acids · protecting groups · regioselectivity

Introduction

Glycosides are ubiquitous and important to life, health, food, materials, energy and the environment. Despite progress, it is still viewed as being important to improve the stereoselective synthesis of glycosides. Previous studies from our laboratory have shown that the presence of a carboxylic acid or a derivative (e.g., ester or amide) at the C-5 of a saccharide, as found in glycuronic acids, leads to a significant increase in the rate of anomerisation promoted by Lewis acids, such as TiCl₄ or SnCl₄. This is explained by chelation of the pyranose ring oxygen atom and C-6 carbonyl group to the Lewis acid facilitating endocyclic cleavage and consequent glycoside bond isomerisation to the thermodynamically more stable anomer (Scheme 1). A study of factors influencing anomerisation of glucose and galactose derivatives has been carried out, with the impact of protecting group (e.g., benzoylation>acetylation) and promoter (TiCl₄>SnCl₄) on the rate and stereoselectivity of the reaction being discussed.

Scheme 1. ■ ■ legend

Results and Discussion

This study commenced with the synthesis of a variety of glycosyl azide and disaccharide substrates. The methyl ester 1 was prepared as previously reported. Its analogous allyl ester 2 was generated via 1 by saponification, which was followed by the base-mediated alkylation of the carboxylic acid and subsequent acetylation. The bromide 3 was prepared from α-galacturonic acid through acetylation, subsequent methyl ester formation and then treatment with HBr/AcOH (Scheme 2). Treatment of this bromide with sodium azide in DMF in an ultrasonic bath gave the azide 4. The β-mannopyranosyl azide 5 was prepared from 5 by a glycosyl iodide. This azide 6 was then subjected to Zemplén deacetylation followed by one pot silylation–benzoylation to give the TBDPS derivative 7. Removal of the the silyl protecting group, followed by oxidation and base-mediated esterification gave 8.

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An approach similar to that used for the mannanuronic acid derivative 8 was adopted for the preparation of the 2-deoxy-N-acetyl-glycuronides (Scheme 3). The α-glycosyl bromides 9 and 10 were converted to the corresponding β-azides using tetrabutylammonium azide in CH₂Cl₂. These azides were then treated with sodium methoxide in methanol to bring about O-deacetylation and this was followed by one pot silylation–benzoylation to give 11 and 12. The TBDPS group was removed from 11 and 12 using HF/pyridine and the resulting primary alcohol was oxidised to the carboxylic acid using TEMPO/BAIB. Initial attempts to prepare the methyl ester by base-mediated esterification as described for other acids above gave low yields. However, the esterification with p-toluenesulphonic acid in MeOH gave the desired azides 13 and 14 in improved yields.

The preparation of the disaccharide 20 was carried out from azide 15. Deacetylation followed by treatment of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSCl) in the presence of pyridine gave 16 in which both 4- and 6-OH groups are protected. The TIPDS group was then rear ranged, using p-toluenesulphonic acid in DMF, so as to protect the 3- and 4-OH groups. Then oxidation of the primary alcohol to the acid using TEMPO/BAIB followed by esterification gave 17. Glycosidation using the trichloroacetimidate donor 18 gave 19. The TIPDS protecting group was removed using HCl/MeOH and subsequent treatment with benzoyl chloride and pyridine gave the disaccharide 20 (Scheme 4).
The synthesis of disaccharide 27 began from the allyl glucoside 21 (Scheme 5).[14] Deacetylation followed by treatment with TBDPSCI in the presence of pyridine and subsequent benzoylation gave 22. Removal of the TBDPS group followed by oxidation and esterification gave 23. The allyl group was removed using PdCl₂ to give a hemiacetal. Subsequent treatment of this hemiacetal with trichloroacetonitrile in the presence of DBU gave donor 24.[15] The disilyloxy derivative 25, prepared from 16 (Scheme 3), was used to give acceptor 26 through regioselective acetylation at the 6-OH. The glycoside bond forming reaction between 24 and 26 then gave the disaccharide 27.

The glucosyl azide 28, prepared by deacetylation of 15, was next regioselectively silylated using TBDPSCI. The remaining hydroxyl groups were benzoylated and removal of the TBDPS group with TBAF gave acceptor 29. The glycoside coupling reaction of 29 with 24 gave disaccharide 30 (Scheme 6).

The diol 25 was used to prepare 31 and 32 (Scheme 7). Thus, the treatment of 25 with acetyl chloride in the presence of collidine led to the regioselective introduction of an acetyl group at the 2-OH.[16] Subsequent glycosidation of this acceptor with 24 gave 31.

Removal of the disiloxo group using HCl/MeOH also led to the selective removal of the acetate from 31 but not the benzoate protecting groups. The subsequent benzoylation of the free OH groups in the aglycon of the intermediate gave 32.

Azide 28 was used to prepare 34 and 35. Treatment of 28 with dimethoxypropane under acidic conditions led to intro-

Scheme 5. ■ ■ legend? ■

Scheme 6. ■ ■ legend? ■

Scheme 7. ■ ■ legend? A Im⁺ above 1st arrow: is this correct? ■


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duction of an acetonide group at the 4- and 6-OH groups. Then treatment with TIPDSCI in pyridine placed the TIPDS protecting group onto the 2- and 3-OH groups. Removal of the acetonide and regioselective acetylation gave 33. The glycoside coupling treatment of 33 with 24 gave disaccharide 34. Concomitant removal of the TIPDS protecting group and the acetate using Amberlyst-15H+ in methanol followed by benzoylation of the free OH groups gave 35 (Scheme 8).

With a series of disaccharides based on glucuronic acid in hand, our attention next turned to preparation of disaccharides based on galacturonic acid. Hence, the donor 37 was required and its preparation was commenced from D-galactose which was first tritylated at the 6-OH group and then the remaining hydroxyl groups then benzoylated. Acid catalysed hydrolysis of the trityl group gave 36. Subsequent oxidation of the primary alcohol and esterification followed by glycosyl bromide formation and silver ion promoted hydrolysis of the bromide gave a hemiacetal. Treatment of the hemiacetal with trichloroacetonitrile in the presence of DBU gave 37. The acceptor 38 was prepared from methyl α-D-galactopyranoside by introduction of a benzylidene at the 4- and 6-OH groups, benzoylation of the 2- and 3-OH groups and then removal of the benzylidene. The glycoside coupling reaction of 37 and diol 38 was regioselective with bond formation occurring at the primary alcohol. Subsequent benzoylation of the initially formed glycoside gave 39 (Scheme 9).

The 4-O-linked disaccharide 44 was prepared starting from thioglycoside 40. Deacetylation of 40 followed by selective introduction of the TBDPS group at the primary alcohol and subsequent benzoylation gave 44. The coupling of 41 with the galactose acceptor 42 gave the disaccharide 43 in good yield. Then the removal of the TBDPS, followed by oxidation, esterification, removal of the benzyl groups and finally benzoylation gave 44 (Scheme 10).
The anomerisation study commenced with a range of substrates in hand. This began with the azide 1 (Table 1, entry 1), which when subjected to treatment with SnCl₄ (0.5 equiv) was only partially converted (~5% conversion) and with high stereoselectivity (ratio of α/β = 95:5, 91%). The use of TiCl₄ at lower or higher amounts gives rise to a reduction in stereoselectivity. The use of TiCl₄ at higher concentrations than 0.5 equiv also enhances the rate, which is most likely important to induce isomerisation of the less reactive substrates as is the case with the glycosyl azides.

Having successfully achieved the anomerisation of the glycosyl azides, we next turned our attention to disaccharide linkages. In previous research we observed the partial anomerisation (~33%) of an acetylated disaccharide using 0.5 equiv TiCl₄ after 24 h in nitromethane. Encouraged that use of 2.5 equivalents of TiCl₄ facilitated the rearrangement of glycosyl azides we explored these conditions with the series of disaccharides shown in Table 2 (entries 1–8). Gratifyingly, these disaccharides were all successfully isomerised to give the 1,2-cis glycosides 52–59. The yields were >75%, and the stereoselectivity greater than 9:1. In a number of cases the selectivity was >95:5, with the β-configured starting disaccharide not being detected in the product mixture by ¹H NMR spectroscopy. In the case of the reaction of 44 conversion of its methyl glycoside to the corresponding glycosyl chloride occurred to a degree (~15%), explaining the lower yield of 56.

Anomerisation of disaccharides with a variety of glycosidic linkages (1–6, 1–4, 1–3 and 1–2) were all achieved and the successful examples included both glucuronic acid and galacturonic acid linkages. In contrast with the azides in Table 1, the glycosyl azide group in each disaccharide in Table 2 did not anomerise. Anomerisation occurred only at the site where efficient chelation to the C-6 carbonyl group could occur. The regiospecific nature of the reaction is worth noting and this provides additional convincing evidence for the rate enhancing effect of the C-6 carbonyl group. The TIPDS protecting group (Table 2, entries 6–8) was also highly compatible with the reaction conditions, especially when located on the aglycon. This contrasted with attempted anomerisation of the azides 17 and 19 (Scheme 3), which were not successful. The TIPDS group may hinder the approach of the Lewis acid at the chelation site when placed on the aglycon.

The results described herein demonstrate a broader application of anomerisation for acylated substrates than heretofore.
The presence of the benzoyl groups in the saccharides in which anomerisation takes place is important as the anomerisation reaction of \( \text{60} \) under the conditions described were not successful. Anomerisation with weaker Lewis acids and also \( \text{SnCl}_4 \) has been reported for pyranosides which have 2,3-trans carbonate or 2,3-trans carbonate groups, which demonstrate increased susceptibility to endocyclic cleavage and anomerisation due to inherent strain.\(^{[18,19]} \) The disaccharides \( \text{61–65} \) were also investigated as part of this work as it had been anticipated that anomerisation would have been fast in these cases given that they contain both the 2,3-trans carbonate and C-6 carbonyl group, both of which promote endocyclic cleavage. However, the reaction of \( \text{61–65} \) led to intractable products when subjected to various Lewis acid promoters. Anomerisation of more reactive saccharides (e.g., benzyl protected saccharides) without the 2,3-trans carbonate or 2,3-trans carbonate, including that promoted by \( \text{TiCl}_4 \), have been carried out previously and this has included some examples of disaccharide anomerisation.\(^{[18,20]} \)

There are reports in which anomerisation with benzylated saccharides give high yields but in other cases they proceed with low yield. It is possible that \( \text{TiCl}_4 \) could cause the removal of benzyl groups, which would complicate the anomerisation of benzylated substrates. In our hands acetyl and benzoyl groups have been found to be stable to \( \text{TiCl}_4 \). Although benzoyl groups are more electron withdrawing than benzyl groups and acetate groups they still confer sufficient reactivity to enable the anomerisation and they are faster than for acetylated substrates. In a previous study the \( \text{SnCl}_4 \) promoted anomerisation of 2,3,4-tri-O-benzoylated glucuronides were 2–3-times faster than corresponding tri-O-acetylated analogues. This contrasts with impact of benzoate groups compared to acetate groups on reactivity in other carbohydrate-based model systems.\(^{[21]} \) It is not clear yet why it is the case that anomerisation becomes possible for the benzoylated disaccharides compared to acetylated derivatives. Aside from our own investigations and that shown herein there has been limited investigation to date on anomerisation of acylated disaccharides.\(^{[22]} \)

In terms of application there is potential for anomerisation of gluconic acids and some applications have been recently described, such as the synthesis of S- and O-glycolipids.\(^{[23]} \) Importantly, homogalacturonan is a major pectic

### Table 2. Anomerisation of disaccharides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (β-anomer)</th>
<th>Product (α-anomer)</th>
<th>Reagents, conditions[^{[b]}]</th>
<th>α/β ratio (yield [%])</th>
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<tr>
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<td>C</td>
<td>&gt; 90:10 (75)</td>
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\[^{[b]}\] B: \( \text{TiCl}_4 \) (2.5 equiv) \( \text{CH}_2\text{Cl}_2 \), \(-15^\circ\text{C}, 48\) h; C: \( \text{TiCl}_4 \) (2.5 equiv), \( \text{CH}_2\text{Cl}_2 \), \(-20^\circ\text{C}, 36\) h.
polymers of α-homogalacturonan and compounds related to O-methyl 2,3,4-tri-
opolymer of a homogalacturonan fragments, which would be important for could be envisaged as building blocks for the synthesis of complex substrates. Although the presence of the uronate is necessary for the most efficient anomerisations,[25] it is possible to subsequently chemically transform the carboxylic acid group of the uronate (e.g., reduction) to increase the diversity of products that can be obtained. The azide group is the precursor to triazole-based conjugates prepared by metal catalysed alkyne–azide cycloaddition reactions.[27] Glycosyl triazoles have been prepared from the corresponding azide and a-glycosyl azides have also been used for the synthesis of a-glycosyl amides.[28–30] The number of α-glycosyl azides is limited in the literature and, until now, these have usually been prepared by nucleophilic substitution of the β-glycosyl halide.[19] In summary, we have described chelation-induced anomerisation of acylated glycosyl azides and disaccharide substrates. The work has included regiospecific or site-directed anomerisation. Further exploration of this reaction, in terms of understanding how the rates can be enhanced, including improving the activity of the promoter is under way. There are intriguing possibilities if regioselective or site-directed anomerisation of higher-order oligosaccharides or polysaccharides can ultimately be achieved. Understanding factors that influence rates of anomerisation will help chemists to achieve isomerisation of glycosidic linkages in increasingly complex substrates.

Experimental Section

Methyl 2,3,4-tri-O-acetyl-1-azido-1-deoxy-β-p-galactopyranuronate (4):
The bromide 3 (0.25 g, 0.63 mmol) and NaN₃ (0.41 g, 6.3 mmol) were placed in a Biotage microwave vial and then DMF (2.5 mL) was added and the vial was sealed and the resulting suspension was placed in an ultrasonic bath and then sonicated for 15–20 min. The vial was opened and the solution was poured on H₂O (15 mL) and extracted twice with EtOAc (15 mL). The combined organic extracts were washed with H₂O (40 mL), brine (40 mL), dried over Na₂SO₄, filtered and the solvent was removed under diminished pressure. Flash chromatography of the residue (petroleum ether/EtOAc 1:1) gave 4 (0.21 g, 92%) as a white solid; [α]₂₀=+16.3 (c 0.6, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 5.74 (dd, 3J /HH= 3.5, 1.4 Hz, 1H-4); 5.19 (dd, 3J /HH= 10.4, 8.8 Hz, 1H-3); 5.09 (dd, 3J /HH= 10.4, 3.5 Hz, 1H-3); 4.07 (dd, 3J /HH= 8.8 Hz, 1H-1, 1H-2); 4.39 (dd, 3J /HH= 1.4 Hz, 1H; H-5); 3.78 (s, 3H; CO₂CH₃); 2.09 (s, 3H; COCH₃); 2.00 ppm (3J /HH= 3H; COCH₃).

¹C NMR (126 MHz, CDCl₃): δ = 170.0 (CO), 169.8, 169.4, 165.9 (3x CO₂CH₃), 88.6 (C-1), 74.2 (C-5), 70.5 (C-3), 68.1 (C-4), 67.8 (C-2), 53.1 (CO₂CH₃), 20.8, 20.7 ppm (2s) (3C/CO₂CH₃). IR (film): ν = 2910, 2115, 1743, 1373, 921 cm⁻¹. ESIMS: m/z 382.0862, found (% 382.0866 [M+Na]+).

6-O-tert-Butylidiphenylsilyl-2,3,4-tri-O-benzoyl-β-p-mannopyranosyl azide (7): Azide 6 (1.4 g, 4.8 mmol) was taken up in MeOH (20 mL) and NaOMe (0.05 g, 0.96 mmol) was added and the mixture was stirred for 1 h. Dimethoxyhexane (10 mL) and HCl (0.2 mL) were added to the reaction mixture and the solution was stirred for 1 h (HCl (0.2 mL) was added slowly). The reaction mixture was then cooled to room temperature and was stirred overnight. The resulting suspension was cooled again and the resulting suspension was washed with EtOAc (50 mL), washed with water (1x HCl (50 mL), satd aqueous NaHCO₃ (50 mL), brine (50 mL), dried over Na₂SO₄, filtered and the solvent was removed under diminished pressure. Flash chromatography of the residue (petroleum ether/ EtOAc, 7:3) gave 7 (2.53 g, 76%) as a foam; [α]₂₀=−19.5 (c 0.1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 8.15–7.13 (ms, 25 H; Ar-H); 6.26 (apt, 1H), 3.74 (d, 3J /HH= 1.4 Hz, 1H; H-5); 3.70 (dd, 3J /HH= 10.4, 1.4 Hz, 1H; H-3); 3.25 (t, 3J /HH= 7.2 Hz, 1H; H-2); 3.18 (dd, 3J /HH= 7.2 Hz, 1H; H-1); 2.50–2.10 ppm (each CO₂CH₃).


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2-Acetamido-6-O-tert-butyldiphenylsilyl-3,4-di-O-benzoyl-2-deoxy-β-D-glucopyranosyl azide (11): Pentaacetyl-n-glucosamine (3 g, 7.7 mmol) was suspended in CHCl₃ (30 mL) and cooled to 0°C. A 33% solution of HBr in AcOH (30 mL) was added and the reaction mixture was stirred for 5 h, keeping the reaction on ice. The reaction was then diluted with CHCl₃ (50 mL) and poured onto ice (100 mL). The layers were separated and the aqueous layer was washed with a further portion of CHCl₃ (30 mL). The combined organic extracts were washed with ice (100 mL), satd. aq. NaHCO₃ (100 mL), brine (100 mL), dried over Na₂SO₄, and the solvent was removed under diminished pressure to give 9. Freshly prepared 9 was dissolved in CHCl₃ (30 mL) and tetrabutylammonium azide (43.8 mg, 0.15 mmol) was added. The reaction mixture was stirred, over night, and the solvent was removed under diminished pressure. Flash chromatography of the residue (EtOAc) gave the intermediate (1.55 g, 54%) as a white solid: [α]₂⁰ = -21.0 (c 0.15, CHCl₃); 1H NMR (500 MHz, CDCl₃): δ = 5.56 (d, J(H-H) = 8.9 Hz, 1H; 1'H); 5.00 (d, J(H-H) = 1.3 Hz, 1H; 1'-H); 3.99–3.88 (m, 3H, 2/H; 2'H); 1.21 ppm (14H, overlapping peaks). 13C NMR (126 MHz, CDCl₃): δ = 211.9, 172.9, 1452, 1259, 1092, 1025 ppm; ESIMS-calced for C₁₄H₂₀N₄O₈Na 395.1179, found m/z (%) 395.1184 [MNa⁺].

2-Acetamido-6-O-tert-butyldiphenylsilyl-3,4-di-O-benzoyl-2-deoxy-β-D-glucopyranosyl azide (12): Treatment of pentaacetyl-n-glucosamine (3.7 g, 7.7 mmol) as described above for the glucosamine gave, via bromide 10, the intermediate azide (1.7 g, 59%) as a white solid: [α]₂⁰ = -30.5 (c 0.04, CHCl₃); 1H NMR (500 MHz, CDCl₃): δ = 5.56 (d, J(H-H) = 8.8 Hz, 1H; 1'H); 5.03 (dd, J(H-H) = 3.3, 1.1 Hz, 1H; 1'-H); 5.24 (dd, J(H-H) = 11.1, 3.3 Hz, 1H; H-1); 4.79 (d, J(H-H) = 9.2 Hz, 1H; H-1); 4.19–4.13 (m, 2H; H-6a, H-6b, overlapping peaks); 4.07–3.97 (m, 2H; H-5, H-2, overlapping peaks); 2.16 (s, 3H; NHCOC₆H₅), 2.06 (s, 3H; COCH₃), 2.01 (s, 3H; COCH₃), 1.99 ppm (s, 3H; COCH₃); 13CNMR (126 MHz, CDCl₃): δ = 170.5, 170.4 (3 × COCH₃), 170.1 (NHCOC₆H₅), 88.7 (C-5), 72.8 (C-5), 69.7 (C-6), 65.4 (C-6), 50.8 (C-2), 23.4 (NHCOC₆H₅), 21.7, 20.7 ppm (2s) (3 × COCH₃); IR (film): ν = 3329, 2907, 1605, 1355, 1240, 1226, 1018 cm⁻¹; ESIMS-calced for C₁₄H₂₀N₄O₈Na 395.1179, found m/z (%) 395.1184 [MNa⁺]. This intermediate (0.9 g, 3.7 mmol) when treated with pyridine (15 mL) and TBDSPCI (1.14 mL, 4.4 mmol) and then benzoyl chloride (0.93 mL, 8.0 mmol) as described above in preparation of 7 gave after chromatography (petroleum ether/EtOAc, 8:4) the title compound 12 (1.79 g, 70%) as a white foam: [α]₂⁰ = -37.8 (c 0.1, CHCl₃); 1H NMR (500 MHz, CDCl₃): δ = 8.08 (d, J(H-H) = 8.0 Hz, 1H; H-1'; H-5'); 7.66 (m, 3H; Ar-H); 7.58–7.47 (m, 5H; Ar-H); 7.42–7.28 (m, 5H; Ar-H); 7.11 (t, J(H-H) = 7.8 Hz, 2H; H-2'), 6.00–5.94 (m, 1H; H-3'), 5.64–5.57 (m, 2H; H-2', NHCOC₆H₅), overlapping peaks), 4.80 (d, J(H-H) = 9.2 Hz, 1H; H-1'), 4.38 (appt, J(H-H) = 11.0, 9.0 Hz, 1H; H-2'), 4.06 (dd, J(H-H) = 7.4, 6.1, 1.2 Hz, 1H; H-5'), 3.86–3.75 (m, 2H; H-6a, H-6b, overlapping peaks); 2.25 ppm (12C, 1H; H-5, overlapping peaks). 13CNMR (126 MHz, CDCl₃): δ = 174.7 (NHCOC₆H₅), 88.6 (C-6), 77.8 (C-5), 75.6 (C-3), 69.4 (C-4), 60.5 (C-6), 35.8 (C-2), 22.0 ppm (NHCOC₆H₅); IR (film): ν = 3299, 2907, 1605, 1553, 1434, 1226, 1018 cm⁻¹; ESIMS-calced for C₁₄H₂₀N₄O₈Na 395.1179, found m/z (%) 395.1184 [MNa⁺].
added 1,3-dichloro-1,1,3,3-tetraisopropylidioxolane (0.99 mL, 20.5 mmol) and the mixture was allowed to warm to room temperature and was then stirred for 5 h at which point MeOH (1 mL) was added and the solvent removed under diminished pressure. The resulting residue was taken up in EtOAc (50 mL) and washed with 1 M HCl (50 mL), NaHCO₃ (50 mL), brine (50 mL), then dried over Na₂SO₄, and the solvent removed under diminished pressure. Flash chromatography of the residue (petro-lem ether/EtOAc, 3:1) gave 16 (47 g, 61%) as a white solid; [α]₂₅D = −80.7 (c 0.2, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃); δ = 4.58 (d, 3JHH = 8.6 Hz, 1H; H-1), 4.09 (dd, 3JHH = 12.7 Hz, 3JHH = 2.1 Hz, 1H; H-6a), 4.00 (dd, 3JHH = 12.7 Hz, 3JHH = 1.5 Hz, 1H; H-6b), 3.83 (appt, 3JHH = 9.1 Hz, 1H; H-4), 3.60 (appt, 3JHH = 9.1 Hz, 1H; H-3), 3.34-3.26 (2m, 2H; H-5, H-2, overlapping peaks), 2.56 (2s, 3JHH = 2 × 0.15, 0.89 ppm (m, 28H; 4 × CH₂(CH₃)₂), overlapping peaks); ¹³C NMR (126 MHz, CDCl₃); δ = 90.8 (C-1, 78.7 (C-5), 76.5 (C-3), 73.5 (C-2), 68.5 (C-4), 60.6 (C-6), 174.3, 173.2, 17.3 (2s), 17.1 (2s) (8 × CO₂CH₃), overlapping peaks), 13.6, 13.2, 12.5 ppm (2s) (4 × CH₃), overlapping peaks); IR (film): ν = 3420, 2986, 2115, 1468, 1248, 1052 cm⁻¹; ESI-HRMS calcld for C₁₄₄H₁₄₂O₃₂Na₂, 1140.5249, found m/z (%) 1140.5235 [M+Na]⁺.

Methyl 1-azido-1-deoxy-3,4-O-(1,1,3,3-tetraisopropyl-1,3-disilylated)-β-D-glucopyranuronate (17): p-TsOH/H₂O (0.17 g, 9.7 mmol) was added to solution of 16 (2 g, 4.45 mmol) in DMF (25 mL) with stirring for 5 h and then it was diluted with EtOAc (50 mL), washed with H₂O (2 × 25 mL), NaHCO₃ (50 mL), dried over Na₂SO₄, and the solvent was removed under diminished pressure. Flash chromatography of the residue (petroleum ether/EtOAc 8:2) gave the 3,4-protected intermediate (1.87 g, 94%) as a clear oil; [α]₂₅D = −4.8 (c 0.17, CHCl₃); ¹H NMR (500 MHz, CDCl₃); δ = 4.60 (d, 3JHH = 8.6 Hz, 1H; H-1), 3.93 (dd, 3JHH = 12.0 Hz, 3JHH = 3.0 Hz, 1H; H-3), 3.77 (appt, 3JHH = 12.0 Hz, 3JHH = 1.5 Hz, 1H; H-5), 2.72, 4.9 Hz, 1H; H-6), 3.73-3.64 (2m, 2H; H-4, H-3, overlapping peaks), 3.45 (dd, 3JHH = 8.9, 4.9, 2.8 Hz, 1H; H-5), 3.38 (appt, 3JHH = 8.6, 2.2 Hz, 1H; H-2), 2.44 (d, 3JHH = 2.3 Hz, 1H; OH), 1.91 (appt, 3JHH = 6.8 Hz, 1H; OH), 1.16-0.86 ppm (m, 28H; 4 × CH₂(CH₃)₂, overlapping peaks); ¹³C NMR (126 MHz, CDCl₃); δ = 89.5 (C-1), 79.8 (C-5), 79.8 (C-3), 73.5 (C-2), 72.1 (C-4), 61.9 (C-6), 17.3 (2s), 17.2 (2s) (4 × CH₂(CH₃)₂, overlapping peaks), 12.9, 12.8, 12.1 ppm (3s) (4 × CH₃), overlapping peaks); IR (film): ν = 3349, 2848, 2114, 1348, 1248, 1052, 987 cm⁻¹; ESI-HRMS calcld for C₁₄₄H₁₄₂O₃₂Na₂, 1140.5249, found m/z (%) 1140.5236 [M+Na]⁺. This intermediate (1.8 g, 4.0 mmol) was dissolved in MeCN/H₂O (60 mL, 3:1) and treated with BAIB (3.24 g, 67%), NaHCO₃ (50 mL), H₂O, and the mixture was stirred under diminished pressure. Flash chromatography of the residue (petroleum ether/EtOAc 3:1) gave the intermediate aldehyde 15 (0.97 g, 67%) as a white foam; [α]₂₅D = 23.0 (c 0.2, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃); δ = 1681 (CO₂CH₃), 1661, 1658, 1651.2 (2s) (4 × CO₃H), 1334.2, 1332 (2a), 1331, 129.9, 128.7, 129.7 (12 × Ar-CH, overlapping peaks), 129.6, 129.8, 128.0 (4 × Ar-C), 128.3, 128.4, 128.3 (8 × Ar-CH, overlapping peaks), 100.1 (C-1), 84.1 (C-1), 79.7 (C-3), 77.5 (C-2), 74.6 (C-4), 73.1 (C-3), 72.5 (2s), 69.6 (C-2s), 62.9 (C-6), 54.2 (CO₂CH₃), 17.5, 17.4, 17.2 (2s), 17.1 (2s) (8 × CH₂CH₃, overlapping peaks); IR (film): ν = 2946, 2119, 1728, 1452, 1249, 1089, 986 cm⁻¹; ESI-HRMS calcld for C₁₄₄H₁₄₂O₃₂Na₂, 1176.0754, found m/z (%) 1176.0766 [M+Na]⁺.
1H NMR (500 MHz, CDCl3): δ = 7.95 (appt, 2J(H,H) = 7.3, 1.4 Hz, 4H; Ar-H), 7.89–7.81 (m, 2H; Ar-H), 7.59–7.47 (m, 2H; Ar-H), 7.46–7.35 (m, 5H; Ar-H), 7.31–7.26 (m, 2H; Ar-H), 5.93 (appt, 3J(H,H) = 9.7 Hz, 1H; H-3), 4.05 (d, 2J(H,H) = 17.0, 10.7, 6.1, 5.0 Hz, 1H; CH2CH2), 5.60–5.39 (m, 2H; Ar-H), 4.18 (q, 2J(C,H) = 7.9 Hz, 1H; H-1), 4.39 (ddt, 2J(H,H) = 13.3 Hz, 3J(H,H) = 5.0, 1.6 Hz, 1H; CH2CH2), 4.19 (ddt, 2J(H,H) = 13.3 Hz, 3J(H,H) = 6.1, 1.4 Hz, 1H; CH2CH2), 3.86 (ddd, 2J(H,H) = 12.4 Hz, 3J(H,H) = 8.8, 1.9 Hz, 1H; H-6a), 3.83–3.68 (m, 2H; H-2, H-5), 3.05 ppm (dd, 2J(H,H) = 8.8, 5.3 Hz, 1H; OH); 13C NMR (126 MHz, CDCl3): δ = 166.0, 165.8, 165.0 (3x COPh), 133.7 (Ar-CH, overlapping peaks), 133.4 (CH2CH2), 133.2 (2x Ar-CH), 129.9, 129.8, 129.7 (6x Ar-CH, overlapping peaks), 129.3, 128.8, 128.6 (3x Ar-CH), 128.5, 128.3 (2x Ar-CH, 167.7, 117.8 (CH2CH2), 100.0 (C-1), 74.6 (C-5), 72.8 (C-7), 71.8 (C-4), 69.6 (C-2), 64.1 ppm (C-6); IR (film): ν = 3300, 2955, 2722, 1451, 1250, 1026 cm⁻¹; ESI-HRMS calculated for C22H29O15N2Na 553.1675; found m/z (%) 553.1673 [M+Na]⁺. This intermediate (14 g, 26.3 mmol) in MeCl2/CH2Cl2 (100 mL, 3:1) was oxidised using BAIB (21.17 g, 65.7 mmol) and 80% H2O2, 2-3 mL. The resulting suspension was filtered through Celite and the filtrate evaporated to dryness. The residue (petroleum ether/EtOAc 9:1) gave 12.2 g of the product (71%).

1H NMR (500 MHz, CDCl3): δ = 7.91 (d, 2J(H,H) = 8.3, 7.0 Hz, 4H; Ar-H), 7.54–7.26 (m, 2H; Ar-H), 7.43–7.33 (m, 5H; Ar-H), 7.28 (2s), 7.26 (2s), 7.24 (2s), 7.22 (2s), 7.20 (2s), 7.18 (3s), 7.15 (3s), 7.12 (3s), 7.09 (3s), 7.07 (3s), 7.05 (3s), 7.02 (3s), 6.98 ppm (2s, 4x CH2CH2), overlapping peaks); 13C NMR (126 MHz, CDCl3): δ = 170.7 (COCH3), 89.6 (C-1), 79.7 (C-3), 76.1 (C-5), 73.7 (C-2), 72.2 (C-4), 62.9 (C-6), 26.9 (C-8), 19.2 ppm (CH2), 17.2 ppm (CH3) overlapping peaks, 128.7, 127.3, 126.3 ppm (3x Ar-CH), 125.8 (2x Ar-CH, overlapping peaks), 118.0 (CH2CH2), 70.1 (C-4), 52.9 ppm (CH2), 3068, 1761, 1726, 1451, 1250, 1026 cm⁻¹; ESI-HRMS calculated for C19H23O12N2Na 434.1745; found m/z (%) 434.1742 [M+Na]⁺.


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2.4-Tris-(4,4,4-tri-0-benzoyl-3,5,5-tri-(methoxy)benzyl)-4-8(-glucopyranosyl)-2-8-(glucopyranosyl) azide (32): Disaccharide (0.25 g, 0.252 mmol) was added to 1.25 mL HCl in methanol (10 mL) at 0°C and the resulting solution was allowed to attain room temperature and stirred for 16 h. The reaction mixture was cooled over an ice-bath, diluted with MeOH (20 mL) and NaHCO3 was added. The resulting slurry was concentrated to dryness and the residue suspended in pyridine and cooled over an ice-bath. BrCl (0.18 mL, 1.5 mmol) was then added and the reaction mixture was allowed to warm to room temperature and was stirred, overnight. Methanol (0.5 mL) was added and the mixture was diluted with EtOAc (10 mL). This layer was washed with 1 mL HCl (2 × mL), satd. aq. NaHCO3 (10 mL), brine (10 mL) and dialyzed over Na2S04, filtered and the solvent was removed under diminished pressure. Flash chromatography (silica; petroleum ether/EtOAc 8:1) gave pure regioselective anomer of azide (0.18 g, 63%). as a glass; [α]D = −15.6 (c 1.25, CH2Cl2); 1H NMR (500 MHz, CDCl3): δ = 8.00 (dd, 3J(H,H) = 8.4, 1.4 Hz, 2H; Ar-H); 7.95–7.9 (m, 2H), 7.79–7.75 (m, 2H), 7.48–7.27 (m, 14H, Ar-H); 5.91 (aptt, 3J(H,H) = 9.3 Hz, 1H; H-3'), 5.79 (aptt, 3J(H,H) = 9.8 Hz, 1H; H-2), 5.04 (d, 3J(H,H) = 9.4 Hz, 1H; H-2'), 4.83 (t, 3J(H,H) = 9.3 Hz, 1H; H-4); 4.65 (d, 3J(H,H) = 9.8 Hz, 1H; H-4'), 5.54 (dd, 3J(H,H) = 9.3 Hz, 1H; H-5'); 3.55 (dd, 3J(H,H) = 9.4 Hz, 1H; H-6a), 3.75 (aptt, 3J(H,H) = 9.3 Hz, 1H; H-1), 3.99–3.91 (m, 1H; H-6a), 3.82–3.71 (m, 3H; H-6b, H-4, H-3, overlapping peaks), 3.45 (dd, 3J(H,H) = 7.9 Hz, 1H; H-1'), 5.2, 2.8, 1.3, 1H, 1.2 H; 3.99 (m, 3H; CO-CH3), 1.89–1.91 (m, 1H; OH), 1.13–1.09 (m, 2J(H,H) = 6.5 Hz, 1J(H,H) = 4.3 Hz, 1H, overlapping peaks), 5.35 (dd, 3J(H,H) = 9.79, 7.9 Hz, 1H, overlapping peaks), 5.40 (dd, 3J(H,H) = 7.91, 7.9 Hz, 1H, 1J(H,H) = 4.3 Hz, 1H, overlapping peaks); 13C NMR (126 MHz, CDCl3): δ = 169.2 (CO2CH3), 167.5, 165.3, 165.3, 166.9 (6 x COCH3), 133.6, 133.4, 130.0, 129.9 (8 x Ar-CH, overlapping peaks), 129.4, 129.0 (8 x Ar-C), 128.6 (2J(H,H) = 12.0 Hz, 1J(CH3) = 6.7 Hz, 1J(CH2) = 5.9 Hz, C-1), 127.9 (6C), 127.2 (7J(C8,C8) = 72.6 (C-5), 69.3 (C-5'), 62.0 (C-6), 28.9, 19.0 (C(CH3)3), 17.3, 17.2, 17.1 (2s), 17.0, 16.8 (8 x CH2CH3), overlapping peaks), 12.9, 12.8, 12.2.
**1.1.** **The Compound (425 mg, 61%) as a White Solid;**

**2.3.3.6-Tri-O-benzoyl-1-deoxy-1-(2,2,2-trichloro-1-iminoethoxy)-3-(6-acetyl)-D-galactopyranosyl bromide (34)**

This intermediate (2 g, 3.2 mmol) was dissolved in DCM (5 mL) and cooled to 0°C under diminished pressure to give the glycosyl bromide as a colourless solid. The combined filtrate were dried over Na2SO4 and the solvent was removed under diminished pressure. Flash chromatography (petroleum ether/EtOAc 2:1) gave the main product as a white solid (243 mg, 44% yield).

**3.2.3-Tri-O-benzoyl-1-deoxy-1-(2,2,2-trichloro-1-iminoethoxy)-b-glucopyranosyl azide (34):**

Removal of the acetyl group gave the above mixture, which was then recrystallized from DCM (5 mL) and cooled to 0°C under diminished pressure to give the glycosyl bromide as a colourless solid. The combined filtrate were dried over Na2SO4 and the solvent was removed under diminished pressure. Flash chromatography (petroleum ether/EtOAc 2:1) gave the main product as a white solid (243 mg, 44% yield).

**4.3.3.6-Tri-O-benzoyl-1-deoxy-1-(2,2,2-trichloro-1-iminoethoxy)-3-(6-acetyl)-D-galactopyranosyl bromide (34)**

This intermediate (2 g, 3.2 mmol) was dissolved in DCM (5 mL) and cooled to 0°C under diminished pressure to give the glycosyl bromide as a colourless solid. The combined filtrate were dried over Na2SO4 and the solvent was removed under diminished pressure. Flash chromatography (petroleum ether/EtOAc 2:1) gave the main product as a white solid (243 mg, 44% yield).
Regiospecific Anomerisation described above gave the intermediate alcohol (165 mg, 77%) as a colorless oil; HRMS calcd for C_{28}H_{25}O_{10} 521.1448, found (mass%) 521.1448. Gas chromatography of the residue (petroleum ether/EtOAc, 3:1) gave the title compound (65 mg, 41%; 92.5 ppm (CH_{3}); ESI-HRMS calcd for C_{56}H_{49}O_{18} 1009.2919, found (mass%) 1009.2655.\[\text{Achtung trennung}\]

J = 11.0 Hz, 3H-H, 2.78 (d, J = 7.9 Hz, 2H-H, Ar-H), 7.51 (t, J = 7.9 Hz, 1H-H, Ar-H), 7.45 (d, J = 7.9 Hz, 1H-H, Ar-H). These are not the final page numbers!
The mixture was filtered through Celite and the filtrate concentrated to dryness. The residue was taken up in pyridine (4 mL) and cooled to 0°C and benzoyl chloride (100 mL, 0.80 mmol) was added and the reaction allowed to attain room temperature for 24 h. Work up as described previously and chromatography (ethyl acetate/CH₂Cl₂) afforded 42 mg (83% yield). 

**4.5-O-Ethyl-6-O-(2,3,4-tri-O-benzoyl-5-O-xylopyranosyl)-β-D-glucopyranosyl azide (55):**  
\[\text{[
\begin{array}{l}
\text{C}_{29} \text{H}_{53} \text{O}_{15} \text{N}_{4} \text{S}\n
\end{array}\]
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Regiospecific Anomerisation

133.2, 130.0, 129.9 (2s), 129.8 (2s) (18/C148Ar-CH, overlapping peaks), 129.1, 1.17–0.83 ppm (m, 28H; 4/C148C)

68.8 (CH3), 55.7 (CH3), 68.5 (CH2), 5.28 ppm (CH2)

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Supporting information

Material presented herein was supported by Science Foundation Ireland (Grant No. 12/1/I198) and the Irish Research Council through an Enterprise Partnership funded by Roche Ireland, Ltd. (M.F.).
There is an example in which a catalytic carboxylic acid led to the inter- and intramolecular promotion of anomeration in the preparation of an acetylated isopropyl glycoside: R. U. Lemieux, O. inter- and intramolecular promotion of anomerisation in the preparation of an acetylated isopropyl glycoside: R. U. Lemieux, O.
Regiospecific Anomerisation of Acylated Glycosyl azides and Benzoylated Disaccharides Using TiCl₄

The place to be: Regiospecific site-directed anomerisation is demonstrated (see scheme). TiCl₄ (2.5 equiv) was employed to induce anomerisation of 15 glycosyl azide and disaccharide substrates of low reactivity, and high yields (>75%) and stereoselectivities (α/β > 9:1) were achieved. The use of benzoylated saccharides was found to be important in disaccharide anomerisation.