Selective electrochemical glycosylation by reactivity tuning

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Electrochemical glycosylation of a selenoglycoside donor proceeds efficiently in an undivided cell in acetonitrile to yield β-glycosides. Measurement of cyclic voltammograms for a selection of seleno-, thio-, and O-glycosides indicates the dependence of oxidation potential on the anomeric substituent allowing the possibility for the rapid construction of oligosaccharides by selective electrochemical activation utilising variable cell potentials in combination with reactivity tuning of the glycosyl donor. A variety of disaccharides are readily synthesised in high yield, but limitations of the use of selenoglycosides as glycosyl donors for selective glycosylation of thioglycoside acceptors are exposed. The first electrochemical trisaccharide synthesis is described.

Introduction

The crucial importance of oligosaccharides in a plethora of biological processes is, in general, contrasted by their availability from natural sources, which in the majority of cases is limited to small amounts. The structural complexity of oligosaccharides, particularly as compared to oligonucleotides and oligopeptides, makes them extremely challenging synthetic targets. Indeed, despite mammoth synthetic efforts over the preceding decades the synthesis of a particular oligosaccharide target remains an extremely time-consuming exercise. However, several promising approaches to oligosaccharide synthesis do promise to facilitate their rapid assembly from pre-formed building blocks. One such approach, which follows on from the development of the armed and disarmed approach to glycosylation of n-pentenyl glycosides developed by Fraser-Reid and co-workers, focuses on the selective chemical activation of particular glycosyl donors in the presence of other less reactive donors in order to allow the rapid, one-pot assembly of tri- and tetra-saccharides. Indeed, following on from the pioneering work of Fraser-Reid, and Ley and colleagues, Wong and co-workers have now developed a computer programme to predict reactivity differences in an attempt to develop a programmable approach to oligosaccharide synthesis using a wide selection of differentially protected glycosyl donors. Inspired by these chemical reactivity differences, we became intrigued as to whether a similar selective type of electrochemical glycosylation reaction was possible. Following on from the early work of Noyori and Kurimoto, and Sinaj and Amatore’s group, we undertook the synthesis and electrochemical investigation of a variety of differentially protected seleno-, thio- and O-glycosides as potential glycosyl donors for use in electrochemical glycosylation reactions. Indeed, published data for a variety of thio-1, seleno-10 and telluro-glycosides,11 which all may in principle be activated electrochemically (Fig. 1), indicated a substantial difference in the corresponding oxidation potentials of the anomeric substituent, allowing the possibility of the selective activation of one type of donor in the presence of the other. This paper contains details of our investigations into the utility of selective electrochemical glycosylation reactions of seleno- and thio- and O-glycosides in order to develop an efficient electrochemically mediated approach to the synthesis of oligosaccharides by reactivity tuning.

Results and discussion

In line with the previously observed differences in chemical reactivity towards the most commonly used electrophilic activators, namely that selenoglycosides are more reactive than thioglycosides, which are in turn more reactive than O-glycosides, the glycosyl donors chosen for investigation were the selenoglycoside

Fig. 1 Electrochemical glycosylation of a thio-/seleno-glycoside at a positive potential of +X Volts.

1, together with a thioglycoside donor/acceptor 2, and an O-glycoside donor/acceptor 3; both of these latter compounds possess a free 6-hydroxyl group (Fig. 2).

Fig. 2 Glycosyl donors and acceptors for electrochemical glycosylation.

In theory the reactivity difference of the anomeric heteroatom could be taken together with the usually observed arming/disarming effect of alcohol protecting groups (i.e. benzyl being more reactive than benzoyl) to allow further levels of reactivity for selective electrochemical glycosylation. In an attempt to investigate and quantify the effect of the hydroxyl protecting group pattern on the oxidation potential, and to see if such effects could be exploited for selective synthesis, the benzoylated selenoglycoside donor 4, the benzoylated thioglycoside donor/acceptor 5 and the perbenzylated thioglycoside donor 6 were also synthesised for electrochemical investigation (Fig. 2). It should be borne in mind that although the use of benzyl protected donors such as 4 and 5 has the advantage

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that an ester protecting group at the 2-position will allow control of stereochemistry during glycosylation by neighbouring group participation, this is offset by the fact that electrochemical glycosylation reactions of donors bearing O-2 ester protecting groups can be problematic due to orthoester formation and protecting group hydrolysis.

Selenoglycosides 1 and 4,14 were synthesised from glucose penta-acetate 7 following literature procedures. Thioglucose 2 with the 6-hydroxyl free in order to be able to act as both a glycosyl donor and acceptor, was synthesised in five steps from glucose penta-acetate 7. Treatment of peracetate 7 with thioreosol and BF$_3$ etherate in dichloromethane produced thioglucose 8 (81% yield). Removal of the acetates by Zeplien deacetylation yielded the tetrol 9 (87% yield), which was then selectively protected by treatment with trityl chloride and DMAP in pyridine to yield a tritol, that was itself immediately benzylated with benzyl bromide and sodium hydride in DMF to yield the completely protected thioglucose 10 (61% yield over two steps). The tritol group was removed by treatment of 10 with aqueous acetic acid to yield the desired alcohol 2 (92% yield, Scheme 1). Benzoylated thioglucose 5 was synthesised from tetrol 9 by a sequence of tritylation and benzoylation to yield fully protected thioglucose 11 (97% yield over two steps) and then treatment with aqueous acid to yield the alcohol 5 (76% yield). The tetrabenzylation of thioglucose 6 was also synthesised from tetrol 9 simply by perbenzoylation with benzyl bromide and sodium hydride in DMF (82% yield). The O-glycoside 3 was accessed from glucose following a route similar to the one used for the synthesis of 1. Treatment of perbenzoylated glucose 12 with phenol and BF$_3$·Et$_2$O in dichloromethane produced the O-glycoside 13 (89% yield). Removal of the benzoxes by Zeplien deacetylation produced the tetrol 14 (90% yield) and this was then followed by selective protection with trityl chloride and DMAP in pyridine to yield the tritol 15 (90% yield). Benzylation with benzyl bromide yielded the completely protected 2-O-glycoside 16 (90% yield), and final removal of the tritol group with iron(II) chloride hexahydrate yielded the desired alcohol 3 (65% yield, Scheme 1).

Cyclic voltammetry

Measurement of the kinetic oxidation potentials of these six glycosyl donors was recorded by cyclic voltammetry versus a Standard Calomel Electrode (vs. SCE) (Table 1). For comparison with previously reported results both peak and mid potentials were recorded. Investigation of the kinetics of oxidation was also undertaken for some of these donors by performing voltammetry at varying scan rates. The measured peak oxidation potential for the perbenzylated selenoglycoside 1 is +1.38 V (vs. SCE). Interestingly, the peak oxidation potential for the perbenzylated selenoglycoside 4 (+1.41 V vs. SCE) is only marginally different, indicating that in the case of these selenoglycosides there is little dependence of the oxidation potential of the anomeric substituent upon the protecting group pattern. Though these measurements are in agreement with the previous measurements of Pirmohamed and Mehta,14,15 the expectation that the electron-withdrawing protecting groups of 4 should disarm this selenoglycoside making it harder to activate the correspondingly fully armed selenoglycoside 1. Measurement of the true thermodynamic oxidation potentials of 1 and 4, as detailed in the accompanying paper,1 in fact does indicate such a protecting group effect. However, since the strategy of reactivity tuning relies on differences in kinetic oxidation potentials to achieve selective activation of the anomeric substituent, it appears that in this case there is little to be gained by the use of both selenoglycoside donors, since no extra level of reactivity differential is achieved. This factor, combined with the knowledge that ester protecting groups have proven rather problematic when undertaking electrochemical glycosylations (vide supra), meant that studies of electrochemical glycosylation of selenoglycosides were focussed solely on the use of the benzyldonor 1. Cyclic voltammetry of the thioglucose 2 showed an oxidation peak at +1.52 V (vs. SCE), indicating a sizable and exploitable difference in oxidation potential. Measurement of the peak oxidation potential of the O-glycoside 3 (+1.89 V vs. SCE) indicated another exploitable difference, which should therefore in theory allow the selective one-pot synthesis of tri- or tetra-saccharides. Finally, cyclic voltammetry of the thioglucoses 5 and 6 (+1.51 and +1.51 V vs. SCE, respectively) again indicated little dependence of peak oxidation potential on protecting group pattern in these particular cases. This final result for thiotolyl glycosides is in contrast to both previously reported measurements for differently protected thiophenyl glycosides,16,17 and our own thermodynamic measurements for thiotolyl glycosides.1

Glycosylation reactions

The use of anhydrous acetonitrile as the solvent for glycosylation reactions favoured the formation of the β-anomers in all cases. In order to reduce any competitive hydrolysis reactions resulting from the presence of trace amounts of water all the reagents were dissolved in the solvent and stirred for 30 min under nitrogen with activated molecular sieves before any potential was applied. Tetraethylammonium perchlorate was used throughout as the supporting electrolyte, in preference to the frequently used alternative of lithium tetrafluoroborate.

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**Scheme 1** Reagents and conditions: (i) p-thioreosol, BF$_3$·Et$_2$O, DCM, 16 h, 81%; (ii) NaOMe, MeOH, 1 h, 87%; (iii) trityl chloride, DMAP, pyridine, 30 h; (iv) BrBz, NaH, DCM, 16 h, 0 °C—RT, 61% over two steps; (v) AcOH, EtOH, 26 h, 80 °C, 92%; (vi) BrBz, NaH, DCM, 72 h, 82%; (vii) trityl chloride, DMAP, pyridine, 20 h; (viii) BzCl, DMAP, pyridine, 24 h, 97% over two steps; (ix) AcOH, EtOH, 24 h, 80 °C, 76%; (x) phenol, BF$_3$·Et$_2$O, DCM, 48 h, 50 °C, 89%; (xi) NaOMe, MeOH, 18 h, 90%; (xii) trityl chloride, DMAP, pyridine, 72 h, 90%; (xiii) BrBz, NaH, DCM, 16 h, 0 °C—RT, 90%; (xiv) FeCl$_3$, DCM, 48 h, 65%. 
Table 1  Oxidation potentials of glycosyl donors vs. Standard Calomel Electrode

<table>
<thead>
<tr>
<th>Glycosyl donor</th>
<th>Peak oxidation potential/V</th>
<th>Mid potential/V</th>
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<tbody>
<tr>
<td>1</td>
<td>1.38</td>
<td>1.26</td>
</tr>
<tr>
<td>2</td>
<td>1.52</td>
<td>1.43</td>
</tr>
<tr>
<td>3</td>
<td>1.89</td>
<td>1.79</td>
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<tr>
<td>4</td>
<td>1.41&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.32&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1.51</td>
<td>1.50</td>
</tr>
<tr>
<td>6</td>
<td>1.52</td>
<td>1.45</td>
</tr>
<tr>
<td>19</td>
<td>1.57</td>
<td>1.48</td>
</tr>
<tr>
<td>PhSeSePh</td>
<td>1.45</td>
<td>1.29</td>
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<sup>a</sup>The oxidation peak is not particularly well-defined; peak error is estimated at ca. 0.02 V.

Initial studies focussed on glycosylation of the selenoglycoside 1 with a variety of non-oxidisable glycosyl acceptors. Electrochemical glycosylation of 1 with methanol proceeded smoothly at +1.7 V to produce the methyl glucoside 17 as predominantly the β-anomer in 65% yield (Scheme 2). The use of diacetone galactose as a carbohydrate acceptor, again at +1.7 V, pleasingly produced the β-disaccharide 18 in an excellent 90% yield.

[Scheme 2 Diagram]

Attention then turned to the possibility of the selective glycosylation of 1 with a glycosyl acceptor/donor that could itself later be activated electrochemically. Unfortunately, attempted selective glycosylation of selenoglycoside 1 with thioglycoside 2 at +1.5 V only produced a disappointing 35% yield of the desired disaccharide product 19. Attempting to improve the yield of the disaccharide product by performing the glycosylation at the slightly higher oxidation potential of +1.7 V, which had proved an optimum potential for the reactions detailed above, unfortunately did not result in the formation of larger amounts of product. Indeed, variation of several reaction parameters in this case did not improve the product yield.

The reasonably small difference in the oxidation potentials of 1 and 2 (ca. 0.2 V) was noted, and it was therefore thought that perhaps the use of a glycosyl acceptor which itself had a significantly higher oxidation potential than 1 may lead to an improvement in the yield of the disaccharide product. An increase in the oxidation potential of 2 could in theory be achieved either by a variation of the aromatic substitution pattern on the thioglycoside, or perhaps by a carbohydrate protecting group exchange, since both of these strategies have been used to achieve selective chemical glycosylation. However, cyclic voltammetry had already revealed that for thioglycosides there was little dependence of kinetic peak oxidation potential on protecting group pattern, i.e. that the benzoylated thioglycoside 5 had a very similar peak oxidation potential (+1.51 V) to that measured for benzylated thioglycoside 2 (+1.52 V). Indeed, attempted glycosylation of 1 with 5 to yield disaccharide 20 was even less successful than glycosylation of 1 with 2.

One solution to this problem would be to use thienyl glycosyl acceptors which display a marked dependence of kinetic oxidation potential on protecting group pattern. However, the use of the O-glucose donor 3 with a significantly higher peak oxidation potential of +1.89 V (vs. SCE) provided an immediate solution to this problem, and glycosylation of selenoglycoside 1 with O-glucose 3 at +1.7 V produced the desired disaccharide 21 in an excellent 79% yield. In fact, similar glycosylation at the slightly lower potential of +1.5 V also produced the desired product 21, albeit in a slightly lower yield (72%).

The rather inefficient synthesis of disaccharides 19 and 20 prompted further investigations that were to reveal potential limitations into the use of selenoglycosides for selective electrochemical glycosylation of thioglycoside acceptors. Any competitive activation of the glycosyl acceptor during glycosylation of the donor would necessarily lead to a reduction in yield of the desired product. Such non-selective electrochemical activation may occur due to an insufficient difference in the oxidation potentials between the donor and the acceptor. It was initially feared that such a process may explain the low yield for the glycosylations of donor 1 (+1.38 V) with either acceptor 2 (+1.52 V) or acceptor 5 (+1.51 V), where the difference in oxidation potentials is merely ca. 0.13 V. Since both these acceptors were not completely recovered from these low-yielding glycosylation reactions we investigated whether activation of the thioglycoside donors 2 and 5 could be a competing process by studying electrochemical activation of similar thioglycoside 6 at +1.7 V. Interestingly, attempted glycosylation of 6 with diacetone galactose under similar conditions used for the synthesis of disaccharides 19 and 20 left 6 largely unchanged, and it was recovered in ca. 93% yield, with only about ca. 5% disaccharide being isolated (Scheme 3). This indicates that 6 is not appreciably electrochemically activated at this cell potential and implies that another factor is responsible for the low yield of disaccharides 19 and 20. Attention therefore turned to potential complications caused by side products arising from glycosylation of the selenoglycoside donor 1 in the low-yielding reactions with thioglycoside acceptors 2 and 5.

[Scheme 3 Diagram]
The side product from electrochemical activation of a selenoglycoside is supposed to be the phenyl selenyl radical, which then presumably dimerises under the reaction conditions, so producing diphenylselenide in situ. Cyclic voltammetry of diphenylselenide revealed its peak oxidation peak to be +1.45 V (vs. SCE, Table 1). We therefore hypothesised that within the cell diphenylselenide produced by electrochemical oxidation of a selenoglycoside may then itself undergo oxidation to produce a species that is capable of chemically activating a thioglycoside donor which itself is not appreciably activated electrochemically at that cell potential. To investigate this hypothesis we reinvestigated glycosylation of thioglycoside donor 6 with diacetone galactose as the acceptor, but with diphenylselenide added to the cell (Scheme 3). In contrast to the earlier experiment, a rapid glycosylation reaction ensued and after 2.5 h disaccharide 18 was isolated in ca. 50% yield. This result provides supporting evidence for the above hypothesis, and indicates that an extra complication may arise from the use of selenoglycosides as donors for selective electrochemical glycosylation with thioglycoside acceptors.

Attention then turned to the synthesis of a trisaccharide by sequential electrochemical glycosylation. Attempted glycosylation of the O-phenyl disaccharide 21 with diacetone galactose as the acceptor at +2.5 V following reported literature procedures unfortunately led to no appreciable reaction. In fact, we were completely unable to achieve trisaccharide synthesis using the O-phenyl disaccharide donor 21, either by performing the reaction at constant high voltage, or at constant current. One explanation may be due to competitive oxidation of the electrolyte at high potential, but the precise reasons for our inability to activate the O-phenyl glycoside electrochemically remain unclear.

Measurement of the peak oxidation potential of perbenzylated disaccharide 19 (+1.57 V, Table 1) revealed only a small change from the measured potential for the monosaccharide acceptor / donor 2 (+1.52 V). Pleasingly disaccharide 19 was glycosylated with diacetone galactose as acceptor at +2.0 V to produce the desired trisaccharide 22 in a very satisfactory 79% yield (Scheme 4). To the best of our knowledge this result represents the first electrochemically mediated trisaccharide synthesis.

**Conclusions**

Electrochemical glycosylation of a protected selenoglycoside has been achieved for a variety of glycosyl acceptors. The use of thioglycoside acceptors as coupling partners produced only moderate yields of disaccharide products, presumably as a result of competitive processes caused by the production of diphenylselenide in situ. However, the use of O-glycosides as acceptors allowed the synthesis of disaccharides in high yield. Subsequent activation of a disaccharide thioglycoside donor allowed the synthesis of a trisaccharide in high yield. This result represents the first electrochemical trisaccharide synthesis, and potentially opens the way for the development of a rapid assembly method for the construction of higher oligosaccharides by a combination of reactivity tuning of the oxidation potentials of the glycosyl donors/acceptors, and the use of variable voltages for electrosynthesis. Investigations into the use of differently protected thioglycoside donors, bearing an array of different aroyl and alkyl groups on the chalcogen atom to allow the establishment of further levels of reactivity tuning for more complex oligosaccharide synthesis are currently in progress, and the results will be published in due course.

**Experimental**

**General**

Melting points were recorded on a Koller hot block. Proton nuclear magnetic resonance (δH) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz), Bruker DPX 400 (400 MHz), Bruker AV 400 (400 MHz), or Bruker AMX 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (δC) spectra were recorded on a Bruker DPX 400 (100.6 MHz) or a Bruker AMX 500 (125.75 MHz) spectrometer. Multiplicities were assigned using APT or DEPT sequence. All chemical shifts are quoted on the δ-scale. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20–250, Micromass Platform 1 APCL, or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH₃, DCI), electron impact (EI), electron spray ionization (ESI), chemical ionization (NH₃, CI), atmospheric pressure chemical ionization (APCI), and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g (100 ml)⁻¹. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Laboratory, Oxford. Thin layer chromatography (t.l.c.) was carried out on Merck glass-backed sheets, pre-coated with 60F₂₅₄ silica. Plates were developed using 0.2% w/v cerium(iv) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and available reagents were dried and purified before use according to standard procedures; dichloromethane was distilled from calcium hydride immediately before use.

**Scheme 4** Reagents and conditions: (i) diacetone galactose, Bu₄NClO₄, 4 Å molecular sieves, MeCN, +2.0 V, 79%.

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**p-Tolyl-2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (8).** Glucose penta-acetate 7 (30 g, 0.08 mol) and p-thioresol (15.2 g, 0.12 mol) were dissolved in dichloromethane (200 ml) under argon in a flame dried flask. The solution was cooled to 0°C and BF₃·Et₂O (14 ml, 0.10 mol) added. The mixture was stirred for 16 h, at which point t.l.c. (ethyl acetate:petrol, 1:1) indicated the formation of a major product (Rf 0.5) and the absence of starting material (Rf 0.4). The reaction mixture was diluted with dichloromethane (200 ml) washed with sodium hydrogen carbonate (2 × 120 ml of a saturated aqueous solution), water (100 ml), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography to afford tetra-acetate 8 (28.2 g, 81%) as a white crystalline solid, m.p. 114–117°C (ethyl acetate/petrol) (lit., 118°C; δH-21 18 (c, 1.0 in CHCl₃); δC-21 21 (c, 2.0 in CHCl₃)); δH (400 MHz, CDCl₃) 1.99, 2.02, 2.09, 2.10 (4 × 3H, 4 × s, 4 × COCH₃), 2.36 (3H, s, PhCH₃), 3.70 (1H, tdd, J₉₋₁₁, J₉₋₂₂, J₁₁₋₂₂ 10.1 Hz, H-1), 2.62 Hz, J₉₋₂₂, J₁₁₋₂₂ 4.8 Hz, H-2), 4.18 (1H, dd, J₁₋₂₂, J₁₋₁₂ 12.3 Hz, H-6), 4.22 (1H, dd, H-6'), 4.64 (1H, d, J₁₋₂₂, J₁₋₁₂ 10.1 Hz, H-1'), 4.94 (1H, at, J₉₋₁₁'H, H-7'), 5.03 (1H, at, J₉₋₁₁'H, H-7'), 5.21 (1H, at, J₉₋₁₁'H, H-7'), 7.13 (2H, d, J₂₋₃ 8.1 Hz, ArH), 7.39 (2H, d, J₂₋₃ 8.1 Hz, ArH).
[α]D 20 −57 (c, 1.5 in pyridine); δH (400 MHz, CDCl3) 2.33 (3H, s, PhCH3), 3.26–3.33 (2H, m, H-4, H-5), 3.39 (1H, at, J = 8.5 Hz, H-3), 3.67 (1H, dd, J = 5.1 Hz, J = 12.0 Hz, H-6), 3.87 (1H, dd, J = 8.8 Hz, J = 9.5 Hz, H-5), 4.36 (1H, at, J = 9.9 Hz, H-4), 5.78 (1H, at, J = 9.9 Hz, H-5), 6.79 (2H, d, J = 8.1 Hz, ArH), 7.19 (2H, d, J = 7.9 Hz, ArH), 7.48 (2H, d, J = 7.9 Hz, ArH).

p-Tolyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (6). Tetr 9 (750 g, 3.50 mol) was dissolved in dimethylformamide (20 ml) under argon in a dry flask and benzyl bromide (1.6 mol, 13 ml) was added portionwise. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (630 mg, 15.7 mmol) was added. The reaction mixture was stirred for 30 min, when point t.l.c. (ethylene acetate:petrol, 1 : 5) indicated the formation of a major product (R 0.3) and the absence of starting material (R 0.1). The reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate (3 x 100 ml) and filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate:petrol, 1 : 4) to afford fully protected thioglycoside 10 (21 g, 61%) as a white crystalline solid, m.p. 144–145 °C (ethyl acetate/petrol); [α]D 20 +23 (c, 1.0 in CHCl3); \( \nu_{\text{max}} \) (KBr disk)/cm\(^{-1}\) 3086, 3058, 3030, 2998, 2864; δH (400 MHz, CDCl3) 2.16 (3H, s, PhCH3), 3.92 (1H, at, J = 10.1 Hz, H-6), 3.37–3.50 (1H, m, H-5), 3.62 (1H, at, J = 9.9 Hz, H-5), 3.67 (1H, dd, J = 9.6 Hz, H-6), 3.70 (1H, at, J = 9.9 Hz, H-6), 3.82 (1H, at, J = 9.9 Hz, H-4), 4.37, 4.71 (2H, ABq, J = 8.8 Hz, PhCH2), 4.70 (1H, d, J = 9.6 Hz, H-1), 4.81, 4.97 (2H, ABq, J = 10.2 Hz, PhCH2), 4.86, 4.91 (2H, ABq, J = 10.8 Hz, PhCH2); δH (100 MHz, CDCl3) 21.2 (s, CH2), 74.5, 75.0, 76.0 (3 x 3, 3 × PhCH3), 77.2, 86.5, 137.7, 138.2, 138.3, 143.9 (6 × s, ArC), 77.8 (d, C-4), 78.8 (d, C-5), 80.7 (d, C-6), 88.2 (c), 87.7 (d, C-1), 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.8, 129.7, 129.8, 132.8 (12 × d, ArCH); \( \nu_{\text{max}} \) (ESI) 821 (M + Na, 100%), 822 (55). [HRMS (ESI) Calc. for C42H39OSNa (MNaH) 816.3723. Found 816.3724.]
Phenyl-2,3,4-tri-O-benzyl-6-O-trityl-a-D-glucopyranoside (13). Penta-O-benzyl-a-D-glucose (10.0 g, 0.014 mol) and phenol (2.7 g, 0.029 mol) were dissolved in dichloromethane (100 ml) under argon in a flame dried flask. The solution was cooled to 0 °C and BF₃·OEt₂ (11.4 mol, 0.043 mol) added. The mixture was heated to 50 °C and refluxed with stirring for 48 h, at which point t.l.c. (ethyl acetate: petrol, 1:2) indicated the formation of a major product (Rf 0.45) the absence of starting material (Rf 0.40). Water (100 ml) was added and the reaction mixture stirred for a further 15 min. The reaction mixture was diluted with dichloromethane (200 ml), washed with water (100 ml), brine (150 ml), dried (MgSO₄) and concentrated in vacuo to afford phenyl glycoside 13 (8.4 g, 89%) as a white crystalline solid, m.p. 169–171 °C (ethyl acetate/petrol) (lit. 172–174 °C); [α]D 22 +81 (c, 1.0 in CHCl₃) [lit. 22 +84 (c, 1.0 in CHCl₃)]; δ(CDCl₃) 1.82 (9H, s, ArCH₃); 7.29 (10 × d, 19 × ArCH), 137.8, 138.9, 139.7, 139.9, 139.3, 138.7, 138.6, 138.4 (10 × d, 19 × ArCH), 136.0, 165.0, 165.8, 165.9, 9.8 Hz, H-2), 3.66–3.77 (3H, m, H-5, H-6, H-6′), 3.88 (1H, ddd, J = 11.0 Hz, J = 9.9 Hz, H-4), 6.05 (1H, d, J = 10.8 Hz, H-3), 6.86–7.60 (18H, m, ArH), 7.93–8.04 (7H, m, ArH).

Phenyl-a-D-glucopyranoside (14). Phenyl glycoside 13 (7.8 g, 0.012 mol) was suspended in methanol (90 ml) under argon in a flame dried flask. To this a solution of sodium (14.8 mmol, 0.63 g) in methanol (90 ml) under argon in a flame dried flask. To this a solution of sodium (1.41 g, 35.3 mmol) was added and the reaction mixture cooled to 0 °C, at which point sodium hydride (1.41 g, 35.3 mmol) was added and the mixture stirred for 1 h, after which time the majority of the solvent was removed in vacuo. The residue was dissolved in dichloromethane (100 ml), washed with water (2 × 100 ml) and the combined aqueous layers re-extracted with dichloromethane (100 ml). The organic phases where then combined and washed with brine (3 × 100 ml), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol then ethyl acetate: petrol, 1:8) to afford fully protected phenyl glycoside 16 (4.4 g, 90%) as a white crystalline solid, m.p. 163–164 °C; [α]D 22 +75 (c, 1.3 in CHCl₃); δ(CDCl₃) 3.08, 303.0, 2929, 2876; δ(CDCl₃) 2.01, 1.0 in CHCl₃; 78.0, 80.1, 82.1, 1.3 Hz, 6.92–7.00 (1H, m, H-5), 4.22 (1H, d, J = 9.3 Hz, H-3), 4.34, 4.76 (2H, ABq, J = 10.2 Hz, PhCH₂), 4.79, 4.88 (2H, ABq, J = 12.7 Hz, PhCH₂), 4.91, 5.07 (2H, ABq, J = 10.6 Hz, PhCH₂), 5.65 (1H, d, J = 1.5 Hz, 7.75–7.78 (45H, m, ArH); 7.23 (100.6 MHz, CDCl₃) 62.3 (t, C-6), 71.0 (d, C-5), 73.2, 75.2, 76.1 (3 × t, PhCH₂), 78.0 (d, C-4), 80.1 (d, C-2), 81.2 (d, C-3), 86.3 (s, Ph), 95.1 (d, C-1), 116.9, 122.3, 126.9, 127.7, 128.7, 128.8, 128.9, 129.5, 129.8 (10 × d, 35 × ArCH), 137.8, 138.1, 138.7, 143.9, 156.8 (s × 7 × ArCH); [m/z (ESI) 791 (M + Na⁺), 100%), 782 (54), 1558 (2M + Na⁺, 37), 1560 (28). [HRMS (ESI) Calc. for C₄₃H₃₉O₁₅Na: 791.3349. Found 791.3363.]

Phenyl-2,3,4-tri-O-benzyl-a-D-glucopyranoside (3). Fully protected phenyl glycoside 16 (2.0 g, 2.60 mmol) was dissolved in dichloromethane (60 ml) and iron(II) chloride (1.40 g, 5.20 mol) was added. The reaction proceeded slowly, but after 48 h, t.l.c. (ethyl acetate: petrol, 1:6) indicated the formation of a major product (Rf 0.1) and only a small amount of remaining starting material. The reaction mixture was washed with water (3 × 50 ml), brine (50 ml), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate: petrol, 1:3) to afford alcohol 3 (0.896 g, 65%) as a white crystalline solid, m.p. 72–74 °C (lit. 73–75 °C); [α]D 22 +49 (c, 1.0 in CHCl₃) [lit. 22 +50 (c, 1.0 in CHCl₃)]; δ(CDCl₃) 144.0 (400 MHz, CDCl₃) 6.38–7.33, 3.81–3.85 (5H, m, H-2, H-4, H-5, H-6, H-6′), 4.27 (1H, d, J = 9.2 Hz, H-3), 4.72, 4.85 (2H, ABq, J = 12.0 Hz, PhCH₂), 4.72, 4.96 (2H, ABq, J = 11.0 Hz, PhCH₂), 4.95, 5.11 (2H, ABq, J = 11.0 Hz, PhCH₂), 5.46 (1H, d, J = 3.6 Hz, H-1), 7.05–7.45 (10H, m, ArH).

Typical procedure for electrochemical glycosylation

The glycosyl donor (100 mg, 0.15 mmol), glycosyl acceptor (0.30 mmol) and tetrabutylammonium perchlorate (855 mg) were dissolved in acetonitrile (25 ml) and transferred to a flame dried cell containing a reticulated carbon working electrode, a nickel mesh counter electrode and a silver wire pseudo reference electrode. A 4 molecular sieves were added and the reaction mixture stirred under nitrogen for 30 min. A defined potential was applied and the reaction monitored by t.l.c. until no starting material remained. At this point the reaction mixture was filtered, and concentrated in vacuo. The residue was taken up in dichloromethane (50 ml), washed with water (50 ml) and brine (50 ml), dried (MgSO₄) and concentrated in vacuo. The crude product was then purified by flash column chromatography (ethyl acetate: petrol).
Methyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (17). Selengoside 1 (100 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.40 mmol) and tetrabutylammonium perchlorate (850 mg), in anisotetritol (25 ml), gave the β-methyl glucoside 17 (57 mg, 65%) as a white crystalline solid, m.p. 66-67 °C (methanol) (lit.20-68-69 °C); ν_H (CDCl_3) 2924, 2796, 1639, 1361, 1358, 1299, 1252, 1202, 1069, 1058, 1041, 1031, 1021, 963, 942, 933, 918, 883, 842, 805, 789, 779, 753, 742, 735, 722, 703, 676, 656, 636, 616, 595, 578, 567, 547, 525, 503, 482, 461, 439, 417, 395, 373, 351, 329, 307, 285, 263, 241, 219, 197, 175, 153, 131, 109, 87, 65, 43, 21 ppm.

The crude product was then purified by flash column chromatography (petrol : ethyl acetate, 3 : 1) to give the product (75), 1068.5 (21), 1069.5 (6). (Found: C, 76.68; H, 6.52. C_{34}H_{40}O_{14} requires C, 76.92, H, 6.35%.)

The residue was taken up in dichloromethane (50 ml), washed with water (50 ml) and the aqueous layer was re-extracted with ethyl acetate. The combined organic phases were washed with brine (50 ml), dried (MgSO_4) and concentrated in vacuo. The residue was then purified by flash column chromatography (petrol : ethyl acetate, 4 : 1) to afford the isomer (78 mg, 92%) of the product, 18 (53%).

At +1.7 V in the presence of PhSeSePh

Thioglycoside 6 (105 mg, 0.16 mmol), diacetoxy galactose (83 mg, 0.32 mmol), dimethyl diselenide (24 mg, 0.077 mmol) and tetrabutylammonium perchlorate (855 mg, 2.5 mol) were dissolved in anisotetritol (25 ml) and transferred to a flame dried cell containing a reticulated carbon working electrode, a nickel mesh counter electrode and a silver wire pseudo reference electrode. 4 Å molecular sieves were added and the reaction mixture stirred under nitrogen for 30 min. A potential of +1.7 V was applied for 2.5 h at which point t.l.c. (petrol : ethyl acetate, 4 : 1) indicated the formation of a minor product (R_0, 3). The reaction mixture was filtered and concentrated in vacuo. The residue was then purified by flash column chromatography (petrol : ethyl acetate, 4 : 1) to afford the isomer (78 mg, 92%) of the product, 18 (53%).

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References and notes

The use of tetrafluoroborate ions in the supporting electrolyte led to an unexpected formation of the &-glycoside product by neighbouring group participation. All oxidation potentials are given for the first scan, at a scan rate of 50 mV s

Acknowledgements

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References and notes

12. For similar investigations that were published during the course of our studies that predominantly use tellurolglycosides as glycosyl donors, see: S. Yamago, K. Koboku, O. Hara, S. Masuda and J. Yoshida, J. Org. Chem., 2002, 67, 8584–8592.
16. The &-O-glycoside is presumably formed as the thermodynamic product of a reversible &-glycosylation with phenol, which counteracts the expected formation of the &-glycoside product by neighbouring group participation.
17. All oxidation potentials are given for the first scan, at a scan rate of 100 mV s
19. The use of tetrafluoroborate ions in the supporting electrolyte led to increased formation of hydrolysis products, together with the production of small amounts of anomeric fluorides, as previously observed by Lubineau and co-workers (ref. 9).
20. In answer to a referee’s comment we add that oxidation of 1 was marginally slower at +1.5 V than at +1.7 V, but the yield of disaccharide produced in both cases was almost identical. Since it had been demonstrated that the acceptor was not activated at +1.7 V, this higher potential was used as it proved more efficient, not because we observed a substantial ohmic drop in the cell.
21. Presumably diphenyliseldene is itself oxidised to a radical cation that can then either disproportionate to produce a species equivalent to PhSe