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Selective electrochemical glycosylation by reactivity tuning[1]

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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[2] 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.[3] 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,[4] 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,[5] 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.[6] 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,[7] and Sinaÿ and Amatore's group,[8] 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-,[9] 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.[12]

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,[13] which are in turn more reactive than *O*-glycosides, the glycosyl donors chosen for investigation were the selenoglycoside

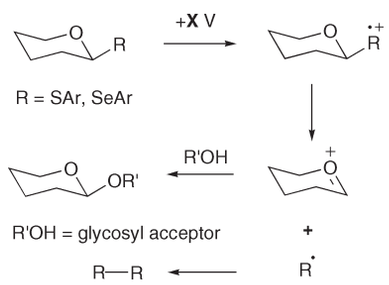

Fig. 1 Electrochemical glycosylation of a thio-/seleno-glycoside at a positive potential of +**X** Volts.

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).

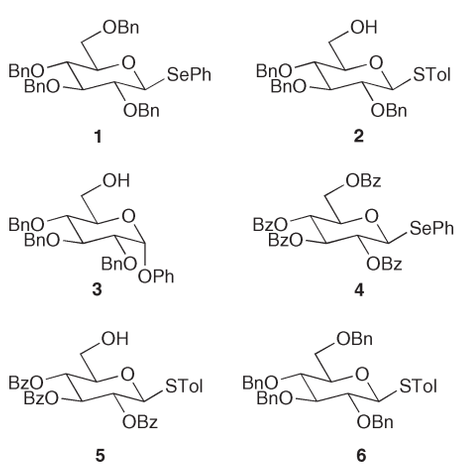

Fig. 2 Glycosyl donors and acceptors for electrochemical glycosylation.

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 benzoyl 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.

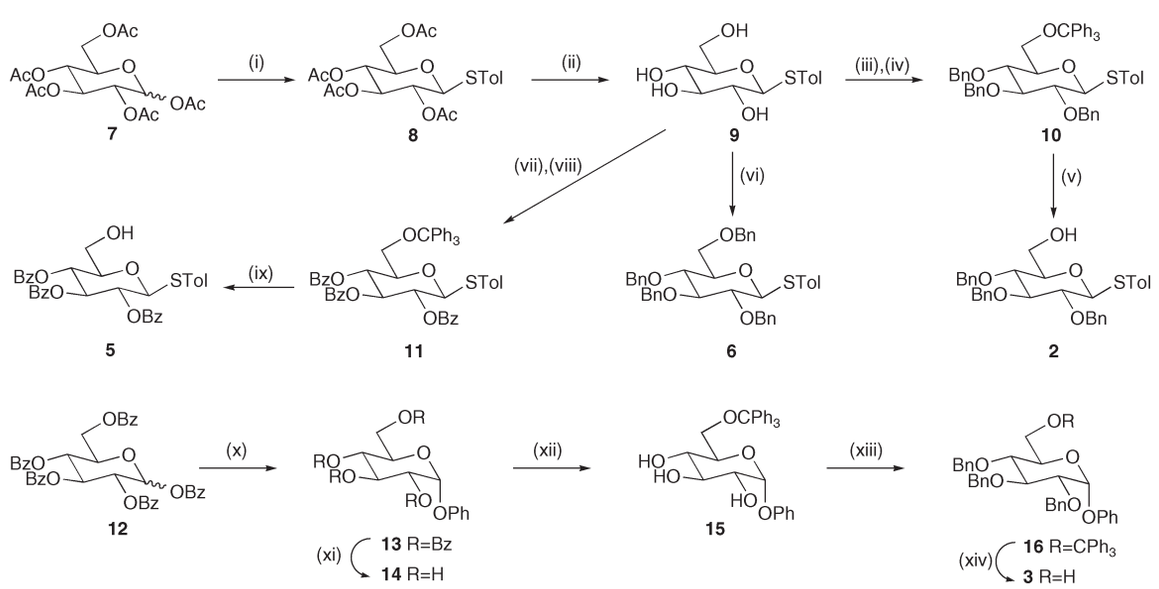
Selenoglycosides **1**[14] and **4**,[15] were synthesised from glucose penta-acetate **7** following literature procedures. Thioglycoside **2**, with the 6-hydroxyl free in order to be able to act as both a glycosyl donor and acceptor, was synthesised in five steps from glucose penta-acetate **7**. Treatment of peracetate **7** with thiocresol and BF_3 etherate in dichloromethane produced thioglycoside **8** (81% yield). Removal of the acetates by Zemplen deacetylation yielded the tetrol **9** (87% yield), which was then selectively protected by treatment with trityl chloride and DMAP in pyridine to yield a triol, that was itself immediately benzylated with benzyl bromide and sodium hydride in DMF to yielded the completely protected thioglycoside **10** (61% yield over two steps). The trityl group was removed by treatment of **10** with aqueous acetic acid to yield the desired alcohol **2** (92% yield, Scheme 1). Benzoylated thioglycoside **5** was synthesised from tetrol **9** by a sequence of tritylation and benzoylation to yield fully protected thioglycoside **11** (97% yield over two steps) and then treatment with aqueous acid to yield the alcohol **5** (76% yield). The tetrabenzylated thioglycoside **6** was also synthesised from tetrol **9** simply by perbenzylation 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 **2**. Treatment of perbenzoylated glucose **12** with phenol and $BF_3{\cdot}OEt_2$ in dichloromethane produced the α-*O*-glycoside **13**[16] (89% yield). Removal of the benzoates by Zemplen deacylation produced the tetrol **14** (90% yield) and this was then followed by selective protection with trityl chloride and DMAP in pyridine to yield the triol **15** (90% yield). Benzylation with benzyl bromide yielded the completely protected *O*-glycoside **16** (90% yield), and finally removal of the trityl group with iron(III) 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).[17] 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.[1] The measured peak oxidation potential for the perbenzylated selenoglycoside **1** is +1.38 V (*vs.* SCE). Interestingly, the peak oxidation potential for the perbenzoylated 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 Pinto and Mehta[10] they do contradict the expectation that the electron-withdrawing protecting groups of **4** should disarm[4] 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 benzylated donor **1**. Cyclic voltammetry of the thioglycoside **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 tetrasaccharides. Finally, cyclic voltammetry of the thioglycosides **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,[9c,12] 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.[18] 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. Tetrabutylammonium perchlorate was used throughout as the supporting electrolyte, in preference to the frequently used alternative of lithium tetrafluoroborate.[19]



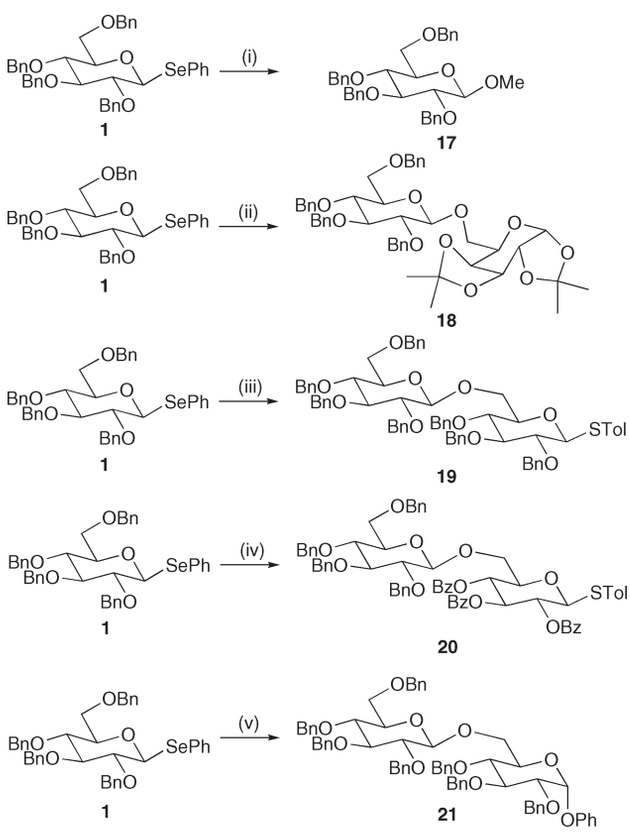
Scheme 1 *Reagents and conditions*: (i) *p*-thiocresol, $BF_3{\cdot}Et_2O$, DCM, 16 h, 81%; (ii) NaOMe, MeOH, 1 h, 87%; (iii) trityl chloride, DMAP, pyridine, 30 h; (iv) BnBr, NaH, DMF, 16 h, 0 °C→RT, 61% over two steps; (v) AcOH, EtOH, 26 h, 80 °C, 92%; (vi) BnBr, NaH, DMF, 72 h, 82%; (vii) trityl chloride, DMAP, pyridine, 20 h; (viii) BzCl, DMAP, pyridine, 24 h, 97% over two steps; (ix) AcOH, EtOH, 24 h, 80 °C, 76%; (x) phenol, $BF_3{\cdot}Et_2O$, DCM, 48 h, 50 °C, 89%; (xi) NaOMe, MeOH, 18 h, 90%; (xii) trityl chloride, DMAP, pyridine, 72 h, 90%; (xiii) BnBr, NaH, DMF, 16 h, 0 °C→RT, 90%; (xiv) $FeCl_3$, DCM, 48 h, 65%.

Table 1 Oxidation potentials of glycosyl donors *vs.* Standard Calomel Electrode

Glycosyl donor	Peak oxidation potential/V	Mid potential/V
1	1.38	1.26
2	1.52	1.43
3	1.89	1.79
4	1.41[a]	1.32[a]
5	1.51	1.50
6	1.52	1.45
19	1.57	1.48
PhSeSePh	1.45	1.29

[a] 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.



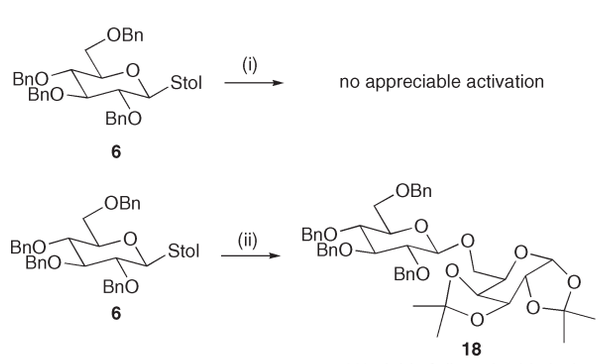
Scheme 2 *Reagents and conditions*: (i) MeOH, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, 65%; (ii) diacetone galactose, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, 90%; (iii) **2**, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, 35%; (iv) **5**, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, <20%; (v) **3**, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, 79%.

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,[20] 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 thiotolyl glycosides 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 thiophenyl glycosyl acceptors which display a marked dependence of kinetic oxidation potential on protecting group pattern.[9c,12] However, the use of the *O*-glycoside 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*-glycoside **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**.

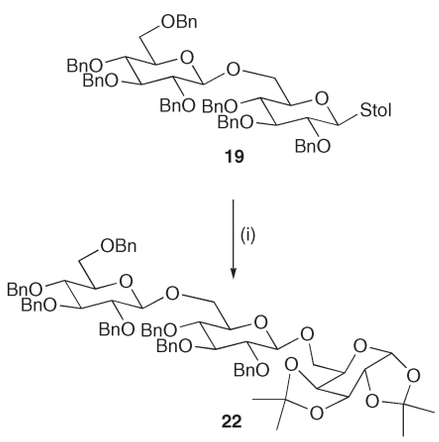


Scheme 3 *Reagents and conditions*: (i) diacetone galactose, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, recovered donor **6**, 93%, disaccharide **18**, 5%; (ii) diacetone galactose, PhSeSePh, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +1.7 V, recovered donor **6**, 48%, disaccharide **18**, *ca.* 50%.

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 diphenyldiselenide *in situ*. Cyclic voltammetry of diphenyldiselenide revealed its peak oxidation peak to be +1.45 V (*vs.* SCE, Table 1). We therefore hypothesised that within the cell diphenyldiselenide 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.[21] To investigate this hypothesis we re-investigated glycosylation of thioglycoside donor **6** with diacetone galactose as the acceptor, but with diphenyldiselenide 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[7] 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.



Scheme 4 *Reagents and conditions*: (i) diacetone galactose, Bu_4NClO_4, 4 Å molecular sieves, MeCN, +2.0 V, 79%.

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 diphenyldiselenide *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 aryl 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 Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AC 200 (200MHz), Bruker DPX 400 (400 MHz), Bruker AV 400 (400 MHz), or Bruker AMX 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (δ_C) 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, Masslab20–250, Micromass Platform 1 APCI, or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH_3 DCI), electron impact (EI), electron spray ionization (ESI), chemical ionization (NH_3 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 $60F_{254}$ 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.

***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*-thiocresol (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 $BF_3{\cdot}Et_2O$ (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 (R_f 0.5) and the absence of starting material (R_f 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 ($MgSO_4$) 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.,[22] 118 °C); $[\alpha]_D^{24}$ −18 (*c*, 1.0 in $CHCl_3$) {lit.,[22] $[\alpha]_D^{20}$ −21 (*c*, 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.99, 2.02, 2.09, 2.10 (4 × 3H, 4 × s, 4 × $COCH_3$), 2.36 (3H, s, PhCH_3), 3.70 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 2.6 Hz, $J_{5,6'}$ 4.8 Hz, H-5), 4.18 (1H, dd, $J_{6,6'}$ 12.3 Hz, H-6), 4.22 (1H, dd, H-6′), 4.64 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.94 (1H, at, *J* 9.7 Hz, H-2), 5.03 (1H, at, *J* 9.9 Hz, H-4), 5.21 (1H, at, *J* 9.5 Hz, H-3), 7.13 (2H, d, *J* 8.1 Hz, ArH), 7.39 (2H, d, *J* 8.1 Hz, ArH).

***p*-Tolyl-1-thio-β-D-glucopyranoside (9).** Acetate **8** (26 g, 0.06 mol) was dissolved in methanol (100 ml) under argon in a flame dried flask. To this a solution of sodium methoxide in methanol (100 ml of a 0.1 M solution) was added and the mixture stirred for 1 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 1) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.5). Ion exchange resin (IR 120+) was added portionwise until the solution was neutralised, at which point the reaction mixture was concentrated *in vacuo* to afford tetrol **9** (14.3 g, 87%) as a white crystalline solid, m.p. 146–148 °C (ethanol/petrol) (lit.,[20] 149 °C); $[\alpha]_D^{25}$ −48 (*c*, 1.0 in MeOH) {lit.,[20]

$[\alpha]_D^{20}$ −57 (*c*, 1.5 in pyridine)}; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, PhCH_3), 3.26–3.33 (2H, m, H-4, H-5), 3.39 (1H, at, *J* 8.5 Hz, H-3), 3.67 (1H, dd, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.87 (1H, dd, $J_{5,6'}$ 2.5 Hz, H-6′), 4.53 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 7.14 (2H, d, *J* 7.9 Hz, ArH), 7.48 (2H, d, *J* 7.9 Hz, ArH).

***p*-Tolyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (10).** Tetrol **9** (12.3 g, 0.04 mol) and trityl chloride (13.2 g, 0.05 mol) were dissolved in pyridine (100 ml) and stirred under argon. After 24 h dimethylaminopyridine (500 mg, 4.67 mmol) and trityl chloride (10 g, 0.04 mol) were added and the mixture stirred for a further 5 h, at which point t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). The reaction mixture was concentrated *in vacuo* and the residue taken up in dichloromethane (200 ml), washed with ammonium chloride (2 × 200 ml of a saturated aqueous solution), sodium hydrogen carbonate (2 × 200 ml of a saturated aqueous solution) and brine (200 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude triol. The crude residue was dissolved in dimethylformamide (100 ml) and benzyl bromide (27 ml, 0.23 mol) was added. The solution was cooled to 0 °C and sodium hydride (11 g of a 60% dispersion in mineral oil, 0.28 mol) was added portionwise to the stirred solution over 15 min. The reaction mixture was allowed to warm to room temperature overnight. After 16 h, t.l.c. (ethyl acetate : petrol, 1 : 3) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). Methanol (100 ml) was added and the solution stirred for 30 min, the reaction mixture was then concentrated *in vacuo* (co-evaporation with toluene, 3 × 100 ml) and the residue taken up in dichloromethane (200 ml). The resulting solution was washed with water (200 ml) and brine (3 × 100 ml), dried ($MgSO_4$) 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); $[\alpha]_D^{25}$ −23 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3086, 3058, 3030, 2998, 2864; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, PhCH_3), 3.32 (1H, dd, $J_{5,6}$ 4.1 Hz, $J_{6,6'}$ 10.1 Hz, H-6), 3.37–3.50 (1H, m, H-5), 3.62 (1H, at, *J* 9.1 Hz, H-2), 3.67 (1H, dd, $J_{5,6'}$ 1.4 Hz, H-6′), 3.70 (1H, at *J* 9.0 Hz, H-3), 3.82 (1H, at, *J* 9.4 Hz, H-4), 4.37, 4.71 (2H, ABq, J_{AB} 10.4 Hz, PhCH_2), 4.70 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.81, 4.97 (2H, ABq, J_{AB} 10.2 Hz, PhCH_2), 4.86, 4.91 (2H, ABq, J_{AB} 10.8 Hz, PhCH_2); δ_C (100.6 MHz, $CDCl_3$) 21.2 (s, CH_3), 62.4 (t, C-6), 75.0, 75.4, 76.0 (3 × t, 3 × PhCH_2), 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-2), 86.8 (C-3), 87.7 (d, C-1), 127.0, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5, 128.8, 129.7, 129.8, 132.8 (12 × d, ArCH); *m*/*z* (ESI) 821 (M + Na^+, 100%), 822 (55). [HRMS (ESI) Calc. for $C_{53}H_{50}O_5S$ (MNH_4^+) 816.3723. Found 816.3724.]

***p*-Tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (2).** Fully protected thioglycoside **10** (2.0 g, 2.51 mmol) was suspended in a mixture of acetic acid : ethanol (20 ml : 10 ml) and refluxed at 80 °C for 26 h at which point t.l.c. (ethyl acetate : petrol, 1 : 4) indicated the formation of a major product (R_f 0.3) and almost complete consumption of starting material (R_f 0.6). The reaction mixture was concentrated *in vacuo* (co-evaporation with toluene) and the residue taken up in dichloromethane (200 ml), washed with sodium hydrogen carbonate (200 ml of a saturated aqueous solution), brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **2** (1.26 g, 92%) as a white crystalline solid, m.p. 97–98 °C (ethyl acetate/petrol); $[\alpha]_D^{24}$ +6.5 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3500, 3084, 3061, 3027, 2960, 2917, 2872; δ_H (400 MHz, $CDCl_3$) 1.98 (1H, at, *J* 6.6 Hz, OH), 3.39 (1H, ddd, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 10.1 Hz, H-6), 3.37–3.50 (1H, m, H-5), 3.62 (1H, at, *J* 9.1 Hz, H-2), 3.67 (1H, dd, $J_{5,6'}$ 2.7 Hz, H-5), 3.48 (1H, dd, $J_{1,2}$ 8.8 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.56 (1H, at, *J* 9.4 Hz, H-4), 3.61–3.74 (1H, m, H-6), 3.74 (1H, at, *J* 9.1 Hz, H-3), 3.90 (1H, ddd, $J_{5,6'}$ 2.3 Hz, $J_{6,6'}$ 11.8 Hz, $J_{6',OH}$ 5.4 Hz, H-6′), 4.67 (1H, d, H-1), 4.67, 4.88 (2H, d ABq, J_{AB} 11.1 Hz, PhCH_2), 4.79, 4.95 (2H, ABq, J_{AB} 10.3 Hz, PhCH_2), 4.89, 4.94 (2H, ABq, J_{AB} 10.8 Hz, PhCH_2), 7.13–7.46 (19H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.1 (s, CH_3), 62.1 (t, C-6), 75.1, 75.5, 75.8 (3 × t, 3 × PhCH_2), 77.6 (d, C-4), 79.2 (d, C-5), 81.1 (d, C-2), 86.6 (C-3), 87.8 (d, C-1), 127.8, 127.9, 128.0, 128.2, 128.5, 129.8, 132.7 (7 × d, 19 × ArCH), 129.4, 137.8, 138.0, 138.1, 138.3 (5 × s, 5 × ArC); *m*/*z* (ESI) 574 (M + NH_4^+, 100%), 579 (M + Na^+, 83), 580 (24), 1130 (2M + NH_4^+, 48), 1135 (2M + Na^+, 83), 1136 (51), 1137 (22). [HRMS (ESI) Calc. for $C_{34}H_{36}O_5S$ (MNH_4^+) 574.2627. Found 574.2628.]

***p*-Tolyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (6).** Tetrol **9** (750 g, 3.50 mmol) was dissolved in dimethylformamide (20 ml) under argon in a dry flask and benzyl bromide (1.6 ml, 13.1 mmol) added. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (630 mg, 15.7 mmol) was added portionwise. The reaction mixture was stirred for 3 d, at which point t.l.c. (ethyl acetate : petrol, 1 : 8) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). Methanol (20 ml) was added and the solution stirred for a further 15 min, after which the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (100 ml) and the resulting solution washed with brine (3 × 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate : petrol, 1 : 8) to afford fully protected thioglycoside **6** (1.4 g, 82%) as a white crystalline solid, m.p. 77–78 °C (ethanol) (lit.,[9b] 80–81 °C); $[\alpha]_D^{25}$ −1.8 (*c*, 1.0 in $CHCl_3$) {lit.,[9b] $[\alpha]_D^{21}$ +2 (*c*, 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.33 (1H, s, PhCH_3), 3.48–3.53 (2H, m, H-2, H-5), 3.66 (1H, at, *J* 9.5 Hz, H-3), 3.72 (1H, at, *J* 8.9 Hz, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.81 (1H,dd, $J_{5,6'}$ 1.7 Hz, H-6′), 4.56, 4.63 (2H, ABq, J_{AB} 12.0 Hz, PhCH_2), 4.61, 4.92 (2H, ABq, J_{AB} 11.0 Hz, PhCH_2), 4.63 (1H, s, $J_{1,2}$ 10.2 Hz, H-1), 4.75, 4.85 (2H, ABq, J_{AB} 10.7 Hz, PhCH_2), 4.87, 4.90 (2H, ABq, J_{AB} 10.2 Hz, PhCH_2), 7.05–7.53 (24H, m, ArH).

***p*-Tolyl-2,3,4-tri-*O*-benzoyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (11).** Tetrol **9** (10.1 g, 0.035 mol), trityl chloride (21.9 g, 0.079 mol) and dimethylaminopyridine (426 mg, 3.49 mmol) were dissolved in pyridine (100 ml) and stirred under argon in a dry flask. After 20 h, t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.5) and the absence of starting material (R_f 0.1). The reaction was cooled to 0 °C, benzoyl chloride (32.5 ml, 0.28 mol) added and the mixture stirred for 24 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 3) indicated the formation of a major product (R_f 0.3). The reaction mixture was diluted with ethyl acetate (400 ml) and washed with hydrochloric acid (3 × 200 ml of a 1M aqueous solution). The aqueous phase was re-extracted with ethyl acetate (200 ml) and the combined organic layers washed with sodium hydrogen carbonate (3 × 200 ml of a saturated aqueous solution), brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate : petrol, 1 : 4→1 : 5) to afford fully protected thioglycoside **11** (28.2 g, 97%) as a white crystalline solid, m.p. 96–97 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ +7.7 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3060, 3033, 2980, 2920, 2874, 1736; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 3.31–3.39 (2H, m, H-6, H-6′), 3.86–3.90 (1H, m, H-5), 4.98 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 5.51 (1H, at, *J* 9.9 Hz, H-2), 5.55 (1H, at, *J* 9.9 Hz, H-4), 5.78 (1H, at, *J* 9.4 Hz, H-3), 7.10–7.57 (28H, m, ArH), 7.69 (2H, d, *J* 8.1 Hz, ArH), 7.81 (2H, d, *J* 8.0 Hz, ArH), 8.00 (2H, d, *J* 7.9 Hz, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.2 (q, CH_3), 62.4 (t, C-6), 69.1 (d, C-4), 70.7 (d, C-2), 74.7 (d, C-3), 78.2 (d, C-5), 86.3 (d, C-1), 86.8 (s, *C*Ph_3), 126.9, 127.7, 128.2, 128.4, 128.6, 129.7, 129.8, 129.9, 133.1, 133.2, 133.8 (11 × d, 34 × ArCH), 128.1, 128.9, 129.0, 129.4, 138.5, 143.6 (6 × s, 8 × ArC), 164.8, 165.1, 165.8 (3 × s, 3 × C=O); *m*/*z* (ESI) 858 (M + NH_4^+, 23%). [HRMS (ESI) Calc. for $C_{53}H_{48}NO_8S$ (MNH_4^+) 858.3101. Found 858.3098.]

***p*-Tolyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (5).** Fully protected thioglycoside **11** (12.0 g, 14.3 mmol) was suspended in a mixture of acetic acid : ethanol (240 ml : 120 ml) and refluxed at 80 °C for 24 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 3) indicated the formation of a major product (R_f 0.2) and the absence

of starting material (R_f 0.5). The reaction was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 ml) and washed with sodium hydrogen carbonate (2 × 100 ml of a saturated aqueous solution), water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate : petrol, 1 : 4) to afford alcohol **5** (6.5 g, 76%) as a white crystalline solid, m.p. 146–147 °C (ethanol); $[\alpha]_D^{22}$ +8.6 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3542, 3093, 3070, 2988, 2949, 2890, 1732, 1722; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 2.51 (1H, br s, OH), 3.73–3.90 (3H, m, H-5, H-6, H-6′), 5.00 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.44–5.49 (2H, m, H-2, H-4), 5.94 (1H, at, *J* 9.7 Hz, H-3), 7.14–7.56 (13H, m, ArH), 7.82 (2H, d, *J* 8.2 Hz, ArH), 7.94 (2H, d, *J* 7.9 Hz, ArH), 7.99 (2H, d, *J* 7.6 Hz, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.2 (q, CH_3), 61.6 (t, C-6), 69.3, 70.6 (2 × d, C-2, C-4), 74.1 (d, C-3), 78.8 (d, C-5), 86.2 (d, C-1), 127.6, 128.5, 128.8, 129.2, 138.9 (5 × s, 5 × ArC), 128.3, 128.4, 128.6, 129.7, 129.8, 129.9, 133.2, 133.3, 133.7, 133.9 (10 × d, 19 × ArCH), 165.0, 165.8, 165.9 (3 × s, 3 × C=O); *m*/*z* (ESI) 616 ($M + NH_4^+$, 45%), 621 ($M + Na^+$, 73), 1220 ($2M + Na^+$, 33). [HRMS (ESI) Calc. for $C_{34}H_{34}NO_8S$ (MNH_4^+) 616.2005. Found 616.2014.]

Phenyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (13). Penta-*O*-benzoyl-D-glucose **12** (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 $BF_3{\cdot}Et_2O$ (11.3 ml, 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 (R_f 0.45) the absence of staring material (R_f 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 ($MgSO_4$) 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.,[23] 172–174 °C); $[\alpha]_D^{24}$ +81 (*c*, 1.0 in $CHCl_3$) {lit.,[23] $[\alpha]_D^{20}$ +84.0 (*c*, 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 4.51 (1H, dd, $J_{5,6}$ 6.1 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 4.59 (1H, dd, $J_{5,6'}$ 2.6 Hz, H-6′), 4.65 (1H, ddd, $J_{4,5}$ 10.2 Hz, H-5), 5.54 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 10.2 Hz, H-2), 5.80 (1H, at, *J* 9.9 Hz, H-4), 6.05 (1H, d, H-1), 6.46 (1H, at, *J* 9.8 Hz, H-3), 6.86–7.60 (18H, m, ArH), 7.93–8.04 (7H, m, ArH).

Phenyl-α-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 (44 mg, 1.91 mol) in methanol (10 ml) was added and the mixture stirred for 18 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 2) indicated the formation of a major product (R_f 0) and the absence of starting material (R_f 0.45). Ion exchange resin (Dowex 50) was added portionwise until the solution was neutralised, at which point the reaction mixture was filtered and concentrated *in vacuo* to afford tetrol **14** (2.8 g, 90%) as a white crystalline solid, m.p. 152 °C (ethanol) (lit.,[24] 160–161 °C); $[\alpha]_D^{22}$ +84 (*c*, 1.5 in MeOH) {lit.,[24] $[\alpha]_D^{21}$ +179 (*c*, 1.25 in H_2O)}; δ_H (400 MHz, $CDCl_3$) 3.45 (1H, at, *J* 9.9 Hz, H-4), 3.58 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.66–3.77 (3H, m, H-5, H-6, H-6′), 3.88 (1H, at, *J* 9.4 Hz, H-3), 4.49 (1H, d, H-1), 7.01 (1H, at, *J* 7.4 Hz, ArH), 7.17 (2H, d, *J* 7.7 Hz, ArH), 7.29 (2H, at, *J* 8.0 Hz, ArH).

Phenyl-6-*O*-trityl-α-D-glucopyranoside (15). Tetrol **14** (2.0 g, 7.81 mmol), trityl chloride (2.43 g, 8.72 mmol) and dimethylaminopyridine (486 mg, 3.98 mmol) were dissolved in pyridine (50 ml) in a dry flask under argon. After 24 h trityl chloride (1.0 g, 3.57 mmol) was added and the reaction mixture stirred for a further 48 h, at which point t.l.c. (ethyl acetate) showed the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.1). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (ethyl acetate) to afford triol **15** (3.5 g, 90%) as a colourless oil; $[\alpha]_D^{22}$ +63 (*c*, 1.4 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3413, br; δ_H (400 MHz, MeOD) 3.20–3.44 (3H, m, H-4, H-6, H-6′), 3.62 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.86 (1H, at, *J* 9.3 Hz, H-3), 3.89–3.92 (1H, m, H-5), 5.58 (1H, d, H-1), 6.98–7.62 (15H, m, ArH); δ_C (100.6 MHz, MeOD) 64.0 (t, C-6), 71.4 (d, C-4), 72.4 (2 × d, C-2, C-5), 74.3 (d, C-3), 86.6 (s, *C*Ph_3), 101.1 (d, C-1), 117.4, 122.4, 126.9, 127.0, 127.6, 127.7, 128.3, 128.9, 129.0, 129.5, 129.6 (11 × d, 15 × ArCH), 114.5 (1 × s, 3 × ArC); *m*/*z* (ESI) 521 ($M + Na^+$, 100%), 1019 ($2M + Na^+$, 62). [HRMS (ESI) Calc. for $C_{31}H_{30}O_6$ (MNa^+) 521.1940. Found 521.1959.]

Phenyl-2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (16). Triol **15** (3.17 g, 6.36 mmol) was dissolved in DMF (50 ml) in a flame dried flask under argon. Benzyl bromide (3 ml, 25.3 mmol) was added and the reaction mixture cooled to 0 °C, at which point sodium hydride (1.41 g, 35.3 mmol) was added portionwise and the reaction mixture was then allowed to warm to room temperature overnight. After 16 h, t.l.c. (ethyl acetate : petrol, 1 : 6) indicated the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0). Methanol (25 ml) was added and the solution stirred for 1 h, after which time the majority of the solvent was removed *in vacuo*. The resulting 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 ($MgSO_4$) 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; $[\alpha]_D^{24}$ +75 (*c*, 1.3 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3087, 3062, 3030, 2929, 2876; δ_H (400 MHz, $CDCl_3$) 3.20 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 10.0 Hz, H-6), 3.48 (1H, dd, $J_{5,6'}$ 1.8 Hz, H-6′), 3.77 (1H, at, *J* 9.5 Hz, H-4), 3.84 (1H, dd, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.96–4.00 (1H, m, H-5), 4.22 (1H, at, *J* 9.3 Hz, H-3), 4.34, 4.76 (2H, ABq, J_{AB} 10.2 Hz, PhCH_2), 4.79, 4.88 (2H, ABq, J_{AB} 12.0 Hz, PhCH_2), 4.91, 5.07 (2H, ABq, J_{AB} 10.6 Hz, PhCH_2), 5.65 (1H, d, H-1), 6.88–7.47 (35H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 62.3 (t, C-6), 71.0 (d, C-5), 73.2, 75.2, 76.1 (3 × t, Ph*C*H_2), 78.0 (d, C-4), 80.1 (d, C-2), 82.1 (d, C-3), 86.3 (s, Ph_3C), 95.1 (d, C-1), 116.9, 122.3, 126.9, 127.7, 127.8, 127.9, 128.2, 128.5, 128.8, 129.5 (10 × d, 35 × ArCH), 137.8, 138.1, 138.7, 143.9, 156.8 (5 × s, 7 × ArC); *m*/*z* (ESI) 791 ($M + Na^+$, 100%), 782 (54), 1558 ($2M + Na^+$, 37), 1560 (28). [HRMS (ESI) Calc. for $C_{52}H_{48}O_6$ (MNa^+) 791.3349. Found 791.3363.]

Phenyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3). Fully protected phenyl glycoside **16** (2.0 g, 2.60 mmol) was dissolved in dichloromethane (60 ml) and iron(III) 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 (R_f 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 ($MgSO_4$) 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.,[25] 74–75 °C); $[\alpha]_D^{24}$ +49 (*c*, 1.0 in $CHCl_3$) {lit.,[25] $[\alpha]_D$ +115 (*c*, 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 3.68–3.73, 3.81–3.85 (5H, m, H-2, H-4, H-5, H-6, H-6′), 4.27 (1H, at, *J* 9.2 Hz, H-3), 4.72, 4.85 (2H, ABq, J_{AB} 12.0 Hz, PhCH_2), 4.72, 4.96 (2H, ABq, J_{AB} 11.0 Hz, PhCH_2), 4.95, 5.11 (2H, ABq, J_{AB} 11.0 Hz, PhCH_2), 5.46 (1H, d, $J_{1,2}$ 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. 4 Å molecular sieves were added and the reaction mixture stirred under nitrogen for 30 min. A defined potential was applied and the reaction monitered 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 ($MgSO_4$) 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). Selenoglycoside **1** (100 mg, 0.15 mmol), anhydrous methanol (0.01 ml, 0.40 mmol) and tetrabutylammonium perchlorate (850 mg), in acetonitrile (25 ml), gave the β-methyl glucoside **17** (57 mg, 65%) as a white crystalline solid, m.p. 66–67 °C (methanol) (lit.,[26] 68–69 °C); $[\alpha]_D^{24}$ +10 (*c*, 1.0 in $CHCl_3$) {lit.,[26] $[\alpha]_D^{20}$ +11 (*c*, 5.3 in dioxan)}; δ_H (400 MHz, $CDCl_3$) 3.47–3.54 (2H, m, H-2, H-5), 3.63 (3H, s, Me), 3.74 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.8 Hz, H-6), 3.81 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-6′), 4.36 (1H, d, $J_{1,2}$ 7.9 Hz, H-1), 4.58, 4.87 (2H, ABq, J_{AB} 10.6 Hz, PhCH_2), 4.60, 4.67 (2H, ABq, J_{AB} 12.3 Hz, PhCH_2), 4.76, 4.99 (2H, ABq, J_{AB} 10.9 Hz, PhCH_2), 4.84, 4.97 (2H, ABq, J_{AB} 11.0 Hz, PhCH_2), 7.19–7.41 (20H, m, ArH). A small amount of the corresponding α-glycoside was also isolated: a colourless oil (11 mg, 13%); $[\alpha]_D^{24}$ +19 (*c*, 0.5 in $CHCl_3$) {lit.,[27] $[\alpha]_D^{20}$ +36 (*c*, 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 3.39 (3H, s, Me), 3.57 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.62–3.68 (2H, m, H-4, H-6), 3.71–3.77 (2H, m, H-5, H-6′), 3.99 (1H, at, *J* 9.2 Hz, H-3), 4.48, 4.84 (2H, ABq, J_{AB} 10.7 Hz, PhCH_2), 4.49, 4.62 (2H, ABq, J_{AB} 12.4 Hz, PhCH_2), 4.64 (1H, d, H-1), 4.68, 4.81 (2H, ABq, J_{AB} 12.1 Hz, PhCH_2), 4.83, 4.99 (2H, ABq, J_{AB} 10.9 Hz, PhCH_2), 7.12–7.38 (20H, m, ArH).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside (18). Selenoglycoside **1** (98 mg, 0.14 mmol), diacetone galactose (75 mg, 0.29 mmol) and tetrabutylammonium perchlorate (855 mg), in acetonitrile (25 ml), gave disaccharide **18** (104 mg, 90%) as a colourless oil: $[\alpha]_D^{22}$ −24 (*c*, 1.0 in $CHCl_3$) {lit.,[28] $[\alpha]_D^{22}$ −22 (*c*, 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33, 1.34 (2 × 3H, 2 × s, 2 × CH_3), 1.48, 1.52 (2 × 3H, 2 × s, 2 × CH_3), 2.11–4.06 (6H, m, H-2_a, H-3_a, H-4_a, H-5_a, H-6_a, H-$6'_a$), 4.11 (1H, ddd, $J_{4,5}$ 7.5 Hz, $J_{5,6}$ 3.4 Hz, $J_{5,6'}$ 1.8 Hz, H-5_b), 4.19 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6_b), 4.27 (1H, dd, $J_{6,6'}$ 8.0 Hz, H-6_b), 4.34 (1H, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 2.4 Hz, H-2_b), 4.48 (1H, d, $J_{1,2}$ 7.7 Hz H-1_a), 4.52 (1H, d, *J* 9.8 Hz, PhC*H*H), 4,55, 4.82 (2H, ABq, J_{AB} 11.8 Hz, PhCH_2). 4.60–4.66 (3H, m, H-3_b, H-4_b, PhCH_2), 4.74, 5.08 (2H, ABq, J_{AB} 11.0 Hz, PhCH_2), 4.80, 4.98 (2H, ABq, J_{AB} 10.9 Hz, PhCH_2), 5.59 (1H, d, $J_{1,2}$ 4.9 Hz H-1_b).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-glucopyranoside (19). Selenoglycoside **1** (100 mg, 0.15 mmol), thioglycoside **2** (167 mg, 0.30 mmol) and tetrabutylammonium perchlorate (872 mg), in acetonitrile (25 ml), gave disaccharide **19** (60 mg, 35%) as a white crystalline solid, m.p. 129–131 °C (petrol/ethyl acetate); $[\alpha]_D^{22}$ +5.0 (*c*, 0.5 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3028, 2907; δ_H (500 MHz, $CDCl_3$) 2.30 (3H, s, Me), 3.46–3.56 (4H, m, H-2_a, H-4_a, H-2_b, H-5_b), 3.63–3.70 (3H, m, H-5_a, H-3_b, H-4_b), 3.73–3.81 (3H, m, H-6_a, H-$6'_a$, H-$6'_b$,), 4.24 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.2 Hz, H-$6'_a$), 4.47 (1H, d, $J_{1,2}$ 7.6 Hz, H-1_b), 4.57–4.67 (4H, m, 2 × PhCH_2), 4.70 (1H, d, $J_{1',2'}$ 9.8 Hz, H-1_a), 4.75–5.02 (10H, m, 5 × PhCH_2), 7.06–7.52 (39H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, Me), 68.6, 68.7 (2 × t, 2 × C-6), 72.5, 73.4, 74.9, 75.1, 75.5, 75.9 (6 × t, 7 × PhCH_2), 78.7, 78.9, 80.2, 80.8, 80.9, 82.2, 84.7, 86.7 (8 × d, 2 × C-2, 2 × C-3, 2 × C-4, 2 × C-5), 87.6 (d, C-1), 103.8 (d, C-1′), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.7, 132.8 (13 × d, 39 × ArCH), 129.7, 137.9, 138.2, 138.9 (3 × s, 9 × ArC); *m*/*z* (ES^+) 1096.6 (M + NH_4^+, 24%), 1101.5 (M + Na^+, 100). [Isotope Distribution Calc. (M + Na^+) 1101.46 (100%), 1102.46 (78), 1103.46 (26), 1104.47 (13). Found 1101.51 (100%), 1102.46 (70), 1103.48 (33), 1104.49 (9).]

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-phenyl-2,3,4-tri-*O*-benzyl-α-glucopyranoside (21). Selenoglycoside **1** (100 mg, 0.15 mmol), phenyl glycoside **3** (150 mg, 0.28 mmol) and tetrabutylammonium perchlorate (855 mg), in acetonitrile (25 ml), gave disaccharide **21** (122 mg, 79%) as a white crystalline solid, m.p. 105–106 °C (petrol/ethyl acetate); $[\alpha]_D^{24}$ +19 (*c*, 0.5 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3030, 2898; δ_H (400 MHz, $CDCl_3$) 3.41–3.44 (1H, m, H-5_a), 3.51 (1H, at, *J* 8.5 Hz, H-2_a), 3.57 (1H, at, *J* 9.1 Hz, H-4_a), 3.62–3.77 (6H, m, H-3_a, H-6_a, H-$6'_a$, H-2_b, H-4_b, H-6_b), 3.96–3.98 (1H, m, H-5_b), 4.15 (1H, dd, $J_{5,6'}$ 1.5 Hz, $J_{6,6'}$ 10.9 Hz, H-$6'_b$), 4.25 (1H, at, *J* 9.3 Hz, H-3_b), 4.31 (1H, d, $J_{1,2}$ 8.1 Hz, H-1_a), 4.32–5.08 (14H, m, PhCH_2), 5.51 (1H, d, $J_{1,2}$ 3.3 Hz, H-1_b), 6.99–7.38 (40H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 68.1, 68.9 (2 × t, 2 × C-6), 70.5, 75.1, 77.6, 77.9, 79.6, 81.8, 81.9, 84.8 (8 × d, 2 × C-2, 2 × C-3, 2 × C-4, 2 × C-5), 73.3, 73.4, 75.0, 75.7 (4 × d, 7 × PhCH_2), 95.4 (d, C-1_b), 103.6 (d, C-1_a), 116.9, 122.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.4 (12 × d, ArCH), 138.0, 138.1, 138.2, 138.3, 138.4, 138.5, 138.9, 156.7 (8 × s, ArC); *m*/*z* (ES^+) 1066.4 (M + NH_4^+, 100%), 1067.5 (75), 1068.5 (21), 1069.5 (6). (Found: C, 76.68; H, 6.52. $C_{67}H_{68}O_{11}$ requires C, 76.69; H, 6.53%).

Attempted glycosylation of 6 with diacetone galactose at +1.7 V in the absence of PhSeSePh

Thioglycoside **6** (100 mg, 0.15 mmol), diacetone galactose (100 mg, 0.38 mmol) and tetrabutylammonium perchlorate (855 mg, 2.5 mol) 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. 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, 3 : 1) indicated the formation of a minor product (R_f 0.3). The reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in ethyl acetate (50 ml), washed with water (50 ml) and the aqueous layer re-extracted with ethyl acetate. The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol : ethyl acetate, 4 : 1) to afford unreacted thioglycoside **6** (93 mg, 93%) and disaccharide **18** (6 mg, 5%).

Attempted glycosylation of 6 with diacetone galactose at +1.7 V in the presence of PhSeSePh

Thioglycoside **6** (105 mg, 0.16 mmol), diacetone galactose (83 mg, 0.32 mmol), diphenyl diselenide (24 mg, 0.077 mmol) and tetrabutylammonium perchlorate (873 mg, 2.6 mol) 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. 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, 3 : 1) indicated the formation of a product (R_f 0.3). The reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in dichloromethane (50 ml), washed with water (50 ml) and the aqueous layer re-extracted with dichloromethane. The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol : ethyl acetate, 7 : 1) to afford thioglycoside **6** (50 mg, 48%) and disaccharide **18** (63 mg, 50%).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-galactopyranoside (22). Disaccharide **20** (120 mg, 0.11 mmol), diacetone galactose (64 mg, 0.25 mmol) and tetrabutylammonium perchlorate (955 mg, 2.79 mol) 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. 4 Å molecular sieves were added and the reaction mixture stirred under nitrogen for 30 min. A potential of 2.0 V was applied for 2.5 h at which point t.l.c. (petrol : ethyl acetate, 3 : 1) indicated the formation of a major product (R_f 0.1). The reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in dichloromethane (50 ml), washed with water (50 ml) and the aqueous layer re-extracted with dichloromethane. The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petrol : ethyl acetate, 1 : 4) afforded trisaccharide **22** (107 mg, 79%) as a white crystalline solid, m.p. 137–139 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ −4.6

(c, 1.0 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3888, 3064, 3030, 2991, 2957, 2892, 2868, 2361, 2341; δ_H (500 MHz, $CDCl_3$) 1.27, 1.35, 1.43, 1.55 (4 × 3H, 4 × s, 4 × CH_3), 3.46–3.55 (4H, m, H-2_a, H-5_a, H-2_b, H-4_b), 3.58–3.61 (1H, m, H-5_b), 3.62–3.78 (7H, m, H-3_a, H-4_a, H-6_a, H-$6'_a$, H-3_b, H-6_b, H6_c), 4.04–4.08 (2H, m, H-4_c, H-5_c), 4.14 (1H, dd, $J_{5,6}$ 3.1 Hz, $J_{6,6'}$ 10.9 Hz, H-$6'_c$), 4.25 (1H, dd, $J_{5,6}$ 1.3 Hz, $J_{6,6'}$ 11.1 Hz, H-$6'_b$), 4.33 (1H, dd, $J_{1,2}$ 4.7 Hz, $J_{2,3}$ 2.5 Hz, H-2_c), 4.46 (1H, d, $J_{1,2}$ 7.9 Hz, H-1_a), 4.48 (1H, d, $J_{1,2}$ 7.6 Hz, H-1_b), 4.55–4.59 (3H, m, H-3_c, 2 × PhC*H*H′), 4.59, 4.66 (2H, ABq, J_{AB} 12.3 Hz, PhCH_2), 4.75–4.83 (5H, m, 4 × PhC*H*H′, PhCH*H*′), 4.86 (1H, d, J_{AB} 11.1 Hz, PhCH*H*′), 4.96 (1H, d, J_{AB} 11.2 Hz, PhCH*H*′), 5.01 (1H, d, J_{AB} 11.0 Hz, PhCH*H*′), 5.04 (1H, d, J_{AB} 11.2 Hz, PhCH*H*′), 5.11 (1H, d, J_{AB} 11.3 Hz, PhCH*H*′), 5.59 (1H, d, $J_{1,2}$ 4.7 Hz, H-1_c), 7.21–7.48 (35H, m, ArH); δ_C (125.7 MHz, $CDCl_3$) 24.2, 24.9, 25.8, 26.0 (4 × q, 4 × CH_3), 67.3 (d, C-5_c), 68.6, 68.8, 69.8 (3 × t, C-6_a, C-6_b, C-6_c), 70.4, 70.6, 71.2 (3 × d, C-2_c, C-3_c, C-4_c), 73.4, 74.1, 74.5, 74.7, 74.9, 75.4, 75.6 (2 × d, 4 × t, C-5_a, C-5_b, 7 × PhCH_2), 77.1, 77.7 (2 × d, C-4_a, C-4_b), 81.4, 81.8 (2 × d, C-2_a, C-2_b), 84.4, 84.7 (2 × d, C-3_a, C-3_b), 96.2 (d, C-1_c), 103.8 (d, C-1_a), 104.3 (d, C-1_b), 108.4, 109.2 [2 × s, 2 × $C(CH_3)_2$], 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.5 (9 × d, 35 × ArCH), 138.1, 138.4, 138.5, 138.6 (4 × s, 7 × ArC); *m*/*z* (ESI) 1232.5 (M + NH_4^+, 100%), 1238.6 (M + Na^+, 57). [Isotope Distribution Calc. (M + NH_4^+) 1232.59 (100%), 1233.60 (84), 1234.60 (37), 1235.60 (11). Found 1232.56 (100%), 1233.56 (76), 1234.59 (25), 1235.58 (6).]

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