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Selective activation of glycosyl donors utilising electrochemical techniques: a study of the thermodynamic oxidation potentials of a range of chalcoglycosides

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A series of six chalcoglycosides (phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside, phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside, phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside, *p*-tolyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside, *p*-tolyl-2,3,4,6-*O*-benzyl-1-thio-β-D-glucopyranoside, and phenyl-2,3,4,6-*O*-benzyl-β-D-glucopyranoside) are voltammetrically interrogated in dimethyl sulfoxide, so as to determine their formal (*i.e.* thermodynamic) redox potentials. The electrochemical oxidation of the chalcoglycoside is shown to follow an overall EC-type mechanism, in which the electro-generated cation radical undergoes an irreversible carbon–chalcogen bond rupture to produce the corresponding glycosyl cation, which may react further. The kinetics of the initial heterogeneous electron transfer process and subsequent irreversible homogeneous chemical degradation of the radical cation are reported, with values for the standard electrochemical rate constant k_0 in the order of 10^{-2} cm s^{-1} and the first order homogeneous rate constant, k_1, of the order of 10^3 s^{-1}. The formal oxidation potentials were found to vary according to the identity of the chalcogenide, such that OPh > SPh ~ STol > SePh.

Introduction

The synthesis of oligosaccharides has received much attention over recent decades due to the wide variety of biological functions in which oligosaccharides play a crucial role.[1,2] While a number of approaches have achieved considerable success in this area a comprehensive methodology for such synthesis is still to be realised.[3]

One promising area of research is the selective activation of one glycoside over another, to give a disaccharide product which can itself be activated as a glycosyl donor without further manipulation. This methodology was first explored by Fraser-Reid using armed and disarmed pentenyl glycosides[4] and subsequently applied to thio glycosides by van Boom.[5] With a sufficient number of glycosyl donors, of decreasing reactivity, it is possible to continue in a similar manner to form longer chain oligosaccharides. This has been shown in practice first by Ley's group[6,7] and subsequently Wong and co-workers,[8] who advanced the scope of the methodology and showed its application to the synthesis of complex oligosaccharides.

This paper sets out to investigate the possible application of such an approach to the activation of glycosides by electrochemical oxidation and deprotection of C-1.[9] It has already been shown that a variety of O,[10] S,[11–15] Se[14] and Te[16] glycosides are readily activated electrochemically over a large range of positive potentials and that variation of the protecting group pattern also affects the potential at which oxidation occurs.[14] Provided that the measurement of the oxidation potentials is possible, and with the potentially large number of differential activation levels, the possibility for expanding on the purely chemical techniques described above is clear. We therefore set out to measure the oxidation potential of a variety of monosaccharides by cyclic voltammetry, in order to establish their formal oxidation potentials and to give an insight into the possible viability of this approach. The formal (or thermodynamic) potential should be distinguished from the peak potential. The former is a pure thermodynamic quantity, whereas the latter (the potential at which the peak of the oxidation wave occurs) is determined by the formal potential, mass transport to the electrode, the electrode kinetics of the electron transfer, and the follow-on homogeneous kinetics. Fig. 1 shows the effect of homogeneous kinetics on the peak potentials for an EC-type oxidation reaction. When $k_1 = 0$, *i.e.* the process is an E-reaction only, the formal potential lies between the anodic and cathodic peak potentials (labelled $E_{p,a}$ and $E_{p,c}$ respectively), although only at the exact mid-point between them in the case that both species in the redox couple have equal diffusion coefficients. As k_1 increases, however, the peaks are shifted to less positive potentials whilst the formal potential (denoted E_f^0 here), of course, remains unchanged.

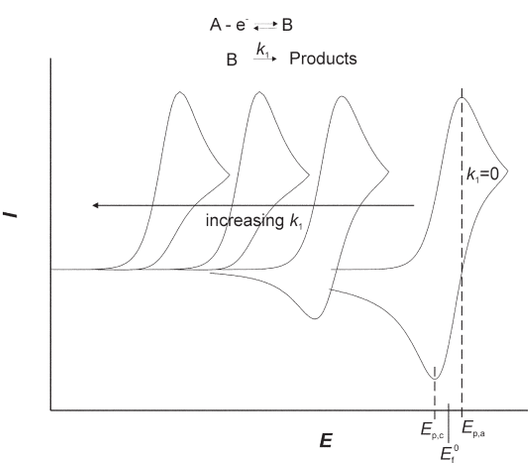

Fig. 1 Schematic cyclic voltammograms for an EC-type oxidation reaction showing the effect of homogeneous kinetics on the formal and peak potentials.

The chalcoglycosides examined in this work are: phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (BzSePh), phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (BnSePh), phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside(BnSPh), *p*-tolyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside (BzSTol), *p*-tolyl-2,3,4,6-*O*-benzyl-1-thio-β-D-glucopyranoside (BnSTol), and phenyl-2,3,4,6-*O*-benzyl-β-D-glucopyranoside (BnOPh). These are listed in Table 1.

Yamago *et al.* have recently investigated these and other glycosides under electrochemical oxidation at glassy carbon macroelectrodes in acetonitrile.[17] Using square wave and cyclic

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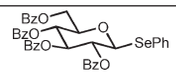
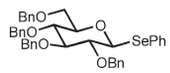
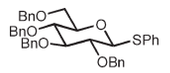
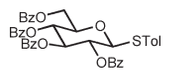
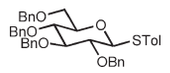
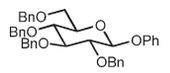
Table 1 Chalcoglycosides under investigation

Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside	BzSePh	
Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside	BnSePh	
Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside	BnSPh	
p-Tolyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside	BzSTol	
p-Tolyl-2,3,4,6-*O*-benzyl-1-thio-β-D-glucopyranoside	BnSTol	
Phenyl-2,3,4,6-*O*-benzyl-β-D-glucopyranoside	BnOPh	

voltammetry they have reported the oxidation (peak) potentials of the various glycosides under irreversible conditions. We report herein the synthesis of a range of representative glycosyl donors and the use of fast scan techniques to investigate their homogeneous kinetics and thereby determine their formal oxidation potentials. This gives as an interesting insight into the oxidative process at the heart of this chemistry and allows us to validate the use of the simpler, slow scan, cyclic voltammetry as a method for determining the relative reactivity of such compounds in a subsequent paper.[18]

Results and discussion

In order to investigate the formal potentials of the chalcoglycosides, and determine their electrochemical kinetics, each was subjected to cyclic voltammetric experiments with subsequent analysis by DigiSim™ software.[19]

A preliminary experiment was conducted to determine the diffusion coefficient of BnSPh in DMSO. A small volume of a 2.3 mM solution of BnSPh and 0.25 M supporting electrolyte [TEAP (tetraethylammonium perchlorate)] in DMSO were placed in the electrochemical cell along with a 3 mm diameter glassy carbon disk working electrode and platinum mesh (counter) and silver wire (reference) electrodes. A series of cyclic voltammograms were recorded at scan rates from 25 to 500 mV s^{-1}, showing chemically irreversible waves but with an apparently reversible (*i.e.* fast) electron transfer. The anodic peak potentials were then plotted against the square root of the scan rate (in Fig. 2) according to the Randles–Sevčik equation,[20]

$$I_p = (2.69 \times 10^5) n^{3/2} \pi r^2 D^{1/2} [A]_{bulk} v^{1/2} \quad (1)$$

where n is the number of electrons transferred, r the radius of the electrode, D the diffusion coefficient, $[A]_{bulk}$ the bulk concentration and v the voltage scan rate. Assuming $n = 1$, this expression results in a diffusion coefficient of $(1.0 \pm 0.1) \times 10^{-5}$ cm^2 s^{-1}, in reasonable agreement with the Wilke–Chang approximation,[21] given by

$$D \approx \frac{\left(7.4 \times 10^{-8}\right) T \sqrt{\phi m_s}}{\eta \sigma^{0.6}} \text{cm}^2\text{s}^{-1} \quad (2)$$

where T is the absolute temperature, ϕ is the solvent affinity factor (unity for aprotic solvents), m_s is the molecular mass of the solvent, η is the solvent viscosity, and σ the molecular volume.[21]

In order to infer the thermodynamic characteristics of the oxidation, it is necessary to reduce the voltammetric timescale of the experiment such that the homogeneous kinetics are outrun. This can be achieved by using fast scan voltammetry at microdisk electrodes. The microelectrode experiments were conducted using a 3.0 mM solution of BnSPh and 0.25 M TEAP in DMSO. The 12.5 μm diameter platinum microdisk was used as the working electrode with the platinum mesh and silver wire electrodes as counter and reference electrodes respectively. A single cyclic voltage scan was applied to the solution at a scan rate of 100 V s^{-1}, which yielded a voltammogram that appeared to be chemically irreversible. Only single voltage scans were used for this work, since initial experiments displayed evidence that continuous voltage sweeping led to fouling of the electrode and inconsistent voltammetry. To further reduce these effects, the electrode was cleaned before the scan was repeated to ensure that consistent cyclic voltammograms were obtained. The electrode was then placed into a separate solution of 0.25 M TEAP in DMSO, and a background voltammogram measured with identical potentiostat settings for scan rate and ohmic compensation. This procedure of measurement was repeated for scan rates in the range 0.1 V s^{-1} to 25 kV s^{-1}.

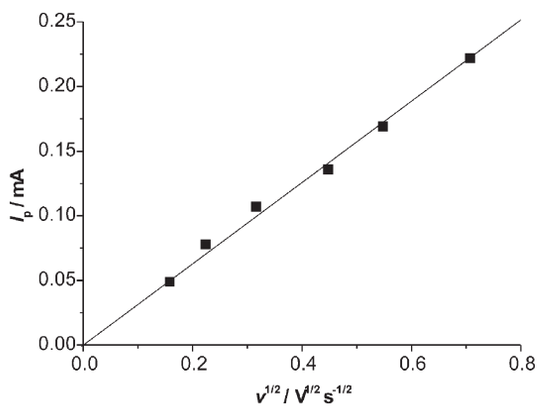


Fig. 2 Randles–Sevčik plot for 2.3 mM BnSPh solution.

In order to analyse the voltammetry of BnSPh, the background voltammograms were first subtracted from the 'full' voltammograms. Then to confirm that the current–voltage response was not due to adsorbed species, a plot of peak currents against the square root of the scan rate was produced. The linear relationship shown in Fig. 3 demonstrates that the voltammograms are due to diffusing species rather than adsorbed.

It is believed that the general mechanism for the oxidation of these chalcoglycosides proceeds according to the EC process shown in Scheme 1.[14] In this scheme, k_1 is the homogeneous rate constant and the electron transfer rates k_f and k_b are related to the standard electrochemical rate constant by

$$k_f = k_0 \exp\left(\frac{(1-\alpha)F}{RT}\left(E - E_f^0\right)\right)$$

and

$$k_b = k_0 \exp\left(\frac{-\alpha F}{RT}\left(E - E_f^0\right)\right)$$

where α is the transfer coefficient. However, in order to confirm that there would be no complications from the oxidation of diphenyl disulfide, which may be formed as a side product by

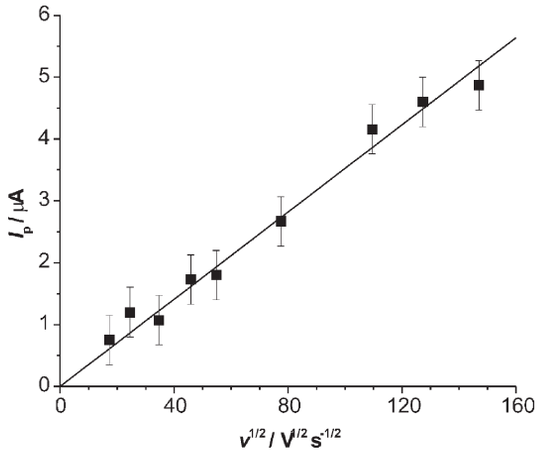
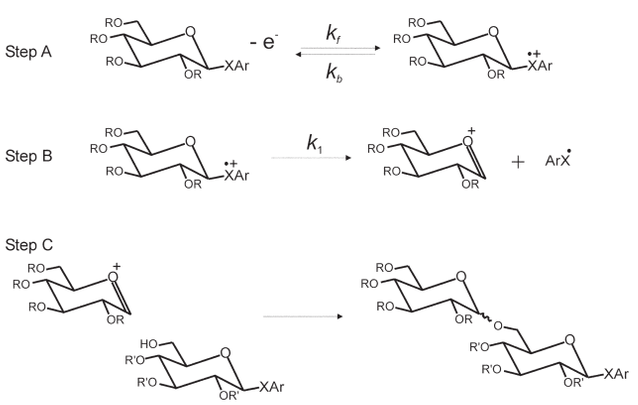


Fig. 3 Plot of I_{peak} *vs.* $\sqrt{v}$ for 3.0 mM BnSPh solution.

coupling of ˙SPh radicals, experiments were conducted using the 12.5 μm diameter platinum microdisk to record cyclic voltammograms of 6.4 mM solutions of Ph_2S_2 in 0.25 M TEAP and DMSO. Fig. 4 shows a typical voltammogram obtained, compared to a similar voltammogram recorded for BnSPh. As can be seen, the oxidation of Ph_2S_2 occurs at higher potential than BnSPh and an analysis for the EC mechanism is pertinent.



Scheme 1 Proposed mechanism for the oxidation of the chalcoglycosides, where R = Bn or Bz, X = O, Se, or S, Ar = Ph or *p*-Tol. Note that this paper only considers steps A and B.

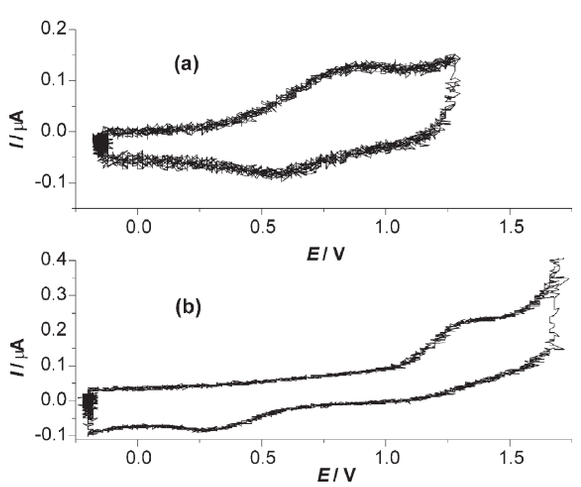


Fig. 4 Comparison of unsubtracted voltammograms at a scan rate of 1 kV s^{-1} for: (a) 3.0 mM BnSPh in 0.25 M TEAP/DMSO, and (b) 6.4 mM Ph_2S_2 in 0.25 M TEAP/DMSO.

The DigiSim™ program was then used to simulate a series of voltammograms for an EC mechanism until a best-fit with the experimental voltammogram was obtained by varying E_f^0, α, k_0 and k_1. The linear diffusion model was used in the DigiSim™ simulations, as the short timescale of the fast scan experiment does not give rise to the convergent diffusion regime normally associated with microdisk electrodes, but rather is approximately planar.[22] Fig. 5 illustrates a typical fit of theory to experiment. The fitting procedure was repeated for each voltammogram with a scan rate in excess of 100 V s^{-1} for BnSPh, and a mean value and standard deviation for each variable was thus obtained. These values were then used to simulate a theoretical response for each scan rate to be compared with the experimental data. Plots of the variation in peak current ratios (anodic to cathodic) with scan rate, and the variation in peak potentials with scan rate, were produced and, as Figs. 6 and 7 show, give a good agreement between theory and experiment.

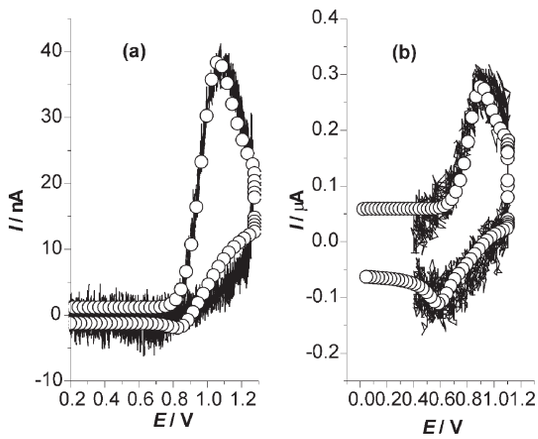


Fig. 5 Voltammogram showing fit between theory (○) and experiment for BnSPh at a scan rate of (a) 300 V s^{-1}, and (b) 2000 V s^{-1}.

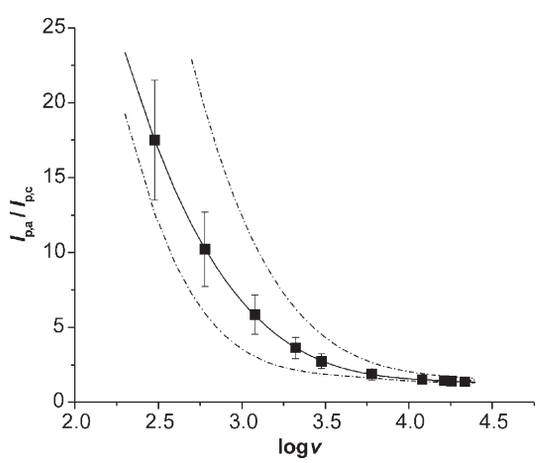


Fig. 6 Plot of theory (–·–, —) *versus* experiment (■) for ratio of peak currents *vs.* scan rate for BnSPh, where the mean theoretical response is shown as the unbroken line, and the maximum and minimum values as broken lines.

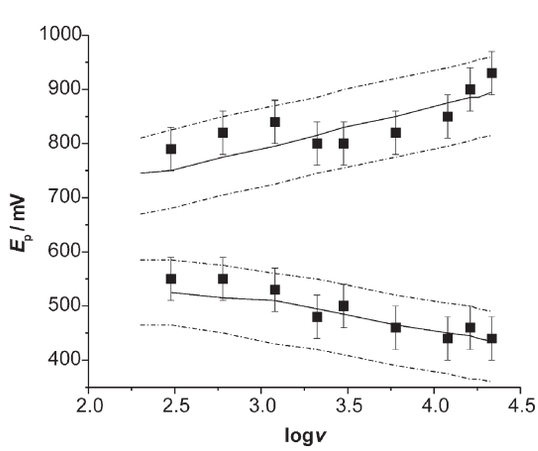


Fig. 7 Plot of theory (–·–, —) *versus* experiment (■) for peak potentials *vs.* scan rate for BnSPh, where the mean theoretical response is shown as the unbroken line, and the maximum and minimum values as broken lines.

The same protocol was repeated for each chalcoglycoside, using a range of scan rates from 0.1 V s^{-1} to 25 kV s^{-1}, with analogous background subtraction and simulation of voltammograms. In each case the diffusion coefficient was found to be approximately 1.0×10^{-5} cm^2 s^{-1}. Fig. 8 illustrates that in the case of the seleno-glycosides, there is no interference from oxidation of the diphenyl diselenide which has a higher oxidation potential, in agreement with literature.[23] The results of these experiments are presented in Table 2, with a high level of agreement between experiment and theory found in each case, as illustrated in Figs. 9 and 10. This shows a clear similarity in the kinetics amongst the compounds, all having a heterogeneous rate constant for electron transfer of the order 10^{-2} cm s^{-1}, and homogeneous rate constants in the order of 10^3 s^{-1}. This is, perhaps, to be expected since the considerations relevant to explaining the rate of electron transfer are obviously very similar for each compound under investigation. The rates of decomposition of the chalcoglycoside radical cation also reflect that there is no significant difference in the stability of the different chalcoglycoside radical cations.

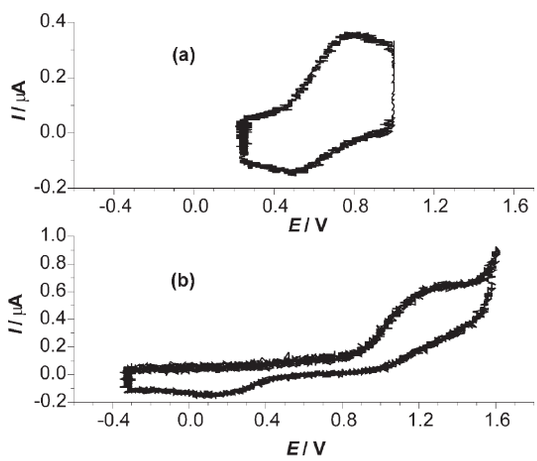


Fig. 8 Comparison of unsubtracted voltammograms at a scan rate of 1 kV s^{-1} for: (a) 3.0 mM BnSePh in 0.25 M TEAP/DMSO, and (b) 7.8 mM Ph_2Se_2 in 0.25 M TEAP/DMSO.

Table 2 Kinetic parameters determined from simulations

Sugar	k_0/cm s^{-1}	k_1/s^{-1}	E_f^0/V (*vs.* Ag)	$E_{p,a}$/V (*vs.* Ag)
BnOPh	0.05 ± 0.03	4550 ± 2730	0.785 ± 0.108	0.982 ± 0.078
BnSPh	0.06 ± 0.02	4800 ± 2910	0.617 ± 0.075	0.841 ± 0.055
BnSePh	0.04 ± 0.03	3910 ± 2190	0.570 ± 0.083	0.840 ± 0.095
BnSTol	0.04 ± 0.02	2180 ± 1100	0.663 ± 0.042	0.928 ± 0.057
BzSePh	0.05 ± 0.02	2740 ± 640	0.724 ± 0.050	0.946 ± 0.082
BzSTol	0.06 ± 0.03	2040 ± 375	0.757 ± 0.024	0.945 ± 0.082

There is, however, a clear trend in the formal potentials, E_f^0, with the identity of the leaving group X. This trend of OPh > STol ~ SPh > SePh, follows the carbon–chalcogenide bond energy (see Fig. 11), and repeats the pattern reported in the literature for the peak potentials for the same compounds, albeit measured using a different electrode material (glassy carbon) in acetonitrile.[17]

Conclusions

The formal oxidation potentials of the series of chalcoglycosides have been found along with homogeneous and heterogeneous kinetic parameters. The trends found amongst the thermodynamic potentials mirror those of the peak potentials, thereby validating the use of peak potentials as a guide for electro-synthetic experiments. Hence, careful choice of reactants enables a strategic electro-synthesis of disaccharides, and opens up the potential for extending this synthetic tactic for the creation of larger oligosaccharides. Part 2 in this series of articles will exploit the results reported herein to achieve these goals.

Experimental

Instrumentation and electrodes

The 'fast scan' potentiostat used was built in-house and has a scan rate of up to 3×10^4 V s^{-1} and was used with minimum filtering.

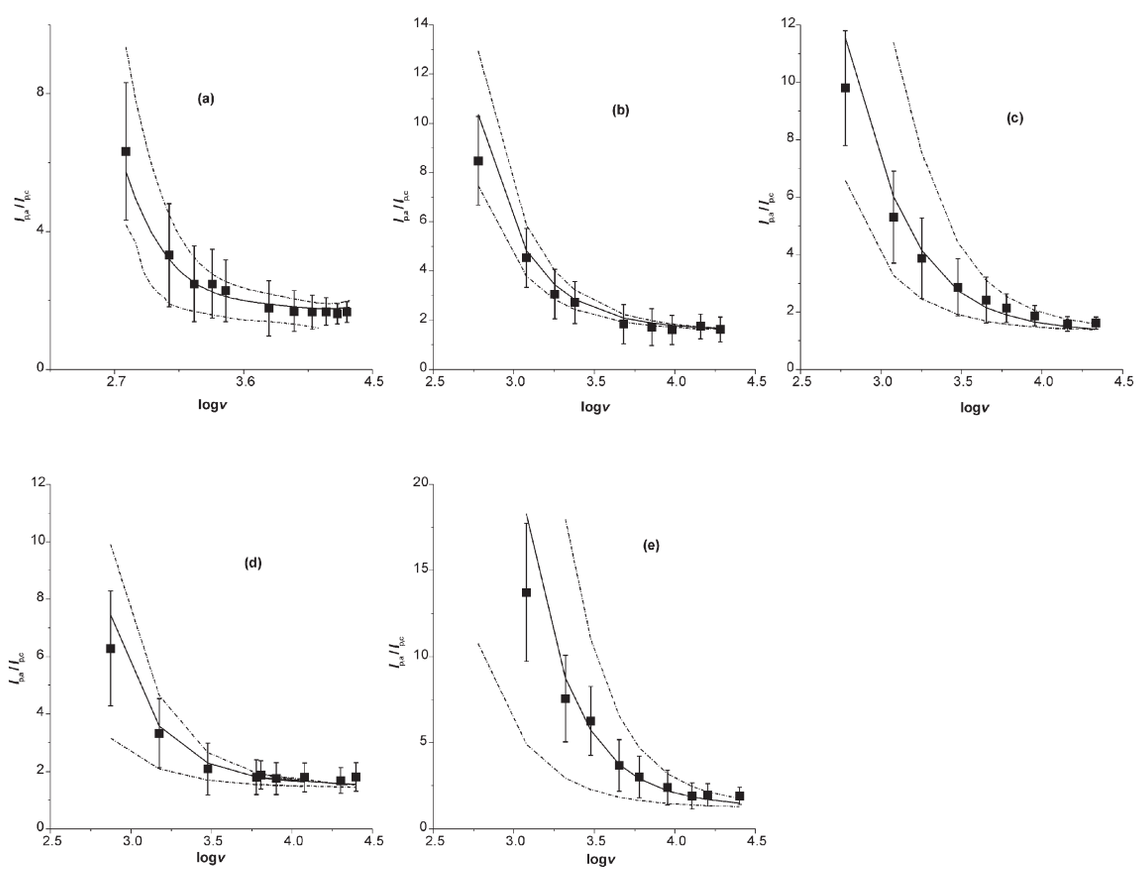


Fig. 9 Plot of theory (– · –, —) *versus* experiment (■) for ratio of peak currents *vs.* scan rate, where the mean theoretical response is shown as the unbroken line, and the maximum and minimum values as broken lines. (a) BzSTol, (b) BzSePh, (c) BnSePh, (d) BnSTol, (e) BnOPh.

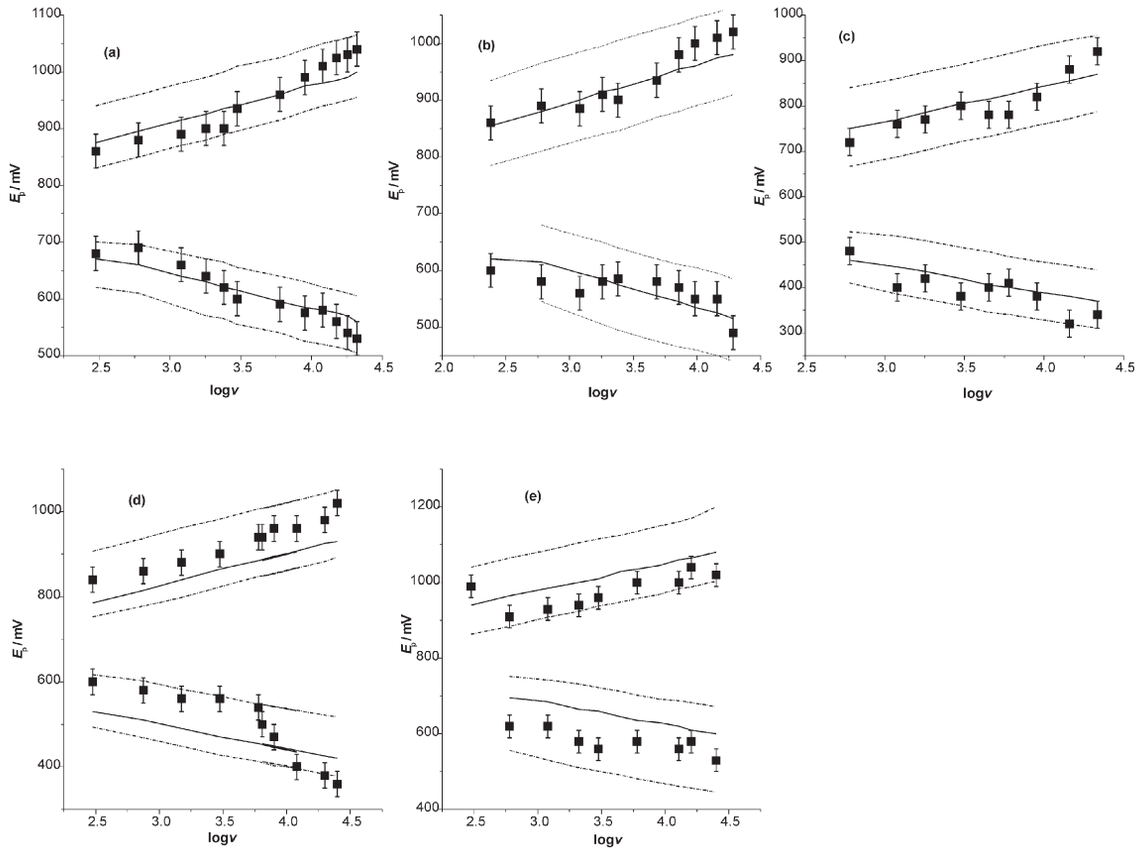


Fig. 10 Plot of theory (–·–, —) *versus* experiment (■) for peak potentials *vs.* scan rate, where the mean theoretical response is shown as the unbroken line, and the maximum and minimum values as broken lines. (a) BzSTol, (b) BzSePh, (c) BnSePh, (d) BnSTol, (e) BnOPh.

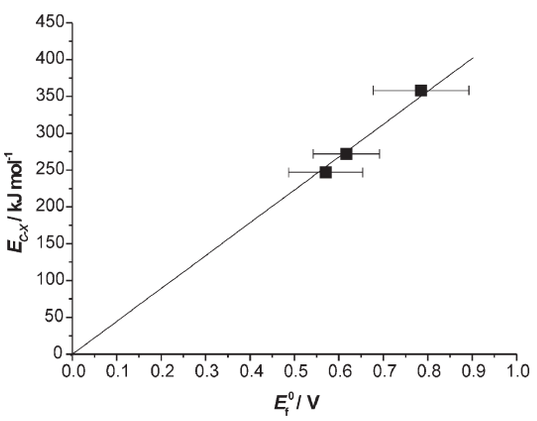


Fig. 11 Plot of formal potential *versus* bond energy (source refs. 24 and 25).

This potentiostat is similar to that described and utilised by Amatore *et al.*[26–28] and is capable of achieving ohmic drop compensation by means of an internal positive feedback circuit. The potential was applied with a TTi TG1304 programmable function generator (Thurlby Thandar Instruments Ltd, Huntingdon, Cambs., UK) and the current was recorded with a Tektronix TDS 3032 oscilloscope (300 MHz band-pass, 2.5 GS s^{-1}).

Voltammograms recorded at scan rates below 50 V s^{-1} utilised a μAutolab Type II (Eco Chemie BV, Utrecht, Netherlands) controlled by a Dell Optiplex GX110 Pentium III computer using General Purpose Electrochemical System v4.8 software (Eco Chemie BV, Utrecht, Netherlands). This software also dealt with data recording and processing. Modelling of voltammograms was carried out using DigiSim™ version 3.0 (Bioanalytical Systems Inc., West Lafayette, Indiana, USA).

The working electrode was a platinum microdisk of diamteter 12.5 μm, constructed by sealing a platinum microwire (99.95%, Johnson Matthey plc, London, UK) into capillary soda glass according to a literature method.[29] Between scans, the electrode was cleaned with ultra-pure water and approximately 30% nitric acid, before being polished using alumina lapping compounds (BDH) of decreasing size from 3 μm down to 0.25 μm on glass and soft lapping pads (Kemet Ltd, UK), and finally rinsed in ultra-pure water and dried carefully and stored under DMSO between each use. The electrode was regularly checked under an optical microscope to ensure that it was not recessed. The counter electrode was a platinum mesh, and a silver wire (99.95%, Johnson Matthey plc, London, UK) was used as a pseudo-reference electrode. Electrochemical experiments were conducted at 294 K ± 2 K, and the cell was housed within a Faraday cage to reduce electrical noise and minimise any photochemical decomposition of the solvent.

Reagents

In addition to the chalcoglycosides, whose preparation and purification are described below, the chemical reagents used were tetraethylammonium perchlorate (TEAP, Fluka, >99%), diphenyl disulfide (Avocado Research Chemicals Ltd, 98%), diphenyl diselenide (Aldrich, 98%), and dimethyl sulfoxide (DMSO, BDH 'Spectrosol', >99.8%). These were of the highest grade available and were used without further purification. The DMSO was stored over activated molecular sieves (Linde 5A, Aldrich) to ensure that the solvent remained dry. Ultra-pure water was used for cleaning (UHQ grade) and had a resistivity of not less than 18 MΩ·cm (Elga, High Wycombe, Bucks., UK).

General method and syntheses of compounds

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 (200 MHz), 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, South Parks Road, 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; methanol was distilled from magnesium methoxide, dichloromethane was distilled from calcium hydride, pyridine was distilled from calcium hydride and stored over potassium hydroxide, and tetrahydrofuran was distilled from a solution of sodium benzophenone ketyl immediately before use.

Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside

Diphenyl diselenide (227 mg, 0.71 mmol) was dissolved in ethanol (50 ml) and sodium borohydride (110 mg, 2.89 mmol) added portionwise. The solution was stirred for 15 min, at which point 2,3,4,6,-tetra-*O*-benzoyl-α-D-glucopyranosyl iodide[30] (2.5 g, 3.54 mmol) was added and the reaction left to stir. After 18 h, t.l.c. (ethyl acetate : petrol, 1 : 2) indicated the formation of a single product (R_f 0.4) and the absence of starting material (R_f 0.5). The reaction mixture was diluted with ethyl acetate (100 ml), washed with sodium thiosulfate (100 ml of a 10% aqueous solution) and water (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 phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (1.82 g, 79%) as a white crystalline solid, m.p. 170 °C (ethanol) (lit.,[31] 169.5–171 °C); $[\alpha]_D^{22}$ +21.4 (*c*, 1.0 in $CHCl_3$) {lit.,[31] $[\alpha]_D^{25}$ +20.5 (*c*, 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 4.13 (1H, ddd, $J_{4,5}$ 10.0 Hz, $J_{5,6}$ 6.0 Hz, $J_{5,6'}$ 2.7 Hz, H-5), 4.50 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.71 (1H, dd, H-6′), 5.08 (1H, d, $J_{1,2}$ 10.2 Hz, H-1), 5.52 (1H, at, *J* 9.7 Hz, H-2), 5.64 (1H, at, H-4), 5.95 (1H, at, H-3), 7.14–8.07 (25H, m, ArH).

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside

Phenyl-2,3,4,6-tetra-*O*-benzoyl-1-seleno-β-D-glucopyranoside (1.2 g, 1.63 mmol) was dissolved in methanol (20 ml) under argon in a dry flask and a solution of sodium (114 mg, 9.35 mmol) in methanol (20 ml) was added. After 5 h, t.l.c. (ethyl acetate : petrol, 1 : 4) showed the formation of a single product (R_f 0) and the absence of starting material (R_f 0.3). The reaction mixture was neutralised with ion exchange resin (Dowex 50), filtered and then concentrated *in vacuo*. The residue was dissolved in dimethylformamide (60 ml), the solution cooled to 0 °C and benzyl bromide (1.0 ml, 8.16 mmol) added. Sodium hydride (60% dispersion in mineral oil, 390 mg, 9.75 mmol) was added portionwise and the reaction mixture allowed to warm slowly to room temperature, with stirring. After 16 h, 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). The reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (3 × 100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate : petrol, 1 : 8) to afford phenyl-2,3,4,6-tetra-*O*-benzyl-1-seleno-β-D-glucopyranoside (1.0 g, 89%) as a white crystalline solid, m.p. 78–79 °C (ethanol) (lit.,[32] 79 °C); $[\alpha]_D^{22}$ −12.8 (*c*, 1.0 in $CHCl_3$) {lit.,[32] $[\alpha]_D^{22}$ +11 (*c*, 1.0 in CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 3.48–3.51 (1H, m, H-5), 3.54 (1H, at, *J* 9.7 Hz, H-6), 3.65–3.73 (2H, m, H-3, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 10.9 Hz H-6), 3.81 (1H, dd, $J_{5,6'}$2.1 Hz, H-6′), 4.55, 4.63 (2H, ABq, J_{AB} 11.9 Hz, PhCH_2), 4.61 (1H, d, *J* 11.0 Hz, PhC*H*H), 4.74 (1H, d, *J* 10.3 Hz, PhC*H*H), 4.83–4.92 (4H, m, 2 × PhCH_2), 4.87 (1H, d, $J_{1,2}$ 9.4 Hz, H-1), 7.19–8.12 (25H, m, ArH).

Phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside

Phenyl-1-thio-β-D-glucopyranoside[33] (1.5 g, 5.52 mmol) was dissolved in dimethylformamide (20 ml) under argon in a dry flask and benzyl bromide (3.3 ml, 27.6 mmol) added. The reaction mixture was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 795 mg, 33.1 mmol) added portionwise and the reaction allowed to warm slowly to room temperature. After 18 h, t.l.c. (ethyl acetate : petrol, 1 : 8) showed the formation of a single product (R_f 0.3) and the absence of starting material (R_f 0). MeOH (50 ml) was added and the reaction mixture stirred for 15 min, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 ml), washed with brine (3 × 100 ml) and the aqueous layer re-extracted with ethyl acetate (100 ml). The combined aqueous layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate : petrol, 1 : 8) to afford phenyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (3.2 g, 92%) as a white crystalline solid, m.p. 90–91 °C (ethyl acetate/petrol) (lit.,[34] 91–92 °C); $[\alpha]_D^{22}$ +0.5 (*c*, 1.0 in $CHCl_3$) {lit.,[35] $[\alpha]_D^{20}$ +0.8 (*c*, 5.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 3.53–3.58 (1H, m, H-5), 3.55 (1H, at, *J* 9.2 Hz, H-2), 3.69 (1H, at, H-3), 3.73–3.78 (2H, m, H-4, H-6), 3.83 (1H, dd, $J_{5,6'}$ 10.9 Hz, $J_{6,6'}$ 1.9 Hz, H-6′), 4.58, 4.65 (2H, ABq, J_{AB} 12.0 Hz, PhCH_2), 4.63, 4.87 (2H, ABq, J_{AB} 10.9 Hz, PhCH_2), 4.71 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.77, 4.93 (2H, ABq, J_{AB} 10.3 Hz, PhCH_2), 4.89, 4.94 (2H, ABq, J_{AB} 10.9 Hz, PhCH_2), 7.22–7.65 (25H, m, ArH).

***p*-Tolyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside**

p-Tolyl-1-thio-glucopyranoside 36 (1.0 g, 3.50 mmol) was dissolved in pyridine (50 ml) under argon in a flame-dried flask and benzoyl chloride (3.3 ml, 28.0 mmol) added. The mixture was stirred for 18 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 3) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0). The reaction was diluted with dichloromethane (100 ml) and washed with HCl (2 × 100 ml of a 0.1 M aqueous solution). The aqueous phase was re-extracted with dichloromethane (100 ml) and the combined organic layers washed with sodium hydrogen carbonate (2 × 100 ml of a saturated aqueous solution), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford *p*-tolyl-2,3,4,6-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.2 g, 88%) as a white crystalline solid, m.p. 186–188 °C (ethanol) (lit.,[14] 186–188 °C); $[\alpha]_D^{25}$ +21 (*c*, 1.0 in $CHCl_3$) {lit.,[14] $[\alpha]_D^{20}$ +23 (*c*, 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, PhCH_3), 4.20 (1H, ddd, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.8 Hz, $J_{5,6'}$ 2.8 Hz, H-5), 4.49 (1H, dd, $J_{6,6'}$ 12.1 Hz, H-6), 4.71 (1H, dd, H-6′), 5.01 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 5.48 (1H, at, *J* 9.7 Hz, H-2), 5.62 (1H, at, *J* 9.8 Hz, H-4), 5.93 (1H, at, *J* 9.6 Hz, H-3), 6.95 (2H, d, *J* 8.0 Hz, ArH), 7.26–7.63 (14H, m, ArH), 7.81 (2H, dd, *J* 1.1 Hz, *J* 8.3 Hz, ArH), 7.91 (2H, dd, *J* 1.2 Hz, *J* 8.1 Hz, ArH), 8.00 (2H, dd, *J* 1.1 Hz, *J* 8.1 Hz, ArH), 8.07 (2H, dd, *J* 1.0 Hz, *J* 8.1 Hz, ArH).

***p*-Tolyl-2,3,4,6-*O*-benzyl-1-thio-β-D-glucopyranoside**

p-Tolyl-1-thio-glucopyranoside[36] (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) 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 was stirred for a further 15 min, the reaction mixture was then 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 *p*-tolyl-2,3,4,6-*O*-benzyl-1-thio-β-

D-glucopyranoside (1.4 g, 82%) as a white crystalline solid, m.p. 77–78 °C (ethanol) (lit.,[14] 80–81 °C); $[\alpha]_D^{25}$ −1.8 (*c*, 1.0 in $CHCl_3$) {lit.,[14] $[\alpha]_D^{20}$ +2 (*c*, 2.5 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).

Phenyl-2,3,4,6-*O*-benzyl-β-D-glucopyranoside

Phenyl-β-D-glucopyranoside[37] (1.0 g, 3.91 mmol) was dissolved in dimethylformamide (40 ml) under argon in a dry flask and benzyl bromide (2.3 ml, 19.5 mmol) added. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil) (940 mg, 23.5 mmol) added portionwise. The reaction mixture was stirred for 18 h, at which point t.l.c. (ethyl acetate : petrol, 1 : 8) indicated the formation of a major product (R_f 0.4) and the absence of starting material (R_f 0). Methanol (50 ml) was added and solution stirred for a further 15 min, then 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 phenyl-2,3,4,6-*O*-benzyl-1-β-D-glucopyranoside (2.1 g, 85%) as a white crystalline solid, m.p. 76–79 °C (ethanol) (lit.,[38] 76 °C); $[\alpha]_D^{25}$ −9.7 (*c*, 1.0 in $CHCl_3$) {lit.,[38] $[\alpha]_D^{?}$ −9.8 (*c*, 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 3.63–3.85 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6′), 4.55–4.64 (3H, m, PhCH_2, PhC*H*H), 4.84–4.90 (3H, m, PhCH_2, PhC*H*H), 4.97–5.10 (3H, m, PhCH_2, H-1), 7.02–7.40 (25H, m, ArH).

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