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Stereoselective synthesis of α-glucosides by neighbouring group participation via an intermediate thiophenium ion

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Dedicated to Professor George Fleet on the occasion of his 65th birthday

ABSTRACT

The use of a 2-*O*-(thiophen-2-yl)methyl protecting group allows highly stereoselective α-glucosylation of a trichloroacetimidate donor; increased stereoselectivity, presumably arising from the intramolecular formation of a transient intermediate thiophenium ion, correlates with increased bulk of the glycosyl acceptor.

1. Introduction

The importance of oligosaccharides in a plethora of fundamental biological processes,[1] taken together with their frequently low natural abundance, a factor which is often compounded by difficulties in isolation and purification, continues to necessitate their total synthesis by chemical and/or enzymatic means. Whilst the use of glycosyl transferases and glycosidases has led to vast improvements in the efficiency of synthetic access to certain oligosaccharides, the availability of enzymes that are capable of performing desired transformation remains a limiting factor in many cases. Therefore, chemical synthesis currently remains the principal synthetic tool available to the scientific community.[2]

Oligosaccharide assembly hinges upon the linking of preformed building blocks by glycosylation. As considerable progress has been made in facilitating the speed of assembly of oligosaccharide structures from these highly functionalised building blocks,[3] the issue of control of anomeric stereochemistry during glycosylation now remains the principal challenge to be addressed. In particular, although 1,2-*trans* glycosidic linkages can usually be synthesised with high levels of stereocontrol by taking advantage of the classical neighbouring group participation (NGP) of 2-*O*-acyl protected glycosyl donors,[4] the stereocontrolled synthesis of 1,2-*cis* glycosidic linkages is considerably more difficult.[5]

Substantial effort has been expended in the search for a general solution to this problem. One promising approach is the use of intramolecular aglycon delivery (IAD),[6] in which glycosyl donor and acceptor are temporarily linked via a protecting group at the 2-postion of the donor; subsequent intramolecular glycosylation[7] usually then enforces the formation of a 1,2-*cis* linkage, provided the linking tether is short enough. Originally developed by Hindsgaul[8] and Stork,[9] several IAD approaches[10] have subsequently been developed including the use of PMB,[11] allyl,[12] propargyl[13] and NAP[14] protection of the 2-hydroxyl of the glycosyl donor, but none has yet to find general application.

Intramolecular approaches to glycosylation suffer the disadvantage of being more protracted than intermolecular glycosylation, necessitating an extra linking step, though one-pot approaches have been developed.[10e] Moreover, linking and glycosylation efficiencies tend to decrease when the technique is applied to more extended donors and acceptors, obviating the utility of the IAD approach for block synthesis.[8c,13b] The current situation is therefore one in which there is still no generally applicable method available for the formation of all 1,2-*cis* glycosidic bonds.

The use of new types of neighbouring group participation[15] to enforce the formation of 1,2-*cis* glycosidic linkages represents an attractive alternative proposition. In theory, such an approach could be applied generally to access α-1,2-*cis* glycosides (e.g., α-*gluco* and α-*galacto*), although perhaps not to synthesise β-1,2-*cis* glycosides, such as β-mannosides. Taken to the extreme the use of cyclic β-glycosyl donors also has the potential to effect high levels of α-stereocontrol during glycosylation,[16] though the reactivity of such donors remains an issue that must be addressed. Boons has been the pioneer of the novel NGP approach, and has recently reported a highly innovative intermolecular glycosylation process in which the stereochemical outcome of the reaction could be controlled by the configuration of a chiral protecting group at the 2-position of the glycosyl donor.[17] For example, *gluco* donors with an (*S*)-(phenylthiomethyl)benzyl moiety at the 2-position gave exclusively α-selectivity due to neighbouring group participation via a cyclic intermediate sulfonium ion.[17b] More recently, Boons also reported[18] the use of acyclic intermediate sulfonium ions to achieve α-glycosylation of donors that did not posses participating groups at the

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2-position. For example, when either phenylthioethyl ether or thiophene was added to the reaction mixture high α-selectivity was achieved during glycosylation of a 2-azido *gluco* trichloroacetimidate.[18]

Although the arguments presented for the potentially widespread utility of the chiral auxiliary approach for the control of anomeric stereochemistry are compelling, we reasoned that perhaps chirality was not necessary in the 2-OH protecting group in order to simply achieve good α-selectivity for the formation of α-1,2-*cis* glycosides. Indeed it was considered that the inherent steric and stereoelectronic preferences for a sulfonium ion to exist in the β-configuration[18] would ensure the formation of a *trans*-decalin sulfonium ion intermediate without the need for a directing stereocentre in the linking chain.[19] We therefore sought to investigate a 'halfway-house' situation following on from the earlier work of Boons, in which thiophene was appended to the 2-position of the glycosyl donor so that reaction could proceed via a thiophenium ion formed intramolecularly (Fig. 1). Such a situation would represent another variant on neighbouring group participation via an intermediate sulfonium ion, but one using the optimum additive that was identified for sulfonium ion mediated glycosylation without neighbouring group participation.[18] The results of a series of preliminary investigations into the potential use of glycosyl donors bearing a 2-*O*-(thiophen-2-yl)methyl group for stereoselective α-glycosylation via putative intermediate thiophenium ions are detailed below.

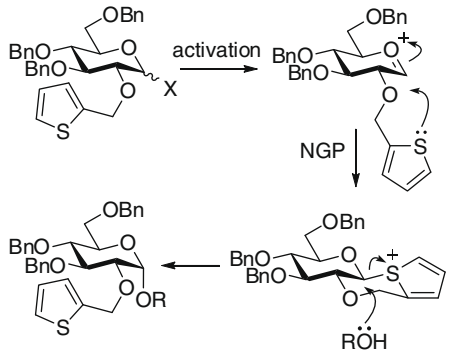
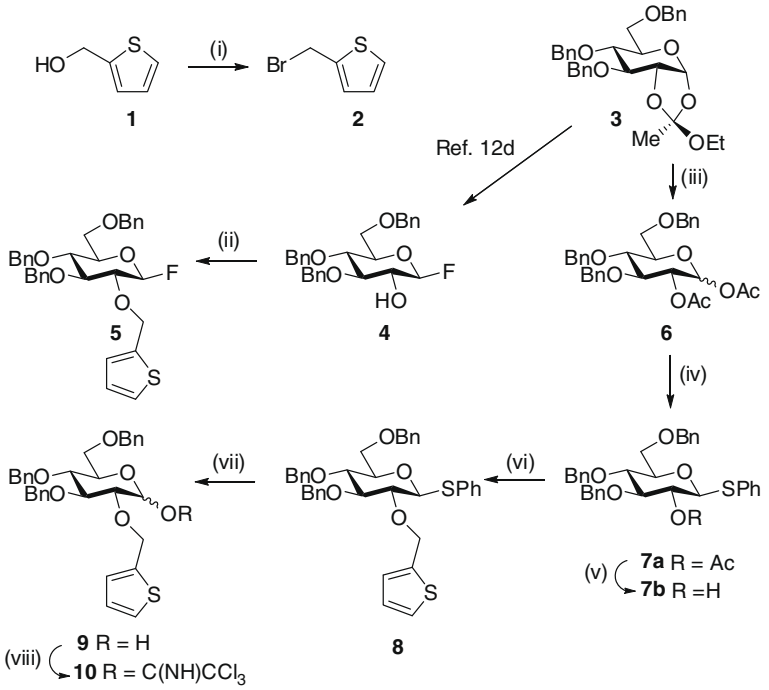


Figure 1. Putative α-selective glycosylation process involving neighbouring group participation (NGP) via an intermediate β-thiophenium ion.

2. Results and discussion

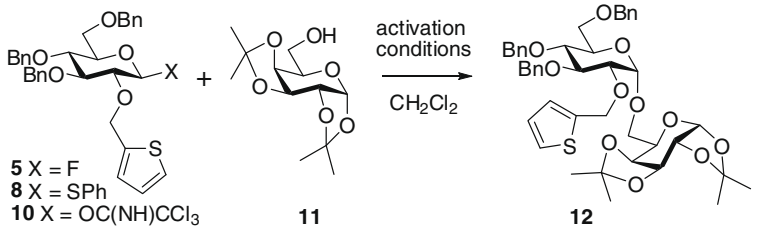
Commercially available 2-thiophene methanol **1** was converted into the bromide **2**,[20] to be used for subsequent alkylation reactions, by treatment with 33% HBr in glacial acetic acid (Scheme 1). Orthoester **3**[21] served as a divergent intermediate allowing access to glycosyl donors in which the 2-position was unprotected for later alkylation with **2**. Glycosyl fluoride alcohol **4**, synthesised from **3** as previously described,[12c] was alkylated by treatment with **2** and sodium hydride in DMF to produce glycosyl fluoride donor **5**. Alternatively treatment of orthoester **3** with aqueous acetic acid produced a mixture of monoacetates, which were immediately converted to an anomeric mixture of diacetates **6**[22] by treatment with acetic anhydride and pyridine. Reaction of **6** with thiophenol and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) produced the β-thiophenyl glycoside **7a**,[23] from which the 2-*O*-acetate was removed by treatment with catalytic methoxide, yielding alcohol **7b**.[24] Alkylation of **7b** with **2**, again achieved by treatment with sodium hydride in DMF, gave the thioglycoside donor **8**. Hydrolysis of **8**, mediated by *N*-iodosuccinimide (NIS) and trifluoroacetic acid (TFA) yielded hemiacetals **9**, which were then converted to the trichloroacetimidate donors **10** by reaction with trichloroacetonitrile and DBU (Scheme 1).

With a selection of glycosyl donors **5**, **8** and **10** in hand preliminary investigations were undertaken into finding suitable activation conditions using diacetone galactose **11** as a model glycosyl acceptor (Table 1). Activation of glycosyl fluoride **5** with supra-stoichiometric quantities of $BF_3{\cdot}OEt_2$ was investigated at a



Scheme 1. Reagents and conditions: (i) HBr/AcOH, Et_2O, 16 h, 85%; (ii) **2**, NaH, DMF, 16 h, 74%; (iii) $AcOH/H_2O$, 16 h; then Ac_2O, DMAP, pyridine, 16 h, 81%; (iv) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 6 h, 89%; (v) NaOMe, MeOH/THF, 16 h, 85%; (vi) **2**, NaH, DMF, 16 h, 78%; (vii) TFA, NIS, CH_2Cl_2/H_2O, 0 °C, 2 h, 84%; (viii) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3 h, 80%.

Table 1
Glycosylation of diacetone galactose with donors **5**, **8** and **10**



Entry	Glycosyl donor	Activation conditions	Time (h)	Temp (°C)	Yield of **12** (%)	α:β Ratio[a]
a	**5**	1.5 equiv $BF_3{\cdot}OEt_2$	0.5	0	45	1:1.25
b	**5**	1.5 equiv $BF_3{\cdot}OEt_2$	1	−41	40	1:1
c	**5**	1.5 equiv $BF_3{\cdot}OEt_2$	1.5	−78	36	2:1
d	**8**	1.5 equiv NIS, 0.5 equiv TMSOTf	1	0	36	1.5:1
e	**8**	1.5 equiv NIS, 0.5 equiv TMSOTf	2	−41	51	2:1
f	**8**	1.5 equiv NIS, 0.5 equiv TMSOTf	3.5	−78	48	6:1
g	**10**	0.1 equiv TMSOTf	0.5	0	93	1:1.25
h	**10**	0.1 equiv TMSOTf	1	−41	84	9:1
i	**10**	0.1 equiv TMSOTf	1.5	−78	71	8:1

[a] Anomeric ratios were determined by integration of appropriate peaks in the ^1H NMR spectra.

range of temperatures in dichloromethane (DCM), but in all cases yields of glycosylation were modest. Moreover, disaccharide **12** was produced as an anomeric mixture of products, and although the α:β ratio increased with decreased reaction temperature, even at −78 °C only very modest selectivity was observed in favour of the desired α-anomer **12α** (α:β ratio, 2:1, Table 1, entry c). Attention turned to the possible use of thioglycoside donor **5**. Activation was achieved by treatment with NIS and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in DCM, but again overall yields for glycosylation were poor, and the formation of numerous by-products indicated the non-orthogonal reactivity profile of the thioglycoside and the thiophene moieties. Moreover, anomeric selectivity was again modest, though at −78 °C the desired α-anomer was favoured (α:β ratio, 6:1, Table 1, entry f). Attention therefore moved to the potential the use of trichloroacetimidate **10** as the donor. Activation of **10** in the presence of **11** with a catalytic amount of TMS triflate at 0 °C in DCM produced disaccharide **12** in an excellent 93% yield, but with low anomeric selectivity actually in favour of the undesired β-anomer (α:β ratio 1:1.25, Table 1, entry g). However, reducing the reaction temperature to −40 °C had a marked effect on the stereoselectivity of glycosylation; now disaccharide **12** was produced in good yield (84%) and with high stereoselectivity in favour of the desired α-anomer (α:β ratio 9:1, Table 1 entry h). Lowering the reaction temperature further (entry i) did not improve either the yield or stereoselectivity, so it was concluded that −40 °C represented the optimum temperature for glycosylation of the trichloroacetimidate **10**.

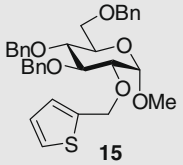
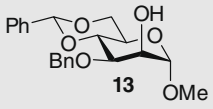
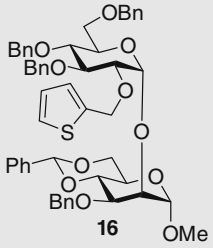
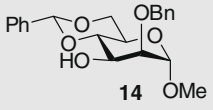
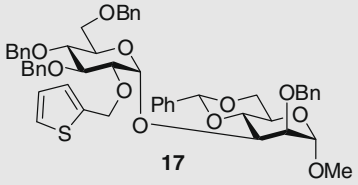
Subsequent investigations focussed on glycosylation of donor **10** with a series of different acceptors at −40 °C in DCM (Table 2). Glycosylation with methanol as acceptor produced methyl glycoside **15** in a good yield but with low stereoselectivity (α:β ratio 1:1.25, Table 2, entry a) indicating that the stereoselectivity of glycosylation was highly dependent on the steric bulk of the glycosyl acceptor. However with carbohydrate alcohols as acceptors the α-stereoselectivity of the process was considerable; glycosylation of the axial 2-hydroxyl of the *manno* acceptor **13**[25] produced disaccharide **16** with very high α-selectivity (α:β ratio 30:1, Table 2, entry b), whilst similar reaction of the *manno* acceptor **14**[25] possessing an equatorial secondary alcohol group produced disaccharide **17** with almost as high selectivity (α:β ratio 28:1, Table 2, entry c).

In order to confirm that the high α-stereoselectivity observed in these reactions was actually due to the presence of the thiophene moiety at the 2-position of the donor, and that it did not simply represent an inherent stereochemical preference arising from steric match/mismatch of the donor/acceptor pairs, a series of control reactions were undertaken using the perbenzylated trichloroacetimidate **18** as donor (Table 3). Glycosylation of **18** with diacetone galactose **11** produced disaccharide **19**[26] as anomeric mixture in favour of the β-anomer (α:β ratio 1:4, Table 3, entry a). This inherent preference for β-selectivity for sterically unhindered acceptors was confirmed by glycosylation of **18** with methanol, which produced methyl glycosides **20**[27] in a 1:8, α:β ratio (Table 3, entry b). Glycosylation with the more hindered secondary carbohydrate acceptors **13** and **14** produced disaccharides **21**[26] and **22** as mixtures in which the α-anomer was actually slightly favoured (Table 3, entries c and d), but in both of these cases the observed stereoselectivity was a factor of 10 lower than that observed for the corresponding 2-*O*-(thiophen-2-yl)methyl donor **10**, confirming the strong α-stereo-directing effect of the thiophene moiety.

3. Conclusions

A series of glycosyl donors possessing a 2-*O*-(thiophen-2-yl)-methyl protecting group at the 2-position were synthesised. Activation of both the glycosyl fluoride and the thioglycoside donors resulted in low-yielding glycosylation processes, indicating the incompatibility of thiophene moiety with those particular activation conditions. However, glycosylation of the trichloroacetimidate donor with a series of glycosyl acceptors resulted in highly α-selective glycosylation; higher α-stereoselectivity being observed with more hindered carbohydrate acceptors. Based on comparison with previous work by Boons, it is postulated that this high α-selectivity results from the intramolecular formation of a transient intermediate β-thiophenium ion, which then undergoes S_N2-like substitution by the glycosyl acceptor. Although the stereocontrol during these glycosylation processes is lower than the optimum results reported by Boons[17b] using the (*S*)-(phenylthiomethyl)benzyl moiety at the 2-position, this procedure does not require the synthesis of a chiral phenyl (phenylsulfanyl)ethyl ester, making such an approach perhaps more amenable to routine synthetic use. Further

Table 2
Glycosylation of various glycosyl acceptors with donor **10** at −40 °C in CH_2Cl_2 with 0.1 equiv TMSOTf as activator

Entry	Acceptor	Product	Yield	α:β Ratio
a	MeOH	 **15**	90	1.5:1
b	 **13**	 **16**	55	30:1
c	 **14**	 **17**	54	28:1

investigations into the use of novel types of neighbouring group participation for the stereoselective synthesis of α-1,2-*cis*-glycosides are currently in progress and the results will be reported in due course.

4. Experimental

4.1. General

Melting points were recorded on a Kofler hot block and are uncorrected. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Bruker DPX 250 (250 MHz), Bruker DPX 400 (400 MHz), Bruker DQX 400 (400 MHz), Bruker AVC 500 (500 MHz) or Bruker AMX 500 (500 MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. Low resolution mass spectra were recorded on a Micromass Platform 1 spectrometer using electrospray ionisation in either positive or negative polarity (ES^+ or ES^-), or using a VG Micromass spectrometer. High resolution mass spectra were recorded on a Walters 2790-Micromass LCT electrospray ionisation mass spectrometer, using either electrospray ionisation (NH_3, Cl) techniques as stated. *m/z* values are reported in Daltons and are followed by their percentage abundance in parentheses. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. Microanalyses were performed by the Inorganic Chemistry Laboratory Elemental Analysis service, Oxford University, UK. Thin Layer Chromatography (TLC) was carried out on Merck Kieselgel $60F_{254}$ pre-coated glass-backed plates. Visualisation of the plates was achieved using a UV lamp (λ_{max} = 254 or 365 nm), and/or ammonium molybdate (5% in 2 M sulfuric acid), or sulfuric acid (5% in ethanol). Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Dichloromethane was distilled from calcium hydride, or dried on an alumina column. Anhydrous THF, DMF, pyridine, methanol and toluene were purchased from Fluka over molecular sieves. 'Petrol' refers to the fraction of light petroleum ether boiling in the range of 40–60 °C.

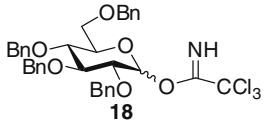
4.2. 2-Bromomethyl thiophene 2[20]

2-Thiophenemethanol **1** (1.66 ml, 17.5 mmol) was dissolved in anhydrous ether (50 ml) under an argon atmosphere. The mixture was cooled to 0 °C and HBr (33% in glacial acetic acid, 4 ml) was added. The reaction was allowed to warm to room temperature. After 16 h, TLC (petrol/ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0.7). The reaction was diluted with ice and water (50 ml), and the aqueous layer was extracted with ether (2 × 25 ml). The combined organic extracts were washed with cold saturated sodium bicarbonate solution until neutral pH and then washed with brine (50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford 2-bromomethyl-thiophene **2** (2.64 g, 85%) as a pale yellow liquid; δ_H (400 MHz, $CDCl_3$) 4.77 (2H, br s, $ArCH_2Br$), 6.96 (1H, dd, *J* 5.31 Hz, *J* 3.54 Hz, Ar-H), 7.13 (1H, d, *J* 3.54 Hz, Ar-H), 7.34 (1H, d, *J* 5.31 Hz, Ar-H); δ_C ($CDCl_3$) 26.8 (t, $ArCH_2Br$), 127.1, 127.2, 128.1 (3 × d, 3 × Ar-CH), 140.4 (s, Ar-C).

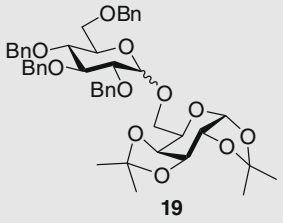
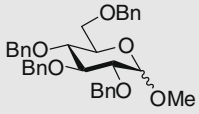
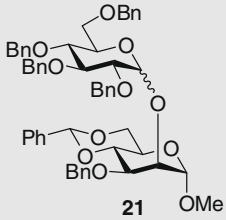
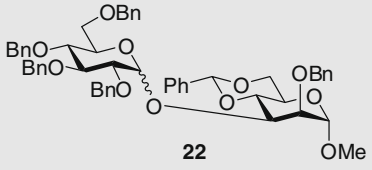
4.3. 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-β-D-glucopyranosyl fluoride 5

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **4**[12c] (0.273 g, 0.603 mmol) was dissolved in anhydrous DMF (2.5 ml) and then slowly added to a suspension of sodium hydride (0.600 g, 0.90 mmol) in anhydrous DMF (2.5 mL) at 0 °C under an argon atmosphere. 2-Bromomethyl-thiophene **13** (0.214 g, 1.206 mmol)

Table 3
Control glycosylation of acceptors with perbenzylated donor **18** at −40 °C in CH_2Cl_2 with 0.1 equiv TMSOTf as activator



18

Entry	Acceptor	Product	Yield	α:β Ratio
a	**11**	 **19**	80	1:4
b	MeOH	 **20**	87	1:8
c	**13**	 **21**	68	2:1
d	**14**	 **22**	60	3:1

was then added slowly as a solution in anhydrous DMF (2.5 ml). Once the addition of the 2-bromomethyl thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, TLC (petrol/ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.3). The reaction was quenched with methanol (5 ml) and concentrated in vacuo. The resulting residue was dissolved in ether (25 ml), washed with water (50 ml), and the aqueous layer extracted with ether (2 × 25 ml). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 15:1) to afford fluoride **5** (0.244 g, 74%) as a pale yellow oil; $[\alpha]_D^{25} = +9.7$ (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.50–3.75 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6′), 4.52, 4.80 (2H, ABq, J_{AB} 10.9 Hz, $ArCH_2$), 4.54, 4.62 (2H, ABq, J_{AB} 12.1 Hz, $ArCH_2$), 4.76, 4.95 (2H, ABq, J_{AB} 11.1 Hz, $ArCH_2$), 4.86, 5.03 (2H, ABq, J_{AB} 11.9 Hz, $ArCH_2$), 5.24 (1H, dd, $J_{1,2}$ 6.6 Hz, $J_{1,F}$ 52.6 Hz, H-1), 6.98 (1H, dd, *J* 5.1 Hz, *J* 3.3 Hz, Ar-H), 7.03 (1H, d, *J* 3.3 Hz, Ar-H), 7.12–7.14 (2H, m, 2 × Ar-H), 7.25–7.35 (14H, m, 14 × Ar-H); δ_C (100 MHz, $CDCl_3$) 68.3 (t, C-6), 68.5, 73.6, 75.1, 75.6 (4 × t, 4 × Ar*C*H_2), 74.8 (dd, $J_{5,F}$ 4.8 Hz, C-5), 76.8 (d, C-4), 81.1 (dd, $J_{2,F}$ 20.8 Hz, C-2), 83.3 (dd, $J_{3,F}$ 11.2 Hz, C-3), 109.8 (dd, $J_{1,F}$ 215.7 Hz, C-1), 126.3, 126.7, 127.1, 127.8, 127.9, 127.9, 128.0, 128.0, 128.4 (9 × d, 9 × Ar-CH), 137.8, 137.8, 138.2, 140.0 (4 × s, 4 × Ar-C); *m/z* (ES^+) 571 ($M+Na^+$, 80) 566 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{32}H_{33}FO_5SNa$ (MNa^+) 571.6546. Found 571.6544). ($C_{32}H_{33}FO_5S$ requires C, 70.05; H, 6.06. Found: C, 70.08; H, 6.06).

4.4. 1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside 6[22]

Orthoester **3**[21] (14.5 g, 27.8 mmol) was dissolved in glacial acetic acid (60% in water, 250 ml) and was stirred at room temperature. After 16 h, TLC (petrol/ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.9). The reaction mixture was co-evaporated with toluene and subsequently left under high vacuum for 2 h. The crude residue and DMAP (0.34 g, 2.79 mmol) were dissolved in anhydrous pyridine (100 ml) and the mixture was cooled to 0 °C under a nitrogen atmosphere. Acetic anhydride (5.27 ml, 55.8 mmol) was then slowly added. Once addition of acetic anhydride was complete, the reaction was allowed to warm to room temperature. After 16 h, TLC (petrol/ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0.6). The reaction was cooled to 0 °C and quenched with ethanol (75 ml). The reaction mixture was concentrated in vacuo. The residue was dissolved in ether (100 ml) and washed with 1 M HCl (100 ml), then with saturated sodium bicarbonate (100 ml) and then with brine (100 ml). The organic phase was then dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (toluene/ethyl acetate, 8:1) to afford diacetate **6**[22] (12.0 g, 81%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [13:1 mixture of α:β anomers observed, major α anomer quoted] 2.00, 2.14 (6H, 2 × s, 2 × CH_3), 3.70 (1H, dd, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.77–3.87 (2H, m, H-4, H-6′), 3.94 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 1.8 Hz, $J_{5,6'}$ 3.3 Hz, H-5), 4.03 (1H, at, *J* 9.5 Hz, H-3), 4.45 (1H, d, *J* 11.37, PhC*H*H′), 4.52–4.67 (3H, m, 1 × PhC*H*H′, 2 × PhCH*H*′), 4.79, 4.88 (2H, ABq, J_{AB} 11.4, $PhCH_2$), 4.85 (1H, d, *J* 10.6, PhC*H*H′), 5.09 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.0 Hz, H-2), 6.34 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.17–7.39 (15H, m, 15 × Ar-H); *m/z* (ES^+) 552 ($M+NH_4^+$, 100%).

4.5. Phenyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 7a[23]

Diacetate **6** (4.06 g, 7.59 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 ml) under a nitrogen atmosphere. Thiophenol (1.16 ml, 11.4 mmol) was added and the mixture was then cooled to 0 °C. Boron trifluoride diethyl etherate (1.40 ml, 9.90 mmol) was added dropwise to the mixture. Once addition of the boron trifluoride diethyl etherate was complete, the mixture was allowed to warm to room temperature. After 6 h, TLC (petrol/ethyl acetate, 7:3) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.7). The reaction was diluted with CH_2Cl_2 (250 ml) and washed with saturated sodium bicarbonate (100 ml), then with water (100 ml) and then with brine (100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 9:1) to afford thioglycoside **7a** (3.97 g, 89%) as a white crystalline solid; mp 112–113 °C (methanol); $[\alpha]_D^{23} = +9.4$ (*c* 1.1 in $CHCl_3$) [Lit. mp 113 °C; $[\alpha]_D^{20} = +10$ (*c* 1.0 in $CHCl_3$)][23]; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 3.54–3.58 (1H, m, H-5), 3.71–3.73 (2H, m, H-3, H-4), 3.77 (1H, dd, $J_{5,6}$ 4.9 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.84 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6′), 4.59 (1H, d, *J* 10.1 Hz, PhC*H*H′), 4.63 (1H, d, $J_{1,2}$ 9.5 Hz, H-1), 4.64–4.72 (3H, m, 3 × PhCH*H*′), 4.81–4.84 (2H, m, 2 × PhC*H*H′), 5.03 (1H, at, *J* 9.5 Hz, H-2), 7.18–7.35 (18H, m, 18 × Ar-H), 7.45–

7.53 (2H, m, 2 × Ar-H); *m/z* (ES^+) 607 ($M+Na^+$, 60) 602 ($M+NH_4^+$, 100%).

4.6. Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 7b[24]

A solution of sodium (0.23 g) in methanol (10 ml) was added to a stirred solution of thioglycoside **7a** (1.50 g, 2.57 mmol) in methanol/THF (20 ml, 1:1). After 16 h, TLC (petrol/ethyl acetate, 7:3) indicated the formation of a single product (R_f 0.7) and complete consumption of starting material (R_f 0.8). Amberlite 120 (H^+) resin was added, and the mixture was stirred for 15 min until pH neutral. The reaction was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 5:1) to afford alcohol **7b** (1.18 g, 85%) as a white crystalline solid; mp 72–73 °C (ethanol); $[\alpha]_D^{23} = -9.7$ (*c* 1.0 in $CHCl_3$) [Lit. mp 71–73 °C; $[\alpha]_D^{20} = -11.5$ (*c* 1.4 in $CHCl_3$)][24]; δ_H (400 MHz, $CDCl_3$) 2.45 (1H, d, $J_{OH,2}$ 2.0 Hz, OH), 3.49–3.58 (2H, m, H-2, H-5), 3.60–3.66 (2H, m, H-3, H-4), 3.76 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.82 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6′), 4.53 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.56–4.66 (3H, m, 3 × PhC*H*H′), 4.84–4.95 (3H, m, 3 × PhCH*H*′), 7.21–7.39 (18H, m, 18 × Ar-H), 7.58–7.61 (2H, m, 2 × Ar-H); *m/z* (ES^+) 565 ($M+Na^+$, 90) 560 ($M+NH_4^+$, 100%).

4.7. Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-1-thio-β-D-glucopyranoside 8

Alcohol **7b** (0.244 g, 0.45 mmol) was dissolved in anhydrous DMF (5 ml) and then slowly added to a suspension of sodium hydride (0.600 g, 0.90 mmol) in anhydrous DMF (5 mL) at 0 °C under an argon atmosphere. 2-Bromomethyl thiophene **2** (0.119 g, 0.67 mmol) was then added slowly as a solution in anhydrous DMF (5 ml). Once the addition of the 2-bromomethyl-thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, TLC (toluene/ethyl acetate, 9:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.6). The reaction was quenched with methanol (5 ml) and concentrated in vacuo. The resulting residue was dissolved in ether (100 ml), washed with water (100 ml), and the aqueous layer was extracted with ether (2 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (toluene/ethyl acetate, 12:1) to afford thioglycoside donor **8** (0.223 g, 78%) as a white crystalline solid; mp 84–85 °C (petrol/ethyl acetate); $[\alpha]_D^{25} = -2.0$ (*c* 1.05 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.49–3.54 (2H, m, H-2, H-5), 3.66 (1H, at, *J* 9.35, H-4), 3.70–3.75 (2H, m, H-3, H-6), 3.80 (1H, dd, $J_{5,6'}$ 1.9 Hz, $J_{6,6'}$ 10.7 Hz, H-6′), 4.56, 4.63 (2H, ABq, J_{AB} 11.9 Hz, $ArCH_2$), 4.60, 4.84 (2H, ABq, J_{AB} 11.3 Hz, $ArCH_2$), 4.65 (1H, d, $J_{1,2}$ 9.6 Hz, H-1) 4.87, 4.97 (2H, ABq, J_{AB} 10.7 Hz, $ArCH_2$), 4.93, 5.03 (2H, ABq, J_{AB} 11.0 Hz, $ArCH_2$), 6.98 (1H, dd, *J* 5.05 Hz, *J* 3.28 Hz, Ar-H), 7.02 (1H, m, Ar-H), 7.19–7.36 (21H, m, 21 × Ar-H); δ_C (100 MHz, $CDCl_3$) 69.0 (t, C-6), 69.5, 73.4, 75.1, 76.0 (4 × t, 4 × $ArCH_2$), 77.7 (d, C-4), 79.1 (d, C-2), 80.5 (d, C-5), 86.6 (d, C-3), 87.5 (d, C-1), 126.2, 126.7, 126.9, 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.4, 128.4, 128.5, 128.9, 132.0 (15 × d, 15 × Ar-CH), 133.7, 138.0, 138.2, 138.4, 140.3 (5 × s, 5 × Ar-C); *m/z* (ES^+) 656 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{38}H_{38}O_5S_2$Na (MNa^+) 661.2053. Found 661.2049). ($C_{38}H_{38}O_5S_2$ requires C, 71.44; H, 6.00. Found: C, 71.46; H, 6.05).

4.8. 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranose 9

Thioglycoside **8** (1.00 g, 1.57 mmol) was dissolved in CH_2Cl_2/H_2O (16.5 mL, 10:1), and the mixture was cooled to 0 °C. *N*-Iodosuccinimide (0.352 g, 1.57 mmol) and TFA (0.12 ml, 1.57 mmol) were added, and the mixture was stirred vigorously. After 2 h, TLC (toluene/ethyl acetate, 9:1) indicated the formation of a single major product (R_f 0.1) and complete consumption of starting material (R_f 0.8). The reaction was quenched with triethylamine (0.5 mL) and then with sodium thiosulfate (5 ml of a 10% solution). The reaction mixture was diluted with CH_2Cl_2 (15 ml), washed with saturated sodium bicarbonate (30 ml), and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 1:1) to afford hemiacetals **9** (0.724 g, 84%) as a clear oil: ν_{max} (KBr) 3510 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.43 (0.5H, at, *J* 8.47, H-2β), 3.53–3.72 (7H, m, H-2α, H-3α, H-4α, H-6α, H-6′α, H-3β, H-4β, H-6β, H-6′β), 4.98–4.09 (1.5H, m, H-5α, H-5β), 4.48–4.62 (4.5H, m, 3 × ArC*H*H′α, 3 × ArC*H*H′β), 4.70 (0.5H, d, $J_{1,2}$ 7.83, H-1β), 4.78–5.02 (7H, m, 5 × ArC*H*H′α, 4 × ArC*H*H′β), 5.13–5.16 (0.5H, m, ArC*H*H′β), 5.19 (1H, br s, H-1α), 6.95–7.04 (2H, m, 3 × Ar-H), 7.13–7.19 (3H, m, 3 × Ar-H), 7.25–7.39 (22H, m, 21 × Ar-H); δ_C (100 MHz, $CDCl_3$) 67.7, 68.7 (2 × t, C-6α, C-6β), 68.8, 73.5, 75.1, 75.8 (4 × t, 4 × $ArCH_2$), 70.2 (d, C-5α/β), 74.6, 77.8, 77.8, 79.5 (4 × d, C-3α, C-3β, C-4α, C-4β), 81.8, (d, C-5α/β), 82.7 (d, C-2α), 84.4 (d, C-2β), 91.4 (d, C-1α), 97.4 (d, C-1 β), 126.0, 126.4, 126.7, 126.8, 126.8, 127.1, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.4, 128.4 (16 × d, 16 × Ar-CH), 137.7, 137.8, 138.2, 138.7, 140.6 (5 × s, 5 × Ar-C); *m/z* (ES^+) 564 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{32}H_{34}O_6$SNa (MNa^+) 569.1968. Found 569.1964). ($C_{32}H_{34}O_6S$ requires C, 70.31; H, 6.27. Found: C, 70.50; H, 6.25).

4.9. *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl) trichloroacetimidate 10

Hemiacetals **9** (0.700 g, 1.28 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 ml) at 0 °C under an argon atmosphere. DBU (0.078 ml, 0.51 mmol) was added followed by trichloroacetonitrile (1.31 ml, 12.8 mmol). After 5 h, TLC (petrol/ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.1). The reaction was concentrated in vacuo and the resulting residue was purified by flash column chromatography (petrol/ethyl acetate, 7:1, with 1% added triethylamine) to afford trichloroacetimidates **10** (0.710 g, 80%) as a pale yellow oil; ν_{max} (KBr) 3345 (w, NH), 1659 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [15:1 mixture of α:β anomers observed, major α anomer quoted] 3.67–3.70 (1H, m, H-5), 3.76–3.83 (3H, m, H-2, H-6, H-6′), 3.98–4.07 (2H, m, H-3, H-4), 4.49, 4.63 (2H, ABq, J_{AB} 12.0 Hz, $ArCH_2$), 4.54, 4.87 (2H, ABq, J_{AB} 10.6 Hz, $ArCH_2$), 4.83, 5.00 (2H, ABq, J_{AB} 10.8 Hz, $ArCH_2$), 4.85, 4.93 (2H, ABq, J_{AB} 12.1 Hz, $ArCH_2$), 6.52 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 6.97 (1H, dd, *J* 5.1, *J* 3.4 Ar-H), 7.00 (1H, m, Ar-H), 7.15–7.17 (2H, m, 2 × Ar-H), 7.27–7.38 (14H, m, 14 × Ar-H), 8.61 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 68.0 (t, C-6), 73.1 (d, C-4), 73.5, 73.6, 75.0, 75.4 (4 × t, 4 × $ArCH_2$), 78.8 (d, C-2), 81.3 (d, C-5), 84.4 (d, C-3), 94.4 (s, OC(NH)CCl_3), 97.6 (d, C-1), 126.2, 126.6, 126.9, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.4, 128.4, 128.6 (12 × d, 12 × Ar-CH), 137.8, 138.0, 138.6, 140.5, (4 × s, 4 × Ar-C), 163.6 (s, C=NH); *m/z* (ES^+) 709 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{34}H_{34}Cl_3NO_6$SNa (MNa^+) 714.0501. Found 714.0504).

4.10. General procedure for glycosylation with donors 10 and 18

A solution of either donor **10** or donor **18** (120 mmol) and the glycosyl acceptor (240 mmol, 2 equiv) in freshly distilled CH_2Cl_2 (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (0.100 g) under argon. The reaction mixture was cooled to −40 °C and stirred for 10 min, before

TMSOTf (0.012 mmol) was added. The reaction was monitored by TLC, and after the donor was consumed the reaction was quenched by the addition of saturated sodium bicarbonate solution and was filtered through Celite®. The mixture was then diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic extracts were then washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo and the resulting residue was purified by flash column chromatography.

4.11. 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(16)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside 12

R_f 0.4 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [1:1 mixture of α:β anomers observed] 1.34 (12H, br s, 2 × CH_3α, 2 × CH_3β), 1.46, 1.47, 1.53, 1.55 (12H, 4 × s, 2 × CH_3α, 2 × CH_3β), 3.44 (1H, m, H-5_bβ), 3.50 (1H, at, *J* 8.4 Hz, H-2_bβ), 3.59–3.86 (10H, m, H-2_aα, H-5_aα, H-2_aβ, H-5_aβ, H-2_bα, H-5_bα, H-6_bα, H-$6'_b$α, H-6_bβ, H-$6'_b$β), 3.99 (1H, at, *J* 9.4 Hz, H-4_bβ), 4.04–4.65 (12H, m, H-3_aα, H-4_aα, H-6_aα, H-$6'_a$α, H-3_aβ, H-4_aβ, H-6_aβ, H-$6'_a$β, H-3_bα, H-4_bα, H-1_aβ, H-3_aβ), 4.74–5.31 (16H, m, 8 × $PhCH_2$α, 8 × $PhCH_2$β), 5.00 (1H, d, $J_{1,2}$ 4.3 Hz, H-1_bα), 5.54 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aβ), 5.60 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aα) 6.95–7.38 (36H, m, 36 × Ar-CH); δ_C (100 MHz, $CDCl_3$) 66.3, 66.9 (2 × t, C-6_aα, C-6_aβ), 68.3, 68.7, (2 × t, C-6_bα, C-6_bβ), 70.0, 73.5, 75.1, 75.8 (4 × t, 4 × ArCH_2), 65.7, 67.4, 70.2, 70.5, 70.7, 70.9, 71.5, 74.7, 77.5, 79.3, 81.2, 81.9, 84.3 (13 × d, C-2_a-C-5_aα/β, C-2_b-C-5_bα/β), 95.4 (d, C-1_aβ), 96.3 (d, C-1_aα), 97.0 (d, C-1_bα), 104.4 (d, C-1_bβ), 125.9, 126.0, 126.5, 126.6, 127.2, 127.6, 127.6, 127.7, 127.7, 127.9, 127.9, 128.1, 128.2, 128.4 (14 × d, 14 × Ar-CH), 137.9, 138.1, 138.3, 138.7, 138.9, 140.9, 141.2 (7 × s, 7 × Ar-C); *m/z* (ES^+) 806 (M+NH_4^+, 100%). (HRMS (ES^+) Calcd for $C_{44}H_{52}O_{11}S_1Na$ (MNa^+) 811.3123. Found 811.3118).

4.12. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranoside 15

R_f 0.6 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [1.5:1 mixture of α:β anomers observed] 3.38–3.50 (3.33H, m, H-2α, H-2β, H-5α, H-5β), 3.60 (5H, br s, OCH_3), 3.61–3.65 (3.33H, m, H-3α, H-3β, H-4α, H-4β), 3.68–3.78 (3.33H, m, H-6α, H-6β, H-6′α, H-6′β), 4.29 (0.66H, d, $J_{1,2}$ 7.8 Hz, H-1β), 4.31 (1H, d, $J_{1,2}$ 3.0 Hz, H-1α), 4.51–4.98 (13.33H, m, 8 × Ar-CHα, 8 × Ar-CHβ), 6.75 (1.66H, m, Ar-CHα, Ar-CHβ), 6.91 (1.66H, m, Ar-CHα, Ar-CHβ), 7.15–7.17 (3.33H, m, 2 × Ar-CHα, 2 × Ar-CHβ), 7.28–7.37 (23.33H, m, 14 × Ar-CHα, 14 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) 57.1 (q, OCH_3), 68.8 (t, C-6), 73.5, 75.1, 75.3, 75.8 (4 × t, 4 × ArCH_2), 74.9 (d, C-5), 77.8 (d, C-3), 81.9 (d, C-2), 84.4 (d, C-4), 104.5 (d, C-1), 126.8, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.4, 129.3 (10 × d, 10 × Ar-CH), 138.0, 138.1, 138.5, 142.9 (4 × s, 4 × Ar-C); *m/z* (ES^+) 578 (M+NH_4^+, 100%). (HRMS (ES^+) Calcd for $C_{33}H_{36}O_6S_1Na$ (MNa^+) 583.2125. Found 583.2119).

4.13. 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(12)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 16

R_f 0.6 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [30:1 mixture of α:β anomers observed, data for the major α-anomer quoted] 3.38 (3H, br s, OCH_3), 3.50 (1H, m, H-5_b), 3.54–3.63 (3H, m, H-2_b, H-3_b, H-4_b), 3.68–3.71 (2H, m, H-6_b, H-$6'_b$), 3.80–3.83 (2H, m, H-5_a, H-6_a), 3.96 (1H, dd, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 9.9 Hz, H-3_a), 4.15 (1H, m, H-4_a), 4.24 (1H, m, H-2_a), 4.33 (1H, m, H-$6'_a$), 4.45, 4.51 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.47, 4.75 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.48 (1H, d, $J_{1,2}$ 4.0 Hz, H-1_b), 4.67, 4.85 (2H, ABq, J_{AB} 12.6 Hz, $PhCH_2$), 4.80, 4.97 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.82, 5.19 (2H, ABq, J_{AB} 11.4 Hz, $PhCH_2$), 4.84 (1H, s, H-1_a), 5.63 (1H, s, PhCH), 6.83 (1H, d, *J* 3.8 Hz, Ar-CH), 6.93 (1H, d, *J* 3.5 Hz, Ar-CH), 7.13–7.15 (2H, m, 2 × Ar-CH), 7.24–7.53 (24H, m, 24 × Ar-CH); selected ^{1}H NMR data for the β-anomer: 5.60 (0.03H, s, PhCH); δ_C (100 MHz, $CDCl_3$) 55.0 (q, OCH_3), 63.9 (d, C-5_a), 68.6, 69.1, 69.1, 71.0, 73.4, 75.2, 75.9 (7 × t, C-6_a, C-6_b, 5 × ArCH_2), 73.7, 74.9, 75.7, 77.4, 78.3, 81.2, 84.4 (7 × d, C-2_a, C-3_a, C-4_a, C-2_b, C-3_b, C-4_b, C-5_b), 99.8 (d, C-1_b), 101.6 (d, Ph*C*H), 102.8 (d, C-1_a), 126.1, 127.4, 127.7, 127.7, 127.9, 127.9, 128.0, 128.1, 128.2, 128.4, 128.4, 128.5, 128.9, 129.6 (14 × d, 14 × Ar-CH), 137.6, 137.8, 137.9, 138.4, 142.3 (5 × s, 5 × Ar-C); *m/z* (ES^+) 918 (M+NH_4^+, 100%). (HRMS (ES^+) Calcd for $C_{53}H_{56}O_{11}S_1Na$ (MNa^+) 923.3436. Found 923.3434).

4.14. 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(13)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 17

R_f 0.57 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [28:1 mixture of α:β anomers observed, data for the major α-anomer quoted] 3.36 (3H, s, OCH_3), 3.47 (1H, m, H-2_b), 3.52–3.69 (4H, m, H-3_b, H-4_b, H-5_b, H-6_b), 3.79–3.99 (4H, m, H-3_a, H-5_a, H-6_a, H-$6'_b$), 4.26 (1H, m, H-$6'_a$), 4.39 (2H, m, H-2_a, H-4_a), 4.47, 4.61 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 4.52, 4.59 (2H, ABq, J_{AB} 11.6 Hz, $PhCH_2$), 4.57 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_b), 4.58, 4.78 (2H, ABq, J_{AB} 10.6 Hz, $PhCH_2$), 4.72, 4.95 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.74 (1H, br s, H-1_a), 4.75, 4.90 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 5.58 (1H, s, PhCH), 6.76 (1H, d, *J* 3.8 Hz, Ar-CH), 6.79 (1H, d, *J* 3.5 Hz, Ar-CH), 7.15–7.48 (26H, m, 26 × Ar-CH); selected ^{1}H NMR data for the β-anomer: 3.37 (0.04H, s, OCH_3), 5.61 (0.04H, s, PhCH); δ_C (100 MHz, $CDCl_3$) 54.9 (q, OCH_3), 64.0 (d, C-5_a), 65.6, 68.6, 68.9, 73.5, 73.8, 75.0, 75.6 (7 × t, C-6_a, C-6_b, 5 × ArCH_2), 70.9, 73.0, 75.2, 77.3, 78.8, 81.2, 84.8 (7 × d, C-2_a, C-3_a, C-4_a, C-2_b, C-3_b, C-4_b, C-5_b), 99.8 (d, C-1_b), 101.3 (d, C-1_a), 102.5 (d, Ph*C*H), 126.0, 126.3, 126.4, 126.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 128.5, 129.0, 129.2, 129.3, 129.4 (24 × d, 24 × Ar-CH), 137.4, 138.0, 138.5, 138.6, 142.7 (5 × s, 5 × Ar-C); *m/z* (ES^+) 918 (M+NH_4^+, 100%). (HRMS (ES^+) Calcd for $C_{53}H_{56}O_{11}S_1Na$ (MNa^+) 923.3436. Found 923.3431).

4.15. 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(16)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside 19[26]

R_f 0.3 (petrol/ethyl acetate, 4:1); δ_H (400 MHz, $CDCl_3$) [1:4 mixture of α:β anomers observed] 1.32, 1.46, 1.51, 1.54 (15H, 4 × br s, 4 × CH_3α, 4 × CH_3β), 3.42–3.49 (2.5H, m, H-2_bα, H-5_bα, H-2_bβ, H-5_bβ), 3.57–3.85 (7.5H, m, H-2_aα, H-4_aα, H-5_aα, H-4_bα, H-6_bα, H-$6'_b$α, H-2_aβ, H-4_aβ, H-5_aβ, H-4_bβ, H-6_bβ, H-$6'_b$β), 3.99 (0.25H, at, *J* 9.2 Hz, H-3_bα), 4.02–4.11 (1.5H, m, H-3_bβ, H-6_aα, H-$6'_a$α), 4.17 (1H, dd, $J_{5,6}$ 3.5 Hz, $J_{6,6'}$ 10.8 Hz, H-6_aβ), 4.25 (1H, m, H-$6'_a$β), 4.31–4.37 (1.25H, m, H-3_aα, H-3_aβ), 4.46 (1H, d, $J_{1,2}$ 7.9 Hz, H-1_bβ), 4.49–5.07 (10H, 4 × $PhCH_2$α, 4 × $PhCH_2$β), 4.58 (0.25H, d, $J_{1,2}$ 2.4 Hz, H-1_bα), 5.53 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aα), 5.57 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aβ), 7.12–7.15 (2.5H, m, 2 × Ar-CHα, 2 × Ar-CHβ), 7.24–7.39 (20H, m, 16 × Ar-CHα, 16 × Ar-CHβ), 7.41–7.44 (2.5H, m, 2 × Ar-CHα, 2 × Ar-CHβ); *m/z* (ES^+) 800 (M+NH_4^+, 100%).

4.16. Methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside 20[27]

R_f 0.4 (petrol/ethyl acetate, 7:1); δ_H (400 MHz, $CDCl_3$) [1:8 mixture of α:β anomers observed, data for the major β-anomer quoted] 3.42–3.48 (2H, m, H-2, H-5), 3.55 (3H, s, OCH_3), 3.60–3.71 (3H, m, H-3, H-4, H-6), 3.76 (1H, dd, $J_{5,6}$ 2.1 Hz, $J_{6,6'}$ 10.9 Hz, H-6′), 4.32 (1H, d, $J_{1,2}$ 7.5 Hz, H-1), 4.53, 4.80 (2H, ABq, J_{AB} 11.3 Hz, $PhCH_2$), 4.56, 4.63 (2H, ABq, J_{AB} 12.3 Hz, $PhCH_2$), 4.72, 4.82 (2H, ABq, J_{AB}

10.9 Hz, $PhCH_2$), 4.92, 4.93 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 7.14–7.17 (2H, m, 2 × PhCH), 7.24–7.36 (18H, m, 18 × PhCH); *m/z* (ES^+) 554 ($M+NH_4^+$, 100%).

4.17. 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(12)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 21[26]

R_f 0.6 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.29 (4.5H, br s, $OCH_3\alpha$, $OCH_3\beta$), 3.57 (1H, dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.6 Hz, H-$2_b\alpha$), 3.60–3.70 (2H, m, H-$5_b\alpha$, H-$2_b\beta$, H-$5_b\beta$), 3.72–3.80 (4H, m, H-$4_b\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$6_b\beta$, H-$6'_b\beta$), 3.83–3.88 (3.5H, m, H-$3_a\alpha$, H-$5_a\alpha$, H-$3_b\beta$, H-$4_b\beta$, H-$5_a\beta$), 4.00–4.04 (3H, m, H-$2_a\alpha$, H-$6_a\alpha$, H-$2_a\beta$, H-$6_a\beta$), 4.20–4.23 (3H, m, H-$4_a\alpha$, H-$6'_a\alpha$, H-$4_a\beta$, H-$6'_a\beta$), 4.27–4.31 (1.5H, m, H-$3_a\alpha$, H-$3_a\beta$), 4.37–5.04 (15.5H, H-$1_a\alpha$, 10 × $PhCH_2\alpha$, 10 × $PhCH_2\beta$), 4.52 (0.5H, s, H-$1_a\beta$), 4.72 (1H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\alpha$), 5.50 (1H, s, PhCHα), 5.58 (1H, d, $J_{1,2}$ 3.8 Hz, H-$1_b\alpha$), 5.65 (0.5H, s, PhCHβ), 7.13–7.19 (6H, m, 4 × Ar-CHα, 4 × Ar-CHβ), 7.24–7.51 (39H, m, 26 × Ar-CHα, 26 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) [data for the major α-anomer quoted] 54.8 (q, OCH_3), 64.3 (d, C-5_a), 68.7, 68.8 (2 × t, C-6_a, C-6_b), 71.4, 73.5, 73.9, 75.2, 75.6 (5 × t, 5 × $ArCH_2$), 70.7, 74.6, 76.7, 77.5, 79.2, 81.4 (6 × d, C-2_a, C-3_a, C-4_a, C-3_b, C-4_b, C-5_b), 79.8 (d, C-2_b), 97.4 (d, C-1_b), 101.1 (d, C-1_a), 101.3 (d, PhCH), 126.0, 127.4, 127.5, 127.6, 127.7, 127.9, 127.9, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.8 (15 × d, 15 × Ar-CH), 137.8, 138.9, 138.2, 138.4, 139.0 (5 × s, 5 × Ar-C); *m/z* (ES^+) 912 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{44}H_{52}O_{11}S_1Na$ (MNa^+) 917.3871. Found 917.3870).

4.18. 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(13)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 22

R_f 0.63 (toluene/ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) [3:1 mixture of α:β anomers observed] 3.33 (1H, s, $OCH_3\beta$), 3.34 (3H, s, $OCH_3\alpha$), 3.52 (1.33H, m, H-$2_b\alpha$, H-$2_b\beta$), 3.56–3.71 (4.33H, m, H-$5_b\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$4_b\beta$, H-$5_b\beta$, H-$6_b\beta$, H-$6'_b\beta$), 3.80–3.90 (5.33H, m, H-$4_b\alpha$, H-$2_a\alpha$, H-$5_a\alpha$, H-$6_a\alpha$, H-$3_b\beta$, H-$2_a\beta$, H-$5_a\beta$, H-$6_a\beta$), 4.00 (1H, at, *J* 9.2 Hz, H-$3_b\alpha$), 4.23–4.39 (4H, m, H-$3_a\alpha$, H-$4_a\alpha$, H-$6'_a\beta$, H-$3_a\beta$, H-$4_a\alpha$, H-$6'_a\beta$), 4.43–4.99 (13.33H, 10 × $PhCH_2\alpha$, 10 × $PhCH_2\beta$), 4.59 (0.33H, d, $J_{1,2}$ 7.8 Hz, H-$1_b\beta$), 4.70 (0.33H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\beta$), 4.72 (1H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\alpha$), 5.47 (1H, s, PhCHα), 5.54 (1H, d, $J_{1,2}$ 3.8 Hz, H-$1_b\alpha$), 5.56 (0.33H, s, PhCHβ), 6.98–7.01 (1.33H, m, Ar-CHα, Ar-CHβ), 7.13–7.48 (38.66H, m, 29 × Ar-CHα, 29 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) [data for the major α-anomer quoted] 54.9 (q, OCH_3), 63.9 (d, C-5_a), 68.7, 69.0 (2 × t, C-6_a, C-6_b), 73.4, 73.5, 73.9, 75.0, 75.5 (5 × t, 5 × $ArCH_2$), 70.9, 72.8, 77.3, 77.4, 78.9 (5 × d, C-2_a, C-3_a, C-4_a, C-4_b, C-5_b), 79.7 (d, C-2_b), 81.4 (d, C-3_b), 96.9 (d, C-1_b), 100.0 (d, C-1_a), 102.4 (d, PhCH), 126.3, 126.4, 127.2, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3, 128.5, 129.3 (17 × d, 17 × Ar-CH), 137.4, 138.0, 138.3, 138.5, 138.7 (5 × s, 5 × Ar-C); *m/z* (ES^+) 912 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{44}H_{52}O_{11}S_1Na$ (MNa^+) 917.3871. Found 917.3868).

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