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Glycosylations Directed by the Armed-Disarmed Effect with Acceptors Containing a Single Ester Group

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A selective glycosylation reaction controlled by the armed-disarmed effect is described by the use of phenyl thioglycosides. The donor thioglycoside is fully protected with benzyl ethers while the acceptor thioglycoside contains benzyl ethers at position 2 and 3 and a strongly electron-withdrawing pentafluorobenzoate ester group at position 6. The coupling can be performed with galactose, glucose, mannose, and phthalimide-protected glucosamine to afford the corresponding 1,4-linked disaccharides in good yield. These disaccharides can act as glycosyl donors for an additional coupling reaction in the same pot if another acceptor and more promoter are added. In this way, two consecutive glycosylations can be achieved to afford trisaccharides in one operation.

Introduction

The role of oligosaccharides in biological processes has been studied intensively over the past two decades.[1] These studies have created an increasing demand for synthetic oligosaccharides and have stimulated research efforts directed toward the development of more efficient syntheses. A large number of glycosyl donors have been exploited[2] together with a variety of glycosylation techniques and strategies.[3] Although very powerful coupling methods have been developed, oligosaccharide synthesis is still plagued by multiple protecting group manipulations which are often necessary in order to control the regio- and diastereoselectivity in the glycosylation reactions.

In 1988, Fraser-Reid and co-workers coined the term "armed-disarmed effect" to describe the differences in reactivity between glycosyl donors depending on their protecting groups.[4] Ether-protected glycosyl donors are more reactive (armed) than ester-protected donors (disarmed) and a selective coupling can be achieved between an armed donor and a disarmed counterpart if the latter contains a free hydroxy group. The concept was initially established with *n*-pentenyl glycosides and later demonstrated with other glycosyl donors.[5] In 1999, the armed-disarmed principle was further developed by Wong and co-workers who described a "programmable one-pot synthesis" of smaller oligosaccharides.[6] The reactivity of a large number of tolyl thioglycosides was measured and these data were used to design selective coupling reactions between more reactive thioglycosides (serving as donors) and less reactive thioglycosides with a free hydroxy group (serving as acceptors).[6] Selective coupling reactions can also be achieved by controlling the reactivity of the leaving group in the glycosyl donor. Several leaving groups can be activated under conditions where others are completely stable, which makes it possible for the glycosyl component to serve either as a donor or as an acceptor depending on the promoter.[7] Thioglycosides are a special case because their reactivity depends on the steric bulk and the electronic properties of the aglycon, which makes it possible to perform a selective coupling reaction between two different thioglycosides.[8]

In the original work on the armed-disarmed effect the donor glycoside was fully protected with ether groups while the acceptor was protected with ester groups at all positions but one.[4] Most importantly, the 2-position in the acceptor always contained an ester group and this electron-withdrawing group close to the anomeric center plays a key role in lowering the reactivity of the acceptor. However, in subsequent coupling reactions this ester group will create a 1,2-*trans* linkage due to neighboring group participation. In our recent syntheses of pectic oligosaccharides we needed a number of galactans with a 1,2-*cis* linkage,[9] and we decided to investigate whether a single ester group at the 6-position would be sufficient to disarm a glycosyl acceptor. Indeed, we were able to show that coupling between **1** and **2** could be performed in 52% yield to give disaccharide **3** as a 6:1 α/β mixture[9b] (Scheme 1, PFBz = pentafluorobenzoyl). Disaccharide **3** was used in further coupling reactions to afford the 1,2-*cis* linked galactans.

Herein, this selective glycosylation reaction will be further explored with a series of phenyl thioglycosides. Perbenzylated phenyl thioglycosides will serve as donors and cou-

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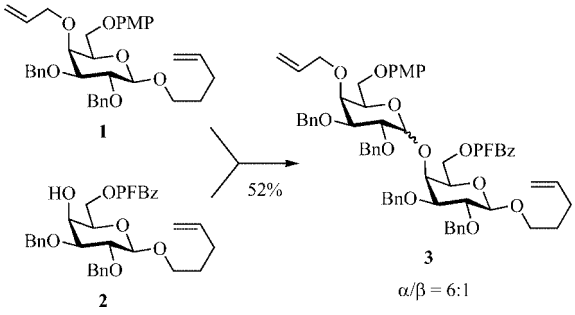
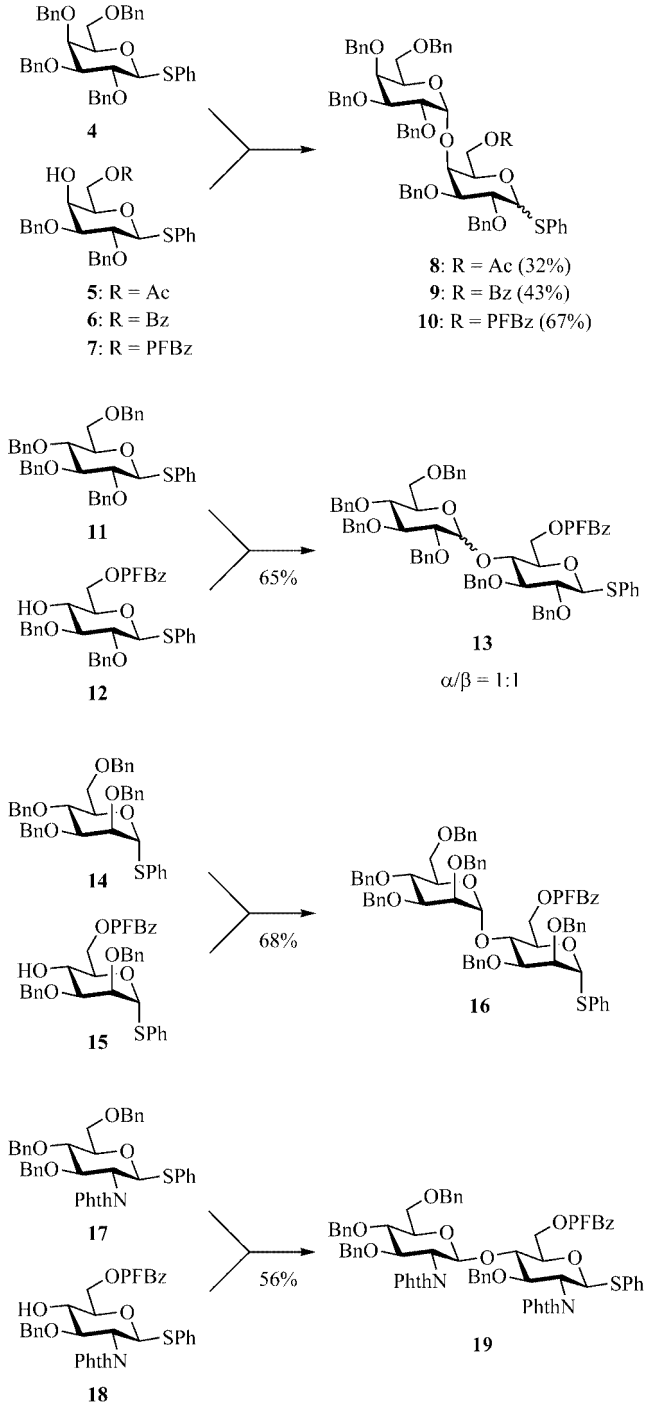


Scheme 1. Reagents and conditions: NIS, TESOTf, CH_2Cl_2, –20 °C.[9b]

pled to the 4-position in phenyl thioglycosides which contain a single ester group at position 6 and ether groups at postion 2 and 3.

Results and Discussion

Thioglycosides are very useful glycosyl donors and have been widely employed in oligosaccharide synthesis.[10] Phenyl thioglycosides are easily prepared from the corresponding peracetylated monosaccharides. Reaction with thiophenol and boron trifluoride etherate in dichloromethane installs the thiophenyl group at the anomeric center in high yield and with complete 1,2-*trans* selectivity directed by the neighboring acetoxy group.[11] Subsequent deacetylation and protection then gives rise to a range of thioglycosides which can serve as donors or acceptors in the selective coupling reactions. A majority of the prepared compounds turned out to be crystalline which further facilitated their synthesis. It was decided to investigate thioglycosides derived from D-galactose, D-glucose, D-mannose, and phthalimide-protected D-glucosamine. Galactose was chosen for the exploratory studies because this monosaccharide was also used in our earlier studies. Three galactosides **5**–**7** containing different ester groups at the 6-position were prepared and submitted to the coupling with the perbenzylated galactoside **4** (Scheme 2). The glycosylation reaction requires a strongly electrophilic promoter system, and it was soon discovered that NIS/TESOTf gave the best results while the weaker electrophiles DMTST and MeOTf reacted sluggishly and gave lower yields. The glycosylations were performed with 1.2 equiv. of the donor, 1.3 equiv. of NIS, and 0.2 equiv. of TESOTf at –20 °C. Under these conditions coupling between **4** and acetyl-protected **5** produced the desired disaccharide **8** in 32% yield. The yield increased to 43% when benzoyl-protected **6** was used in the coupling. In both cases, smaller amounts of byproducts were observed by TLC but were not further characterised. Fortunately, when the ester group was changed to the more electron-withdrawing pentafluorobenzoyl group, the yield of the cross-coupled product improved to 67%. This is in accordance with our earlier observations where the coupling with the pentafluorobenzoyl group gave a significantly higher yield than with the acetyl and the benzoyl group.[9b] The three glycosylations were performed with diethyl ether (short "ether" in the sequel) as the solvent. Notably, when the solvent was changed to dichloromethane, the yield in the last coupling fell to 56%. In all cases, only the α-anomer was observed at the new glycosidic linkage. However, some anomerisation of the thiophenyl linkage took place in the coupling with **7**. It is known that thioglycosides can undergo this epimerisation in the presence of an electrophile to form the more stable α-anomer.[12] The anomeric configurations were determined from the J_{CH} coupling constants



Scheme 2. Reagents and conditions: NIS, TESOTf, Et_2O, –20 °C.

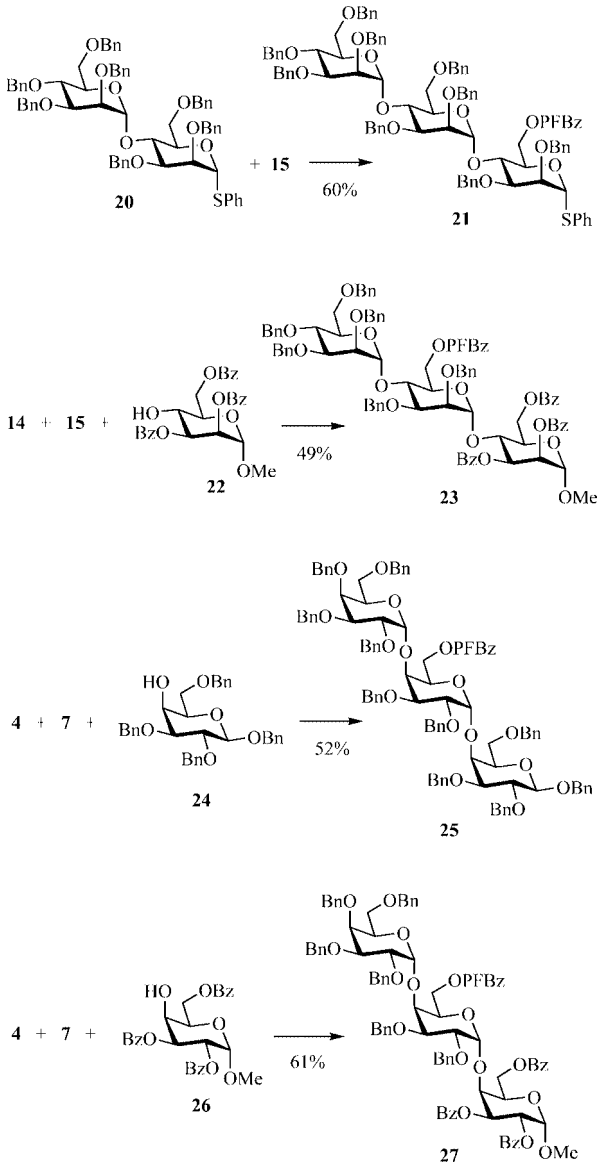
of the anomeric carbons. For the α-anomers the $J_{C-1,H-1}$ value was measured to about 170 Hz while the value for the β-anomer was around 160 Hz.[13]

To further explore the use of a single ester group to disarm the glycosyl acceptor, the selective coupling was also studied with glucose, mannose and glucosamine (Scheme 2). In these cases, only the pentafluorobenzoyl group was employed for protection of the acceptor. With glucose, the reaction between **11** and **12** furnished the disaccharide **13** in 65% yield when ether was used as the solvent. In dichloromethane the yield was only 42% while the coupling in acetonitrile gave 33% yield. Surprisingly, a 1:1 α/β mixture at the newly generated glycosidic linkage was obtained in all three solvents even though ether is supposed to favour the α-product and acetonitrile the β-product.[14] In this case, no epimerisation was observed around the thiophenyl linkage. With mannose, coupling between **14** and **15** gave disaccharide **16** in 68% yield when ether was used as the solvent while the yield dropped to 57% in dichloromethane. With phthalimide-protected glucosamine, reaction between **17** and **18** gave the chitibiose-derivative **19** in 56% yield with ether as the solvent and 45% yield with dichloromethane as the solvent. These results clearly show that the preferred solvent is ether which is known to decrease the rate of a glycosylation as compared to dichloromethane.[14]

Following the successful synthesis of several disaccharides by the selective coupling it was decided to extend the investigation to the synthesis of trisaccharides. First, it was studied whether a disaccharide could serve as the donor. Thus, dimannan **16** was converted into the corresponding perbenzylated compound **20** (Scheme 3). Subsequent coupling with acceptor **15** gave trimannan **21** in 60% yield. The reaction was carried out in ether and other solvents were not investigated in this case.

Another approach to trisaccharides would involve two consecutive glycosylations with monosaccharides in the same pot.[15] Therefore, monosaccharides **14** and **15** were mixed in ether at –20 °C followed by addition of NIS and TESOTf. After 35 min TLC showed the formation of disaccharide **16** which was not isolated. Instead, monosaccharide **22** and more NIS were added and the mixture was stirred at –20 °C for an additional 40 min. This resulted in trimannan **23** in 49% yield. It was also attempted to form the trisaccharide by mixing the three monosaccharides **14**, **15**, and **22** in the same flask followed by addition of excess NIS/TESOTf. However, only a very small amount of trimannan **23** was formed in this case while the main product resulted from a coupling between **14** and **22**. This disaccharide was isolated in 55% yield which indicates that tribenzoyl mannoside **22** is more reactive as an acceptor than pentafluorobenzoyl mannoside **15**.

The same experiments were also performed with galactose. Monosaccharides **4** and **7** were reacted in ether for 10 min followed by addition of **24** and more NIS. This gave the trigalactan **25** in 52% yield with a 1,2-*cis* linkage at the two new glycosidic bonds. When the tribenzoyl galactoside **26** was added to the reaction mixture the yield of the corresponding trigalactan increased to 61%. Again, it was attempted to form the trisaccharide by reacting **4**, **7**, and **26** at the same time. However, this experiment gave the same result as observed with mannose and the main product was a disaccharide from coupling between **4** and **26**. As a result, the step-wise addition procedure is necessary in order to achieve two glycosylations in the same pot.



Scheme 3. Reagents and conditions: NIS, TESOTf, Et_2O, –20 °C.

Conclusions

In summary, we have further developed a selective glycosylation reaction based on the armed-disarmed effect. Two phenyl thioglycosides can be coupled in good yield when the reactivity of the acceptor is decreased by a single pentafluorobenzoate ester at the 6-position. An additional glycosylation reaction can be performed in the same pot if another acceptor and more promoter are added to the reac-

tion mixture. This method gives easy access to a number of useful di- and trisaccharide building blocks for oligosaccharide synthesis.

Experimental Section

General: CH_2Cl_2 was dried by distillation from CaH_2 while diethyl ether was dried by distillation from sodium/benzophenone. NIS was recrystallised from dioxane/CCl_4. Reactions were conducted under nitrogen when anhydrous solvents were used. All reactions were monitored by TLC using aluminium plates precoated with silica gel 60. Compounds were visualized by dipping in a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $Ce(SO_4)_2$ (10 g/L) in 10% aqueous H_2SO_4 followed by heating. Melting points are uncorrected. Flash column chromatography was performed with E. Merck silica gel 60 (particle size 0.040–0.063 mm). Optical rotations were measured with a Perkin–Elmer 241 polarimeter while IR spectra were recorded with a Perkin–Elmer 1720 Infrared Fourier Transform spectrometer. NMR spectra were recorded with a Varian Mercury 300 instrument. Me_4Si was used as the internal standard in ^1H NMR while $CDCl_3$ (δ = 77.16 ppm) served as the internal standard in ^{13}C NMR spectroscopy. Microanalyses were obtained at the Microanalytical Laboratory, University of Vienna while high-resolution mass spectra were recorded at the Department of Physics and Chemistry, University of Southern Denmark. The glycosyl donors **4**, **11**, **14**, and **17** were prepared according to literature procedures.[16]

Phenyl 6-*O*-Acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (5): To an ice-cooled solution of phenyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside[17] (1.50 g, 3.31 mmol) in CH_2Cl_2 (12 mL) were added Et_3N (0.65 mL, 4.66 mmol) and Ac_2O (0.33 mL, 3.49 mmol). The mixture was stirred at 5 °C for 18 h and then washed with 0.1 M HCl (2 × 20 mL), dried ($MgSO_4$), and concentrated to afford a crystalline residue, which was recrystallised from heptane/EtOAc to give 1.39 g (85%) of **5**. R_f = 0.17 (heptane/EtOAc, 7:3). M.p. 135–137 °C (heptane/EtOAc). $[\alpha]_D^{20}$ = +8.1 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1717, 1275, 1090, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.21 (m, 15 H), 4.85–4.70 (m, 4 H), 4.61 (d, *J* = 9.8 Hz, 1 H), 4.36–4.32 (m, 2 H), 3.98 (d, *J* = 3.2 Hz, 1 H), 3.73 (t, *J* = 9.2 Hz, 1 H), 3.64 (d, *J* = 5.6 Hz, 1 H), 3.58 (dd, *J* = 3.2, 8.9 Hz, 1 H), 2.42 (br. s, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.94, 138.09, 137.53, 133.86, 131.95–127.54 (15 C), 87.68, 82.30, 76.95, 75.88, 75.70, 72.45, 66.73, 63.51, 20.99 ppm. $C_{28}H_{30}O_6S$ (494.6): calcd. C 67.99, H 6.11, S 6.48; found C 67.41, H 6.52, S 6.09.

Phenyl 6-*O*-Benzoyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (6): Phenyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside[17] (1.50 g, 3.31 mmol) was treated with BzCl (0.40 mL, 3.44 mmol) as described above to give the crude product as a solid, which was recrystallised from heptane/EtOAc to furnish 1.69 g (92%) of **6**. R_f = 0.28 (heptane/EtOAc, 7:3). M.p. 161–164 °C (heptane/EtOAc) (ref.[18] M.p. 151.5–152 °C). $[\alpha]_D^{20}$ = –1.7 (*c* = 1.0, $CHCl_3$) [ref.[18] $[\alpha]_D^{20}$ = –3.8 (*c* = 1.1, $CHCl_3$)]. IR (KBr): $\tilde{\nu}$ = 1709, 1285, 1119, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04–7.09 (m, 20 H), 4.81 (d, *J* = 10.3 Hz, 1 H), 4.70 (d, *J* = 10.3 Hz, 1 H), 4.67–4.65 (m, 2 H), 4.60 (d, *J* = 9.8 Hz, 1 H), 4.57–4.48 (m, 2 H), 4.04 (d, *J* = 3.2 Hz, 1 H), 3.80–3.73 (m, 2 H), 3.61 (dd, *J* = 3.2, 8.9 Hz, 1 H), 2.54 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.47, 138.11, 137.57, 134.16, 133.31, 131.65–127.40 (20 C), 87.98, 82.30, 77.14, 75.96, 75.88, 72.59, 67.00, 64.10 ppm. $C_{33}H_{32}O_6S$ (556.7): calcd. C 71.20, H 5.79, S 5.76; found C 70.93, H 5.91, S 5.48.

Phenyl 2,3-Di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-β-D-galactopyranoside (7): To an ice-cooled solution of phenyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside[17] (5.00 g, 11.0 mmol) and Et_3N (2.17 mL, 15.6 mmol) in CH_2Cl_2 (25 mL) was added pentafluorobenzoyl chloride (1.64 mL, 11.4 mmol) in a dropwise fashion over 45 min. The mixture was stirred for 1 h at room temperature and then washed with 0.1 M HCl (2 × 20 mL), dried ($MgSO_4$), and concentrated to afford a crystalline residue, which was recrystallised from heptane/EtOAc to give 4.98 g (70%) of **7**. R_f = 0.26 (heptane/EtOAc, 4:1). M.p. 152–153 °C. $[\alpha]_D^{20}$ = +5.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3036, 1733, 1497, 1009, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.21 (m, 15 H), 4.83 (d, *J* = 10.3 Hz, 1 H), 4.72 (d, *J* = 10.3 Hz, 1 H), 4.69–4.64 (m, 3 H), 4.61 (d, *J* = 9.7 Hz, 1 H), 4.54 (dd, *J* = 4.8, 11.6 Hz, 1 H) 4.02 (d, *J* = 3.0 Hz, 1 H), 3.75–3.71 (m, 2 H), 3.61 (dd, *J* = 3.2, 8.9 Hz, 1 H), 2.49 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.83, 138.09, 137.48, 133.70, 132.05–127.61 (15 C), 88.01, 82.12, 76.96, 75.96, 75.40, 72.66, 66.84, 65.53 ppm. $C_{33}H_{27}F_5O_6S$ (646.6): calcd. C 61.30, H 4.21, F 14.69, S 4.96; found C 61.08, H 4.13, F 14.78, S 4.74.

General Procedure for Glycosylation Reactions: A mixture of the perbenzylated donor (0.93 mmol) and the ester-protected acceptor (0.77 mmol) was dried azeotropically with toluene and stored under high vacuum for 1 h. The mixture was dissolved in anhydrous Et_2O (15 mL) under a nitrogen atmosphere, cooled to –20 °C, followed by addition of NIS (0.23 g, 1.02 mmol) and TESOTf (0.04 mL, 0.18 mmol). The dark red solution was stirred at –20 °C until TLC revealed full conversion of the donor (10–45 min). The reaction was quenched with Et_3N, diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous $Na_2S_2O_3$ (2 × 20 mL) and saturated aqueous $NaHCO_3$ (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated and the residue purified by flash chromatography.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (8): The coupling between **4** and **5** was performed according to the general procedure and stopped after 20 min to afford 32% yield of **8**. R_f = 0.18 (heptane/EtOAc, 4:1). $[\alpha]_D^{20}$ = +8.1 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3030, 1709, 1454, 1098, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.19 (m, 35 H), 5.72 (d, *J* = 5.2 Hz, 1 H), 4.91 (d, *J* = 11.2 Hz, 1 H), 4.86–4.00 (m, 20 H), 3.89 (dd, *J* = 2.5, 10.2 Hz, 1 H), 3.72 (dd, *J* = 2.6, 9.9 Hz, 1 H), 3.52 (t, *J* = 7.9 Hz, 1 H), 3.23 (dd, *J* = 4.8, 8.2 Hz, 1 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.51, 138.95, 138.81, 138.66, 138.31, 138.08, 138.00, 134.35, 131.74–127.10 (35 C), 100.55 (d, *J* = 171.1 Hz), 86.90 (d, *J* = 158.9 Hz), 79.47, 77.95, 76.27, 75.74, 75.22, 74.91, 74.58, 74.17, 73.28, 73.00, 72.51, 72.43, 69.82, 69.61, 67.90, 62.49, 20.88 ppm. $C_{62}H_{64}O_{11}S$ (1017.3): calcd. C 73.21, H 6.34, S 3.15; found C 72.81, H 6.37, S 2.47.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (9): The coupling between **4** and **6** was performed according to the general procedure and stopped after 20 min to afford 43% yield of **9**. R_f = 0.24 (heptane/EtOAc, 4:1). $[\alpha]_D^{20}$ = –1.7 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3030, 1709, 1453, 1097, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.07 (m, 40 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.93 (d, *J* = 11.7 Hz, 1 H), 4.92 (d, *J* = 11.7 Hz, 1 H), 4.81–4.52 (m, 12 H), 4.35 (dd, *J* = 5.2, 8.4 Hz, 1 H), 4.17–4.11 (m, 4 H), 4.04 (dd, *J* = 2.4, 9.9 Hz, 1 H), 3.81–3.70 (m, 2 H), 3.57–3.46 (m, 2 H), 3.27 (dd, *J* = 4.8, 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.13, 138.87, 138.78, 138.47, 138.29, 138.26, 137.96, 134.04, 133.30, 131.66–127.33 (40 C), 100.80 (d, *J* = 171.0 Hz), 87.53 (d, *J*

= 159.2 Hz), 82.60, 79.38, 76.60, 76.17, 75.98, 75.66, 75.31, 74.97, 74.36, 74.25, 73.30, 72.60, 72.12, 69.56, 67.98, 62.79 ppm. $C_{67}H_{66}O_{11}S$ (1079.3): calcd. C 74.56, H 6.16, S 2.97; found C 74.64, H 6.65, S 2.76.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-α/β-D-galactopyranoside (10α and 10β): The coupling between **4** and **7** was performed according to the general procedure and stopped after 45 min to give 67% yield of **10** as a 4:3 α/β mixture.

For 10α: R_f = 0.15 (heptane/EtOAc, 17:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.04 (m, 35 H), 5.64 (d, J = 6.8 Hz, 1 H), 4.83–4.45 (m, 13 H), 4.34 (t, J = 5.9 Hz, 1 H), 4.23 (dd, J = 3.9, 7.1 Hz, 1 H), 4.13–3.93 (m, 6 H), 3.81 (dd, J = 2.4, 10.3 Hz, 1 H), 3.63 (dd, J = 2.6, 9.8 Hz, 1 H), 3.45 (t, J = 8.6 Hz, 1 H), 3.18 (dd, J = 3.7, 7.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.94, 138.78, 138.64, 138.29, 138.11, 137.98, 134.37, 131.21–126.85 (35 C), 100.75 ($J_{C,H}$ = 170.4 Hz), 86.79 ($J_{C,H}$ = 170.2 Hz), 79.57, 77.77, 76.43, 76.22, 75.18, 75.02, 74.56, 74.53, 73.38, 73.16, 72.66, 72.44, 69.78, 69.65, 67.98, 64.45 ppm. HRMS: calcd. for $C_{67}H_{65}F_5NO_{11}S$ $[M + NH_4]^+$ 1186.4194; found 1186.4185.

For 10β: R_f = 0.18 (heptane/EtOAc, 17:3). $[\alpha]_D^{20}$ = +34.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.02 (m, 35 H), 4.85–4.79 (m, 2 H), 4.69–4.29 (m, 12 H), 4.17 (dd, J = 5.1, 8.4 Hz, 1 H), 4.08–3.87 (m, 6 H), 3.63 (t, J = 9.4 Hz, 1 H), 3.55 (t, J = 6.2 Hz, 1 H), 3.42 (t, J = 8.6 Hz, 1 H), 3.36 (dd, J = 1.9, 9.2 Hz, 1 H), 3.18 (dd, J = 5.3, 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.90, 138.77, 138.53, 138.28, 138.28, 138.00, 133.67, 132.11–127.40 (35 C), 100.75 ($J_{C,H}$ = 171.0 Hz), 87.58 ($J_{C,H}$ = 160.4 Hz), 82.29, 80.59, 79.43, 79.41, 76.39, 75.92, 75.68, 75.00, 74.48, 74.39, 73.38, 72.60, 72.19, 69.75, 68.10, 64.55 ppm. HRMS: calcd. for $C_{67}H_{65}F_5NO_{11}S$ $[M + NH_4]^+$ 1186.4194; found 1186.4186.

Phenyl 2,3-Di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-β-D-glucopyranoside (12): Phenyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside[19] (10.6 g, 23.4 mmol) was treated with pentafluorobenzoyl chloride (3.6 mL, 25.0 mmol) as described above for **7**. The crude product was crystallised from heptane/EtOAc to afford 14.2 g (94%) of **12**. R_f = 0.26 (heptane/EtOAc, 4:1). M.p. 119–120 °C (heptane/EtOAc). $[\alpha]_D^{20}$ = –32.3 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3031, 1734, 1494, 1008, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.20 (m, 15 H), 4.96 (d, J = 11.5 Hz, 1 H), 4.95 (d, J = 11.2 Hz, 1 H), 4.74 (d, J = 8.3 Hz, 1 H), 4.72–4.66 (m, 3 H), 4.57 (dd, J = 4.1, 12.5 Hz, 1 H), 3.57–3.49 (m, 4 H), 2.38 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.11, 137.73, 133.29, 132.13–127.74 (15 C), 87.88, 85.82, 80.48, 76.91, 75.58, 75.45, 69.59, 65.40 ppm. $C_{33}H_{27}F_5O_6S$ (646.6): calcd. C 61.30, H 4.21, F 14.69, S 4.96; found C 61.12, H 4.13, F 14.52, S 4.74.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-β-D-glucopyranoside (13): The coupling between **11** and **12** was performed according to the general procedure and stopped after 10 min to give 65% yield of **13** as a 1:1 α/β mixture which could not be separated. R_f = 0.18 (heptane/EtOAc, 9:1). IR (KBr): $\tilde{\nu}$ = 3063, 1742, 1498, 1071, 737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.10 (m, 70 H), 5.43 (d, J = 3.7 Hz, 1 H), 5.14 (d, J = 11.2 Hz, 1 H), 4.98 (d, J = 11.7 Hz, 1 H), 4.91–4.34 (m, 29 H), 3.98–3.39 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.95, 138.95, 138.76, 138.57, 138.51, 138.36, 138.26, 138.08, 138.08, 138.08, 137.83, 137.79, 133.26, 133.06, 132.69–126.59 (70 C), 102.91 ($J_{C,H}$ = 159.8 Hz), 98.57 ($J_{C,H}$ = 169.6 Hz), 87.51 ($J_{C,H}$ = 160.1 Hz, 2 C), 86.02, 85.08, 84.54, 82.84, 81.93, 80.81, 80.18, 79.20, 77.90, 77.70, 76.93, 76.56, 75.94, 75.84, 75.71, 75.63, 75.58, 75.48, 75.33, 75.23, 75.12, 74.79, 73.63, 73.58, 73.36, 71.73, 68.86, 68.27, 65.73, 65.70, 64.48, 64.45 ppm. $C_{67}H_{61}F_5O_{11}S$ (1169.3): calcd. C 68.82, H 5.26, F 8.12, S 2.74; found C 68.98, H 5.28, F 8.09, S 2.61.

Phenyl 2,3-Di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-α-D-mannopyranoside (15): Phenyl 2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside[20] (3.00 g, 6.63 mmol) was treated with pentafluorobenzoyl chloride (1.01 mL, 7.01 mmol) as described above for **7**. The crude product was purified by flash chromatography (heptane/EtOAc, 4:1) to give 2.98 g (70%) of **15** as a solid. R_f = 0.26 (heptane/EtOAc, 4:1). M.p. 116–118 °C (heptane/EtOAc). $[\alpha]_D^{20}$ = +40.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3069, 1742, 1497, 1010, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.23 (m, 15 H), 5.68 (d, J = 1.7 Hz, 1 H), 4.75–4.50 (m, 6 H), 4.42 (ddd, J = 2.4, 5.3, 9.4 Hz, 1 H), 4.15 (t, J = 9.6 Hz, 1 H), 4.08 (dd, J = 1.7, 2.9 Hz, 1 H), 3.73 (dd, J = 2.9, 9.4 Hz, 1 H), 2.61 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.12, 137.64, 137.58, 134.08, 131.32–127.62 (15 C), 85.79, 79.54, 75.37, 72.12, 71.78, 71.25, 66.64, 65.79 ppm. $C_{33}H_{27}F_5O_6S$ (646.6): calcd. C 61.30, H 4.21, F 14.69, S 4.96; found C 61.25, H 4.29, F 14.59, S 4.86.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-α-D-mannopyranoside (16): The coupling between **14** and **15** was performed according to the general procedure and stopped after 35 min to afford 68% yield of **16**. R_f = 0.25 (heptane/EtOAc, 17:3). $[\alpha]_D^{20}$ = +60.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3063, 1740, 1498, 1104, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.02 (m, 35 H), 5.47 (d, J = 1.6 Hz, 1 H), 5.17 (d, J = 1.8 Hz, 1 H), 4.71 (d, J = 10.7 Hz, 1 H), 4.48–4.31 (m, 10 H), 4.24–4.16 (m, 4 H), 4.07 (t, J = 9.3 Hz, 1 H), 3.94 (t, J = 9.2 Hz, 1 H), 3.88–3.84 (m, 1 H), 3.77 (dd, J = 1.7, 9.3 Hz, 1 H), 3.71–3.52 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.78, 138.78, 138.57, 138.51, 137.70, 137.70, 134.01, 131.33–127.30 (35 C), 100.83 ($J_{C,H}$ = 171.0 Hz), 85.41 ($J_{C,H}$ = 169.0 Hz), 79.80, 79.79, 75.79, 75.79, 75.29, 75.17, 74.67, 73.33, 73.26, 72.21, 72.10, 71.99, 71.42, 70.34, 68.91, 65.84 ppm. $C_{67}H_{61}F_5O_{11}S$ (1169.3): calcd. C 68.82, H 5.26, S 2.74; found C 68.62, H 5.44, S 2.56.

Phenyl 3-*O*-Benzyl-2-deoxy-6-*O*-pentafluorobenzoyl-2-phthalimido-1-thio-β-D-glucopyranoside (18): Phenyl 3-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[21] (5.00 g, 10.2 mmol) was treated with pentafluorobenzoyl chloride (1.55 mL, 10.8 mmol) as described above for **7**. The crude product was purified by flash chromatography (heptane/EtOAc, 7:3) to afford 5.09 g (73%) of **18** as a solid. R_f = 0.23 (heptane/EtOAc, 7:3). M.p. 149–151 °C (heptane/EtOAc). $[\alpha]_D^{20}$ = +40.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3063, 1751, 1764, 1715, 1389, 1087, 719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.70 (m, 4 H), 7.34–6.95 (m, 10 H), 5.55 (d, J = 10.0 Hz, 1 H), 4.76–4.62 (m, 3 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.32–4.19 (m, 2 H), 3.79 (ddd, J = 2.2, 4.9, 9.9 Hz, 1 H), 3.69 (dd, J = 7.9, 9.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.41, 167.36, 137.79, 134.29–123.56 (17 C), 83.76, 80.23, 77.38, 74.94, 71.50, 65.39, 54.42 ppm. $C_{34}H_{24}F_5NO_7S$ (685.6): calcd. C 59.56, H 3.53, F 13.86, N 2.04, S 4.68; found C 59.69, H 3.59, F 13.83, N 2.08, S 4.64.

Phenyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-pentafluorobenzoyl-2-phthalimido-1-thio-β-D-glucopyranoside (19): The coupling between **17** and **18** was performed according to the general procedure and stopped after 15 min to afford 56% yield of **19**. R_f = 0.12 (heptane/EtOAc, 17:3). $[\alpha]_D^{20}$ = +25.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3062, 1777, 1744, 1716, 1387, 1084, 721 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.53 (m, 8 H), 7.40–6.74 (m, 25 H), 5.35 (d, J = 9.9 Hz, 1 H), 5.33 (d, J = 7.9 Hz, 1 H), 4.91 (d, J = 13.0 Hz, 1 H),

4.81–4.10 (m, 12 H), 4.02 (dd, J = 8.6, 9.4 Hz, 1 H), 3.93–3.70 (m, 4 H), 3.58–3.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.89 (2 C), 167.73 (2 C), 138.51, 138.13, 137.97, 137.94, 133.05–123.36 (38 C), 97.73 ($J_{C,H}$ = 160.6 Hz), 83.54 ($J_{C,H}$ = 159.2 Hz), 80.27, 79.53, 78.97, 78.24, 75.19, 75.08, 75.03, 74.95, 73.40, 71.47, 68.22, 64.11, 56.63, 54.69 ppm. $C_{69}H_{55}F_5N_2O_{13}S$ (1247.3): calcd. C 66.45, H 4.44, F 7.62, N 2.25, S 2.57; found C 66.39, H 4.62, F 7.88, N 2.20, S 2.46.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (20): To a solution of **16** (0.86 g, 0.74 mmol) in MeOH (25 mL) was added sodium (70 mg, 3.0 mmol) and the mixture was heated to 50 °C for 20 min. The reaction was cooled to room temperature and quenched with Amberlite IR-120 (H^+) ion-exchange resin (10 mL). The mixture was stirred for 10 min, filtered and concentrated. The residue was purified by flash chromatography (heptane/EtOAc, 7:3) to give 0.72 g (0.74 mmol) of a syrup (R_f = 0.20, heptane/EtOAc, 7:3). To an ice-cooled solution of this in DMF (9 mL) were added Bu_4NI (20 mg, 0.06 mmol), NaH (50 mg of a 50% oil dispersion, 1.0 mmol) and BnBr (0.17 mL, 1.4 mmol). The reaction was stirred at room temperature for 16 h and then quenched with AcOH. The mixture was diluted with Et_2O (20 mL), washed with water (2 × 25 mL), dried ($MgSO_4$), evaporated to dryness, and purified by flash chromatography (heptane/EtOAc, 4:1) to afford 0.61 g (78%) of **20** as a syrup. R_f = 0.23 (heptane/EtOAc, 3:1). $[\alpha]_D^{20}$ = +41.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.15 (m, 40 H), 5.59 (d, J = 1.7 Hz, 1 H), 5.32 (d, J = 1.8 Hz, 1 H), 4.86 (d, J = 10.8 Hz, 1 H), 4.68–4.31 (m, 13 H), 4.13 (t, J = 9.3 Hz, 1 H), 4.01–3.65 (m, 10 H), 3.58 (dd, J = 1.7, 10.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.82, 138.80, 138.71, 138.67, 138.57, 137.88, 137.81, 134.18, 132.11–127.35 (40 C), 100.21 (d, J = 170.2 Hz), 85.48 (d, J = 170.8 Hz), 80.20, 79.96, 75.83, 75.34, 75.17, 75.03, 74.87, 73.50, 73.15, 73.10, 72.22, 72.16, 72.02, 71.78, 71.21, 70.15, 69.38 ppm. $C_{67}H_{68}O_{10}S$ (1065.3): calcd. C 75.54, H 6.43, S 3.01; found C 75.82, H 6.76, S 2.56.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-1-thio-α-D-mannopyranoside (21): The coupling between **20** and **15** was performed according to the general procedure and stopped after 25 min to afford 60% yield of **21**. R_f = 0.17 (heptane/EtOAc, 4:1). $[\alpha]_D^{20}$ = +37.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3030, 1741, 1498, 1052, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.13 (m, 50 H), 5.62 (d, J = 1.6 Hz, 1 H), 5.30 (d, J = 1.7 Hz, 1 H), 5.29 (d, J = 1.7 Hz, 1 H), 4.81 (dd, J = 3.0, 11.2 Hz, 1 H), 4.68 (dd, J = 4.6, 12.0 Hz, 1 H), 4.63–4.02 (m, 21 H), 3.98 (d, J = 9.6 Hz, 1 H), 3.85–3.60 (m, 11 H) 3.46 (dd, J = 1.6, 10.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.07, 138.99, 138.96, 138.86, 138.70, 138.68, 138.43, 137.78, 137.73, 134.11, 131.38–127.29 (50 C), 100.65 ($J_{C,H}$ = 170.7 Hz), 100.11 ($J_{C,H}$ = 169.6 Hz), 85.35 ($J_{C,H}$ = 170.2 Hz), 80.30, 79.93, 75.85, 75.58, 75.27, 74.95, 74.90, 74.44, 74.41, 73.58, 73.39, 73.04, 72.18, 72.14, 72.14, 72.11, 71.40, 70.67, 70.13, 70.10, 69.19, 65.98, 65.95, 65.91 ppm. $C_{94}H_{89}F_5O_{16}S$ (1601.8): calcd. C 70.49, H 5.60, S 2.00; found C 69.99, H 5.81, S 1.85.

Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-α-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (23): The glycosylation between **14** and **15** was carried out in accordance with the general procedure. A solution of **22**[22] (1.1 equiv.) in Et_2O and more NIS (1.5 equiv.) were added after 35 min and the mixture was stirred at –20 °C for an additional 40 min. The reaction was worked up as described above to afford 49% yield of **23**. R_f = 0.28 (heptane/EtOAc, 7:3). $[\alpha]_D^{20}$ = +7.1 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3064, 1727, 1498, 1070, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–6.81 (m, 45 H), 5.78 (dd, J = 3.3, 9.6 Hz, 1 H), 5.57 (dd, J = 1.8, 3.2 Hz, 1 H), 4.92 (dd, J = 1.9, 11.9 Hz, 1 H), 4.88 (d, J = 1.8 Hz, 1 H), 4.79 (d, J = 10.7 Hz, 1 H), 4.73 (d, J = 11.9 Hz, 1 H), 4.65–4.31 (m, 9 H), 4.31–4.25 (m, 3 H), 4.21–3.96 (m, 6 H), 3.87 (d, J = 4.5 Hz, 1 H), 3.85 (dd, J = 2.8, 9.4 Hz, 1 H), 3.78–3.69 (m, 5 H), 3.58 (dd, J = 3.7, 12.3 Hz, 1 H), 3.51 (t, J = 2.4 Hz, 1 H), 3.47 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.94, 165.36, 165.23, 138.84, 138.74, 138.52, 138.50, 137.82, 137.76, 133.82, 133.64, 133.29, 129.78–126.94 (45 C), 100.76 ($J_{C,H}$ = 171.0 Hz), 100.67 ($J_{C,H}$ = 171.0 Hz), 98.49 ($J_{C,H}$ = 170.1 Hz), 79.94, 79.25, 75.79, 75.15, 74.92, 74.73, 74.64, 73.98, 73.32, 73.19, 72.76, 72.70, 72.56, 72.16, 71.37, 71.16, 70.46, 69.60, 68.80, 65.98, 62.97, 55.58 ppm. HRMS: calcd. for $C_{89}H_{85}F_5NO_{20}$ $[M + NH_4]^+$ 1582.5580; found 1582.5534.

Benzyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (25): The glycosylation between **4** and **7** was carried out in accordance with the general procedure. A solution of **24**[23] (1.1 equiv.) in Et_2O and more NIS (1.5 equiv.) were added after 10 min and the mixture was stirred at –20 °C for an additional 10 min. The reaction was worked up as described above to afford 52% yield of **25**. R_f = 0.08 (heptane/EtOAc, 17:3). $[\alpha]_D^{20}$ = +39.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3061, 1741, 1498, 1098, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.14 (m, 50 H), 5.09 (d, J = 3.0 Hz, 1 H), 4.97–4.51 (m, 18 H), 4.43–4.29 (m, 6 H), 4.12–3.87 (m, 10 H), 3.68–3.48 (m, 4 H), 3.55 (dd, J = 2.7, 9.9 Hz, 1 H), 3.16 (dd, J = 4.6, 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.90, 138.84, 138.84, 138.80, 138.68, 138.59, 138.34, 138.22, 138.17, 137.75, 128.58–127.28 (50 C), 102.96 ($J_{C,H}$ = 160.9 Hz), 100.63 ($J_{C,H}$ = 169.6 Hz), 100.20 ($J_{C,H}$ = 169.6 Hz), 79.91, 79.72, 79.34, 77.50, 76.32, 76.05, 75.33, 75.22, 75.17, 75.02, 74.44, 74.33, 73.62, 73.44, 73.24, 73.24 72.49, 72.35, 72.29, 71.17, 71.13, 69.51, 68.89, 68.10, 67.69 ppm. HRMS: calcd. for $C_{95}H_{95}F_5NO_{17}$ $[M + NH_4]^+$ 1616.6516; found 1616.6487.

Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzyl-6-*O*-pentafluorobenzoyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (27): The glycosylation between **4** and **7** was carried out in accordance with the general procedure. A solution of **26**[22] (1.1 equiv.) in Et_2O and more NIS (1.5 equiv.) were added after 10 min and the mixture was stirred at –20 °C for an additional 10 min. The reaction was worked up as described above to afford 61% yield of **27**. R_f = 0.12 (heptane/EtOAc, 4:1). $[\alpha]_D^{20}$ = +82.3 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3031, 1724, 1452, 1099, 713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–7.12 (m, 45 H), 5.64–5.60 (m, 2 H), 5.19 (d, J = 3.1 Hz, 1 H), 4.96 (d, J = 3.2 Hz, 1 H), 4.91–4.00 (m, 25 H) 3.92 (dd, J = 3.2, 10.2 Hz, 1 H), 3.80 (dd, J = 2.6, 10.2 Hz, 1 H), 3.52 (t, J = 8.7 Hz, 1 H), 3.41 (s, 3 H), 3.23 (dd, J = 4.6, 8.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.27, 166.19, 166.06, 138.95, 138.75, 138.65, 138.29, 138.25, 138.12, 133.35, 133.33, 133.30, 129.96–127.37 (45 C), 100.50 ($J_{C,H}$ = 169.6 Hz), 97.49 ($J_{C,H}$ = 169.6 Hz), 97.49 ($J_{C,H}$ = 171.0 Hz), 79.46, 77.47, 76.64, 75.95, 75.02, 74.70, 74.44, 74.19, 73.93, 73.31, 72.86, 72.23, 70.81, 69.65, 69.14, 68.58, 67.77, 67.74, 63.85, 63.40, 63.38, 55.50 ppm. HRMS: calcd. for $C_{89}H_{85}F_5NO_{20}$ $[M + NH_4]^+$ 1582.5580; found 1582.5549.

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