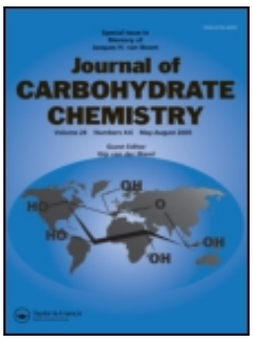

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A Novel Selectfluor-Mediated Regioselective *O*-Benzyl Ether Acetolysis of Perbenzylated Monosaccharides

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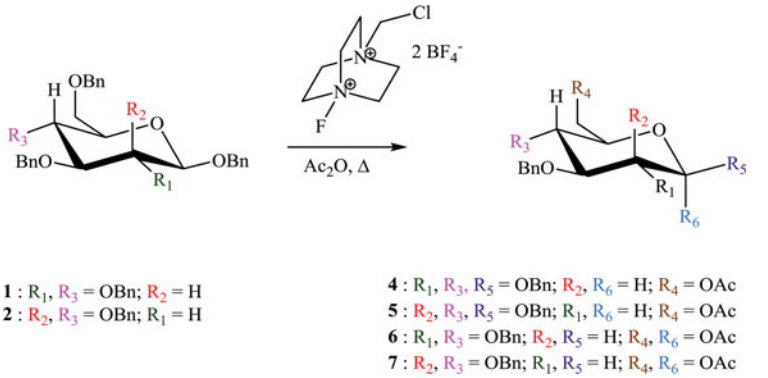
GRAPHICAL ABSTRACT



1 : R_1, R_3 = OBn; R_2 = H
2 : R_2, R_3 = OBn; R_1 = H

4 : R_1, R_3, R_5 = OBn; R_2, R_6 = H; R_4 = OAc
5 : R_2, R_3, R_5 = OBn; R_1, R_6 = H; R_4 = OAc
6 : R_1, R_3 = OBn; R_2, R_5 = H; R_4, R_6 = OAc
7 : R_2, R_3 = OBn; R_1, R_5 = H; R_4, R_6 = OAc

Selectfluor, a source of the super electrophile F^+, has replaced conventional reagents that supply F^+ for fluorination due to its attractive physical and chemical properties. This study is the first report of using Selectfluor as a debenzylating reagent. Selectfluor has been found to effect regioselective *O*-benzyl acetolysis from the per-*O*-benzylated derivatives of glucose and mannose, which are among the most commonly occurring monosaccharides. For both derivatives, one equivalent of Selectfluor first cleaves the primary benzyl, while a second equivalent subsequently removes the anomeric benzyl. Regioselective removal at higher equivalents proved difficult, with complex mixtures being obtained. The reaction proceeded under mild conditions with good yields

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and high regioselectivity, resulting in quick access to partially benzylated monosaccharide derivatives. This study provides shortened access to attractive building blocks for oligosaccharide synthesis.

Keywords Selectfluor; Oligosaccharides; Monosaccharides; Benzyl group; Regioselective deprotection

INTRODUCTION

Synthetic carbohydrates have found widespread applications due to their importance in many biological and physiological roles. Carbohydrates and their derivatives are involved in cell recognition, signal transduction, adhesion processes, and energy storage.[1–3] A major problem encountered in carbohydrate synthesis is that the monosaccharide building blocks are polyhydroxylated molecules with multiple centers of reactivity.[4–6] This increases the susceptibility of competing glycosylation reactions, and it is therefore necessary to develop protecting group strategies to synthesize particular targets.[7] Apart from the Fischer glycosylation and installation of bulky protecting groups on the primary position,[5–8] very few other reactions display high regioselectivity for a particular hydroxyl group on the sugar. Synthetic routes generally require multiple steps with judicious choice of protecting groups, featuring expensive and time-consuming purification steps and low overall yields.[8]

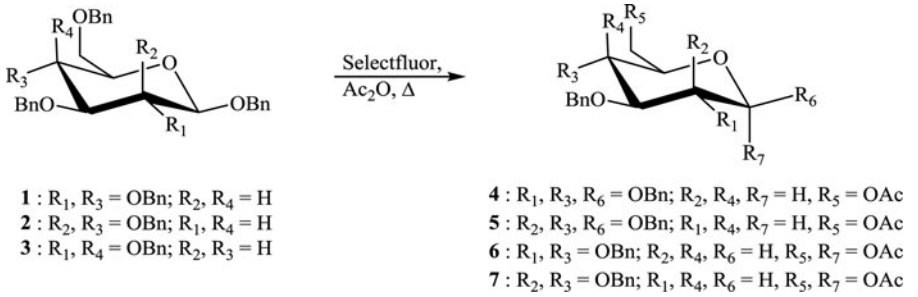
Sakai and coworkers have shown that acetolysis using Ac_2O containing 1% (v/v) H_2SO_4 can be used to effect stepwise acetolysis of benzyl ethers from per-*O*-benzylated derivatives.[9] This method, however, requires the use of H_2SO_4 and needs careful monitoring since product degradation can occur, resulting in reduced yields. In another study,[10] Cao and Yamada utilized a similar method as an easy route to obtain partially protected derivatives following stepwise deprotection of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside. They found that the order of debenzylation was 6-O-Bn > 3-OBn > 4-O-Bn > 2-O-Bn. Pastore and coworkers utilized I_2 and Et_3SiH to effect the regioselective de-*O*-benzylation of a range of carbohydrate substrates, with the least sterically accessible benzyl group being cleaved in most cases.[11] Mechanistic investigation reveals that when I_2 and Et_3SiH are used, anhydrous HI is generated and functions as the promoter. Lecourt and coworkers demonstrated the use of diisobutylaluminium hydride and triisobutylaluminium hydride as effective reagents for regioselective *O*-benzyl removal.[12] Various per-*O*-benzylated mono- and disaccharide derivatives were examined, and their method showed high regioselectivity toward a single benzyl group. They demonstrated the effectiveness of their method to produce novel cyclodextrin derivatives by treating per-*O*-benzylated α and β cyclodextrin with triisobutylaluminium hydride. This facilitated the regioselective de-*O*-benzylation on the primary rim of the

cyclodextrin, leading to the formation of an A-D diol. Yang and coworkers utilized the combination of $ZnCl_2$ and Ac_2O-HOAc and demonstrated its effectiveness for regioselective removal of the primary benzyl from a variety of substrates while the secondary benzyl groups are preserved.[13] The method showed good orthogonality with other protecting groups and works well at room temperature. Giordano and coworkers developed a method for the regioselective deprotection of benzylated derivatives using iodine and silane.[14] This method utilized isopropyl acetate instead of the usual acetic anhydride and acidic conditions employed under acetolytic conditions, and the preservation of *O*-glycosidic bonds is a particularly attractive feature of this method.

Other methods exist that are often used in the preparation of partially benzylated carbohydrate derivatives. Complexation by Lewis acids, such as $TiCl_4$ or $SnCl_4$, has been effectively used in the regioselective deprotection of benzyl ethers.[7,15] However, this often involves the use of toxic and/or expensive reagents. The use of boron trichloride has been reported as a novel method for the regioselective deprotection of *C*-glycosides containing 1,2-cis or 1,3-cis benzyl groups by Xiea and coworkers.[16]

A glycosyl acceptor bearing a free primary hydroxyl group can be prepared from selective ring opening of a 4,6-*O*-benzylidene acetal using $LiAlH_4$ and $AlCl_3$[17] or by initially protecting the primary position with sterically bulky groups (e.g., silyl and trityl groups), followed by deprotection at a later stage of the synthesis.[15–20] Catalytic transfer hydrogenation (CTH) is an effective and mild method that can be used to prepare protected derivatives bearing a free anomeric hydroxyl group.[21] A suitable leaving group can then be appended for use as a glycosyl donor.

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluorob orate) (Selectfluor)[22] is an electrophilic fluorinating reagent and has largely replaced previously used sources of F^+.[23] It is easy to handle (free-flowing white crystals), very stable, and commercially available on a large scale.[23–25] Fluorine substitution has been previously shown to significantly alter the physical and chemical properties of many molecules.[24–28] Selectfluor has also been effectively used in the preparation of glycosyl fluorides, fluorination of aromatic compounds, fluorination of alkenes, and many oxidation reactions.[23] However, in this study, Selectfluor was found to be an effective reagent in the regioselective *O*-benzyl removal of per-*O*-benzylated monosaccharides. Selectfluor was utilized at both catalytic and stoichiometric equivalents to determine its effect on the fully benzylated derivatives of glucose, mannose, and galactose. Per-*O*-benzylated monosaccharides are easy to prepare in good yield in a single step from the free monosaccharide. The benzyl ether is a popular protecting group and is well known for its robustness and stability to a wide range of conditions. Using Selectfluor, we demonstrate that the benzyl group on the primary position was removed first followed by the anomeric benzyl group.



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3 : R_1, R_4 = OBn; R_2, R_3 = H

4 : R_1, R_3, R_6 = OBn; R_2, R_4, R_7 = H, R_5 = OAc
5 : R_2, R_3, R_6 = OBn; R_1, R_4, R_7 = H, R_5 = OAc
6 : R_1, R_3 = OBn; R_2, R_4, R_6 = H, R_5, R_7 = OAc
7 : R_2, R_3 = OBn; R_1, R_4, R_6 = H, R_5, R_7 = OAc

Scheme 1: Reactions of Selectfluor and **1**–**3**.

RESULTS AND DISCUSSION

The per-*O*-benzylated glucopyranose and mannopyranose derivatives **1** and **2** were prepared by treating the free sugar with excess NaH and BnBr in DMF in good yields. The galactopyranoside **3** could not be obtained using this method since the α furanoside was the major product along with an inseparable mixture of the β furanoside, β pyranoside, and α pyranoside.[29,30] Derivative **3** was prepared according to literature protocols starting from free galactose.[31,32] Compounds **1**, **2,** and **3** were used as the starting material for the regioselective de-*O*-benzylation studies with Selectfluor. Scheme 1 outlines the reactions utilized to investigate the effect of Selectfluor on the per-*O*-benzylated derivatives.

When **1**–**3** were each treated with catalytic amounts of Selectfluor, only starting material persisted. Stoichiometric amounts were then investigated, and when 1 equivalent of Selectfluor in Ac_2O was utilized at room temperature, no significant reaction was observed (Tables 1–3). The experiment was then repeated with gentle heating, and TLC analysis revealed the appearance of a spot below that of the starting material. The reaction was allowed to continue; however, product formation was very slow even with prolonged reaction times. Optimization studies were then carried out as shown in Tables 1

Table 1: Optimization of reaction between 1 equivalent of Selectfluor and **1**

Starting material	Eq. Selectfluor	Temperature/°C	Time	Product (yield%)
1	1	RT	Overnight	No reaction
1	1	30	Overnight	**4** (< 5)
1	1	60	6 h	**4** (58)
1	1	60	Overnight	**4** (67)
1	1	Reflux	2 h	**4** (65)
1	1	Reflux	Overnight	**4** (52)

through 3 to vary the temperature and time in order to maximize product formation.

When **1** or **2** was used as the starting material, the major product of the reaction was its monoacetylated derivative **4** or **5**, respectively. The benzyl group at C-6 was the first to be acetolyzed due to its greater steric accessibility. The reaction was heated at 60°C, and after 6 h, considerable reaction progress was observed. The derivatives **4** and **5** were obtained in a yield of 58% and 55%, respectively, and unreacted starting material was recovered. The reaction was repeated at 60°C overnight and improved yields were obtained.

The reaction was then repeated under reflux and conversion was rapid; after 2 h, most of the starting material was consumed and products **6** and **7** were obtained in a yield of 65% and 61%, respectively. The yields of **4** and **5** were lower when the reaction was performed under extensive reflux as product degradation occurred. A complex mixture of partially benzylated derivatives was detected after column chromatography, as elucidated by ^{1}H and ^{13}C NMR.

When the reaction was carried out with galactoside **3** using the conditions optimized for **1** and **2**, poor regioselectivity was observed and the monoacetylated derivative was obtained only in minor yield. This proved difficult to purify since the desired product eluted with other partially benzylated derivatives, possibly bearing a single acetate group at a nonprimary position.

Table 2: Optimization of reaction between 1 equivalent of Selectfluor and **2**

Starting material	Eq. Selectfluor	Temperature/°C	Time	Product (yield%)
2	1	RT	Overnight	No reaction
2	1	30	Overnight	**5** (< 5)
2	1	60	6 h	**5** (55)
2	1	60	Overnight	**5** (63)
2	1	Reflux	2 h	**5** (61)
2	1	Reflux	Overnight	**5** (51)

Table 3: Optimization of reaction between 1 equivalent of Selectfluor and **3**

Starting material	Eq. Selectfluor	Temperature/°C	Time	Yield%
3	1	RT	Overnight	No reaction
3	1	30	Overnight	< 5
3	1	60	6 h	Complex mixture
3	1	60	Overnight	Complex mixture
3	1	Reflux	2 h	Complex mixture
3	1	Reflux	Overnight	Complex mixture

Tables 4 through 6 detail the reaction conditions and the results of the experiments with 2 equivalents of Selectfluor when **1**, **2,** and **3** were used as the substrates. The anomeric benzyl was the second benzyl to be cleaved, resulting in the 1,6-di-*O*-acetates **6** and **7** as the major product (60% and 59% yields, respectively). As previously reported with **3**, poor regioselectivity was observed and attempts at further benzyl group acetolysis using higher equivalents of Selectfluor proved difficult, since there was a loss of regioselectivity and complex mixtures were obtained. Despite the unsuccessful attempts with **3**, many literature protocols exist for the regioselective acetolysis of highly benzylated galacto-derivatives.[11–16] We postulate that the lone pair of electrons on the carbonyl oxygen of acetic anhydride attacks the F^+, facilitating the activation of the carbonyl centre. This is typical of known acetolysis pathways and the oxygen of the substrate is then able to attack the activated nucleophilic center, effecting benzyl group acetolysis.[9,10,13,14]

Deacetylation of the Product

Partially benzylated derivatives are useful synthetic intermediates. Scheme 3shows that **4** and **6** could be readily converted to **8** and **9** in a yield of 97% and 82%, respectively, as useful glycosyl acceptor and donor for the synthesis of oligosaccharides Scheme 2.

Table 4: Optimization of reaction between 2 equivalents of Selectfluor and **1**

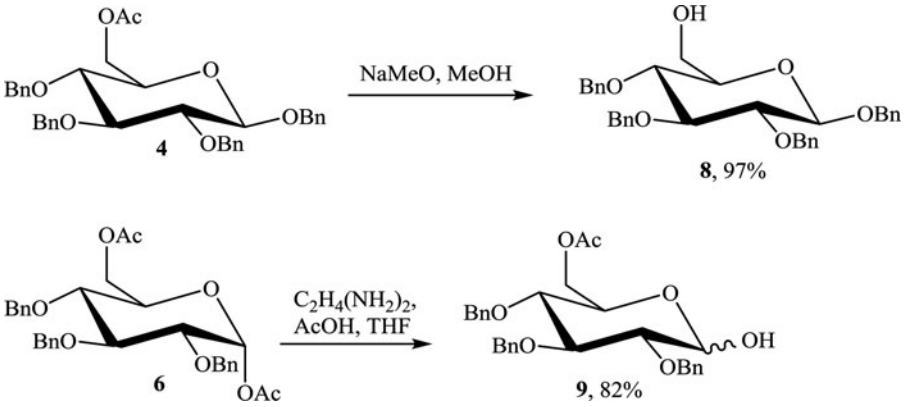
Starting material	Eq. Selectfluor	Temperature/°C	Time	Product (yield%)
1	2	RT	Overnight	No reaction
1	2	30	Overnight	**6** (< 5)
1	2	60	6 h	**6** (50)
1	2	60	Overnight	**6** (54)
1	2	Reflux	2 h	**6** (60)
1	2	Reflux	Overnight	**6** (44)

Table 5: Optimization of reaction between 2 equivalents of Selectfluor and **2**

Starting material	Eq. Selectfluor	Temperature/°C	Time	Product (yield%)
2	2	RT	Overnight	No reaction
2	2	30	Overnight	**7** (< 5)
2	2	60	6 h	**7** (54)
2	2	60	Overnight	**7** (60)
2	2	Reflux	2 h	**7** (59)
2	2	Reflux	Overnight	**7** (40)

Table 6: Optimization of reaction between 2 equivalents of Selectfluor and **3**

Starting material	Eq. Selectfluor	Temperature/°C	Time	Yield%
3	2	RT	Overnight	No reaction
3	2	30	Overnight	< 5
3	2	60	6 h	Complex mixture
3	2	60	Overnight	Complex mixture
3	2	Reflux	2 h	Complex mixture
3	2	Reflux	Overnight	Complex mixture



Scheme 2: Deacetylation reactions of **4** and **6**.

CONCLUSION

Selectfluor-mediated benzyl group acetolysis was proved to be a mild and easy method to obtain partially benyzlated and partially acetylated glucose and mannose derivatives. These are useful intermediates and can be used for oligosaccharide synthesis. The primary benzyl ether was the first to be acetolyzed followed by the benzyl ether linkage at the anomeric position. This method has limitations at higher equivalents of Selectfluor, as under these conditions the reactions were complex and could not afford regioselective benzyl ether acetolysis.

EXPERIMENTAL

General Methods

All chemicals used were reagent grade and used as purchased unless otherwise stated. DMF was dried over calcium hydride for 24 h, distilled under reduced pressure in an inert atmosphere of nitrogen, and stored over 4 Å molecular sieves under argon. TLC was performed using precoated silica gel 60 F_{254} plates with compounds visualized using acidic ammonium molybdate solution

[ammonium molybdate (VI) tetrahydrate (25 g) in 1 M H_2SO_4 (500 mL)]. ^1H, ^{13}C, COSY, and HSQC NMR experiments were recorded on a Bruker 600, 400, or 300 NMR spectrometer in the deuterated solvents stated. Chemical shifts are stated in ppm. Multiplicities are stated as s (singlet), bs (broad singlet), *p*s (pseudo singlet), d (doublet), apptd (apparent doublet), t (triplet), apptt (apparent triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), ABq (AB quartet), or m (multiplet). High-resolution mass spectral (HRMS) analyses were obtained using a Bruker Daltonics micrOToF-Q instrument in the electron spray ionization mode. Column chromatography was performed using high-purity-grade silica gel, 70–250 mesh/60 Å.

Benzyl 2,3,4,6-tetra-O-*benzyl-β-D-glucopyranoside (1)*

D-Glucose (5 g, 27.8 mmol) was suspended in 100 mL anhydrous DMF in a 250 mL round-bottom flask. The reaction vessel was flushed with argon and cooled in an ice bath to 5°C. NaH (60% dispersion in mineral oil; 6.6 g, 166.5 mmol) was then added over a period of 10 min. This was allowed to stir for 60 min followed by the addition of BnBr (19.8 mL, 166.5 mmol) over a 30-min period and stirring continued for 24 h. Methanol (20 mL) was then added to the reaction and the DMF removed under high vacuum. The crude residue was dissolved in CH_2Cl_2 (100 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **1** (14.18 g, 81%); R_f (Pet. Ether: EtOAc; 4:1) = 0.44; ^1H NMR (600 MHz, $CDCl_3$): δ: 3.47 (1H, ddd, $J_{4,5}$ = 9.4 Hz, $J_{5,6a}$ = 5.5, $J_{5,6b}$ = 4.2 Hz, H-5), 3.53 (1H, t, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 7.8 Hz, H-2), 3.64 (2H, m, H-3, H-4), 3.71 (1H, dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,6b}$ = 10.8, H-6b), 3.76 (1H, dd, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 10.8, H-6a), 4.52 (1H, d, $J_{1,2}$ = 7.8 Hz, H-1), 4.54, 4.72 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.57, 4.63 (2H, ABq, J = 12.2 Hz, PhCH_2O-), 4.67, 4.98 (2H, ABq, J = 11.9 Hz, PhCH_2O-), 4.78, 4.92 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.82, 4.96 (2H, ABq, J = 10.8 Hz, PhCH_2O-), 7.16–7.39 (25H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 69.0 (1C, C-6), 71.2 (1C, Ph*C*H_2O), 73.5 (1C, Ph*C*H_2O), 74.91 (1C, Ph*C*H_2O), 74.94 (1C, Ph*C*H_2O), 75.0 (1C, C-5), 75.7 (1C, Ph*C*H_2O), 77.9 (1C, C-4), 82.3 (1C, C-2), 84.8 (1C, C-3), 102.6 (1C, $J_{C1\text{-}H1}$ = 160.0 Hz, C-1), 127.6–128.4 (25C, Ar-C), 137.5 (1C, Ar-*quat*), 138.1 (1C, Ar-*quat*), 138.2 (1C, Ar-*quat*), 138.4 (1C, Ar-*quat*), 138.6 (1C, Ar-*quat*). HRMS calculated for $C_{41}H_{42}O_6Na$: 653.2879; found: 653.2874 $(M + Na)^+$.

Benzyl 2,3,4,6-tetra-O-*benzyl-β-D-mannopyranoside (2)*

D-Mannose (5 g, 27.8 mmol) was suspended in 100 mL anhydrous DMF in a 250 mL round-bottom flask. The reaction vessel was flushed with argon

and cooled in an ice bath to 5°C. NaH (60% dispersion in mineral oil; 6.6 g, 166.5 mmol) was then added over a period of 10 min. This was allowed to stir for 60 min followed by the addition of BnBr (19.8 mL, 166.5 mmol) over a 30-min period and stirring continued for 24 h. Methanol (20 mL) was then added to the reaction and the DMF removed under high vacuum. The crude residue was dissolved in CH_2Cl_2 (100 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **2** (13.65 g, 78%); R_f (EtOAc : Pet. Ether; 2:3) = 0.57; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 3.45 (1H, ddd, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 6.0 Hz, H-5), 3.49 (1H, dd, $J_{2,3}$ = 5.6 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.78 (1H, dd, $J_{5,6b}$ = 6.0 Hz, $J_{6a,6b}$ = 10.8, H-6b), 3.83 (1H, dd, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 10.8, H-6a), 3.90 (1H, t, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.92 (1H, dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 5.6 Hz, H-2), 4.43, 4.50 (2H, ABq, J = 11.8 Hz, PhCH_2O-), 4.44 (1H, s, H-1), 4.54, 4.90 (2H, ABq, J = 10.8 Hz, PhCH_2O-), 4.59, 5.00 (2H, ABq, J = 12.0 Hz, PhCH_2O-), 4.60, 4.65 (2H, ABq, J = 12.1 Hz, PhCH_2O-), 4.89, 5.01 (2H, ABq, J = 12.3 Hz, PhCH_2O-), 7.18–7.46 (25H, m, Ar-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ: 69.8 (1C, C-6), 71.0 (1C, Ph*C*H_2O), 71.6 (1C, Ph*C*H_2O), 73.6 (1C, Ph*C*H_2O), 73.9 (1C, Ph*C*H_2O), 74.0 (1C, C-4), 75.0 (1C, C-2), 75.2 (1C, Ph*C*H_2O), 76.1 (1C, C-5), 82.5 (1C, C-3), 100.4 (1C, $J_{C1\text{-}H1}$ = 152.4 Hz, C-1), 127.6–128.5 (25C, Ar-C), 137.6 (1C, Ar-*quat*), 138.3 (1C, Ar-*quat*), 138.5 (1C, Ar-*quat*), 138.6 (1C, Ar-*quat*), 138.9 (1C, Ar-*quat*). HRMS calculated for $C_{41}H_{42}O_6Na$: 653.2879; found: 653.2874 $(M + Na)^+$.

*Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (3)*

Benzyl-β-D-galactopyranoside, **11**. (2 g, 7.40 mmol) was suspended in 10 mL anhydrous DMF in a 100 mL round-bottom flask. The reaction vessel was flushed with argon and cooled in an ice bath to 5°C. NaH (60% dispersion in mineral oil; 1.5 g, 37.0 mmol) was then added over a period of 10 min. This was allowed to stir for 60 min followed by the addition of BnBr (4.4 mL, 37.0 mmol) over a 30-min period and stirring continued for 24 h. Methanol (20 mL) was then added to the reaction and the DMF removed under high vacuum. The crude residue was dissolved in CH_2Cl_2 (100 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **3** (3.9 g, 84%); R_f (Pet. Ether: EtOAc; 4:1) = 0.42; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 3.51 (1H, dd, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.0 Hz, H-3), 3.53 (1H, m, H-5), 3.60 (1H, m, H-6a), 3.63 (1H, dd, $J_{5,6b}$ = 6.5 Hz, $J_{6,6b}$ = 9.7, H-6b), 3.90 (2H, m, H-2, H-4), 4.42, 4.46 (2H, ABq, J = 11.8 Hz, PhCH_2O-), 4.47 (1H, d, $J_{1,2}$ = 7.7 Hz, H-1),

4.60, 4.96 (2H, ABq, J = 12.3 Hz, PhCH_2O-), 4.63, 4.94 (2H, ABq, J = 11.7 Hz, PhCH_2O-), 4.69, 4.47 (2H, ABq, J = 11.8 Hz, PhCH_2O-), 4.77, 4.92 (2H, ABq, J = 10.8Hz, PhCH_2O-), 7.23–7.36 (25H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 69.0 (1C, C-6), 71.0 (1C, PhCH$_2$O), 73.2 (1C, PhCH$_2$O), 73.6 (2C, C-5, PhCH$_2$O), 73.7 (1C, C-4), 74.6 (1C, PhCH$_2$O), 75.4 (1C, PhCH$_2$O), 79.7 (1C, C-2), 82.4 (1C, C-3), 103.0 (1C, $J_{C1\text{-}H1}$ = 158.5 Hz, C-1), 127.6–128.5 (25C, Ar-C), 137.8 (1C, Ar-*quat*), 138.1 (1C, Ar-*quat*), 138.6 (1C, Ar-*quat*), 138.7 (1C, Ar-*quat*), 138.8 (1C, Ar-*quat*). HRMS calculated for $C_{41}H_{42}O_6Na$: 653.2879; found: 653.2874 $(M + Na)^+$.

*Benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (4)*

Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (2 g, 3.2 mmol) was dissolved in 15 mL Ac_2O in a 100 mL round-bottom flask. Selectfluor (1.12 g, 3.2 mmol) was added and the reaction heated under reflux for 2 h. The Ac_2O was removed under high vacuum and the crude residue dissolved in CH_2Cl_2 (25 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **4** (1.2 g, 65%); R_f (Pet. Ether : EtOAc; 8:2) = 0.38; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 2.05 (3H, s, CH_3CO-), 3.50 (1H, m, $J_{4,5}$ = 9.3 Hz, $J_{5,6a}$ = 2.1, $J_{5,6b}$ = 4.9 Hz, H-5), 3.52 (1H, dd, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 3.56 (1H, t, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.3 Hz, H-4), 3.67 (1H, t, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.3 Hz, H-3), 4.25 (1H, dd, $J_{5,6b}$ = 4.9 Hz, $J_{6a,6b}$ = 11.9, H-6b), 4.37 (1H, dd, $J_{5,6a}$ = 2.1 Hz, $J_{6a,6b}$ = 11.9, H-6a), 4.51 (1H, d, $J_{1,2}$ = 7.8 Hz, H-1), 4.57, 4.86 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.66, 4.93 (2H, ABq, J = 11.9 Hz, PhCH_2O-), 4.73, 4.95 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.79, 4.96 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 7.26–7.37 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 20.9 (1C, CH$_3$CO-), 63.1 (1C, C-6), 71.2 (1C, PhCH$_2$O), 72.8 (1C, C-5), 74.9 (1C, PhCH$_2$O), 75.0 (1C, PhCH$_2$O), 75.7 (1C, PhCH$_2$O), 77.3 (1C, C-4), 82.2 (1C, C-2), 84.7 (1C, C-3), 102.4 (1C, $J_{C1\text{-}H1}$ = 158.5 Hz, C-1), 127.9–128.5 (20C, Ar-C), 137.1 (1C, Ar-*quat*), 137.7 (1C, Ar-*quat*), 138.2 (1C, Ar-*quat*), 138.4 (1C, Ar-*quat*), 170.8 (1C, CH$_3$$C$O-). HRMS calculated for $C_{36}H_{38}O_7Na$: 605.2512; found: 605.2467 $(M + Na)^+$.

*Benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-mannopyranoside (5)*

Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannoopyranoside (2 g, 3.2 mmol) was dissolved in 15 mL Ac_2O in a 100 mL round-bottom flask. Selectfluor (1.12 g, 3.2 mmol) was added and the reaction heated under reflux for 2 h. The Ac_2O was removed under high vacuum and the crude residue dissolved in CH_2Cl_2 (25 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected

to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **5** (1.1 g, 61%); R_f (Pet. Ether : EtOAc; 8:2) = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 2.03 (3H, s, CH_3CO-), 3.44 (1H, ddd, $J_{4,5} = 9.4$ Hz, $J_{5,6a} = 5.7$, $J_{5,6b} = 2.0$ Hz, H-5), 3.47 (1H, dd, $J_{2,3} = 3.0$, $J_{3,4} = 9.3$ Hz, H-3), 3.92 (2H, m, H-2, H-4), 4.41 (2H, m, H-1, H-6b), 4.40, 4.48 (2H, ABq, $J = 11.8$ Hz, PhCH_2O-), 4.43 (1H, dd, $J_{5,6a} = 5.7$ Hz, $J_{6,6b} = 11.8$, H-6a), 4.57, 4.96 (2H, ABq, $J = 12.0$ Hz, PhCH_2O-), 4.59, 4.94 (2H, ABq, $J = 10.9$ Hz, PhCH_2O-), 4.87, 5.00 (2H, ABq, $J = 12.5$ Hz, PhCH_2O-), 7.22–7.33 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 20.9 (1C, CH$_3$CO-), 63.7 (1C, C-6), 70.8 (1C, PhCH$_2$O), 71.3 (1C, PhCH$_2$O), 73.6 (1C, C-5), 73.7 (1C, C-2), 73.8 (1C, PhCH$_2$O), 74.5 (1C, C-4), 75.1 (1C, PhCH$_2$O), 82.3 (1C, C-3), 100.1 (1C, $J_{C1\text{-}H1} = 153.9$ Hz, C-1), 127.4–128.4 (20C, Ar-C), 137.2 (1C, Ar-*quat*), 138.0 (1C, Ar-*quat*), 138.1 (1C, Ar-*quat*), 138.6 (1C, Ar-*quat*), 170.8 (1C, CH$_3$*C*O-). HRMS calculated for $C_{36}H_{38}O_7Na$: 605.2512; found: 605.2523 $(M + Na)^+$.

*Acetyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6)*

Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (2 g, 3.2 mmol) was dissolved in 15 mL Ac_2O in a 100 mL round-bottom flask. Selectfluor (2.25 g, 6.3 mmol) was added and the reaction heated under reflux for 2 h. The Ac_2O was removed under high vacuum and the crude residue dissolved in CH_2Cl_2 (25 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **6** (1.02 g, 60%); R_f (EtOAc : Pet. Ether; 3:2) = 0.57; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 2.02 (3H, s, CH_3CO-), 2.15 (3H, s, CH_3CO-), 3.57 (1H, dd, $J_{3,4} = 9.3$ Hz, $J_{4,5} = 10.2$ Hz, H-4), 3.67 (1H, dd, $J_{1,2} = 3.6$ Hz, $J_{2,3} = 9.3$ Hz, H-2), 3.94 (1H, ddd, $J_{4,5} = 10.2$ Hz, $J_{5,6a} = 2.3$, $J_{5,6b} = 4.0$ Hz, H-5), 3.98 (1H, t, $J_{2,3} = 9.3$ Hz, $J_{3,4} = 9.3$ Hz, H-3), 4.24 (1H, dd, $J_{5,6a} = 2.3$ Hz, $J_{6a,6b} = 12.2$, H-6a), 4.28 (1H, dd, $J_{5,6b} = 4.0$ Hz, $J_{6a,6b} = 12.2$, H-6b), 4.57, 4.89 (2H, ABq, $J = 10.7$ Hz, PhCH_2O-), 4.64, 4.71 (2H, ABq, $J = 10.5$ Hz, PhCH_2O-), 4.83, 4.99 (2H, ABq, $J = 10.8$ Hz, PhCH_2O-), 6.32 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 7.26–7.35 (15H, m, Ar-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ: 20.9 (1C, CH$_3$CO-), 21.2 (1C, CH$_3$CO-), 62.7 (1C, C-6), 71.2 (1C, C-5), 73.3 (1C, PhCH$_2$O), 75.4 (1C, PhCH$_2$O), 75.8 (1C, PhCH$_2$O), 76.6 (1C, C-4), 78.9 (1C, C-2), 81.7 (1C, C-3), 89.7 (1C, $J_{C1\text{-}H1} = 173.6$ Hz, C-1), 127.9–128.6 (15C, Ar-C), 138.5 (1C, Ar-*quat*), 137.7 (1C, Ar-*quat*), 137.5 (1C, Ar-*quat*), 169.4 (1C, CH$_3$*C*O-), 170.7 (1C, CH$_3$*C*O-). HRMS calculated for $C_{31}H_{34}O_8Na$: 557.2151; found: 557.2092 $(M + Na)^+$.

*Acetyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (7)*

Benzyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranoside (2 g, 3.2 mmol) was dissolved in 15 mL Ac_2O in a 100 mL round-bottom flask. Selectfluor (2.25 g,

6.3 mmol) was added and the reaction heated under reflux for 2 h. The Ac_2O was removed under high vacuum and the crude residue dissolved in CH_2Cl_2 (25 mL), transferred to a separatory funnel, and washed with H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **7** (1.00 g, 59%); R_f (EtOAc : Pet. Ether; 3:2) = 0.57; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.98 (3H, s, CH_3CO-), 2.00 (3H, s, CH_3CO-), 3.75 (1H, m, H-2), 3.88 (1H, m, H-3, H-5), 4.00 (1H, t, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 9.6 Hz, H-4), 4.30 (1H, dd, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 12.0, H-6b), 4.33 (1H, dd, $J_{5,6}$ = 2.3 Hz, $J_{6a,6b}$ = 12.0, H-6a), 4.57 (2H, appts, PhCH_2O-), 4.60, 4.94 (2H, ABq, J = 10.8 Hz, PhCH_2O-), 4.70, 4.74 (2H, ABq, J = 12.3 Hz, PhCH_2O-), 6.20 (1H, d, $J_{1,2}$ = 2.0 Hz, H-1), 7.12–7.39 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 20.8 (1C, CH$_3$CO-), 20.9 (1C, CH$_3$CO-), 63.1 (1C, C-6), 71.9 (1C, PhCH$_2$O), 72.3 (2C, C-5, PhCH$_2$O), 73.1 (1C, C-2), 73.7 (1C, C-4), 75.2 (1C, PhCH$_2$O), 79.0 (1C, C-3), 91.5 (1C, $J_{C1\text{-}H1}$ = 175.1 Hz, C-1), 127.7–128.4 (15C, Ar-C), 137.7 (1C, Ar-*quat*), 137.9 (2C, Ar-*quat*), 168.7 (1C, CH$_3$$C$O-), 170.7 (1C, CH$_3$$C$O-). HRMS calculated for $C_{31}H_{34}O_8Na$: 557.2151; found: 557.2156 $(M + Na)^+$.

*Benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (8)*

Benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside, **4** (1 g, 11.4 mmol) was dissolved in 10 mL of an 8:2 mixture of MeOH:CH_2Cl_2. To this, NaOMe (0.1 g, 2.0 mmol) was added and the reaction monitored via TLC until complete consumption of the starting material was observed. The reaction mixture was neutralized to pH 7 using Amberlyst H^+ exchange resin and filtered, and the solvent was removed in vacuo. The crude residue was subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **8** (0.90 g, 97%); R_f (EtOAc : Pet. Ether; 2 : 3) = 0.39; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.81 (1H, bs, OH-6), 3.36 (1H, ddd, $J_{4,5}$ = 8.4 Hz, $J_{5,6a}$ = 4.4, $J_{5,6b}$ = 2.7 Hz, H-5), 3.49 (1H, t, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.4 Hz, H-2), 3.57 (1H, t, $J_{3,4}$ = 8.4 Hz, $J_{4,5}$ = 8.4 Hz, H-4), 3.66 (1H, dd, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 3.71 (1H, dd, $J_{5,6a}$ = 4.4 Hz, $J_{6,6b}$ = 12.0, H-6a), 3.87 (1H, dd, $J_{5,6b}$ = 2.7 Hz, $J_{6,6b}$ = 12.0, H-6b), 4.57 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1), 4.64, 4.86 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.69, 4.92 (2H, ABq, J = 11.9 Hz, PhCH_2O-), 4.73, 4.95 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 4.81, 4.94 (2H, ABq, J = 10.9 Hz, PhCH_2O-), 7.23, 7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 62.0 (1C, C-6), 71.6 (1C, PhCH$_2$O), 74.9 (2C, PhCH$_2$O), 75.0 (1C, C-5), 75.7 (1C, PhCH$_2$O), 77.5 (1C, C-4), 82.3 (1C, C-2), 84.5 (1C, C-3), 102.8 (1C, $J_{C1\text{-}H1}$ = 162.0 Hz, C-1), 127.6–128.4 (20C, Ar-C), 137.2 (1C, Ar-*quat*), 137.9 (1C, Ar-*quat*), 138.2 (1C, Ar-*quat*), 138.4 (1C, Ar-*quat*). HRMS calculated for $C_{34}H_{36}O_6Na$: 563.2410; found: 563.2427 $(M + Na)^+$.

*6-*O*-acetyl-2,3,4,-tri-*O*-benzyl-α,β-D-glucopyranose (9)*

Acetyl 2,3,4,-tri-*O*-benzyl-6-*O*-acetyl-α-D-glucopyranoside (2 g, 3.7 mmol) was dissolved in THF (25 mL) in a 100 mL round-bottom flask. To this was added AcOH (0.3 mL, 5.2 mmol) and ethylenediamine (0.3 mL, 4.5 mmol). This was allowed to stir for 24 h and then the THF was removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (25 mL), transferred to a separatory funnel, and washed with 2M HCl (100 mL) and saturated sodium bicarbonate (100 mL), followed by H_2O (3 × 150 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated in vacuo and the crude residue subjected to purification by column chromatography using petroleum ether/ethyl acetate (gradient elution) to afford **9** (1.51 g, 82%) (α:β, 2:1); R_f (EtOAc : Pet. Ether; 3:2) = 0.45; ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.95 (6H, m, (α + β) CH_3CO-), 3.42 (1H, dd, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 8.9 Hz, H-2β), 3.48 (2H, m, H-5β, OH-1α), 3.51 (2H, m, H-4α, H-4β), 3.54 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.2 Hz, H-2α), 3.65 (1H, t, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 8.9 Hz, H-3β), 4.06 (1H, t, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3α), 4.08 (1H, ddd, $J_{4,5}$ = 10.2 Hz, $J_{5,6a}$ = 2.2, $J_{5,6b}$ = 4.2 Hz, H-5α), 4.16 (1H, dd, $J_{5,6b}$ = 4.7 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6b-β), 4.23 (1H, dd, $J_{5,6b}$ = 4.2 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b-α), 4.29 (1H, dd, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a-α), 4.34 (1H, dd, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 11.9 Hz, H-6a-β), 4.56, 4.85 (2H, ABq, J = 10.8 Hz, PhCH_2O-β), 4.58, 4.87 (2H, ABq, J = 11.0 Hz, PhCH_2O-α), 4.64 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1β), 4.66, 4.70 (2H, ABq, J = 12.0 Hz, PhCH_2O-α), 4.74, 4.97 (2H, ABq, J = 11.1 Hz, PhCH_2O-β), 4.80, 4.94 (2H, ABq, J = 10.9 Hz, PhCH_2O-β), 4.83, 4.98 (2H, ABq, J = 10.9 Hz, PhCH_2O-α), 5.17 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1α), 127.5–128.3 (30H, m, (α + β) Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 20.7 (2C, (α + β) CH_3CO-), 63.0 (2C, C-6α, C-6β), 68.4 (1C, C-5α), 72.6 (1C, C-5β), 72.8 (1C, PhCH_2O-α), 74.5 (2C, PhCH_2O-β), 74.8 (1C, PhCH_2O-α), 75.5 (2C, (α + β) PhCH_2O-), 77.0 (2C, C-4α, C-4β), 79.8 (1C, C-2α), 81.4 (1C, C-3α), 82.8 (1C, C-2β), 84.3 (1C, C-3β), 90.7 (1C, $J_{C1\text{-}H1}$ = 169.0 Hz, C-1α), 97.2 (1C, $J_{C1\text{-}H1}$ = 163.0 Hz, C-1β), 127.5–128.3 (30C, (α + β) Ar-C), 137.4–138.3 (6C, (α + β) Ar-*quat*), 170.8 (2C, (α + β) CH_3CO-). HRMS calculated for $C_{29}H_{32}O_7Na$: 515.2046; found: 515.2007 $(M + Na)^+$.

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