2-[Dimethyl(2-naphthylmethyl)silyl]ethoxy Carbonate (NSEC) as a New Mode of Hydroxyl Group Protection

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2-[Dimethyl(2-naphthylmethyl)silyl]ethoxy carbonate (NSEC) is a novel protecting group to mask hydroxyl groups. NSECCl is available in three steps from chlorodimethylvinylsilane and 2-(bromomethyl)naphthalene. Introduction and removal of the NSEC group are performed easily and rapidly in the presence of most protecting groups currently used in carbohydrate chemistry. The removal of NSEC can be carried out under mild conditions in the presence of various ether and ester protecting groups. Additionally, the NSEC group is stable to glycosylation conditions using glycosyl phosphates. The synthesis of disaccharide **18** containing NSEC has been accomplished.

INTRODUCTION

The synthesis of complex, branched carbohydrates requires an orthogonal protecting group pattern that masks hydroxyl groups that serve as connecting points. Since each monosaccharide presents up to four functional groups with similar reactivity, the differential protection of these functional groups remains a major challenge in the assembly of large carbohydrate structures. In addition to protecting group orthogonality, the steric and electronic nature of the protecting

groups are important because they influence the reactivity of the building blocks and the outcome of the glycosylation reactions. A variety of different protecting groups that can be removed selectively has been disclosed.[1] Benzyl ethers are typically used as permanent protecting groups, which mask hydroxyl groups during the entire synthesis and are removed at the late stages of oligosaccharide assembly. Various esters, silyl ethers, and allyl ethers commonly are employed as temporary protecting groups. The choice of an orthogonal protecting group pattern represents a key issue in planning and executing the synthesis of the target molecule. Silyl ether-based protecting groups have achieved great popularity in organic synthesis.

Silyl-based modes of protection are relatively stable under basic or neutral conditions, and many silyl-based groups even tolerate weak acidic reaction conditions. In addition, a range of cleavage conditions for silyl ether bonds is available.[2] The removal of silyl groups by fluoride ions has been used commonly, because the formation of the Si-F bond is energetically favored. The use of silyl ethers has already been established for solid-phase oligonucleotide[3] and oligosaccharide[4] syntheses.

UV-active protecting groups have been applied to solid support oligosaccharide synthesis since real-time monitoring of coupling reactions is of particular utility for automated oligosaccharide assembly. Therefore, the 9-fluorenylmethoxycarbonyl (Fmoc) group has been used as a temporary protecting group in the automated synthesis of Lewis antigens.[5] The UV-active dibenzofulvene moiety released after Fmoc cleavage allows for real-time monitoring of the reaction progress.[6]

The trimethylsilylethoxy carbonate (Teoc) group is a useful protecting group for hydroxyl[7] and amino groups in peptide[8] and oligonucleotide[9,10] assembly. It is readily introduced in good yields using mild basic conditions. Facile, selective removal of Teoc in the presence of other carbonate-based protecting groups such as Fmoc has been achieved by treatment with acetic acid-buffered TBAF solutions.[11]

Here, we present 2-[dimethyl(2-naphthylmethyl)silyl]ethoxy carbonate (NSEC) as a novel, silyl-based, temporary protecting group (Fig. 1). NSEC combines the advantages of a silyl-based protecting group—facile and selective cleavage—with the use of a highly UV-sensitive chromophoric tag for UV monitoring during automated synthesis.

Figure 1: Design of a UV active, silyl-based protecting group.

RESULTS AND DISCUSSION

2-[Dimethyl(2-naphthylmethyl)silyl]ethyl chloroformate (NSECCl) was synthesized in three steps (Sch. 1). Preparation of the Grignard reagent 2-naphtylmethyl magnesium bromide and addition to chlorodimethylvinylsilane afforded vinylsilane **1** in 69% yield. A hydroboration-oxidation protocol followed by reaction of the resulting alcohol with phosgene led to the desired chloroformate **2** (NSECCl) in good yield.

To test the stability of the NSEC group under conditions used to cleave standard hydroxyl protecting groups, NSEC protected glucose **5** containing a free hydroxyl group in C2 was prepared (Sch. 2). Introduction of the NSEC group at the C6 hydroxyl position of the 1,2-anhydrosugar **3**[12] proceeded smoothly under mild basic conditions using DMAP to give **4** (98% yield). Epoxidation of the double bond with dimethyldioxirane (DMDO) and opening of the epoxide with methanol yielded 81% of the desired glucose building block **5**.

The introduction of different ester and carbonate protecting groups at the C2 hydroxyl group of **5** was achieved in the presence of the NSEC protecting group and furnished fully protected monosaccharides **6a−e** (Table 1).

Unfortunately, ether protecting groups like allyl and *p*-methoxybenzyl (PMB) could not be introduced successfully. Treatment of **5** with sodium hydride and allyl bromide in DMF at 0°C gave only 18% of the desired product **6f**, as cleavage of NSEC under these basic conditions occured. Allylation in the presence of allyl trichloroacetimidate[13] (AllTCA) allows for protection of hydroxyl groups under acidic conditions. However, the reaction of **5** and AllTCA promoted by TfOH in CH₂Cl₂/hexanes[13] or by TMSOTf yielded only 24% and 19% of **6f**, respectively, due to incomplete conversion.

To prepare the C2 *O*-allyl and *O*-PMB-protected glucose derivatives, a different synthetic route was chosen (Sch. 3). The C6 hydroxyl group of **3** was protected with TIPS before epoxidation with DMDO and epoxide opening with methanol afforded **7**.[14] The C2 hydroxyl group of **7** was then protected using *p*-methoxybenzyl chloride or allyl bromide and sodium hydride to give monosaccharides **8a** and **8b**. Desilylation with TBAF and C6 hydroxyl protection with NSECCl in the presence of DMAP yielded the desired monosaccharides **9** and **6f**.
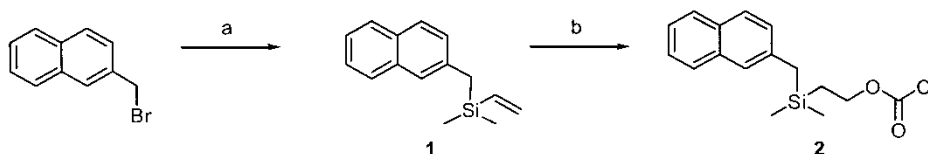
Scheme 1: (a) Mg, Et₂O, 3 hr, then chlorodimethylvinylsilane, Et₂O, reflux, 69%; (b) 1. 9-BBN, THF, 1 hr; 2. H₂O₂, NaOH, H₂O, THF, reflux, 1.5 hr, 60%; 3. phosgene, Et₂O, −15°C to rt, 2.5 hr, 63%.
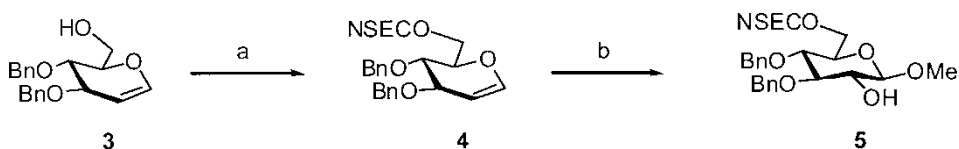
Scheme 2: (a) NSECCl, DMAP, CH_2Cl_2, rt, 15 hr, 98%; (b) 1. DMDO, CH_2Cl_2, 0°C, 1 hr; 2. MeOH, CH_2Cl_2, rt, 15 hr, 81% (2 steps).

To evaluate if NSEC is useful even at hindered hydroxyl groups, two monosaccharides with free C2 hydroxyl group were prepared (Sch. 4). Epoxidation of **10** with DMDO followed by opening of the epoxide with methanol and subsequent NSEC protection gave **11**, albeit in low yield. Benzylated thioglycoside **12**[14] was NSEC protected to provide **13** (59% yield). These results indicate that the NSEC group may be difficult to introduce in sterically demanding positions.

A method for the removal of the NSEC group was developed using monosaccharides **6a–f** and **9** (Table 2). Treatment with TBAF at 0°C allowed for NSEC cleavage in the presence of most hydroxyl protecting groups. Esters, including levulinoyl, benzoyl, pivaloyl, and acetyl esters, but also allyl and PMB ethers are not affected under these conditions, and monosaccharides **14a–d** and **8a,b** were obtained in excellent yield.

However, the NSEC group cannot be selectively removed in the presence of Fmoc. Reaction of **6e** with HF-pyridine fails to remove NSEC even after 7 d. Treatment with TBAF/acetic acid results in Fmoc cleavage, as a mixture of **5** (38%) and the monosaccharide diol (41%) was obtained.

Table 1: Protection of **5** with common hydroxyl protecting groups in the presence of NSEC.
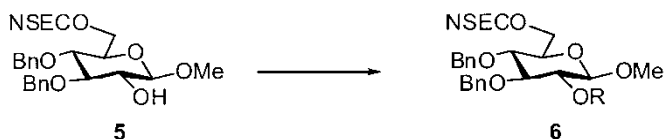
Product	R	Conditions	Yield (%)
6a	Lev	LevOH, DIPC, DMAP, CH_2, Cl_2, 0°C to rt, 15 hr	90
6b	Bz	BzCl, DMAP, CH_2Cl_2, 0°C to rt, 1.5 hr	86
6c	Piv	PivCl, DMAP, CH_2Cl_2, 0°C to rt, 3 hr	86
6d	Ac	AcCl, DMAP, CH_2Cl_2, 0°C to rt, 3 hr	93
6e	Fmoc	FmocCl, pyridine, rt, 2 d	66
6f	All	AllTCA,[a] TfOH, CH_2, Cl_2, hexanes, rt, 5 hr	24

[a]Allyl trichloroacetimidate.[13]
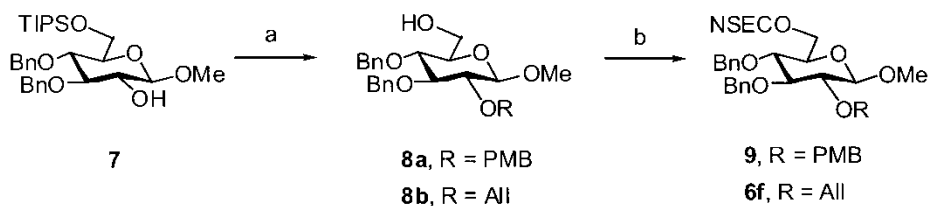
Scheme 3: (a) R = PMB: 1. PMBCl, NaH, DMF, 0°C to rt, 1 hr, 88%; 2. TBAF, AcOH, THF, 1 hr, 66% (2 steps); R = All: 1. AllBr, NaH, DMF, 0°C to rt, 1 hr; 2. TBAF, THF, 1 hr, 99% (2 steps); (b) NSECCl, DMAP, CH$_2$Cl$_2$, rt, 15 hr, 66% (R = PMB); 58% (R = All).

The stability of the NSEC group under conditions commonly used to cleave other modes of protection was studied. The NSEC group is not affected under deprotection conditions that facilitate the removal of levulinoyl (Lev), Fmoc, allyl, and PMB groups (Table 3). Monosaccharide alcohol **5** was obtained in good yield in all cases. For ester-type protecting groups (Bz, Piv, Ac) selective deprotection was not possible. These groups are usually cleaved under strongly basic conditions that also cleave the NSEC carbonate, thus leading to the monosaccharide diol.

With effective protocols to place and remove the NSEC group in hand, we used the new protecting group in the assembly of a disaccharide (Sch. 5). The phosphate glycosylating agent **15** was prepared via a one-pot procedure from the corresponding NSEC protected glucal **4** by epoxidation, subsequent epoxide opening with dibutyl phosphate, and benzoylation.[15] Protection of the C2 hydroxyl group proved difficult and furnished **15** in 20 to 47% yield. The C2 unprotected glycosyl phosphate was isolated as a byproduct in about 20% yield. Coupling of **15** with 4-penten-1-ol proceeded smoothly in the
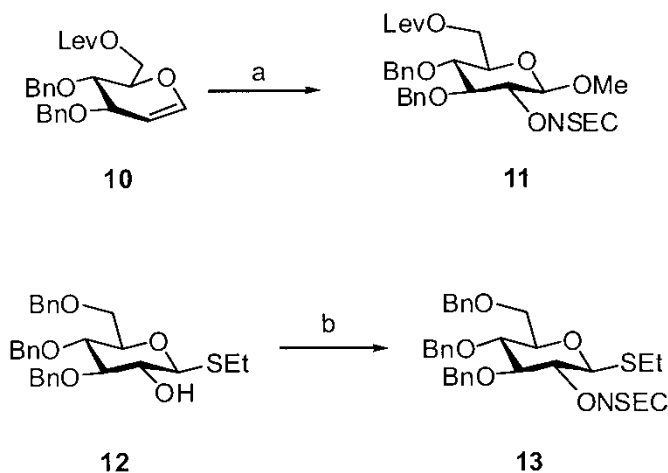
Scheme 4: (a) 1. DMDO, CH$_2$Cl$_2$, 0°C, 1 hr; 2. MeOH, CH$_2$Cl$_2$, rt, 15 hr; 3. NSECCl, DMAP, pyridine, CH$_2$Cl$_2$, rt, 2d, 25% (3 steps); (b) NSECCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt, 1d, 59%.

Table 2: Removal and functional group compatibility of NSEC protected monosaccharides.

Starting material	Product	R	Yield (%)
6a	**14a**	Lev	quant[a]
6b	**14b**	Bz	85[a]
6c	**14c**	Piv	91[a]
6d	**14d**	Ac	93[a]
6e	**14e**	Fmoc	—[b]
6f	**8b**	All	92[a]
9	**8a**	PMB	95[a]

[a]TBAF, THF, 0°C;
[b]Acetic acid-buffered TBAF was used. These conditions resulted in loss of Fmoc.

presence of TBSOTf to give **16** in 70% yield. Removal of the NSEC group with TBAF (96%) and subsequent glycosylation of **17** with phosphate **15** using TBSOTf yielded the desired disaccharide **18** in 83% yield.

CONCLUSION

In conclusion, a novel silyl-based protecting group to mask hydroxyl groups—2-[dimethyl(2-naphthylmethyl)silyl]ethoxy carbonate (NSEC)—is reported. This group can be readily introduced and removed in the presence of most commonly

Table 3: Stability of NSEC protected monosaccharides under various conditions.
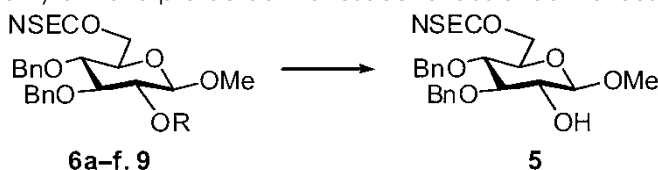
Starting material	R	Conditions	Yield (%)
6a	Lev	NH$_2$NH$_2$-HOAc, MeOH, CH$_2$Cl$_2$, rt, 1 hr	quant
6e	Fmoc	20% piperidine in DMF, rt, 30 min	95
6f	All	PdCl$_2$, H$_2$O, AcOH, NaOAc, 80°C, 40 min	83
9	PMB	DDQ, CH$_2$Cl$_2$, H$_2$O, rt, 3 hr	72
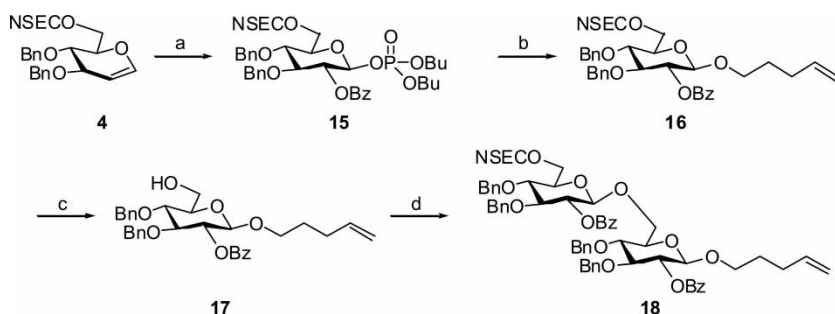
Scheme 5: (a) 1. DMDO, CH_2Cl_2, 0°C, 30 min; 2. $HOP(O)(OBu)_2$, CH_2Cl_2, −78°C, 30 min; 3. BzCl, DMAP, 0°C, 3 hr, 47% (3 steps); (b) 4-Penten-1-ol, TBSOTf, CH_2Cl_2, −78° to −30°C, 3 hr, 70%; (c) TBAF, THF, 0°C, 50 min, 96%; (d) **15**, TBSOTf, CH_2Cl_2, −78° to −30°C, 2 hr, 83%.

used hydroxyl protecting groups. The NSEC group can be selectively removed using TBAF in the presence of various ester and ether protecting groups. Other carbonates such as Fmoc are also cleaved under these conditions. The NSEC group is stable under a range of deprotection conditions, but strongly basic conditions result in the removal of the NSEC group.

The NSEC carbonate is compatible with glycosylation conditions using glycosyl phosphates and should find application in the synthesis of complex carbohydrates and combinatorial oligosaccharide libraries. This protecting group should be particularly useful for automated assembly of oligosaccharides, as its cleavage can be followed by UV.

EXPERIMENTAL

General

All chemicals were reagent grade and used as supplied unless otherwise noted. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were purified by a J. C. Meyer Solvent Dispensing System (two packed columns of neutral alumina, or in the case of toluene, one packed column of alumina followed by one packed column of Q5 reactant, i.e., a copper oxide oxygen scavenger). Solvents for chromatography and work-up procedures were distilled from commercially available technical grade solvents. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by UV or by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Fluka silica gel 60 (40–63 μm). 1H NMR spectra were recorded using a Varian Mercury XL 300 spectrometer (300 MHz) and a Bruker DRX2500 spectrometer (500 MHz) and are reported

in ppm (δ) relative to CHCl$_3$ (7.25 ppm) as an internal reference. Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were obtained using a Varian Mercury XL 300 spectrometer (75 MHz) and a Bruker DRX2500 spectrometer (125 MHz) and are reported in δ relative to CDCl$_3$ (77.0 ppm) as an internal reference. ^{31}P NMR spectra were obtained using a Varian Mercury XL 300 spectrometer (121 MHz) and are reported in d relative to H$_3$PO$_4$ (0.0 ppm) as an external reference. Optical rotations were measured on a Perkin-Elmer 241 polarimeter or a Jasco DIP-370 polarimeter (10 cm, 1 mL cell). IR spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer. High-resolution mass spectral (HRMS) analyses were performed by the MS-service at the Laboratory for Organic Chemistry at ETH Zürich. ESI-MS, EI-MS, and MALDI-MS were obtained on an IonSpec Ultra instrument. In the case of MALDI-MS, 2,5-dihydroxybenzoic acid (DHB) served as the matrix.

General Procedures

Protection of Alcohols with Acyl Chlorides: General Procedure A

To a solution of alcohol **5** in anhydrous CH$_2$Cl$_2$ (ca 14 mL/mmol) DMAP (2.2 to 2.3 equiv.) was added, followed by addition of the corresponding acyl chloride (1.9 to 2.1 equiv) at 0°C. The solution was stirred for 5 min at 0°C and then at rt until TLC analysis showed complete conversion. The mixture was diluted with hexanes/EtOAc (1 : 1) and filtered through a plug of silica gel. The solvents were evaporated and the crude product was purified by flash silica gel column chromatography.

NSEC Deprotection: General Procedure B

To a solution of the carbonate (1.0 equiv.) in THF (ca 20 mL/mmol) at 0°C a solution of TBAF in THF (1 M, 1.2 to 1.3 equiv) was added and the mixture was stirred at 0°C until TLC analysis showed complete conversion. Ethyl acetate was added and the organic layer was washed with saturated aqueous NaHCO$_3$ solution and water. The organic phase was dried with MgSO$_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography.

Dimethyl(2-naphthylmethyl)vinylsilane (1). The glassware was dried in the oven just before use. Magnesium (1.09 g, 45.2 mmol) was poured in a round bottom flask and diethyl ether (100 mL) was added. A few pellets of iodine were added several times until the brownish color persisted. 2-(Bromomethyl)-naphthalene (8.33 g, 37.7 mmol) was added and the solution was warmed in a water bath until boiling started. After 2 hr, chlorodimethylvinylsilane (5.70 g, 45.5 mmol) was added and the suspension was refluxed for 24 hr. The reaction was quenched with aqueous NH$_4$Cl solution (0.5 M) and the aqueous

phase was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica gel column chromatography (hexanes/EtOAc 20 : 1) to give **1** (5.92 g, 69%) as a colorless oil; $R_f = 0.50$ (hexanes/EtOAc 20 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.70 (m, 3 H), 7.46–7.37 (m, 3 H), 7.19 (dd, $J = 1.6$, 8.5 Hz, 1 H), 6.23–5.95 (m, 2 H), 5.74–5.65 (m, 1 H), 2.32 (s, 2 H), 0.09 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.9, 134.0, 132.6, 131.3, 128.2, 127.8, 127.7, 127.2, 126.0, 125.6, 124.6, 26.4, −3.4. IR ($CHCl_3$): ν_{max} cm^{-1} 3155, 2253, 1793, 1630, 1598, 1466, 1380, 1097. EI-MS: m/z (M^+) calcd 226.1178, obsd 226.1171.

2-[Dimethyl(2-naphthylmethyl)silyl]ethyl chloroformate (2). A solution of silane **1** (4.79 g, 21.2 mmol) in THF (15 mL) was added to a solution of 9-BBN in THF (0.5 M, 43 mL, 21.2 mmol) at rt under nitrogen.[16] After 1 hr, ethanol (5 mL), water (2 mL), and an aqueous NaOH solution (3 M, 18 mL) were added. H_2O_2 (30%, 0.45 mL) was added dropwise at rt and the solution was heated to reflux. After 1 hr, the mixture was cooled to rt, diluted with aqueous $NaHCO_3$ solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by flash silica gel column chromatography (hexanes/EtOAc 3 : 2) gave 2-[dimethyl(2-naphthylmethyl)silyl]ethanol (3.02 g, 12.4 mmol, 58%) as a colorless oil, which was azeotroped with toluene three times and dried under high vacuum for 30 min. The compound was dissolved in diethyl ether (50 mL) and slowly cannulated into a solution of phosgene in toluene (20%, 13 mL, 24.8 mmol) at −15°C. After addition, the solution was warmed to rt under argon. After 2.5 hr, the solution was degassed with nitrogen, equipping the system with an exhaust line into an alkaline bath. After 30 min, the solvent was evaporated and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc 3 : 1) to yield **2** (2.40 g, 37%, 3 steps) as a colorless oil; $R_f = 0.75$ (hexanes/EtOAc 3 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.71 (m, 3 H), 7.46–7.36 (m, 3 H), 7.15 (d, $J = 6.5$ Hz, 1 H), 4.40–4.34 (m, 2 H), 2.31 (s, 2 H), 1.19–1.13 (m, 2 H), 0.09 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 136.9, 134.0, 131.4, 128.2, 127.8, 127.8, 127.3, 126.2, 125.6, 124.9, 71.0, 26.0, 16.0, −3.1. IR ($CHCl_3$): ν_{max} cm^{-1} 3158, 2253, 1768, 1632, 1466, 1374, 1149, 1092, 913. EI-MS: m/z (M^+ - CO_2) calcd 262.0945, obsd 262.0941.

3,4-Di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-D-glucal (4). A solution of NSECCl (1.00 g, 3.26 mmol) in CH_2Cl_2 (10 mL) was added to a solution of 3,4-di-*O*-benzyl-D-glucal **3** (1.00 g, 3.06 mmol) in CH_2Cl_2 (10 mL), followed by DMAP (0.560 g, 4.59 mmol) before the reaction was stirred at rt overnight. After 15 hr, the solution was diluted with ethyl acetate (60 mL) and washed with HCl (5% aqueous, 60 mL), saturated aqueous $NaHCO_3$ solution (60 mL), and brine (2 × 60 mL). The combined organic layers were dried over

MgSO$_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc 6 : 1) to yield **4** (1.78 g, 98%) as a colorless oil; R$_f$ = 0.67 (hexanes/EtOAc 3 : 1); [α]$_D$ +0.34 (*c* 0.85, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78–7.71 (m, 3 H), 7.44–7.29 (m, 13 H), 7.16 (dd, *J* = 1.8, 6.6 Hz, 1 H), 6.40 (dd, *J* = 1.2, 5.0 Hz, 1 H), 4.91 (dd, *J* = 2.8, 3.4 Hz, 1 H), 4.86 (d, *J* = 11.3 Hz, 1 H), 4.64–4.69 (m, 2 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.45–4.43 (m, 2 H), 4.25–4.21 (m, 3 H), 4.15–4.12 (m, 1 H), 3.82–3.79 (m, 1 H), 2.30 (s, 2 H), 1.12–1.08 (m, 2 H), 0.07 (s, 6 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.0, 144.4, 138.2, 137.9, 137.1, 133.8, 131.1, 128.5, 128.5, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.0, 125.9, 125.3, 124.5, 100.0, 75.1, 74.9, 74.0, 73.6, 70.4, 66.2, 65.8, 25.8, 15.9, −3.4. IR (CHCl$_3$): v_{max} cm^{-1} 2964, 1739, 1646, 1251, 1067. ESI-MS: *m/z* (M + Na)$^+$ calcd 619.2486, obsd 619.2477.

Methyl 3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxy-carbonyl}-β-D-glucopyranoside (5). Glucal **4** (0.740 g, 1.24 mmol) was coevaporated with toluene three times, dried under high vacuum for 1 hr, and was then dissolved in anhydrous CH$_2$Cl$_2$ (10 mL). The solution was cooled to 0°C and dimethyldioxirane (33 mL of a 0.08 M solution in acetone, 2.64 mmol) was added. After 1 hr, the solution was concentrated and the product dried for 10 min under high vacuum. CH$_2$Cl$_2$ (10 mL) followed by methanol (10 mL) were added at 0°C, and the solution was warmed to rt and stirred overnight. After 15 hr, the solvent was removed and the crude product was purified by flash silica gel column chromatography (hexanes/ EtOAc 3 : 1 to 3 : 2) to yield **5** as a colorless solid (0.683 g, 81%); mp. 83–84°C; R$_f$ = 0.30 (hexanes/EtOAc 3 : 2); [α]$_D$ +2.52 (*c* 0.95, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78–7.70 (m, 3 H), 7.44–7.27 (m, 13 H), 7.16 (dd, *J* = 1.6, 6.9 Hz, 1 H), 4.95–4.85 (m, 3 H), 4.61 (d, *J* = 10.9 Hz, 1 H), 4.44–4.42 (m, 1 H), 4.24–4.18 (m, 4 H), 3.61–3.53 (m, 7 H), 2.30–2.29 (m, 3 H), 1.11–1.08 (m, 2 H), 0.07 (s, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.2, 138.7 137.9, 137.3, 134.0, 131.3, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.2, 126.1, 125.6, 124.8, 103.8, 84.6, 77.5, 75.3, 75.3, 74.8, 73.4, 66.5, 66.4, 57.4, 26.0, 16.1, -3.1. IR (CHCl$_3$): v_{max} cm^{-1} 3067, 1741, 1600, 1269, 1224, 1112. ESI-MS: *m/z* (M + Na)$^+$ calcd 667.2698, obsd 667.2707.

Methyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)-silyl]ethoxycarbonyl}-β-D-glucopyranoside (6a). Levulinic acid (0.016 mL, 0.15 mmol) and DMAP (0.020 g, 0.161 mmol) were dissolved in CH$_2$Cl$_2$ (1 mL) and the solution was cooled to 0°C. DIPC (0.023 mL, 0.15 mmol) was added under vigorous stirring. After 10 min, a solution of glucose **5** (0.094 g, 0.146 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise and the reaction was stirred at rt overnight. After 15 hr, the solution was diluted with ethyl acetate, the precipitate was filtered through Celite, and the solution was concentrated. The residue was diluted with hexanes/EtOAc

(3 : 2), filtered through a silica pad, and concentrated to yield **6a** (0.096 g, 90%) as a colorless oil; $R_f = 0.31$ (hexanes/EtOAc 3 : 2); $[\alpha]_D$ −5.52 (*c* 1.15, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78–7.70 (m, 3 H), 7.44–7.26 (m, 13 H), 7.16 (dd, *J* = 1.8, 8.5 Hz, 1 H), 5.00–4.96 (m, 1 H), 4.84 (d, *J* = 10.9 Hz, 1 H), 4.78 (d, *J* = 11.5 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 10.9 Hz, 1 H), 4.43 (dd, *J* = 2.1, 11.6 Hz, 1 H), 4.30–4.20 (m, 4 H), 3.72–3.69 (m, 1 H), 3.63–3.60 (m, 1 H), 3.58–3.55 (m, 1 H), 3.45 (s, 3 H), 2.72–2.68 (m, 2 H), 2.58–2.46 (m, 2 H), 2.30 (s, 2 H), 2.16 (s, 3 H), 1.11–1.08 (m, 2 H), 0.07 (s, 6 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.4, 171.7, 155.2, 138.3, 137.8, 137.3, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.2, 126.1, 125.6, 124.8, 101.9, 83.0, 77.1, 75.3, 75.2, 73.6, 73.3, 66.4, 66.3, 57.0, 38.1, 30.0, 28.2, 26.0, 16.1, −3.1. IR (CHCl$_3$): v_{max} cm^{-1} 3054, 2896, 1747, 1718, 1455, 1359, 1241, 1152, 1073. ESI-MS: *m/z* (M + Na)$^+$ calcd 765.3065, obsd 765.3056.

Methyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthyl-methyl)silyl]ethoxycarbonyl}-β-D-glucopyranoside (6b). Following General Procedure A, alcohol **5** (0.090 g, 0.14 mmol), DMAP (0.038 g, 0.31 mmol), and benzoyl chloride (0.032 mL, 0.28 mmol) were reacted in CH$_2$Cl$_2$ (2 mL) for 90 min at rt. Purification by flash silica gel column chromatography (hexanes/EtOAc 4 : 1) gave **6b** (0.090 g, 86%) as a colorless oil; $R_f = 0.25$ (hexanes/EtOAc 4 : 1); $[\alpha]_D$ +28.7 (*c* 0.46, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.01 (d, *J* = 7.4 Hz, 2 H), 7.77–7.68 (m, 3 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.45–7.24 (m, 10 H), 7.16–7.10 (m, 6 H), 5.25 (dd, *J* = 7.8, 9.2 Hz, 1 H), 4.86 (d, *J* = 10.8 Hz, 1 H), 4.73 (d, *J* = 11.1 Hz, 1 H), 4.66 (d, *J* = 11.1 Hz, 1 H), 4.60 (d, *J* = 10.8 Hz, 1 H), 4.48–4.43 (m, 2 H), 4.30–4.18 (m, 3 H), 3.84 (t, *J* = 9.1 Hz, 1 H), 3.71–3.59 (m, 2 H), 3.43 (s, 3 H), 2.29 (s, 2 H), 1.12–1.06 (m, 2 H), 0.06 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.0, 154.8, 137.5, 137.4, 137.0, 133.6, 133.0, 131.0, 129.7, 129.7, 128.4, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 125.8, 125.2, 124.4, 101.7, 82.7, 77.5, 75.1, 75.0, 73.5, 73.1, 66.2, 66.1, 56.8, 25.9, 15.9, −3.2. IR (CHCl$_3$): v_{max} cm^{-1} 3036, 2995, 1733, 1451, 1395, 1318, 1256, 1092, 1067. ESI-MS: *m/z* (M + Na)$^+$ calcd 771.2965, obsd 771.2969.

Methyl 3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]-ethoxycarbonyl}-2-*O*-pivaloyl-β-D-glucopyranoside (6c). Following General Procedure A, alcohol **5** (0.090 g, 0.14 mmol), DMAP (0.038 g, 0.31 mmol) and pivaloyl chloride (0.034 mL, 0.27 mmol) were reacted in CH$_2$Cl$_2$ (2 mL) for 3 hr at rt. Flash silica gel column chromatography (hexanes/EtOAc 4 : 1) gave **6c** (0.086 g, 86%) as a colorless solid; mp 82–83°C; $R_f = 0.20$ (hexanes/EtOAc 4 : 1); $[\alpha]_D$ −3.5 (*c* 0.49, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74–7.65 (m, 3 H), 7.40–7.18 (m, 13 H), 7.11 (dd, *J* = 1.7, 8.3 Hz, 1 H), 5.01 (dd, *J* = 7.9, 8.9 Hz, 1 H), 4.78 (d, *J* = 10.8 Hz, 1 H), 4.71 (d, *J* = 11.1 Hz, 1 H), 4.66 (d, *J* = 11.1 Hz, 1 H), 4.53 (d, *J* = 10.8 Hz, 1 H), 4.40 (dd, *J* = 2.0,

11.5 Hz, 1 H), 4.27–4.14 (m, 4 H), 3.71–3.50 (m, 3 H), 3.41 (s, 3 H), 2.25 (s, 2 H), 1.16 (s, 9 H), 1.09–1.01 (m, 2 H), 0.02 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 176.9, 155.0, 137.9, 137.6, 137.1, 133.8, 131.1, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 127.6, 127.5, 127.4, 127.0, 125.9, 125.3, 124.5, 102.0, 83.1, 77.3, 75.0, 74.8, 73.1, 72.9, 66.2, 66.1, 56.8, 38.8, 27.0, 25.8, 15.8, -3.4. IR (CHCl$_3$): ν_{max} cm^{-1} 2954, 1739, 1456, 1395, 1359, 1262, 1139, 1092. ESI-MS: m/z (M + Na)$^+$ calcd 751.3278, obsd 751.3262.

Methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)-silyl]ethoxycarbonyl}-β-D-glucopyranoside (6d). Following General Procedure A, alcohol **5** (0.080 g, 0.12 mmol), DMAP (0.033 g, 0.27 mmol), and acyl chloride (0.018 mL, 0.25 mmol) were stirred in CH$_2$Cl$_2$ (2 mL) for 90 min at rt. Flash silica gel column chromatography (hexanes/EtOAc 4 : 1) yielded **6d** (0.079 g, 93%) as a colorless oil; R$_f$ = 0.25 (hexanes/EtOAc 4 : 1); $[\alpha]_D$ +5.4 (*c* 0.24, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.77–7.68 (m, 3 H), 7.44–7.24 (m, 13 H), 7.14 (dd, J = 1.9, 8.3 Hz, 1 H), 4.97 (dd, J = 8.2, 8.6 Hz, 1 H), 4.83 (d, J = 10.8 Hz, 1 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.67 (d, J = 11.4 Hz, 1 H), 4.58 (d, J = 10.8 Hz, 1 H), 4.43 (dd, J = 2.1, 11.4 Hz, 1 H), 4.29–4.17 (m, 4 H), 3.70–3.49 (m, 3 H), 3.43 (s, 3 H), 2.28 (s, 2 H), 1.97 (s, 3 H), 1.11–1.05 (m, 2 H), 0.05 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 169.4, 154.8, 137.8, 137.3, 137.0, 133.7, 131.0, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 127.4, 126.9, 125.8, 125.2, 124.4, 101.5, 82.9, 77.6, 75.1, 75.0, 73.0, 72.8, 66.2, 66.0, 56.7, 25.9, 21.0, 15.9, -3.2. IR (CHCl$_3$): ν_{max} cm^{-1} 2964, 2933, 1728, 1456, 1380, 1272, 1128, 1072. ESI-MS: m/z (M + Na)$^+$ calcd 709.2809, obsd 709.2812.

Methyl 3,4-di-*O*-benzyl-2-*O*-(9-fluorenylmethoxycarbonyl)-6-*O*-{2-[di-methyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-D-glucopyranoside (6e). To a solution of **5** (0.100 g, 0.155 mmol) in anhydrous pyridine (3 mL) FmocCl (0.080 g, 0.31 mmol) was added at 0°C and the white suspension was stirred at rt. After 24 hr, additional FmocCl (0.040 g, 0.15 mmol) was added. The clear solution was diluted with ethyl acetate (40 mL) after an additional 24 hr, washed with HCl (3% aqueous, 2 × 30 mL), saturated aqueous NaHCO$_3$ solution (2 × 30 mL) and brine (2 × 30 mL), dried over MgSO$_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc 3 : 1, then toluene/EtOAc 40 : 1) to yield **6e** (0.089 g, 66%) as a colorless oil; R$_f$ = 0.30 (toluene/EtOAc 25 : 1); $[\alpha]_D$ −6.3 (*c* 0.16, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.80–7.71 (m, 5 H), 7.64–7.57 (m, 2 H), 7.46–7.22 (m, 17 H), 7.17 (dd, J = 1.6, 8.4 Hz, 1 H), 4.88–4.72 (m, 4 H), 4.61 (d, J = 11.0 Hz, 1 H), 4.54–4.20 (m, 8 H), 3.77 (t, J = 9.0 Hz, 1 H), 3.67–3.55 (m, 2 H), 3.50 (s, 3 H), 2.31 (s, 2 H), 1.14–1.08 (m, 2 H), 0.08 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 154.9, 154.4, 143.4, 143.2, 141.3, 137.8, 137.4, 137.1, 133.8, 131.1, 128.5, 128.3, 128.1, 128.0, 127.8, 127.8, 127.8,

127.7, 127.7, 127.6, 127.6, 127.1, 127.0, 125.9, 125.3, 125.1, 125.0, 124.5, 120.0, 101.5, 82.7, 77.5, 77.4, 75.2, 75.1, 73.1, 70.1, 66.2, 65.9, 56.9, 46.7, 25.8, 15.8, −3.4. IR (CHCl$_3$): v_{max} cm^{-1} 3005, 1749, 1446, 1385, 1256, 1087, 1072. ESI-MS: m/z (M + Na)$^+$ calcd 884.4, obsd 884.2.

Methyl 2-*O*-allyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)-silyl]ethoxycarbonyl}-β-D-glucopyranoside (6f). Procedure 1: Glucose **5** (0.049 g, 0.075 mmol) and freshly prepared allyl trichloroacetimidate[13] (0.079 g, 0.39 mmol) were dissolved in CH$_2$Cl$_2$ (2 mL). The solution was cooled to 0°C and TMSOTf (0.008 mL, 0.038 mmol) was added. The reaction was warmed to rt and stirred overnight. After 15 hr, a second aliquot of allyl trichloroacetimidate (0.070 g, 0.35 mmol) and TMSOTf (0.010 mL, 0.040 mmol) was added at 0°C. The reaction was then warmed to rt. After 1 hr, a few drops of Et$_3$N were added, the reaction mixture was concentrated, and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc 3:1) to give **6f** (10 mg, 19%) as a colorless oil.

Procedure 2: Glucose **5** (40 mg, 0.062 mmol) and allyl trichloroacetimidate[13] (0.049 g, 0.124 mmol) were dissolved in CH$_2$Cl$_2$ (1 mL), and hexanes (2 mL) and triflic acid (0.005 mL, 0.06 mmol) were added. The reaction was stirred at rt overnight. After 15 hr, the reaction mixture was filtered and the filtrate was washed with saturated aqueous NaHCO$_3$ solution and water, dried over MgSO$_4$, filtered, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 3:1) gave **6f** (10 mg, 24%) as a colorless oil.

Procedure 3: A solution of NSECCl (0.174 g, 0.52 mmol) in CH$_2$Cl$_2$ (3 mL) was added to a solution of **8b** (0.154 g, 0.37 mmol) in CH$_2$Cl$_2$ (5 mL) followed by DMAP (0.068 g, 0.56 mmol) and the reaction was stirred at rt overnight. After 15 hr, the solution was diluted with ethyl acetate (20 mL) and washed with HCl (5% aqueous, 40 mL), saturated aqueous NaHCO$_3$ solution (40 mL), and brine (40 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc 6:1 to 3:1) to yield **6f** (0.144 g, 58%) as a colorless oil; R$_f$ = 0.78 (hexanes/EtOAc 3:2); $[\alpha]_D$ −2.19 (*c* 3.2, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71−7.63 (m, 3 H), 7.37−7.10 (m, 13 H), 7.09 (dd, *J* = 1.7, 8.5 Hz, 1 H), 5.91−5.83 (m, 1 H), 5.24−5.23 (m, 1 H), 5.20 (m, 1 H), 5.11−5.09 (m, 1 H), 4.90 (d, *J* = 10.9 Hz, 1 H), 4.80 (d, *J* = 10.9 Hz, 1 H), 4.72 (d, *J* = 10.9 Hz, 1 H), 4.51 (d, *J* = 10.9 Hz, 1 H), 4.35−4.30 (m, 2 H), 4.19−4.09 (m, 6 H), 3.56 (t, *J* = 8.9 Hz, 1 H), 3.45−3.41 (m, 5 H), 3.25−3.22 (m, 1 H), 2.23 (s, 2 H), 1.04−1.00 (m, 2 H), 0.06 (s, 6 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.2, 138.7, 138.0, 137.3, 135.2, 134.0, 131.3, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.2, 126.1, 125.6, 124.8, 117.2, 104.6, 84.8, 82.1, 77.7, 75.9, 75.3, 73.8, 73.1, 66.6, 66.3, 57.3, 26.0, 16.1, −3.1. IR (CHCl$_3$): v_{max} cm^{-1} 3415, 3025, 2390, 1739, 1523, 1451, 1251, 1066, 1046. ESI-MS: m/z (M + Na)$^+$ calcd 707.3011, obsd 707.3021.

Methyl 3,4-di-*O*-benzyl-6-*O*-tri-isopropylsilyl-β-D-glucopyranoside (7). 3,4-Di-*O*-benzyl-D-Glucal[17] (0.348 g, 1.07 mmol) was dissolved in DMF. Imidazole (0.145 g, 2.14 mmol) followed by TIPSCl (0.28 mL, 1.28 mmol) were added; and the reaction was stirred at rt overnight. After 23 hr, water was added (60 mL) and the solution was extracted with ethyl acetate (2 × 60 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (70 mL), water (70 mL), and brine (70 mL), dried over MgSO$_4$, filtered, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 3 : 2) gave the TIPS protected glycal as a colorless oil (0.502 g), which was coevaporated with toluene three times and dried under high vacuum for 1 hr. The glycal was dissolved in CH$_2$Cl$_2$ (10 mL) and the solution was cooled to 0°C. Dimethyldioxirane (26 mL of a 0.08 M solution in acetone, 2.1 mmol) was added. After 1 hr, the solvents were removed and the product was dried for 10 min under high vacuum. CH$_2$Cl$_2$ (10 mL) followed by methanol (10 mL) were added at 0°C, and the solution was warmed to rt and stirred overnight. After 15 hr, the solvent was removed and the crude product was purified by flash silica gel column chromatography (hexanes/ EtOAc 3 : 2) to give **7** (0.538 g, 95%, 3 steps) as a colorless solid. The spectral data are consistent with previously reported data.[18]

Methyl 3,4-di-*O*-benzyl-2-*O*-*para*-methoxybenzyl-β-D-glucopyranoside (8a). Glucose **7** (0.198 g, 0.37 mmol) was dissolved in DMF (5 mL) and the solution was cooled to 4°C. NaH (0.030 g of a 60% suspension in mineral oil, 0.74 mmol) and *p*-methoxybenzyl chloride (0.080 mL, 0.56 mmol) were added and the solution was warmed to rt. After 1 hr, the reaction was quenched by addition of water (20 mL) at 0°C and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (50 mL), dried over MgSO$_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc 3 : 2 to 2 : 3) to give methyl 3,4-di-*O*-benzyl-2-*O*-*para*-methoxybenzyl-6-*O*-triisopropylsilyl-β-D-glucopyranoside (0.211 g). The product was dissolved in THF (5 mL) and TBAF (0.70 mL of a 1 M solution in THF, 0.64 mmol) was added at rt. After 10 min, acetic acid (0.020 mL, 0.32 mmol) was added and the solution was stirred for 1 hr. Water (20 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (40 mL), dried over MgSO$_4$, filtered, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 3 : 2 to 2 : 3) gave **8a** (0.118 g, 66%, 2 steps) as a colorless oil. Characterization data were consistent with literature data.[19]

Methyl 2-*O*-allyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (8b). Glucose **7** (0.185 g, 0.35 mmol) was dissolved in DMF (5 mL) and the solution was cooled to 4°C. NaH (0.030 g of a 60% suspension in mineral oil, 0.70 mmol)

and allyl bromide (0.050 mL, 0.52 mmol) were added and the solution was warmed to rt. After 1 hr, the reaction was quenched by addition of water (20 mL) at 0°C. After extraction with ethyl acetate (3×20 mL), the organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue (0.205 g) was dissolved in THF (5 mL), TBAF (0.80 mL of a 1 M solution in THF, 0.74 mmol) was added at rt, and the reaction was stirred for 1 hr. Water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give **8b** as a colorless oil (0.144 g, 99%). Characterization data were consistent with literature data.[19]

Methyl 3,4-di-*O*-benzyl-2-*O*-*para*-methoxybenzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-D-glucopyranoside (9). A solution of NSECCl (0.140 g, 0.33 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **8a** (0.118 g, 0.24 mmol) in CH_2Cl_2 (5 mL), followed by addition of DMAP (0.044 g, 0.36 mmol), and the reaction was stirred at rt overnight. After 15 hr, the solution was diluted with ethyl acetate (20 mL) and washed with HCl (5% aqueous, 40 mL), saturated aqueous $NaHCO_3$ solution (40 mL), and brine (40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash silica gel column chromatography (hexanes/EtOAc 6:1) gave **9** (0.122 g, 66%) as a colorless oil; $R_f = 0.27$ (hexanes/EtOAc 3:1); $[\alpha]_D$ +15.7 (*c* 2.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.64 (m, 3 H), 7.37–7.18 (m, 12 H), 7.09 (dd, $J = 1.8, 8.4$ Hz, 1 H), 6.78–6.76 (m, 2 H), 4.87 (d, $J = 11.1$ Hz, 1 H), 4.79 (d, $J = 10.8$ Hz, 1 H), 4.76 (d, $J = 10.7$ Hz, 1 H), 4.71 (d, $J = 11.1$ Hz, 1 H), 4.56 (d, $J = 10.7$ Hz, 1 H), 4.51 (d, $J = 10.8$ Hz, 1 H), 4.34–4.33 (m, 1 H), 4.24–4.14 (m, 4 H), 3.73 (s, 3 H), 3.72–3.57 (m, 1 H), 3.49 (s, 3 H), 3.46–3.33 (m, 1 H), 2.23 (s, 2 H), 1.04–1.01 (m, 2 H), 0.07 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 155.2, 138.8, 138.0, 130.0, 128.7, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.2, 126.1, 125.6, 124.8, 114.0, 104.9, 84.8, 82.1, 76.9, 75.8, 75.3, 74.6, 73.1, 66.6, 66.4, 57.3, 55.5, 26.1, 16.1, -3.1. IR ($CHCl_3$): ν_{max} cm^{-1} 3008, 1741, 1513, 1454, 1067. ESI-MS: m/z $(M + Na)^+$ calcd 787.3273, obsd 787.3285.

Methyl 2-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-3,4-di-*O*-benzyl-6-*O*-levulinoyl-β-D-glucopyranoside (11). Glucal **10**[20] (0.360 g, 0.85 mmol) was coevaporated with toluene three times, dried under high vacuum for 1 hr and then dissolved in CH_2Cl_2 (10 mL). The solution was cooled to 0°C and dimethyldioxirane (21 mL of a 0.08 M solution in acetone, 1.70 mmol) was added. After 1 hr, the solvent was removed under reduced pressure and the product was dried for 10 min under high vacuum. CH_2Cl_2 (7 mL) followed by methanol (7 mL) were added at 0°C and the

solution was stirred for 3 hr. The solvent was removed and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc 3:2 to 2:3) to give methyl 3,4-di-*O*-benzyl-6-*O*-levulinoyl-β-D-glucopyranoside (0.333 g). An aliquot of the obtained compound (0.049 g) was redissolved in CH_2Cl_2 (2 mL), and pyridine (0.5 mL) and DMAP (0.050 g, 0.41 mmol) were added. The solution was stirred for 1 hr, and then a solution of NSECCl (0.130 g, 0.41 mmol) in CH_2Cl_2 (0.5 mL) was added. The reaction was stirred for 2 d, diluted with ethyl acetate (10 mL), and washed with HCl (5% aqueous, 10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 2:3) gave **11** (0.024 g, 25%, 3 steps) as a colorless oil; $R_f = 0.26$ (hexanes/EtOAc 2:3); $[\alpha]_D$ −2.67 (*c* 4.5, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.78−7.69 (m, 3 H), 7.44−7.25 (m, 13 H), 7.15 (dd, $J = 1.7, 8.4$ Hz, 1 H), 4.85−4.74 (m, 4 H), 4.60 (d, $J = 10.8$ Hz, 1 H), 4.38 (dd, $J = 2.2, 11.9$ Hz, 1 H), 4.33 (d, $J = 9.6$ Hz, 1 H), 4.28−4.20 (m, 3 H), 3.74−3.70 (m, 1 H), 3.64−3.58 (m, 1 H), 3.54−3.51 (m, 1 H), 3.48 (s, 3 H), 2.77−2.72 (m, 2 H), 2.60 (t, $J = 6.5$ Hz, 2 H), 2.29 (s, 2 H), 2.19 (s, 3 H), 1.09−1.05 (m, 2 H), 0.06 (d, $J = 3.0$ Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 206.5, 172.6, 154.5, 138.8, 137.8, 137.3, 134.0, 131.3, 128.7, 128.6, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.2, 126.1, 125.6, 124.8, 101.9, 83.3, 77.6, 77.4, 75.5, 75.3, 73.3, 66.7, 63.1, 57.2, 38.1, 30.1, 28.1, 25.9, 16.0, −3.2, −3.2. IR (CHCl₃): v_{max} cm⁻¹ 3035, 1744, 1251, 1159, 1067, 1026. ESI-MS: m/z (M + Na)⁺ calcd 765.3065, obsd 765.3080.

Thioethyl 2-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (13). Glucose **12**[14] (0.050 g, 0.10 mmol) was dissolved in CH_2Cl_2 (1.5 mL). A solution of NSECCl (0.070 g, 0.20 mmol) in CH_2Cl_2 (1 mL) followed by Et₃N (0.021 mL, 0.15 mmol) and DMAP (0.0024 g, 0.02 mmol) was added, and the solution was stirred at rt. After 24 hr, the reaction was diluted with ethyl acetate (20 mL) and washed with HCl (5% aqueous, 20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 6:1 to 3:1) gave product **13** (0.045 g, 59%) as a colorless oil; $R_f = 0.42$ (hexanes/EtOAc 3:1); $[\alpha]_D$ +0.75 (*c* 10.7, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.80−7.71 (m, 3 H), 7.47−7.15 (m, 19 H), 4.89−4.75 (m, 4 H), 4.66−4.55 (m, 3 H), 4.44 (d, $J = 10.0$ Hz, 1 H), 4.28−4.22 (m, 2 H), 3.81−3.69 (m, 4 H), 3.54−3.50 (m, 1 H), 2.80−2.69 (m, 2 H), 2.30 (s, 2 H), 1.30 (t, $J = 7.4$ Hz, 3 H), 1.12−1.06 (m, 2 H), 0.07 (s, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 154.1, 138.0, 138.0, 137.7, 137.0, 133.7, 131.0, 128.9, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 126.9, 125.8, 125.2, 124.5, 84.5, 83.4, 79.4, 77.6, 75.9, 75.4, 75.1, 73.5, 68.8, 66.6, 25.9,

24.2, 15.9, 15.1, −3.2. IR (CHCl$_3$): $v_{\max}$ cm^{-1} 3008, 1748, 1600, 1451, 1359, 1251, 1087. ESI-MS: m/z (M + Na)$^+$ calcd 787.3095, obsd 787.3100.

Methyl 3,4-di-*O*-benzyl-2-*O*-*para*-methoxybenzyl-β-D-glucopyranoside (8a). Following General Procedure B, **9g** (0.026 g, 0.034 mmol) was treated with TBAF (0.040 mL of a 1 M solution in THF, 0.040 mmol) in THF (1 mL) for 45 min. Purification by flash silica gel chromatography (hexanes/EtOAc 3 : 2) gave **8a** (0.015 g, 95%) as a colorless oil. The spectroscopic data are consistent with those reported above.

Methyl 2-*O*-allyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (8b). Following General Procedure B, **6j** (0.029 g, 0.042 mmol) was treated with TBAF (0.050 mL of a 1 M solution in THF, 0.051 mmol) in THF (1 mL) for 40 min. Purification by flash silica gel chromatography (hexanes/EtOAc 3 : 2 to 2 : 3) gave **8b** (0.016 g, 92%) as a colorless oil. The spectroscopic data are consistent with those reported above.

Methyl 3,4-di-*O*-benzyl-2-*O*-levulinoyl-β-D-glucopyranoside (14a). Following General Procedure B, **6a** (0.046 g, 0.060 mmol) was treated with TBAF (0.075 mL of a 1 M solution in THF, 0.070 mmol) in THF (1.2 mL) for 30 min. Purification by flash silica gel chromatography (hexanes/EtOAc 2 : 3) gave **14a** (0.028 g, quantitative yield) as a colorless oil. Characterization data were consistent with literature data.[19]

Methyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (14b). Following General Procedure B, **6b** (0.035 g, 0.047 mmol) was treated with TBAF (0.060 mL of a 1 M solution in THF, 0.060 mmol) for 30 min. Flash silica gel column chromatography (hexanes/EtOAc 3 : 2) gave **14b** (0.019 g, 85%) as a colorless solid; mp 94–95°C. Characterization data were consistent with literature data.[21]

Methyl 3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (14c). Following General Procedure B, **6c** (0.080 g, 0.11 mmol) was treated with TBAF (0.14 mL of a 1 M solution in THF, 0.14 mmol) for 45 min. Flash silica gel column chromatography (hexanes/EtOAc 3 : 1) gave **14c** (0.047 g, 91%) as a colorless solid; mp 73–74°C. Characterization data were consistent with literature data.[18]

Methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (14d). Following General Procedure B, **6d** (0.062 g, 0.090 mmol) was treated with TBAF (0.11 mL of a 1 M solution in THF, 0.11 mmol) for 45 min. Flash silica gel column chromatography (hexanes/EtOAc (2 : 1) gave **14d** (0.035 g, 93%) as a colorless solid; mp 79–80°C. Characterization data were consistent with literature data.[21]

Removal of the levulinoyl group: Methyl 3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl (2-naphthylmethyl)silyl]ethoxycarbonyl}-β-ᴅ-glucopyranoside (5). A solution of hydrazine acetate in methanol (0.3 M) was prepared and an aliquot (0.10 mL, 0.030 mmol) was added to a solution of glucose **6a** (0.020 g, 0.027 mmol) in CH₂Cl₂ (1 mL). After 1.5 hr, the reaction was quenched by addition of a few drops of acetone, diluted with CH₂Cl₂, and concentrated. Flash silica gel column chromatography (hexanes/EtOAc 3 : 1) gave **5** (0.039 g, quantitative yield). Spectroscopic data are consistent with the data reported above.

Removal of the Fmoc group: Methyl 3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl-(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-ᴅ-glucopyranoside (5). A solution of **6e** (0.036 g, 0.042 mmol) in anhydrous DMF (1.6 mL) and piperdine (0.4 mL) was stirred for 30 min at rt. Water (2 mL) was added and the mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), dried with MgSO₄, filtered, and evaporated. Purification by flash silica gel column chromatography (hexanes/EtOAc 5 : 1 to 2 : 1) yielded **5** (0.026 g, 95%). Spectroscopic data are consistent with the data reported above.

Removal of the allyl ether group: Methyl 3,4-Di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-ᴅ-glucopyrano-side (5). Glucose **6j** (0.041 g, 0.060 mmol) was dissolved in AcOH/H₂O (9 : 1, 4 mL). PdCl₂ (0.030 g, 0.15 mmol) followed by NaOAc (0.030 g, 0.36 mmol) were added and the solution was heated to 80°C. After 40 min, the reaction was cooled to rt, diluted with ethyl acetate, and washed with saturated aqueous NaHCO₃ solution (3 × 30 mL), brine (30 mL), and water (30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield **5** (0.032 g, 83%). Spectroscopic data are consistent with the data reported above.

Removal of the PMB ether group: Methyl 3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-ᴅ-glucopyrano-side (5). Glucose **8g** (0.010 g, 0.013 mmol) was dissolved in CH₂Cl₂ (1 mL). Water (0.060 mL) followed by DDQ (0.0046 g, 0.020 mmol) were added and the reaction was stirred for 3 hr. A solution of ascorbic acid sodium salt (0.1 M, 5 mL) in water was added to quench excess DDQ. The solution was diluted with CH₂Cl₂ (10 mL) and washed with aqueous ascorbic acid solution (0.1 M, 2 × 20 mL) and brine (20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. Purification by flash silica gel column chromatography (hexanes/EtOAc 3 : 1 to 3 : 2) gave **5** (0.006 g, 72%). Spectroscopic data are consistent with the data reported above.

Dibutyl   2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthyl-methyl)silyl]ethoxycarbonyl}-β-ᴅ-glucopyranosyl   phosphate   (15).

Glycal **4** (0.400 g, 0.670 mmol) was azeotroped with toluene (5 × 5 mL) and then dried under vacuum overnight. A solution of the glycal in anhydrous CH_2Cl_2 (8 mL) was cooled to 0°C and dimethyldioxirane (13 mL of a 0.08 M solution in acetone, 1.0 mmol) was added. After 30 min at 0°C, the volatiles were removed under vacuum and the resulting oil was dried for 30 min. The residue was redissolved in anhydrous CH_2Cl_2 (23 mL) and cooled to −78°C. A solution of dibutyl phosphate (0.155 g, 0.737 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise within 5 min. After 30 min, the reaction was warmed to 0°C, and DMAP (0.327 g, 2.68 mmol) followed by benzoyl chloride (0.16 mL, 1.4 mmol) was added. The mixture was stirred for 3 hr, while warming to rt and then diluted with ethyl acetate. The precipitate was filtered through a plug of silica gel and the solvents were removed under vacuum. The residue was purified by flash silica gel column chromatography (deactivated with 1% Et_3N for loading, hexanes/EtOAc 5:1 to 3:1 to 1:1) to yield phosphate **15** (0.290 g, 47%) as a colorless oil; $R_f = 0.40$ (hexanes/EtOAc 1:1); $[\alpha]_D$ +22.7 (*c* 0.37, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.6 Hz, 2 H), 7.77−7.69 (m, 3 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.45−7.24 (m, 10 H), 7.17−7.09 (m, 6 H), 5.39−5.29 (m, 2 H), 4.88−4.60 (m, 4 H), 4.46 (dd, *J* = 1.4, 11.5 Hz, 1 H), 4.28−4.16 (m, 3 H), 4.08−3.91 (m, 2 H), 3.86−3.59 (m, 5 H), 2.29 (s, 2 H), 1.62−1.53 (m, 3 H), 1.42−1.21 (m, 4 H), 1.11−0.91 (m, 3 H), 0.85 (t, *J* = 7.4 Hz, 3 H), 0.66 (t, *J* = 7.3 Hz, 3 H), 0.06 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 154.7, 137.2, 136.9, 133.7, 133.2, 131.0, 129.7, 129.2, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.7, 127.5, 127.4, 126.9, 125.8, 125.2, 124.4, 96.4 (d, $3J_P$ = 5.0 Hz), 82.0, 82.0, 76.9, 75.2, 73.7, 73.2 (d, $2J_P$ = 8.6 Hz), 67.9 (d, $2J_P$ = 6.3 Hz), 67.8 (d, $2J_P$ = 6.3 Hz), 66.2, 65.4, 32.0 (d, $3J_P$ = 7.5 Hz), 31.8 (d, $3J_P$ = 7.3 Hz) 25.8, 18.6, 18.3, 15.9, 13.6, 13.4, −3.2. ^{31}P NMR (121 MHz, $CDCl_3$): δ −2.2. IR ($CHCl_3$): v_{max} cm^{-1} 3005, 2954, 1733, 1600, 1451, 1262, 1097, 1031. ESI-MS: *m/z* $(M + Na)^+$ calcd 949.3724, obsd 949.3721.

Pent-4-enyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-D-glucopyranoside (16). Phosphate **15** (0.110 g, 0.119 mmol) was azeotroped with anhydrous toluene (3 × 5 mL) and dried under vacuum overnight. Pent-4-en-1-ol (0.025 mL, 0.24 mmol) and CH_2Cl_2 (2 mL) were added, the solution was cooled to −78°C, and TBSOTf (0.030 mL, 0.13 mmol) was added. The mixture was stirred for 3 hr while slowly warming to −30°C and then neutralized by addition of Et_3N. The solvents were evaporated and purification by flash silica gel column chromatography (hexanes/EtOAc 7:1) gave **16** (0.067 g, 70%) as a colorless oil; $R_f = 0.14$ (hexanes/EtOAc 7:1); $[\alpha]_D$ +19.6 (*c* 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.4 Hz, 2 H), 7.79−7.71 (m, 3 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.47−7.27 (m, 10 H), 7.18−7.16 (m, 6 H), 5.65−5.62 (m, 1 H), 5.28 (dd, *J* = 7.9, 9.3 Hz, 1 H), 4.89 (d, *J* = 10.9 Hz, 1 H), 4.84−4.67 (m, 3 H), 4.72 (d, *J* = 8.4 Hz, 1 H), 4.63 (d, *J* = 10.9 Hz, 1 H), 4.51 (d, *J* = 7.9 Hz, 1 H), 4.47 (dd, *J* = 2.0, 11.5 Hz,

1 H), 4.31–4.21 (m, 3 H), 3.89–3.81 (m, 2 H), 3.73–3.60 (m, 2 H), 3.44 (ddd, $J = 6.2$, 7.1, 9.6 Hz, 1 H), 2.31 (s, 2 H), 2.01–1.87 (m, 2 H), 1.67–1.48 (m, 2 H), 1.14–1.09 (m, 2 H), 0.08 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.1, 155.0, 137.9, 137.6, 137.5, 137.1, 133.8, 133.1, 131.1, 129.9, 129.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.0, 125.9, 125.3, 124.5, 114.7, 101.0, 82.7, 77.6, 75.1, 75.0, 73.6, 73.1, 69.0, 66.2, 29.7, 28.5, 25.8, 15.8, −3.4. IR (CHCl$_3$): v_{max} cm^{-1} 3035, 2892, 1733, 1446, 1313, 1262, 1092, 1021. ESI-MS: m/z (M + Na)$^+$ calcd 825.3435, obsd 825.3417.

Pent-4-enyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (17). Following General Procedure B, **16** (0.063 g, 0.078 mmol) was treated with TBAF (0.10 mL of a 1 M solution in THF, 0.10 mmol) in THF (1.5 mL) for 50 min. Flash silica gel column chromatography (hexanes/EtOAc 5 : 1 to 1 : 1) gave **17** (0.040 g, 96%) as a colorless solid; mp 58–58.5°C; R$_f$ = 0.20 (hexanes/EtOAc 3 : 1); [α]$_D$ +11.5 (*c* 0.26, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.01 (d, $J = 7.4$ Hz, 2 H), 7.57 (t, $J = 7.4$ Hz, 1 H), 7.46–7.41 (m, 2 H), 7.38–7.27 (m, 5 H), 7.13 (s, 5 H), 5.68–5.55 (m, 1 H), 5.24 (dd, $J = 8.0$, 9.3 Hz, 1 H), 4.87 (d, $J = 10.9$ Hz, 1 H), 4.84–4.74 (m, 4 H), 4.68 (d, $J = 10.9$ Hz, 1 H), 4.54 (d, $J = 8.0$ Hz, 1 H), 3.93–3.70 (m, 5 H), 3.49–3.41 (m, 2 H), 2.02–1.84 (m, 3 H), 1.65–1.49 (m, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.2, 137.8, 137.7, 133.1, 129.9, 129.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 114.8, 101.2, 82.5, 77.7, 75.3, 75.1, 75.0, 73.8, 69.2, 61.9, 29.7, 28.5. IR (CHCl$_3$): v_{max} cm^{-1} 3005, 2872, 1728, 1451, 1359, 1267, 1087, 1026. ESI-MS: m/z (M + Na)$^+$ calcd 555.2359, obsd 555.2345.

Pent-4-enyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-{2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl}-β-D-glucopyranosyl-(1 → 6)-2-*O*-benzoyl-3,4-di-*O*-benzyl-6-β-D-glucopyranoside (18). Phosphate **15** (0.073 g, 0.079 mmol) and **17** (0.035 g, 0.066 mmol) were coevaporated with anhydrous toluene (5 × 5 mL) and then dried under vacuum overnight. Anhydrous CH$_2$Cl$_2$ (2 mL) was added, the solution was cooled to −78°C and TBSOTf (0.019 mL, 0.083 mmol) was added. The mixture was stirred for 2 hr while slowly warming to −30°C, and then neutralized with Et$_3$N and concentrated. Purification by silica gel column chromatography (toluene/EtOAc 10 : 1) gave disaccharide **18** (0.069 g, 83%) as a colorless oil; R$_f$ = 0.35 (toluene/EtOAc 10 : 1); [α]$_D$ +17.6 (*c* 0.33, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.99–7.95 (m, 4 H), 7.78–7.69 (m, 3 H), 7.55 (t, $J = 7.4$ Hz, 1 H), 7.50 (t, $J = 7.4$ Hz, 1 H), 7.44–7.26 (m, 15 H), 7.20–7.08 (m, 13 H), 5.63–5.50 (m, 1 H), 5.33 (dd, $J = 7.8$, 9.0 Hz, 1 H), 5.16 (d, $J = 7.8$, 9.2 Hz, 1 H), 4.88 (d, $J = 10.8$ Hz, 1 H), 4.80–4.57 (m, 9 H), 4.51–4.45 (m, 2 H), 4.35–4.14 (m, 4 H), 4.31 (d, $J = 7.9$ Hz, 1 H), 3.84 (t, $J = 8.9$ Hz, 1 H), 3.75–3.41 (m, 7 H), 3.19–3.12 (m, 1 H), 2.29 (s, 2 H), 1.86–1.78 (m, 2 H), 1.45–1.27 (m, 2 H), 1.11–1.06 (m, 2 H), 0.06 (s, 6 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.9, 164.8, 154.8,

137.8, 137.6, 137.6, 137.4, 137.4, 137.0, 133.6, 133.0, 132.8, 131.0, 129.8, 129.6, 129.6, 129.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 126.9, 125.8, 125.2, 125.2, 124.4, 114.5, 100.8, 100.7, 82.7, 82.6, 77.9, 77.5, 75.1, 75.0, 74.8, 74.8, 73.6, 73.5, 73.2, 68.4, 67.9, 66.2, 66.1, 29.8, 28.5, 25.8, 15.9, -3.2. IR (CHCl$_3$): v_{max} cm^{-1} 3015, 2882, 1728, 1451, 1262, 1092, 1067. ESI-MS: m/z (M + Na)$^+$ calcd 1271.5164, obsd 1271.5165.

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