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N-Tetrachlorophthaloyl (TCP) for Ready Protection/ Deprotection of Amino Sugar Glycosides†

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Abstract—The tetrachlorophthaloyl (TCP) group can be utilized when imidic protection of an amine is desired and durability of the protecting group to conditions ranging from mildly basic to harshly acidic is required. Installation can be accomplished in two steps by treating the free base with the commercially available TCP anhydride, and then closing the imidic ring with acetic anhydride and pyridine. Cleavage is effected by 2–4 eq of ethylenediamine under very mild conditions under which esters and glycopeptides have been shown to be stable, and racemization of amino acid residues does not occur. Unsubstituted phthalimides, even within the same molecule, are also unaffected during TCP cleavage. TCP protecting groups serve as β-directors on donors and can also be present on acceptor species during electrophilic couplings in oligosaccharide synthesis. Copyright © 1996 Elsevier Science Ltd

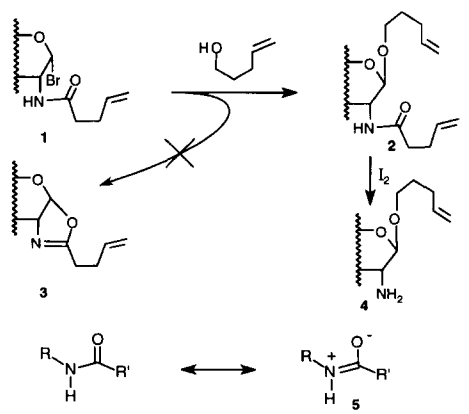
Introduction

Amine protection and deprotection are major problems in organic synthesis as may be judged by the disproportionate amount of space devoted to the topics in popular reference texts.[1] The problems are compounded in the case of glycoproteins[2] by the preponderance of sensitive functionalities that must survive the protection or deprotection event. The easiest method of amine protection is undoubtedly acylation; but the conditions for de-N-acylation require the use of strong acid or base[1] which threatens the saccharide moiety. 2-Amino-2-deoxy sugars are ubiquitous components of glycoproteins. An additional level of complexity arises in protecting the 2-amino group in these compounds, because neighboring group participation by the 2-N-acyl moiety during reactions at the adjacent anomeric center frequently results in the formation of oxazolines.[3] Recent projects in our laboratory[4] have sensitized us to the problems of amine protection/deprotection, and in this manuscript we describe some pertinent studies.

With respect to the problem of de-N-acylation, we have recently explored a procedure that provides a solution.[5] Our work on n-pentenyl glycosides (NPGs)[6] had led to strategies for hydroxyl[7] and diol[8] protection/deprotection, which in turn prompted the development of the 4-pentenoyl moiety for protection of primary and secondary amines.[5] The ease of the procedure is exemplified in Scheme 1. Thus the conversion of **1** into **2** is achieved under standard conditions, notably without formation of oxazoline **3**, and de-N-acylation, **2**→**4**, occurs rapidly and quantitatively with the use of molecular iodine.[5] Although the latter reaction is an oxidative process, the deprotection procedure does not affect commonly used oxidizable moieties such as *p*-methoxybenzyl and thioalkyl.[5]

Its success notwithstanding, the study in Scheme 1 presented us with a new problem stemming from the chemoselective cleavage of the 4-pentenamide residue of **2**, leaving the pentenyl glycosidic moiety intact. This chemoselectivity is readily rationalized by the resonance form **5**, which renders the amide carbonyl group much more nucleophilic than the glycosidic oxygen, thereby enhancing reaction with the respective cyclic iodonium ion intermediate.

Although the above chemoselectivity may be of value in certain cases, it was a disappointing corollary for us,



Scheme 1.

†Conference reports on the use of TCP group for amine protection (a) Debenham, J. S.; Fraser-Reid, B., XVIIth International Carbohydrate Symposium, Ottawa, Canada, July 1994, paper B1.38; (b) Debenham, J. S; Fraser-Reid, B., 209th National Meeting of the American Chemical Society, Anaheim, California, April **1995**, paper CARB 008. Preliminary publications (a) Debenham, J.S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.*, **1995**, *117*, 3302–3303; (b) Debenham, J.S.; Fraser-Reid, B. *J. Org. Chem.*, in press.

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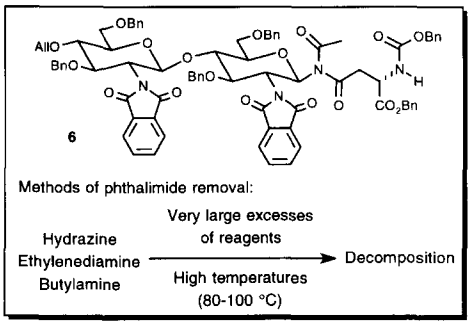
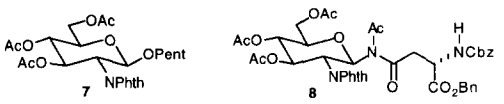
in that an NPG could not be used as a glycosyl donor in the presence of 4-pentenamide, since the preferred site of reaction would be the latter. This circumstance prompted us to develop an amine protection strategy that would permit the use of NPGs as glycosyl donors. In this context, the problem of neighboring group participation by the 2-N-acyl residue had to be addressed.

2-N-Acyl participation during glycoside coupling frequently results in formation of oxazolines such as **3**, except when the glycosyl acceptor is a primary alcohol as in **1**→**2**.[3] Lemieux and co-workers had popularized the use of phthaloyl protection of 2-amino-2-deoxy sugars,[9] and this procedure has seen wide application.[10] Not only was oxazoline formation obviated, but the difficulty of deprotection was lessened since hydrazine could be used for cleavage in keeping with the Ing–Manske variation of the Gabriel synthesis.[11]



Even so, in complex systems where other base sensitive sites exist, the use of hydrazine may cause major problems.[12] This is exemplified for glycopeptides such as **6**[13] where the indicated standard methods of phthaloyl cleavage all result in decomposition.

A procedure for cleaving phthalimides by the use of sodium borohydride had been developed by Ganem,[14] and Garegg and Ogawa independently applied it to glucosamine derivatives.[15] Their procedure was reasonably successful for compound **7**, but only decomposition was observed for the more complex glycopeptide **8**.



It seemed to us that phthalimide cleavage would be facilitated by the presence of electron withdrawing groups on the aromatic ring, the most likely candidates being halogen and nitro.[16] To test the idea, the phthalimide **9**, was deprotected to give amine **10** which was treated under standard Lemieux conditions[9] to give the 4-nitrophthalimido derivative **11**. Several cleavage conditions were tested with varying degrees of success. However these reactions were not always easy to monitor by TLC. The fact that initial attack on the carbonyl groups of the 4-nitrophthalimides (e.g. **11** or **13a**) leads to regioisomeric intermediates, was probably responsible for the many 'spots' seen on TLC. Consequently, nitro (**12a**) and other monosubstituted phthalic anhydrides were eliminated from further consideration.

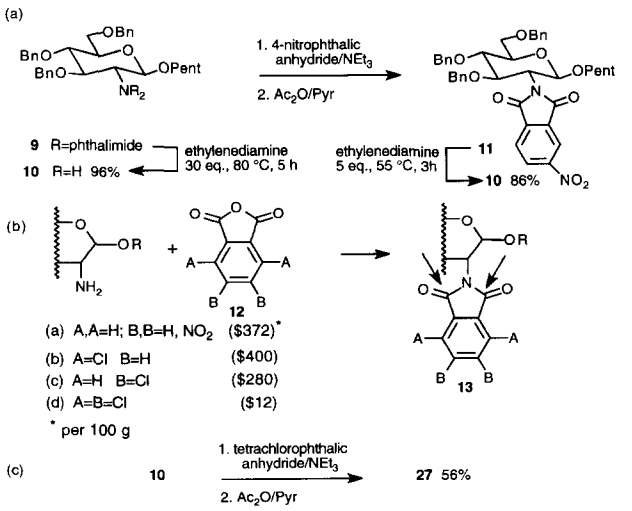
3,6 or 4,5-Disubstituted and 3,4,5,6-tetrasubstituted reagents (**12b**, **c** and **d**, respectively) would give symmetrical derivatives; but the cost of these reagents was now an added concern, since our aim was to install the protecting group in bulk, as soon as possible in the reaction sequence. In light of the costs[17] shown in Scheme 2b, we decided to concentrate further attention on tetrachlorophthaloyl (TCP).[18]

Preparation of TCP derivatives

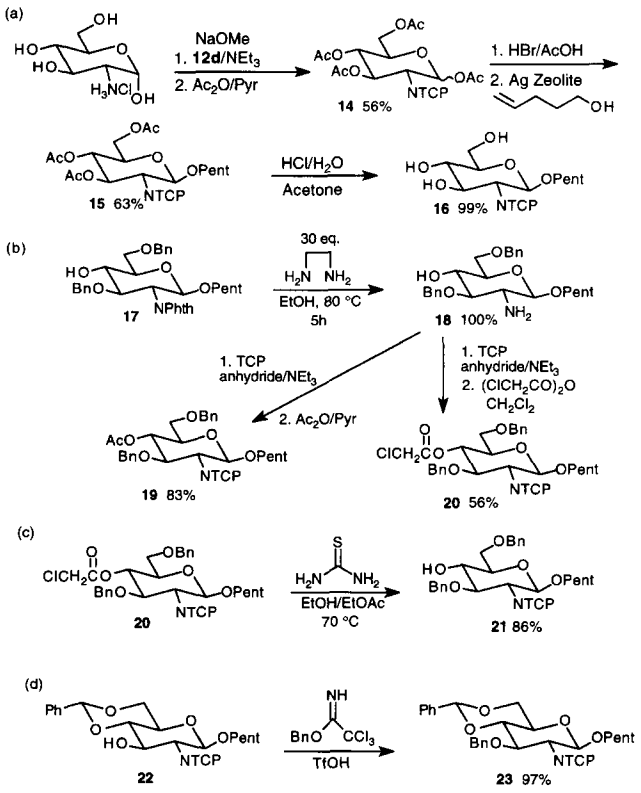
The preparation of TCP derivatives follows the standard procedures used for the unsubstituted analogue. Thus application of Lemieux's two-stage reaction[9] to glucosamine hydrochloride and TCP anhydride **12d** (Scheme 3a) afforded the tetraacetate **14** in 56% overall yield which is similar to the yield obtained with the unsubstituted analogue.[9] Standard Koenigs–Knorr strategy then afforded NPG **15**. Additionally, for the latter reaction silver zeolite was the promoter of choice.

In view of the TCP group's sensitivity to strongly basic conditions, such as metal hydride mediated benzylations, an alternative is to use unsubstituted phthaloyl for the problematic steps and then replace it at an appropriate time with TCP, as exemplified in Scheme 3b.

It is useful to note the use of chloroacetic anhydride for installing the TCP group under reaction conditions which simultaneously esterify the hydroxyl in the preparation of **20**. As indicated by the formation of **21**, the chloroacetyl ester can be chemoselectively cleaved under the usual conditions, and thus may be used



Scheme 2.

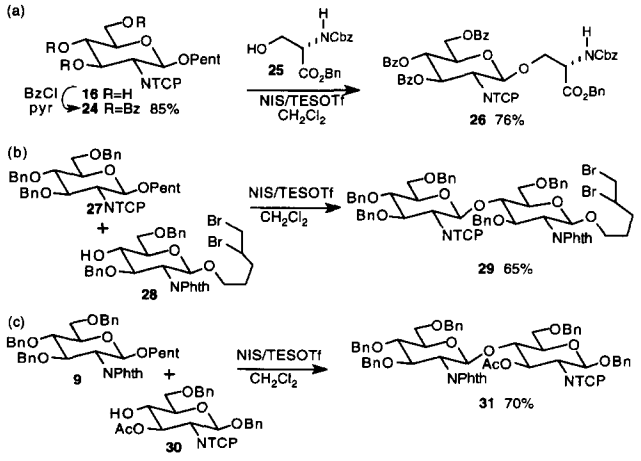


Scheme 3.

where the synthetic strategy requires the presence/removal of an ester, or the removal of one ester in the presence of another.

Similarly since the use of sodium hydride is problematic with TCP, we have demonstrated with **22** (Scheme 3d) that benzylation can be quantitatively effected by use of benzyltrichloracetimidate.[19]

In view of the fact that C2-electron withdrawing esters such as trichloroacetyl do not participate in reactions at the anomeric center,[20] it was necessary to establish that 1,2-trans coupling products would still predominate in the presence of TCP groups. In the examples summarized in Scheme 4, β-glycosides were the only



Scheme 4.

detectable coupling products with NPG glycosyl donors and a variety of glycosyl acceptors. Notably the TCP group may be placed either on the donor, as in **24** and **27**, or acceptor, as in **30**.

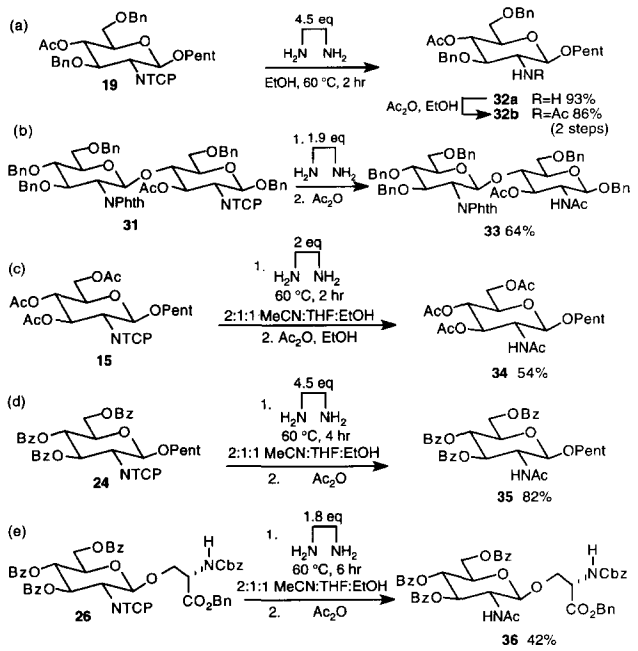
Deprotection

We now set out to develop conditions for specific TCP cleavage. In this connection, Schmidt and coworkers[21] examined TCP protected glycosyl trichloroacetimidates as glycosyl donors and applied the Ganem[14]–Ogawa-Garreg[15] method for TCP deprotection. The recommended steps are sodium borohydride reduction, acid-catalysed phthalide formation, followed by treatment with acetic anhydride and pyridine. Since the last conditions are also O-acetylating, it would not have been possible to judge whether the substrate's esters had survived the dephthaloylation. The question of chemoselective dephthaloylation was also not addressed. We were interested in both of these possibilities.

Recently Barany[22] and Meldal[23] and their coworkers have reported the use of the dithiosuccinyl (Dts) function in the synthesis of 1,2-*trans*-amino sugar glycosides. Among the advantages, are the procedures for cleaving the protecting group by solvolysis (with dithiothreitol), or reduction (with sodium borohydride). The Dts protecting group shows promise for solid-phase syntheses, for which it was first developed by Barany and Merrifield.[24] Unfortunately the reagents needed to install the Dts group are not commercially available, furthermore, four steps and two silica gel purifications are needed in the process. By contrast, the TCP reagent is commercially available, inexpensive, and can be installed in two steps from glucosamine·HCl with a single recrystallization for purification. Additionally, it remains to be seen whether the Dts group has sufficient durability to survive the hydroxyl group manipulations that are essential in oligosaccharide synthesis.

Experimentation with various amines (hydrazine, methylhydrazine, ethylenediamine) in various solvents (ethanol, isopropanol, DMF, acetonitrile, THF) at various temperatures, revealed that suitable conditions were ethylenediamine (2–4 eq) in MeCN/THF/EtOH (2:1:1)[25] at 60°. An ideal test example is seen in Scheme 5a, where reaction of **19** gave amine **32a** in quantitative yield. These conditions are much milder than those required for cleaving the unsubstituted phthalimide, e.g. Schemes 2a and 3b, where ethylenediamine is virtually a cosolvent.

In order to prevent the possibility of O→N acyl transfer and also to facilitate the ease of isolation we decided to N-acetylate all products directly as shown in Scheme 5b–e. Compound **31** gave us an opportunity to test for chemoselective dephthaloylation and the isolation of **33** in 64% yield provided a convincing demonstration. Thus cleavages such as this provide a new route to differentially N-functionalized chitobiosyl derivatives.



Scheme 5.

The isolation of **32a** made it clear that an acetate could survive the aminolysis conditions. That this result was not fortuitously related to the hindered location of the ester in precursor **19**, was reinforced with triacetate **15** which gave **34** in 54% yield. Not surprisingly, benzoate esters survived even better as exemplified in Scheme 5d for the 82% conversion of **24**→**35**. Further optimization to enhance the durability of esters during the cleavage process is ongoing in our laboratories.

The case of the O-linked glycoamino acid **26** was of interest (Scheme 5e). In light of the three base-sensitive sites on the serine residue (ester, carbamate and epimerizable center) in addition to the three benzoate esters, the recovery of **36** in 42% yield is encouraging, particularly when the demands of any alternative route to **36** are considered.

Summary

We have found that there are many advantages to using the TCP protecting group in synthetic manipulations of aminodeoxy sugars. The required reagent is commercially available, inexpensive and can be installed in two steps on glucosamine without the need for chromatography. Many of the derivatives are highly crystalline, so purification is facilitated. The derivatives are stable to mildly basic to very acidic conditions but react readily with certain bases. The latter property has been used advantageously to develop efficient cleavage by treatment with 2–4 equivalents of ethylenediamine under conditions so mild that most esters survive. Chemoselectivity in TCP cleavage can also achieved since unsubstituted phthalimides are untouched by these cleavage conditions.

Experiments to extend and optimize the use of TCP protection/deprotection are underway and will be reported in due course.

Experimental

General procedures

All reactions were conducted under a dry argon atmosphere. THF was distilled from sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. Cyclohexane and absolute ethanol were stored over 4 Å molecular sieves. Solutions of compounds in organic solvents were dried over sodium sulfate prior to rotary evaporation. TLC plates were Kieselgel 60 F254 (Merck Art. 5554). Carbohydrate compounds were visualized on the TLC plate by charring with H_2SO_4–EtOH–H_2O (1:10:10). Flash column chromatography was done with silica gel 60 (230–400 mesh, Merck). Optical rotations were determined at the sodium D line with a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer operating at 3k resolution for low resolution fast atom bombardment (FAB) mass spectra or a Hewlett-Packard 5988A mass spectrometer using chemical ionization with ammonia as the reagent gas. FAB mass spectra were conducted using a *m*-nitrobenzyl alcohol matrix with xenon as the fast atom. Accurate mass measurements were made using FAB at 10k resolution. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300, Inova-400 or GE QE-300 spectrometer. Coupling constants are reported in Hertz and chemical shifts are in ppm on the delta scale. ^1H and ^{13}C chemical shifts are reported relative to internal tetramethylsilane (0.00 ppm). Elemental analyses were conducted by Atlantic Microlab, Inc. (P.O. Box 2288, Norcross, GA 30091, U.S.A.). The preparation of **29** can be found elsewhere.[26]

Pent-4-enyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (9). To pent-4-enyl 2-deoxy-2-phthalimido-β-D-glucopyranoside[13] (dried by azeotroping with toluene) (3.15 g, 8.36 mmol) in 20 mL DMF was added benzyl bromide (6.0 mL, 50.4 mmol), tetrabutyl ammonium iodide (0.31 g, 0.84 mmol) and sodium hydride (1.5 g, 37.6 mmol) at 0 °C. After stirring for 30 min, the solution was allowed to warm to room temperature and then stirred an additional 2.5 h. The reaction was quenched with 4 mL of glacial acetic acid, and the DMF was removed in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and satd aq. $NaHCO_3$ (50 mL) solution. The aqueous portion was extracted CH_2Cl_2 (2×40 mL). The concentrated reaction mixture was purified via flash chromatography eluting with 15:85 EtOAc/petroleum ether affording **9** as a clear oil (4.35 g, 80%). R_f=0.45 (25:75 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +40.3° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.84 (m, 4H), 7.21–7.39 (m, 10H), 6.84–7.02 (m, 5H), 5.48–5.62 (m, 1H), 5.12 (d, *J*=8.4 Hz, 1H), 4.56–4.86 (m, 8H), 4.11–4.46 (m, 3H), 3.62–3.84 (m, 4H), 3.34–3.42 (m,

1H), 1.81–1.85 (m, 2H), 1.44–1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.85 (bs), 140.93, 137.76, 137.73, 137.60, 133.55, 128.27, 128.19, 127.85, 127.81, 127.71, 127.67, 127.62, 127.44, 127.25, 127.14, 126.73, 123.01, 114.44, 98.04, 79.52, 79.07, 74.78, 74.57, 73.28, 68.55, 68.48, 64.84, 55.73, 29.63, 28.27; MS (CI) *m/e* 665 $(M+NH_4)^+$. Anal. calcd for $C_{40}H_{41}O_7N$: C, 74.17; H, 6.38%; found C, 73.91; H, 6.32%.

Pent-4-enyl 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (10). To **9** (2.34 g, 3.45 mmol) in 10 mL ethanol was added ethylenediamine (6.9 mL, 103.5 mmol). The soln was heated to 80 °C and stirred for 5 h. The ethanol and excess ethylenediamine were removed in vacuo. The concd reaction mixture was purified via flash chromatography eluting with 2:98 CH_3OH/ CH_2Cl_2 affording **10** as a clear oil (1.71 g, 96%). R_f 0.43 (45:55 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +4.9° (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.40 (m, 15H), 5.75–5.86 (m, 1H), 4.95–5.06 (m, 3H), 4.54–4.81 (m, 5H), 4.18 (d, J=7.9 Hz, 1H), 3.89–3.97 (m, 1H), 3.42–3.77 (m, 6H), 2.88 (dd, J=8, 9.7 Hz, 1H), 2.10–2.17 (m, 2H), 1.67–1.77 (m, 2H), 1.52 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.25, 138.01, 137.95, 137.79, 128.42, 128.32, 128.21, 127.82, 127.68, 127.47, 114.76, 103.76, 85.08, 78.52, 75.21, 75.09, 74.67, 73.37, 69.07, 68.75, 56.85, 30.07, 28.68; MS (FAB) *m/e* 518.2 MH^+.

Pent-4-enyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-(4-nitrophthalimido)-β-D-glucopyranoside (11). To **10** (0.934g, 1.80 mmol) in 18 mL CH_2Cl_2 was added tetrachlorophthalic anhydride (0.383, 1.98 mmol). After stirring 10 min, NEt_3 (0.28 mL, 1.98 mmol) was added and the reaction stirred an additional 45 min. The soln was concentrated and then diluted with pyridine (12 mL) before adding acetic anhydride (0.65 mL, 6.68 mmol). After stirring 12 h, the pyridine was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with H_2O (1 × 15 mL) and sat. aq. $NaHCO_3$ (1 × 15 mL) solution, back extracting the combined aqueous portions with CH_2Cl_2 (3 × 15 mL). The concd soln was purified via flash chromatography eluting with 18:82 EtOAc–petroleum ether affording **11** as an oil (1.11 g, 89%); R_f 0.47 (20:80 EtOAc:petroleum ether); $[\alpha]_D^{20}$ +38.5° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ8.56–7.68 (m, 3H), 7.40–7.20 (m, 10H), 7.40–6.70 (m, 5H), 5.62–5.51 (m, 1H), 5.15 (d, J=8.5 Hz, 1H), 4.84 (dd, J=8.5, 10.6 Hz, 1H), 4.78–4.56 (m, 6H), 4.45–4.14 (m, 3H), 3.84–3.76 (m, 4H), 3.67–3.62 (m, 1H), 3.43–3.35 (m, 1H), 1.90–1.75 (m, 2H), 1.58–1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.35, 151.26, 138.07, 137.95, 137.70, 137.56, 135.79, 132.57, 128.64, 128.35, 128.25, 127.95, 127.89, 127.78, 127.65, 127.51, 127.08, 125.84, 124.17, 118.37, 114.57, 97.77, 79.63, 79.27, 74.94, 74.73, 73.37, 68.58, 68.44, 56.35, 29.67, 28.31; HRMS calcd for $C_{40}H_{39}N_2O_9$ $(M-H)^+$ 691.2656, found 691.2673.

(10) via 4-nitrophthalimido cleavage. To **11** (50.0 mg, 0.0722 mmol) in 2 mL ethanol was added ethylenediamine (24.1 μL, 0.361 mmol). The solution was heated to 55 °C and stirred for 3 h. The ethanol and excess ethylenediamine were removed in vacuo. The concd reaction mixture was purified via flash chromatography eluting with 2:98 methanol/CH_2Cl_2 affording **10** as a film (34.7 mg, 86%).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-D-glucopyranoside (14). Glucosamine•HCl (10.0 g, 46.37 mmol) was added to methoxide solution, Na (1.07 g 46.54 mmol) in MeOH (50mL), which stirred 8 min before filtering into another vessel containing tetrachlorophthalic (TCP) anhydride (4.64 g, 16.23 mmol). Once the filtration was complete TCP anhydride (4.64 g, 16.23 mmol) was added. The reaction stirred 10 minutes before addition of NEt_3 (6.50 ml, 46.63 mmol) and TCP anhydride (4.64 g, 16.23 mmol). The reaction mixture stirred an additional 3 h before removing the MeOH in vacuo. To the white foam was added pyridine (55 mL) and acetic anhydride (60 mL, 543 mmol). The solution stirred for 7.5 h before removal of the pyridine in vacuo. The residue was diluted with $CHCl_3$ (120 mL) and washed with 5% aq. HCl (2 × 40 mL) back extracting the aq. phase with $CHCl_3$ (1 × 40 mL) and then with satd aq. $NaHCO_3$ (80 mL) back extracting the aq. phase with $CHCl_3$ (1 × 40 mL) . The organic phase was concd, and the residue recrystallized from EtOH. Compound **14** was recovered as a white solid (α anomer) (16 g, 56%). mp 219.5°; R_f=0.59 (45:55 EtOAc:petroleum ether); $[\alpha]_D^{20}$ +157.5° (*c* 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (dd, J=9.6, 12.1 Hz, 1H), 6.26 (d, J=3.4 Hz, 1H), 5.17 (t, J=9.9 Hz, 1H), 4.72 (dd, J=3.4, 14.9 Hz, 1H), 4.13–4.40 (m, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.41, 169.54, 169.42, 169.27, 162.49, 140.51, 129.93, 126.53, 90.24, 70.07, 69.01, 66.74, 61.26, 53.20, 20.81, 20.64, 20.56, 20.48; MS (FAB) *m/e* 622.0 $(M+Li)^+$; Anal. calcd for $C_{22}H_{19}NO_{11}Cl_4$: C, 42.95; H, 3.11%; found: C, 43.02; H, 3.14%.

Pent-4-enyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (15). To **14** (25.22 g, 40.99 mmol) was added HBr (266 mmol, 53.2 mL, 30 wt. % in acetic acid) in acetic anhydride (110.7 mmol, 10.4 mL). After stirring in darkness for 27 h, the reaction mixture was diluted with $CHCl_3$ (300 mL) and poured onto ice cold H_2O (300 mL). The layers were separated and the organic portion was washed with H_2O (2 × 300 mL) and with satd aq. $NaHCO_3$ (1 × 250 mL) dried and concd to a syrup. To the crude glycosyl bromide was added pent-4-enyl alcohol (123 mmol, 12.7 mL) and Ag zeolite powder (33.1 g) in CH_2Cl_2 (120 mL). The reaction stirred in darkness for 36 h at reflux and was then filtered through Celite. After concentration of the CH_2Cl_2 solution, the solid was recrystallized from methanol affording **15** as a white solid (16.66 g, 63%); R_F 0.54 (30:70 EtOAc:petroleum ether); mp 161 °C; R_f=0.54 (30:70 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +34.1° (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66–5.72 (m, 2H), 5.34 (d, J=8.4 Hz,

1H), 5.19 (t, $J=10.0$ Hz, 1H), 4.82–4.88 (m, 2H), 4.14–4.36 (m, 3H), 3.79–3.85 (m, 2H), 3.45–3.53 (m, 2H), 2.12 (s, 3H), 2.04 (s, 3H), 1.90 (s, 3H), 1.90–2.0 (m, 2H), 1.55–1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.46, 170.38, 169.18, 163.3 (bs), 162.3 (bs), 140.36, 137.40, 129.77, 126.75, 114.72, 97.56, 71.65, 70.75, 69.10, 68.50, 61.75, 55.22, 29.62, 28.20, 20.61, 20.45, 20.35; MS (FAB) *m/e* 648.1 $(M+Li)^+$. Anal. calcd for $C_{25}H_{25}NO_{10}Cl_4$: C, 46.82; H, 3.93%; found: C, 46.98; H, 3.88%.

Pent-4-enyl 2-amino-2-deoxy-3,6-di-*O*-benzyl-β-D-glucopyranoside (18). To pent-4-enyl 2-deoxy-2-phthalimido-3,6-di-*O*-benzyl-β-D-glucopyranoside[13] (1.52 g, 2.72 mmol) in 20 mL ethanol was added ethylenediamine (9.1 mL, 136 mmol). The soln was heated to 80 °C and stirred for 5.5 h. The ethanol and excess ethylenediamine were removed in vacuo. The concd reaction mixture was purified via flash chromatography eluting with 7:93 CH_3OH/CH_2Cl_2 affording **18** as a clear oil (1.14 g, 98%). $R_f=0.41$ (45:55 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −16.9° (*c* 1.05, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.38 (m, 10H), 5.76–5.81 (m, 1H), 4.95–5.05 (m, 3H), 4.54–4.78 (m, 3H), 4.2 (d, $J=8.1$ Hz, 1H), 3.87–3.90 (m, 1H), 3.69–3.85 (m, 3H), 3.44–3.53 (m, 2H), 3.34 (t, $J=9.5$ Hz, 1H), 2.90–3.20 (bs, 1H), 2.80–2.85 (m, 1H), 2.11–2.16 (m, 2H), 1.63–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.31, 137.61, 137.56, 128.08, 127.98, 127.27, 114.54, 103.11, 84.41, 74.46, 74.33, 73.17, 71.94, 69.80, 68.68, 55.90, 29.77, 28.41; HRMS calcd for $C_{25}H_{34}NO_5$ MH^+ 428.2437; found 428.2427.

Pent-4-enyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (19). To **18** (0.15 g, 0.36 mmol) in 6 mL CH_2Cl_2 was added **12d** (0.12 g, 0.38 mmol). After stirring for 4 min, NEt_3 (55 μL, 0.39 mmol) was added and the reaction stirred an additional 1 h. The soln was concd and then diluted with pyridine (5 mL) before adding acetic anhydride (0.2 mL, 2.14 mmol). After stirring 20 h, the pyridine was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with satd aq. $NaHCO_3$ (2 × 15 mL) solution back extracting the combined aq. portions with CH_2Cl_2 (1 × 15 mL). The concd soln was purified via flash chromatography eluting with 20:80 EtOAc–petroleum ether affording **19** as a slightly yellow oil (0.22 g, 83%). $R_f=0.25$ (15:85 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +69.6° (*c* 0.994, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.36 (m, 5H), 6.70–7.05 (m, 5H), 5.56–5.67 (m, 1H), 5.08–5.14 (m, 2H), 4.73–4.83 (m, 3H), 4.56 (s, 2H), 4.11–4.33 (m, 3H), 3.61–3.82 (m, 4H), 3.36–3.44 (m, 1H), 2.02 (s, 3H), 1.85–1.93 (m, 2H), 1.49–1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.49, 163.25, 162.04, 138.13, 137.71, 137.61, 128.29, 128.27, 128.23, 127.95, 127.93, 127.87, 127.83, 127.75, 114.68, 97.67, 77.81, 74.59, 73.57, 73.54, 73.29, 72.71, 69.45, 68.76, 56.05, 29.73, 28.31, 20.84; MS (FAB) *m/e* 744.1 $(M+Li)^+$. Anal. calcd for $C_{35}H_{33}NO_8Cl_4$: C, 57.00; H, 4.51; N, 1.90%; found: C, 57.03; H, 4.49; N, 1.94%.

Pent-4-enyl 4-*O*-chloroacetyl-3,6-di-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (20). To **18** (95.8 mg, 0.225 mmol) in 5 mL CH_2Cl_2 was added **12d** (74.0 mg, 0.247 mmol). After stirring for 6 min, NEt_3 (31 μL, 0.247 mmol) was added and the reaction stirred an additional 1 h. Chloroacetic anhydride (0.231 g, 1.35 mmol) and pyridine (73 μL, 0.898 mmol) were then added. After stirring for 3.5 h, the reaction was quenched with satd aq. $NaHCO_3$ (5 mL) and the soln was diluted with an additional 10 mL CH_2Cl_2. The layers were sepd and the aq. portion extracted (2 × 10 mL CH_2Cl_2). The concd soln was purified via flash chromatography eluting with 15:85 EtOAc–petroleum ether affording **20** as a clear glass (96.3 mg, 56%); R_f 0.33 (15:85 EtOAc:petroleum ether); $[\alpha]_D^{20}$ +24.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–6.90 (m, 10H), 5.76–5.62 (m, 1H), 5.18 (t, $J=9.9$ Hz, 1H), 4.94–4.82 (m, 2H), 4.7 (d, $J=12.7$ Hz, 1H), 4.6 (d, $J=7.9$ Hz, 1H), 4.52 (s, 2H), 4.38 (d, $J=12.3$ Hz, 1H), 4.18 (dd, $J=7.9$, 9.6 Hz, 1H), 3.90–3.70 (m, 5H), 3.66–3.62 (m, 2H), 3.52–3.44 (m, 1H), 2.01–1.95 (m, 2H), 1.63–1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.17, 141.14, 138.44, 137.84, 137.67, 128.39, 127.93, 127.90, 127.79, 127.35, 127.05, 114.85, 101.84, 82.68, 75.07, 73.72, 73.06, 69.89, 68.97, 65.46, 40.58, 29.79, 28.48; HRMS calcd for $C_{35}H_{33}NO_8Cl_4$ MH^+ 772.0624, found 772.0624.

Pent-4-enyl 3,6-di-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (21). To **20** (46.2 mg, 0.060 mmol) in ethanol (2.2 mL) and EtOAc (0.3 mL) was added thiourea (11 mg, 0.14 mmol) and $NaHCO_3$ (10.1 mg, 0.12 mmol) before heating to 75 °C. The reaction was stirred for 5 h at which point it was allowed to cool to room temperature. The reaction mixture was concd, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (10 mL) back extracting the aq portion with CH_2Cl_2 (2 × 15 mL). The reaction mixture was concd, and the residue was purified by flash chromatography eluting with 25:75 EtOAc–petroleum ether. Compound **21** was recovered as a film (36 mg, 86%); R_f 0.20 (20:80 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +32.0° (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74–7.40 (m, 10H), 5.57–5.65 (m, 1H), 5.10 (d, $J=8$ Hz, 1H), 4.76–4.87 (m, 3H), 4.62 (dd, $J=11.9$, 21.4 Hz, 2H), 4.43 (d, $J=12.83$ Hz, 1H), 4.06–4.12 (m, 2H), 3.59–3.87 (m, 5H), 3.36–3.41 (m, 1H), 3.13 (bd, $J=2.4$ Hz, 1H), 1.83–1.92 (m, 2H), 1.47–1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.27, 162.45, 139.59, 138.60, 137.69, 137.40, 129.30, 129.20, 128.50, 128.06, 127.93, 127.88, 127.80, 126.85, 114.69, 97.80, 79.36, 74.95, 74.76, 73.78, 73.31, 70.63, 68.73, 55.96, 29.77, 28.36; MS (Fab) *m/e* 702.08 $(M+Li)^+$; Anal. calcd for $C_{33}H_{31}NO_7Cl_4$: C, 57.00; H, 4.49; N, 2.01%; found: C, 57.01; H, 4.52; N, 2.03%.

Pent-4-enyl 4,6-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (22). To **15** (40.10 g, 62.53 mmol) in acetone (800 mL) was added HCl (75 mL, conc.) in H_2O (260 mL). After refluxing 1 h H_2O (150 mL) was added. The reaction was refluxed

an additional 15 h before removing the acetone in vacuo. The aq. soln was extracted with EtOAc (4 × 190 mL) and the combined organic portion was washed with with satd aq. $NaHCO_3$ (2 × 250 mL) back extracting the combined aq portions with EtOAc (1 × 200 mL). The soln was concd affording **16** as a white foam (31.90 g, 99%). **16** was then dissolved in acetonitrile (250 mL) before addition of benzaldehyde dimethyl acetal (25.1 mL, 168.8 mmol) and *p*-toluenesulfonic acid (0.476 g, 2.50 mmol). After refluxing for 10 h, the reaction was quenched with NEt_3 (0.75 mL) and concd to 1/4 of its original volume before diluting with EtOAc (550 mL). The organic soln was washed with sat. aq. $NaHCO_3$ (2 × 200 mL) soln back extracting the combined aq. portions with EtOAc (2 × 200 mL). The concd soln was purified via flash chromatography eluting with 12:88 EtOAc–petroleum ether affording **22** as a yellow foam (29.50 g, 79%); R_f 0.30 (20:80 EtOAc:petroleum ether); $[\alpha]_D^{20}$ −26.4° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.55–7.35 (m, 5H), 5.74–5.88 (m, 1H), 5.56 (s, 1H), 5.22 (d, *J* = 8.4 Hz, 1H), 4.90–4.80 (m, 2H), 4.64–4.54 (m, 1H), 4.44–4.36 (m, 1H), 4.24 (dd, *J* = 8.4, 10.6 Hz, 1H), 3.88–3.78 (m, 2H), 3.68–3.56 (m, 2H), 3.50–3.42 (m, 1H), 2.55 (bs, 1H), 1.97–1.90 (m, 2H), 1.62–1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.00 (bd), 140.20, 137.52, 136.66, 129.07, 128.10, 125.79, 114.74, 101.40, 98.39, 81.83, 69.04, 68.49, 67.91, 66.00, 57.01, 29.69, 28.36; MS (FAB) *m/e* 603.99 MH^+; Anal. calcd for $C_{26}H_{23}NO_7Cl_4$: C, 51.76; H, 3.84%; found: C, 51.76; H, 3.88.

Pent-4-enyl 3-*O*-benzyl-4,6-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (23). To **22** (12.90 g, 21.38 mmol) in CH_2Cl_2 (18 mL) and cyclohexane (72 mL) was added benzyl 2,2,2-trichloroacetimidate (7.95 mL, 42.76 mmol) and triflic acid (49 μL, 0.56 mmol). The reaction mixture was stirred for 3 h and an additional amount of benzyl 2,2,2-trichloroacetimidate (4.0 mL, 21.38 mmol) and triflic acid (49 μL, 0.56 mmol) were added. After stirring an additional 7 h the reaction was quenched with 0.3 mL of pyridine and diluted with CH_2Cl_2 (250 mL). The reaction mixture was washed with 5% aq. HCl (80 mL) back extracting the aq. phase with CH_2Cl_2 (1 × 40 mL) and then with satd aq. $NaHCO_3$ (100 mL) back extracting the aq. phase with CH_2Cl_2 (1 × 40 mL). The organic phase was concd, and the residue was purified by flash chromatography eluting with a gradient of 6→7% EtOAc–petroleum ether. Compound **23** was recovered as a white foam (14.38 g, 97%); R_f 0.19 (6:94 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +48.6° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.82–7.56 (m, 10H), 5.29–5.63 (m, 2H), 5.19 (d, *J* = 8.6 Hz, 1H), 4.14–4.85 (m, 4H), 3.90–3.41 (m, 5H), 1.80–1.92 (m, 2H), 1.45–1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.86, 162.10, 139.71, 138.15, 137.56, 137.16, 128.99, 128.32, 128.22, 127.85, 127.02, 126.43, 125.97, 114.76, 101.29, 98.36, 82.68, 75.09, 74.39, 69.05, 68.62, 66.07, 56.43, 29.71, 28.35; MS (FAB) *m/e* 693.05 M^-; Anal. calcd for $C_{33}H_{29}NO_7Cl_4$: C, 57.16; H, 4.22; N, 2.02%; found: C, 57.28; H, 4.26; N, 2.08%.

Pent-4-enyl 3,4,6-tri-*O*-benzoyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (24). To **16** (6.435 g, 12.49 mmol) in 40 mL pyridine was added benzoyl chloride (6.85 mL, 48.71 mmol). After stirring for 17 h the reaction was quenched with H_2O (10 mL) before removing the pyridine in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with 5% aq. HCl (2 × 50 mL) back extracting the aq. phase with CH_2Cl_2 (1 × 20 mL) and then with satd aq. $NaHCO_3$ (2 × 50 mL) back extracting the aq. phase with CH_2Cl_2 (1 × 20 mL). The concd solution was purified via flash chromatography eluting with 15:85 EtOAc–petroleum ether affording **24** as a white foam (8.770 g, 85%). R_f 0.40 (20:80 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +52.0° (*c* 1.13°, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–8.04 (m, 15H), 6.15–6.22 (m, 1H), 5.61–5.75 (m, 2H), 5.54 (d, *J* = 8.4 Hz, 1H), 4.82–4.88 (m, 2H), 4.90–4.67 (m, 3H), 4.18–4.25 (m, 1H), 3.83–3.90 (m, 1H), 3.50–3.58 (m, 1H), 1.91–1.98 (m, 2H), 1.57–1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.98, 165.88, 165.02, 162.91 (bs), 161.77 (bs), 140.34, 137.48, 133.39, 133.02, 132.93, 129.96, 129.82, 129.71, 129.62, 129.46, 128.56, 128.28, 128.19, 126.85, 114.84, 97.85, 71.96, 71.21, 69.95, 69.23, 63.01, 55.55, 29.73, 28.35; MS (Fab) *m/e* 834.14 $(M+Li)^+$; Anal. calcd for $C_{40}H_{31}NO_{10}Cl_4$: C, 58.06; H, 3.78%; found: C, 57.87; H, 3.79%.

1-*O*-[*N*-(Benzyloxycarbonyl)-L-serine benzyl ester] 3,4,6-tri-*O*-benzoyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (26). To **24** (0.35 g, 0.43 mmol) and **25** (0.10 g, 0.30 mmol) (both dried by azeotroping together with toluene) in 3 mL CH_2Cl_2 was added *N*-iodosuccinimide (0.124 g, 0.553 mmol) and triethylsilyl triflate (58 μL, 0.26 mmol). After stirring for 30 min at room temperature the glycosyl donor had been consumed, and the reaction was quenched with 1.5 mL 10% aq. $Na_2S_2O_3$ and 1.5 mL of satd aq. $NaHCO_3$ soln. The mixture was stirred for an additional 5 min before separating the layers and extracting the aq. portion with CH_2Cl_2 (3 × 10 mL). The concd soln was purified via flash chromatography eluting with a gradient of 25→30% EtOAc–petroleum ether affording **26** as a white foam (0.25 g, 76%); R_f 0.45 (30:70 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +54.8° (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–8.03 (m, 25H), 6.14 (dd, *J* = 9.9, 10.4 Hz, 1H), 5.67 (t, *J* = 10.0 Hz, 1H), 5.55 (d, *J* = 8.4 Hz, 1H), 5.28 (bd, *J* = 7.49 Hz, 1H), 4.98–5.10 (m, 4H), 4.39–4.62 (m, 4H), 3.97–4.24 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.14, 165.90, 165.75, 164.90, 155.59, 163.73 (bs), 162.31 (bs), 140.17 (bs), 140.13 (bs), 135.97, 134.83, 133.40, 133.34, 132.99, 129.81, 129.68, 129.61, 129.32, 128.45, 128.34, 128.24, 128.09, 128.01, 127.96, 127.77, 127.01, 97.94, 71.96, 70.90, 69.55, 69.03, 67.33, 66.80, 62.63, 55.21, 54.46; MS (FAB) *m/e* 1077.1 $(M+Li)^+$; Anal. calcd for $C_{53}H_{40}N_2O_{14}Cl_4$: C, 59.45; H, 3.77%; found: C, 59.20; H, 3.61%.

Pent-4-enyl 3,4,6-tri-*O*-benzyl-2-dexoy-2-tetrachlorophthalimido-β-D-glucopyranoside (27). To **10** (1.71 g, 3.31 mmol) in 11 mL CH_2Cl_2 was added **12d** (1.08 g, 3.64 mmol). After stirring for 11 min, NEt_3 (0.51 mL,

3.64 mmol) was added and the reaction stirred for an additional 1 h. The solution was concd and then diluted with pyridine (11 mL) before adding acetic anhydride (1.2 mL, 11.57 mmol). After stirring 20 h, the pyridine was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (80 mL) and washed with 5% HCl (2 × 30 mL), back extracting with CH_2Cl_2 (1 × 30 mL), and then washed with satd aq. $NaHCO_3$ soln (2 × 30 mL), back extracting with CH_2Cl_2 (1 × 30 mL). The concd soln was purified via flash chromatography eluting with 10:90 EtOAc–petroleum ether affording **27** as a slightly yellow oil (1.51 g, 58%); R_f 0.55 (15:85 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +31.6° (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.66–7.39 (m, 15H), 5.58–5.67 (m, 1H), 5.08 (d, *J* = 8.3 Hz, 1H), 4.55–4.91 (m, 8H), 4.06–4.37 (m, 3H), 3.56–3.81 (m, 4H), 3.34–3.42 (m, 1H), 1.85–1.92 (m, 2H), 1.47–1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.79, 162.02, 140.34, 138.98, 138.24, 137.74, 137.55, 137.43, 128.98, 128.87, 128.05, 127.74, 127.70, 127.60, 127.49, 126.90, 126.34, 126.29, 114.47, 97.47, 79.84, 79.34, 74.82, 74.69, 74.64, 73.12, 68.28, 68.20, 56.13, 29.56, 28.17; HRMS calcd for $C_{40}H_{37}NO_7Cl_4$ M^- 785.1302, found 785.1293.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside. Prepared as above for **15** starting with **14** affords a white foam (11.35 g, 69%); R_f 0.5 (30:70 EtOAc:petroleum ether); $[\alpha]^{20}_D$ −8.1° (*c* 1.09, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.08–7.38 (m, 5H), 5.70 (dd, *J* = 9.8, 11.2 Hz, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 5.2 (t, *J* = 9.6 Hz, 1H), 4.87 (d, *J* = 12.3 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.17–4.38 (m, 3H), 3.81–3.86 (m, 1H), 2.14 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.61, 170.37, 169.30, 162.8 (bs), 162.3 (bs), 136.57, 129.74, 128.41, 128.18, 127.98, 127.77, 126.83, 126.75, 97.09, 71.83, 71.80, 70.56, 68.52, 61.83, 55.39, 20.71, 20.52, 20.42; MS (FAB) *m/e* 662.93 M^-; Anal. calcd for $C_{27}H_{23}NO_{10}Cl_4$: C, 48.89; H, 3.50%; found: C, 49.00; H, 3.51%.

Benzyl 4,6-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside. Prepared as above for **22** starting with benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside affords a white foam (14.564 g, 87%); R_f 0.35 (20:80 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −59.8° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.02 (m, 10H), 5.54 (s, 1H), 5.20 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.64–4.36 (m, 3H), 4.24 (dd, *J* = 8.6, 10.6 Hz, 1H), 3.88–3.54 (m, 3H), 2.7 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.00, 162.23, 139.40, 139.21, 136.68, 136.53, 128.76, 127.83, 127.59, 127.26, 126.69, 126.44, 125.57, 101.01, 97.78, 81.34, 71.52, 68.21, 67.44, 65.77, 57.07; MS (FAB) *m/e* 625.01 M^-; Anal. calcd for $C_{28}H_{21}NO_7Cl_4$: C, 53.78; H,3.39%; found: C, 53.65; H, 3.40%.

Benzyl 3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (30). To benzyl 4,6-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (3.626 g, 5.794 mmol) in pyridine (16 mL) was added acetic anhydride (1.90 mL, 20.3 mmol). The reaction stirred 3 h before removing the pyridine in vacuo. The residue was dissolved in CH_2Cl_2 (100 ml) and washed with 5% aq. HCl (1 × 30 mL), back extracting with CH_2Cl_2 (1 × 10 mL), and then washed with satd aq. $NaHCO_3$ (2 × 30 mL) soln, back extracting with CH_2Cl_2 (1 × 10 mL). The concd soln was purified *via* flash chromatography eluting with 100% CH_2Cl_2 →2:98 EtOAc/ CH_2Cl_2 affording a white foam (3.611 g, 93%). To the foam (3.473 g, 5.204 mmol) in THF (50 mL) and ether (100 mL) was added 3 Å molecular sieves (1.6 g) and $NaCNBH_3$ (3.270 g, 52.04 eq). HCl_g was bubbled through the solution until the foaming had stopped at which point it was diluted with $CHCl_3$ (200 mL) and washed with with satd aq. $NaHCO_3$ (1 × 150 mL) solution, back extracting with $CHCl_3$ (1 × 40 mL), and with 5% aq HCl (1 × 150 mL), back extracting with $CHCl_3$ (1 × 40 mL). The concd soln was purified via flash chromatography eluting with 30:70 EtOAc–petroleum ether affording **30** as a white foam (3.045 g, 87%); R_f 0.30 (30:70 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −33.8° (*c* 1.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.08 (m, 10H), 5.55 (dd, *J* = 1.8, 8.8 Hz, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 4.84 (d, *J* = 12.3 Hz, 1H), 4.69–4.58 (m, 2H), 4.47 (d, *J* = 12.3 Hz, 1H), 4.24 (dd, *J* = 2.2, 8.4 Hz, 1H), 3.88–3.67 (m, 4H), 2.94 (bs, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.32, 162.95, 162.63, 140.06, 137.53, 136.93, 128.44, 128.13, 127.89, 127.84, 127.70, 127.65, 126.85, 97.19, 74.04, 73.71, 73.31, 71.66, 70.95, 69.87, 55.40, 20.68; MS (FAB) *m/e* 668.96 M ; Anal. calcd for $C_{30}H_{25}NO_8Cl_4$: C, 53.83; H, 3.76%; found: C, 53.70; H, 3.83%.

Benzyl (3,4,6-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (31). To **9** (1.258 g, 1.942 mmol) and **30** (1.000 g, 1.494 mmol) (both dried by azeotroping together with toluene) in 10 mL CH_2Cl_2 was added *N*-iodosuccinimide (0.57 g, 2.52 mmol) and triethylsilyl triflate (101 μL, 0.45 mmol). After stirring for 25 min at room temperature the glycosyl donor had been consumed and the reaction was quenched with 5 mL 10% aq. $Na_2S_2O_3$ and 5 mL of satd aq. $NaHCO_3$ solution. The mixture was stirred for an additional 5 min before separating the layers and extracting the aq. phase with CH_2Cl_2 (3 × 15 mL). The concentrated CH_2Cl_2 soln was purified via flash chromatography eluting with 25:75 EtOAc–petroleum ether affording **31** as a white foam (1.28 g, 70%); R_f 0.22 (25:75 EtOAc–petroleum ether); $[\alpha]_D^{20}$ +15.2° (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (bs, 4H), 6.85–7.33 (m, 25H), 5.58 (dd, *J* = 9.5, 11.3 Hz, 1H), 5.19–5.27 (m, 2H), 3.41–4.81 (m, 21H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.44, 167.70 (bs), 162.75 (bs), 162.56 (bs), 140.02, 139.75, 138.01, 137.87, 137.76, 136.87, 133.63, 131.45, 129.59, 129.40, 128.28, 128.23, 128.06, 128.00, 127.88, 127.70, 127.62, 127.48, 127.19, 126.86, 123.12, 97.18, 96.92, 79.08, 78.79, 74.70, 74.62, 74.25, 73.76, 73.12, 72.57, 71.43, 71.22, 68.10, 67.53, 56.08, 55.74, 20.50; MS (FAB) *m/e* 1237.2 $(M+Li)^+$; Anal. calcd for $C_{65}H_{56}N_2O_{14}Cl_4$: C, 63.42; H, 4.59%; found: C, 63.34; H, 4.64%.

Pent-4-enyl 4-*O*-acetyl-2-amino-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (32a). To **19** (0.135 g, 0.184 mmol) in 2 mL ethanol was added ethylenediamine (55.0 μL, 0.83 mmol). The reaction was heated to 60 °C for 2 h and then allowed to cool to room temperature. The reaction mixture was concentrated, and the residue was purified by flash chromatography eluting with 5:95 methanol:CH_2Cl_2. Compound **32a** was recovered as a film (86.3 mg, 93%); R_f 0.31 (45:55 EtOAc:petroleum ether); $[\alpha]_D^{20}$ −8.5° (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.40 (m, 10H), 5.71–5.90 (m, 1H), 4.92–5.10 (m, 3H), 4.60–4.75 (m, 2H), 4.23 (d, J=7.8 Hz, 1H), 3.88–3.98 (m, 1H), 3.45–3.65 (m, 5H), 2.90–2.98 (m, 1H), 2.09–2.18 (m, 2H), 1.90 (s, 3H), 1.62–1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.95, 137.99, 137.88, 128.56, 128.34, 127.92, 127.85, 127.75, 127.68, 114.94, 103.64, 82.91, 74.31, 73.62, 71.63, 69.89, 69.37, 63.91, 56.46, 30.15, 28.74, 20.96; HRMS calcd for $C_{27}H_{35}NO_6$ MH^+ 470.2543, found 470.2563.

Pent-4-enyl 2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (32b). To **19** (0.135 g, 0.184 mmol) in 2 mL ethanol was added ethylenediamine (55.0 μL, 0.83 mmol). The reaction was heated to 60 °C for 2 h after which it was allowed to cool to room temperature. Acetic anhydride (0.34 mL, 3.67 mmol) was added, and the soln was allowed to stir for an additional 20 min. The reaction mixture was concd and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq. $NaHCO_3$ (15 mL). The layers were sepd, and the aq. portion extracted with CH_2Cl_2 (2 × 20 mL). The product was purified by flash chromatography eluting with 20:80 EtOAc–dichloromethane. Compound **32b** was recovered as an off white film (80.4 mg, 86%); R_f 0.39 (22:78 EtOAc: CH_2Cl_2); $[\alpha]_D^{20}$ +11.6° (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.32 (m, 10H), 5.69–5.80 (m, 2H), 4.94–5.02 (m, 4H), 4.53–4.60 (m, 4H), 4.36 (t, J=9.7 Hz, 1H), 3.85–3.89 (m, 1H), 3.47–3.68 (m, 4H), 3.15–3.18 (m, 1H), 2.06–2.13 (m, 2H), 1.89 (s, 3H), 1.87 (s, 3H), 1.64–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.19, 169.36, 137.50, 127.99, 127.85, 127.43, 127.34, 127.32, 127.17, 114.47, 98.78, 76.15, 73.6, 73.06, 72.73, 71.43, 69.17, 68.17, 57.65, 29.53, 28.21, 23.10, 20.42; MS (CI) *m/e* 512 $(M+H)^+$, 529 $(M+NH_4)^+$; HRMS calcd for $C_{29}H_{38}NO_7$ MH^+ 512.2648, found 512.2633.

Benzyl (3,4,6-tri-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (33). To **13** (100 mg, 0.0812 mmol) in 0.7 mL of 2:1:1 acetonitrile:ethanol:tetrahydrofuran was added ethylenediamine (10.0 μL, 0.15 mmol) before heating to 60 °C. The reaction mixture was stirred for 22 h, allowed to cool to room temperature, concd and then filtered through a short column of silica gel with 3:97 methanol–CH_2Cl_2. The residue was treated with acetic anhydride (76 μL, 0.81 mmol) and triethylamine (23 μL, 0.16 mmol) in pyridine (1 mL) for 3 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with satd aq. $NaHCO_3$ (8 mL) back extracting the aq. portion with CH_2Cl_2 (2 × 15 mL). The product was purified by flash chromatography eluting with 35:65 EtOAc–CH_2Cl_2. Compound **33** was recovered as a film (52 mg, 64%); R_f 0.24 (18:82 EtOAc:dichloromethane); $[\alpha]_D^{20}$ −1.3° (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (bs, 4H), 6.84–7.34 (m, 25H), 5.39 (d, J=9.5 Hz, 1H), 5.30 (d, J=9.1 Hz, 1H), 4.92 (t, J=9 Hz, 1H), 3.73–4.82 (m, 18H), 3.32–3.49 (m, 4H), 1.97 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.13, 169.93, 167.90, 138.14, 137.95, 137.85, 137.19, 133.69, 131.52, 128.40, 128.35, 128.27, 128.14, 127.98, 127.80, 127.69, 127.63, 127.28, 123.19, 99.69, 97.34, 79.23, 78.86, 74.81, 74.73, 74.64, 73.45, 73.30, 72.67, 69.91, 68.38, 67.88, 56.23, 53.33, 23.25, 20.82; HRMS calcd for $C_{59}H_{61}N_2O_{13}$ MH^+ 1005.4174, found 1005.4129. Anal. calcd for $C_{59}H_{60}N_2O_{13}\cdot 2H_2O$: C, 68.06; H, 6.20%; found: C, 68.54; H, 6.01%.

Pent-4-enyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (34). To **15** (0.164 g, 0.256 mmol) in 1.65 mL 2:1:1 acetonitrile–ethanol–tetrahydrofuran was added ethylenediamine (77.0 μL, 1.15 mmol) before heating to 60 °C. The reaction was stirred for 100 min and then allowed to cool to room temperature. The reaction mixture was concd and filtered through a short column of silica gel with 10:90 methanol–CH_2Cl_2. The residue was treated with acetic anhydride (144 μL, 1.53 mmol) in ethanol (2 mL) for 30 min. The reaction mixture was concd and the residue was purified by flash chromatography eluting with 50:50 EtOAc–CH_2Cl_2. Compound **34** was recovered as an off-white film (56.7 mg, 54%); R_f 0.29 (50:50 EtOAc–dichloromethane); $[\alpha]_D^{20}$ −12.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.9 (bs, 1H), 5.68–5.77 (m, 1H), 5.26 (t, J=9.7 Hz, 1H), 4.88–5.03 (m, 3H), 4.64 (d, J=8.4 Hz, 1H), 4.05–4.23 (m, 2H), 3.64–3.84 (m, 3H), 3.41–3.48 (m, 1H), 2.02 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.75, 170.65, 170.17, 169.33, 137.83, 114.88, 100.64, 72.36, 71.60, 68.98, 68.76, 62.17, 54.66, 29.82, 28.52, 23.18, 20.54–20.62 (m, 3C); HRMS calcd for $C_{19}H_{30}NO_9$ MH^+ 416.1921, found 416.1924.

Pent-4-enyl 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (35). To **24** (0.153 g, 0.185 mmol) in 2.3 mL of 2:1:1 acetonitrile–ethanol–tetrahydrofuran was added ethylenediamine (56.0 μL, 0.85 mmol) before heating to 60 °C. The reaction mixture was stirred for 4.5 h, allowed to cool to room temperature, concentrated and then filtered through a short column of silica gel with 8:92 methanol:CH_2Cl_2. The residue was treated with acetic anhydride (53 μL, 0.54 mmol) and triethylamine (52 μL, 0.38 mmol) in CH_2Cl_2 (2 mL) for 30 min. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with satd aq. $NaHCO_3$ (8 mL) back extracting the aqueous portion with CH_2Cl_2 (2 × 15 mL). The reaction mixture was concd, and the residue was purified by flash chromatography eluting with 20:80 EtOAc–petroleum ether. Compound **35** was recovered as an off white film (80.4 mg, 86%); R_f 0.51 (10:90 EtOAc:dichloromethane); $[\alpha]_D^{20}$ −33.3° (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.27–8.03 (m, 15H), 5.59–5.82 (m, 4H), 4.85–5.02 (m, 3H), 4.44–4.63 (m, 2H), 4.07–4.16 (m, 2H), 3.88–3.95 (m, 1H), 3.51–3.59 (m, 1H), 2.06–2.13 (m, 2H), 1.90 (s, 3H), 1.66–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.32, 166.59, 166.13, 165.12, 137.82, 133.46, 133.38, 133.32, 133.28, 133.22, 133.08, 133.06, 132.98, 129.77, 129.62, 129.50, 128.76, 128.74, 128.33, 128.21, 114.90, 100.92, 72.89, 71.83, 69.85, 68.99, 63.24, 54.86, 29.86, 28.54, 23.21; MS (FAB) *m/e* 602.22 MH^+ HRMS calcd for $C_{34}H_{36}NO_9$ MH^+ 602.2390, found 602.2385.

1-*O*-[*N*-(benzyloxycarbonyl)-L-serine benzyl ester] 2-acetamido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-D-glucopyranoside (36). To **26** (0.110 g, 0.103 mmol) in 0.7 mL of 2:1:1 acetonitrile–ethanol–tetrahydrofuran was added ethylenediamine (12.0 L, 0.18 mmol) before heating to 60 °C. The reaction was stirred for 13 h at which point it was allowed to cool to room temperature. The reaction mixture was concd and filtered through a short plug of silica gel with 2:98 methanol–CH_2Cl_2. The residue was treated with acetic anhydride (76 μL, 0.82 mmol) in CH_2Cl_2 (1 mL) for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with satd aq. $NaHCO_3$ (8 mL) back extracting the aqueous portion with CH_2Cl_2 (2×15 mL). The product was purified by flash chromatography eluting with 50:50 EtOAc–CH_2Cl_2 to give **36** as a film (36.1 mg, 42%); R_f 0.46 (55:45 EtOAc–petroleum ether); $[\alpha]_D^{20}$ −22.1° (*c* 0.936, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–8.00 (m, 25H), 5.55–5.90 (m, 4H), 5.09–5.18 (m, 4H), 4.88 (d, J=8.2 Hz, 1H), 4.28–4.60 (m, 4H), 3.92–4.02 (m, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.79, 169.55, 166.50, 166.09, 165.09, 156.01, 136.19, 135.23, 133.47, 133.39, 133.08, 129.94, 129.79, 129.68, 129.46, 128.83, 128.74, 128.66, 128.52, 128.42, 128.35, 128.20, 128.14, 128.07, 127.99, 100.86, 72.45, 72.04, 71.98, 69.42, 68.91, 67.41, 66.96, 62.96, 54.88, 54.29, 23.14; MS (FAB) *m/e* 845.2 MH^+. HRMS calcd for $C_{47}H_{44}N_2O_{13}$ MH^+ 845.2922, found 845.2935.

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