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Note

Synthesis of cyclopropyl glycosides and their use as novel glycosyl donors

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ABSTRACT

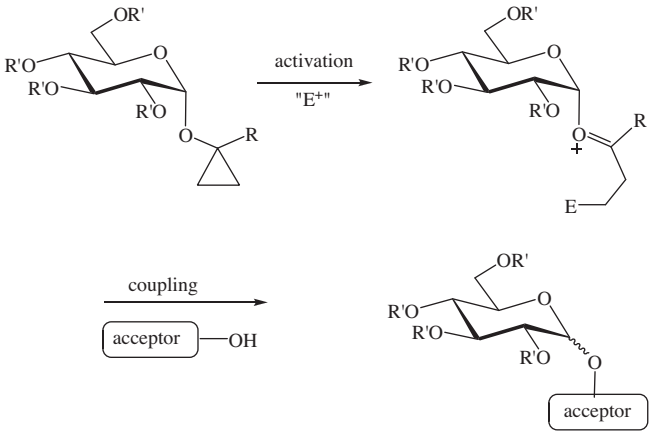
Methods for the synthesis of cyclopropyl glycosides and their use as glycosyl donors are described. Cyclopropyl glycosides containing different substituents were prepared by cyclopropanation of the corresponding vinyl glycosides, or by glycosidation of cyclopropyl alcohols that are synthesized by the Kulinkovich reaction. 1-Methyl- and 1-phenyl-substituted cyclopropyl glycosides undergo coupling to Fmoc-protected serine and threonine and to partially protected monosaccharides in the presence of TMS triflate to give glycosidated products.

Cyclopropanols and alkoxycyclopropanes have been used as homoenols and homoenolate equivalents in a variety of transformations in organic synthesis that are initiated by ring-opening.[1,2] Recent applications include the conversion of oxygen-substituted cyclopropanes to spirocyclobutanones by Prins-type reactions,[3] to oxepanes by Petasis–Ferrier rearrangement,[4] and to α-methylketones.[5] Among cyclopropanated carbohydrates, those in which the cyclopropane ring is fused at C2–C3 on the pyranose ring are the most widely studied, and have been successfully used to synthesize 2-C alkyl branched-chain sugars, oxepines, heptoses, and other products.[2,6–9] We considered that cyclopropyl glycosides, which are available from vinyl glycosides and by other means, may undergo glycosidation under Lewis-acid activation (Scheme 1).

In their work on the structure of the plant toxin helminthosporoside, Curini and Pellicciari demonstrated that a carboethoxy-substituted cyclopropyl glycoside underwent fragmentation in methanolic hydrogen chloride to produce methyl 4,4-dimethoxybutanoate (Scheme 2),[10] presumably through loss of the cyclopropyl group by an analogous process. Conceptually, the ring opening-fragmentation pathway illustrated in Scheme 1 resembles the cleavage of 1-methylcyclopropyl ethers (MCP ethers) and (1-methyl)cyclopropyl carbamates, which have been used as hydroxyl and amino protecting groups, respectively.[11,12] MCPM (1-methyl 1′-cyclo propylmethyl) ethers have also been used as hydroxyl protecting groups, and are cleaved under acidic conditions.[13]

There have been no reports of the use of cyclopropyl glycosides as glycosyl donors. We considered that the reactivity exemplified in Scheme 1 may allow activation and coupling under mild activating conditions by treatment with a Lewis acid. Cyclopropyl glycosides would be expected to be stable to a variety of conditions, and should be accessible by cyclopropanation of vinyl glycosides, from cyclopropyl alcohols, or from allyl glycosides once the double bond is isomerized. In this paper we describe the synthesis of unsubstituted and substituted cyclopropyl glycosides, and their use as glycosyl donors toward Fmoc-protected serine and threonine and monosaccharides.

Cyclopropyl glycosides were prepared by three methods. The first of these involves the conversion of tetra-*O*-benzyl-D-glucopyranose to mixed acetals by treatment with ethyl vinyl ether or



Scheme 1. Glycosidation via cyclopropyl glycosides.

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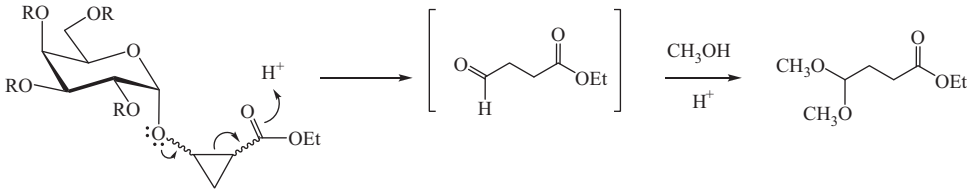
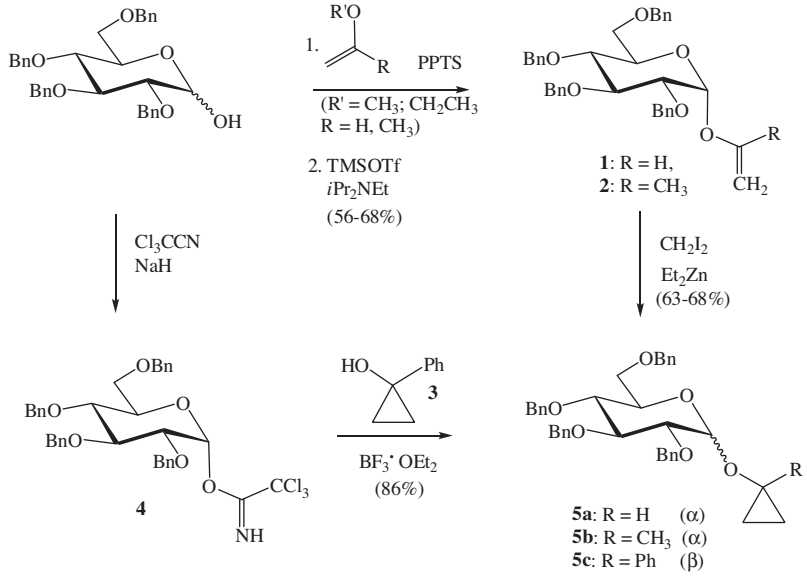


Scheme 2. Fragmentation of a cyclopropyl glycoside.



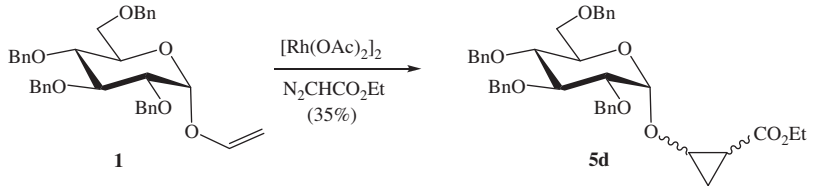
Scheme 3. Synthesis of cyclopropyl glycosides.

2-methoxypropene. The mixed acetals are then cleaved by trimethylsilyl trifluoromethanesulfonate in the presence of an amine base to give the vinyl glycosides **1** and **2** (Scheme 3). We previously described this two-step sequence as a mercury-free method for the preparation of vinyl glycosides and other vinyl-substituted carbohydrates that were used as substrates in hetero-Diels–Alder reactions.[14,15]

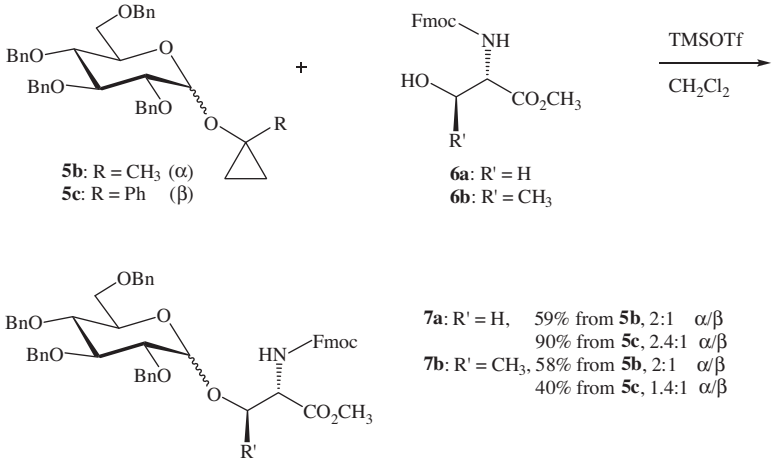
Cyclopropanation of the vinyl glycosides was carried out with diethyl zinc and methylene diodide[8] to give the corresponding cyclopropyl glycosides **5a** (R = H) and **5b** (R = CH_3). Initially, it was difficult to isolate acceptable yields of the 1-methylcyclopropyl glycoside **5b** by this method, which involves quenching the reaction with 1 M HCl. The replacement of the acid hydrolysis of the reaction mixture with the addition of pyridine[16] to precipitate the zinc salts gave higher and more reproducible yields of **5b**, which could be prepared in gram quantities as a crystalline solid that was stable indefinitely in the freezer (−10 °C). Compound **5b** is stable to amine and aqueous bases, and to Grignard reagents at 0 °C.

Vinyl glycoside synthesis followed by cyclopropanation was a convenient method to prepare unsubtituted and 1-methyl-substituted cyclopropyl glycosides **5a** and **5b**; however, the sequence proved to be less practical for the preparation of the 1-phenyl-substituted analog **5c**. In this case, preparation of 1-phenylcyclopropanol by the Kulinkovich reaction,[1,17] followed by Schmidt glycosidation[18]**5c** was successful. Synthesis of carboethoxy-substituted cyclopropyl glycoside **5d** was performed by treatment of vinyl glycoside **1** with rhodium acetate and ethyl diazoacetate (Scheme 4).[19,20] Cyclopropyl glycosides **5a** and **5b** were obtained as α anomers, **5c** as the β anomer, and **5d** as a mixture of diastereomers.

To study glycosidation using cyclopropyl glycosides, we initially chose protected amino acid acceptors to avoid potential side reactions that might result from the sensitivity of some carbohydrate acceptors toward acidic reagents that may be required to activate the cyclopropyl ring toward cleavage. Additionally, glycosidations of serine and threonine are known to be problematic, thus successful coupling reactions involving them would be synthetically useful. In this study, coupling reactions of the cyclopropyl glycosides were carried out using Fmoc-protected serine and threonine methyl esters. Previously, low yields in the synthesis of serine O-glycosides by the Koenigs–Knörr procedure have been ascribed to poor nucleophilicity of the hydroxyl group that results from intramolecular hydrogen bonding.[21] Improved yields were obtained by the use of imine derivatives of the amino acid acceptors in glycosidations with glycosyl halides, as well as through the use of other donors.[22,23] We were interested in observing if cyclopropyl glycosides could be used to glycosidate serine and threonine derivatives for possible application to glycopeptide synthesis.[24]. Initial results were not encouraging, as the unsubstituted cyclopropyl glycoside (**5a**), as well as the carboethoxy-substituted compound (**5d**) failed to undergo coupling with either Fmoc serine or threonine in the presence of trimethylsilyl triflate (TMS triflate, TMSOTf) or *N*-bromosuccinimide. Decomposition of the cyclopropyl glycosides was observed but no products of coupling were isolated. However, methyl- and phenyl-substituted cyclopropyl glycosides, **5b** and **5c**, underwent coupling with both Fmoc serine and threonine methyl esters **6a** and **6b** in the presence of TMS triflate to give glycosidated amino acids **7a** and **7b** (Scheme 5). Glycosidation of Fmoc serine methyl ester with **5c** proceeded in 90% yield. In all cases, α glycosides were obtained as the major products over β. While stereoselectivities are modest, we are encouraged by the



Scheme 4. Synthesis of a carboethoxy-substituted cyclopropyl glycoside.



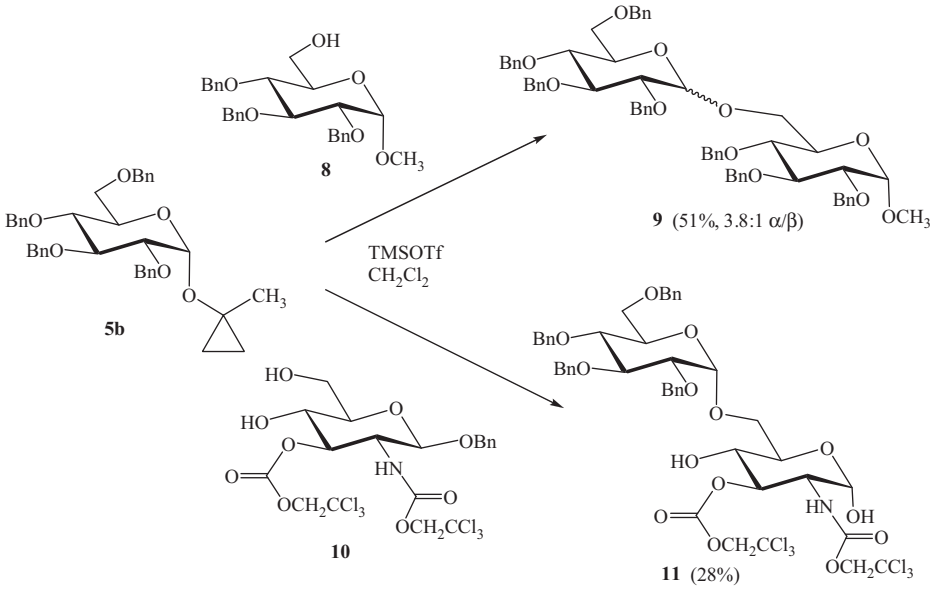
Scheme 5. Coupling of cyclopropyl glycosides with Fmoc serine/threonine.

ease with which glycosidation occurs from these readily accessible donors. The Fmoc protecting group, shown previously to be well suited to the efficient glycosidation of Fmoc serine benzyl ester with glycosyl bromides,[25] also works well in glycosidations with cyclopropyl glycosides.

Trichloroacetimidate derivatives have been used successfully to glycosidate Fmoc-protected serine esters with perbenzylated sugars. The TCA derivative of a disaccharide was used to glycosidate Fmoc-serine methyl ester in 86% yield, with ~2:1 α/β selectivity.[23] Isopropenyl glycosides, used in our study for the preparation of cyclopropyl glycosides, have been used as glycosyl donors in their own right.[26] For an additional comparison, we carried out the glycosidation of **6a** with isopropenyl glycoside **2**, using TMSOTf as the catalyst in dichloromethane. The ratio of α/β glycosides was again 2:1 and the isolated yield after chromatographic purification was 64%. We observed that the glycosidation of **6a** with isopropenyl glycoside **2** occurred more rapidly than with cyclopropyl glycoside donor **5b** or **5c**. Glycosidations with isopropenyl glycosides are known to proceed in either dichloromethane or acetonitrile, and with higher β-selectivity in the latter. Due to solubility problems of the reactants in acetonitrile, we were unable to attempt glycosidations in this solvent alone; however, the glycosidation of **5b** with **6a** was successful in a mixture of 8:1 acetonitrile–dichloromethane. The reaction proceeded more slowly than it did in dichloromethane, and the yield (48%) and stereoselectivity (α/β ratio = 4:1) were also different. Clearly there are differences in reactivity between the cyclopropyl and isopropenyl glycosides. While it is difficult to be definitive without additional examples, our results do suggest that cyclopropyl glycosides are less reactive toward activation with TMSOTf than isopropenyl glycosides, and that the preference for α-glycoside formation is not as solvent-dependent.

The mechanism of glycosidation with cyclopropyl glycoside donors likely follows the pathway suggested by Scheme 1. Reagents such as mercury(II) trifluoroacetate, *N*-iodosuccinimide and TMSOTf have been shown to initiate the ring-opening of cyclopropanated carbohydrates derived from glycals,[2,6] and products resulting from addition of the electrophile to a cyclopropyl carbon are obtained in some examples. One question that is pertinent to our study is whether or not it is TMSOTf or simply triflic acid that is activating the cyclopropyl glycosides in the coupling reactions. In the glycosidation of a cytovaricin subunit with a triethylsilyl glycoside using trityl perchlorate as the catalyst, it was shown that no reaction took place in the presence of 2,6-di-*tert*-butylpyridine or molecular sieves, which suggested that the true catalyst was perchloric acid.[27]. This was confirmed by successful glycosidations of the same donor with Brønsted acids. Control experiments that we conducted with 1-methylcyclopropyl donor **5a** and Fmoc serine methyl ester were less clear. While glycosidation did not occur in the presence of an amine base, tetramethylurea, or molecular sieves, coupling also did not take place when triflic acid was used to activate the cyclopropyl sugar. Attempted glycosidations using cyclopropyl sugars in the presence of other catalysts, including bismuth and aluminum triflates, were also unsuccessful. The development of milder conditions would expand the utility of cyclopropyl glycosides as donors, especially in oligosaccharide synthesis, as illustrated in Scheme 6.

Glycosidation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[28,29] **8** with 1-methylcyclopropyl glycoside **5b** occurred smoothly to give the 1,6-linked disaccharide **9**[26,30] in 51% yield after chromatography. However, the attempted glycosidation of bis-Troc-protected acceptor **10**[31,32] gave a mixture of products from which only α-linked disaccharide **11** could be isolated in 28% yield based on recovered **5b**. Glycosidation of **10** was of interest to us because it has been used as a glycosyl acceptor in the synthesis of lipid A analogs. Selective glycosidation of the C-6 hydroxyl in the presence of the unprotected C-4 hydroxyl was achieved through the use of glycosyl halides.[31] That debenzylation occurred and that the anomeric configurations at C1 in both carbohydrates in the disaccharide are α were established by extensive NMR analysis using both 1D and 2D techniques. Debenzylation is likely the result of the sensitivity of this acceptor to triflic acid that is



Scheme 6. Disaccharide synthesis with cyclopropyl glycosides as donors.

produced in the glycosidation. Given that other products were not characterized, it is not possible to ascertain the stereoselectivity of the coupling of **5b** and **10**. However, the loss of the aglycone from the acceptor and apparent absence of a β-linked disaccharide indicate sensitivity of the glycosidic linkages at both anomeric positions. It is worth noting that a recent comparison of relative rates of hydrolysis of methyl glucopyranoside derivatives that were substituted at the C2 position revealed a greater rate for hydrolysis of glucosides with C2 carbamate groups than that observed with alkyl or alkanoyl groups.[33]

In this study, we have synthesized 1-substituted cyclopropyl glycosides by cyclopropanation of isopropenyl glycosides and by glycosidation of 1-substituted cyclopropanols. The use of pyridine in the processing of the cyclopropanation of isopropenyl glycosides rather than acid was critical, and allowed the crystalline 1-methylcyclopropyl glycoside to be prepared efficiently. We have shown that 1-methyl and 1-phenylsubstituted cyclopropyl glycosides can be activated with TMSOTf and used as glycosyl donors in coupling reactions. Both Fmoc-protected serine and threonine methyl esters undergo glycosidation smoothly with these novel donors. Carbohydrate acceptors were also used successfully, albeit in a limited number of trials. Additional experiments are needed to assess the scope and synthetic utility of cyclopropyl glycosides in glycosidation with carbohydrates that possess more diverse substitution patterns.

1. Experimental

1.1. General procedures

Melting points were recorded on a Thomas-Hoover apparatus and they are uncorrected. Thin-layer chromatography was carried out on aluminum foil-backed silica gel plates (EMD) coated with a fluorescent indicator. Plates were developed with cerium molybdate stain. Flash chromatography was carried out using 230–400 mesh silica gel. NMR spectra were recorded on a Varian (Agilent) Mercury 300 Plus spectrometer in $CDCl_3$ for ^1H NMR at 300.0 MHz, tetramethylsilane reference, $\delta = 0.0$ ppm, and, ^{13}C NMR 70.0 MHz, $CDCl_3$ reference, $\delta = 76.9$ ppm. Spectral assignments were confirmed using gCOSY, DEPT, ^{13}C detected HETCOR, and gHMBC experiments.

1.2. Cyclopropyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 5a

To a stirring solution of vinyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **1** (0.73 g, 1.3 mmol) in anhydrous diethyl ether (2 mL) was added diiodomethane (1.0 mL, 12.7 mmol) followed by diethyl zinc (2.0 mL, 1 M in hexanes) under argon. The reaction mixture was stirred for 19 h at rt then ether (5 mL) was added and the reaction cooled to 0 °C. Pyridine (0.17 mL, 2.1 mmol) was added and the solution became yellow in color. After stirring for an additional hour at rt, the reaction was again cooled and a second portion of pyridine (0.17 mL, 2.1 mmol) was added, turning the solution orange. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure to give crude product that was purified by flash chromatography with 1:14:85 triethylamine–EtOAc–hexanes as the eluent. Cyclopropyl glycoside **5a** was obtained as an oil; yield, 0.73 g (97%). A second chromatography with 1:19:80 triethylamine–EtOAc–hexanes was used to provide 0.51 g (68%) of analytically pure material for characterization. R_f 0.48 (20% EtOAc–hexanes), $[\alpha]_D$ +122 (*c* 1.0, chloroform), ^1H NMR δ 7.34–7.11 (m, 20H, Ph-H), 4.96, 4.79 (ABq, 2H, $J = 10.8$, $PhCH_2$), 4.87 (d, 1H, $J_{1,2} = 3.7$, H-1), 4.75, 4.61 (ABq, 2H, $J = 12.2$, $PhCH_2$), 4.83, 4.47 (ABq, 2H, $J = 10.8$, $PhCH_2$), 4.60, 4.47 (ABq, 2H, $J = 12.2$, $PhCH_2$), 3.94 (dd, 1H, $J_{3,2} = 9.7$, $J_{3,4} = 9.1$, H-3), 3.85 (ddd, 1H, $J_{5,4} = 10.1$, $J_{5,6} = 3.8$, $J_{5,6'} = 2.1$, H-5), 3.72 (dd, 1H, $J_{6,5} = 3.8$, $J_{6,6'} = 10.6$, H-6), 3.65 (dd, 1H, $J_{6',5} = 2.1$, $J_{6',6} = 10.6$, H-6′), 3.63 (dd, 1H, $J_{4,3} = 9.1$, $J_{4,5} = 10.1$, H-4), 3.55 (dd, 1H, $J_{2,1} = 3.7$, $J_{2,3} = 9.7$, H-2), 3.42 (m, 1H, cyclopropyl), 0.844 (m, 1H, cyclopropyl), 0.637–0.391 (m, 3H, cyclopropyl); ^{13}C NMR δ 2 × 138.8, 138.2, 138.1 (Ph-*ipso*'s), 128.3–127.4, 20C, overlapped (Ph-CH's), 97.3 (C-1), 81.9 (C-3), 79.7 (C-2), 77.7 (C-4), 75.5, 74.9, 73.4, 73.0 ($PhCH_2$'s), 70.4 (C-5), 68.5 (C-6), 51.0 (cyclopropyl), 5.71 (cyclopropyl), 4.63 (cyclopropyl).

Anal. calcd for $C_{37}H_{40}O_6$: C, 76.66; H, 6.78. Found: C, 76.55; H, 6.85.

1.3. 1-Methylcyclopropyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 5b

To a stirring solution of isopropenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **2** (0.37 g, 0.64 mmol) in anhydrous diethyl ether (6 mL) was added diiodomethane (0.51 mL, 6.3 mmol) and diethyl

zinc (0.97 mL, 1 M in hexanes, 5.7 mmol) dropwise with stirring under argon. The reaction mixture was stirred for 14 h at rt then cooled to 0 °C. Pyridine (0.08 mL) was added and the solution became yellow in color. After stirring for an additional hour at rt, the reaction was again cooled and a second portion of pyridine (0.08 mL) was added, turning the solution orange. The reaction mixture was filtered through Celite and using an additional portion of ether (5 mL) and filtrate was concentrated under reduced pressure to an oil that was purified by flash chromatography using 1:10:89 triethylamine–EtOAc–hexanes to give 0.34 g (89%) of product as a colorless oil that solidified on storage at 0 °C. Recrystallization from 80:20 hexanes–EtOAc gave white solid (0.24 g, 63%). In subsequent preparations it was found that the solid product obtained after chromatography was suitable for coupling reactions: mp 83–86 °C, R_f 0.46 (20% EtOAc–hexanes), $[\alpha]_D$ +51.8 (*c* 1.0, dichloromethane), ^{1}H NMR δ 7.34–7.11 (m, 20H, Ph-H), 4.95, 4.79 (ABq, 2H, J = 10.7, $PhCH_2$), 5.09 (d, 1H, $J_{1,2}$ = 3.7, H-1), 4.82, 4.45 (ABq, 2H, J = 10.5, $PhCH_2$), 4.73, 4.64 (ABq, 2H, J = 12.2, $PhCH_2$), 4.62, 4.45 (ABq, 2H, J = 12.0, $PhCH_2$), 3.92 (dd, 1H, $J_{3,2}$ = 9.7, $J_{3,4}$ = 9.1, H-3), 3.85 (ddd, 1H, $J_{5,4}$ = 10.0, $J_{5,6}$ = 3.5, $J_{5,6'}$ = 2.2, H-5), 3.72 (dd, 1H, $J_{6,5}$ = 3.5, $J_{6,6'}$ = 10.5, H-6), 3.60 (dd, 1H, $J_{6',5}$ = 2.2, $J_{6,6'}$ = 10.5, H-6′), 3.63 (dd, 1H, $J_{4,3}$ = 9.1, $J_{4,5}$ = 10.0, H-4), 3.51 (dd, 1H, $J_{2,1}$ = 3.7, $J_{2,3}$ = 9.7, H-2), 1.45 (br s, 3H, CH_3), 1.07 (m, 1H, cyclopropyl), 0.75 (m, 1H, cyclopropyl), 0.41 (m, 2H, cyclopropyl); ^{13}C NMR δ 138.6, 138.0, 137.9, 137.7 (Ph-*ipso*'s), 128.2–127.2, 20C, overlapped (Ph-CH's), 95.9 (C-1), 81.9 (C-3), 79.5 (C-2), 77.7 (C-4), 75.4, 74.8, 73.1, 73.3 ($PhCH_2$'s), 70.1 (C-5), 68.4 (C-6), 58.5 (cyclopropyl), 22.1 (CH_3). 13.8 (cyclopropyl), 12.3 (cyclopropyl).

HRMS calcd for $C_{38}H_{46}NO_6$ $[M+NH_4]^+$: 612.3309. Found: 612.3325.

1.4. 1-(2-Ethoxycarbonylcyclopropyl) 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 5d

To a stirring solution of vinyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (500 mg, 0.89 mmol) and rhodium(II) acetate dimer (39 mg, 0.088 mmol) in dichloroethane (5 mL) was added a solution of ethyl diazoacetate (93.5 μL, 1.5 equiv) in dichloroethane (1 mL) over the course of 1 h at 60 °C with stirring. The reaction was stirred for 4 h at 60 °C, then concentrated to an oil that purified by flash chromatography; yield, 205 mg (35%). The carboethoxy-substituted was obtained as an inseparable mixture of diastereomers: R_f 0.3 (25% EtOAc–hexanes), ^{1}H NMR (isomer A) δ 7.35–7.10 (m, both diastereomers, Ph-H), 4.94, 4.79 (ABq, 2H, J = 10.9, $PhCH_2$), 4.82, 4.45 (ABq, 2H, J = 10.8, $PhCH_2$), 4.82 (d, 1H, $J_{1,2}$ = 3.7, H-1), 4.78, 4.60 (ABq, 2H, J = 12.1, $PhCH_2$), 4.61, 4.45 (ABq, 2H, J = 12.0, $PhCH_2$), 3.89 (dd, 1H, $J_{3,2}$ = 9.7, $J_{3,4}$ = 8.8, H-3), 3.82 (ddd, 1H, J = 2.0, 4.3, 6.9, cyclopropyl-1), 3.81 (m, 1H, H-5), 3.66 (m, 1H, H-4), 3.76–3.62(m, 2H, H-6, H-6′), 3.54 (dd, 1H, $J_{2,1}$ = 3.7, $J_{2,3}$ = 9.7, H-2), 4.11 (q, 2H, J_{vic} = 7.2, OCH_2), 1.73 (ddd, 1H, J = 2.0, 6.1, 9.6, cyclopropyl-2), 1.44 (m, 1H, cyclopropyl-3a), 1.30 (m, 1H, cyclopropyl-3b), 1.27 (t, 3H, J_{vic} = 7.2, CH_3); ^{13}C NMR δ 138.4, 137.8, 137.6, 137.48 (Ph-*ipso*'s), 128.3–127.3, (19 resonances, overlapped C for both diastereomers, Ph-CH), 97.8 (C-1), 81.7 (C-3), 79.4 (C-2), 77.2 (C-4), 75.6, 74.9, 73.5, 73.4 ($PhCH_2$'s), 70.6 (C-5), 67.9 (C-6), 60.5 (OCH_2), 57.8 (cyclopropyl-1), 20.6 (cyclopropyl-2), 15.5 (cyclopropyl-3), 14.1 (CH_3);(isomer B) δ 7.35–7.10 (m, both diastereomers, Ph-H), 4.95, 4.79 (ABq, 2H, J = 10.8, $PhCH_2$), 4.82, 4.45 (ABq, 2H, J = 10.8, $PhCH_2$), 4.84 (d, 1H, $J_{1,2}$ = 3.7, $J_{2,3}$ = 9.7, H-1), 4.79, 4.60 (ABq, 2H, J = 12.1, $PhCH_2$), 4.62, 4.46 (ABq, 2H, J = 12.2, $PhCH_2$), 3.89 (dd, 1H, $J_{3,2}$ = 9.7, $J_{3,4}$ = 8.7, H-3), 3.74 (m, 1H, H-5), 3.69 (ddd, 1H, cyclopropyl-1), 3.67 (m, 1H, H-4), 3.76–3.62(m, 2H, H-6, H-6′), 3.55 (dd, 1H, $J_{2,1}$ = 3.7, $J_{2,3}$ = 9.7, H-2), 4.09 (q, 2H, J_{vic} = 7.2, OCH_2), 1.97 (ddd, 1H, J = 2.2, 6.1, 9.8, cyclopropyl-2), 1.23 (t, 3H, J_{vic} = 7.2, CH_3), 1.21(m, 1H, cyclopropyl-3a), 1.14 (m, 1H, cyclopropyl-3b); ^{13}C NMR δ 138.4, 137.8, 137.7, 137.52 (Ph-*ipso*'s), 128.3–127.3 (19 resonances, overlapped C for both diastereomers, Ph-CH), 97.5 (C-1), 81.7 (C-3), 79.4 (C-2), 77.3 (C-4), 75.6 ($PhCH_2$), 74.9 ($PhCH_2$), 73.3 ($PhCH_2$), 73.3 ($PhCH_2$), 70.7 (C-5), 67.9 (C-6), 60.47 (OCH_2), 58.5 (cyclopropyl-1), 21.0 (cyclopropyl-2), 15.5 (cyclopropyl-3), 14.2 (CH_3). HRMS calcd for $C_{40}H_{44}O_8$ Na $[M+Na]^+$: 675.2933. Found: 675.2942.

1.5. 1-Phenylcyclopropyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside 5c

To a stirring solution of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate[17] (1.54 g, 2.25 mmol) in anhydrous dichloromethane (11 mL) was added 1-phenyl-1-cyclopropanol[16] (155 mg, 1.15 mmol). The solution was cooled to 0 °C and boron trifluoride diethyl etherate (150 μL) was added under argon. The reaction mixture was allowed to warm to rt, and stirred for 2 h, after which another 155 mg of 1-phenyl-1-cyclopropanol was added. The reaction mixture was again cooled to 0 °C and additional boron trifluoride diethyl etherate (150 μL) was added. After 2 h the reaction was quenched with 3 mL saturated sodium carbonate solution. The organic layer was separated and dried over $MgSO_4$ then concentrated to yield a viscous brown oil which was purified by flash chromatography (1:2:97 triethylamine–EtOAc–hexanes) to yield a yellow oil (0.59 g, 40%): R_f 0.72 (25% EtOAc–hexanes), $[\alpha]_D$ +11.8 (*c* 1.0, chloroform), ^{1}H NMR δ 7.48–7.11 (m, 25H, Ph-H), 4.92, 4.73 (ABq, 2H, J = 10.8, $PhCH_2$), 4.88, 4.76 (ABq, 2H, J = 10.4, $PhCH_2$), 4.79, 4.54 (ABq, 2H, J = 11.2, $PhCH_2$), 4.59 (d, 1H, $J_{1,2}$ = 8.1, H-1), 4.53, 4.43 (ABq, 2H, J = 12.3, $PhCH_2$), 3.61 (m, 1H, H-6), 3.58 (m, 1H, $J_{4,3}$ = ND, $J_{4,5}$ = 9.8, H-4), 3.54 (m, 1H, H-6′), 3.58 (m, 1H, $J_{3,2}$ = 8.1, $J_{3,4}$ = ND, H-3), 3.43 (dd, 1H, $J_{2,1}$ = 8.1, $J_{2,3}$ = 9.3, H-2), 3.30 (m, 1H, H-5), 1.68 (m, 1H, J_{gem} = 11.6, J_{vic} = 6.9, 5.2, cyclopropyl-2a), 1.32 (m, 1H, cyclopropyl-3a), 1.04 (m, 1H, cyclopropyl-2b), 0.93 (m, 1H, cyclopropyl-3b); ^{13}C NMR δ 141.0 (CP-Ph *ipso*), 138.4, 2 × 138.2, 138.0 (Ph-CH_2*ipso*), 128.8–128.2 (25C, Ph-CH), 102.0 (C-1), 84.8 (C-3), 82.1 (C-2), 77.7 (C-4), 75.4, 74.8, 74.7 ($PhCH_2$'s), 74.6 (C-5), 73.3 ($PhCH_2$), 68.7(C-6), 63.7 (cyclopropyl-1), 14.6 (cyclopropyl-2), 14.4 (cyclopropyl-3).

HRMS calcd for $C_{43}H_{44}NaO_6$ $[M+Na]^+$: 679.3037. Found: 679.3036.

1.6. Methyl 3-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyloxy)-(*S*)-2-(9-fluorenyl-methoxycarbonylamino)-propanoate 7a

From ***5b***: To a stirring solution of cyclopropyl glycoside **5b** (59 mg, 0.1 mmol) in anhydrous dichloromethane (2 mL) was added Fmoc-protected serine methyl ester **6a** (17 mg, 0.05 mmol) and the solution was flushed with argon and cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (0.01 mL, 0.05 mmol) was added and the reaction mixture was allowed to warm to rt. After 2 h, additional **6a** (17 mg, 0.05 mmol) and TMS triflate (0.01 mL, 0.05 mmol) were added at −78 °C and the reaction was stirred for an additional 2 h. Saturated sodium carbonate solution was added followed by diethyl ether (10 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to an oil that was purified by flash chromatography using 30% EtOAc–hexanes to give unseparated anomers of **7a** (51 mg, 59%, 2:1 α/β): R_f 0.37 (30% EtOAc–hexanes), ^{1}H NMR (α anomer) δ 7.74–7.10 (m, 28H, Ph), 6.08 (m, 1H, J = 8.7, NH), 4.96, 4.82 (ABq, 2H, J = 10.8, $PhCH_2$), 4.82, 4.47 (ABq, 2H, J = 10.6, $PhCH_2$), 4.76 (d, 1H, $J_{1,2}$ = 3.5, H-1), 4.71, 4.60 (ABq, 2H, J 12.0, $PhCH_2$), 4.57, 4.45 (ABq, 2H, J = 12.3, $PhCH_2$), 4.56 (dd, 1H, J = 3.4, 3.7, CHN), 4.42–4.25 (m, 2H, $OCOCH_2$), 4.22 (m, 1H, $CHCH_2O$), 4.12 (dd, 1H, J = 3.7, 10.7, CHO), 3.93 (dd, 1H, $J_{3,2}$ = 9.7, $J_{3,4}$ = 8.8, H-3), 3.87 (dd, 1H, J = 3.4, 10.7, CHO), 3.73 (m, 1H, $J_{5,4}$ = 10.1, H-5), 3.70 (s, 3H, OCH_3), 3.69 (m, 2H, H-6,6′), 3.63 (dd, 1H, $J_{4,3}$ = 8.8, $J_{4,5}$ = 10.1, H-4), 3.56 (dd, 1H, $J_{2,3}$ = 9.7,

$J_{3,4}$ = 8.8 H-2); ^{13}C NMR (α anomer) δ F = (fluorenyl) 170.2 (OC═O), 155.8 (NC═O), 143.6 (F8a,9a), 141.0 (F4a,4b), 138.4–137.5 (both isomers, 8C, Ph-*ipso*), 128.2–127.4 (both isomers, Ph-CH_2 + F3,6), 126.9 (F2,7), 125.0 (F1,8), 119.7 (F4,5), 98.6 (C-1), 81.6 (C-3), 79.7 (C-2), 77.3 (C-4), 75.6, 75.1, 73.4, 73.0 (4C, $PhCH_2$'s), 70.8 (C-5), 69.9 (CH_2O), 68.2 (C-6), 67.1 ($OCOCH_2$), 54.5 (CHN), 52.6 (OCH_3), 47.0 ($CHCH_2$).

^{1}H NMR (β anomer) δ 7.74–7.10 (m, 28H, Ph), 5.84 (m, 1H, *J* = 7.9, NH), 4.93, 4.82 (ABq, 2H, *J* = 10.8, $PhCH_2$), 4.88, 4.73 (ABq, 2H, *J* = 11.0, $PhCH_2$), 4.81, 4.53 (ABq, 2H, *J* 10.8, $PhCH_2$), 4.59, 4.26 (ABq, 2H, *J* = 12.2, $PhCH_2$), 4.55 (m, 1H, *J* = 3.4, CHN), 4.42–4.25 (m, 2H, $OCOCH_2$), 4.36 (d, 1H, $J_{1,2}$ = 7.8, H-1), 4.19 (m, 1H, $CHCH_2O$), 4.35 (m, 1H, *J* = 3.5, CHO), 3.93 (m, 1H, H-3), 3.89 (dd, 1H, *J* = 3.4, 10.7, CHO), 3.42 (m, 1H, H-5), 3.76 (s, 3H, OCH_3), 3.69 (m, 2H, H-6,6′), 3.63 (m, 1H, H-4), 3.45 (m, 1H, H-2); ^{13}C NMR (β anomer) δ, F = (fluorenyl), 170.1 (OC═O), 155.7 (NC═O), 143.5 (F8a,9a), 141.0 (F4a,4b), 138.4–137.5 (both isomers, 8C, Ph-*ipso*), 128.2–127.4 (both isomers, Ph-CH_2 + F3,6), 126.9 (F2,7), 124.9 (F1,8), 119.7 (F4,5), 103.8 (C-1), 84.5 (C-3), 81.6 (C-2), 77.5 (C-4), 75.6 ($PhCH_2$), 74.9 ($PhCH_2$), 74.8 (C-5), 73.4 ($PhCH_2$), 73.0 ($PhCH_2$), 69.8 (CH_2O), 68.4 (C-6), 67.2 ($OCOCH_2$), 54.5 (CHN), 52.6 (OCH_3), 47.0 ($CHCH_2$). HRMS calcd for $C_{53}H_{54}NO_{10}$ $[M+H]^+$: 864.3748. Found: 864.3748.

From ***5c***: To a stirring solution of **5c** (85 mg, 0.13 mmol) in anhydrous dichloromethane (2.5 mL) was added Fmoc-protected serine methyl ester **6a** (25 mg, 0.073 mmol). The solution was flushed with argon and cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (0.015 mL, 0.075 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h, additional **6a** (25 mg, 0.073 mmol) and TMS triflate (0.015 mL, 0.075 mmol) were added at −78 °C and the reaction was stirred for an additional 2 h. Saturated sodium carbonate solution was added followed by diethyl ether (10 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to an oil that was purified by flash chromatography using 30% EtOAc–hexanes to give inseparable anomers of **7a** (116 mg, 90%, 2.4:1 α/β).

1.7. Methyl (*R*)-3-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyloxy)-(*S*)-2-(9-fluorenyl-methoxycarbonylamino)butanoate 7b

From ***5b***: To a stirring solution of cyclopropyl glycoside **5b** (120 mg, 0.2 mmol) in anhydrous dichloromethane (4 mL) was added Fmoc-protected threonine methyl ester **6b** (36 mg, 0.1 mmol) and the solution was flushed with argon and cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (0.02 mL, 0.1 mmol) was added and the reaction mixture was allowed to warm to rt. After 2 h, an additional **6b** (36 mg, 0.1 mmol) and TMS triflate (0.02 mL, 0.1 mmol) were added at −78 °C and the reactions was stirred for an additional 2 h. Saturated sodium carbonate solution was added followed by dichloromethane (5 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to an oil that was purified by flash chromatography using a gradient of 10% EtOAc–hexanes to 30% EtOAc–hexanes to give unseparated anomers of **7a** (100 mg, 58%, 2:1 α/β): R_f 0.42 (30% EtOAc–hexanes), ^{1}H NMR (α anomer) δ 7.70–7.10 (m, 28H, Ph), 5.98 (m, 1H, *J* = 8.1, NH), 4.96, 4.84 (ABq, 2H, $PhCH_2$), 4.89 (d, 1H, $J_{1,2}$ = 3.7, H-1), 4.81, 4.44 (ABq, 2H, $PhCH_2$), 4.61, 4.60 (ABq, 2H, $PhCH_2$), 4.57, 4.45 (ABq, 2H, $PhCH_2$), 4.43 (m, 2H, $OCOCH_2$), 4.38 (m, 1H, *J* = 6.4, CH_3CHO), 4.34 (m, 1H, CHN), 4.23 (m, 1H, *J* = 7.0, $CHCH_2O$), 3.95 (m, 1H, $J_{3,2}$ = 9.8, $J_{3,4}$ = 9.2, H-3), 3.85 (m, 1H, $J_{5,6}$ = 3.4, H-5), 3.75 (m, 1H, $J_{6,6'}$ = 10.6, H-6), 3.70 (s, 3H, OCH_3), 3.67 (m, 1H, $J_{4,3}$ = 9.2, $J_{4,5}$ = 9.8, H-4), 3.60 (m, 1H, H-6′), 3.50 (dd, 1H, $J_{2,1}$ = 3.7, $J_{2,3}$ = 9.8, H-2), 1.31 (d, 3H, J_{vic} = 6.4, CH_3CH); ^{13}C NMR (α anomer) δ, F = (fluorenyl) δ 170.7 (OC═O), 156.4 (NC═O), 143.62, 143.50 F8a, F9a, 141.0 F4a, F4b, 138.4–137.5 (both isomers, 8C, Ph-*ipso*), 128.8 (F2, F7), 128.2–127.4 (both isomers, Ph-CH_2 + F3,6), 124.9 (F1, F8), 119.7 (F4, F5), 97.95 (C-1), 81.6 (C-3), 79.2 (C-2), 77.4 (C-4), 75.6 (CHO), 75.4, 75.1, 73.4, 73.0 (4C, $PhCH_2$'s), 70.8 (C-5), 68.1 (C-6), 67.0 ($OCOCH_2$), 58.8 (CHN), 52.4 (OCH_3), 47.0 ($CHCH_2$), ^{1}H NMR (β anomer) δ 7.73–7.10 (m, 28H, Ph), 5.82 (m, 1H, *J* = 8.6, NH), 4.90, 4.79 (ABq, 2H, $PhCH_2$), 4.88, 4.71 (ABq, 2H, $PhCH_2$), 4.79, 4.52 (ABq, 2H, $PhCH_2$), 4.53, 4.46 (ABq, 2H, $PhCH_2$), 4.43 (m, 1H, *J* = 6.4, CH_3CHO), 4.42 (d, 1H, $J_{1,2}$ = 8.0, H-1), 4.40 (m, 1H, CHN), 4.39 (m, 2H, $OCOCH_2$), 4.23 (m, 1H, *J* = 7.0, $CHCH_2O$), 3.76 (s, 3H, OCH_3), 3.65 (m, 3H, H-3, H-4, H-5), 3.6 (m, 2H, H-6, 6′), 3.43 (dd, 1H, H-2) 1.31 (d, 3H, CH_3CH); ^{13}C NMR δ 138.4–137.5 (8C, Ph); ^{13}C NMR (β anomer) δ 170.5 (OC═O), 156.4 (NC═O), 143.66, 143.45 F8a, F9a, 141.0, 141.0 F4a, F4b, 138.4–137.5 (both isomers, 8C, Ph-*ipso*), 128.8 (F2, F7), 128.2–127.4 (both isomers, Ph-CH_2 + F3,6), 124.9 (F1, F8), 119.7 (F4, F5), 101.4 (C-1), 84.4 (C-3), 81.6 (C-2), 77.3 (C-4), 75.5 ($PhCH_2$), 74.9 ($PhCH_2$), 74.9 ($PhCH_2$), 74.6 (CHO), 74.5 (C-5), 73.3 ($PhCH_2$), 68.6 (C-6), 67.1 ($OCOCH_2$), 58.6 (CHN), 52.3 (OCH_3), 47.0 ($CHCH_2$). HRMS calcd for $C_{54}H_{56}NO_{10}$ $[M+H]^+$: 878.3904. Found: 878.3865.

From ***5c***: To a stirring solution of **5c** (85 mg, 0.13 mmol) in anhydrous dichloromethane (2.5 mL) was added Fmoc-protected threonine methyl ester **6a** (28 mg, 0.079 mmol). The solution was flushed with argon and cooled to −78 °C. Trimethylsilyl trifluoromethanesulfonate (0.015 mL, 0.075 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h, additional **6a** (28 mg, 0.079 mmol) and TMS triflate (0.015 mL, 0.075 mmol) were added at −78 °C and the reaction was stirred for an additional 2 h. Saturated sodium carbonate solution was added followed by diethyl ether (10 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to an oil that was purified by flash chromatography using 30% EtOAc–hexanes to give inseparable anomers of **7a** (35 mg, 39%, 1.4:1 α/β).

1.8. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside 9[26,30]

To a stirring solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **8**[28,29] (35 mg, 0.075 mmol) and 1-phenylcyclopropyl 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranoside **5c** (0.042 g, 0.064 mmol) in anhydrous dichloromethane (2 mL) was added trimethylsilyl trifluoromethanesulfonate (0.01 mL, 0.05 mmol) under argon at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, after which some more of **8** (35 mg, 0.075 mmol) in dichloromethane was added, and the reaction mixture was again cooled to 0 °C and more trimethylsilyl trifluoromethanesulfonate was added (0.01 mL, 0.05 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another 2 h. Saturated sodium carbonate solution (1 mL) was then added, the mixture was diluted with 10 mL dichloromethane, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil (0.086 g) that was purified by flash chromatography on silica gel to give **9** as a mixture of anomers; yield, 32 mg (51%, 3.8:1 α/β): R_f 0.63 (30% EtOAc–hexanes), ^{1}H NMR (α anomer): δ 7.36–7.08 (m, 35H, Ph-H), 4.97 (d, 1H, *J* = 3.6, H-1), 4.95, 4.81 (ABq, 2H, $PhCH_2$), 4.94, 4.77 (ABq, 2H, $PhCH_2$), 4.91, 4.64 (ABq, 2H, $PhCH_2$), 4.82, 4.45 (ABq, 2H, $PhCH_2$), 4.71, 4.57 (ABq, 2H, $PhCH_2$), 4.66 (ABq, 2H, tight pair, $PhCH_2$), 4.57, 4.42 (ABq, 2H, $PhCH_2$), 4.54 (d, 1H, *J* = 3.9, H-1′), 3.98 (m, 1H, H-3′), 3.95 (m, 1H, H-3), 3.82–3.49 (m, 6H, H-5′, H-5, H-6_a, H-6_b, H-$6_{a'}$, H-$6_{b'}$), 3.65 (m, 1H, H-4′), 3.62 (m, 1H, H-4), 3.54 (m, 1H, H-2), 3.44 (m, 1H, H-2′), 3.35 (s, 3H, CH_3O). HRMS calcd for $C_{62}H_{66}O_{11}$ $[M+Na]^+$: 1009.4503. Found: 1009.4487.

1.9. 2-Deoxy-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-3-*O*-(2,2,2-trichloroethoxycarbonyl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranose 11

To a stirring solution of benzyl 2-deoxy-3-*O*-(2,2,2-trichloroethoxycarbonyl)-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside **10**[31,32] (100 mg, 0.16 mmol. and 1-methylcyclopropyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **5b** (120 mg, 0.20 mmol) in 5 mL methylene chloride was added trimethylsilyl trifluoromethanesulfonate (35 μL, 0.19 mol) under argon at 0 °C. The reaction flask was allowed to warm to room temperature and stirred for 1.5 h, after which additional **10** (100 mg, 0.16 mmol) was added in dichloromethane, the reaction mixture was again cooled to 0 °C and more trimethylsilyl trifluoromethanesulfonate (35 μL, 0.19 mol) was added. The reaction mixture was allowed to warm to room temperature and stirred for another 2 h. Saturated sodium carbonate solution (1 mL) was then added, the mixture was diluted with 10 mL dichloromethane, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a yellow oil which was purified by flash chromatography on silica gel using 1:8:91 triethylamine–EtOAc–hexanes as eluant to yield a waxy, colorless solid (0.0378 g, 0.036 mmol, 28% based on recovery of unreacted **5b**: R_f 0.61 (30% EtOAc–hexanes, ^{1}H NMR δ 7.38–7.09 (m, 20H, Ph), 6.6 (br d, 1H, $J_{2,NH}$ = 8.8, NH), 5.51 (d, 1H, J = 1.8, H-1), 5.01, 4.86 (ABq, 2H, J = 10.7, $PhCH_2$), 4.98, 4.72 (ABq, 2H, J = 12.3, $PhCH_2$), 4.87, 4.74 (ABq, 2H, J = 12.0, C2-Troc), 4.86, (d, 1H, J = 3.8, H-1′), 4.83, 4.46 (ABq, 2H, J = 11.0, $PhCH_2$), 4.72 (m, 1H, H-3), 4.7, 4.57 (ABq, 2H, J = 12.3, C3-Troc), 4.54, 4.45 (ABq, 2H, J = 12.3, $PhCH_2$), 4.53 (ddd, 1H, $J_{5,4}$ = 2.0, $J_{5,6a}$ = 0.9, $J_{5,6b}$ = 5.4, H-5), 4.11 (dd, 1H, $J_{5,6a}$ = 0.9, $J_{6a,6b}$ = 7.9, H-6a), 4.08 (t, 1H, $J_{3,2}$ = 9.7, $J_{3,4}$ = 9.3, H-3′), 3.96 (br d, 1H, $J_{2,NH}$ = 8.8, H-2), 3.9 (ddd, 1H, $J_{5,4}$ = 10.0, $J_{5,6a'}$ = 4.2, $J_{5,6b''}$ = 2.1, H-5′), 3.77 (dd, 1H, $J_{6a,5}$ = 0.9$J_{6a,6b}$ = 7.9, H-6b), 3.67 (dd, 1H, $J_{6'a,5'}$ = 4.2, $J_{6'a,6'b}$ = 10.8, H-6a′), 3.64 (m, 1H, H-4), 3.60 (t, 1H, $J_{4',3'}$ = 9.3 $J_{4',5'}$ = 10.0, H-4′ 3.60 (dd, 1H, $J_{6'b,5'}$ = 2.1, $J_{6'a,6'b}$ = 10.8, H-6b′), 3.57 (dd, 1H, $J_{2,1}$ = 3.8, $J_{2,3}$ = 9.7, H-2′); ^{13}C NMR δ 154.2 (C3 C═O), 153.4 (C═O), 138.9, 138.2, 137.9, 137.7 (*ipso*'s), 129.0–127.9 (20C, Ph), 99.4 (C-1), 96.9 (C-1′), 95.5 (CCl_3), 94.3 (CCl_3), 81.9 (C3′), 77.8 (C2′), 77.2(C-4′), 76.9 (CH_2-Troc), 75.7 ($PhCH_2$), 75.1 ($PhCH_2$), 74.8 (C5), 74.6 (C3), 73.7 ($PhCH_2$), 73.4 ($PhCH_2$), 73.2 (C3), 71.8 (C4), 71.4 (C5′), 68.2 (C6′), 64.7 (C6), 50.4 (C2). ESMS calcd for $C_{46}H_{50}NO_{14}Cl_6$ $[M+H]^+$: 1050.14. Found: 1050.1.

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