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Synthesis of Neoglycoconjugates by the Desulfurative Rearrangement of Allylic Disulfides

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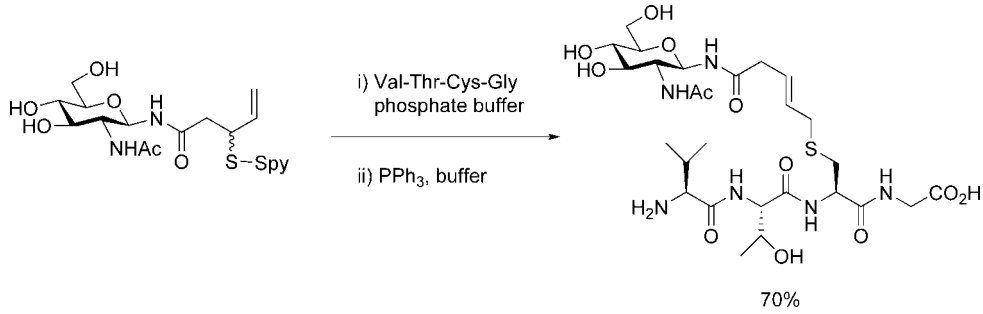
Received July 11, 2008



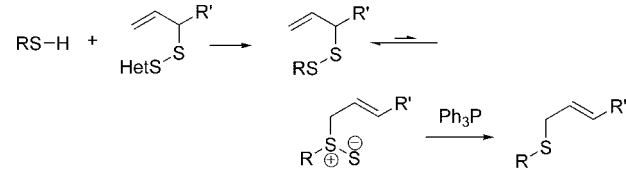
Two series of neoglycosyl donors are prepared on the basis of connection of an allylic disulfide motif to the anomeric center via a simple *O*-glycosyl linkage or *N*-glycosyl amide unit. Conjugation of both sets of donors to cysteine in peptides is demonstrated through classical disulfide exchange followed by the phosphine-mediated desulfurative allylic rearrangement resulting in neoglycopeptides characterized by a simple thioether spacer. The conjugation reaction functions in the absence of protecting groups on both the neoglycosyl donor and peptide in aqueous media at room temperature.

Introduction

We have introduced the desulfurative rearrangement of allylic disulfides (Scheme 1) as a facile means of electrophile-free, permanent functionalization of thiols suitable for the modification of cysteine and other thiols.[1] Herein we report on the extension of this chemistry to the ligation of carbohydrates to cysteine in peptides and proteins.

The ability to prepare glycosylated peptides and proteins is critical to the pursuit and advancement of glycomics and glycoscience.[2] The generation of native linkages between oligosaccharides and peptides typically requires the assembly of preglycosylated peptide building blocks into larger peptides, as exemplified by recent groundbreaking syntheses employing the method of native chemical ligation,[3] whereas the synthesis of neoglycoconjugates in principle allows the conjugation of oligosaccharides to fully assembled peptides and even proteins.[4] Among the many elegant methods devised,[5] the disulfide ligation, as applied to peptides and proteins by the Boons and Davis groups,[6] stands out for the mildness of conditions and broad functional group tolerance. The impermanence of the disulfide ligation, due to the ease of reduction and/or scrambling processes, has promoted the search

SCHEME 1. Ligation via the Desulfurative Allylic Disulfide Rearrangement



(1) (a) Crich, D.; Krishnamurthy, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2006**, *128*, 2544–2545. (b) Crich, D.; Zou, Y.; Brebion, F. *J. Org. Chem.* **2006**, *71*, 9172–9177. (c) Crich, D.; Krishnamurthy, V.; Brebion, F.; Karatholuvhu, M.; Subramanian, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2007**, *129*, 10282–10294. (d) Li, Z.; Wang, C.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* **2008**, *73*, 6127–6136.

(2) (a) Paulson, J. C.; Blixt, O.; Collins, B. E. *Nature Chem. Biol.* **2006**, *2*, 238–248. (b) Dwek, R. A.; Butters, T. D. *Chem. Rev.* **2002**, *102*, 283–284. (c) Varki, A. *Glycobiology* **1993**, *3*, 97–130. (d) Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds. *Essentials of Glycobiology*; Cold Spring Harbor Press: Cold Spring Harbor, 1999. (e) Buskas, T.; Ingale, S.; Boons, G.-J. *Glycobiology* **2006**, *16*, 113R–136R. (f) Werz, D. B.; Seeberger, P. H. *Chem. Biol.* **2007**, *2*, 661–691. (g) Ernst, B., Hart, G. W., Sinaÿ, P., Eds. *Carbohydrates in Chemistry and Biology*; Wiley-VCH: Weinheim, 2000. (h) Fraser-Reid, B., Kuniaki, T., Thiem, J., Eds. *Glycoscience: Chemistry and Chemical Biology*; Springer-Verlag: Berlin, 2001. (i) Fukuda, M., Hindsgaul, O., Eds. *Molecular and Cellular Glycobiology*; Oxford University Press: Oxford, 2000. (j) Demchenko, A. V., Ed. *Frontiers in Modern Carbohydrate Chemistry*; American Chemical Society: Washington, DC, 2007. (k) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–601. (l) Murrey, H. E.; Hsieh-Wilson, L. C. *Chem. Rev.* **2008**, *108*, 1708–1731.

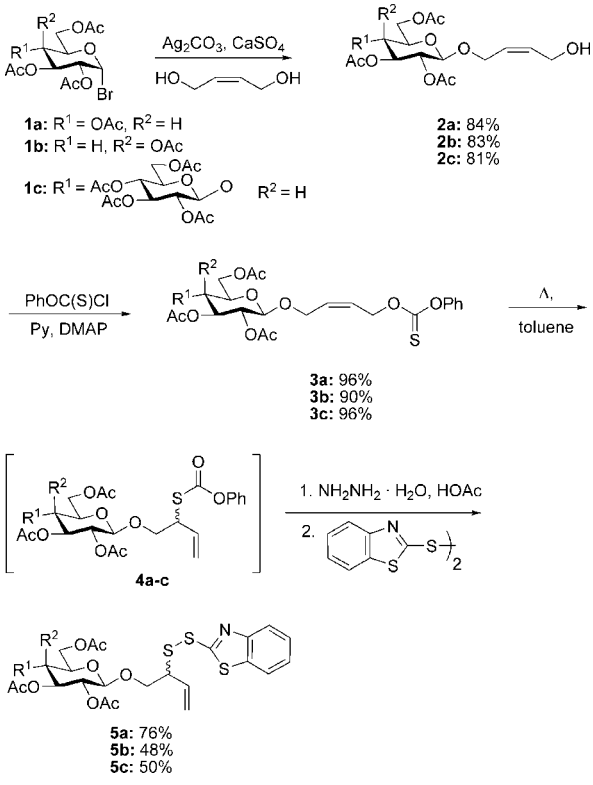
10.1021/jo8015314 CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/27/2008

for methods to convert the disulfide to a simple thioether, which have so far been marred by a loss of stereochemical integrity of the cysteine residue involved in the linkage.[7] The application of the desulfurative allylic rearrangement that we describe here combines the broad functional group compatibility of the disulfide ligation with the formation of a permanent thioether-type bond, and the maintenance of stereochemical integrity of the peptide chain.

Results and Discussion

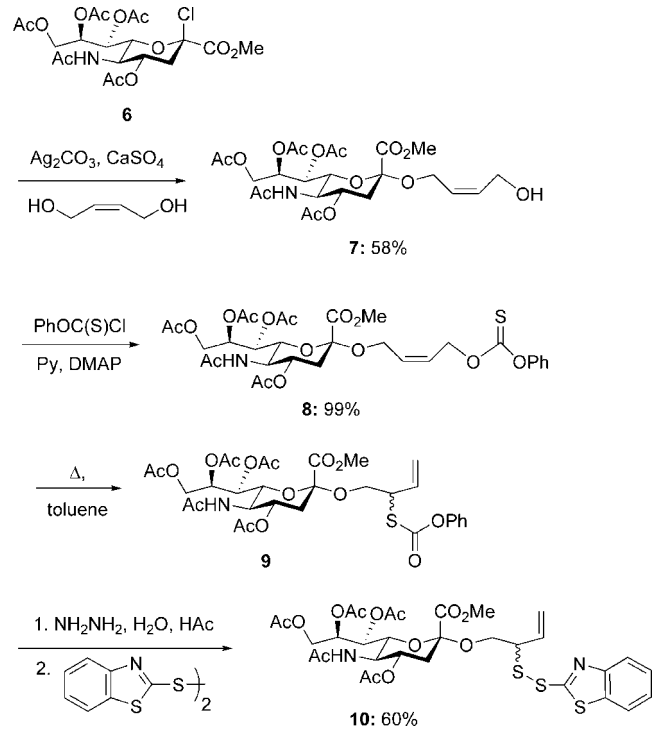
In our approach to neoglycoconjugate synthesis, we envisaged the use of a short spacer, resulting from the ligation reaction itself, to link the carbohydrate to the peptide. We preferred to accommodate the inherent requirement of the desulfurative allylic disulfide rearrangement for an allylic sulfide through the use of an appropriate tether, rather than attempt incorporation of this functionality into the saccharide itself to limit the number of chemical manipulations prior to the ligation reaction. To this end, in a first generation approach, a series of glycosyl bromides were coupled in β-selective reactions to *cis*-butene-1,4-diol (Scheme 2). Subsequent functionalization of the residual alcohol as a thionocarbonate ester was followed by heating in toluene at reflux to provoke [3,3]-sigmatropic rearrangement[8] and the formation of allylic thiolcarbonates as mixtures of stereoisomers at the newly generated stereogenic center. Selective hydrazinolysis of the thiolcarbonate gave the corresponding allylic thiols which were not isolated but immediately converted to the benzothiazolyl disulfides in high yield (Scheme 2).

SCHEME 2. First-Generation Approach to Precursor Synthesis



Exactly analogous chemistry with a sialosyl chloride gave an α-sialyl glycoside carrying the allylic disulfide moiety at the anomeric position (Scheme 3).

SCHEME 3. First-Generation Approach Applied to a Sialic Acid Derivative



A more efficient second-generation protocol involved application of the allylic thionocarbonate rearrangement to the

(3) (a) Yamamoto, N.; Tanabe, Y.; Okamoto, R.; Dawson, P. E.; Kajihara, Y. *J. Am. Chem. Soc.* **2008**, *130*, 501–510. (b) Krauss, I. J.; Joyce, J. G.; Finnefrock, A. C.; Song, H. C.; Dudkin, V. Y.; Geng, X.; Warren, D. J.; Chastain, M.; Shiver, J. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 11042–11044. (c) Haase, C.; Seitz, O. *Top. Curr. Chem.* **2007**, *267*, 1–36.

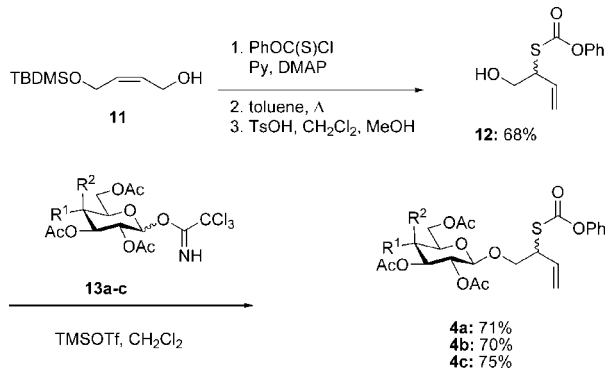
(4) (a) Stowell, C. P.; Lee, Y. C. *Adv. Carbohydr. Chem. Biochem.* **1980**, *37*, 225–281. (b) Lee, Y. C., Lee, R. T., Eds. *Neoglycoconjugates:Preparation and Applications*; Academic Press: San Diego, 1994. (c) Roy, R. In *Carbohydrate Chemistry*; Boons, G.-J., Ed.; Blackie Academic and Professional: London, 1998; pp 243−321. (d) Specker, D.; Wittman, V. *Top. Curr. Chem.* **2007**, *267*, 65–108.

(5) (a) Zhu, X. M.; Pachamuthu, K.; Schmidt, R. R. *Org. Lett.* **2004**, *6*, 1083–1085. (b) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160–187. (c) Doores, K. J.; Gamblin, D. P.; Davis, B. G. *Chem. Eur. J.* **2006**, *12*, 656–665. (d) Peri, F.; Nicotra, F. *Chem. Commun* **2004**, 623–627. (e) Ohnishi, Y.; Ichikawa, M.; Ichikawa, Y. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1289–1291. (f) Jobron, L.; Hummel, G. *Org. Lett.* **2000**, *2*, 2265–2267. (g) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405–407. (h) Knapp, S.; Myers, D. S. *J. Org. Chem.* **2002**, *67*, 2995–2999. (i) Zhu, X. M.; Schmidt, R. R. *Chem. Eur. J.* **2004**, *10*, 875–887. (j) Thayer, D. A.; Yu, H. N.; Galan, M. C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4596–4599. (k) Yang, Y.-Y.; Ficht, S.; Brik, A.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 7690–7701. (l) Ficht, S.; Payne, R. J.; Brik, A.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5975–5979. (m) Ichikawa, Y.; Matsukawa, Y.; Isobe, M. *J. Am. Chem. Soc.* **2006**, *128*, 3934–3938. (n) Ladmiral, V.; Mantovani, G.; Clarkson, G. J.; Cauet, S.; Irwin, J. L.; Haddleton, D. M. *J. Am. Chem. Soc.* **2006**, *128*, 4823–4830. (o) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364–367. (p) Ichikawa, Y.; Ohara, F.; Kotsuki, H.; Nakano, K. *Org. Lett.* **2006**, *8*, 5009–5012. (q) Wittrock, S.; Becker, T.; Kunz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5226–5230. (r) Ni, J.; Song, H.; Wang, Y.; Stamatos, N. M.; Wang, L.-X. *Bioconjugate Chem.* **2006**, *17*, 493–500. (s) Kolomiets, E.; Johansson, E. M. V.; Renaudet, O.; Darbre, T.; Reymound, J.-L. *Org. Lett.* **2007**, *8*, 14656–11468. (t) Samantaray, S.; Marathe, U.; Dasgupta, S.; Nandicoori, V. K.; Roy, R. P. *J. Am. Chem. Soc.* **2008**, *130*, 2132–2133.

(6) (a) Macindoe, W. M.; van Oijen, A. H.; Boons, G.-J. *Chem. Commun.* **1998**, 847–848. (b) Gamblin, D. P.; Garnier, S. J.; Ward, N. J.; Oldham, A. J.; Fairbanks, A. J.; Davis, B. G. *Org. Biomol. Chem.* **2003**, *1*, 3642–3644. (c) Gamblin, D. P.; Garnier, P.; van Kasteren, S.; Oldham, N. J.; Fairbanks, A. J.; Davis, B. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 828–833. (d) van Kasteren, S. I.; Kramer, H. B.; Jensen, H. H.; Campbell, S. J.; Kirkpatrick, J.; Oldham, N. J.; Anthony, D. C.; Davis, B. G. *Nature* **2007**, *446*, 1105–1109. (e) Bernardes, G. J. L.; Chalker, J. M.; Errey, J. C.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 5052–5053.

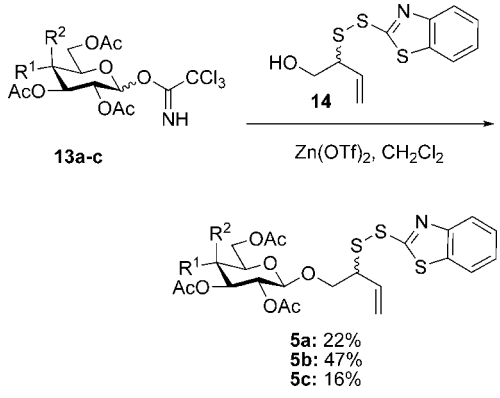
mono(*tert*-butyldimethylsilyl) ether of *cis*-butene-1,4-diol and desilylation followed by glycosylation by the trichloroacetimidate method[9] to intercept the first-generation method at the stage of the glycosylated thiolcarbonates **4a**−**c** (Scheme 4).[10]

SCHEME 4. Second-Generation Approach



The ideal approach (third generation) involved direct glycosylation of the known[3] hydroxylated allylic disulfide **14**, accessible from **12** by cleavage of the thiolcarbonate and sulfenylation in the usual manner, with glycosyl donors **13a**−**c**. Unfortunately, while this approach was successful (Scheme 5), it provided the desired products in only moderate yield and resulted in complications in a subsequent step (vide infra).

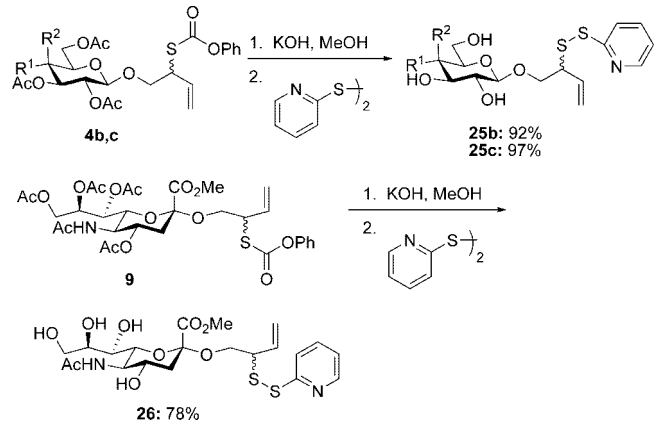
SCHEME 5. Third-Generation Approach



With four protected neoglycosyl donors in hand, a series of couplings were attempted to model cysteine-containing peptides. These reactions were conducted at room temperature by mixing the peptide and the neoglycosyl donor in acetonitrile/methanol (1:1) as solvent and, after the sulfenyl transfer stage was complete, adding triphenylphosphine to provoke the key rearrangement and render the ligation complete. Initial reactions were conducted with protected peptides before compatibility with free glutathione was tested in an aqueous medium. In all cases, the ligation proceeded efficiently, with the products being obtained in a highly trans-selective manner with respect to the linker (Table 1).

Deprotection of the neoglycoconjugate donors encountered several problems owing to the sensitivity of both disulfides[11] and allylic thiols[8c] to basic conditions. Thus, Zemplen-type cleavage of disulfides **5a**−**c** and **10** gave complex reaction mixtures from which only low yields of the desired products could be isolated. Optimal conditions were eventually found involving a mild saponification at the level of the thiolcarbonates **4b**,**c** and **9**, with concomitant removal of the thiolcarbonate and direct sulfenylation of the released thiol without isolation (Scheme 6). The optimum synthesis of the free neoglycosyl donors is therefore the combination of the second-generation approach to the protected donor (Scheme 3), followed by saponification and sulfenylation (Scheme 6).

SCHEME 6. Preparation of Unprotected Neoglycosyl Donors



Conjugation of the fully deprotected neoglycosyl donors **25** and **26** to the model peptide glutathione was achieved without issue in pH 8.0 phosphate buffer by simply mixing to achieve sulfenyl transfer and adding triphenylphosphine to bring about the sigmatropic rearrangement (Table 2). Interestingly, the yields in the protecting group free reactions conducted in phosphate buffer (Table 2) are routinely higher than those conducted with protected neoglycosyl donors in organic solvent mixtures (Table 1), which we attribute to the established facilitation of the desulfurative allylic disulfide rearrangement in polar solvents[1c] at the expense of the background phosphine-mediated disulfide cleavage reaction.

A second allylic disulfide linker was prepared as set out in Scheme 7 with a view to mimicking the *N*-glycosylamide linkage. Thus, aldol **31** was subjected to the thio-Mitsunobu reaction[12] to give the thioacetate **32**. Saponification and sulfenylation then afforded disulfide **33** which was converted to the free acid **34** by exposure to trifluoroacetic acid.

SCHEME 7. Preparation of an Alternative Linker

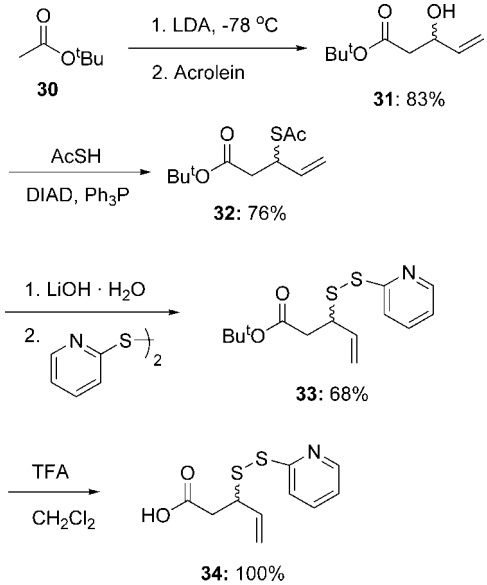
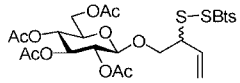
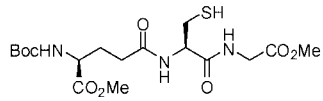
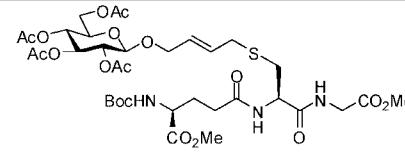
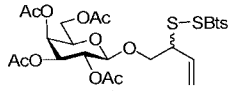
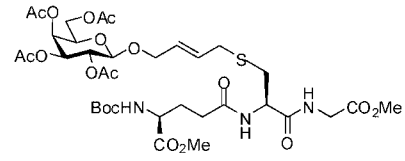
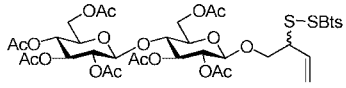
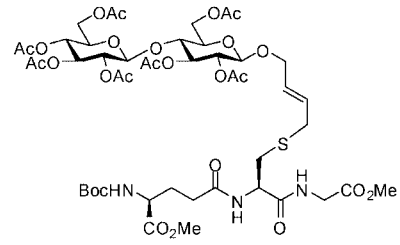
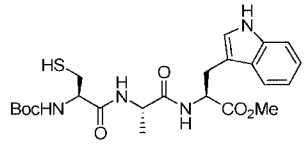
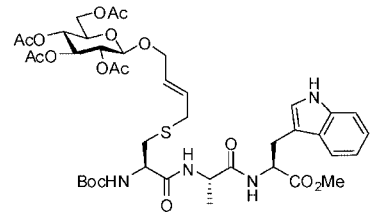
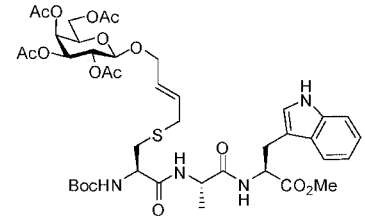
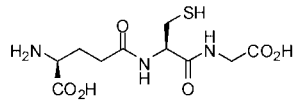
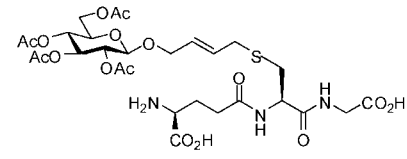
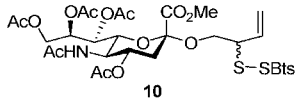
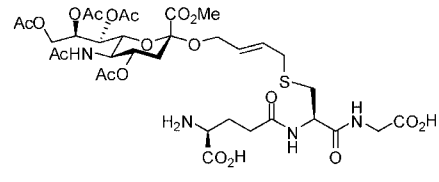
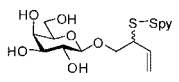
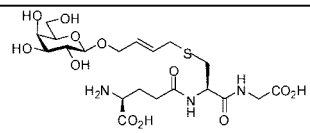
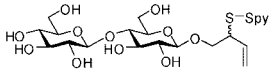
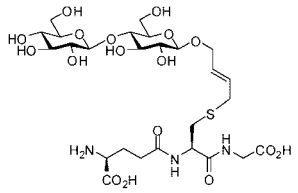
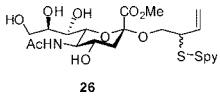
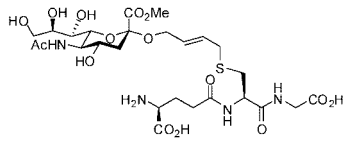


TABLE 1. Neoglycoconjugate Formation with Protected Donors

Neoglycosyl Donor	Peptides	Solvent	Neoglycopeptide (Yield)
 **5a**	 **15**	MeCN/ MeOH (1:1)	 **16** (79%)
 **5b**	**15**	MeCN/ MeOH (1:1)	 **17** (67%)
 **5c**	**15**	MeCN/ MeOH (1:1)	 **18** (70%)
5a	 **19**	MeCN/ MeOH (1:1)	 **20** (59%)
5b	**19**	MeCN/ MeOH (1:1)	 **21** (66%)
5a	 **22**	MeCN/ Tris buffer pH 8.0 (1:1)	 **23** (75%)
 **10**	**22**	MeCN/ Tris buffer pH 8.0 (1:1)	 **24** (71%)

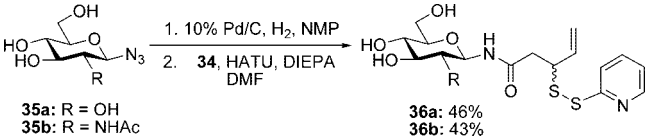
Standard peptide coupling reactions then enabled acid **34** to be affixed to glycosylamines in the complete absence of protecting groups (Scheme 8). Although the yields for this coupling process are only moderate at the present time, it possesses the very obvious

TABLE 2. Protecting Group-Free Neoglycoconjugate Preparation with Glutathione in Phosphate Buffer

Neoglycosyl Donor	Neoglycopeptide (Yield)
 **25b**	 **27** (90%)
 **25c**	 **28** (92%)
 **26**	 **29** (94%)

advantages of convergency and the direct provision of neoglycosyl donors ready for conjugation without the need for further protecting group manipulation.

SCHEME 8. Preparation of Amide-Based Neoglycosyl Donors



35a: R = OH
35b: R = NHAc

36a: 46%
36b: 43%

Neoglycoconjugate synthesis with donors **36** was conducted in aqueous buffer and proceeded in excellent yield (Table 3).

Experimental Section

General Methods. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. All reactions were conducted under an atmosphere of dry nitrogen. Organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature.

General Procedure for the Reaction of Glycosyl Bromides with *cis*-But-2-ene-1,4-diol (2a−c, 7).[13] *cis*-But-2-ene-1,4-diol (10 mL, 120 mmol), Ag_2CO_3 (750 mg, 2.7 mmol), $CaSO_4$ (2 g), and an iodine crystal were stirred with the exclusion of moisture and light for 0.5 h at room temperature before a glycosyl bromide (**1a−c**) (1.9 mmol) or the sialyl chloride (**6**) was added. The reaction mixture was stirred at room temperature for 24 h and then diluted with dichloromethane (25 mL) and filtered through Celite and the filtrate washed with water. The solvent was removed by evaporation, and the mixture was purified by chromatography over silica gel to afford the glycosides (**2a−c** and **7**).

(*Z*)-4-Hydroxybut-2-enyl tetra-*O*-acetyl-β-D-glucopyranoside (2a): white solid, eluted from silica gel with hexane/ethyl acetate (2:1) in 84% yield; mp 97 °C; $[\alpha]^{25}_D$ −15.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.60 (m, 1H), 5.18 (t, J = 9.5 Hz, 1H), 5.06 (t, J = 9.5 Hz, 1H), 4.97 (dd, J = 8.0, J = 9.5 Hz, 1H), 4.55 (d, J = 8.0 Hz, 1H), 4.34 (dd, J = 6.0, J = 12.5 Hz, 1H), 4.24 (m, 2H), 4.17 (d, J = 6.5 Hz, 2H), 4.14 (dd, J = 2.0, J = 10.0 Hz, 1H), 3.69 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 169.5, 133.4, 126.7, 99.3, 72.8, 71.8, 71.2, 68.4, 64.3, 62.0, 58.5, 20.8, 20.7, 20.6. Anal. Calcd for $C_{18}H_{26}O_{11}$: C, 51.33; H, 6.28; N, 2.49. Found: C, 51.22; H, 6.01; N, 2.44.

(*Z*)-4-Hydroxybut-2-enyl tetra-*O*-acetyl-β-D-galactopyranoside (2b): syrup, eluted from silica gel with hexane/ethyl acetate (2:1) in 83% yield; $[\alpha]^{15}_D$ −9.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 5.52 (m, 1H), 5.30 (d, J = 3.5 Hz, 1H), 5.11 (dd, J = 8.0, J = 10.5 Hz, 1H), 4.93 (dd, J = 3.5, J = 10.5 Hz, 1H), 4.45 (d, J = 8.0 Hz, 1H), 4.28 (dd, J = 7.5, J = 12.5 Hz, 1H), 4.20 (dd, J = 7.5, J = 12.5 Hz, 1H), 4.11−4.02 (m, 1H), 3.86 (t, J = 6.5 Hz, 1H), 2.07 (s, 3H), 1.98 (s, 6H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.3, 170.1, 169.6, 133.5, 126.4, 99.6, 70.9, 70.6, 68.7, 67.1, 64.2, 61.4, 58.3, 20.7, 20.64, 20.5; ESIHRMS calcd for $C_{18}H_{26}O_{11}Na$ $[M + Na]^+$ 441.1368, found 441.1361.

(*Z*)-4-Hydroxybut-2-enyl hepta-*O*-acetyl-β-D-cellobioside (2c): white solid, eluted from silica gel with hexane/ethyl acetate (1:3) in 81% yield; mp 171 °C; $[\alpha]^{15}_D$ −21.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.60 (m, 1H), 5.15 (m, 2H), 5.05 (t, J = 9.5 Hz, 1H), 5.90 (m, 2H), 4.55−4.50 (m, 3H), 4.35(dd, J = 4.5, J = 12.5 Hz, 1H), 4.31(dd, J = 6.0, J = 13.0 Hz, 1H), 4.23(dd, J = 7.5, J = 12.5 Hz, 1H), 4.17 (d, J = 6.5 Hz, 2H), 4.09−4.03 (m, 2H), 3.76 (t, J = 9.5 Hz, 1H), 3.64 (m, 1H), 3.59 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.003 (s, 3H), 1.998 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 170.2, 169.8, 169.7, 169.3, 169.1, 133.5, 126.6, 100.7, 99.1, 76.4, 72.9, 72.7, 72.4, 71.9, 71.6, 71.5, 67.7, 64.3, 61.8, 61.5, 58.4, 20.9, 20.70, 20.66, 20.5; ESIHRMS calcd for $C_{30}H_{42}O_{19}Na$ $[M + Na]^+$ 729.2218, found 729.2191.

(*Z*)-4-Hydroxybut-2-enyl (methyl 4,7,8,9-tetra-*O*-acetyl-5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate) (7): white solid, eluted from silica gel with ethyl acetate in 58% yield; mp 130.1 °C; $[\alpha]24_D$ −11.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (m, 1H), 5.57 (m, 1H), 5.44 (m, 1H), 5.30 (dd, J = 0.5, J = 8.5 Hz, 1H), 5.25 (dd, J = 0.5, J = 9.5 Hz, 1H), 4.83 (m, 1H), 4.34 (m, 1H), 4.20 (m, 1H), 4.12 (dd, J = 6.5, J = 13.5 Hz, 1H), 4.05 (m, 4H), 3.78 (s, 3H), 2.59 (dd, J = 4.5, J = 12.5 Hz, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.04, 170.96, 170.5, 170.3, 168.4 (C-1, $J_{C\text{-}1,H\text{-}3ax}$ = 5.0 Hz), 131.8, 127.5, 98.4, 72.4, 69.0, 68.4, 67.3, 62.7, 61.1, 58.3, 52.8, 49.4, 38.1, 23.2, 21.2, 20.9, 20.8. Anal. Calcd for $C_{24}H_{35}NO_{14}$: C, 51.33; H, 6.28; N, 2.49. Found: C, 51.22; H, 6.01; N, 2.44.

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(10) The glycosylation reaction was accompanied by partial cleavage of the O-2 acetate, which was detrimental to the yield of the product. Therefore, an acetylation step was included in the workup protocol to reinstall any missing acetates.

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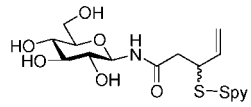
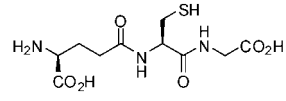
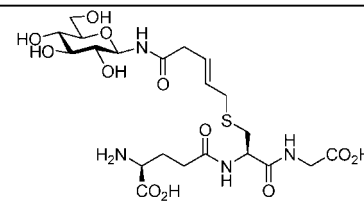
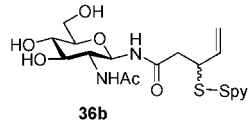
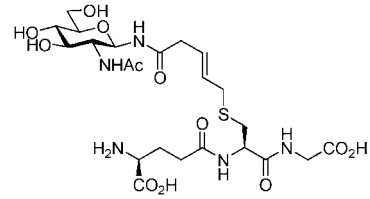
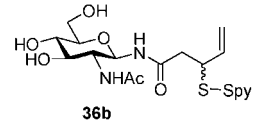
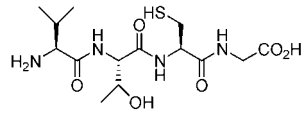
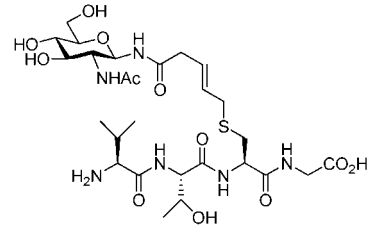
TABLE 3. Amide-Based Neoglycopeptide Synthesis

Neoglycosyl Donor	Peptide	Neoglycopeptide (Yield)
 **36a**	 **22**	 **37** (70%)
 **36b**	**22**	 **38** (85%)
 **36b**	 **39**	 **40** (70%)

General Procedure for the Reaction of Hydroxybutenyl Glycosides with Phenyl Thionochloroformate (3a−c, 8). A solution of phenyl chlorothionocarbonate (158 μL, 1.14 mmol) in dichloromethane (3 mL) was added to a solution of the alcohols **2a−c** (0.38 mmol), pyridine (184 μL, 2.28 mmol), and DMAP (6 mg) in dichloromethane (2 mL), and the resulting yellow solution was stirred at room temperature for 5 h. The reaction mixture was poured into H_2O (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried, filtered, evaporated, and purified by chromatography over silica gel.

(*Z*)-4-(Phenyloxythionocarbonyloxy)-2-butenyl tetra-*O*-acetyl-*β*-D-glucopyranoside (3a): yellow syrup, eluted from silica gel with hexane/ethyl acetate (1:1) in 96% yield; $[\alpha]^{21}_D$ −9.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 8.0 Hz, 2H), 5.87 (m, 1H), 5.80 (m, 1H), 5.19 (t, J = 9.5 Hz, 1H), 5.09 (m, 3H), 5.00 (dd, J = 8.0, J = 9.5 Hz, 1H), 4.56 (d, J = 8.0 Hz, 1H), 4.38 (dq, J = 5.5, J = 13.5 Hz, 2H), 4.25 (dd, J = 4.5, J = 12.0 Hz, 1H), 4.15 (dd, J = 2.0, J = 12.0 Hz, 1H), 3.69 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 170.7, 170.3, 169.41, 169.39, 153.4, 130.6, 129.6, 126.7, 126.1, 121.9, 99.5, 72.8, 71.9, 71.2, 69.2, 68.3, 64.6, 61.9, 20.79, 20.75, 20.6; ESIHRMS calcd for $C_{25}H_{30}O_{12}SNa$ [M + Na]$^+$ 577.1356, found 577.1338.

(*Z*)-4-(Phenyloxythionocarbonyloxy)-2-butenyl tetra-*O*-acetyl-*β*-D-galactopyranoside (3b): yellow syrup, eluted from silica gel with hexane/ethyl acetate (1:1) in 90% yield; $[\alpha]^{15}_D$ −3.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.26 (dt, J = 1.0, J = 7.5 Hz, 1H), 7.07 (m, 2H), 5.81 (m, 2H), 5.34 (dd, J = 0.5, J = 3.5 Hz, 1H), 5.19 (dd, J = 8.0, J = 10.5 Hz, 1H), 5.07 (m, 2H), 4.97 (dd, J = 3.5, J = 10.5 Hz, 1H), 4.50 (d, J = 8.0 Hz, 1H), 4.39 (dd, J = 5.5, J = 12.5 Hz, 1H), 4.32 (dd, J = 6.5, J = 12.5 Hz, 1H), 4.12(d, J = 7.0 Hz, 1H), 3.88 (dt, J = 1.5, J = 6.5 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 170.3, 170.2, 170.1, 169.4, 153.4, 130.7, 129.6, 126.7, 125.9, 121.9, 100.0, 70.9, 70.8, 69.2, 68.7, 67.1, 64.6, 61.3, 20.8, 20.7, 20.6; ESIHRMS calcd for $C_{25}H_{30}O_{12}SNa$ [M + Na]$^+$ 577.1356, found 577.1344.

(*Z*)-4-(Phenyloxythionocarbonyloxy)-2-butenyl hepta-*O*-acetyl-*β*-D-cellobioside (3c): yellow syrup, eluted from silica gel with hexane/ethyl acetate (1:1) in 96% yield; $[\alpha]^{15}_D$ −18.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, J = 8.0 Hz, 2H), 7.30 (m, 1H), 7.09 (m 2H), 5.87 (m, 1H), 5.79 (m, 1H), 5.19−5.03 (m, 5H), 4.91 (m, 2H), 4.54−4.48 (m, 3H), 4.40−4.31(m, 3H), 3.78 (t, J = 9.5 Hz, 1H), 3.64 (m, 1H), 3.58 (m, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 170.5, 170.33, 170.26, 169.8, 169.7, 169.3, 169.1, 153.4, 130.6, 129.6, 126.7, 126.1, 121.9, 100.8, 99.3, 76.4, 72.9, 72.8, 72.5, 72.0, 71.6, 71.4, 69.2, 67.8, 64.6, 61.8, 61.5, 21.0, 20.8, 20.7, 20.6; ESIHRMS calcd for $C_{37}H_{46}O_{20}SNa$ [M + Na]$^+$ 865.2201, found 865.2173.

(*Z*)-4-(Phenyloxythionocarbonyloxy)-2-butenyl (methyl 4,7,8,9-tetra-*O*-acetyl-5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate) (8): yellow syrup, eluted from silica gel with dichloromethane/methanol (10:1) in 99% yield; $[\alpha]^{24}_D$ −12.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41(d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 5.79 (m, 1H), 5.43 (m, 1H), 5.32 (dd, J = 2.0, J = 8.5 Hz, 1H), 5.24 (d, J = 9.0 Hz, 1H), 5.14 (dd, J = 1.5, J = 6.5 Hz, 2H), 4.85 (m, 1H), 4.41(dd, J = 5.0, J = 13.5 Hz, 1H), 4.29 (dd, J = 2.5, J = 12.5 Hz, 1H), 4.06 (m, 4H), 3.79 (s, 3H), 2.60 (dd, J = 4.5, J = 13.0 Hz, 2H), 2.16 (s, 3H), 2.12 (s, 3H), 2.023 (s, 3H), 2.017 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 171.0, 170.7, 170.24, 170.18, 170.1, 168.2, 153.5, 130.3, 129.6, 126.6, 125.5, 121.9, 98.5, 72.5, 69.8, 69.0, 68.3, 67.2, 61.0, 52.9, 49.4, 38.0, 23.2, 21.2, 20.9, 20.8; ESIHRMS calcd for $C_{31}H_{39}NO_{15}SNa$ [M + Na]$^+$ 720.1933, found 720.1928.

General Procedure for the [3,3]-Sigmatropic Rearrangement Reaction of Allylic Thionocarbonates (4a−c, 9). A solution of **3a−c** or **8** in toluene was heated at reflux for 8−12 h. Evaporation of the solvent afforded **4a−c** or **9** as yellow syrups in quantitative yield.

2-(Phenyloxycarbonylthioxy)-3-butenyl Tetra-*O*-acetyl-β-D-glucopyranoside (4a). An approximately 1:1 mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2 × 2H), 7.24 (t, J = 7.5 Hz, 2 × 1H), 7.15 (m, 2 × 2H), 5.90 (m, 2 × 1H), 5.39 (dd, J = 3.5, J = 17.0 Hz, 2 × 1H), 5.22 (m, 2 × 2H), 5.08 (dt, J = 3.5, J = 10.0 Hz, 2 × 1H), 5.02 (dt, J = 2.0, J = 8.0 Hz, 2 × 1H), 4.58 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 8.0 Hz, 1H), 4.16 (m, 2 × 4H), 3.79 (m, 2 × 1H), 3.70 (m, 2 × 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.018 (s, 3H), 2.017 (s, 3H), 2.003 (s, 3H), 2.000 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 169.4, 169.3, 169.0, 168.96, 168.92, 168.31, 168.29, 151.1, 133.6, 129.6, 126.3, 121.3, 119.0, 118.9, 101.3, 100.5, 72.7, 72.6, 71.9, 71.8, 71.04, 71.98, 70.5, 68.4, 68.3, 61.9, 61.8, 48.5, 47.9, 20.8, 20.6; ESIHRMS calcd for $C_{25}H_{30}O_{12}SNa$ $[M + Na]^+$ 577.1356, found 577.1339.

2-(Phenyloxycarbonylthioxy)-3-butenyl Tetra-*O*-acetyl-β-D-galactopyranoside (4b). An approximately 1:1 mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2 × 2H), 7.25 (t, J = 7.5 Hz, 2 × 2H), 7.15 (m, 2 × 2H), 5.92 (m, 2 × 1H), 5.39 (m, 2 × 2H), 5.24 (m, 2 × 2H), 5.02 (m, 2 × 1H), 4.53 (d, J = 8.5 Hz, 1H), 4.51 (d, J = 8.5 Hz, 1H), 4.21−4.10 (m, 2 × 4H), 3.91 (m, 2 × 1H), 3.79 (m, 2 × 1H), 2.513 (s, 3H), 2.148 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.3, 170.2, 169.5, 169.4, 168.9, 151.1, 133.8, 133.4, 129.6, 126.3, 121.3, 118.9, 118.8, 101.8, 101.1, 71.7, 70.83, 70.76, 70.5, 68.6, 68.5, 67.0, 61.3, 48.6, 48.0, 20.88, 20.83, 20.7, 20.6; ESIHRMS calcd for $C_{25}H_{30}O_{12}SNa$ $[M + Na]^+$ 577.1356, found 577.1331.

2-(Phenyloxycarbonylthioxy)-3-butenyl Hepta-*O*-acetyl-β-D-cellobioside (4c). An approximately 1:1 mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 8.0 Hz, 2 × 2H), 7.24 (t, J = 7.5 Hz, 2 × 1H), 7.14 (m 2 × 2H), 5.87 (m, 2 × 1H), 5.36 (d, J = 17.5 Hz, 1H), 5.35 (d, J = 17.5 Hz, 1H), 5.24−5.11 (m, 2 × 3H), 5.05 (m, 2 × 1H), 4.91 (m, 2 × 2H), 4.54−4.49 (m, 2 × 3H), 4.35 (dd, J = 4.5, J = 12.5 Hz, 2 × 1H), 4.21−4.02 (m, 2 × 4H), 3.76 (m, 2 × 2H), 3.65 (m, 2 × 1H), 3.59 (m, 2 × 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.024 (s, 3H), 2.015 (s, 2 × 3H), 2.01 (s, 2 × 3H), 2.00 (s, 2 × 3H), 1.97 (s, 2 × 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.3, 170.2, 169.8, 169.6, 169.5, 169.3, 169.1, 168.92, 168.87, 151.1, 133.7, 133.4, 129.6, 129.3, 121.3, 118.9, 118.8, 101.2, 100.8, 100.3, 72.9, 72.8, 72.34, 72.29, 72.0, 71.7, 71.6, 71.3, 71.2, 70.4, 67.8, 61.74, 61.7, 61.6, 48.4, 47.9, 20.9, 20.74, 20.72, 20.68, 20.6; ESIHRMS calcd for $C_{37}H_{46}O_{20}SNa$ $[M + Na]^+$ 865.2201, found 865.2164.

2-(Phenyloxycarbonylthioxy)-3-butenyl (Methyl 4,7,8,9-tetra-*O*-acetyl-5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate) (9). An approximately 1:1 mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 8.0 Hz, 2 × 2H), 7.22 (m, 2 × 1H), 7.15 (d, J = 8.0 Hz, 2 × 2H), 5.92 (m, 2 × 1H), 5.39 (m, 2 × 2H), 5.32 (m, 2 × 1H), 5.21 (m, 2 × 1H), 4.86 (m, 2 × 1H), 4.27 (t, J = 12.5 Hz, 2 × 1H), 4.15−4.01 (m, 2 × 6H), 3.80 (s, 3H), 3.78 (s, 3H), 3.58 (m, 2 × 1H), 2.61 (m, 2 × 1H), 2.12 (s, 2 × 3H), 2.11 (s, 2 × 3H), 2.03 (s, 2 × 3H), 2.01 (s, 2 × 3H), 1.864 (s, 3H), 1.861 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.9, 170.45, 170.37, 170.2, 169.0, 168.4, 168.3, 151.4, 134.4, 134.0, 129.7, 129.3, 128.5, 126.4, 121.6, 118.7, 118.6, 98.9, 98.8, 72.8, 69.3, 68.7, 67.5, 66.5, 66.4, 62.6, 62.5, 53.11, 53.07, 49.7, 48.8, 48.5, 38.1, 23.5, 21.3, 21.10, 21.06, 21.0; ESIHRMS calcd for $C_{31}H_{39}NO_{15}SNa$ $[M + Na]^+$ 720.1933, found 720.1936.

General Procedure for the Conversion of Allylic Thiocarbonates to Allylic Benzothiazolyl Disulfides. The thiocarbonate (0.48 mmol) and $NH_2NH_2 \cdot H_2O$ (36 μL, 0.72 mmol) were dissolved with stirring in DMF (3 mL), followed after 2 min by the dropwise addition of glacial acetic acid (41 μL, 0.72 mmol) at room temperature over 0.5 h. The resulting solution was added dropwise to a well-stirred suspension of 2,2′-dithiobis(benzothiazole) (242 mg, 0.72 mmol) in dichloromethane (3 mL) over 15 min, followed by stirring at room temperature until completion (∼3 h). The solvent was evaporated, and the residue was taken up in dichloromethane and washed with water. The combined organic phases were dried, filtered, evaporated, and purified by chromatography over silica gel.

2-(Benzothiazol-2-yldisulfanyl)-3-enyl tetra-*O*-acetyl-β-D-glucopyranoside (5a): yellow foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with hexane/ethyl acetate (2:1) in 76% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (m, 2 × 2H), 7.44 (t, J = 7.5 Hz, 2 × 1H), 7.35 (t, J = 7.5 Hz, 2 × 1H), 5.84 (m, 1H), 5.75 (m, 1H), 5.33−5.18 (m, 2 × 3H), 5.10−5.01 (m, 2 × 2H), 4.55 (d, J = 8.0 Hz, 1H), 4.54 (d, J = 8.0 Hz, 1H), 4.26−4.17 (m, 2 × 2H), 4.12 (dt, J = 2.0, J = 12.0 Hz, 2 × 1H), 3.85−3.75 (m, 2 × 2H), 3.68 (m, 2 × 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.024 (s, 3H), 2.021 (s, 3H), 2.009 (s, 3H), 2.008 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 172.4, 170.1, 170.3, 169.41, 169.35, 155.0, 135.9, 132.6, 132.3, 126.4, 124.7, 122.23, 122.18, 121.2, 120.7, 120.5, 101.1, 100.8, 72.7, 72.6, 72.0, 71.0, 70.3, 70.1, 68.3, 54.2, 20.8, 20.6; ESIHRMS calcd for $C_{25}H_{29}NO_{10}S_3Na$ $[M + Na]^+$ 622.0846, found 622.0851.

2-(Benzothiazol-2-yldisulfanyl)-3-enyl tetra-*O*-acetyl-β-D-galactopyranoside (5b): yellow foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with hexane/ethyl acetate (2:1) in 48% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (m, 2 × 1H), 7.82 (d, J = 8.0 Hz, 2 × 1H), 7.44 (m, 2 × 1H), 7.33 (m, 2 × 1H), 5.85 (m, 1H), 5.76 (m, 1H), 5.39 (2s, 2 × 1H), 5.34−5.22 (m, 2 × 3H), 5.01 (m, 2 × 1H), 4.51 (d, J = 8.0 Hz, 1H), 4.50 (d, J = 8.0 Hz, 1H), 4.22 (m, 2 × 1H), 4.19−4.09 (m, 2 × 2H), 3.89 (m, 2 × 1H), 3.85 (m, 2 × 1H), 3.78 (d, J = 10.0 Hz, 1H), 3.77 (d, J = 10.0 Hz, 1H), 2.514 (s, 3H), 2.148 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 2 × 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 172.3, 170.4, 170.3, 170.2, 169.5, 169.4, 155.0, 135.9, 132.7, 132.3, 126.38, 126.35, 124.8, 124.7, 122.24, 122.18, 121.2, 120.7, 120.5, 101.6, 101.3, 70.84, 70.79, 70.7, 70.2, 70.1, 68.5, 66.9, 61.2, 54.2, 20.98, 20.95, 20.7, 20.6; ESIHRMS calcd for $C_{25}H_{29}NO_{10}S_3Na$ $[M + Na]^+$ 622.0846, found 622.0836.

2-(Benzothiazol-2-yldisulfanyl)-3-enyl hepta-*O*-acetyl-β-D-cellobioside (5c): yellow foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with hexane/ethyl acetate (1:1) in 50% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (m, 2 × 2H), 7.43 (t, J = 7.5 Hz, 2 × 1H), 7.34 (t, J = 7.5 Hz, 2 × 1H), 5.83−5.70 (m, 2 × 1H), 5.31−5.22 (m, 2 × 2H), 5.18−5.11 (m, 2 × 2H), 5.06 (m, 2 × 1H), 4.93 (m, 2 × 2H), 4.53−4.47 (m, 2 × 3H), 4.38 (m, 1H), 4.35 (m, 1H), 4.13 (m, 2 × 1H), 4.10−4.02 (m, 2 × 2H), 3.85−3.73 (m, 2 × 3H), 3.65 (m, 2 × 1H), 3.55 (m, 2 × 1H), 2.17 (s, 3H), 2.10 (s, 3H), 2.082 (s, 3H), 2.079 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.023 (s, 3H), 2.020 (s, 3H), 2.015 (s, 2 × 3H), 2.00 (s, 2 × 3H), 1.98 (s, 2 × 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 172.4, 170.5, 170.29, 170.26, 169.8, 169.61, 169.56, 169.3, 169.1, 155.0, 135.9, 132.7, 132.4, 126.3, 124.7, 122.21, 122.18, 121.2, 120.6, 120.5, 100.8, 100.6, 72.9, 72.8, 72.33, 72.26, 72.0, 71.6, 71.3, 70.2, 70.1, 67.8, 61.7, 61.6, 54.24, 54.21, 20.88, 20.83, 20.80, 20.7, 20.6; ESIHRMS calcd for $C_{37}H_{46}O_{18}NS_3$ $[M + H]^+$ 888.1877, found 888.1834.

2-(Benzothiazol-2-yldisulfanyl)-3-enyl (methyl 4,7,8,9-tetra-*O*-acetyl-5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate) (10): yellow foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with dichloromethane/methanol (10:1) in 60% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85(dd, J = 3.0, J = 8.0 Hz, 2 × 1H), 7.81 (d, J = 8.0 Hz, 2 × 1H), 7.42 (t, J = 8.0 Hz, 2 × 1H), 7.33 (t, J = 8.0 Hz, 2 × 1H), 5.83 (m, 2 × 1H), 5.40 (m, 2 × 1H), 5.31 (m, 2 × 2H), 5.24 (m, 2 × 1H), 5.19 (m, 2 × 1H), 4.89 (m, 2 × 1H), 4.28(m, 2 × 1H), 4.10 (m, 2 × 4H), 3.79 (s, 3H), 3.76 (s, 3H), 3.68 (m, 1H), 3.59 (m, 1H), 2.61 (m, 2 × 1H), 2.12 (m, 2 × 6H), 2.03 (m, 2 × 6H), 1.98 (t, J = 12.50 Hz, 2 × 1H), 1.88 (s, 2 × 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.6, 170.3, 170.1, 168.1, 155.1, 135.9, 132.8, 132.6, 126.2, 124.6, 122.1, 121.1, 120.3, 120.2, 98.7, 98.5, 69.0, 68.5, 68.4, 67.2, 65.8, 68.4, 67.2, 65.8, 65.5, 62.4, 54.8, 54.7, 52.9, 49.4, 37.9, 23.2, 21.1, 20.9, 20.8; ESIHRMS calcd for $C_{31}H_{38}N_2O_{19}S_3Na$ $[M + Na]^+$ 765.1429, found 765.1423.

2-(Phenoxycarbonylthioxy)-3-butenol (12). A solution of phenyl chlorothionocarbonate (5 g, 29 mmol) in dichloromethane (3 mL) was added to a solution of (*E*)-4-(*tert*-butyldimethylsiloxy)but-2-en-1-ol[14] (1.95 g, 9.65 mmol), pyridine (4.6 mL, 58 mmol), and 4-(dimethylamino)pyridine (236 mg) in dichloromethane (48 mL). The yellow solution was stirred for 5 h and then was poured into H_2O and extracted with dichloromethane. The combined organic phases were dried, filtered, evaporated. The residue was taken up in toluene (200 mL) and heated at reflux for 4 h at room temperature. Evaporation of the solvent afforded a yellow syrup which was dissolved in dichloromethane/methanol (9:1), and *p*-TsOH·H_2O (1.87 g, 9.65 mmol) was added in one portion. On completion, the reaction mixture was poured into H_2O and extracted with dichloromethane. The combined organic phases were dried, filtered, evaporated, and purified by chromatography over silica gel, eluting with with hexane/ethyl acetate (2:1), to give the title compound as a yellow liquid in (1.2 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 8.0 Hz, 2 × 2H), 7.25 (t, J = 7.5 Hz, 2 × 1H), 7.16 (d, J = 8.0 Hz, 2 × 2H), 5.92 (m, 2 × 1H), 5.44 (d, J = 17.0 Hz, 2 × 1H), 5.32 (d, J = 10.0 Hz, 2 × 1H), 4.14 (m, 2 × 1H), 3.89 (m, 2 × 2H), 1.92 (t, J = 6.0 Hz, 2 × 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 151.3, 133.7, 129.8, 126.5, 121.5, 119.7, 64.6, 51.3; ESIHRMS calcd for $C_{11}H_{12}O_3SNa$ $[M + Na]^+$ 247.0405, found 247.0430.

General Procedure for the Glycosylation of 2-(Phenoxycarbonylthioxy)-3-butenol with Glycosyl Trichloroacetimidates. The trichloroacetimidate (0.2 mmol), alcohol **12** (0.4 mmol), and activated 4 Å powdered molecular sieves were mixed in dichloromethane (2 mL) and stirred at room temperature for 0.5 h before TMSOTf (0.06 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2−4 h, when TLC showed the donor to hae been consumed. 4-(Dimethylamino)pyridine (0.4 mmol) and Ac_2O (0.4 mmol) were added at 0 °C and stirring continued for 4 h at room temperature before saturated aqueous $NaHCO_3$ was added at 0 °C, and the reaction mixture was filtered and washed with brine. The organic layer was dried and concentrated under reduced pressure, and the glycosides were isolated by silica gel column chromatography (hexane/ethyl acetate from 95:5 to 2:1).

General Procedure for the Glycosylation of 2-(Benzothiazol-2-yldisulfanyl)but-3-enol with Glycosyl Trichloroacetimidates. The trichloroacetimidate (0.2 mmol), 2-(benzothiazol-2-yldisulfanyl)but-3-en-1-ol[1c] (0.4 mmol), and activated 4 Å powdered molecular sieves were mixed in dichloromethane (2 mL) and stirred at room temperature for 0.5 h before $Zn(OTf)_2$ (74 mg, 0.2 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 8−12 h until TLC indicated consumption of the donor.[15] The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C, filtered, and washed with brine. The organic layer was dried and concentrated under reduced pressure, and the glycosides were isolated by silica gel column chromatography (hexane/ethyl acetate from 95:5 to 2:1).

General Procedure for the Ligation of Protected Neoglycosyl Donors with Protected Peptides. A solution of cysteine containing peptide (0.05 mmol) and neoglycosyl donor (0.075 mmol) in methanol/acetonitrile (0.5 mL/0.5 mL) was stirred at room temperature until TLC indicated completion, after which triphenylphosphine (39 mg, 0.15 mmol) was added and the reaction mixture was stirred at room temperature for 10−24 h. The solution was evaporated and the mixture purified by chromatography eluting with dichloromethane/methanol (100:1).

***S*-[4-(Tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-2*E*-butenyl] *N*-(*tert*-butyloxycarbonyl)-*γ*-L-Glu-(α-OMe)-L-Cys-Gly-OMe (16):** 79% yield; $[\alpha]^{23}_D$ −40.8 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (m, 2H), 5.27 (t, J = 9.5 Hz, 1H), 5.04 (t, J = 10.0 Hz, 1H), 4.92 (m, 1H), 4.76 (d, J = 8.0 Hz, 1H), 4.73 (m, 1H), 4.30 (m, 2H), 4.16 (m, 3H), 3.98 (d, J = 5.5 Hz, 2H), 3.88 (m, 1H), 3.73 (s, 6H), 3.40 (m, 2H), 3.21 (dd, J = 5.0 Hz, J = 14.0 Hz, 1H), 2.91 (m, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.14 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.93 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.94, 172.90, 171.2, 170.8, 170.6, 170.0, 169.54, 169.46, 155.8, 129.7, 128.8, 99.5, 80.3, 72.8, 71.7, 71.4, 69.1, 68.4, 62.0, 60.4, 52.6, 52.5, 52.44, 52.36, 41.3, 33.6, 32.5, 32.2, 28.9, 28.7, 28.3, 27.8, 21.1, 20.8, 20.7; ESIHRMS calcd for $C_{35}H_{53}N_3O_{18}SNa$ $[M + Na]^+$ 858.2943, found 858.2936.

***S*-[4-(Tetra-*O*-acetyl-*β*-D-galactopyranosyloxy)-2*E*-butenyl] *N*-(*tert*-butyloxycarbonyl)-*γ*-L-Glu-(α-OMe)-L-Cys-Gly-OMe (17):** 67% yield; $[\alpha]^{23}_D$ −36.6 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.70 (m, 2H), 5.37 (m, 1H), 5.20 (dd, J = 3.5 Hz, J = 11.0 Hz, 1H), 5.09 (m, 1H), 4.74 (d, J = 7.5 Hz, 1H), 4.54 (m, 1H), 4.29 (m, 1H), 4.14 (m, 5H), 3.722 (s, 3H), 3.716 (s, 3H), 3.31 (m, 2H), 2.98 (dd, J = 5.5 Hz, J = 14.0 Hz, 1H), 2.69 (m, 1H), 2.39 (t, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.13 (m, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.94 (s, 3H), 1.93 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.5, 173.2, 171.9, 170.8, 170.7, 170.2, 170.13, 170.10, 170.0, 156.7, 129.6, 128.6, 99.2, 79.3, 71.0, 70.4, 69.1, 68.3, 67.6, 61.3, 53.1, 52.4, 51.4, 51.3, 40.5, 32.6, 31.8, 31.5, 27.3, 27.0, 19.4, 19.3, 19.1; ESIHRMS calcd for $C_{35}H_{53}N_3O_{18}SNa$ $[M + Na]^+$ 858.2943, found 858.2940.

***S*-[4-(Hepta-*O*-acetyl-*β*-D-cellobiosyloxy)-2*E*-butenyl] *N*-(*tert*-butyloxycarbonyl)-*γ*-L-Glu-(α-OMe)-L-Cys-Gly-OMe (18):** 70% yield; $[\alpha]^{21}_D$ −15.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 5.69−5.61 (2H, m), 5.24−5.16 (m, 2H), 5.00 (t, J = 9.6 Hz, 1H), 5.09 (m, 1H), 4.80 (t, J = 8.4 Hz, 2H), 4.70 (dd, J = 2.4, J = 8.0 Hz, 1H), 4.61 (dd, J = 4.0, J = 8.0 Hz, 1H), 4.53 (m, 2H), 4.39 (m, 1H), 4.26 (m, 1H), 4.14 (m, 3H), 4.04 (dd, J = 2.0, J = 12.4 Hz, 1H), 3.97 (s, 2H), 3.89−3.81 (m, 2H), 3.78 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.18 (m, 2H), 2.96 (m, 1H), 2.67 (m, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.12 (m, 4H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.93 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.7, 173.3, 171.8, 171.7, 171.2, 171.0, 170.7, 170.4, 170.1, 170.0, 169.8, 156.5, 133.5, 126.1, 100.7, 99.0, 79.5, 76.9, 73.3, 73.1, 72.8, 71.9, 71.8, 71.7, 68.1, 64.1, 62.4, 61.6, 57.5, 55.74, 55.70, 53.3, 51.6, 51.5, 40.8, 40.7, 31.7, 27.6, 27.2, 25.8, 19.8, 19.6, 19.53, 19.5, 19.40, 19.38; ESIHRMS calcd for $C_{47}H_{69}N_3O_{26}SNa$ $[M + Na]^+$ 1146.3788, found 1146.3786.

***S*-[4-(Tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-2*E*-butenyl] *N*-(*tert*-butyloxycarbonyl)-L-Cys-L-Ala-L-Trp-OMe (20):** 59% yield; $[\alpha]^{23}_D$ −19.9 (*c* 0.9, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.50 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.09 (m, 2H), 7.02 (m, 1H), 5.63 (m, 2H), 5.25 (t, J = 10.0 Hz, 1H), 4.99 (t, J = 10.0 Hz, 1H), 4.73 (m, 1H), 4.64 (d, J = 8.0 Hz, 1H), 4.42 (m, 1H), 4.24 (m, 2H), 4.17 (m, 1H), 4.09 (m, 3H), 3.76 (m, 1H), 3.64 (s, 3H), 3.27 (m, 1H), 3.22 (m, 1H), 3.10 (d, J = 2.5 Hz, 1H), 2.81 (m, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.44 (s, 9H), 1.32 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 172.2, 171.6, 171.0, 170.3, 169.9, 169.8, 156.3, 136.6, 129.3, 128.5, 127.4, 123.3, 121.1, 118.5, 117.8, 111.0, 109.1, 99.2, 79.5, 72.9, 71.5, 71.3, 68.6, 68.4, 61.7, 60.2, 53.8, 53.4, 51.3, 48.9, 32.7, 32.4, 27.3, 27.1, 19.5, 19.4, 19.3, 19.2, 16.8, 13.1; ESIHRMS calcd for $C_{41}H_{57}N_4O_{16}S$ $[M + H]^+$ 893.3485, found 893.3488.

***S*-[4-(Tetra-*O*-acetyl-*β*-D-galactopyranosyloxy)-2*E*-butenyl] *N*-(*tert*-butyloxycarbonyl)-L-Cys-L-Ala-L-Trp-OMe (21):** 66% yield; $[\alpha]^{21}_D$ −10.5 (*c* 1.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 5.63 (m, 2H), 5.38 (d, J = 3.0 Hz, 1H), 5.32 (d, J = 7.0 Hz, 1H), 5.23 (m, 1H), 5.13 (dd, J = 3.5, J = 10.5 Hz, 1H), 4.88 (m, 1H), 4.61 (d, J = 7.5 Hz, 1H), 4.50 (t, J = 7.2 Hz, 1H), 4.33 (d, J = 11.5 Hz, 1H), 4.20 (m, 2H), 4.11 (m, 2H), 4.01 (m, 2H), 3.69 (s, 3H), 3.42 (dd, J = 5.0, J = 15.0 Hz, 1H), 3.28 (dd, J = 5.5, J = 14.5 Hz, 1H), 3.07 (d, J = 4.5 Hz, 2H), 2.75 (d, J = 6.0 Hz, 2H), 2.11 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.47 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H);

(14) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906–4911.

(15) When TLC indicated orthoester formation, TMSOTf (0.1 equiv) was added before the reaction was quenched.

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 171.5, 170.8, 170.5, 170.0, 136.3, 129.8, 129.1, 127.7, 123.6, 122.3, 119.7, 118.6, 111.6, 109.7, 99.9, 80.7, 71.1, 70.7, 69.3, 69.1, 67.4, 61.6, 53.0, 52.7, 49.1, 33.8, 33.2, 29.9, 28.5, 27.6, 21.1, 20.88, 20.85, 20.8, 18.1; ESIHRMS calcd for $C_{41}H_{57}N_4O_{16}S$ $[M + H]^+$ 893.3485, found 893.3480.

General Procedure for the Ligation of Protected Neoglycosyl Donors with Glutathione. A solution of glutathione (0.05 mmol) and neoglycosyl donor (0.075 mmol) in Tris buffer (pH 8.0)/acetonitrile (0.5 mL/0.5 mL) was stirred at room temperature until completion. Triphenylphosphine (39 mg, 0.15 mmol) dissolved in tetrahydrofuran (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 10−24 h. The solution was evaporated and the residue purified by reversed-phase HPLC using a gradient of 50% A to 100% A developed over 50 min (A, 0.1%TFA/CH_3CN; B, 0.1% TFA/H_2O; column: Varian Microsorb C_{18} 250 × 21.4 mm; flow rate: 8 mL/min; UV detection: 215nm).

***S*-[4-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (23):** 75% yield; $[\alpha]^{24}_D$ −13.3 (*c* 0.6, MeOH); ^{1}H NMR (500 MHz, D_2O) δ 5.60 (m, 2H), 5.24 (t, J = 9.5 Hz, 1H), 4.98 (t, J = 9.5 Hz, 1H), 4.84 (t, J = 8.5 Hz, 1H), 4.76 (d, J = 8.5 Hz, 1H), 4.42 (m, 1H), 4.23 (m, 2H), 4.10 (m, 2H), 3.91 (m, 3H), 3.85 (t, J = 6.5 Hz, 1H), 3.10 (d, J = 6.0 Hz, 2H), 2.87 (dd, J = 5.4, J = 14.0 Hz, 1H), 2.68 (m, 1H), 2.44 (m, 2H), 2.08 (m, 2H), 1.99 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 174.3, 173.7, 173.1, 172.85, 172.77, 172.66, 171.9, 130.6, 128.2, 98.8, 73.1, 71.5, 71.1, 69.5, 68.3, 61.8, 52.8, 52.5, 41.0, 32.6, 31.4, 30.9, 25.5, 20.14, 20.11, 20.03, 19.99; ESIHRMS calcd for $C_{28}H_{41}N_3O_{16}SNa$ $[M + Na]^+$ 730.2105, found 730.2102.

***S*-[4-(Methyl 4,7,8,9-tetra-*O*-acetyl-5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (24):** 71% yield; $[\alpha]^{24}_D$ −9.2 (*c* 0.6, MeOH/H_2O, 1:1); ^{1}H NMR (500 MHz, D_2O) δ 5.64 (m, 2H), 5.29 (m, 2H), 4.80 (m, 2H), 4.45 (m, 1H), 4.26 (m, 1H), 4.15 (m, 3H), 3.99 (t, J = 6.5 Hz, 1H), 3.95 (m, 1H), 3.92 (s, 2H), 3.83 (t, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.13 (d, J = 6.5 Hz, 2H), 2.89 (dd, J = 5.5, J = 14.0 Hz, 2H), 2.71 (m, 1H), 2.63 (dd, J = 5.0, J = 13.0 Hz, 1H), 2.50 (m, 2H), 2.16 (m, 2H), 2.11 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 175.1, 174.5, 173.9, 173.7, 173.6, 173.2, 173.1, 172.6, 169.0, 132.7, 126.5, 98.8, 71.8, 69.4, 68.5, 67.5, 62.4, 57.4, 55.8, 53.9, 53.6, 49.0, 41.6, 37.2, 26.1, 25.5, 22.0, 20.7, 20.4, 20.3; ESIHRMS calcd for $C_{34}H_{50}N_4O_{19}SNa$ $[M + Na]^+$ 873.2688, found 873.2699.

General Procedure for Preparation of Deprotected Neoglycosyl Donors from Acetylated Allylic Thiocarbonates. The peracetyl glycosyl thiolcarbonate (0.2 mmol) was dissolved in MeOH (1 mL) at 0 °C with stirring and 1 M KOH in MeOH (1.2 mmol−2.1 mmol, 1.5 equiv per acetate group) was added dropwise. After 10−15 min, the pH of the reaction mixture was adjusted to 7 by careful addition of Amberlyst-15. The reaction mixture was then filtered, and the filtrate was added dropwise over 15 min to a well-stirred solution of 2,2′-dipyridyl disulfide (68 mg, 0.3 mmol) in MeOH (1 mL) at room temperature and the resulting solution stirred until completion (TLC, ∼3 h). The solvent was removed in vacuo and the residue taken up in H_2O and washed with ether several times. Evaporation of the aqueous phase followed by chromatographic purification gave the products.

2-(2-Pyridyldisulfanyl)-3-enyl β-D-galactopyranoside (25b): white foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with dichloromethane/methanol (20:1) in 92% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (m, 2 × 1H), 7.94 (m, 2 × 1H), 7.81(m, 2 × 1H), 7.20 (m, 2 × 1H), 5.86 (m, 1H), 5.81 (m, 1H), 5.23 (m, 2 × 1H), 5.14 (d, J = 10.5 Hz, 2 × 1H), 4.24 (m, 2 × 1H), 4.13 (m, 2 × 1H), 3.80 (m, 2 × 3H), 3.72 (m, 2 × 2H), 3.55 (2 × 1H, m), 3.47(m, 2 × 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 160.6, 148.8, 138.0, 134.24, 134.20, 121.0, 120.4, 118.4, 118.2, 104.04, 103.96, 75.6, 73.8, 71.3, 70.1, 69.1, 61.3, 61.2, 54.3; ESIHRMS calcd for $C_{15}H_{21}NO_6S_2Na$ $[M + Na]^+$ 398.0708, found 398.0706.

2-(2-Pyridyldisulfanyl)-3-enyl β-D-cellobioside (25c): white foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with dichloromethane/methanol (15:1) in 92% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (m, 2 × 1H), 8.13(m, 2 × 2H), 7.50 (m, 2 × 1H), 5.86 (m, 2 × 1H), 5.28 (m, 2 × 1H), 5.18 (m, 2 × 1H), 4.41 (d, J = 7.5 Hz, 2 × 1H), 4.32 (dd, J = 8.0, J = 17.0 Hz, 2 × 1H), 4.16 (m, 1H), 4.09 (m, 1H), 3.90 (m, 2 × 4H), 3.80 (m, 2 × 2H), 3.66 (m, 2 × 1H), 3.52 (m, 2 × 2H), 3.36 (m, 2 × 3H), 3.25(m, 2 × 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 160.6, 148.8, 138.0, 134.2, 134.1, 121.1, 120.4, 118.5, 118.3, 103.4, 103.2, 79.5, 76.9, 76.7, 75.4, 75.2, 73.7, 73.6, 70.2, 70.1, 61.3, 60.7, 54.2, 54.1; ESIHRMS calcd for $C_{21}H_{31}NO_{11}S_2Na$ $[M + Na]^+$ 560.1236, found 560.1255.

2-(2-Pyridyldisulfanyl)-3-enyl (methyl 5-acetylamino-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate (26): white foam, eluted from silica gel as an approximately 1:1 mixture of diastereomers with dichloromethane/methanol (20:1) in 78% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (m, 2 × 1H), 7.87 (m, 2 × 1H), 7.81 (m, 2 × 1H), 7.21 (m, 2 × 1H), 5.77 (m, 2 × 1H), 5.20 (m, 2 × 2H), 4.05 (m, 2 × 1H), 3.82 (m, 2 × 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.64 (m, 2 × 4H), 3.54 (m, 2 × 1H), 3.49 (m, 2 × 1H), 2.66 (m, 2 × 1H), 1.994 (s, 3H), 1.991 (s, 3H), 1.71(m, 2 × 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.0, 169.47, 169.49, 160.5, 160.4, 148.97, 148.89, 138.0, 133.91, 133.86, 121.2, 121.1, 120.24, 120.21, 118.7, 118.5, 99.05, 99.00, 73.9, 71.2, 71.1, 68.98, 68.9, 67.3, 64.9, 64.87, 63.6, 63.5, 54.2, 53.9, 52.6, 52.3, 40.3, 40.28, 21.5; ESIHRMS calcd for $C_{21}H_{30}N_2O_9S_2Na$ $[M + Na]^+$ 541.1290, found 541.1305.

General Procedure for the Ligation of Unprotected Neoglycosyl Donors with Glutathione. A solution of glutathione (21.7 mg, 0.07 mmol) and neoglycosyl donor (0.11 mmol) in phosphate buffer (pH 8.0)/acetonitrile (0.5 mL/0.5 mL) was stirred at room temperature until completion (12−24 h). Triphenylphosphine (27.5 mg, 0.11 mmol) dissolved in THF (0.1 mL) was added, and the reaction mixture was stirred at room temperature for 10−24 h. The solution was evaporated and the mixture purified by reverse phase HPLC using a gradient of 100% B to 50% B developed over 50 min (A, 0.1%TFA/CH_3CN; B, 0.1% TFA/H_2O; column: Varian Microsorb C_{18} 250 × 21.4 mm; flow rate: 8 mL/min; UV detection: 215nm).

S-[4-(β-D-Galactopyranosyloxy)-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (27): 90% yield; $[\alpha]^{23}_D$ −18.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 5.77 (m, 2H), 4.52 (m, 1H), 4.38 (d, J = 8.4 Hz, 1H), 4.35 (dd, J = 3.2, J = 12.0 Hz, 1H), 4.20 (m, 1H), 4.08 (t, J = 6.4 Hz, 1H), 3.99 (s, 2H), 3.88 (d, J = 3.2 Hz, 1H), 3.73 (m, 2H), 3.61 (m, 2H), 3.48 (m, 1H), 3.20 (d, J = 5.6 Hz, 2H), 2.96 (m, 1H), 2.79 (m, 1H), 2.56 (m, 2H), 2.22 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 174.5, 173.13, 173.07, 171.7, 130.7, 130.0, 102.0, 75.4, 73.1, 71.0, 69.7, 68.91, 61.2, 53.2, 52.4, 41.4, 33.0, 31.8, 31.1, 25.7; ESIHRMS calcd for $C_{20}H_{31}N_3O_{12}S$ $[M - H]^-$ 538.1707, found 538.1689.

***S*-[4-(β-D-Cellobiosyloxy)-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (28):** 92% yield; $[\alpha]^{23}_D$ −0.4 (*c* 1.7, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.76 (m, 2H), 4.57 (m, 1H), 4.40 (d, J = 8.0 Hz, 1H), 4.35 (m, 2H), 4.16 (m, 1H), 4.05 (m, 1H), 3.94 (s, 2H), 3.86 (m, 2H), 3.66 (m, 1H), 3.54 (m, 2H), 3.39 (m, 2H), 3.31 (m, 3H), 3.25 (m, 2H), 3.19 (d, J = 5.6 Hz, 2H), 2.95 (m, 1H), 2.71 (m, 1H), 2.57 (m, 2H), 2.20 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.2, 171.9, 171.5, 170.3, 129.6, 129.3, 103.5, 101.9, 79.6, 76.9, 76.7, 75.3, 75.2, 73.7, 73.6, 70.2, 68.9, 61.2, 60.6, 53.0, 52.3, 48.7, 40.6, 33.1, 32.2, 31.1, 25.9; ESIHRMS calcd for $C_{26}H_{42}N_3O_{17}S$ $[M - H]^-$ 700.2235, found 700.2229.

***S*-[4-(Methyl (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate)-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (29):** 94% yield; $[\alpha]^{23}_D$ −13.8 (*c* 1.4, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 5.77 (m, 2H), 4.51 (m, 1H), 4.27 (m, 1H), 4.06 (m, 2H), 3.99 (s, 2H), 3.83 (m, 7H), 3.71 (m, 1H), 3.62 (m, 1H), 3.52 (d, J = 9.2 Hz, 1H), 3.18 (d, J = 5.6 Hz, 1H), 2.94 (m, 1H), 2.77 (m, 1H), 2.67 (m, 1H), 2.56 (m, 2H), 2.22 (m, 2H), 2.00 (s, 3H), 1.78 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 175.3, 174.5, 173.1,

173.0, 171.7, 170.3, 130.5, 128.7, 99.1, 73.2, 70.9, 68.5, 67.4, 65.0, 63.4, 53.7, 53.2, 52.4, 52.0, 41.3, 39.6, 33.0, 31.8, 31.1, 25.7, 22.3; ESIHRMS calcd for $C_{26}H_{42}N_4O_{15}SNa$ $[M + Na]^+$ 705.2265, found 705.2265.

***tert*-Butyl 3-Acetylthio-4-pentenoate (32).** Diisopropyl azodicarboxylate (5.1 mL, 26 mmol) was added to a stirred solution of triphenylphosphine (6.85 g, 26 mmol) in tetrahydrofuran (46 mL) at 0 °C over 0.5 h, resulting in the formation of a white precipitate. A solution of alcohol **31**[16] (3.0 g, 17.4 mmol) and thiolacetic acid (1.87 mL, 26 mmol) in tetrahydrofuran (20 mL) was then added dropwise, and the mixture was stirred for 1 h at 0 °C and at room temperature for 13 h resulting in a clear yellow solution. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried, filtered, evaporated, and purified by chromatography (eluting with hexane/ethyl acetate, 10:1) to give **32** (3.06 g, 76%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (m, 2 × 1H), 5.26 (d, J = 17.0 Hz, 2 × 1H), 5.10 (d, J = 10.5 Hz, 2 × 1H), 4.42 (q, J = 7.5 Hz, 2 × 1H), 2.63 (m, 2 × 2H), 2.31 (s, 2 × 3H), 1.43(s, 2 × 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 169.8, 136.6, 116.7, 81.4, 42.5, 40.2, 30.8, 28.3; ESIHRMS calcd for $C_{11}H_{18}O_3SNa$ $[M + Na]^+$ 253.0874, found 253.0895.

***tert*-Butyl 3-[(2-Pyridinyl)disulfanyl]-4-pentenoate (33).** Lithium hydroxide monohydrate (30 mg, 0.71 mmol) was added in one portion to a stirred solution of thiolacetate **32** (163 mg, 0.71 mmol) in methanol (3.5 mL) at 0 °C. After 0.5 h, the pH of the solution was adjusted to 7 with 3 M HCl, and the resulting solution was added dropwise to a stirred solution of 2,2′-dipyridyl disulfide (239 mg, 1.06 mmol) in dichloromethane (3 mL) over 15 min. After the solution was stirred for 3 h, the solvent was removed. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried, filtered, evaporated, and purified by chromatography on silica gel[17] (eluting with hexane/ethyl acetate, 10:1) to afford **33** (144 mg, 68%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, J = 0.5, J = 4.5 Hz, 2 × 1H), 7.72 (d, J = 7.5 Hz, 2 × 1H), 7.63 (dt, J = 2.0, J = 7.5 Hz, 2 × 1H), 7.08 (dt, J = 1.0, J = 7.5 Hz, 2 × 1H), 5.76 (m, 2 × 1H), 5.18 (d, J = 17.0 Hz, 2 × 1H), 5.10 (d, J = 10.0 Hz, 2 × 1H), 3.86 (q, J = 8.5 Hz, 2 × 1H), 2.77 (dd, J = 6.5, J = 15.5 Hz, 2 × 1H), 2.59 (dd, J = 8.5, J = 16.0 Hz, 2 × 1H), 1.43(s, 2 × 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 160.6, 149.6, 137.1, 135.6, 120.9, 120.0, 118.3, 81.5, 50.0, 39.8, 28.3; ESIHRMS calcd for $C_{14}H_{19}NO_2S_2Na$ $[M + Na]^+$ 320.0755, found 320.0766.

3-[(2-Pyridinyl)disulfanyl]-4-pentenoic Acid (34). Trifluoroacetic acid (1.36 mL, 17.5 mmol) was added dropwise over 20 min into a stirred solution of ester **33** (208 mg, 0.7 mmol) in dichloromethane (1.4 mL) at 0 °C. The reaction mixture was stirred for 4−5 h at room temperature and then concentrated, taken up in toluene, and concentrated again to afford **34** (169 mg, 100%) as yellow syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (br. s, 2 × 1H), 8.59 (d, J = 4.8 Hz, 2 × 1H), 7.87 (m, 2 × 2H), 7.35 (t, J = 6.0 Hz, 2 × 1H), 5.80 (m, 2 × 1H), 5.20 (m, 2 × 2H), 3.93 (q, J = 7.2 Hz, 2 × 1H), 2.82(m, 2 × 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 147.1, 140.3, 134.7, 122.7, 122.4, 119.2, 50.0, 38.4, 29.9; ESIHRMS calcd for $C_{10}H_{11}NO_2S_2Na$ $[M + Na]^+$ 264.0129, found 264.0147.

General Procedure for Formation of *N*-Glycosyl 3-[(2-Pyridinyl)disulfanyl]-4-pentenamides.[18] A solution of β-D-glucopyranosyl azide or 2-acetamido-2-deoxy-β-D-glucopyranosyl azide (1.18 mmol) in *N*-methylpyrrolidone (4 mL) was stirred with 10% Pd/C under H_2 (1 atm) at room temperature until TLC indicated completion (~5 h). After filtration, the reaction mixture was added dropwise over 0.5 h to a stirred, premixed solution of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (231 mg, 0.59 mmol) and diisopropylethylamine (202 μL, 1.18 mmol) and acid **34** (142 mg, 0.59 mmol) in DMF (1.7 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight and then concentrated and the residue taken up in toluene and concentrated again to give yellow oil, which was lyophilized to remove *N*-methylpyrrolidone and then subjected to flash chromatography to afford the pure *N*-glycosylamide.

***N*-(β-D-Glucopyranosyl) 3-[(2-pyridinyl)disulfanyl]-4-pentenamide (36a):** white foam, eluted from silica gel with dichloromethane/methanol (3:1) as an approximately 1:1 mixture of diastereomers in 46% yield: ^{1}H NMR (400 MHz, D_2O) δ 8.34 (d, J = 4.8 Hz, 2 × 1H), 7.79 (m, 2 × 2H), 7.25 (m, 2 × 1H), 5.73 (m, 2 × 1H), 5.13 (d, J = 17.2 Hz, 2 × 1H), 5.04 (d, J = 9.6 Hz, 2 × 1H), 3.87 (m, 2 × 2H), 3.69 (m, 2 × 1H), 3.50 (m, 2 × 2H), 3.35 (m, 2 × 2H), 2.77 (m, 2 × 2H); ^{13}C NMR (100 MHz, D_2O) δ 174.4, 159.0, 149.1, 138.8, 135.1, 122.2, 121.8, 118.6, 118.5, 79.6, 77.9, 76.8, 72.0, 69.5, 60.8, 49.93, 49.86, 39.5, 39.4; ESIHRMS calcd for $C_{16}H_{22}N_2O_6S_2Na$ $[M + Na]^+$ 425.0817, found 428.0824.

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl) 3-[(2-pyridinyl)disulfanyl]-4-pentenamide (36b):** white foam, eluted from silica gel with dichloromethane/methanol (3:1) as an approximately 1:1 mixture of diastereomers in 43% yield: ^{1}H NMR (400 MHz, D_2O) δ 8.37 (m, 2 × 1H), 7.83 (m, 2 × 2H), 7.28 (m, 2 × 1H), 5.72 (m, 2 × 1H), 5.07 (m, 2 × 3H), 3.88 (m, 2 × 2H), 3.77 (m, 2 × 2H), 3.60 (m, 2 × 1H), 3.35 (m, 2 × 2H), 2.74 (m, 2 × 2H), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1, 173.0, 171.5, 160.24, 160.15, 149.0, 148.9, 137.91, 137.87, 135.6, 135.5, 121.2, 121.1, 120.20, 120.15, 117.5, 117.3, 79.1, 79.0, 78.62, 78.59, 75.20, 75.16, 70.61, 70.58, 61.5, 54.9, 50.2, 50.0, 39.7, 39.6, 21.9, 21.8; ESIHRMS calcd for $C_{18}H_{25}N_3O_6S_2Na$ $[M + Na]^+$ 466.1082, found 466.1100.

General Procedure for Ligation of *N*-Glycosyl 3-[(2-Pyridinyl)disulfanyl]-4-pentenamides with Peptides. A solution of cysteine containing peptide (0.05 mmol) and the *N*-glycosylamide (0.075 mmol) in phosphate buffer (pH 8.0)/acetonitrile (0.5 mL/0.5 mL) was stirred at room temperature until completion (12−24 h). Triphenylphosphine (26 mg, 0.1 mmol) dissolved in THF (0.1 mL) was then added, and the reaction mixture was stirred at room temperature for 10−24 h. The solution was evaporated and the residue purified by reverse phase HPLC using a gradient of 100% B to 50% B developed over 70 min (A, 0.1% TFA/CH_3CN; B, 0.1% TFA/H_2O; column: Varian Microsorb C_{18} 250 × 21.4 mm; flow rate: 8 mL/min; UV detection: 215nm).

***S*-[*N*-(β-D-Glucopyranosyl)-5-carboxamido-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (37):** 70% yield; $[\alpha]^{23}_D$ −18.5 (*c* 0.6, MeOH/H_2O 1:1); ^{1}H NMR (400 MHz, D_2O) δ 5.66 (m, 2H), 4.94 (d, J = 8.8 Hz, 1H), 4.53 (m, 1H), 4.04 (t, J = 6.4 Hz, 1H), 4.00 (s, 2H), 3.86 (m, 1H), 3.70 (dd, J = 4.8, J = 12.0 Hz, 1H), 3.51 (m, 1H), 3.59 (t, J = 8.4 Hz, 1H), 3.38 (m, 2H), 3.27 (m, 2H), 3.20 (d, J = 6.4 Hz, 2H), 3.11 (d, J = 4.8 Hz, 1H), 2.97 (dd, J = 5.4, J = 14.2 Hz, 1H), 2.80 (m, 1H), 2.57 (m, 2H), 2.22 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 176.1, 174.6, 173.2, 173.1, 172.2, 130.6, 126.1, 79.6, 77.9, 76.8, 72.0, 69.5, 60.8, 53.2, 52.8, 47.8, 41.4, 39.2, 33.2, 31.6, 31.2, 25.9; ESIHRMS calcd for $C_{21}H_{35}N_4O_{12}S$ $[M + H]^+$ 567.1972, found 567.1967.

***S*-[*N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-carboxamido-2*E*-butenyl] γ-L-Glu-L-Cys-Gly (38):** 85% yield; $[\alpha]^{23}_D$ −3.4 (*c* 0.7, MeOH/H_2O 1:1); ^{1}H NMR (400 MHz, D_2O) δ 5.52 (m, 2H), 5.03 (d, J = 9.6 Hz, 1H), 4.52 (m, 1H), 4.04 (t, J = 6.4 Hz, 1H), 4.00 (s, 2H), 3.86 (dd, J = 1.6, J = 12.0 Hz, 1H), 3.80 (t, J = 10.0 Hz, 1H), 3.73 (dd, J = 4.8, J = 12.0 Hz, 1H), 3.59 (t, J = 8.4 Hz, 1H), 3.48 (m, 2H), 3.19 (d, J = 5.6 Hz, 2H), 3.03 (d, J = 4.8 Hz, 2H), 3.00 (dd, J = 5.6, J = 14.0 Hz, 1H), 2.78 (dd, J = 8.8, J = 14.4 Hz, 1H), 2.57 (m, 2H), 2.22 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 175.5, 175.0, 174.6, 173.2, 173.1, 130.7, 126.0, 78.8, 77.9, 74.4, 69.8, 60.8, 54.6, 53.2, 52.7, 41.4, 39.3, 33.3, 31.8, 31.2, 25.8, 22.3; ESIHRMS calcd for $C_{23}H_{37}N_5O_{12}SNa$ $[M + Na]^+$ 630.2057, found 630.2072.

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(17) This compound showed a tendency to undergo allylic rearrangement during silica gel chromatography when moisture was not fully excluded.[1c]

(18) Wen, S.; Guo, Z. *Org. Lett.* **2001**, *3*, 3773–3776.

***S*-[*N*-(2-Acetamido-2-deoxy-*β*-D-glucopyranosyl)-5-carboxamido-2*E*-butenyl] L-Val-L-Thr-L-Cys-Gly (40):** 70% yield; $[\alpha]^{23}_{D}$ −8.9 (*c* 0.2, MeOH/H_2O 1:1); ^{1}H NMR (500 MHz, D_2O) δ 5.50 (m, 2H), 4.92 (d, J = 10.0 Hz, 1H), 4.45 (m, 1H), 4.32 (d, J = 6.5 Hz, 1H), 4.03 (m, 1H), 3.88 (s, 2H), 3.80 (d, J = 5.5 Hz, 1H), 3.75 (m, 1H), 3.69 (t, J = 10.0 Hz, 1H), 3.62 (dd, J = 4.5, J = 12.0 Hz, 1H), 3.48 (t, J = 9.2 Hz, 1H), 3.37 (m, 2H), 3.07 (d, J = 6.0 Hz, 2H), 2.92 (d, J = 4.5 Hz, 2H), 2.86 (d, J = 5.0 Hz, J = 14.0 Hz, 1H), 2.69 (m, 1H), 2.12 (m, 1H), 1.87 (s, 3H), 1.10 (d, J = 6.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, D_2O) δ 175.3, 174.9, 173.1, 172.3, 171.2, 169.7, 130.6, 125.8, 78.7, 77.8, 74.3, 69.7, 67.3, 60.7, 59.3, 58.6, 54.5, 52.9, 50.6, 41.4, 39.2, 30.5, 24.0, 22.2, 19.0, 17.9, 17.0; ESIHRMS calcd for $C_{27}H_{47}N_6O_{12}S$ [M + H]$^+$ 679.2973, found 679.2997.

Acknowledgment. We thank the NIH (GM62160) for partial support of this work and Dr. Franck Brebion for help and advice in the initial stages of the project.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8015314