

# Click Azide–Nitrile Cycloaddition as a New Ligation Tool for the Synthesis of Tetrazole-Tethered C-Glycosyl α-Amino Acids<sup>†</sup>

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galacto-ribo series

Glycoproteins play a key role in a multitude of biological events in living organisms. Hence, neoglycopeptides obtained from unnatural *C*-glycosyl  $\alpha$ -amino acids can be used as synthetic probes in studies aiming at clarifying the role of the carbohydrate domain in glycoprotein biological activity. A new class of *C*-glycosyl  $\alpha$ -amino acids featuring a nitrogenated heterocycle ring holding the carbohydrate and glycinyl moiety was designed in our laboratory. Having previously prepared isoxazole-, 1,2,3-triazole-, and pyridine-tethered compounds, the family has now been enlarged by a group of newcomers represented by tetrazole derivatives. Two sets of compounds have been prepared, one being constituted of *C*-galactosyl and *C*-ribosyl *O*-tetrazolyl serines while the other contains *S*-tetrazolyl cysteine derivatives. In both cases, the synthetic scheme involved a two-step route, the first one being the thermal cycloaddition of a sugar azide with *p*-toluensulfonyl cyanide (TsCN) to give a 1-substituted 5-sulfonyl tetrazole and the second the replacement of the tosyl group with a serine or cysteine residue. For the high efficiency and operational simplicity, the azide—TsCN cycloaddition appears to be a true click process. Finally, one of the amino acids prepared was incorporated into a tripeptide.

### Introduction

A great deal, about 50%, of proteins in humans are glycosylated.<sup>1</sup> A variety of oligosaccharides that are mostly branched are introduced in the protein backbone mainly through *O*- and *N*-glycosyl amino acids, being serine, threonine, hydroxyproline, and asparagine, the most common derivatives. The carbohydrate domain in glycoproteins is key to vital biological processes including cell-cell recognition and interaction and it affects protein folding, conformation, stability, and biological activity.<sup>2</sup> In this context, defects in the attachment of carbohydrate to protein in humans may be the main cause of undesired biochemical events that result in serious diseases.<sup>3</sup> A striking example is represented by the disease known as congenital disorder of glycosylation (CDG) syndrome. Specifically, following the original observations of a pediatrician in Belgium in the beginning of the 1980s, further studies have revealed that congenital underglycosylation of proteins causes severe health problems in children and typically results in multisystemic presentation involving interference with normal development of the brain and functions of the liver, stomach, and nervous and intestinal systems.<sup>4</sup> On the other hand, the beneficial effects of glycosylation in neuropeptides (e.g., enkephalins) in terms of improved blood—brain barrier penetration and analgesic potency have been recently discussed.<sup>5</sup> The role of antifreeze glycoproteins<sup>6</sup> in Teleost fish is crucial to prevent in vivo ice growth in organisms inhabiting subzero environments. Conse-

<sup>&</sup>lt;sup>†</sup> Dedicated to the fond memory of Albert I. Meyers.

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quently, efficient protection of these organisms against cryoinjury and death is achieved. In general, however, numerous mechanisms of carbohydrate action in glycoproteins are at present poorly understood.<sup>1</sup> Natural and unnatural glycopeptides with a well-defined structure and composition can serve as probes in biochemical studies, while the latter are also potential leads for the developments of new drugs against carbohydratebased metabolic disorders. Hence, a great deal of efforts are made toward the search of efficient synthetic methods of natural O- and N-linked glycosyl amino and glycopeptides<sup>2b,7</sup> as well as of unnatural C-linked analogues<sup>8</sup> to be incorporated into peptidic chains. Attention is also drawn to the synthesis of S-linked glycosyl amino acids and thioglycopeptides.<sup>9</sup> While in early studies we have carried out the synthesis of methylene isosteres of glycosyl serines<sup>10</sup> and ethylene isosteres of glycosyl asparagines,<sup>10c,11</sup> more recently we have started a program focused on the synthesis of a newly designed family of C-glycosyl amino acids that feature a nitrogenated heterocycle as a tether of the carbohydrate and glycinyl moiety (Figure 1). In our view, the heterocycle should serve not only as a passive yet robust linker but can also act as an additional site of interaction with target substrates through dipolar interactions and hydrogen bonding. Therefore, glycopeptides in which such amino acids are embedded may give rise to highly selective molecular recognition processes. Synthetic approaches to these

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FIGURE 1. Heterocycle-tethered C-glycosyl amino acids.

glycosyl amino acids having isoxazole,<sup>12</sup> 1,2,3-triazole,<sup>12</sup> and pyridine rings<sup>13</sup> as linkers have been reported and reviewed.<sup>14</sup> In this paper, we report on the first synthesis of tetrazole-tethered *C*-glycosyl amino acids that relies on an very efficient azide—nitrile cycloaddition as a key step for the heterocyclic ring formation. This ligation strategy is quite attractive because tetrazole is a lipophilic and highly stable unit under a variety of reaction conditions and being densely nitrogenated may induce strong intermolecular interactions via an extensive set of hydrogen bondings. The biological relevance of the tetrazole ring is well-recognized as a metabolically stable surrogate for a carboxylic or amide group.<sup>15</sup>

### **Results and Discussion**

Formation of tetrazole rings by the Huisgen 1,3-dipolar cycloaddition between nitriles and organic azides<sup>16</sup> is in principle the most direct method. However, this reaction is limited in scope because only nitriles activated by strong electronwithdrawing groups can be effectively engaged as dipolarophilic partners by organic azides. A few years ago, Demko and Sharpless have shown for the first time the existence of a reaction window by coupling under solvent-free conditions p-toluenesulfonyl cyanide (TolSO<sub>2</sub>-CN, TsCN)<sup>17</sup> and acyl cyanides<sup>18</sup> with various aromatic and aliphatic azides to give exclusively the corresponding 1,5-disubstituted tetrazoles. As the reactions were carried out using 1 equiv of each reagent and gave nearly quantitative conversion into almost pure products, the process was considered as a case of click chemistry transformation as defined by Sharpless and co-workers.<sup>19</sup> Moreover, earlier work of Gol'tsberg and Koldobskii had previously demonstrated that the 5-sulfonyl substituent in tetrazoles can be readily replaced by a wide range of nucleo-

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SCHEME 1. Azide—Nitrile Cycloaddition-Based Approach toward the Synthesis of *C*-Glycosylmethyl Tetrazole Serines and Cysteines



philes.<sup>20</sup> The click azide—TsSCN cycloaddition together with the tosyl substitution in the formed 1-substituted 5-sulfonyl tetrazole established a two-step route toward the synthesis of a variety of 1,5-disubstituted tetrazoles that were hardly accessible by the direct Huisgen azide—nitrile cycloaddition. Recently, we have validated the effectiveness of this click ligation route for the synthesis of complex molecules such as glycoclusters installed on a calix[4]arene platform through tetrazole tethers.<sup>21</sup>

With this in mind, we planned the synthesis of target C-glycosylmethyl tetrazole serines 5 and cysteines 6 as shown in Scheme 1. This consisted of the click cycloaddition of benzylated and acetylated glycosylmethyl azides (azidomethyl glycosides) 1 and 2 with TsCN to give 1-glycosylmethyl-5tosyl tetrazoles 3 and 4 followed by the replacement of the tosyl group by serine and cysteine derivatives acting as O- and S-nucleophile, respectively. Azides 1 and 2 as starting materials were selected in order to introduce a methylene bridge between the carbohydrate and tetrazole ring, thus creating a robust C-glycosidic linkage that would preserve the final product from chemical and enzymatic degradation. Another point of great importance was the careful choice of orthogonal protective groups PG<sup>1</sup> and PG<sup>2</sup> in the carbohydrate and glycinyl moiety in order to make the formed amino acids suitable building blocks in peptide synthesis.

A. Synthesis of Glycosylmethyl Azides 1 and 2. Although the preparation of  $\beta$ -azidomethyl glycosides was reported in previous papers from our laboratory starting from formyl  $\beta$ -*C*glycosides,<sup>22</sup> we have developed a new and more efficient, general method starting from glycosyl cyanides. These *C*glycosides are available as either  $\alpha$ - or  $\beta$ -anomers by cyanation of glycosyl acetates with trimethylsilyl cyanide (TMSCN).<sup>23</sup> Benzylated galactosyl and ribosyl cyanides 7 were reduced in SCHEME 2. Synthesis of Perbenzylated Glycosylmethyl Azides



nearly quantitative yields by lithium aluminum hydride to amines **8**, and these were transformed in very good yields (62–87%) into azides **1** by diazotransfer reaction using imidazole-1-sulfonyl azide (ISA) hydrochloride<sup>24</sup> (Scheme 2). Key in our method was this new, efficient, and shelf-stable diazotransfer reagent. The ISA reagent provided a safer, more effective azide transfer than the commonly used diazo transfer reagent trifluoromethanesulfonyl azide, whose preparation and manipulation require special caution.<sup>25</sup> Following Scheme 2, we have prepared a set of four benzylated glycosylmethyl azides **1a**–**d** with  $\alpha$ - and  $\beta$ -galacto and  $\alpha$ - and  $\beta$ -ribo configurations.

In order to modulate the orthogonal protecting group setting in the final amino acid, acetylated glycosylmethyl azides 2a-dwere conveniently prepared employing aminomethyl glycosides 8 (Scheme 3). Debenzylation of these compounds by hydrogenation over Pd(OH)<sub>2</sub> afforded the amines 9 that, as crude material, were subjected to the diazotransfer reaction with ISA hydrochloride to give the azides 10. These compounds were acetylated to give good overall yields (62–74%) of azides 2a-d.

**B.** Synthesis of *C*-Glycosylmethyl *O*-Tetrazolyl Serines **5.** The method and conditions for the synthesis of these compounds are illustrated by the synthesis of the  $\beta$ -D-galactosylmethyl derivative **5b** (Scheme 4). Neat tetrabenzyl  $\beta$ -Dgalactosylmethyl azide **1b** and TsCN (2.0 equiv) were heated at 100 °C (oil bath). At this temperature, a homogeneous liquid resulted so that the mixture was efficiently stirred by a magnetic bar. As the reaction proceeded, the mixture solidified. The excess of TsCN was simply removed by sublimation under vacuum so that nearly pure 1-galactosylmethyl-5-tosyl tetrazole **3b** was

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isolated (93% yield) as the sole regioisomer. The 1,5-substitution pattern in the tetrazole ring was assumed on the basis of previous observations.<sup>17,18,26</sup> A highly performing click azide-nitrile cycloaddition appeared to take place as well with a complex alkyl azide such as 1b.<sup>27</sup> As the substitution of the tosyl group by an O-nucleophile required strong basic conditions, this prevented the use of a protected serine derivative such as N-Boc-L-serine methyl ester. The tosyl group of **3b** was replaced by reaction with N-Boc-N,O-isopropylidene-D-serinol  $11^{28}$  and NaH. This reaction provided the masked serine derivative 12b. It has been demonstrated that compound 11 functions as a configurationally stable equivalent of serine by virtue of the easy transformation of the N-Boc oxazolidine ring into the glycinyl group.<sup>10,11</sup> Unexpectedly, treatment of 12b with the Jones reagent (H<sub>2</sub>SO<sub>4</sub>-H<sub>2</sub>O, CrO<sub>3</sub>) at room temperature to achieve one-pot cleavage of the oxazolidine ring and oxidation of the amino alcohol afforded the target amino acid in very poor yield (15%). In addition, the use of aqueous 60-80% AcOH<sup>10</sup> to remove the acetonide protecting group gave poor results (25% yield of the corresponding alcohol). Fortunately, a recent method for cleaving protected cyclic N,O-aminals by using catalytic BiBr<sub>3</sub> was available.<sup>29</sup> To our satisfaction, treatment of 12b with BiBr3 in acetonitrile at room temperature, then oxidation of the alcohol with the Jones reagent, and finally esterification with diazomethane afforded the orthogonally protected N-Boc methyl serinate 5b in 60% isolated overall yield. This final product displayed all prerequisites for being a suitable building block in N-Boc-based peptide synthesis. Debenzylation of the carbohydrate moiety of **5b** by palladium-

which the cycloadduct **12b** was isolated in very low yield (18%). (28) Dondoni, A.; Perrone, D. Org. Synth. **1999**, 77, 64–70.





catalyzed hydrogenolysis proved to be compatible with the presence of basic nitrogen atoms of the tetrazole ring, thus leading to the amino ester 5b'.

The cycloaddition—substitution sequence was successfully applied to the other three benzylated glycosylmethyl azides prepared, i.e., the  $\alpha$ -D-galactosyl derivative **1a** and the  $\alpha$ -D- and  $\beta$ -D-ribosyl derivatives **1c** and **1d**. As quoted in Table 1, uniformly high yields of intermediates **3** and **12** and amino esters **5** were observed in all cases, thus confirming the efficiency of the method.

**C.** Synthesis of *C*-Glycosylmethyl *S*-Tetrazolyl Cysteines 6. Having in mind the final role of the amino acids under preparation, i.e., their use in cotranslational modification of glycopeptides, we decided to use peracetylated glycosylmethyl azides 2 as starting material. We envisaged the acetyl group removal by saponification of either the final amino acid or the peptide in which it was introduced.<sup>30</sup> In this way, we avoided the risk that the removal of the carbohydrate benzyl groups by Pd-catalyzed hydrogenation could fail due to the presence of the cysteine sulfur atom. Hence, a typical synthesis of a model

<sup>(26)</sup> Butler, R. N. In *Comprehensive Heterocyclic Compounds*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1966; Vol. 4.

<sup>(27)</sup> The proficuous choice of thermal conditions to perform the cycloaddition of **1b** with TsCN became apparent when the reaction was carried out under Cu(1) catalysis as described by Bosch and Vilarrasa: Bosch, L.; Vilarrasa, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3926–3930. In our hands, treatment of **1b** with TsCN (2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (room temperature) in the presence of Cu<sub>2</sub>(OTf)  $_2$ ·C<sub>6</sub>H<sub>6</sub> (0.1 equiv) as the catalyst produced a complex reaction mixture from which the cycloadduct **12b** was isolated in very low yield (18%).

<sup>(29)</sup> Cong, X.; Hu, F.; Liu, K.-G.; Liao, Q.-J.; Yao, Z.-J. J. Org. Chem. **2005**, 70, 4514–4516. It is worth noting that errors in some references cited in this paper as author given names instead of family names have been reported.







<sup>a</sup> See the Experimental Section for details. <sup>b</sup> Isolated yield by chromatography.

compound is succinctly illustrated here (Scheme 5). The reaction of the tetraacetyl azidomethyl  $\beta$ -D-galactoside **2b** with excess TsCN (2.0 equiv) was run neat at 100 °C, and the isolated 5-tosyl tetrazole **4b** (93% yield) was treated with *N*-fluorenylmethoxycarbonyl (*N*-Fmoc) cysteine **13**<sup>31</sup> (1.1 equiv) under mild basic conditions (K<sub>2</sub>CO<sub>3</sub>) at room temperature. The cysteine **13** was added in two portions to **4b** in order to reduce its transformation into *N*-Fmoc cysteine **6b** was isolated in high yield (90%) without any apparent loss of configurational integrity of the glycinyl group. This approach appeared to be more straightforward than that followed in the synthesis of the serine derivatives **5** (see previous section) in which a masked amino acid nucleophile had to be employed because of the strong basic conditions required for the substitution of the tosyl group.

The same reaction sequence was applied to the other peracetylated glycosylmethyl azides shown in Scheme 3, i.e., compounds **2a**, **2c**, and **2d**. Both the cycloadducts **4a**, **4c**, and **4d** and the tetrazole-tethered *C*-glycosyl cysteines **6a**, **6c**, and **6d** were isolated in good to excellent yields (Table 2). It is worth noting that the set of orthogonal protective groups in amino acids **6a**–**d** makes these compounds all suitable for the *N*-Fmocbased automated peptide synthesis.<sup>30</sup>

**D.** Synthesis of Tetrazole-Tethered Glycopeptides. In order to demonstrate the potential of the prepared *C*-glycosyl amino

<sup>(31)</sup> Lumbierres, M.; Palomo, J.; Kragol, G. S. R.; Müller, O.; Waldmann, H. *Chem.–Eur. J.* **2005**, *11*, 7405–7415.



acids as orthogonally protected building blocks for the cotranslational modification of glycopeptides, the *O*-serine derivative

<sup>(30)</sup> As a selected example of this protection strategy in glycopeptide synthesis, see: Liu, S.; Ben, R. N. Org. Lett. 2005, 7, 2385–2388.

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 TABLE 2.
 Glycosylmethyl Tetrazole Cysteines Prepared<sup>a</sup>



<sup>a</sup> See the Experimental Section for details. <sup>b</sup> Isolated yield by chromatography.

14 was selected as a prototype in this crucial validating test (Scheme 6). A crude sample of this amino acid as obtained from the cleavage of the oxazolidine precursor 12b was employed in the coupling with phenylalanine ethyl ester hydrochloride (H-Phe-OEt • HCl). The reaction was carried out at ambient temperature under activation of the condensation agent (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) in the presence of the Hünig's base (diisopropylethyl amine, DIPEA). From this reaction, the dipeptide 15 was isolated by chromatography in very good yield (80%). The removal of the N-Boc protective group from 15 was readily carried out upon treatment with diluted trifluoroacetic acid (TFA). The amine that formed was used in the condensation with N-Boc alanine (Boc-Ala-OH) under the same coupling conditions described above. The tetrazole-tethered glycopeptide 16 was isolated after chromatography in 72% yield. This tripeptide can be inserted in a more complex peptide via N-Bocbased peptide synthesis.

### Conclusions

In summary, we have demonstrated the efficiency of the Sharpless–Demko azide–sulfonyl cyanide cycloaddition/sulfonyl substitution route for the synthesis of tetrazole-tethered *C*-glycosyl  $\alpha$ -amino acids. A new ligation tool has been established for unnatural *C*-glycosyl  $\alpha$ -amino acid synthesis, the building blocks required for the cotranslational modification of glycopeptides. The key step in this strategy was the thermal azide–cyanide cycloaddition, a reaction that is highlighted as a click process when the organic cyanide is activated by a strong



electron-withdrawing substituent such as the sulfonyl group. This and previous work reported from our laboratory<sup>21</sup> demonstrated the fidelity of this thermally induced metal-free process even when applied to complex systems. This reaction combined with the sulfonyl group substitution step appears to have its own value as a new ligation tool. The tetrazole ring that is formed plays the role of a robust molecular keystone holding the biologically active residues. So far the glycosyl amino acids prepared were serine and cysteine derivatives. It can be envisaged that substitution of the sulfonyl group with *N*-, *Se*-, and *C*nucleophile amino acids or their synthetic equivalents will expand the scope of this new synthetic method.

#### **Experimental Section**

Cyanides 7a-d,<sup>23</sup> amines 8b,<sup>22a</sup> 8d,<sup>22a</sup> and 9a,<sup>32a</sup> 9b,<sup>32</sup> azides 1b,<sup>22a</sup> 1d,<sup>22a</sup> and 2b,<sup>22b</sup> tetrazoles  $3b^{21}$  and 3d,<sup>21</sup> serinol 11,<sup>28</sup> and cysteine  $13^{31}$  are known compounds, and their spectroscopic data were identical to those reported.

General Procedure for the Synthesis of Benzylated Amines 8. To a stirred suspension of LiAlH<sub>4</sub> (304 mg, 8.00 mmol) in anhydrous THF (10 mL) was slowly added a solution of cyanide 7 (1.10 g, 2.00 mmol) in anhydrous THF (4 mL). The resulting mixture was stirred under reflux until disappearance of starting cyanide (TLC analysis, typically 1 h), cooled to room temperature, and then diluted with 28% aqueous NH<sub>4</sub>OH (2 mL). The resulting mixture was stirred at room temperature until the formation of a white precipitate was observed (typically 30 min). The mixture was then filtered over a pad of Celite and washed thoroughly with AcOEt. The combined filtrates were concentrated to give the corresponding crude amine 8 in almost quantitative yield. Each amine 8 was used in the next step without any purification.

(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)methylamine (8a). <sup>1</sup>H NMR:  $\delta = 7.50-7.20$  (m, 20 H, Ph), 4.75 and 4.61 (2 d, 2 H, *J* = 11.8 Hz, PhCH<sub>2</sub>), 4.73 and 4.51 (2 d, 2 H, *J* = 12.0 Hz, PhCH<sub>2</sub>), 4.66 and 4.64 (2 d, 2 H, *J* = 11.5 Hz, PhCH<sub>2</sub>), 4.56 and 4.52 (2 d, 2 H, *J* = 12.2 Hz, PhCH<sub>2</sub>), 4.10-4.04 (m, 1 H, H-5), 4.02 (dd, 1 H, *J*<sub>4,5</sub> = 2.8 Hz, *J*<sub>3,4</sub> = 3.8 Hz, H-4), 3.95-3.81 (m, 2 H, H-2, H-3), 3.81-3.71 (m, 2 H, H-1, H-6a), 3.66 (dd, 1 H, *J*<sub>5,6b</sub> = 4.2 Hz, *J*<sub>6a,6b</sub> = 10.5 Hz, H-6b), 2.97 (dd, 1 H, *J*<sub>1,1'a</sub> = 8.9 Hz, *J*<sub>1'a,1'b</sub> = 13.5 Hz, H-1'a), 2.78 (dd, 1 H, *J*<sub>1,1'b</sub> = 4.2 Hz, H-1'b).

(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)methylamine (8c). <sup>1</sup>H NMR:  $\delta$  = 7.40–7.25 (m, 15 H, Ph), 4.78 and 4.59 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*<sub>2</sub>), 4.62 and 4.52 (2 d, 2 H, *J* = 12.0 Hz, PhC*H*<sub>2</sub>), 4.57 and 4.54 (2 d, 2 H, *J* = 12.2 Hz, PhC*H*<sub>2</sub>), 4.20 (ddd, 1 H, *J*<sub>3,4</sub> = 7.0 Hz, *J*<sub>4,5a</sub> = 3.3 Hz, *J*<sub>4,5b</sub> = 4.10 Hz, H-4), 4.08 (dd, 1 H, *J*<sub>1,2</sub> = 4.8 Hz, *J*<sub>2,3</sub> = 4.8 Hz, H-2), 4.06–3.98 (m, 2 H, H-1, H-3), 3.60 (dd, 1 H, *J*<sub>5a,5b</sub> = 10.6 Hz, H-5a), 3.49 (dd, 1 H, H-5b), 3.01 (dd, 1 H, *J*<sub>1,1'a</sub> = 6.7 Hz, *J*<sub>1'a,1'b</sub> = 13.2 Hz, H-1'a), 2.92 (dd, 1 H, *J*<sub>1,1'b</sub> = 5.1 Hz, H-1'b).

General Procedure for the Synthesis of Benzylated Azides 1. A mixture of crude amine 8 (553 mg, ~1.00 mmol), imidazole-1-sulfonyl azide hydrochloride (251 mg, 1.20 mmol), K<sub>2</sub>CO<sub>3</sub> (235 mg, 1.70 mmol), CuSO<sub>4</sub>•5H<sub>2</sub>O (2.5 mg, 0.01 mmol), and MeOH (5 mL) was stirred at room temperature for 4 h. The mixture was then concentrated, diluted with H<sub>2</sub>O (15 mL), acidified with concd HCl, and extracted with AcOEt (3 × 25 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding azide 1.

(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)methyl azide (1a). Column chromatography with 9:1 cyclohexane–AcOEt afforded 1a (452 mg, 79%) as white foam. [α]<sub>D</sub> = 16.2 (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  = 7.42–7.20 (m, 20 H, Ph), 4.72 and 4.59 (2 d, 2 H, *J* = 12.0 Hz, PhCH<sub>2</sub>), 4.70 and 4.51 (2 d, 2 H, *J* = 11.8 Hz, PhCH<sub>2</sub>), 4.62 and 4.60 (2 d, 2 H, *J* = 11.5 Hz, PhCH<sub>2</sub>), 4.60 and 4.53 (2 d, 2 H, *J* = 12.2 Hz, PhCH<sub>2</sub>), 4.22–4.08 (m, 2 H, H-1, H-5), 4.05 (dd, 1 H, *J*<sub>4.5</sub> = 2.7 Hz, *J*<sub>3.4</sub> = 4.2 Hz, H-4), 3.92(dd, 1 H,  $J_{5,6a} = 7.3$  Hz,  $J_{6a,6b} = 10.7$  Hz, H-6a), 3.82 - 3.70 (m, 3 H, H-2, H-3, H-6b), 3.60 (dd, 1 H,  $J_{1,1'a} = 8.5$  Hz,  $J_{1'a,1'b} = 12.9$  Hz, H-1'a), 3.27 (dd, 1 H,  $J_{1,1'b} = 4.8$  Hz, H-1'b). <sup>13</sup>C NMR:  $\delta = 138.3$  (2C), 137.8 (2C), 128.5 - 127.4 (20C), 75.9, 75.5, 73.7, 73.3, 73.1, 73.2, 73.0, 72.9, 70.2, 66.6, 49.2. MALDI-TOF MS: 602.9 (M<sup>+</sup> + Na). Anal. Calcd for  $C_{35}H_{37}N_3O_5$  (579.27): C, 75.52; N, 7.25; H, 6.43. Found: C, 75.50; N, 7.27; H, 6.41.

(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)methyl Azide (1c). Column chromatography with 9:1 cyclohexane–AcOEt afforded 1c (285 mg, 62%) as a white foam. [α]<sub>D</sub> = 40.3 (*c* 2.8, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 7.40–7.20 (m, 15 H, Ph), 4.77 and 4.55 (2 d, 2 H, *J* = 11.5 Hz, PhCH<sub>2</sub>), 4.62 and 4.54 (2 d, 2 H, *J* = 11.8 Hz, PhCH<sub>2</sub>), 4.57 and 4.49 (2 d, 2 H, *J* = 12.0 Hz, PhCH<sub>2</sub>), 4.25 (ddd, 1 H, *J*<sub>3,4</sub> = 5.5 Hz, *J*<sub>4,5a</sub> = 3.6 Hz, *J*<sub>4,5b</sub> = 3.4 Hz, H-4), 4.21 (ddd, 1 H, *J*<sub>1,2</sub> = 4.8 Hz, H-2), 4.07 (dd, 1 H, H-3), 3.65 (dd, 1 H, *J*<sub>1'a,1'b</sub> = 12.8 Hz, H-1'a), 3.59 (dd, 1 H, H-3), 3.65 (dd, 1 H, *J*<sub>1'a,1'b</sub> = 12.8 Hz, H-1'a), 3.59 (dd, 1 H, H-3), 7.5, 7.3.4, 7.3.1, 72.6, 69.9, 50.9. MALDI-TOF MS: 460.4 (M<sup>+</sup> + H). Anal. Calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub> (459.22): C, 70.57; N, 9.14; H, 6.36. Found: C, 70.53; N, 9.11; H, 6.38.

General Procedure for the Synthesis of Unprotected Amines 9. A vigorously stirred mixture of amine 8 (553 mg,  $\sim$ 1.00 mmol), 20% palladium hydroxide on carbon (227 mg), and AcOH (8 mL) was degassed under vacuum and saturated with hydrogen (by a H<sub>2</sub>-filled balloon) three times. The suspension was stirred at room temperature for 12 h under a positive pressure of hydrogen (8 bar), filtered through a plug of cotton, and concentrated to give crude amine 9 in almost quantitative yield. Each amine 9 was used in the next step without any purification.

(**α-D-Ribofuranosyl)methylamine** (**9c**). <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  = 4.19 (dd, 1 H,  $J_{1,2}$  = 4.0 Hz,  $J_{2,3}$  = 4.5 Hz, H-2), 4.15 (ddd, 1 H,  $J_{1,1'a}$  = 6.0 Hz,  $J_{1,1'b}$  = 4.5 Hz, H-1), 4.03 (dd, 1 H,  $J_{3,4}$  = 7.8 Hz, H-3), 3.81 (ddd, 1 H,  $J_{4,5a}$  = 2.8 Hz,  $J_{4,5b}$  = 5.4 Hz, H-4), 3.66 (dd, 1 H,  $J_{5a,5b}$  = 12.5 Hz, H-5a), 3.49 (dd, 1 H, H-5b), 3.15 (dd, 1 H,  $J_{1'a,1'b}$  = 13.0 Hz, H-1'a), 3.11 (dd, 1 H, H-1'b). <sup>13</sup>C NMR (D<sub>2</sub>O):  $\delta$  = 81.9, 75.9, 72.5, 71.8, 61.5, 39.6.

(*β*-D-Ribofuranosyl)methylamine (9d). <sup>1</sup>H NMR:  $\delta = 3.93$  (dd, 1 H,  $J_{1,2} = 5.1$  Hz,  $J_{2,3} = 5.0$  Hz, H-2), 3.90 (ddd, 1 H,  $J_{1,1'a} = 3.2$ Hz,  $J_{1,1'b} = 13.3$  Hz, H-1), 3.84 (dd, 1 H,  $J_{3,4} = 5.2$  Hz, H-3), 3.82 (ddd, 1 H,  $J_{4,5a} = 3.2$  Hz,  $J_{4,5b} = 4.9$  Hz, H-4), 3.17 (dd, 1 H,  $J_{1'a,1'b} = 13.3$  Hz, H-1'a), 2.91 (dd, 1 H, H-1'b). <sup>13</sup>C NMR (D<sub>2</sub>O):  $\delta = 84.4$ , 78.5, 72.7, 71.2, 61.5, 41.7.

General Procedure for the Synthesis of Acetylated Azides 2. A mixture of crude amine 9 (193 mg, ~1.00 mmol), imidazole-1-sulfonyl azide hydrochloride (251 mg, 1.20 mmol), K<sub>2</sub>CO<sub>3</sub> (235 mg, 1.70 mmol), CuSO<sub>4</sub>•5H<sub>2</sub>O (2.5 mg, 0.01 mmol), and MeOH (5 mL) was stirred at room temperature for 4 h. The mixture was then concentrated and coevaporated with toluene (2 × 10 mL). Acetic anhydride (3 mL) and pyridine (3 mL) were added to the residue, and the resulting mixture was stirred for an additional 5 h, diluted with H<sub>2</sub>O (10 mL), and extracted with AcOEt (3 × 25 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding azide 2.

(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)methyl azide (2a). Column chromatography with 2:1 cyclohexane–AcOEt afforded **2a** (248 mg, 64%) as a yellow syrup.  $[α]_D = 53.0$  (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta = 5.44$  (dd, 1 H,  $J_{3,4} = 3.3$  Hz,  $J_{4,5} = 3.5$  Hz, H-4), 5.27 (dd, 1 H,  $J_{1,2} = 4.6$  Hz,  $J_{2,3} = 8.5$  Hz, H-2), 5.21 (dd, 1 H, H-3), 4.39 (dd, 1 H,  $J_{5.6a} = 8.0$  Hz,  $J_{6a,6b} = 11.7$  Hz, H-6a), 4.37 (ddd, 1 H,  $J_{1,1'a} = 8.8$  Hz,  $J_{1,1'b} = 3.7$  Hz, H-1), 4.24 (ddd, 1 H,  $J_{5.6b} = 4.7$  Hz, H-5), 4.10 (dd, 1 H, H-6b), 3.61 (dd, 1 H,  $J_{1'a,1'b} = 13.5$  Hz, H-1'a), 3.28 (dd, 1 H, H-1'b), 2.12, 2.10, 2.07, and 2.05 (4s, 12 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 170.7$ , 169.8, 169.6, 169.5, 70.8, 69.9, 67.7, 67.6, 66.9, 60.7, 48.3, 20.7 (3C), 20.6. MALDI-TOF MS: 426.4 (M<sup>+</sup> + K). Anal. Calcd for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>9</sub> (387.13): C, 46.51; N, 10.85; H, 5.46. Found: C, 46.50; N, 10.88; H, 5.45. (2,3,5-Tri-*O*-acetyl-α-D-ribofuranosyl)methyl Azide (2c). Column chromatography with 2.5:1 cyclohexane—AcOEt afforded 2c (208 mg, 66%) as a white foam. [α]<sub>D</sub> = 55.8 (*c* 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 5.54 (dd, 1 H,  $J_{1,2}$  = 4.7 Hz,  $J_{2,3}$  = 5.0 Hz, H-2), 5.32–5.26 (m, 1 H, H-3), 4.38 (ddd, 1 H,  $J_{1,1'a}$  = 7.2 Hz,  $J_{1,1'b}$  = 5.5 Hz, H-1), 4.33–4.24 (m, 2 H, H-4, H-5a), 4.16–4.08 (m, 1 H, H-5b), 3.51 (dd, 1 H,  $J_{1'a,1'b}$  = 13.0 Hz, H-1'a), 3.40 (dd, 1 H, H-1'b), 2.16, 2.12, and 2.08 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  = 170.6, 169.6, 169.5, 77.8, 77.6, 71.8, 71.5, 63.4, 50.2, 20.8, 20.6, 20.5. MALDI-TOF MS: 338.1 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>7</sub> (315.11): C, 45.71; N, 13.33; H, 5.43. Found: C, 45.74; N, 13.35; H, 5.40.

(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)methyl azide (2d). Column chromatography with 2.5:1 cyclohexane–AcOEt afforded 2d (214 mg, 68%) as a white foam. [α]<sub>D</sub> = -76.3 (*c* 1.7, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta = 5.18-5.13$  (m, 2 H, H-2, H-3), 4.34 (dd, 1 H,  $J_{4,5a} = 2.9$  Hz,  $J_{5b,5a} = 11.9$  Hz, H-5a), 4.21 (ddd, 1 H,  $J_{3,4} = 5.5$  Hz,  $J_{4,5b} = 5.0$  Hz, H-4), 4.15 (dd, 1 H, H-5b), 4.13 (ddd, 1 H,  $J_{1,2} = 5.5$  Hz,  $J_{1,1'a} = 3.1$  Hz,  $J_{1,1'b} = 4.2$  Hz, H-1), 3.60 (dd, 1 H,  $J_{1'a,1'b} = 13.3$  Hz, H-1'a), 3.36 (dd, 1 H, H-1'b), 2.11, 2.09, and 2.07 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 170.6$ , 169.7, 169.6, 80.6, 79.4, 71.6, 71.4, 63.2, 51.6, 20.7, 20.5 (2C). MALDI-TOF MS: 338.4 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>7</sub> (315.11): C, 45.71; N, 5.43; H, 35.5. Found: C, 45.73; N, 13.34; H, 5.44.

General Procedure for the Synthesis of 1-Glycosylmethyl-5tosyl tetrazoles 3 and 4. A mixture of either azide 1 or 2 (0.50 mmol) and commercially available *p*-toluensulfonyl cyanide (181 mg, 1.00 mmol) was stirred at 100 °C in the absence of solvent under a nitrogen atmosphere and then cooled to room temperature. The excess of *p*-toluensulfonyl cyanide was then removed by sublimation under vacuum to give nearly pure tetrazole 3 or 4. Analytical quality samples of 3 and 4 were obtained by eluting the corresponding crude derivative from a column of silica gel with the suitable elution system.

1-(2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosylmethyl)-5-(p-toluensulfonyl)-1H-tetrazole (3a). Column chromatography with 4.5:1 cyclohexane-AcOEt afforded 3a (319 mg, 84%) as a white amorphous solid.  $[\alpha]_{\rm D} = 47.1 \ (c \ 1.1, \text{CHCl}_3)$ . <sup>1</sup>H NMR (400 MHz):  $\delta = 8.00-7.90$  (m, 2 H, Ar), 7.50–7.20 (m, 20 H, Ar), 7.18–7.10 (m, 2 H, Ar), 5.10 (dd, 1 H,  $J_{1,1'a} = 10.3$  Hz,  $J_{1'a,1'b} = 14.2$  Hz, H-1'a), 4.89 (dd, 1 H,  $J_{1,1'b} = 3.6$  Hz, H-1'b), 4.75 and 4.57 (2 d, 2 H, J = 11.8 Hz, PhCH<sub>2</sub>), 4.74 and 4.67 (2 d, 2 H, J = 11.5 Hz, PhCH<sub>2</sub>), 4.71 and 4.66 (2 d, 2 H, *J* = 11.8 Hz, PhCH<sub>2</sub>), 4.65 (ddd, 1 H,  $J_{1,2} = 4.5$  Hz, H-1), 4.30 and 4.23 (2 d, 2 H, J = 12.0 Hz, PhCH<sub>2</sub>), 4.18–4.08 (m, 2 H, H-4, H-5), 4.03 (dd, 1 H, J<sub>2,3</sub> = 7.5 Hz, H-2), 3.79 (dd, 1 H, J<sub>3.4</sub> = 2.6 Hz, H-3), 3.63 (dd, 1 H, J<sub>5.6a</sub> = 6.0 Hz,  $J_{6a,6b} = 10.4$  Hz, H-6a), 3.60 (dd, 1 H,  $J_{5,6b} = 7.0$  Hz, H-6b), 2.43 (s, 3 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 155.1$ , 147.2, 138.3, 138.1, 137.6, 137.5, 134.4, 130.3 (2C), 129.2 (2C), 127.9-127.0 (20C), 75.2, 75.1, 73.7, 73.6, 73.4, 73.2, 72.9, 72.8, 70.9, 66.9, 47.7, 21.9. MALDI-TOF MS: 783.4 ( $M^+$  + Na). Anal. Calcd for C43H44N4O7S (760.29): C, 67.88; N, 7.36; H, 5.83; S, 4.21. Found: C, 67.89; N, 7.32; H, 5.81; S, 4.23.

1-(2,3,5-Tri-O-benzyl-α-D-ribofuranosylmethyl)-5-(p-toluensulfonyl)-1H-tetrazole (3c). Column chromatography with 4:1 cyclohexane-AcOEt afforded 3c (256 mg, 80%) as a white amorphous solid.  $[\alpha]_D = 43.6$  (c 2.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta =$ 8.00-7.90 (m, 2 H, Ar), 7.50-7.30 (m, 15 H, Ar), 7.30-7.10 (m, 2 H, Ar), 5.37 (dd, 1 H,  $J_{1,1'a} = 9.9$  Hz,  $J_{1'a,1'b} = 14.2$  Hz, H-1'a), 4.82 (dd, 1 H,  $J_{1,1'b} = 2.8$  Hz, H-1'b), 4.74 and 4.59 (2 d, 2 H, J = 11.8 Hz, PhCH<sub>2</sub>), 4.70 and 4.63 (2 d, 2 H, J = 12.0 Hz, PhCH<sub>2</sub>), 4.64 (ddd, 1 H,  $J_{1,2} = 6.5$  Hz, H-1), 4.53 (ddd, 1 H,  $J_{3,4} = 2.8$  Hz,  $J_{4,5a} = 3.6$  Hz,  $J_{4,5b} = 4.0$  Hz, H-4), 4.51 and 4.43 (2 d, 2 H, J =12.2 Hz, PhCH<sub>2</sub>), 4.29 (dd, 1 H,  $J_{2,3} = 5.5$  Hz, H-2), 4.06 (dd, 1 H, H-3), 3.47 (dd, 1 H,  $J_{5a,5b} = 10.5$  Hz, H-5a), 3.44 (dd, 1 H, H-5b), 2.45 (s, 3 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 155.4$ , 147.1, 137.9, 137.7, 137.4, 134.2, 130.2 (2C), 129.1 (2C), 128.5-127.6 (15C), 81.6, 78.2, 77.9, 77.8, 73.5, 72.9, 72.4, 70.2, 50.7, 21.8. MALDI-TOF MS: 641.3 (M<sup>+</sup> + H). Anal. Calcd for  $C_{35}H_{36}N_4O_6S$  (640.24): C, 65.61; N, 8.74; H, 5.66; S, 5.00. Found: C, 65.63; N, 8.71; H, 5.67; S, 5.02.

1-(2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosylmethyl)-5-(p-toluensulfonyl)-1H-tetrazole (4a). Column chromatography with 2:1 cyclohexane-AcOEt afforded 4a (267 mg, 94%) as a white amorphous solid.  $[\alpha]_D = 59.7 (c \ 1.0, CHCl_3)$ . <sup>1</sup>H NMR (400 MHz):  $\delta = 8.01 - 7.97$  (m, 2 H, Ar), 7.49 - 7.42 (m, 2 H, Ar), 5.49 (dd, 1 H,  $J_{3,4} = 3.3$  Hz,  $J_{4,5} = 3.2$  Hz, H-4), 5.43 (dd, 1 H,  $J_{1,2} = 4.8$  Hz,  $J_{2,3} = 8.5$  Hz, H-2), 5.28 (dd, 1 H, H-3), 5.06 (dd, 1 H,  $J_{1,1'a} =$ 10.8 Hz,  $J_{1'a,1'b} = 14.5$  Hz, H-1'a), 4.95 (dd, 1 H,  $J_{1,1'b} = 3.0$  Hz, H-1'b), 4.75 (ddd, 1 H, H-1), 4.35 (ddd, 1 H, J<sub>5.6a</sub> = 8.5 Hz, J<sub>5.6b</sub> = 4.5 Hz, H-5), 4.21 (dd, 1 H,  $J_{6a.6b}$  = 11.8 Hz, H-6a), 4.04 (dd, 1 H, H-6b), 2.49 (s, 3 H, CH<sub>3</sub>), 2.21, 2.11, 2.08 and 1.93 (4s, 12 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  =170.6, 169.8, 169.7, 169.6, 154.9, 147.6, 134.1, 130.4 (2C), 129.3 (2C), 70.4, 69.7, 67.3, 67.0, 66.8, 60.4, 46.4, 21.9, 20.7 (2C), 20.6 (2C). MALDI-TOF MS: 607.5 (M<sup>+</sup> + K). Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>11</sub>S (568.15): C, 48.59; N, 9.85; H, 4.96; S, 5.64. Found: C, 48.57; N, 9.83; H, 4.92; S, 5.66.

**1-(2,3,4,6-Tetra-***O*-acetyl-β-D-galactopyranosylmethyl)-5-(*p*-toluensulfonyl)-1*H*-tetrazole (4b). Column chromatography with 2:1 cyclohexane–AcOEt afforded 4b (264 mg, 93%) as a white amorphous solid. [α]<sub>D</sub> = -7.8 (*c* 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  = 8.01–7.95 (m, 2 H, Ar), 7.47–7.42 (m, 2 H, Ar), 5.42 (dd, 1 H,  $J_{3,4}$  = 3.3 Hz,  $J_{4,5}$  = 0.5 Hz, H-4), 5.28 (dd, 1 H,  $J_{1,2}$  = 9.8 Hz,  $J_{2,3}$  = 9.9 Hz, H-2), 5.13 (dd, 1 H, H-3), 5.08 (dd, 1 H,  $J_{1,1'a}$  = 9.2 Hz,  $J_{1'a,1'b}$  = 14.5 Hz, H-1'a), 4.87 (dd, 1 H,  $J_{1,1'b}$  = 2.5 Hz, H-1'b), 4.05–3.90 (m, 3 H, H-1, 2H-6), 3.79 (ddd, 1 H,  $J_{5,6a}$  = 6.7 Hz,  $J_{5,6b}$  = 6.8 Hz, H-5), 2.49 (s, 3 H, CH<sub>3</sub>), 2.18, 2.15, 2.01, and 1.94 (4s, 12 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  = 170.6, 170.5, 170.4, 170.2, 155.4, 147.6, 134.3, 130.4 (2C), 129.3 (2C), 76.4, 74.2, 71.5, 67.4, 67.3, 61.1, 50.6, 21.9, 20.7, 20.6, 20.5, 20.4. MALDI-TOF MS: 591.4 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>11</sub>S (568.15): C, 48.59; N, 9.85; H, 4.96; S, 5.64. Found: C, 48.57; N, 9.83; H, 4.92; S, 5.66.

**1-(2,3,5-Tri-***O*-acetyl-α-D-ribofuranosylmethyl)-5-(*p*-toluensulfonyl)-1*H*-tetrazole (4c). Column chromatography with 1.5:1 cyclohexane–AcOEt afforded 4c (243 mg, 98%) as a white amorphous solid. [α]<sub>D</sub> = 48.8 (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 8.01–7.97 (m, 2 H, Ar), 7.47–7.42 (m, 2 H, Ar), 5.56 (dd, 1 H,  $J_{1,2}$  = 5.5 Hz,  $J_{2,3}$  = 5.2 Hz, H-2), 5.34 (dd, 1 H,  $J_{3,4}$  = 5.0 Hz, H-3), 5.23 (dd, 1 H,  $J_{1,1'a}$  = 9.8 Hz,  $J_{1'a,1'b}$  = 14.5 Hz, H-1'a), 4.88–4.80 (m, 2 H, H-1, H-1'b), 4.46 (ddd, 1 H,  $J_{4,5a}$  = 3.2 Hz,  $J_{4,5b}$  = 4.8 Hz, H-4), 4.22 (dd, 1 H,  $J_{5a,5b}$  = 12.2 Hz, H-5a), 4.14 (dd, 1 H, H-5b), 2.50 (s, 3 H, CH<sub>3</sub>), 2.19, 2.14, and 2.09 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  = 170.4, 169.7, 169.3, 155.5, 147.5, 134.3, 130.3 (2C), 129.2 (2C), 79.1, 77.4, 71.9, 71.0, 63.2, 49.3, 21.9, 20.7, 20.6, 20.4. MALDI-TOF MS: 497.4 (M<sup>+</sup> + H). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub>S (496.13): C, 48.38; N, 11.28; H, 4.87; S, 6.46. Found: C, 48.35; N, 11.26; H, 4.85; S, 6.47.

**1-(2,3,5-Tri-***O*-acetyl-β-D-ribofuranosylmethyl)-5-(*p*-toluensulfonyl)-1*H*-tetrazole (4d). Column chromatography with 1.5:1 cyclohexane–AcOEt afforded 4d (223 mg, 90%) as a white amorphous solid. [α]<sub>D</sub> = -23.6 (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 8.02–7.97 (m, 2 H, Ar), 7.45–7.40 (m, 2 H, Ar), 5.19–5.12 (m, 3 H, H-2, H-3, H-1'a), 5.03 (dd, 1 H,  $J_{1,1'b}$  = 5.8 Hz,  $J_{1'a,1'b}$  = 14.1 Hz, H-1'b), 4.54–4.48 (m, 1 H, H-1), 4.20 (ddd, 1 H,  $J_{3,4}$  = 4.0 Hz,  $J_{4,5a}$  = 3.2 Hz,  $J_{4,5b}$  = 3.0 Hz, H-4), 4.11 (dd, 1 H,  $J_{5a,5b}$  = 12.3 Hz, H-5a), 4.06 (dd, 1 H, H-5b), 2.48 (s, 3 H, CH<sub>3</sub>), 2.10, 2.08, and 2.03 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  = 170.5, 169.7 (2C), 155.7, 147.5, 134.5, 130.3 (2C), 129.3 (2C), 80.7, 78.1, 71.9, 71.7, 63.0, 50.2, 21.8, 20.7, 20.5, 20.3. MALDI-TOF MS: 519.7 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub>S (496.13): C, 48.38; N, 11.28; H, 4.87; S, 6.46. Found: C, 48.35; N, 11.26; H, 4.85; S, 6.47.

General Procedure for the Synthesis of Masked Glycosyl Amino Acids 12 (Table 1). To a stirred solution of D-serinol 11 (92 mg, 0.40 mmol) in anhydrous DMF (4 mL) was added NaH (32 mg, 0.80 mmol of a 60% dispersion in oil). The mixture was stirred at room temperature for 30 min and then diluted with a solution of sugar tetrazole 3 (304 mg, 0.40 mmol) in anhydrous DMF (2 mL). The resulting solution was stirred at room temperature

for 16 h, diluted with saturated aqueous NH<sub>4</sub>Cl (10 mL), and extracted with AcOEt (3  $\times$  50 mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding adduct **12**.

(4R)-2,2-Dimethyl-4-[1-(2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosylmethyl)-1*H*-tetrazol-5-yloxymethyl)]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (12a). Column chromatography with 3:1 cyclohexane-AcOEt afforded 12a (268 mg, 80%) as a white foam.  $[\alpha]_D = 37.4 (c \ 1.3, CHCl_3)$ . <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 120 °C) selected data:  $\delta = 7.40-7.20 (m, 20 H, Ph), 4.72 and 4.62 (2 d, 2 H,$ *J*=11.5 Hz, PhC*H*<sub>2</sub>), 4.70 and 4.54 (2 d, 2 H,*J*= 11.8 Hz, PhC*H*<sub>2</sub>),4.25–4.18 (m, 1 H), 4.16–4.08 (m, 1 H), 3.64 (d, 2 H,*J*= 6.0Hz), 1.45 and 1.43 (2s, 6 H), 1.42 (s, 9 H). MALDI-TOF MS:858.8 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>47</sub>H<sub>57</sub>N<sub>5</sub>O<sub>9</sub> (835.42): C, 67.53;N, 8.38; H, 6.87. Found: C, 67.55; N, 8.34; H, 6.81.

(4R)-2,2-Dimethyl-4-[1-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosylmethyl)-1H-tetrazol-5-yloxymethyl)]oxazolidine-3-carboxylic Acid tert-Butyl Ester (12b). Column chromatography with 3:1 cyclohexane-AcOEt afforded 12b (284 mg, 85%) as a yellow syrup. [α]<sub>D</sub> = 1.5 (*c* 2.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 120 °C):  $\delta$ = 7.40-7.10 (m, 20 H, Ph), 4.92 and 4.56 (2 d, 2 H, J = 11.5 Hz, PhC $H_2$ ), 4.83 and 4.67 (2 d, 2 H, J = 11.2 Hz, PhC $H_2$ ), 4.81 and 4.72 (2 d, 2 H, J = 12.0 Hz, PhCH<sub>2</sub>), 4.54 and 4.42 (2 d, 2 H, J = 10.5 Hz, PhCH<sub>2</sub>), 4.46-4.34 (m, 3 H), 4.28-4.14 (m, 2 H), 4.06 (dd, 1 H, J = 1.0 Hz, J = 2.5 Hz), 3.92 (d, 2 H, J = 4.5 Hz), 3.82–3.72 (m, 3 H), 3.67 (ddd, 1 H, J = 1.0 Hz, J = 6.0 Hz, J = 7.5 Hz), 3.56 (dd, 1 H, J = 6.0 Hz, J = 10.5 Hz), 3.46 (dd, 1 H, J = 6.5 Hz, J = 10.5 Hz), 1.49 and 1.43 (2s, 6 H), 1.42 (s, 9 H). MALDI-TOF MS: 836.7 ( $M^+$  + H). Anal. Calcd for C<sub>47</sub>H<sub>57</sub>N<sub>5</sub>O<sub>9</sub> (835.42): C, 67.53; N, 8.38; H, 6.87. Found: C, 67.54; N, 8.33; H, 6.82.

(4*R*)-2,2-Dimethyl-4-[1-(2',3',5'-tri-*O*-benzyl-α-D-ribofuranosylmethyl)-1*H*-tetrazol-5-yloxymethyl)]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (12c). Column chromatography with 3:1 cyclohexane–AcOEt afforded 12c (237 mg, 83%) as a white foam. [α]<sub>D</sub> = 49.2 (*c* 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 120 °C):  $\delta$  = 7.40–7.20 (m, 15 H, Ph), 4.75 and 4.62 (2 d, 2 H, *J* = 11.5 Hz, PhC*H*<sub>2</sub>), 4.68 and 4.62 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*<sub>2</sub>), 4.57 (dd, 1 H, *J* = 4.5 Hz, *J* = 10.5 Hz), 4.52–4.30 (m, 5 H), 4.48 (s, 2 H, PhC*H*<sub>2</sub>), 4.22–4.15 (m, 2 H), 4.12 (t, 1 H, *J* = 4.5 Hz), 4.00–3.88 (m, 2 H), 3.51 (d, 2 H, *J* = 5.5 Hz), 1.45 and 1.43 (2s, 6 H), 1.42 (s, 9 H). MALDI-TOF MS: 836.7 (M<sup>+</sup> + K). Anal. Calcd for C<sub>39</sub>H<sub>49</sub>N<sub>5</sub>O<sub>8</sub> (715.36): C, 65.44; N, 9.78; H, 6.90. Found: C, 65.44; N, 9.72; H, 6.93.

(4*R*)-2,2-Dimethyl-4-[1-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosylmethyl)-1*H*-tetrazol-5-yloxymethyl)]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (12d). Column chromatography with 3:1 cyclohexane–AcOEt afforded 12d (223 mg, 78%) as a white foam. [α]<sub>D</sub> = -3.4 (*c* 1.3, CHCl<sub>3</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 120 °C):  $\delta$  = 7.40–7.20 (m, 15 H, Ph), 4.62 and 4.53 (2 d, 2 H, *J* = 11.5 Hz, PhC*H*<sub>2</sub>), 4.58 (dd, 1 H, *J* = 3.2 Hz, *J* = 10.0 Hz), 4.56 (s, 2 H, PhC*H*<sub>2</sub>), 4.48 (s, 2 H, PhC*H*<sub>2</sub>), 4.44 (dd, 1 H, *J* = 7.0 Hz, *J* = 10.0 Hz), 4.34–4.18 (m, 4 H), 4.14–4.08 (m, 1 H), 4.02–3.94 (m, 4 H), 3.47 (dd, 1 H, *J* = 4.5 Hz, *J* = 10.5 Hz), 3.43 (dd, 1 H, *J* = 5.0 Hz, *J* = 10.5 Hz), 1.48 and 1.44 (2s, 6 H), 1.42 (s, 9 H). MALDI-TOF MS: 738.4 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>39</sub>H<sub>49</sub>N<sub>5</sub>O<sub>8</sub> (715.36): C, 65.44; N, 9.78; H, 6.90. Found: C, 65.41; N, 9.73; H, 6.92.

General Procedure for the Synthesis of Glycosylmethyl Tetrazole Serines 5 (Table 1). To a stirred solution of adduct 12 (167 mg, 0.20 mmol) in MeCN (2 mL) was added BiBr<sub>3</sub> (9 mg, 0.02 mmol) in one portion. The resulting mixture was stirred at room temperature for 6 h, diluted with saturated aqueous NaHCO<sub>3</sub> solution (5 mL), and extracted with AcOEt ( $3 \times 25$  mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give the corresponding crude *N*-Boc amino alcohol.

To a cooled (0 °C), stirred solution of the above crude *N*-Boc amino alcohol (159 mg,  $\sim$ 0.20 mmol) in acetone (6 mL) freshly

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prepared 1 M Jones reagent (0.60 mL, 0.60 mmol) was added in one portion. The mixture was allowed to warm to room temperature in 30 min, stirred at room temperature for an additional 1.5 h, and then diluted with *i*-PrOH (0.5 mL). The suspension was neutralized with saturated aqueous NaHCO<sub>3</sub>, diluted with AcOEt (80 mL), and then washed with brine ( $2 \times 5$  mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford the corresponding crude carboxylic acid derivative.

To a stirred, cooled (0 °C) solution of the above crude carboxylic acid in  $CH_2Cl_2$  (2.0 mL) was added an ethereal solution of  $CH_2N_2$  until a pale yellow color persisted. The solution was stirred for an additional 15 min at 0 °C and then dried under vacuum. The residue was eluted from a column of silica gel with the suitable elution system to give the corresponding glycosylmethyl tetrazole serine **5**.

(2S)-2-tert-Butoxycarbonylamino-3-[1-(2',3',4',6'-tetra-O-benzylα-D-galactopyranosylmethyl)-1H-tetrazol-5-yloxy]propionic Acid Methyl Ester (5a). Column chromatography with 2.5:1 cyclohexane-AcOEt afforded **5a** (102 mg, 62%) as a white foam.  $[\alpha]_D$ = 16.1 (c 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 7.44–7.14 (m, 20 H, Ph), 6.07 (d, 1 H,  $J_{2,\rm NH} = 7.5$  Hz, NH), 4.80–4.62 (m, 5 H, 2H-3, 3 CHPh), 4.62-4.46 (m, 4 H, H-2, 3 CHPh), 4.45-4.36 (m, 1 H, H-1'), 4.35 (s, 2 H,  $CH_2Ph$ ), 4.25 (d, 2 H, J = 8.0 Hz, 2H-1"), 4.16-4.09 (m, 1 H, H-5'), 4.02-3.94 (m, 2 H, H-2', H-4'), 3.76 (dd, 1 H,  $J_{2',3'} = 7.6$  Hz,  $J_{3',4'} = 2.7$  Hz, H-3'), 3.70–3.60 (m, 1 H, H-6'a), 3.68 (s, 3 H, CH<sub>3</sub>), 3.54 (dd, 1 H,  $J_{5',6'b} = 4.5$  Hz,  $J_{6'a,6'b} = 11.5$  Hz, H-6'b), 1.43 (s, 9 H, *t*-Bu). <sup>13</sup>C NMR:  $\delta = 169.5$ , 161.1, 155.3, 138.0 (2C), 137.7, 137.6, 128.6-127.4 (20C), 80.2, 75.3, 73.8, 73.5, 73.4, 73.3, 73.0, 72.9, 72.3, 70.5, 68.1, 53.1, 52.7, 43.6, 29.7, 28.3 (3C). MALDI-TOF MS: 846.7 (M<sup>+</sup> + Na). Anal. Calcd for C<sub>45</sub>H<sub>53</sub>N<sub>5</sub>O<sub>10</sub> (823.38): C, 65.60; N, 8.50; H, 6.48. Found: C, 65.62; N, 8.53; H, 6.41.

(2S)-2-tert-Butoxycarbonylamino-3-[1-(2',3',4',6'-tetra-O-benzyl- $\beta$ -D-galactopyranosylmethyl)-1*H*-tetrazol-5-yloxy]propionic Acid Methyl Ester (5b). Column chromatography with 3:1 cyclohexane-AcOEt afforded **5b** (99 mg, 60%) as a white foam.  $[\alpha]_{D}$ = 4.5 (c 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta$  = 7.45–7.10 (m, 20 H, Ph), 5.85 (d, 1 H,  $J_{2,\rm NH}$  = 8.5 Hz, NH), 5.02 and 4.74 (2 d, 2 H, J = 11.2 Hz, PhCH<sub>2</sub>), 4.90 and 4.52 (2 d, 2 H, J = 11.5 Hz, PhC $H_2$ ), 4.80–4.69 (m, 2 H, 2H-3), 4.76 and 4.66 (2 d, 2 H, J =11.8 Hz, PhCH<sub>2</sub>), 4.66-4.59 (m, 1 H, H-2), 4.42 and 4.36 (2 d, 2 H, J = 11.8 Hz, PhCH<sub>2</sub>), 4.32 (dd, 1 H,  $J_{1',1''a} = 2.8$  Hz,  $J_{1''a,1''b} =$ 14.1 Hz, H-1"a), 4.09 (dd, 1 H,  $J_{1',1''b} = 8.0$  Hz, H-1"b), 3.96 (dd, 1 H,  $J_{3',4'} = 2.6$  Hz,  $J_{4',5'} = 0.5$  Hz, H-4'), 3.80 (dd, 1 H,  $J_{1',2'} = 9.0$ Hz,  $J_{2',3'} = 9.5$  Hz, H-2'), 3.67 (dd, 1 H, H-3'), 3.65 (ddd, 1 H, H-1'), 3.60 (s, 3 H, CH<sub>3</sub>), 3.52-3.45 (m, 3 H, H-5', 2H-6'), 1.45 (s, 9 H, *t*-Bu). <sup>13</sup>C NMR:  $\delta = 169.4$ , 161.5, 155.1, 138.5, 138.0, 137.9, 137.8, 129.0-127.0 (20C), 84.6, 80.5, 77.4, 76.6, 75.7, 75.1, 74.6, 73.4, 72.1, 68.5, 53.2, 52.8, 47.0, 26.7, 28.3 (3C). MALDI-TOF MS: 824.2 ( $M^+$  + H). Anal. Calcd for  $C_{45}H_{53}N_5O_{10}$  (823.38): C, 65.60; N, 8.50; H, 6.48. Found: C, 65.62; N, 8.53; H, 6.41.

(2S)-2-tert-Butoxycarbonylamino-3-[1-(2',3',5'-tri-O-benzyl-α-Dribofuranosylmethyl)-1H-tetrazol-5-yloxy]propionic Acid Methyl Ester (5c). Column chromatography with 2:1 cyclohexane-AcOEt afforded **5c** (94 mg, 67%) as a white foam.  $[\alpha]_D = 44.9$  (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta = 7.40-7.20$  (m, 15 H, Ph), 5.63 (d, 1 H,  $J_{2,\rm NH}$  = 8.5 Hz, NH), 4.83 (d, 2 H, J = 3.0 Hz, 2H-3), 4.71 and 4.52 (2 d, 2 H, J = 11.5 Hz, PhCH<sub>2</sub>), 4.74-4.67 (m, 1 H, H-2), 4.67 and 4.61 (2 d, 2 H, J = 12.0 Hz, PhCH<sub>2</sub>), 4.50-4.34 (m, 6 H, 2H-1", H-1', H-4', PhC $H_2$ ), 4.22 (dd, 1 H,  $J_{1',2'} = 5.5$  Hz,  $J_{2',3'} = 5.3$  Hz, H-2'), 4.02 (dd, 1 H,  $J_{3',4'} = 3.5$  Hz, H-3'), 3.66 (s, 3 H, CH<sub>3</sub>), 3.52 (dd, 1 H,  $J_{4',5'a} = 4.5$  Hz,  $J_{5'a,5'b} = 10.5$  Hz, H-5'a), 3.47 (dd, 1 H,  $J_{4',5'b} = 4.0$  Hz, H-5'b), 1.41 (s, 9 H, t-Bu). <sup>13</sup>C NMR:  $\delta = 169.5, 161.5, 155.1, 137.8, 137.6, 137.5, 128.5 - 127.5$ (15C), 81.4, 80.5, 77.9, 77.6, 73.5, 72.9, 72.8, 72.3, 70.3, 53.2, 52.8, 46.4, 28.2 (4C). MALDI-TOF MS: 742.8 (M<sup>+</sup> + K). Anal. Calcd for C<sub>37</sub>H<sub>45</sub>N<sub>5</sub>O<sub>9</sub> (703.32): C, 63.14; N, 9.95; H, 6.44. Found: C, 63.17; N, 9.91; H, 6.45.

(2S)-2-tert-Butoxycarbonylamino-3-[1-(2',3',5'-tri-O-benzyl-β-Dribofuranosylmethyl)-1H-tetrazol-5-yloxy]propionic Acid Methyl Ester (5d). Column chromatography with 2:1 cyclohexane-AcOEt afforded **5d** (86 mg, 61%) as a white foam.  $[\alpha]_{D} = -38.5$  (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta = 7.50-7.10$  (m, 15 H, Ph), 5.83 (d, 1 H,  $J_{2,NH} = 8.5$  Hz, NH), 4.89 (dd, 1 H,  $J_{2,3a} = 2.8$  Hz,  $J_{3a,3b}$ = 10.3 Hz, H-3a), 4.62 (ddd, 1 H,  $J_{2,3b}$  = 3.4 Hz, H-2), 4.95 and 4.55 (2 d, 2 H, J = 11.5 Hz, PhCH<sub>2</sub>), 4.54 (dd, 1 H, H-3b), 4.45 (s, 2 H, PhC $H_2$ ), 4.38 and 4.20 (2 d, 2 H, J = 12.0 Hz, PhC $H_2$ ), 4.33–4.27 (m, 3 H, H-1', 2H-1"), 4.16 (ddd, 1 H,  $J_{3',4'} = 2.2$  Hz,  $J_{4',5'a} = 3.8$  Hz,  $J_{4',5'b} = 3.3$  Hz, H-4'), 3.84 (dd, 1 H,  $J_{1',2'} = 8.0$ Hz,  $J_{2',3'} = 5.0$  Hz, H-2'), 3.75 (s, 3 H, CH<sub>3</sub>), 3.63 (dd, 1 H, H-3'), 3.17 (dd, 1 H,  $J_{5'a,5'b} = 10.2$  Hz, H-5'a), 3.13 (dd, 1 H, H-5'b), 1.48 (s, 9 H, *t*-Bu). <sup>13</sup>C NMR:  $\delta$  = 169.6, 161.6, 155.3, 137.5 (3C), 128.5-127.6 (15C), 82.3, 80.4, 78.1, 78.0, 77.2, 73.3, 72.8, 71.8, 69.3, 53.0, 52.9, 45.6, 28.3 (4C). MALDI-TOF MS: 726.4 (M<sup>+</sup> + Na). Anal. Calcd for  $C_{37}H_{45}N_5O_9$  (703.32): C, 63.14; N, 9.95; H, 6.44. Found: C, 63.13; N, 9.94; H, 6.43.

(2S)-2-tert-Butoxycarbonylamino-3-[1-(β-D-galactopyranosylmethyl)-1H-tetrazol-5-yloxy]propionic Acid Methyl Ester (5b'). A vigorously stirred mixture of 5b (165 mg, 0.20 mmol), 20% palladium hydroxide on carbon (80 mg), and MeOH (4 mL) was degassed under vacuum and saturated with hydrogen (by an H2filled balloon) three times. The suspension was stirred at room temperature for 4 h under a slightly positive pressure of hydrogen (balloon) and then filtered off through a plug of cotton and washed thoroughly with MeOH (5 mL) and water (2 mL). The combined filtrates were concentrated to afford crude 5b' (88 mg, 95%) at least 90% pure as established by <sup>1</sup>H NMR analysis. <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta = 4.83 - 4.75$  (m, 2 H, 2H-3), 4.72-4.65 (m, 1 H, H-2), 4.51 (dd, 1 H,  $J_{1',1''a} = 3.5$  Hz,  $J_{1''a,1''b} = 14.0$  Hz, H-1''a), 4.31 (dd, 1 H,  $J_{1',1''b} = 7.5$  Hz, H-1"b), 3.85 (dd, 1 H,  $J_{3',4'} = 3.5$ Hz,  $J_{4',5'} = 0.5$  Hz, H-4'), 3.70–3.40 (m, 6 H, H-1', H-2', H-3', H-5', 2H-6'), 3.77 (s, 3 H, CH<sub>3</sub>), 1.45 (s, 9 H, t-Bu). <sup>13</sup>C NMR (CD<sub>3</sub>OD):  $\delta = 169.6, 161.1, 155.8, 78.8, 77.5, 74.7, 71.9, 69.2,$ 68.9, 61.1, 53.1, 51.9, 47.1, 27.4 (4C). MALDI-TOF MS: 464.8  $(M^+ + H)$ , 486.1  $(M^+ + Na)$ .

General Procedure for the Synthesis of Glycosylmethyl Tetrazole Cysteines 6 (Table 2). To a stirred mixture of glycosylmethyl tetrazole 4 (142 mg, 0.25 mmol),  $K_2CO_3$  (103 mg, 0.75 mmol), and anhydrous MeCN (2.5 mL) was added cysteine 13 (45 mg, 0.13 mmol) in one portion. The resulting mixture was stirred at room temperature for 2 h, and then a second portion of cysteine 13 (45 mg, 0.13 mmol) was added. The mixture was stirred for an additional 3 h and then concentrated. The resulting residue was eluted from a column of silica gel with the suitable elution system to give the corresponding glycosylmethyl tetrazole cysteine 6.

(2R)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-[1-(2',3',4',6'tetra-O-acetyl- $\alpha$ -D-galactopyranosylmethyl)-1*H*-tetrazol-5-ylsulfanyl)propionic Acid (6a). Column chromatography with 32.3:1 AcOEt-AcOH afforded 6a (174 mg, 92%) as a white amorphous solid.  $[\alpha]_D = 47.7$  (*c* 0.6, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta =$ 7.79-7.73 (m, 2 H, Ar), 7.64-7.55 (m, 2 H, Ar), 7.44-7.36 (m, 2 H, Ar), 7.35–7.28 (m, 2 H, Ar), 6.44 (d, 1 H,  $J_{2,\text{NH}} = 6.4$  Hz, NH), 5.45 (dd, 1 H, *J* = 3.0 Hz, *J* = 3.5 Hz, H-4'), 5.34–5.21 (m, 2 H, H-2', H-3'), 4.82-4.68 (m, 1 H, H-2), 4.66-4.57 (m, 1 H, H-1'), 4.57-4.43 (m, 2 H, 2H-1"), 4.43-4.27 (m, 4 H, FmocCH<sub>2</sub>, 2H-6'), 4.27-4.19 (m, 1 H, FmocCH), 3.97-3.77 (m, 3 H, 2H-3, H-5'), 2.15, 2.09, and 1.97 (3s, 12 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 171.3$ , 169.7 (2C), 169.6 (2C), 156.3, 154.1, 143.6 (2C), 141.3 (2C), 127.8 (2C), 127.1 (2C), 125.2 (2C), 120.0 (2C), 70.5, 68.6, 67.8, 67.5, 67.3, 66.3, 59.9, 47.0, 45.8, 36.0, 20.7 (2C), 20.6 (2C). MALDI-TOF MS: 778.4 (M<sup>+</sup> + Na). Anal. Calcd for  $C_{34}H_{37}N_5O_{13}S$ (755.21): C, 54.03; N, 9.27; H, 4.93; S, 4.24. Found: C, 54.01; N, 9.26; H, 4.94; S, 4.23.

(2*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-[1-(2',3',4',6'tetra-*O*-acetyl-β-D-galactopyranosylmethyl)-1*H*-tetrazol-5-ylsulfanyl)propionic Acid (6b). Column chromatography with 24:1 AcOEt–AcOH afforded 6b (170 mg, 90%) as a white amorphous solid. [α]<sub>D</sub> = 15.8 (*c* 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta$  = 7.80–7.73 (m, 2 H, Ar), 7.63–7.55 (m, 2 H, Ar), 7.45–7.35 (m, 2 H, Ar), 7.35–7.27 (m, 2 H, ar), 6.39 (d, 1 H, *J*<sub>2,NH</sub> = 6.5 Hz, NH), 5.40 (dd, 1 H, *J*<sub>3',4'</sub> = 3.0 Hz, *J*<sub>4',5'</sub> = 0.5 Hz, H-4'), 5.15 (dd, 1 H, *J*<sub>1',2'</sub> = 9.5 Hz, *J*<sub>2',3'</sub> = 9.8 Hz, H-2'), 5.05 (dd, 1 H, H-3'), 4.81–4.70 (m, 1 H, H-2), 4.50–4.26 (m, 4 H, 2H-1", FmocCH<sub>2</sub>), 4.22 (t, 1 H, *J* = 7.0 Hz, FmocCH), 4.04 (dd, 1 H, *J*<sub>5',6'a</sub> = 6.5 Hz, *J*<sub>6'a,6'b</sub> = 11.0 Hz, H-6'a), 3.98–3.80 (m, 3 H, H-3a, H-1', H-6'b), 3.79–3.61 (m, 2 H, H-3b, H-5'), 2.10, 2.00, and 1.90 (3s, 12 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta$  = 171.4, 171.0, 170.1, 170.0, 169.9, 156.2, 155.4, 143.6 (2c), 141.3 (2C), 127.8 (2C), 127.1 (2C), 125.1 (2C), 120.0 (2C), 76.2, 74.2, 71.4, 67.4, 67.2, 67.1, 61.3, 53.8, 48.7, 47.0, 35.7, 20.7, 20.6, 20.5 (2C). MALDI-TOF MS: 801.6 (M<sup>+</sup> + K). Anal. Calcd for C<sub>34</sub>H<sub>37</sub>N<sub>5</sub>O<sub>13</sub>S (755.21): C, 54.03; N, 9.27; H, 4.93; S, 4.24. Found: C, 54.03; N, 9.25; H, 4.91; S, 4.24.

(2R)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-[1-(2',3',5'-tri-O-acetyl- $\alpha$ -D-ribofuranosylmethyl)-1H-tetrazol-5-ylsulfanyl)propionic Acid (6c). Column chromatography with 19:1 AcOEt-AcOH afforded **6c** (155 mg, 91%) as a white amorphous solid.  $[\alpha]_D = 36.8$ (c 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR:  $\delta = 7.74 - 7.60$  (m, 2 H, Ar), 7.56-7.40 (m, 2 H, Ar), 7.37-7.20 (m, 2 H, Ar), 7.29-7.10 (m, 2 H, Ar), 6.42 (d, 1 H,  $J_{2,\text{NH}} = 7.5$  Hz, NH), 5.49 (dd, 1 H,  $J_{1',2'} = 5.0$  Hz,  $J_{2',3'} =$ 5.5 Hz, H-2'), 5.27 (dd, 1 H,  $J_{3',4'} = 5.5$  Hz, H-3'), 4.74 (ddd, 1 H,  $J_{2,3a} = 3.5$  Hz,  $J_{2,3b} = 6.5$  Hz, H-2), 4.59 (ddd, 1 H,  $J_{1',1"a} = 6.0$  Hz,  $J_{1',1"b} = 6.0$  Hz, H-1'), 4.46 (d, 2 H, 2H-1"), 4.42-4.28 (3 H, H-4', FmocCH<sub>2</sub>), 4.22-4.12 (m, 2 H, H-5'a, FmocCH), 4.07 (dd, 1 H, J<sub>4',5'a</sub> = 4.5 Hz,  $J_{5'a,5'b}$  = 8.5 Hz, H-5'b), 3.93 (dd, 1 H,  $J_{3a,3b}$  = 14.5 Hz, H-3a), 3.76 (dd, 1 H, H-3b), 2.11, 2.05, and 2.01 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 171.8, 170.8, 169.6, 169.5, 156.2, 154.6, 143.6, 143.5,$ 141.2, 141.1, 127.7 (2C), 127.1 (2C), 125.1 (2C), 120.0 (2C), 78.5, 77.2, 71.9, 71.1, 67.3, 63.2, 54.0, 47.3, 46.9, 35.8, 20.7, 20.5 (2C). MALDI-TOF MS: 684.6 (M<sup>+</sup> + H). Anal. Calcd for  $C_{31}H_{33}N_5O_{11}S$ (683.19): C, 54.46; N, 10.24; H, 4.87; S, 4.69. Found: C, 54.48; N, 10.23; H, 4.81; S, 4.64.

(2R)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-[1-(2',3',5'tri-O-acetyl- $\beta$ -D-ribofuranosylmethyl)-1H-tetrazol-5-ylsulfanyl)propionic Acid (6d). Column chromatography with 24:1 AcOEt-AcOH afforded **6d** (154 mg, 90%) as a white foam.  $[\alpha]_{D} = -17.4$  (c 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz):  $\delta = 7.77 - 7.68$  (m, 2 H, Ar), 7.65-7.55 (m, 2 H, Ar), 7.41-7.35 (m, 2 H, Ar), 7.30-7.25 (m, 2 H, Ar), 6.55 (d, 1 H,  $J_{2,\text{NH}} = 7.5$  Hz, NH), 5.05 (dd, 1 H,  $J_{2',3'} =$ 5.5 Hz,  $J_{3',4'} = 4.0$  Hz, H-3'), 4.96 (dd, 1 H,  $J_{1',2'} = 7.5$  Hz, H-2'), 4.73 (ddd, 1 H,  $J_{2,3a} = 3.5$  Hz,  $J_{2,3b} = 7.0$  Hz, H-2), 4.55 (dd, 1 H,  $J_{1',1''a} = 4.0$  Hz,  $J_{1''a,1''b} = 14.5$  Hz, H-1''a), 4.50 (dd, 1 H,  $J_{1',1''b} =$ 4.5 Hz, H-1"b), 4.40-4.30 (m, 3 H, H-1', FmocCH<sub>2</sub>), 4.25-4.10 (m, 3 H, H-4', H-5'a, FmocCH), 4.05 (dd, 1 H,  $J_{4',5'b} = 3.5$  Hz,  $J_{5'a,5'b} = 12.0$  Hz, H-5'b), 3.83 (dd, 1 H,  $J_{3a,3b} = 14.5$  Hz, H-3), 3.73 (dd, 1 H, H-3b), 1.99, 2.06, and 2.07 (3s, 9 H, CH<sub>3</sub>). <sup>13</sup>C NMR:  $\delta = 171.9, 170.9, 169.8 (2C), 156.3, 155.4, 143.6 (2C), 141.2 (2C),$ 127.7 (2C), 127.1 (2C), 125.2 (2C), 119.9 (2C), 80.6, 78.2, 71.4, 67.5, 63.2, 53.9, 48.1, 47.0, 35.6, 20.7, 20.5, 20.4. MALDI-TOF MS: 706.4 ( $M^+$  + Na). Anal. Calcd for  $C_{31}H_{33}N_5O_{11}S$  (683.19): C, 54.46; N, 10.24; H, 4.87; S, 4.69. Found: C, 54.44; N, 10.21; H, 4.87; S, 4.63.

**Dipetide (15).** To a cooled (0 °C), stirred solution of crude acid **14** (81 mg, ~0.10 mmol), L-phenylalanine ethyl ester hydrochloride (34 mg, 0.15 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (62 mg, 0.12 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added *N*,*N*-diisopropylethylamine (52  $\mu$ L, 0.30 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H<sub>2</sub>O (2 × 10 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give dipeptide **15** (79 mg, 80%) as a white foam. [ $\alpha$ ]<sub>D</sub> = 5.5 (*c* 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz) selected data:  $\delta$  = 7.40–7.00 (m, 25 H, Ar), 6.90 (bs, 1 H, NH), 5.60 (bs, 1 H, NH), 5.01 and 4.70 (2 d, 2 H, *J* = 11.5 Hz, PhCH<sub>2</sub>), 4.88 and 4.72 (2 d, 2 H, *J* = 12.0 Hz, PhCH<sub>2</sub>), 4.42 and 4.34 (2 d, 2 H, *J* = 11.8 Hz, PhCH<sub>2</sub>), 4.08 (q, 2 H, J = 7.0 Hz,  $CH_2CH_3$ ), 3.86 (dd, 1 H,  $J_{3,4} = 3.5$  Hz,  $J_{4,5} = 0.5$  Hz, H-4<sub>sug</sub>), 3.81 (dd, 1 H,  $J_{1,2} = 9.0$  Hz,  $J_{2,3} = 9.5$  Hz, H-2<sub>sug</sub>), 3.68 (ddd, 1 H,  $J_{1,1'a} = 1.5$  Hz,  $J_{1,1'b} = 2.0$  Hz, H-1<sub>sug</sub>), 3.62 (dd, 1 H, H-3<sub>sug</sub>), 3.52–3.46 (m, 3 H, H-5<sub>sug</sub>, 2H-6<sub>sug</sub>), 3.06 (dd, 1 H, J = 6.0 Hz, J = 14.5 Hz), 2.98 (dd, 1 H, J = 7.0 Hz, J = 14.5 Hz), 1.40 (s, 9 H, *t*-Bu), 1.18 (t, 3 H, J = 7.0 Hz,  $CH_2CH_3$ ). MALDI-TOF MS: 985.8 (M<sup>+</sup> + H). Anal. Calcd for C<sub>55</sub>H<sub>64</sub>N<sub>6</sub>O<sub>11</sub> (984.46): C, 67.06; N, 8.53; H, 6.55. Found: C, 67.03; N, 8.52; H, 6.58.

**Tripeptide** (16). To a cooled (0 °C), stirred solution of dipeptide 15 (79 mg, 0.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was slowly added a solution of TFA–CH<sub>2</sub>Cl<sub>2</sub> (0.50 mL–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, and then the solution was warmed to room temperature. After 30 min at room temperature, the solution was neutralized at 0 °C with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give the corresponding crude free amine (70 mg), which was used for the following reaction without any purification.

To a cooled (0 °C), stirred solution of the above crude amine (70 mg, ~0.08 mmol), *tert*-butoxycarbonyl-L-alanine (22 mg, 0.12 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (73 mg, 0.14 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added *N*,*N*-diisopropylethylamine (60  $\mu$ L, 0.35 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (10 mL) and

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brine (10 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and eluted from a column of silica gel with 1.5:1 cyclohexane–AcOEt to give tripeptide **16** (60 mg, 72% from **15**).  $[\alpha]_D = -14.8$  (*c* 0.7, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz) selected data:  $\delta = 7.40-7.00$  (m, 27 H, Ar, 2 NH), 5.08 (bs, 1 H, NH), 5.00 and 4.70 (2 d, 2 H, J = 11.5 Hz, PhCH<sub>2</sub>), 4.80 and 4.56 (2 d, 2 H, J = 11.0 Hz, PhCH<sub>2</sub>), 4.09 (q, 2 H, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.98 (dd, 1 H,  $J_{3,4} = 3.5$  Hz,  $J_{4,5} = 0.5$  Hz, H-4<sub>sug</sub>), 3.80 (dd, 1 H,  $J_{1,2} = 9.0$  Hz,  $J_{2,3} = 9.5$  Hz, H-2<sub>sug</sub>), 3.73–3.64 (m, 2 H, H-1<sub>sug</sub>, H-3<sub>sug</sub>), 3.52–3.40 (m, 3 H, H-5s, 2H-6s), 3.10 (dd, 1 H, J = 6.0 Hz, J = 14.5 Hz), 3.00 (dd, 1 H, J = 7.0 Hz, CH<sub>3</sub>), 1.17 (t, 3 H, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>). MALDI-TOF MS: 1056.9 (M<sup>+</sup> + H). Anal. Calcd for C<sub>58</sub>H<sub>69</sub>N<sub>7</sub>O<sub>12</sub> (1055.50): C, 65.95; N, 9.28; H, 6.58. Found: C, 65.93; N, 9.23; H, 6.56.

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**Supporting Information Available:** General experimental methods and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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