Stereospecific Solution- and Solid-Phase Glycosylations. Synthesis of β-Linked Saccharides and Construction of Disaccharide Libraries Using Phenylsulfenyl 2-Deoxy-2-Trifluoroacetamido Glycopyranosides as Glycosyl Donors[1]

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An efficient strategy to construct β-*O*-2-amino-2-deoxyglycopyranosidic linkages using glycosyl sulfoxides is demonstrated. Phenylsulfenyl 2-deoxy-2-trifluoroacetamido glycopyranosides were found to be reactive glycosyl donors in both solid- and solution-phase glycosylations, affording the corresponding β-glycosides exclusively and in high yield. The trifluoroacetamido group was removed under mild conditions, allowing orthogonal derivatization of multiple protected amino groups on an oligosaccharide or glycoconjugate. On the basis of the results with these glycosyl donors, a solid-phase β-linked disaccharide library was constructed. The scope and flexibility of this approach will be discussed.

Carbohydrates and glycoconjugates play key roles in crucial biological processes, such as cellular trafficking and cell surface recognition,[2] and have been identified as medicinally important antitumor and antibiotic agents.[3] As part of the current investigation of naturally occurring or novel carbohydrate motifs, rapid exploration of oligosaccharide molecular diversity requires flexible solution- and solid-phase combinatorial strategies.[4] The glycosylation methods used in such endeavors should proceed in high yield, be predictably stereospecific in the construction of new glycosidic linkages, and utilize building blocks that permit further introduction of chemical diversity around the oligosaccharide core.[5]

Among the various available glycosylation methods, the sulfoxide glycosylation method has attracted attention because of mild reaction conditions, high reactivity of its activated glycosylating agent, generally good to excellent anomeric stereocontrol, and compatibility with both solution- and solid-phase glycosylations.[6,7] In our attempts to expand the scope of the sulfoxide glycosylation method, we examined the stereospecific construction of β-glycosides using 2-amino-2-deoxy monosaccharide donors, based on saccharides such as glucosamine and galactosamine. These amino sugars are ubiquitously present in naturally occurring molecules such as bacterial lipid A and cell wall peptidoglycan,[8] O- and N-linked glycoproteins,[9] proteoglycans,[10] sialyl-Lewis oligosaccharides,[11] antitumor agents and antibiotics.[12] Unfortunately, solid-phase construction of β-2-amino-2-deoxy glycosides remains a challenge for the various existing glycosylation methods.[13] For such glycosides, amino protective groups that ensure high β selectivity tend to decrease the reactivity of the activated glycosyl donor dramatically, leading to sluggish reactions and disappointingly poor yields. Furthermore, removal of the amino protective group may not be compatible with solid-phase supports and often lead to incomplete deprotection

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(13) Danishefsky and co-workers have made important contributions in this area based on the glycal technology. For example, reducing β-2-acetamido-1-amino-2-deoxyglucose derivatives were generated on solid phase using iodosulfonamidation of polymer-bound of glucals as a key step. The anomeric amino group was then coupled to diverse peptides using IIDQ as a coupling reagent.: (a) Roberge, J. Y.; Beebe, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 3915−3927. More recently, these researchers developed a solid-phase sequence where a solid-phase bound glycal was converted in two steps to the ethylsulfanyl 2-phenylsulfonamido glycosyl donor, which was then coupled to different glycosyl acceptors using methyl triflate as a promoter. In this study the oligosaccharides were cleaved off the resin as the N-protected sulfonamides: (b) Zheng, C., Seeberger, P. H., Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 786−789.

10.1021/jo9903499 CCC: $18.00
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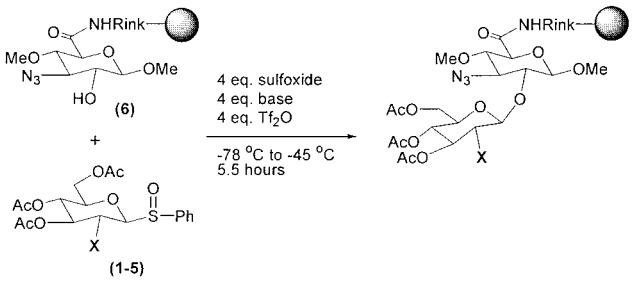
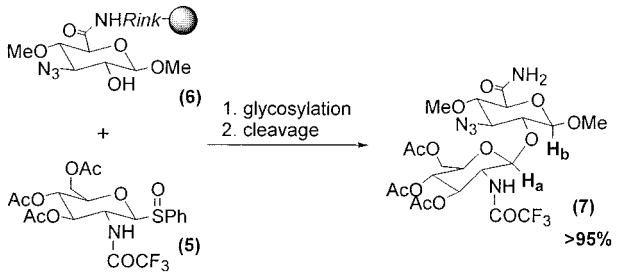


sulfoxide donor	conversion (LSD integration)
(**1**), X = NHFmoc	2%
(**2**), X = $NHCO_2CH_2CH{=}CH_2$ (NHAlloc)	3%
(**3**), X = NPhth	11%
(**4**), X = $NPhthCl_4$	31%
(**5**), X = $NHCOCF_3$ (NHTFAc)	>95%

Figure 1. Model solid-phase glycosylation using phenylsulfenyl 2-deoxy-2-*N*-protected-3,4,6-tri-*O*-acetylglucopyranosides **1**−**5** as glycosyl donors. The glycosylation conversion yield was calculated by cleaving the product from the resin and analyzing the mixture by LC-MS.

and product decomposition.[14] In summary, a method that allows both stereochemical formation of β-2-amino-2-deoxy glycosidic linkages and subsequent exploration of chemical diversity around the 2-amino group of the donor sugar has not been reported.

In our studies we investigated solution- and solid-phase glycosylations using as glycosyl donors phenylsulfenyl 2-amino-2-deoxy glycopyranosides **1**−**5**, containing different removable amino protective groups (Figure 1).[15] Solution-phase glycosylations using 2-propanol and *N*,*N*-diethyldeoxycholamide as acceptors showed that donors **1**−**5** afforded high yields (80+%) of the corresponding β-glycosides exclusively (results not shown). However, solid-phase glycosylations using donors **1**−**5** and the glucuronic acid acceptor **6**[16] immobilized on Rink Amide resin produced variable conversion yields of the respective disaccharide products. While donors **1**−**4** afforded poor to modest disaccharide yields, the trifluoroacetamido (TFAc) donor sulfoxide **5** showed a nearly quantitative conversion yield (Figure 1).[17] ^{1}H NMR analysis of the cleaved disaccharide **7** confirmed that only the β-glycoside was formed in the reaction (Figure 2). Subsequent studies indicated that the TFAc group could be easily removed in solution and solid phases using LiOH in THF−MeOH solution. These mild conditions allow for the orthogonal deprotection of the trifluoroacetamido group in the presence of other N-containing groups and open the possibility of orthogonal deprotection and derivatization of amino groups in oligosaccharide libraries.[18] As additional attractive features of donor **5**, this crystalline solid can be prepared in multigram scale in 6 steps from commercially available glucosamine hydrochloride (Scheme 1) and is indefinitely stable at room temperature.



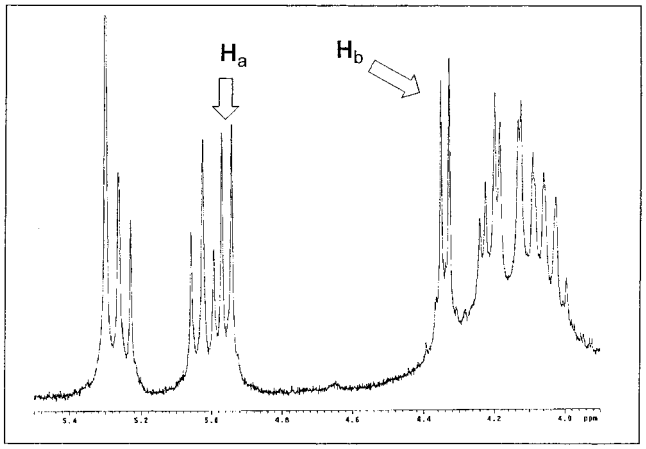


Figure 2. Detail of the ^{1}H NMR spectrum of cleaved **7**. The large coupling constant for the anomeric proton of the donor ring (H_a, J = 8.4 Hz) establishes the new glycosidic linkage as β.

To explore the flexibility of phenylsulfenyl 2-deoxy-2-trifluoroacetamido glycopyranosides as building blocks in the synthesis of solid-phase carbohydrate libraries, disaccharide **7** was submitted to the reaction sequence illustrated in Scheme 2. Upon removal of all base-sensitive groups, the free amino group in **13** was selectively derivatized as the corresponding amide **14** using HATU as a coupling agent,[19] and the free hydroxyl groups were protected as acetate groups to yield **15**. The azido group on the acceptor ring was then reduced to the free amine and converted to the urea **16**. The identity and purity of each reaction product was confirmed by cleaving the product off the resin and analyzing it by HPLC, LC-MS, and NMR.

Following the chemistry described in Scheme 2, a 48-member combinatorial library was designed around disaccharide **7**, using 6 different isocyanates and 8 different carboxylic acids as elements of diversity (Figure

(14) For an extensive review on recent progress in N-protection for amino sugar synthesis, see: Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann.* **1997**, 791−802.

(15) In the present article we only report on glucosamine-derived glycosyl donors. However, the use of 2-deoxy-2-trifluoroacetamido glycosyl sulfoxides as donors is general in nature, affording comparable results in the galactosamine and fucosamine series: Silva, D. J.; Sofia, M. J. Unpublished results.

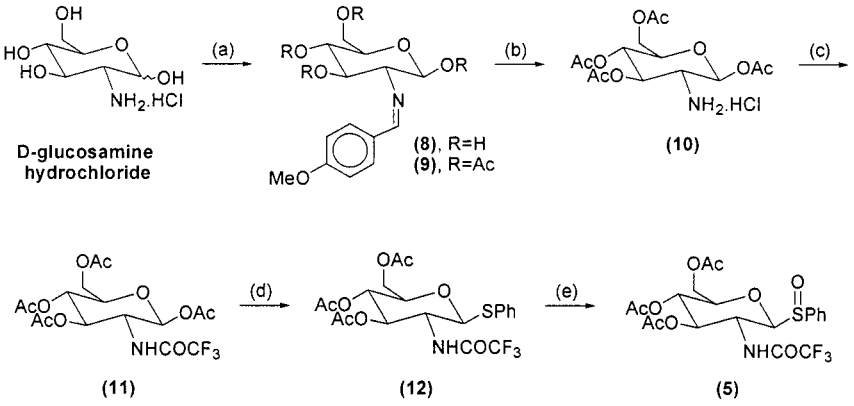
(16) Methyl 3-azido-3-deoxy-4-*O*-methyl-β-D-glucopyranosiduronic acid was prepared in 10 steps from 1,2:5,6-di-*O*-isopropylidene-D-allofuranose: Jain, R. K., Sofia, M. J. Unpublished results.

(17) We found that donor concentration had a dramatic effect on the yields of solid-phase sulfoxide glycosylations, with higher donor concentrations leading to higher glycosylation yields. For donor **5**, best results were obtained with concentrations in the range of 0.06−0.3 M.

(18) Due to the different deprotection conditions for the nitrogen-containing N_3, FmocNH, and NHTFAc groups, it is possible to conceive a deprotection−derivatization sequence for a library containing these three groups and consequently at least three diversity points. The Fmoc and TFAc groups could be deprotected under different basic conditions: mild treatment with piperidine in DMF would remove the Fmoc group exclusively and a posterior treatment with LiOH in MeOH−THF would cleanly remove the trifluoroacetamido group. The azido group could be independently unmasked under reducing conditions. This strategy is being currently pursued and will be reported in due time: Silva, D. J.; Sofia, M. J. Unpublished results.

(19) Under the HATU coupling conditions used for amide formation, ester formation by the uncapped hydroxyl groups was virtually absent. In the cases where trace amounts of esters were indeed observed, they were selectively cleaved by posterior treatment with LiOH in THF−MeOH solution.

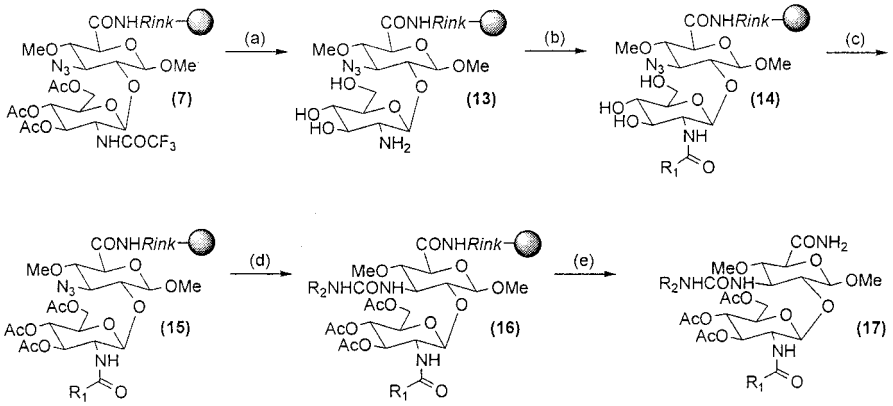
Scheme 1[a]



[a] Key: (a) (i) *p*-$OMeC_6H_4CHO$, 1M NaOH (72%), (ii) Ac_2O, pyridine, DMAP (77%); (b) 5N HCl, acetone (100%); (c) $(CF_3CO)_2O$, pyridine, CH_2Cl_2 (100%); (d) PhSH, $BF_3.OEt_2$, CH_2Cl_2 (92%); (e) mCPBA, CH_2Cl_2, -78 °C to -25 °C (95%).

[a] Key: (a) (i) *p*-$OMeC_6H_4CHO$, 1M NaOH (72%), (ii) Ac_2O, pyridine, DMAP (77%); (b) 5N HCl, acetone (100%); (c) $(CF_3CO)_2O$, pyridine, CH_2Cl_2 (100%); (d) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (92%); (e) mCPBA, CH_2Cl_2, −78 °C to −25 °C (95%).

Scheme 2[a]



[a] Key: (a) LiOH, MeOH, THF; (b) R_1COOH, HATU, DIPEA, DMF; (c) Ac_2O, pyridine, DMAP, toluene, CH_2Cl_2; (d) (i) PMe_3, THF, EtOH, H_2O, (ii) R_2-NCO, toluene; (e) 20% TFA-CH_2Cl_2.

[a] Key: (a) LiOH, MeOH, THF; (b) R_1COOH, HATU, DIPEA, DMF; (c) Ac_2O, pyridine, DMAP, toluene, CH_2Cl_2; (d) (i) PMe_3, THF, EtOH, H_2O, (ii) R_2-NCO, toluene; (e) 20% TFA-CH_2Cl_2.

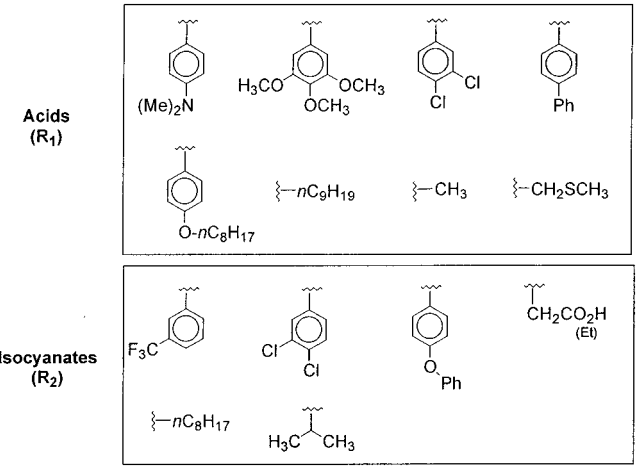


Figure 3. Building blocks used in the construction of the solid-phase disaccharide library. R_1 and R_2 groups are the same as those shown in Scheme 2.

3). After cleavage using a TFA−CH_2Cl_2 mixture, the library products were characterized by LC-MS. The desired derivatized disaccharides were all obtained as the major products in greater than 85% purity.

In summary, we have described the use of the phenylsulfenyl 2-deoxy-2-trifluoroacetamido glycopyranosides as donors in solution- and solid-phase glycosylations. To our knowledge, this is the first instance where an easily deprotectable 2-amino-2-deoxy glycopyranosyl donor was shown to afford high yields of β-glycosides on a solid-phase support. Since the trifluoroacetamido group can be deprotected under mild conditions, this method allows for orthogonal deprotection and derivatization of amino groups in an oligosaccharide or glycoconjugate. The increased synthetic flexibility provided by this method expands the range of derivatized oligosaccharides accessible by solution- and solid-phase methods, facilitating the exploration of diversity around an oligosaccharide core toward the discovery of new biologically active saccharides.

Experimental Section

General Methods. All moisture-sensitive reactions were carried out under an atmosphere of nitrogen gas in oven-dried glassware. THF was freshly distilled from sodium−benzophe-

none ketyl; ethyl acetate, toluene, and CH_2Cl_2 were freshly distilled from CaH_2. Amine-free DMF and 20% piperidine in DMF were purchased from PerSeptive Systems. Rink Amide polystyrene resin (FmocNH capped, 0.46 mmol/g) was purchased from NovaBiochem. On-bead product quality control was performed by Kaiser tests, % N determination, and IR analyses. Products were cleaved off resin by treatment with 20% TFA−CH_2Cl_2 for 30 min and analyzed by solution-phase ^1H and ^{13}C NMR spectroscopy and liquid chromatography (LC) with light-scattering (LSD) and mass spectrometry (MS) detectors. Conversion yields and purities were estimated by integrating the LSD traces. ^1H NMR spectra were obtained at 300 MHz, and ^{13}C NMR spectra were obtained at 75.4 MHz.

Immobilization of Methyl 3-Azido-3-deoxy-4-*O*-methyl-β-D-glucopyranosiduronic Acid on Rink Amide Resin (6). Rink Amide polystyrene resin (500 mg, 0.23 mmol) was treated with 4 mL of a 20% solution of piperidine in DMF for 30 min. The resin was washed with DMF (3×), THF (3×), and CH_2Cl_2 (3×). Removal of the Fmoc group was confirmed by a positive Kaiser test of the resin. To the resin were sequentially added amine-free DMF (4 mL), methyl 3-azido-3-deoxy-4-*O*-methyl-β-D-glucopyranosiduronic acid (114 mg, 0.46 mmol), HATU (174 mg, 0.46 mmol), and DIPEA (distilled from CaH_2, 80 μL, 0.46 mmol). The reaction mixture was stirred overnight. The resin was washed with DMF (3×), THF (3×), and CH_2Cl_2 (3×) and dried under high vacuum. Complete derivatization of the resin amino groups was confirmed by a negative Kaiser test. IR (bead, cm^{-1}): 2191, 2104. Anal. Calcd for $C_8H_{14}N_4O_5$ (on bead): N, 2.58. Found: N, 2.54 (98% loading). A sample of the resin was cleaved with 20% TFA−CH_2Cl_2 for analytical analysis. ES for $C_8H_{14}N_4O_5$: [MH] calcd *m*/*z* 247, found 247. ^1H NMR ($CDCl_3$): 6.64 (s, br, 1H), 6.32 (s, br, 1H), 5.14 (d, J = 5.1 Hz, 1H), 3.98 (d, J = 7.5 Hz, 1H), 3.50 (d, J = 9.0 Hz, 1H), 3.28 (s, br, 6H), 3.19 (t, J = 9.6 Hz, 1H), 3.06−2.94 (m, 2H). ^{13}C NMR ($CDCl_3$): 169.9, 103.3, 80.2, 74.5, 71.2, 67.8, 59.7, 56.6.

Typical Glycosylation Procedure. Rink Amide resin (20 mg; 9 μmol) containing the glycosyl acceptor was dried under high vacuum and kept under argon. To the resin was added a solution of the glycosyl donor **1**−**5** (4 equiv; concentration of 0.14 M) and 2,6-di-*tert*-butyl-4-methylpyridine (4.5 mg; 2 equiv) in a 5:1 mixture of methylene chloride and ethyl acetate (total volume of 300 μL). The mixture was stirred at room temperature for 5 min and cooled to −78 °C. Trifluoromethanesulfonic anhydride (7 μL; 4 equiv) was slowly added and the system was kept at −70 °C for 1 h. The temperature was slowly raised to −45 °C and kept constant for 5.5 h. The reaction was quenched with 100 μL of a 2:1 mixture of methanol and DIPEA at −45 °C. The reaction mixture was allowed to warm to room temperature and the resin was washed with DMF (3×), THF (2×), CH_3OH (2×), and CH_2Cl_2 (2×). Data for **7**: IR (bead, cm^{-1}) 2193, 2105. Anal. Calcd for $C_{22}H_{29}F_3N_5O_{13}$ (on bead): N, 2.71. Found: N, 2.69 (99% loading). For analytical purposes, a sample of **7** was cleaved with 20% TFA−CH_2Cl_2. LC-MS for the cleaved material is reproduced in Figure 4 (Supporting Information). ES for $C_{22}H_{30}F_3N_5O_{13}$: [MH] calcd *m*/*z* 630, found 630. ^1H NMR ($CDCl_3$): 9.06 (d, J = 9 Hz, 0.8H), 6.75 (s, br, 1H), 6.28 (s, br, 1H), 5.26 (t, J = 10.2 Hz, 1H), 5.03 (t, J = 9.9 Hz, 1H), 4.96 (d, J = 8.4 Hz, 1H), 4.34 (d, J = 7.2 Hz, 1H), 4.20 (dd, J = 12.6 Hz, 5.1 Hz, 1H), 4.11 (dd, J = 12.6 Hz, 2.4 Hz, 1H), 4.04 (m, 1H), 3.80−3.6 (m, 3H), 3.51 (s, 3H), 3.49 (s, 3H), 3.45−3.40 (m, 1H), 3.30 (q, J = 7.8 Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$): 170.6, 170.4, 170.2, 169.3, 155.0 (J = 38 Hz), 113.0 (J = 288 Hz), 102.6, 100.4, 81.2, 78.9, 74.6, 72.0, 71.7, 68.4, 66.8, 62.0, 60.3, 57.3, 54.4, 20.7, 20.5, 20.4.

Removal of Base-Sensitive Groups (13). The glycosylated resin **7** (1.0 g) was treated with 16 mL of 0.5 M LiOH in 1:1 THF−MeOH overnight. The resin was drained and washed with 1:1 THF−MeOH (3×), THF (3×), and CH_2Cl_2 (3×). As expected, the resin gave a strongly positive Kaiser test. Anal. Calcd for $C_{14}H_{25}N_5O_9$ (on bead): N, 3.22. Found: N, 3.20 (99% loading).

Design of Library. Derivatized resin **13** (20 mg; 9 μmol) was added to each of 48 Irori MicroKans containing radio frequency tags. The MicroKans were then sealed, drained, dried under vacuum, and scanned into the Irori combinatorial chemistry software through an Irori AccuTag 100 scanning station.

Formation of Amide Groups (14). The cans containing **13** were sorted into 8 different containers, each corresponding to a different carboxylic acid. To each container were added in sequence 9 mL of DMF, 0.225 mmol of R_1COOH, 0.225 mmol of HATU (85 mg), and 0.225 mmol of DIPEA (40 μL). The containers were shaken overnight at room temperature. The supernatants were drained, and the cans were washed with DMF (2×), MeOH (2×), THF (2×), and CH_2Cl_2 (2×).

Per-*O*-Acetylation (15). The MicroKans were combined and treated with 30 mL of CH_2Cl_2, 30 mL of toluene, 9 mL of Ac_2O, 9 mL of pyridine, and 30 mg of DMAP for 3 h at room temperature. The supernatant was drained, and the cans were washed with CH_2Cl_2 (4×) and THF (2×).

Data for R_1 = 4-phenyl-benzoyl: IR (bead, cm^{-1}) 2189, 2105. Anal. Calcd for $C_{33}H_{39}N_5O_{13}$ (on bead): N, 2.60. Found: N, 2.50 (96% loading). For analytical purposes, a sample of the resin was cleaved with 20% TFA−CH_2Cl_2. ES for $C_{33}H_{39}N_5O_{13}$: [MH] calcd *m*/*z* 714, found 714. ^1H NMR ($CDCl_3$−DMSO-d_6): 8.56 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.73 (two sets of t, J_{app} = 8.4 Hz, 4H), 7.59 (s, br, 0.8H), 7.50 (t, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 7.34 (s, br, 0.8H), 5.34 (t, J = 9.6 Hz, 1H), 5.10 (d, J = 8.7 Hz, 1H), 5.00 (t, J = 9.9 Hz, 1H), 4.45 (d, J = 7.5 Hz, 1H), 4.26 (dd, J = 12 Hz, 4.5 Hz, 1H), 4.14−4.10 (m, 2H), 3.85−3.74 (m, 3H), 3.59 (t, J = 9.6 Hz, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 3.29 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$−DMSO-d_6): 169.7, 169.4, 169.2, 168.9, 166.2, 142.7, 139.2, 133.3, 128.7, 127.7, 127.5, 126.7, 126.2, 102.0, 100.1, 79.9, 78.8, 74.2, 72.7, 71.0, 68.4, 66.2, 61.9, 59.2, 56.4, 54.1, 20.4, 20.3, 20.2.

Reduction of Azide Groups and Urea Formation (17). The MicroKans were combined and treated with 7.5 mL of THF, 30 mL of EtOH, 7 mL of water, and 22.5 mL of a 1.0 M solution of PMe_3 in THF. The MicroKans were shaken for 4 h at room temperature. The supernatant was drained, and the cans were washed with THF (2×), DMF (2×), and CH_2Cl_2 (3×) and dried under high vacuum overnight. The resin yielded a strong Kaiser test. Data for R_1 = 4-phenylbenzoyl: IR (bead, cm^{-1}) no absorption in the 2200−2000 cm^{-1}. Anal. Calcd for $C_{33}H_{41}N_3O_{13}$ (on bead): N, 1.60. Found: N, 1.57 (98% loading). For analytical purposes, a sample of the resin was cleaved with 20% TFA−CH_2Cl_2. ES for $C_{33}H_{41}N_3O_{13}$: [MH] calcd *m*/*z* 688, found 688.

The MicroKans were sorted into 6 different containers. To each container were added in sequence 12 mL of toluene, 6 mmol of R_2NCO, and 0.2 mL of DIPEA. The reaction vessels were shaken for 2 h. The supernatant was drained, and the cans were washed with DMF (3×), MeOH (2×), and CH_2Cl_2 (4×). The cans were dried under vacuum and kept under argon. Data for R_1 = 4-phenylbenzoyl and R_2 = 3-(trifluoromethyl)phenyl: Anal. Calcd for $C_{41}H_{45}F_3N_4O_{14}$ (on bead): N, 1.99. Found: N, 1.90 (95% loading). For analytical purposes, a sample of the resin was cleaved with 20% TFA−CH_2Cl_2. ES for $C_{41}H_{45}F_3N_4O_{14}$: [MH] calcd *m*/*z* 875, found 875. ^1H NMR (DMSO-d_6): 8.47 (d, J = 9.6 Hz, 1H), 7.9−7.1 (m, 15H), 5.28 (t, J = 9.9 Hz, 1H), 5.14 (d, J = 8.4 Hz, 1H), 4.98 (t, J = 9.9 Hz, 1H), 4.45 (d, J = 6.3 Hz, 1H), 4.27 (dd, J = 12.6 Hz, 4.5 Hz, 1H), 4.12 (d, br, J_{app} = 11.1 Hz, 1H), 4.04 (q, J = 9.9 Hz, 1H), 3.9−3.6 (m, 5H), 3.5−3.3 (m, 2H), 3.44 (s, 3H), 3.25 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (DMSO-d_6): 170.5, 170.2, 170.0, 169.7, 166.5, 154.6, 142.7, 141.2, 139.3, 133.2, 129.7, 129.2, 128.2, 128.0, 127.0, 126.6, 126.3, 121.2, 117.4, 113.7, 103.0, 99.7, 77.9, 78.3, 75.2, 73.4, 71.1, 68.7, 62.1, 59.0, 56.5, 54.7, 54.2, 20.7, 20.6, 20.5.

Supporting Information Available: Text and figures giving experimental procedures and characterization data for glycosylation studies and solid-phase derivatization studies (10 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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