Generation of C-Glycoside Peptide Ligands for Cell Surface Carbohydrate Receptors Using a Four-Component Condensation on Solid Support

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Introduction

Interest in cell surface carbohydrates[1] has steadily increased over the past two decades as a result of the cloning of numerous glycosylated receptors. These oligosaccharides are known to play important roles in adhesion events such as the recruitment of leukocytes in inflammation,[2] metastasis,[3] and recognition of cells by viral[4] and bacterial pathogens.[5] The wide variety of biological functions involving carbohydrates makes inhibitors for the receptors that bind them attractive therapeutic targets. In order to explore therapeutics aimed at the general class of cell surface carbohydrate receptors, we have applied the concepts of combinatorial chemistry to carbohydrate drug discovery.[6] Typical of combinatorial chemistry approaches, a rapid and flexible strategy that generates defined compounds with variability at different sites in the final structure would be advantageous.

This note describes a combinatorial approach to the synthesis of glycomimetic candidiates that bear a structural resemblance to cell surface carbohydrates. This approach uses the Ugi[7] four-component condensation,[8] performed on a solid support, to cluster C-glycosides and other functionalities around a predictable core structure. This solid phase methodology is demonstrated first through the synthesis of eight fully deprotected monosaccharides and disaccharides that can be targeted toward a variety of cell surface carbohydrate receptors, highlighting the generality of the strategy. Second, with this methodology in place, a 96-well, 192-compound[9] focused library of glycomimetics targeting the receptors of sialyl Lewis x (NeuAcα2,3Galβ1,4(Fucα1,3)GlcNAc, compound **1**, Figure 1) is discussed.

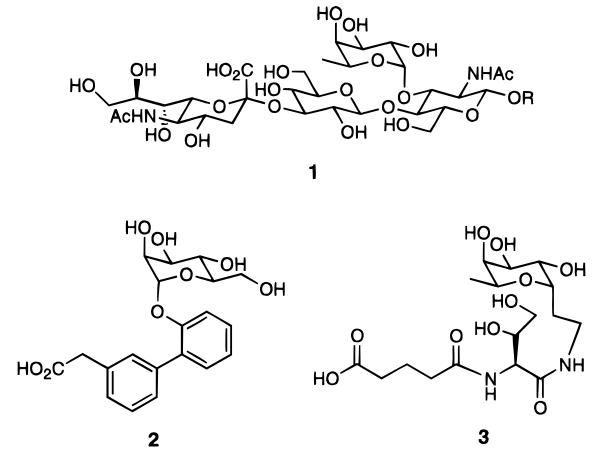

Figure 1.

Background

Cell surface carbohydrates themselves make poor drug candidates due to their biological instability in the gut and poor binding affinities to their receptors. Approaches to circumvent these problems have included multivalent ligands,[10] the use of alternate frameworks to appropriately position individual sugars,[11] and the use of C-glycosides.[12] Our approach utilizes C-glycosides as the carbohydrate-based component. These compounds are resistant to both chemical and enzymatic hydrolysis and do not stray from their O-glycosidic counterparts either in binding affinity to natural ligands or in solution conformation.[13]

Experimental studies on the energetics of carbohydrate−receptor binding has shed light on the contributing factors involved in this important binding event.[14] One hypothesis involving carbohydrate−receptor binding concludes that sugar hydroxyl groups contribute little to the overall binding energy due to favorable solvation of the ligand by water in solution and that hydrophobic interactions can drive complexation. Thus, ligands presenting a mix of mono or oligo C-saccharides that are required for binding along with other nonpolar functionalities may yield more potent sugar ligands. Glycomimetics which have a peptide or non-peptide core structure serving as a scaffold to display the external sugars have recently been reported and have biological activities similar to that of their target blood group determinants.[10c,f] As an example, compounds **2** and **3** (Figure 1), designed to mimic the biologically relevant oligosaccharide sialyl Lewis x **1**, have been reported and are inhibitors of

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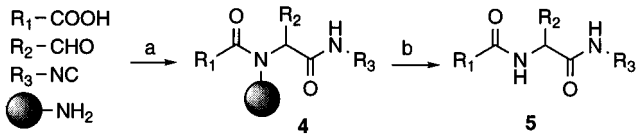


Figure 2. Reagents and conditions: (a) (i) MeOH/CH_2Cl_2, rt, 24 h; (ii) wash polymer; (b) 20% TFA in CH_2Cl_2.

E-selectin with relative binding potencies of 1.5 and 0.8, respectively, in comparison to the IC_{50} of 1 mM for **5**.

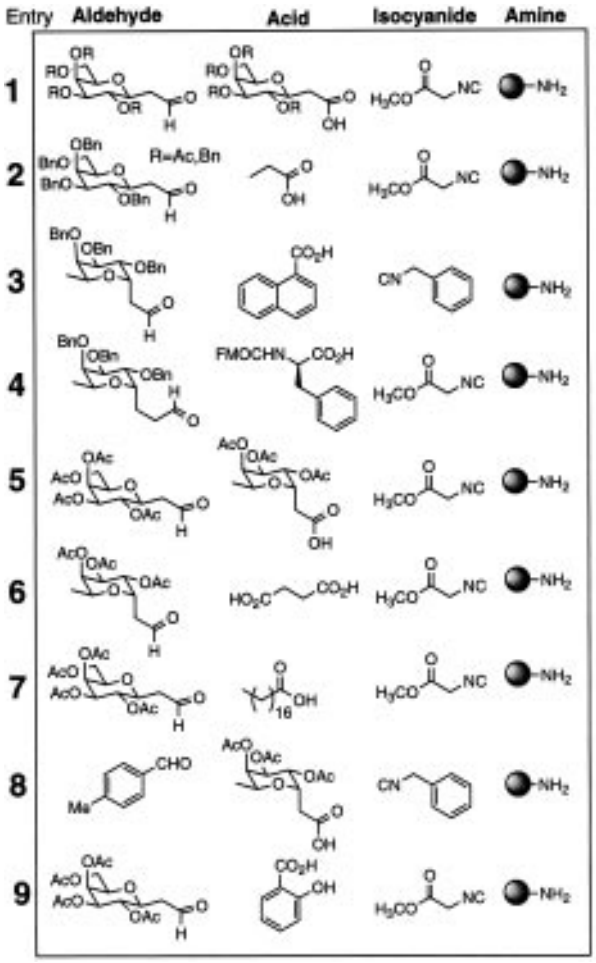
The Ugi reaction is a multiple component condensation (MCC) reaction that combines an aldehyde, carboxylic acid, isocyanide, and amine, resulting in α-acylamino amide **4** (Figure 2). It allows the rapid generation of a large number of compounds based on a common core structure and displaying varied functionality. Research in our laboratories has led to the adaptation of this reaction to solid-support through the utilization of Rink[15] resin as the amine component, yielding acylamino amide **5** upon removal from the polymer.[16] By employing solid support, the use of excess reagents to drive reactions to completion and the elimination of chromatography allow for the rapid generation of pure compounds in moderate yield in a 96-well plate format easily adaptable to high throughput screening.

Results

Prior to performing a focused library of sialyl Lewis x glycomimetics, a more general approach was taken to investigate the behavior of protected carbohydrate components in the Ugi reaction. This allowed for a general understanding of expected yields, purities, and diastereoselectivities that one would expect when moving to a larger library format. One main issue to address was the protection−deprotection scheme for the carbohydrates that would provide compounds of reasonable purity and acceptable yield, eliminating the need for chromatography.

Table 1 shows examples of the components that were used in the preliminary Ugi reactions. The C-glycoside components used were synthesized through standard methods.[17] The corresponding acids were obtained via a buffered sodium chlorite oxidation of the aldehyde precursors.[18] Products of the reactions in Table 1 can be identified by referring to the α-acylamino amide core in Figure 1 and enlisting the appropriate components in each entry. For example, the product for entry 4, tripeptide **7** (Figure 3), is derived from a reaction with Rink resin, methyl isocyanoacetate (MICA), *N*-FMOC-L-phenylalanine, and the fucose aldehyde **6**.[19] This is a one-step synthesis of a tripeptide with a C-glycosylated serine analog as the center amino acid.[20]

Table 1. Components for Solid Phase Reactions[a]



[a] The product corresponding to each entry results from the condensation of the four components listed in each row. All products are in the deprotected form except for entries 3 and 4.

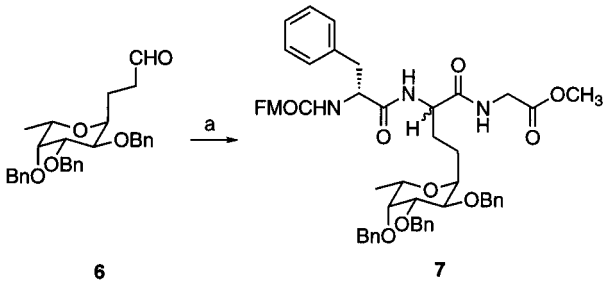


Figure 3. Product from entry 4 in Table 1. Reagents and conditions: (a) (i) MeOH/CH_2Cl_2, rt, 24 h, *N*-FMOC-phenylalanine, MICA, and Rink resin amine; (ii) wash polymer; (b) 20% TFA in CH_2Cl_2.

Compounds in Table 1 were obtained in fair to high yields depending on the stoichiometry of the reacting components relative to the Rink amine resin.[21] The highest yield obtained was 71% in entry 5 when 3 equiv of each sugar to 1 equiv of the resin bound amine was

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(21) Yields are as follows: entry 1, R = Bn, 56%; R = Ac, 77%; entry 2, 54%; entry 3, 33%; entry 4, 17%; entry 5, 71.5%; entry 6, 56%; entry 7, 65%; entry 8, 24%; entry 9, 53% yield.

used.[22] When the equivalency of sugar is dropped to two, the yields were consistently 50% ± 10%. We have observed that in most cases the products are ≥95% pure.[23] The diastereoselectivity of these reactions ranged from 4:1 in tetrabenzyl-β-C-galactoside found in entry 2 to 1:1 in entry 4 when the homologated tribenzyl-α-C-fucoside was used. As a general rule, chiral aldehydes have the greatest effect on the diastereoselecivity due to the proximity they have to the newly formed stereocenter while the sugar acids have little effect (approximately 1:1 ratios of diastereomers). The α-substituted C-glycosides induce little to no diastereoselectivity.

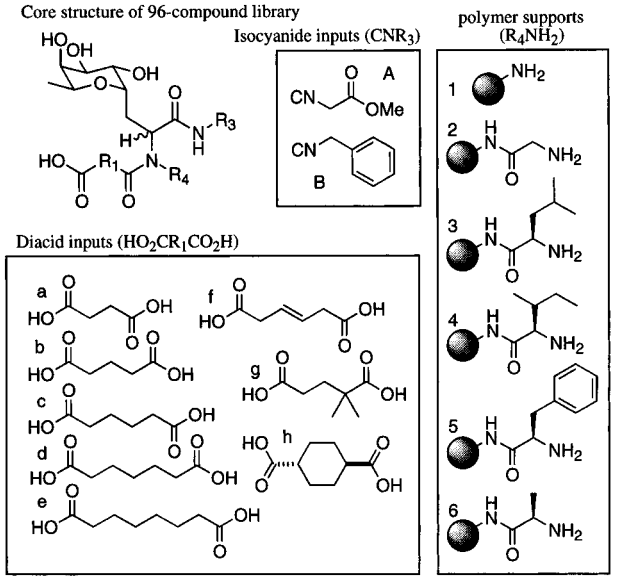
The generality of this strategy is demonstrated by the diversity of products, including the disaccharide compounds in entries 1 and 5, the fatty acid derivative in entry 7, and the use of a diacid in entry 6 which, if the MCC is performed in solution, would result in Ugi reactions at both carboxyl termini. Should a biological assay identify an active compound in the two diastereomer mix, the appropriate acylamino amide would need to be synthesized through a more rigorous enantioselective synthesis or the diastereomers separated by chromatography in order to deconvolute the result. Many alternatives exist for the synthesis of optically active amino acids.[24]

Two strategies for the deprotection of the sugar hydroxyl protecting groups (benzyl and acetate) were investigated. For both deprotection strategies, chromatography was not needed. Because solution phase hydrogenation proceeds in high yields and with few side reactions, the benzyl ethers could be removed efficiently following TFA cleavage with H_2 and $Pd(OH)_2$ on carbon. After filtration of the Pd catalyst, compounds of high purity were observed.

Protocols for removal of protecting groups while the compounds remained on the polymer were also developed. Alternate homogeneous debenzylation methods suitable for solid phase either result in low yields or are not compatible with the variety of functional groups used.[25] However, acetylated C-glycosides are easy to synthesize and are good candidates for deprotection on the polymer. Deacetylation was achieved with 1 M NaOMe in a 1:1 MeOH/THF mixture to give completely deprotected compounds that could then be cleaved from the polymer. We found this on-polymer deprotection scheme to be the more convenient of the two approaches; however, the benzylated structures are useful alternatives that can be employed for substrates that may be unstable to the basic deacetylation conditions or in cases where orthogonal protecting groups are desired.

We next turned our attention to the combinatorial library of sialyl Lewis x blood group glycomimetics using entry 6 in Table 1 as a model. Using the easily obtainable fucose aldehyde and a variety of components (Table 2), 192 compounds were prepared. On the basis of precedence, this core structure was an ideal starting point for library generation. It is presently understood that both the fucose and the carboxylate functionalities are

Table 2. Combinatorial Library Directed toward Sialyl Lewis x[a]



[a] Schematic representing the 96-compound library. Individual wells contain a single reagent from each box, and all wells contain the acetylated C-fucose as the aldehyde component.

important in the binding of sialyl Lewis x to E-selectin and are intended to mimic the corresponding carboxylate of *N*-acetylneuraminic acid along with the sugar.[19] As illustrated in compounds **2** and **3**, provided that the three hydroxyl residues of the fucose and the carboxylate are retained and displayed to the receptor with the appropriate conformation and distance from one another, competitive binding can be observed.

We envisioned the synthesis of ligands that would vary the distance from carboxylate to fucose using diacids of increasing length and a fucose aldehyde in a solid phase Ugi reaction. A MCC can, in addition to scanning this distance requirement, probe the active site for other favorable interactions by changing the amine and isocyanide components. To do this the Rink polymer amine component was coupled to five different *N*-FMOC amino acids under DCC conditions, providing five different amines after FMOC deprotection. Eight diacids of variable lengths were chosen along with two isocyanides, methyl isocyanoacetate (MICA) and benzyl isocyanide. All reagents were added as 1 M solutions in 1 mL wells containing 1 equiv of resin bound amine. Diacids were dissolved in 1:1 MeOH/THF, a solvent system necessary to obtain reasonable yields. Two and one-half equivalents of the C-fucose as the aldehyde were added in CH_2Cl_2, followed by 5.0 equiv of the isocyanide, 30 min later. After 36 h the polymer was washed and treated with 1 mL of a 1 M NaOMe solution for 4 h. The compounds were cleaved from the polymer with 2 mL of 20% TFA in CH_2Cl_2, rinsed with 0.5 mL of methanol,[26] and dried in a vacuum oven. All expected products were formed in roughly 50% yield and in high purity except in those wells containing the olefinic diacid where no product was observed.[27] This illustrates that this method can be used for preparing large numbers of glycomimetics in a preliminary screening program.

(22) In all cases the equivalency of the resisn bound amine was determined by the loading level indicated by the manufacturer in mmol/g.

(23) The product from entry 3 was found be 85% pure with excess napthyl peaks in the NMR, most likely due to insufficient rinsing of the pollymer suport.

(24) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: New York, Oxford, 1989.

(25) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991.

(26) This caused some methyl ester formation of the free acid from concentration of TFA and methanol. In subsequent experiments this methanol wash was deleted from the procedure.

Conclusion

The solid phase synthesis of glycomimetics has been demonstrated. Central to this work is the solid phase Ugi four-component condensation with a variety of functionalized C-glycosides which can accommodate different protecting group strategies. We feel this is a simple and powerful way to achieve rapid diversity in libraries that target carbohydrate receptor ligands. Assaying the compounds in Table 2 should provide insight into binding requirements for the sialyl Lewis x blood group tetrasaccharide. However, compounds synthesized according to this strategy are not limited to blood group determinants but all cell surface carbohydrates. We are presently working toward these goals as well as expanding the scope of this process to other functionalized components and carbohydrate clustering.

Experimental Section

General Procedures. The procedures requiring anhydrous conditions were the debenzylations and the preparation of the 1 M sodium methoxide. For these reactions, flame-dried flasks were used and an inert atmosphere of nitrogen was maintained. Solvents were distilled immediately prior to use: THF from sodium/benzophenone ketyl and methanol from magnesium turnings. Anhydrous DMF was purchased from Aldrich and used directly. For all other procedures reagent-grade solvents are sufficient. Rink resin was purchased from Advanced ChemTech. The loading level of the polymer was 0.56 mmol/g. Thin layer chromatography was performed on silica gel with precoated glass plates (E. Merck Brinkman, Kieselgel 60 F254, 0.25 mm) and visualized with UV light, *p*-anisaldehyde, and/or ninhydrin staining. NMR spectra were obtained with a Bruker ARX-500, ARX-400, or AM-360 spectrometer in $CDCl_3$ or CD_3OD. Spectra was referenced to residual $CHCl_3$ and CH_3OH at 7.26 and 3.3 ppm respectively. Unless otherwise noted spectra were taken in $CDCl_3$. Coupling constants are listed in hertz. IR spectra were obtained with a Nicolet 510P FT-IR spectrometer. Optical rotations were obtained with a Perkin-Elmer 241MC polarimeter using a 1 dm pathlength at room temperature (24 °C). Concentrations are reported in g/mL.

Representative Procedure for Debenzylation of Compound in Entry 2. The C-glycoside (11 mg) was azeotroped with toluene and dissolved in 100 μL of distilled MeOH. $Pd(OH)_2$ on carbon (7 mg, Aldrich) was added under a N_2 atmosphere. The solution was bubbled with H_2 gas for 5 min and then stirring was continued for 24 h under an atmosphere of H_2 gas. The solution was filtered through a small bed of Celite followed by excessive rinsing with MeOH. The solvent was evaporated, giving 9 mg of a clear yellow oil.

Representative Procedure for Coupling FMOC Amino Acids to Rink Resin. The FMOC amino acid (4.6 mmol), DCC (4.6 mmol), and HOBt (3.45 mmol) were combined in THF and stirred for 20 min. The white DCU was filtered, transferring the filtrate to 2.05 g of Rink (Advanced Chemtech, 0.56 mmol/g). After 18 h of gentle stirring, the resin was washed with alternating DMF, MeOH, and CH_2Cl_2.

General Procedure for C-Glycoside Aldehyde Oxidation. The aldehyde (1.0 equiv) was dissolved in tBuOH (20 mL per 4.5 mmol of aldehyde), water (2 mL per 4.5 mmol of aldehyde), and 2-methyl-2-butene (6.7 equiv). $Na_2H_2PO_4$ (1.3 equiv) and $NaClO_2$ (1.3 equiv) were added to the solution and allowed to stir overnight. The tBuOH was then evaporated, and the residue was redissolved in 25 mL of EtOAc and transferred to a separatory funnel. Then 20 mL of saturated NH_4Cl was added and extracted three times with equal portions of EtOAc. The combined organic layers were dried with Na_2SO_4 and evaporated to yield a clear oil.

Tetraacetyl C-galactose acid: yield = 95%. IR (neat): ν max 2950, 2928, 2817, 2361, 1749, 1437, 1371, 1221, 1101, 1051, 952, 906, 800, 738 cm^{-1}. ^1H NMR (400 MHz): δ 5.41 (d, 1H, J = 3.2 Hz), 5.11 (dd, 1H, J = 9.8, 9.9 Hz), 5.03 (dd, 1H, J = 3.3, 10.0 Hz), 4.20−4.07 (m, 2H), 4.04 (dd, 1H, J = 6.6, 11.3Hz), 3.92 (m, 1H), 2.61 (dd, 1H, 8.4, 16.1 Hz), 2.55 (dd, 1H, J = 3.9, 16.1 Hz), 2.14 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H). ^{13}C NMR: δ 174.8, 170.5, 170.3, 170.1, 169.9, 74.7, 74.2, 71.8, 68.8, 67.5, 61.3, 37.1, 20.6, 20.6, 20.6, 20.5. HRMS (EI): M + H calcd 391.1240, found 391.1231.

Triacetyl C-fucose acid: yield >95%, crude was used in all reactions. IR (neat): υ max 3476, 2988, 1747, 1373, 1227, 1059 cm^{-1}. ^1H NMR (360 MHz): δ 8.16 (bs, 1H), 5.24 (dd, 1H, J = 5.7, 9.9 Hz), 5.15 (dd, 1H, J = 2.1, 3.2 Hz), 5.06 (dd, 1H, J = 6.6, 9.9 Hz), 4.58 (m, 1H), 3.94 (m, 1H), 2.65 (dd, 1H, J = 8.7, 15.4 Hz), 2.56 (dd, 1H, J = 5.7, 15.4 Hz), 2.04 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H), 1.03 (d, 3H, J = 6.4 Hz). ^{13}C NMR (90.5 MHz): δ 174.5, 170.5, 170.0, 169.6, 70.1, 69.3, 68.1, 67.0, 66.5, 20.3, 15.4. HRMS (FAB): M + H calcd 333.1186, found 333.1197.

Tetrabenzyl C-galactose acid: yield > 95%, crude was used in all reactions. IR (neat): ν max 3030, 2870, 1713, 1455, 1271, 1101 cm^{-1}. ^1H NMR (360 MHz): δ 7.44−7.26 (m, 20H), 5.02 (d, 1H, J = 11.1 Hz), 4.98 (d, 1H, J = 11.6 Hz), 4.80 (d, 1H, J = 11.7 Hz), 4.70 (d, 1H, J = 11.6 Hz), 4.68 (d, 1H, J = 11.0 Hz), 4.67 (d, 1H, J = 11.6 Hz), 4.50 (d, 1H, J = 11.7 Hz), 4.43 (d, 1H, J = 11.7 Hz), 4.06 (d, 1H, J = 2.3 Hz), 3.8−3.6 (m, 6H), 2.84 (dd, 1H, J = 2.7, 16.0 Hz), 2.56 (dd, 1H, J = 7.9, 15.8 Hz). ^{13}C NMR (90.5 MHz): δ 176.1, 138.5, 138.0, 138.0, 137.7, 128−127 (m, 12C), 84.5, 77.8, 77.1, 75.9, 75.2, 74.5, 73.6, 73.4, 72.1, 68.5, 37.4. HRMS (FAB): M + H calcd 583.2696, found 583.2704.

Tribenzyl C-fucose aldehyde (6): yield 85%. ^1H NMR (500 MHz): δ 9.76 (t, 1H, J = 1.4 Hz), 7.34−7.26 (m, 15H), 4.77 (d, 1H, J = 11.8 Hz), 4.75 (d, 1H, J = 11.9 Hz), 4.68 (d, 1H, J = 12.0 Hz), 4.65 (d, 1H, J = 11.8 Hz), 4.61 (d, 1H, J = 11.8 Hz), 4.53 (d, 1H, J = 11.8 Hz), 3.95 (dt, 1H, J = 10.9, 3.8 Hz), 3.86 (m, 1H), 3.81 (m, 1H), 3.77−3.74 (m, 2H), 2.48 (dddd, 1H, J = 1.7, 6.6, 6.6, 14.4 Hz), 2.43 (dddd, 1H, J = 1.2, 6.8, 6.8, 14.4 Hz), 1.98 (m, 1H), 1.82 (m, 1H), 1.23(d, 3H, J = 6.6 Hz).

General Procedure for Compounds in Table 1 (see compound data for equivalents used). Carboxylic acid in 1 M MeOH, de-FMOCed Rink (1 equiv), isocyanide, and aldehyde in 1 M CH_2Cl_2 were combined. After 24 h of stirring and then evaporation to near dryness, the polymer was washed repeatedly with CH_2Cl_2 and MeOH. Treatment of the polymer with 15 mL of 20% trifluroaceticacid in CH_2Cl_2 and slow filtration followed by vacuum evaporation provides the benzylated product. Debenzylation with $Pd(OH)_2$ on carbon with H_2 gas gives the polyol. **For acetylated compounds:** the polymer is rinsed after the MCC reaction and then stirred with 4 mL of freshly prepared 1 M NaOMe for 2 h. After the solution is filtered and washed with 5% HCl/MeOH and excess MeOH and CH_2Cl_2, TFA is then used to remove the compound from the resin.

Entry 1, R = Bn: acid of C-galactose (2.0 equiv), aldehyde of C-galactose (2.0 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); 56% yield, crude was taken directly on. **Debenzyl:** yield 99%, both diastereomers. IR (neat): ν max 3366, 2930, 1678, 1547, 1439, 1410, 1377, 1206, 1140, 1092, 1051 cm^{-1}. ^1H NMR (500 MHz, D_2O/CD_3OD 5/1): δ 4.53 (dd, 0.3H), 4.39 (dd, 0.7H, J = 8.2, 8.2 Hz), 3.86 (d, 0.7 H), 3.79−3.40 (m, 20H), 3.29−3.10 (m, 5H), 2.75−2.60 (m, 2H), 2.42−2.21 (m, 2H), 2.15 (t, 1H), 1.71 (m, 1H). ^{13}C NMR (125.7 MHz, D_2O/CD_3OD 5/1): δ 175.3, 175.1, 174.5, 172.7, 129.7, 79.6, 79.6, 79.5, 78.0, 77.7, 77.5, 77.4, 77.2, 75.0, 74.9, 74.8, 72.0, 71.6, 71.5, 71.4, 70.2, 70.2, 70.1, 62.5, 62.4, 62.3, 62.1, 53.6, 53.4, 52.7, 42.1, 39.4, 38.1, 34.4. HRMS (FAB): M + H calcd 863.2933, found 863.2915.

Entry 2: propionic acid (5.0 equiv), aldehyde of C-galactose (2.0 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 54%, crude. ^1H NMR (500 MHz): δ 7.59 (br, 1H), 7.39−7.26 (m, 20H), 7.12 (br, 1H), 4.97−4.31 (8H), 4.1−3.5 (sugar ring H, 7H), 3.65 (s, 3H), 3.28 (d, 0.2 H, J = 5.8 Hz), 3.16 (d, 0.8 H, J = 8.7 Hz), 2.82 (bd, 1H, J = 14.4 Hz), 2.40 (br, 2H), 2.27 (br, 1H), 2.26 (br, 2H), 1.94 (br, 1H), 1.14 (t, 3H, J = 7.1 Hz). **Major diastereomer:** yield = 20%, off prep TLC. IR (neat): ν max 3326, 2922, 2872, 1752, 1653, 1539, 1454, 1366, 1208, 1105 cm^{-1}.

(27) Forty-eight of the 96 wells were checked for successful formation of product with positive ion electrospray mass spectroscopy, giving a 86% success rate with all failures attributed to the wells containing the olefinic diacid. In addition, yields and purities were confirmed by the isolation and characterization (^1H NMR and mass spectra) of compounds from eight larger scale reactions. (Bd6) 17.4 mg, 55.8% yield; (Bh4) 14.0 mg, 47.4% yield; (Bd4) 11.0 mg, 38.0% yield; (Bf6) 9.1 mg, 32.3% yield; (Bh1) 5.0 mg, 17.4% yield; (Bb1) 8.7 mg, 28.4% yield; (Bg5) 9.7 mg, 31.6% yield; (Bg4) 2.6 mg, 9.0% yield.

^{1}H NMR (400 MHz): δ 7.36−7.25(m, 20H), 6.27 (br, 1H), 4.95 (d, 1H, J = 11.9 Hz), 4.91 (d, 1H, J = 11.0 Hz), 4.75 (d, 1H, J = 11.8 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.64 (d, 1H, J = 10.9 Hz), 4.61 (d, 1H, J = 11.9 Hz), 4.47 (d, 1H, J = 10.8 Hz), 4.32 (d, 1H, J = 10.9 Hz), 3.92 (dd, 1H, J = 7.0, 17.6 Hz), 3.80 (d, 1H, J = 2.6 Hz), 3.76−3.59 (m, 7H), 3.64 (s, 3H), 3.53 (brdd, 1H, J = 8.0, 14.6 Hz), 3.18 (dd, 1H, J = 2.1, 9.2 Hz), 2.95 (dd, 1H, J = 4.3, 17.6 Hz), 2.19 (q, 2H, J = 7.4 Hz), 2.05 (m, 2H), 1.13 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100.6 MHz) (note: carbonyl carbons absent due to very long T1's): δ 138.4, 138.3, 138.3, 137.3, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.6, 84.7, 79.9, 75.4, 75.2, 74.2, 74.0, 72.8, 71.3, 52.0, 50.0, 40.3, 35.3, 29.6, 9.7. $[\alpha]_D$: +2.14 (c 0.015, $CHCl_3$).

Entry 2, debenzyl: yield = 95%, crude. IR (neat): ν max 3359, 2932, 1744, 1651, 1541, 1223, 1090 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 4.58 (dd, 1H, J = 6.4, 9.3 Hz), 3.80 (m, 1H), 3.71 (t, 3H), 3.62 (dd, 1H, J = 3.6, 15.0 Hz), 3.55 (ddd, 1H, J = 0.9, 3.5, 9.1 Hz), 3.42−3.34 (m, 3H), 2.32 (ddd, 1H, J = 2.5, 9.4, 14.0 Hz), 2.24 (q, 2H, J = 7.6 Hz), 1.83 (ddd, 1H, J = 2.9, 6.5, 14.0 Hz), 1.10 (t, 3H, J = 7.6 Hz). ^{13}C NMR (100.6 MHz, CD_3-OD): δ 176.7, 174.8, 171.7, 80.4, 77.9, 76.3, 73.0, 71.1, 63.3, 52.6, 52.4, 41.9, 35.5, 29.8, 10.2. HRMS (FAB): M + H calcd 379.1717, found 379.1718. $[\alpha]_D$: +18.4 (c 0.0076, CH_3OH).

Entry 3: napthoic acid (5.0 equiv), aldehyde of C-fucose (2.0 equiv), Rink polymer (1.0 equiv), benzyl isocyanide (5.0 equiv); yield = 33%, crude. IR (neat): ν max 3285, 2928, 1636, 1533, 1455, 1356, 1244, 1101, 785, 733, 696 cm^{-1}. ^{1}H NMR (400 MHz): δ 8.4−7.2 (m, 27H), 6.86 (t, 1H, J = 5.9 Hz), 4.84 (d, 1H, J = 11.7 Hz), 4.77 (d, 1H, J = 12 Hz), 4.74 (d, 1H, J = 11.7 Hz), 4.67 (d, 1H, J = 11.7 Hz), 4.63 (d, 1H, J = 11.7 Hz), 4.56 (d, 1H, J = 11.5 Hz), 4.38 (dd, 1H, J = 5.4, 14.9 Hz), 4.24 (dt, 1H, J = 4.7, 11.1 Hz), 4.14 (ddd, 1H, J = 2.4, 6.4, 13.0 Hz), 4.03 (dd, 1H, J = 5.0, 8.0 Hz), 3.85 (dd, 1H, J = 2.9, 8.1 Hz), 3.79 (t, 1H, J = 2.7 Hz), 2.46 (ddd, 1H, J = 6.0, 11.4, 14.4 Hz), 2.10 (ddd, 1H, J = 4.0, 9.6, 14.0 Hz), 1.22 (t, 3H, 6.5 Hz). ^{13}C NMR (100.6 MHz): δ 170.8, 169.3, 138.5, 138.3, 138.1, 137.8, 134.1, 133.7, 133.4, 131.0, 130.1, 128.7−127 (m), 127.2, 126.4, 126.2, 126.0, 125.5, 125.4, 124.6, 124.5, 77.9, 77.2, 76.3, 76.1, 73.9, 73.4, 73.1, 69.1, 68.7, 51.4, 43.6, 30.3, 16.1. HRMS (FAB): M + H calcd 749.3591, found 749.3604. $[\alpha]_D$ = −36.7 (c 0.0171, $CHCl_3$).

Entry 4: FMOC-alanine (4.0 equiv), aldehyde of C-fucose (1.0 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 17%, crude. IR (neat): ν max 3293, 2924, 1739, 1691, 1645, 1537, 1453, 1260, 1090 cm^{-1}. ^{1}H NMR (400 MHz): δ 7.74 (d, 2H, J = 6.1 Hz), 7.50 (t, 2H, J = 8.4 Hz), 7.39 (t, 2H, J = 7.4 Hz), 7.32−7.21 (m, 21H), 7.16 (br, 1H), 6.78 (br, 0.5H), 6.62 (br, 0.5H), 5.30 (m, 1H), 4.71 (d, 1H, J = 12.1 Hz), 4.67 (d, 1H, J = 12.1 Hz), 4.62 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.4 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.68 (1H), 4.42 (dd, 2H, J = 4.4, 11.5 Hz), 4.26 (br, 1H), 4.15 (t, 1H, J = 6.4 Hz), 4.05 (m, 2H), 3.87 (m, 1H), 3.77 (m, 2H), 3.69 (s, 3H), 3.05 (br, 2H). HRMS (FAB): M + H calcd 960.4435, found 960.4417.

Entry 5: acid of C-fucose (3.0 equiv), aldehyde of C-galactose (3.0 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 71.5%, crude. IR (neat): ν max 3345, 1682, 1539, 1435, 1206, 1138 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 4.49 (dd, 0.3H, J = 4, 11 Hz), 4.40 (dd, 0.7H, J = 6, 6 Hz), 4.20 (m, 0.7H), 4.05 (m, 0.3H), 3.8−3.1 (m, 12H), 3.11 (s), 2.7−2.3 (m), 2.2 (m), 2.1 (m), 1.85−1.55 (m), 1.0 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100.6 MHz, CD_3OD): two diastereomers δ 179.1, 174.5, 174.3, 173.6, 172.4, 121.7, 121.1, 121.1, 118.8, 115.9, 113.1, 83.6, 79.7, 79.6, 77.4, 77.3, 75.0, 74.7, 74.3, 72.5, 72.2, 72.0, 71.8, 71.7, 71.3, 70.9, 70.5, 70.2, 70.1, 69.0, 68.3, 62.5, 52.3, 42.0, 33.5, 33.3, 16.6, 15.7.

Entry 6: succinic acid (5.0 equiv), aldehyde of C-fucose (2.5 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 56%, crude. ^{1}H NMR (360 MHz, CD_3OD): δ 4.50 (m, 1H), 4.10 (m, 1H), 4.05−3.83 (bm, 4H), 3.74−3.61 (bm, 2H), 2.67−2.53 (bm, 4H), 2.17 (b, 1H), 2.02 (b, 1H); major diastereomer 3.65 (s, 3H), 1.21 (d, 3H, J = 7.0 Hz), minor diastereomer 3.76 (s, 3H), 1.22 (s, 3H, J = 7.0 Hz). HRMS (FAB) for acetylated methyl ester: M + H calcd 547.2139, found 547.2126. IR (neat): ν max 2930, 1747, 1667, 1539, 1373, 1227, 1088, 1057 cm^{-1}.

Entry 7: stearic acid (5.0 equiv), aldehyde of C-galactose (2.8 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 65.2%, ^{1}H NMR (400 MHz, CD_3OD): δ 4.67 (m, 1H, minor diastereomer) 4.57 (dd, 1H, J = 6.2, 8.5 Hz, major diastereomer), 4.06−3.34 (m, 10H), 2.34−2.13 (m, 2H), 1.98−1.79 (m, 2H), 1.58 (m, 2H), 1.27 (bm, 30H), 0.87 (m, 3H). ^{13}C NMR (100.6 MHz, CD_3OD): two diastereomers, δ 176.4, 176.1, 175.0, 174.6, 172.8, 80.2, 78.1, 77.8, 76.2, 72.9, 72.4, 71.1, 70.9, 63.3, 63.0, 52.4, 52.0, 41.8, 37.0, 36.8, 30.7, 36.8, 35.4, 34.8, 33.0, 30.8, 30.7, 30.6, 30.5, 30.5, 30.4, 30.3, 24.2, 23.7, 14.4. HRMS (EI) for tetra-acetylated compound: M + H calcd 757.4487, found 757.4485. IR (neat): ν max 3061, 2924, 2853, 1747, 1651, 1539, 1466, 1439, 1371, 1226, 1097, 1051, 910, 738, 704 cm^{-1}.

Entry 8: *p*-toulualdehyde (5.0 equiv), fucose acid (3.0 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 24%, crude. IR (neat): ν max 3291, 2926, 1636, 1539, 1516, 1455, 1377, 1204, 1140, 1065, 689 cm^{-1}. ^{1}H NMR (500 MHz, 5:1 $CDCl_3$:CD_3OD): δ 7.19 (m, 6H), 7.06 (m, 4H), 5.33 (bm, 1H), 4.30 (bm, 3H), 3.83 (bm, 1H), 3.76 (bm, 1H), 3.58 (m, +CD_3OH), 3.52 (bm, 1H), 2.53 (m, 2H), 2.26 (s, 3H), 1.12 (m, 3H). ^{13}C NMR (100.6 MHz): two diastereomers, δ 1171.6, 170.5, 170.4, 137.9, 137.6, 134.3, 129.7, 129.3, 128.3, 127.2, 127.2, 126.9, 77.2, 71.9, 70.7, 69.6, 68.0, 67.9, 56.7, 56.7, 43.2, 34.7, 33.1, 33.0, 29.5, 20.8, 15.8, 15.7. HRMS (FAB): M + H calcd 443.2182, found 443.2194.

Entry 9: salicylic acid (6.1 equiv), aldehyde of C-galactose (3.8 equiv), Rink polymer (1.0 equiv), MICA (5.0 equiv); yield = 53.1%, crude. IR (neat): ν max 3375, 2928, 1684, 1541, 1495, 1441, 1207, 1140, 845, 802, 758, 725 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 7.86 (d, 1H, J = 4.5 Hz), 7.37 (m, 1H), 6.90 (d, 2H, J = 4.6 Hz), 4.11−3.21 (bm, 12H), 2.47 (bm, 1H), 2.03 (bm, 1H). ^{13}C NMR (100.6 MHz, CD_3OD): two diastereomers, δ 160.5, 134.9, 129.9, 120.3, 118.2, 117.4, 80.3, 78.1, 76.2, 73.0, 71.0, 63.1, 52.7, 35.8. HRMS (EI) for tetraacetylated compound: M + H calcd 610.2010, found 610.1994

HRMS for select compounds from Table 2: Bd6 (FAB) M + H calcd 560.2584, found 560.2585; Bh4 (CI) M + H calcd 592.3234, found 592.3219; Bd4 (CI) M + H calcd 580.3234, found 580.3232; Bf6 (FAB) M + Na calcd 544.2271, found 544.2277; Bh1 (FAB) M + H calcd 479.2393, found 479.2403; Bb1 (FAB) M + H calcd 439.2080, found 439.2087; Bg5 (FAB) M + Na calcd 636.2897, found 636.2895; Bg4 (FAB) M + H calcd 602.3054, found 602.3050.

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Supporting Information Available: ^{1}H NMR spectra for sugar components, compounds generated in Table 1, and select compounds from Table 2 (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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