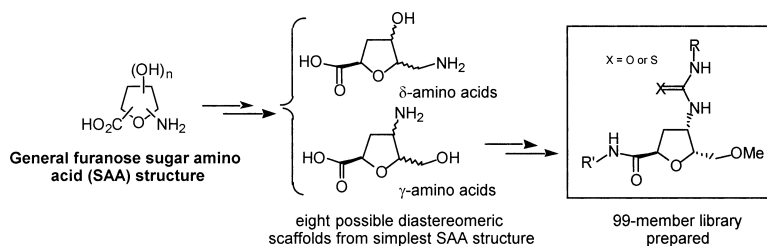## Article

Tetrahydrofuran-Based Amino Acids as Library Scaffolds

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Tetrahydrofuran-Based Amino Acids as Library Scaffolds

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A furanose sugar amino acid (SAA) has been utilized as a library scaffold for the first time. Two furanose SAA scaffolds were examined to illustrate their potential for derivatization. The resulting 99-member library contained three orthogonal points of diversification that allowed easy access to ethers and carbamates from a hydroxyl moiety, a range of ureas from an azide (via an amine), and a range of amides from a methyl ester. The novel amide formation (by displacement of the methoxide from the methyl ester moiety) was achieved in good yield and purity with high structural confidence. Full characterization of several library intermediates (including a crystal structure) was obtained. The library was submitted for antibacterial screening.

Introduction

Carbohydrates have been frequently utilized as structurally diverse scaffolds with up to five points of diversity in combinatorial synthesis.[1−3] Simple modification of carbohydrate scaffolds can cause dramatic changes in biological activity.[4] Additionally, a wide range of stereochemistries can be employed.[5,6] As a result, they are valuable scaffolds for biological probes.[7,8] Literature indicates that pyranose scaffolds[9−11] are more frequently employed than their furanose counterparts.[12,13] Sugar amino acids (SAAs)[14−17] have been utilized in peptidomimetics, as carbopeptoid foldamers,[18,19] and to a lesser extent as molecular scaffolds[20] since their potential as building blocks was highlighted by McDevitt et al. (Figure 1).[21] The incorporation of amine and acid functions into the sugar scaffold simplified orthogonal protection requirements and aided manipulation via established library methodology. SAAs have been employed in structural analogues, for example, in mimics of Leu−enkephalin,[22−24] integrin antagonists (RGD),[25] somatostatin[26] and cyclodextrins;[27] and as pharmacophore mapping libraries.[28−30] The Fleet group have prepared numerous furanose SAAs[31−33] in addition to the vast number of SAA structures prepared elsewhere since 1955.[34] Recently, the removal of one of the hydroxyl groups in the furanose scaffold (**1**) gave access to a simple SAA (**2**) with three points of diversity (Figure 2).[31] In contrast to the work of Sofia et al., we have focused on the preparation of a 99-member library from a furanose-based SAA. The target library was prepared (without rational design) in solution phase with resin scavenging to produce a novel small molecule library to exemplify the potential of furanose SAAs as convenient stereodiverse library scaffolds (Figure 2).

Results and Discussion

Scaffold Synthesis. The sugar amino acid scaffolds utilized for library formation were two γ-amino acids (L-*arabino* **3** and L-*lyxo* **4**) based upon the simplest THF scaffold (deoxygenated at one position). The fully protected analogues of SAAs **3** and **4** (**5** and **6**) were prepared efficiently from L-gulonolactone (**7**) over 7 steps (32% yield) and 8 steps (28% yield), respectively, to afford 20−30 g quantities of the fully protected scaffolds **5** and **6** (Scheme 1). Further synthetic details for these (and other diastereomeric) novel scaffolds are detailed in an earlier publication.[31] It is of note that several of the intermediates in the synthetic strategy to obtain **5** and **6** also are potential scaffolds, for example, the selectively protected diol (**8**).

Development of a Practical Synthetic Route. The presence of the amine (prepared from the azides **5** and **6** by hydrogenation with 10% palladium on activated charcoal (Pd/C) in ethyl acetate) allowed formation of ureas using iso(thio)cyanates with subsequent scavenging with aminopolystyrene (AMPs) (Scheme 2). Reactions of the amine with acid chlorides and sulfonyl chlorides were also shown to be successful. Subsequent deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group from the urea using tetrabutylammonium fluoride (TBAF) was successful, although an aqueous workup was not effective in removal of the TBDPS impurities. The TBDPS group of **5** and **6** could be efficiently removed on large scale using 3% HCl in methanol to give the desired deprotected alcohols **9** and **10** in 76 and 73% yields, respectively (Scheme 2).

The hydroxyl moiety was originally intended to be alkylated as one possible point of diversity, but many standard procedures (alkyl halides with sodium hydride[35] or potassium carbonate, trichloroacetimidates[36,37] and Mitsunobu conditions)[38] were found to be problematic. One reason was that the removal of the proton of the hydroxyl required a particularly strong base, which caused epimerization of the
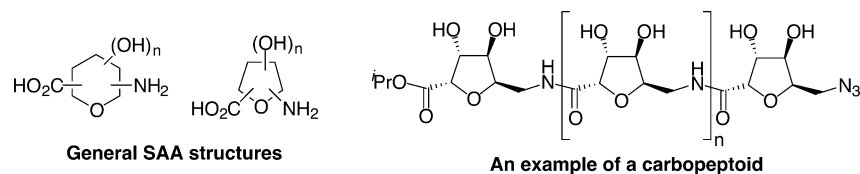
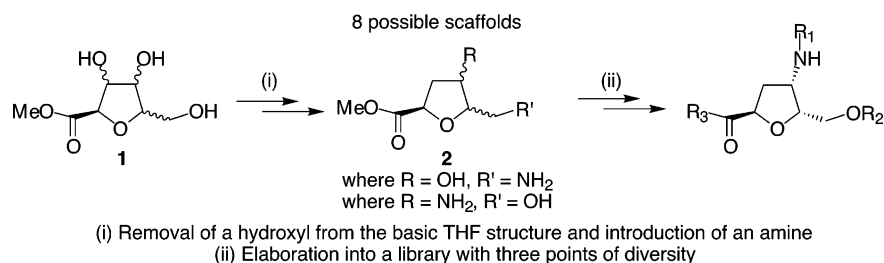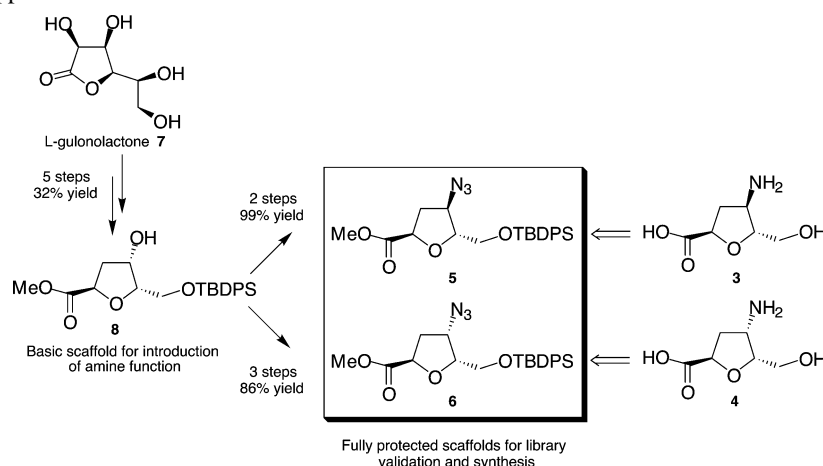**Figure 1.** Sugar amino acids (SAAs) and carbopeptoids.

Figure 2. Potential of furanose SAAs as scaffolds.

Scheme 1. Synthetic Approach to Formation of the Protected SAAs **3** and **4**

acid moiety (shown by nOe difference experiments). Alkylation conditions employing a 1:1 solution of methyl iodide and acetonitrile with silver (I) oxide at 80 °C gave quantitative conversion of the alcohols (**9** and **10**) to the methyl ethers (**11** and **12**).[39] The formation of a carbamate at the hydroxyl position (**13**) was also found to be successful (Scheme 2).[40] Due to the potential for migration of the carbamate onto the amine (generated from the azide) in the next step, only the methyl ethers **11** and **12** were reacted to the corresponding urea derivatives.

Since the optimal alkylation conditions were unsuitable for the parallel synthetic approach, the alkyl group on the primary hydroxyl was fixed, and only the alkyl groups of the urea (from the amine) and amide (from the methyl ester) were varied to create a 10 × 10 library. To avoid multiple hydrogenation reactions, the urea was formed prior to the amide. Dithiothreitol (DTT) reductions were examined as an alternative to the Pd/C hydrogenation conditions, but reactions did not go to completion with a reasonable excess of DTT and resin-bound amine.[41,42]

Aminolysis of the methyl ester was attempted by heating in the presence of an amine to give the corresponding amide (Scheme 2). The optimal conditions required methanol as the solvent, 10 equiv of the amine, and heating at 60 °C (then at 80 °C if necessary). Resin scavenging of the excess amine[43] gave highest purity when anhydride resin with high
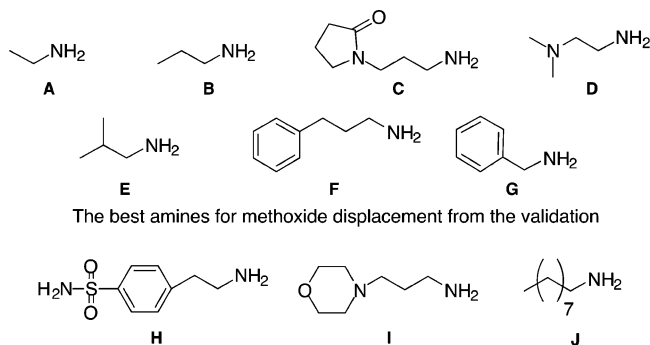
loading was utilized. Methoxide displacement of the phenyl urea **14** was validated with 12 different amines in order to find amines suitable for the final library synthesis. The amines that gave rise to the desired products (after removal of excess amine by AMPs) with purity >80% were selected for the final library synthesis. Seven of the 12 amines passed these criteria, and a further three amines were selected on the basis of previous experience (Chart 1).

Although library approaches were validated for both the L-*arabino* and L-*lyxo* amino acids (**5** and **6**), only one of the two scaffolds was utilized for library preparation. Here, the L-*lyxo* scaffold **6** was employed for library synthesis due to the identification of a minor side product during the urea formation on the L-*arabino* scaffold. The side product was believed to be a dimeric SAA (**15**) formed by the intermolecular reaction of the amine with the methyl ester forming the linking amide bond; formation of the urea at the second amine function could occur either before or after the coupling reaction (Figure 3). The formation of a library based upon a dimeric SAA may have potential as a scaffold, particularly due to the successful utilization of several disaccharide scaffolds in the literature.[44,45]

Final Library Synthesis. Validation indicated that the most feasible library approach required TBDPS deprotection of the primary hydroxyl and subsequent reprotection with an acid stable protecting group (such as a methyl ether or

Scheme 2. Development of the Synthetic Route for the Library from SAAs **5** and **6**[a]
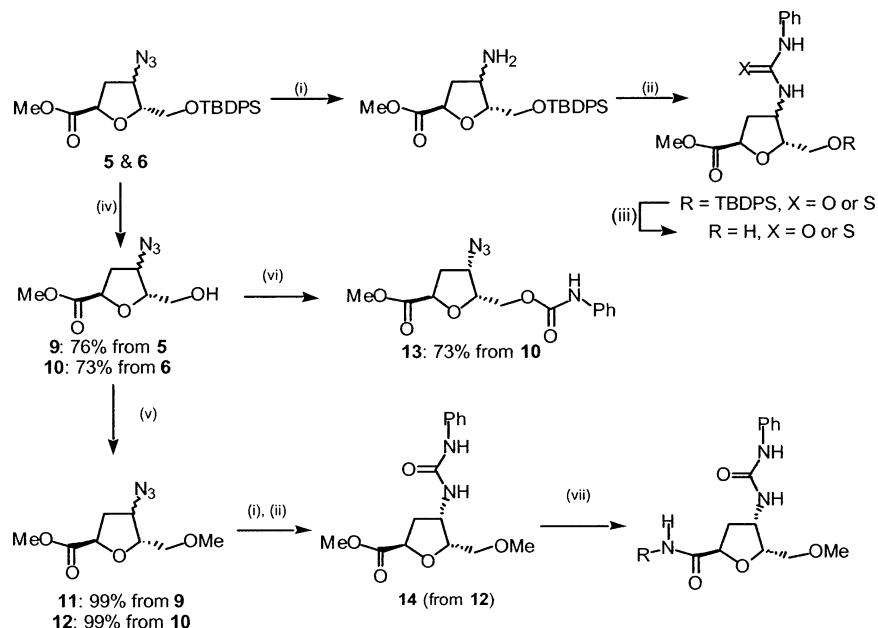
[a] Reagents and conditions: (i) 10% Pd/C, H$_2$, ethyl acetate; (ii) phenyl iso(thio)cyanate, dichloromethane at room temperature, then scavenging with AMPs; (iii) tetrabutylammonium fluoride, THF, then aqueous workup; (iv) 3% HCl in methanol, room temperature; (v) methyl iodide/acetonitrile (1:1), silver (I) oxide, 80 °C; (vi) phenyl isocyanate, pyridine, room temperature; (vii) amine (10 equiv; see Chart 1), methanol, 60 or 80 °C.

Chart 1. Amines Selected for Library Synthesis

The best amines for methoxide displacement from the validation

Further amines selected according to knowledge of successful reactions

Scheme 3. Synthetic Approach Utilized for Library Preparation[a]

[a] Reagents and conditions: (i) 3% HCl in methanol, room temperature; (ii) methyl iodide/acetonitrile (1:1), silver (I) oxide, 80 °C; (iii) 10% Pd/C, H$_2$, ethyl acetate; (iv) iso(thio)cyanate (10 different), dichloromethane at room temperature, then AMPs; (v) amine (**A**–**J**), methanol, 60 or 80 °C, then anhydride resin in dichloromethane.

carbamate) prior to introduction of the urea, followed by amide formation (Scheme 3).

Therefore, the synthetic precursor **12** for the library synthesis was obtained from **6** in 72% yield by treatment with acidic methanol with subsequent formation of the methyl ether (Scheme 3). The urea derivatives were obtained by reaction of an aliquot of the amine (prepared from the azide **12** by treatment with 10% Pd/C in ethyl acetate under a hydrogen atmosphere) with an iso(thio)cyanate in dichlo-
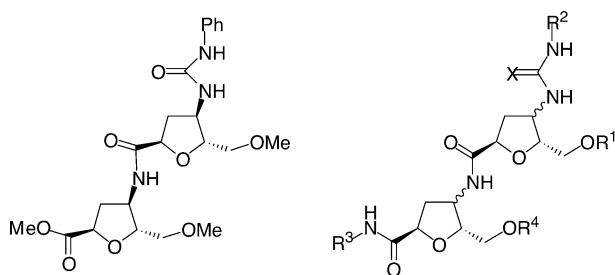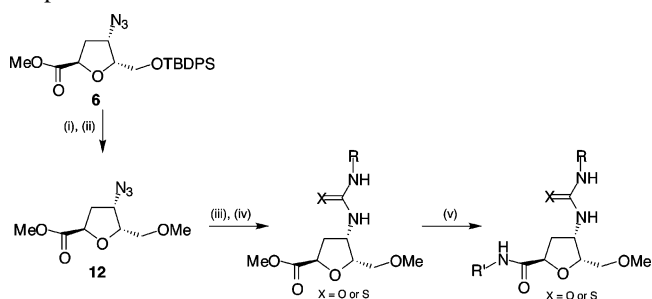

15: Observed side product   Potential of dimeric species as a scaffold

Figure 3. Dimeric SAA species **15** identified as a side product from urea formation on the L-*arabino* scaffold.

romethane overnight, followed by resin scavenging with AMPs and purification by flash column chromatography (where required). Further details are available in the Supporting Information. The penultimate library intermediates (**16**–**25**) generated are shown in Figure 4. Displacement of the methoxide of each urea (**16**–**25**) was then conducted with each of the 10 amines shown in Chart 1 (as described in the Experimental Section) to generate the final library.

After synthesis, the purity was obtained of the final residue of each library member was determined by LC at 215 nm, the results of which are shown in Table 1. The crude yields of the final library compounds were, in general, less than 100%, with the exception of library compounds generated from amine **A** (ethylamine) and amine **H** (2-[4-sulfamoylphenyl]ethylamine) (Supporting Information). This has been attributed to the unexpectedly poor removal of amine **A** by concentration in vacuo and of amine **H** by poor resin scavenging in DMF. These poorer purification results are indicated in bold in Table 1.
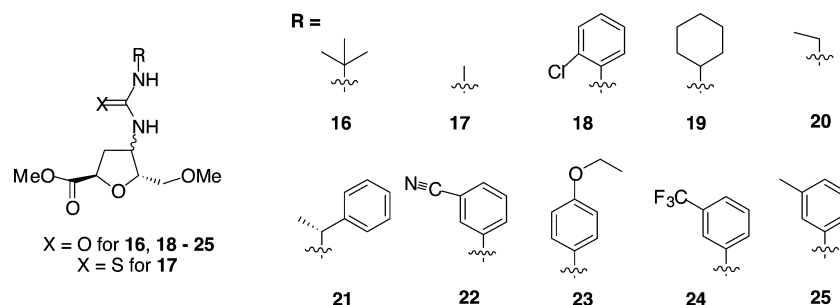
Figure 4. The array of urea compounds (**16–25**) generated at the first point of diversity.

Table 1. Purity (%) of the Final Library Members Detected by LC at 215 nm

amine	16	17	18	19	20	21	22	23	24	25	av
					urea						
A	0	49	84	0	61	65	80	72	70	79	**56**
B	64	92	88	48	0	84	90	82	80	85	71
C	43	41	91	69	79	88	89	82	81	93	76
D	29	48	91	0	95	85	95	82	78	85	69
E	39	93	80	46	0	84	87	77	80	84	67
F	84	92	89	80	85	85	81	85	84	NA[a]	85
G	69	93	65	79	84	87	86	81	81	85	81
H	46	48	64	37	61	68	76	70	48	58	**58**
I	36	46	89	53	91	88	93	78	83	90	75
J	41	92	91	47	0	81	80	71	78	83	66
av	45	69	83	46	56	82	86	78	76	82	70

[a] Reaction not performed.

Table 2. Evidence for the Poor Detection at 215 nm for Several Library Members

compd	crude yield, %	purity,[a] %		yield,[b] %
		215 nm	ELS	
16A	>100	0	97	78
19A	>100	0	97	75

[a] Purity calculated by area under the curve. [b] Yield calculated by calibrated ^{1}H NMR with TMS.

For several library members, the purity has been stated as 0% by LC at 215 nm. It is believed that this was due to the absence of chromophores in several final library products. To establish the structural integrity of such compounds, library members **16A** and **19A** were analyzed by ELS as well as by their yield (calculated by calibrated ^{1}H NMR)
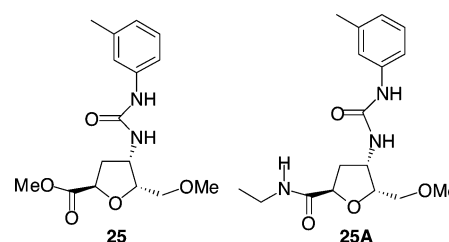

Figure 5. Resynthesis targets for additional structural integrity evidence.

(Table 2) and their ^{1}H NMR peaks listed. (The ELS data for the entire library is given in the Supporting Information).

To obtain a data set representative of the entire library, one row and two columns were chosen at random (Table 3). The reaction yields for the library members in the sampled data were obtained via integration of a ^{1}H NMR spectrum containing an internal standard (tetramethylsilane) of known concentration.

Confirmation of the structural integrity of the library has been achieved by listing the ^{1}H NMR signals of the sampled data set (with the exception of **18H** and **22H**, which were complicated by the excess amine **H** still present) and the presence of the $[M + H]^+$ ion (100%) by LC/MS. Additional peaks observed in some spectra were attributed to $[2M + H]^+$ and $[2M + Na]^+$. Additional structural information was obtained when library intermediate **25** was purified and fully characterized and a crystal structure was obtained[46] (Supporting Information). Urea **25** was then reacted with ethylamine to generate **25A**, which was also purified and fully characterized (Figure 5). The library has been submitted for antibacterial screening at Prolysis Ltd.[47]

Table 3. Randomly Selected Library Data Set for Characterization Purposes

compd	crude yield, %	purity,[a] %	yield,[b] %	compd	crude yield, %	purity,[a] %	yield,[b] %
16G	76	69	59	**18E**	86	80	78
17G	87	90	70	**18F**	89	89	83
18G	90	65	71	**18H**	>100	64	90
19G	>100	79	55	**18I**	80	89	74
20G	82	84	64	**18J**	97	91	83
21G	71	87	53	**22A**	>100	79	69
22G	87	86	63	**22B**	88	90	70
23G	89	81	64	**22C**	48	82	30
24G	82	81	56	**22D**	36	92	23
25G	66	85	56	**22E**	84	87	65
18A	>100	84	83	**22F**	82	81	55
18B	93	88	78	**22H**	>100	66	89
18C	72	91	60	**22I**	71	93	44
18D	55	91	50	**22J**	97	80	63

[a] Purity calculated by area under the curve by UV at 215 nm. [b] Yield calculated by calibrated ^{1}H NMR with TMS.

Conclusion

Two γ-amino acids based on a tetrahydrofuran scaffold were validated as library scaffolds, illustrating the stereochemical diversity possible from a sugar-derived scaffold. A 99-member library was successfully prepared from the L-*lyxo* scaffold **6** with a good level of purity (despite inefficient removal of two amines in the final synthetic step). A high degree of structural integrity existed despite problems resulting from the absence of chromophores in some final library members. Initial biological screening of the library indicated the biological potential of SAA furanose scaffolds.

Experimental Section

General. All reactions were carried out in standard glassware or screw-top vials (10 mL volume) for parallel library synthesis. Reactions at room temperature were performed with orbital spinners (for vials) or shakers (for round-bottomed flasks) when resin was present; otherwise, magnetic stirrer hotplates were employed. Reaction heating was undertaken using magnetic stirrer hot plates equipped with a 24-well metal block used to transfer heat to the vials. In these circumstances, it is the external reaction temperature that is quoted. The small reaction volume and the good quality seal of the vials allowed heating to be carried out without any condensation apparatus. A Genevac apparatus was employed for solvent removal from vials. Commercial reagents were used without further purification. ^{1}H NMR and ^{13}C NMR were recorded using CDCl$_3$ (unless stated otherwise) at 400 and 100 MHz, respectively, on a Bruker Avance 400 spectrometer. Proton and carbon chemical shifts are reported in parts per million using residual CHCl$_3$ as an internal standard in the absence of tetramethylsilane. All coupling constants are given in Hertz. Flash column chromatography was performed using Sorbsil C60 40/60 silica (0.040−0.063 mesh) from Merck. Aminopolystyrene (AMPs) resin (1.1 mmol/g) was prepared by Evotec OAI, and the anhydride resin (6.3 mmol/g) was obtained from Novabiochem. Library members were coded by the urea (**16**−**25**) and the amide (**A**−**J**). Detailed experimental data for general procedures 1−5 are given in the Supporting Information.

1. General Procedure for Deprotection of the TBDPS Group. The TBDPS ether **5** (14.0 g, 3.19 mmol) was dissolved in a solution of 3% HCl in methanol (280 mL) and stirred at room temperature. When the reaction was complete [3 h 15 min by TLC in ethyl acetate/hexane, 1:1], sodium bicarbonate (25 g) was added to neutralize the reaction mixture. The reaction mixture was then filtered through Celite (eluent: methanol) and concentrated in vacuo. The reaction was purified by flash column chromatography (ethyl acetate/hexane, 1:2 to 1:1) to afford the alcohol **9** (4.87 g, 76%) as a colorless oil. This procedure was also employed to generate alcohol **10** from TBDPS ether **6** in 73% yield as a colorless oil.

2. General Procedure for the Formation of the Methyl Ether. Alkylation using methyl iodide was carried out on the unprotected L-*arabino* azide **9** following a literature procedure.[39] The azide **9** (4.01 g, 20 mmol) was heated to 80 °C in the presence of silver (I) oxide (6.94 g, 30 mmol) with acetonitrile/methyl iodide (1:1, 120 mL) as solvent.

After 19 h, TLC (ethyl acetate/hexane, 1:1) indicated the absence of starting material and the formation of a single product. Subsequent workup (filtration then concentration in vacuo) followed by flash column chromatography (ethyl acetate/hexane; 1:3) afforded the desired product **11** (4.23 g, 99%) as a clear colorless oil. The methyl ether of the *arabino* azide (**12**) was obtained from alcohol **10** by the same procedure in similar yield.

3. Formation of the Carbamate. Functionalization of the hydroxyl as a carbamate was achieved in good yield by treating the unprotected *lyxo* azide **10** (151 mg, 0.75 mmol) with phenyl isocyanate (81 μL, 0.75 mmol) in pyridine (2.0 mL) at room temperature.[40] After 20 h, the reaction mixture was concentrated in vacuo, diluted with ethyl acetate, then washed with 0.5 M HCl and water. The organic layer was dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/hexane; 1:4) to give the desired product **13** (190 mg, 75%) as an oil, which crystallized on standing.

4. Hydrogenation and Capping to Form Ureas. Formation of the Amine. A solution of azide **12** (3.01 g, 14 mmol) in ethyl acetate (120 mL) was vigorously stirred under an atmosphere of hydrogen in the presence of palladized carbon (10%, 301 mg). After 22 h 30 min, TLC (ethyl acetate/hexane, 1:1) indicated the absence of starting material. The reaction was degassed, purged with nitrogen, and filtered through Celite (eluent: ethyl acetate). The solution was concentrated in vacuo to give the crude amine, which was reacted without further purification. Eleven aliquots of the amine were prepared in dichloromethane for reaction with nine different isocyanates and one isothiocyanate. The 11th aliquot was reacted with *m*-tolyl isocyanate to provide material for full characterization.

Formation of 25. *m*-Tolyl isocyanate (490 μL, 3.8 mmol) was added to a solution of the crude amine in dichloromethane (17.0 mL) and shaken overnight. Aminopolystyrene (AMPs, 1.1 mmol/g) (3.46 g, 3.8 mmol) was added to the reaction mixture and shaken overnight. The AMPs was removed by filtration (eluent: dichloromethane), and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/hexane; 1:1 to 3:1) to give the *m*-tolyl urea **25** (364 mg, 89%) as a white crystalline solid.

5. Displacement of Methoxide by an Amine. The appropriate amine (10 equiv) was added to the urea (one of 10 × 1.5 mL aliquots in methanol), except in the case of ethylamine (1.5 mL of 2.0 M solution in methanol) and propylamine (5 equiv of the amine in 1.5 mL methanol). Reaction progress was monitored by LC/MS after overnight reaction at 60 °C. All reactions went to completion after heating for 1 day at 60 °C or with an additional 1 or 2 days at 80 °C (Supporting Information). Once no starting material was visible by LC/MS, the reactions were concentrated in vacuo. Residues from reaction with amines B, C, D, E, F, G, I, and J were dissolved in dichloromethane, and the excess amine was removed by scavenging with anhydride resin. Amine H was insoluble in DCM; therefore, DMF was used as the solvent in the scavenging step. Amine A was volatile and, thus, did not require resin scavenging. After filtration

to remove the resin and concentration in vacuo, the samples were weighed and analyzed by LC/MS with detection by UV spectroscopy at 215 nm and by ELS.

Formation of 25A. A solution of ethylamine (**A**) in methanol (2.0 M, 4.00 mL) was added to the *m*-tolyl urea **25** (121 mg, 0.38 mmol) and stirred at 60 °C overnight. By LC/MS, no starting material remained. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/methanol; 99:1) to give library member **25A** (88.6 mg, 70%) as an amorphous solid.

6. Spectral Data for the Sampled Library Members.
***N*-Benzyl 2,5-Anhydro-4-(3-*tert*-butylureido)-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (16G).** ^{1}H NMR: **δ** 1.30 (s, 9H), 2.26 (dd, J = 8.0, 5.6, 2H), 3.35 (s, 3H), 3.49 (dd, J = 10.6, 6.4, 1H), 3.60 (dd, J = 10.6, 2.8, 1H), 4.22 (a−dt, J = 6.0, 2.8, 1H), 4.38 (dd, J = 15.0, 6.0, 1H), 4.43 (m, 1H), 4.48 (m, 1H), 4.59 (t, J = 8.0, 1H), 5.07 (s, 1H), 5.59 (d, J = 8.0, 1H), 7.19−7.36 (m, 6H). LC/MS: *m/z* 364 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-6-*O*-methyl-4-(3-methylthioureido)-L-*lyxo*-hexonamide (17G).** ^{1}H NMR: δ 2.93 (m, 2H), 2.95 (bs, 3H), 3.38 (s, 3H), 3.54 (dd, J = 10.4, 3.6, 1H), 3.70 (dd, J = 10.4, 2.4, 1H), 4.34 (m, 1H), 4.42 (dd, J = 15.0, 6.0, 1H), 4.47 (dd, J = 15.0, J = 6.0, 1H), 4.63 (t, J = 7.6, 1H), 5.12 (bs, 1H), 6.69 (bs, 1H), 7.05−7.16 (m, 2H), 7.25−7.37 (m, 5H). LC/MS: *m/z* 338 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-4-[3-(*o*-chlorophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (18G).** ^{1}H NMR: δ 2.36 (dd, J = 8.0, 5.6, 2H), 3.32 (s, 3H), 3.53 (dd, J = 10.6, 6.2, 1H), 3.64 (dd, J = 10.6, 2.6, 1H), 4.28 (a−dt, J = 5.8, 3.0, 1H), 4.42 (dd, J = 14.6, 5.8, 1H), 4.51 (dd, J = 14.6, 6.2, 1H), 4.61−4.67 (m, 2H), 6.73 (d, J = 7.6, 1H), 6.95 (m, 1H), 7.19−7.35 (m, 8H), 8.02 (s, 1H), 8.10 (dd, J = 8.4, 1.2, 1H). LC/MS: *m/z* 418 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-4-(3-cyclohexylureido)-6-*O*-methyl-L-*lyxo*-hexonamide (19G).** ^{1}H NMR: δ 1.02−1.18 (m, 3H), 1.26−1.38 (m, 2H), 1.60 (a−dt, J = 12.8, 3.8, 1H), 1.70 (a−dt, J = 13.2, 3.6, 2H), 1.91 (a−dd, J = 12.0, 2.4, 2H), 2.32 (dd, J = 7.4, 5.8, 2H), 3.38 (s, 3H), 3.44 (m, 1H), 3.52 (dd, J = 10.8, 5.6, 1H), 3.63 (dd, J = 10.8, 2.8, 1H), 4.23 (a−dt, J = 5.6, 2.8, 1H), 4.42 (dd, J = 9.0, 5.6, 1H), 4.47 (dd, J = 9.0, 5.6, 1H), 4.51−4.56 (m, 1H), 4.61 (t, J = 7.8, 1H), 5.48 (d, J = 8.0, 1H), 7.13 (t, J = 5.8, 1H), 7.25−7.37 (m, 6H). LC/MS: *m/z* 390 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-4-(3-ethylureido)-6-*O*-methyl-L-*lyxo*-hexonamide (20G).** ^{1}H NMR: δ 1.10 (t, J = 7.0, 3H), 2.29−2.33 (m, 2H), 3.16 (q, J = 7.0, 2H), 3.37 (s, 3H), 3.51 (dd, J = 10.8, 5.2, 1H), 3.62 (dd, J = 10.8, 3.2, 1H), 4.23 (a−dt, J = 5.4, 3.2, 1H), 4.42 (dd, J = 14.6, 6.0, 1H), 4.46 (dd, J = 14.6, 6.0, 1H), 4.53 (m, 1H), 4.60 (t, J = 7.6, 1H), 5.69 (bd, J = 4.8, 1H), 7.21 (t, J = 6.0, 1H), 7.25−7.36 (m, 6H). LC/MS: *m/z* 336 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-6-*O*-methyl-4-{3-[(S)-α-methylbenzyl]ureido}-L-*lyxo*-hexonamide (21G).** ^{1}H NMR: δ 1.42 (d, J = 6.0, 3H), 2.18−2.26 (m, 2H), 3.20 (s, 3H), 3.25 (m, 1H), 3.45 (dd, J = 10.6, 2.6, 1H), 4.15 (a−dt,

J = 6.4, 3.4, 1H), 4.35 (dd, J = 14.8, 6.0, 1H), 4.43 (dd, J = 14.8, 6.4, 1H), 4.48 (m, 1H), 4.53 (t, J = 7.2, 1H), 4.76 (a-quintet, J = 6.7, 1H), 5.46 (bd, J = 7.2, 1H), 5.52 (d, J = 7.2, 1H), 7.11 (t, J = 5.8, 1H), 7.21−7.35 (m, 10H). LC/MS: *m/z* 412 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-4-[3-(*m*-cyanophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (22G).** ^{1}H NMR: δ 2.26−2.37 (m, 2H), 3.34 (s, 3H), 3.55 (dd, J = 10.8, 5.2, 1H), 3.67 (dd, J = 10.8, 2.8, 1H), 4.33 (m, 1H), 4.49 (d, J = 6.4, 2H), 4.64 (t, J = 8.0, 1H), 4.68 (m, 1H), 6.43 (d, J = 8.4, 1H), 7.20−7.42 (m, 8H), 7.47 (ddd, J = 8.0, 2.0, 1.6, 1H), 7.75 (t, J = 1.8, 1H), 8.29 (s, 1H). LC/MS: *m/z* 409 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-4-[3-(*p*-ethoxyphenyl)ureido]-6-*O*-methyl-L-*lyxo*-hexonamide (23G).** ^{1}H NMR: δ 1.40 (t, J = 6.8, 3H), 2.32 (dd, J = 7.0, 6.0, 2H), 3.23 (s, 3H), 3.47 (dd, J = 10.8, 5.6, 1H), 3.61 (dd, J = 10.8, 2.8, 1H), 3.98 (q, J = 6.8, 2H), 4.23 (a−dt, J = 5.0, 3.0, 1H), 4.40 (dd, J = 14.8, 6.0, 1H), 4.70 (dd, J = 14.8, 6.0, 1H), 4.56−4.63 (m, 2H), 6.01 (d, J = 7.6, 1H), 6.79−6.83 (m, 2H), 7.14−7.21 (m, 3H), 7.21−7.36 (m, 6H). LC/MS: *m/z* 428 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-6-*O*-methyl-4-[3-(*m*-trifluoromethylphenyl)ureido]-L-*lyxo*-hexonamide (24G).** ^{1}H NMR: δ 2.29−2.34 (m, 2H), 3.33 (s, 3H), 3.54 (dd, J = 10.8, 5.6, 1H), 3.67 (dd, J = 10.8, 2.4, 1H), 4.33 (m, 1H), 4.48 (d, J = 6.0, 2H), 4.63−4.71 (m, 2H), 6.45 (d, J = 8.4, 1H), 7.20−7.39 (m, 8H), 7.45 (m, 1H), 7.71 (s, 1H), 8.21 (s, 1H). LC/MS: *m/z* 452 (M + H)[+].

***N*-Benzyl 2,5-Anhydro-3,4-dideoxy-6-*O*-methyl-4-(3-*m*-tolylureido)-L-*lyxo*-hexonamide (25G).** ^{1}H NMR: δ 2.27 (s, 3H), 2.33 (m, 2H), 3.30 (s, 3H), 3.52 (dd, J = 10.8, 5.6, 1H), 3.65 (dd, J = 10.8, 2.4, 1H), 4.30 (m, 1H), 4.47 (d, J = 5.6, 2H), 4.59−4.67 (m, 2H), 6.20 (d, J = 8.0, 1H), 6.84 (m, 1H), 7.05 (m, 1H), 7.11−7.16 (m, 2H), 7.25−7.37 (m, 6H), 7.51 (s, 1H). LC/MS: *m/z* 398 (M + H)[+].

***N*-Ethyl 2,5-Anhydro-4-[3-(*o*-chlorophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (18A).** ^{1}H NMR: δ 1.14 (t, J = 7.4, 3H), 2.22−2.33 (m, 2H), 3.18−3.37 (m, 5H), 3.53 (dd, J = 10.8, 6.4, 1H), 3.66 (dd, J = 10.8, 2.8, 1H), 4.27−4.31 (m, 1H), 4.53 (t, J = 8.2, 1H), 4.58−4.64 (m, 1H), 6.91−7.02 (m, 3H), 7.19−7.23 (m, 1H), 7.30 (dd, J = 8.2, 1.8, 1H), 7.62 (s, 1H), 8.10 (dd, J = 8.2, 1.4, 1H). LC/MS: *m/z* 356 (M + H)[+].

***N*-Propyl 2,5-Anhydro-4-[3-(*o*-chlorophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (18B).** ^{1}H NMR: δ 0.90 (t, J = 7.4, 3H), 1.52 (sextet, J = 7.4, 2H), 2.26−2.38 (m, 2H), 3.16−3.31 (m, 2H), 3.36 (s, 3H), 3.54 (dd, J = 10.8, 6.8, 1H), 3.66 (dd, J = 10.8, 2.8, 1H), 4.30−4.33 (m, 1H), 4.58 (t, J = 8.0, 1H), 4.61−4.67 (m, 1H), 6.82 (d, J = 8.8, 1H), 6.89−6.97 (m, 2H), 7.20−7.24 (m, 1H), 7.31 (dd, J = 8.2, 2.0, 1H), 7.53 (s, 1H), 8.09 (dd, J = 8.2, 2.0, 1H). LC/MS: *m/z* 370 (M + H)[+].

***N*-[3-(2-Oxopyrrolidin-1-yl)-propyl] 2,5-Anhydro-4-[3-(*o*-chlorophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (18C).** ^{1}H NMR: δ 1.68−1.76 (m, 2H), 1.99−2.07 (m, 2H), 2.27−2.42 (m, 4H), 3.12−3.43 (m, 9H), 3.58 (dd, J = 10.8, 6.4, 1H), 3.68 (dd, J = 10.8, 3.2, 1H), 4.32−4.35 (m, 1H), 4.57 (t, J = 7.8, 1H), 4.58−4.65 (m, 1H),

6.85 (d, *J* = 8.4, 1H), 6.91−6.95 (m, 1H), 7.19−7.24 (m, 1H), 7.29 (dd, *J* = 8.4, 1.6, 1H), 7.60 (s, 1H), 7.72 (t, *J* = 6.2, 1H), 8.12 (dd, *J* = 8.4, 2.0, 1H). LC/MS: *m/z* 453 (M + H)$^+$.

N-(2-Dimethylaminoethyl) 2,5-Anhydro-4-[3-(o-chlorophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18D). ^{1}H NMR: δ 2.24 (s, 6H), 2.34 (a−dd, *J* = 7.8, 5.8, 2H), 2.43 (t, *J* = 6.2, 2H), 3.29−3.44 (m, 5H), 3.55 (dd, *J* = 10.8, 5.6, 1H), 3.67 (dd, *J* = 10.8, 2.8, 1H), 4.31 (a−dt, *J* = 5.6, 2.8, 1H), 4.60 (t, *J* = 8.0, 1H), 4.62−4.67 (m, 1H), 6.67 (d, *J* = 7.6, 1H), 6.95 (a−dt, *J* = 7.6, 1.6, 1H), 7.20−7.25 (m, 1H), 7.28−7.33 (m, 2H), 7.43 (s, 1H), 8.08 (dd, *J* = 8.2, 1.8, 1H). LC/MS: *m/z* 399 (M + H)$^+$.

N-Isobutyl 2,5-Anhydro-4-[3-(o-chlorophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18E). ^{1}H NMR: δ 0.89 (d, *J* = 6.4, 6H), 1.77 (septet, *J* = 6.4, 1H), 2.27−2.37 (m, 2H), 3.10 (t, *J* = 6.6, 2H), 3.36 (s, 3H), 3.54 (dd, *J* = 10.8, 6.0, 1H), 3.66 (dd, *J* = 10.8, 3.2, 1H), 4.29−4.33 (m, 1H), 4.59 (t, *J* = 7.8, 1H), 4.60−4.66 (m, 1H), 6.78 (d, *J* = 8.0, 1H), 6.92−6.97 (m, 2H), 7.20−7.24 (m, 1H), 7.31 (dd, *J* = 8.0, 1.2, 1H), 7.53 (s, 1H), 8.09 (dd, *J* = 8.0, 1.2, 1H). LC/MS: *m/z* 384 (M + H)$^+$.

N-(3-Phenylpropyl) 2,5-Anhydro-4-[3-(o-chlorophenyl)-ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18F). ^{1}H NMR: δ 1.83 (quintet, *J* = 7.6, 2H), 2.23−2.35 (m, 2H), 2.62 (t, *J* = 7.6, 2H), 3.23−3.38 (m, 5H), 3.52 (dd, *J* = 10.6, 6.4, 1H), 3.65 (dd, *J* = 10.6, 2.4, 1H), 4.24−4.28 (m, 1H), 4.56 (t, *J* = 8.2, 1H), 4.59−4.65 (m, 1H), 6.77 (d, *J* = 8.0, 1H), 6.89 (t, *J* = 6.0, 1H), 6.94 (a−dt, *J* = 8.0, 2.0, 1H), 7.13−7.31 (m, 7H), 7.52 (s, 1H), 8.10 (dd, *J* = 8.6, 1.4, 1H). LC/MS: *m/z* 446 (M + H)$^+$.

N-[2-(p-Sulfamoylphenyl)ethyl] 2,5-Anhydro-4-[3-(o-chlorophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18H). ^{1}H NMR (DMSO-*d*$_6$): The region of 6.0 to 9.5 ppm should contain all the NH and Ar−C*H* peaks, which should equal 13H; however, the region integrates to ∼19H. Since the carbohydrate region contained the required amount of protons, the additional protons were attributed to excess amine that was not fully removed by the resin scavenging. This meant that the spectrum could not be fully assigned for the purpose of characterization. LC/MS: *m/z* 511 (M + H)$^+$.

N-(3-Morpholin-4-ylpropyl) 2,5-Anhydro-4-[3-(o-chlorophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18I). ^{1}H NMR: δ 1.66−1.73 (m, 2H), 2.30−2.34 (m, 2H), 2.39−2.47 (m, 6H), 3.22−3.30 (m, 1H), 3.35 (s, 3H), 3.44−3.51(m, 1H), 3.54 (dd, *J* = 10.8, 6.4, 1H), 3.66 (dd, *J* = 10.8, 3.2, 1H), 3.67−3.78 (m, 4H), 4.34 (m, 1H), 4.58 (t, *J* = 7.8, 1H), 4.63−4.69 (m, 1H), 6.81 (d, *J* = 8.0, 1H), 6.92−6.97 (m, 1H), 7.20−7.25 (m, 1H), 7.31 (dd, *J* = 8.0, 1.2, 1H), 7.53 (s, 1H), 7.77 (t, *J* = 5.8, 1H), 8.10 (dd, *J* = 8.0, 0.8, 1H). LC/MS: *m/z* 455 (M + H)$^+$.

N-Nonyl 2,5-Anhydro-4-[3-(o-chlorophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (18J). ^{1}H NMR: δ 0.88 (t, *J* = 6.8, 3H), 1.24 (m, 12H), 1.45−1.50 (m, 2H), 2.26−2.37 (m, 2H), 3.18−3.33 (m, 2H), 3.36 (s, 3H), 3.54 (dd, *J* = 10.6, 6.4, 1H), 3.66 (dd, *J* = 10.6, 2.8, 1H), 4.30−4.33 (m, 1H), 4.58 (t, *J* = 8.2, 1H), 4.62−4.68 (m, 1H), 6.83 (d, *J* = 8.0, 1H), 6.88 (t, *J* = 6.0, 1H), 6.94 (dt, *J* =

8.0, 2.0, 1H), 7.19−7.24 (m, 1H), 7.30 (dd, *J* = 8.2, 1.4, 1H), 7.54 (s, 1H), 8.09 (dd, *J* = 8.2, 1.8, 1H). LC/MS: *m/z* 454 (M + H)$^+$.

N-Ethyl 2,5-Anhydro-4-[3-(m-cyanophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22A). ^{1}H NMR: δ 1.17 (t, *J* = 7.2, 3H), 2.22 (dd, *J* = 8.0, 5.2, 2H), 3.27−3.33 (m, 2H), 3.36 (s, 3H), 3.51 (dd, *J* = 10.8, 6.8, 1H), 3.65 (dd, *J* = 10.8, 2.4, 1H), 4.27−4.31 (m, 1H), 4.48 (t, *J* = 8.0, 1H), 4.55−4.61 (m, 1H), 6.54 (d, *J* = 8.4, 1H), 7.11 (t, *J* = 5.8, 1H), 7.21 (dt, *J* = 7.2, 1.2, 1H), 7.31 (t, *J* = 8.0, 1H), 7.62−7.66 (m, 1H), 7.75 (t, *J* = 1.8, 1H), 8.66 (s, 1H). LC/MS: *m/z* 347 (M + H)$^+$.

N-Propyl 2,5-Anhydro-4-[3-(m-cyanophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22B). ^{1}H NMR: δ 0.95 (t, *J* = 7.6, 3H), 1.57 (sextet, *J* = 7.6, 2H), 2.25−2.30 (m, 2H), 3.23−3.28 (m, 2H), 3.38 (s, 3H), 3.55 (dd, *J* = 10.4, 5.6, 1H), 3.69 (dd, *J* = 10.4, 2.4, 1H), 4.34 (dt, *J* = 5.6, 2.0, 1H), 4.55−4.59 (m, 1H), 4.63−4.69 (m, 1H), 6.45 (d, *J* = 8.0, 1H), 7.07 (t, *J* = 6.0, 1H), 7.24 (dt, *J* = 7.6, 1.6, 1H), 7.33 (t, *J* = 8.2, 1H), 7.62−7.65 (m, 1H), 7.76 (t, *J* = 1.8, 1H), 8.43 (s, 1H). LC/MS: *m/z* 361 (M + H)$^+$.

N-[3-(2-Oxopyrrolidin-1-yl)-propyl] 2,5-Anhydro-4-[3-(m-cyanophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22C). ^{1}H NMR: δ 1.73 (sextet, *J* = 6.8, 2H), 2.00−2.10 (m, 2H), 2.29−2.33 (m, 2H), 2.41 (t, *J* = 8.2, 2H), 3.16−3.46 (m, 9H), 3.57 (dd, *J* = 10.8, 5.6, 1H), 3.66 (dd, *J* = 10.8, 3.2, 1H), 4.35−4.38 (m, 1H), 4.56 (t, *J* = 7.8, 1H), 4.58−4.65 (m, 1H), 6.46 (bs, 1H), 7.22 (dt, *J* = 8.0, 1.2, 1H), 7.32 (t, *J* = 8.0, 1H), 7.64−7.70 (m, 2H), 7.76 (t, *J* = 1.8, 1H), 8.62 (s, 1H). LC/MS: *m/z* 444 (M + H)$^+$.

N-(2-Dimethylaminoethyl) 2,5-Anhydro-4-[3-(m-cyanophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22D). ^{1}H NMR: δ 2.26 (ddd, *J* = 13.2, 8.8, 6.4, 1H), 2.35 (ddd, *J* = 13.2, 7.0, 2.0, 1H), 2.58 (s, 6H), 2.77−2.87 (m, 2H), 3.37 (s, 3H), 3.39−3.59 (m, 2H), 3.63−3.68 (m, 2H), 4.30−4.33 (m, 1H), 4.63−4.71 (m, 2H), 6.84 (d, *J* = 8.0, 1H), 7.23 (a−d, *J* = 8.4, 1H), 7.32 (t, *J* = 8.4, 1H), 7.61−7.64 (m, 1H), 7.75 (t, *J* = 6.0, 1H), 7.88 (t, *J* = 1.6, 1H), 8.62 (s, 1H). LC/MS: *m/z* 390 (M + H)$^+$.

N-Isobutyl 2,5-Anhydro-4-[3-(m-cyanophenyl)ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22E). ^{1}H NMR: δ 0.94 (d, *J* = 6.4, 6H), 1.82 (septet, *J* = 6.4, 1H), 2.22−2.34 (m, 2H), 3.06−3.19 (m, 2H), 3.37 (s, 3H), 3.56 (dd, *J* = 10.8, 5.6, 1H), 3.69 (dd, *J* = 10.8, 2.6, 1H), 4.35 (a−dt, *J* = 5.6, 2.6, 1H), 4.57 (t, *J* = 8.2, 1H), 4.64−4.70 (m, 1H), 6.42 (d, *J* = 8.4, 1H), 7.06 (t, *J* = 6.4, 1H), 7.24 (dt, *J* = 8.0, 1.6, 1H), 7.33 (t, *J* = 8.0, 1H), 7.62−7.66 (m, 1H), 7.76 (t, *J* = 1.8, 1H), 8.43 (s, 1H). LC/MS: *m/z* 375 (M + H)$^+$.

N-(3-Phenylpropyl) 2,5-Anhydro-4-[3-(m-cyanophenyl)-ureido]-3,4-dideoxy-6-O-methyl-L-*lyxo*-hexonamide (22F). ^{1}H NMR: δ 1.89 (quintet, *J* = 7.6, 2H), 2.16−2.29 (m, 2H), 2.66 (t, *J* = 7.6, 2H), 3.28−3.34 (m, 2H), 3.35 (s, 3H), 3.53 (dd, *J* = 10.8, 5.6, 1H), 3.66 (dd, *J* = 10.8, 3.2, 1H), 4.29 (a−dt, *J* = 6.2, 2.8, 1H), 4.50−4.54 (m, 1H), 4.60−4.66 (m, 1H), 6.38 (d, *J* = 8.8, 1H), 6.98 (t, *J* = 6.0, 1H), 7.15−7.32 (m, 7H), 7.57−7.60 (m, 1H), 7.76 (t, *J* = 1.6, 1H), 8.39 (s, 1H). LC/MS: *m/z* 437 (M + H)$^+$.

N-[2-(*p*-Sulfamoylphenyl)ethyl] 2,5-Anhydro-4-[3-(*m*-cyanophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (22H). ^{1}H NMR (DMSO-d_6): The region of 6.0–9.5 ppm should contain all the NH and Ar–C*H* peaks, which should equal 13H; however, the region integrates to ~18H. Since the carbohydrate region contained the required amount of protons, the additional protons were attributed to excess amine that was not fully removed by the resin scavenging. This meant that the spectrum could not be fully assigned for the purpose of characterization. LC/MS: *m/z* 502 (M + H)[+].

N-(3-Morpholin-4-yl-propyl) 2,5-Anhydro-4-[3-(*m*-cyanophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (22I). ^{1}H NMR: δ 1.73 (m, 2H), 2.26–2.32 (m, 2H), 2.49–2.58 (m, 6H), 3.27–3.36 (m, 1H), 3.37 (s, 3H), 3.47–3.54 (m, 1H), 3.56 (dd, *J* = 10.6, 5.2, 1H), 3.68 (dd, *J* = 10.6, 2.4, 1H), 3.71–3.81 (m, 4H), 4.37 (a–dt, *J* = 5.2, 3.0, 1H), 4.56 (t, *J* = 8.2, 1H), 4.65–4.71 (m, 1H), 6.42 (d, *J* = 8.0, 1H), 7.24 (dt, *J* = 8.0, 1.2, 1H), 7.34 (t, *J* = 8.0, 1H), 7.67–7.70 (m, 1H), 7.72 (t, *J* = 1.8, 1H), 8.04 (m, 1H), 8.46 (s, 1H). LC/MS: *m/z* 446 (M + H)[+].

N-Nonyl 2,5-Anhydro-4-[3-(*m*-cyanophenyl)ureido]-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (22J). ^{1}H NMR: δ 0.88 (t, *J* = 6.8, 3H), 1.25–1.29 (m, 12H), 1.49–1.56 (m, 2H), 2.21–2.32 (m, 2H), 3.27 (a–ddd, *J* = 13.4, 7.6, 3.0, 2H), 3.37 (s, 3H), 3.55 (dd, *J* = 10.8, 6.0, 1H), 3.68 (dd, *J* = 10.8, 2.8, 1H), 4.35 (dt, *J* = 6.0, 2.8, 1H), 4.55 (t, *J* = 8.0, 1H), 4.62–4.68 (m, 1H), 6.49 (d, *J* = 8.4, 1H), 7.00 (t, *J* = 6.0, 1H), 7.23 (dt, *J* = 7.6, 1.2, 1H), 7.32 (t, *J* = 7.6, 1H), 7.60–7.63 (m, 1H), 7.79 (t, *J* = 1.8, 1H), 8.51 (s, 1H). LC/MS: *m/z* 445 (M + H)[+].

N-Ethyl 2,5-Anhydro-(3-*tert*-butyl-ureido)-3,4-dideoxy-6-*O*-methyl-4-L-*lyxo*-hexonamide (16A). ^{1}H NMR: δ 1.14 (t, *J* = 7.2, 3H), 1.32 (s, 9H), 2.18–2.21 (m, 2H), 3.21–3.33 (m, 2H), 3.39 (s, 3H), 3.47 (dd, *J* = 10.4, 6.4, 1H), 3.62 (dd, *J* = 10.4, 2.0, 1H), 4.22–4.26 (m, 1H), 4.43–4.50 (m, 2H), 5.22 (s, 1H), 5.67 (d, *J* = 8.0, 1H), 6.94 (t, *J* = 5.8, 1H). LC/MS: *m/z* 302 (M + H)[+].

N-Ethyl 2,5-Anhydro-4-(3-cyclohexyl-ureido)-3,4-dideoxy-6-*O*-methyl-L-*lyxo*-hexonamide (19A). ^{1}H NMR: δ 1.06–1.39 (m, 8H), 1.57–1.62 (m, 1H), 1.67–1.71 (m, 2H), 1.88–1.92 (m, 2H), 2.22 (dd, *J* = 7.8, 5.4, 2H), 3.19–3.36 (m, 2H), 3.39 (s, 3H), 3.42–3.54 (m, 2H), 3.63 (dd, *J* = 10.8, 3.2, 1H), 4.22–4.25 (m, 1H), 4.44–4.51 (m, 2H), 5.25 (d, *J* = 8.0, 1H), 5.76 (d, *J* = 8.4, 1H), 6.95 (t, *J* = 5.8, 1H). LC/MS: *m/z* 328 (M + H)[+].

Supporting Information Available. The additional information includes detailed experimental data for general procedures 1–5, the yields and purity of ureas **16**–**25**, data concerning the reaction conditions required for the final synthetic step for each library member, and ELS purity data and crude yields for the final library members and the data for the crystal structure of **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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