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Synthesis and Structural Analysis of the Anilides of Glucuronic Acid and Orientation of the Groups on the Carbohydrate Scaffolding

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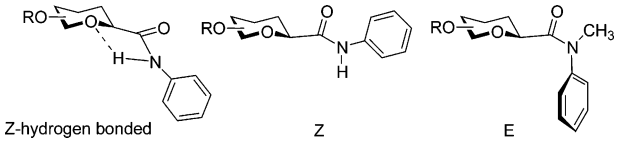

The synthesis of anilides derived from glucuronic acid is described. Secondary anilides had a *Z* configuration in the solid state and showed intramolecular and intermolecular hydrogen bonding. However, on the basis of NMR and IR studies, there was generally no evidence for the same hydrogen bonding in solution. Tertiary anilides showed a strong preference for the *E* configuration on the basis of NOE studies and molecular mechanics calculations. The alkylation of the secondary anilides induces a configurational switch that alters the orientation of the aromatic group with respect to the pyranose, which has relevance for presentation or orientation of pharmacophoric groups on carbohydrate scaffolds.

1. Introduction

The use of carbohydrates as scaffolds in peptidomimetic research was first experimentally explored by Hirschmann, Nicolaou, Smith, and co-workers.[1] A broad range of research topics in which carbohydrate scaffolds are of interest have since been explored.[2−4] The strategies generally involve the development of synthetic sequences in solution or on a solid phase for placement or grafting of the pharmacophoric groups onto saccharide scaffolds; the scaffolds project the attached groups in the direction of the binding sites. The saccharides have been shown to be privileged scaffolds, and the results published indicate that monosaccharide and higher-order saccharide scaffolds hold promise for being universally useful as drug discovery platforms. In addition, there has also been interest in carbohydrate mimetics and *carbohybrids*.[5] In this area, the focus is the development of compounds that bind with high affinities to carbohydrate receptors, and this can deal with attachment of a hydrophobic or other group to the carbohydrate of interest. In such contexts, the study of preferred structural orientations of the groups attached to monosaccharides would be important, but this has not been investigated with any great detail; the exceptions are the previous determinations of the saccharide ring conformation and the determination of the preferences displayed for glycosidic torsion angles.[6] We have previously reported, as an extension of earlier studies carried out by other

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(2) (a) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503. (b) Kallus, C.; Opatz, T.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Tetrahedron Lett.* **1999**, *40*, 7783. (c) Opatz, T.; Kallus, C.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Eur. J. Org. Chem.* **2003**, 1527. (d) Opatz, T.; Kallus, C.; Wunberg, T.; Kunz, H. *Tetrahedron* **2004**, *60*, 8613. (e) Hunger, U.; Ohnsmann, J.; Kunz, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1104. (f) Sofia, M. J. *Mol. Diversity* **1998**, *3*, 75. (g) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H. M.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802. (h) Sofia, M. J. *Med. Chem. Res.* **1998**, *8*, 362. (i) Sofia, M. J.; Silva, D. J. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 365−376. (j) Silva, D. J.; Sofia, M. J. *Tetrahedron Lett.* **2000**, *41*, 855. (k) Jain, R.; Kamau, M.; Wang, C. G.; Ippolito, R.; Wang, H. M.; Dulina, R.; Anderson, J.; Gange, D.; Sofia, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2185. (l) Baizman, E. R.; Branstrom, A. A.; Longley, C. B.; Allanson, N.; Sofia, M. J.; Gange, D.; Goldman, R. C. *Microbiology (Reading, U.K.)* **2000**, *146*, 3129. (m) Ghosh, M.; Dulina, R. G.; Kakarla, R.; Sofia, M. J. *J. Org. Chem.* **2000**, *65*, 8387.

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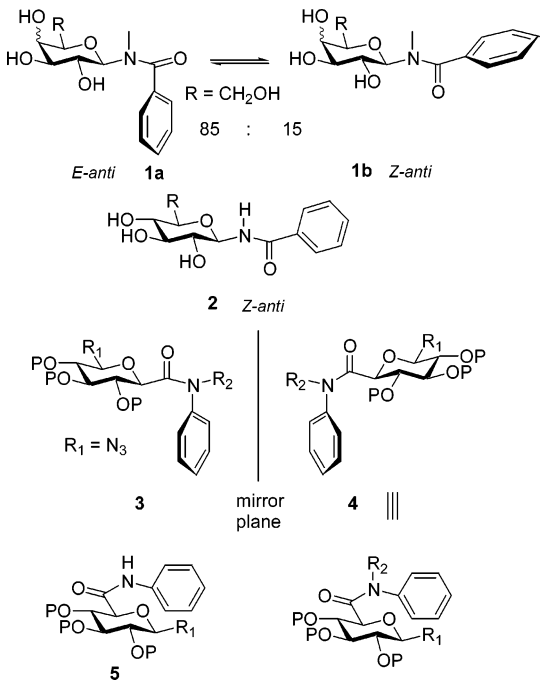
researchers,[7] the structural preferences for glycosyl aromatic amides, which are shown to diverge depending on the nature of the amide; tertiary amides strongly prefer the *E*-anti structure, **1a**, whereas secondary amides prefer the *Z*-anti structure, **2** (Chart 1).[8] This results in a diverging spatial relationship between the aromatic and pyranose groups when **1a** and **2** are compared and could be relevant to the biological activity displayed by such amides.[9] The preferred directional properties of the aromatic ring or groups attached to the aromatic ring of amides depend on the molecule having either a secondary or tertiary amide, and this could be considered in the design of bioactive molecules on carbohydrate templates, depending on the orientation required for the aromatic group. The N-alkylation of the secondary amides related to **2**, used for the synthesis of the tertiary amides, can be unreliable, and its success depends, to a large degree, on the nature of the protecting groups and the reaction conditions; this approach was not successful in our hands for the preparation of hindered tertiary amides (e.g., *N*-isopropyl-*N*-glycosylbenzamides). Because of the synthetic difficulties, we have studied the synthesis and structural preferences of **4** which is a pseudoenantiomer of β-D-glucopyranose-*C*-carboxamide[10] **3**, and they are described herein. It seemed interesting to determine if the aromatic groups and saccharide ring would, as in **1a**, prefer a similar spatial arrangement and if this arrangement would be different than that of the secondary anilide **5**.[11]

CHART 1



2. Results and Discussion

2.1. Synthesis of Amides. Anhydride **6**[12] was used as an intermediate in the synthesis of the D-glucuronic acid derivatives (Scheme 1). Secondary amides **8** and **9**, but not tertiary amide **10**, were obtained from the reaction of **6** with the appropriate amine in dichloromethane; treatment of **6** with *N*-methylaniline produced the acid **7** as a result of the more hindered nucleophile reacting at the carbonyl group of the anhydride furthest from the saccharide. Both secondary amides and tertiary amides, **8**−**10**, were prepared via a DCC-promoted coupling reaction of acid **7**, which was obtained by the hydrolysis of **6**.[12] The yields for secondary amides **8** and **9** are similar whether anhydride **6** or acid **7** is used. The reaction from anhydride **6** produces a mixture from which product isolation and purification is more straightforward. The coupling of **7** with aniline in the presence of ethyl chloroformate and triethylamine[13]

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(6) For a review, see: Imberty, A.; Pérez, S. *Chem. Rev.* **2000**, *100*, 4567.

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(8) The *E* and *Z* nomenclature refer to the amide configuration. For the *Z* isomer the groups of highest priority according to Cahn Ingold Prelog rules (for **1** and **2** these are the pyranose group and oxygen atom, respectively) are on same side of the plane defined by the N−C bond; for the *E* isomer these groups are on opposite sides of the N−C bond. The syn and anti nomenclature refers to torsion angle defined by H_1−C_1−N−H. For the anti (antiperiplanar) isomer, this angle is 180 ± 90°; for the syn (synperiplanar) isomer, this angle is 0 ± 90°.

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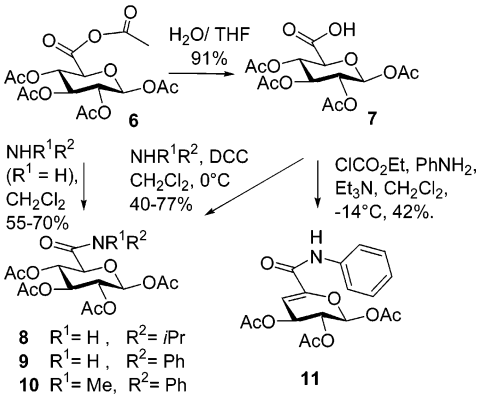
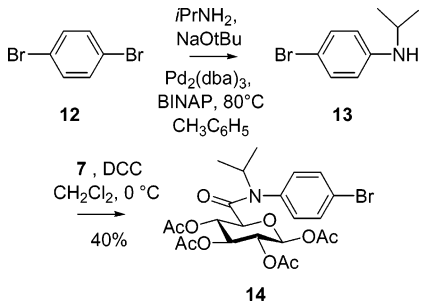
SCHEME 1



SCHEME 2



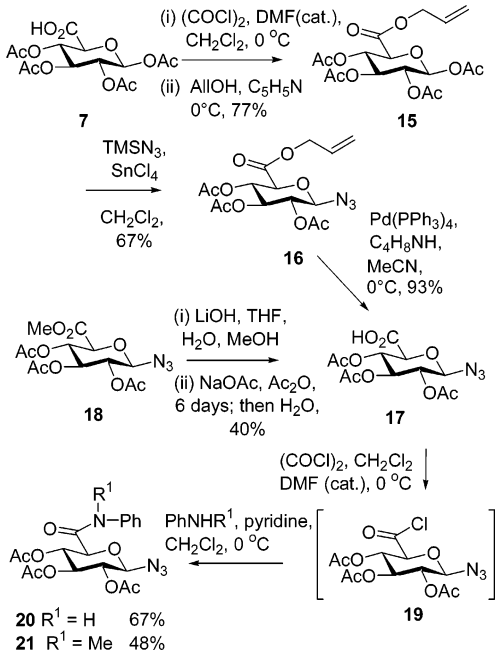
produced the 4,5-unsaturated amide **11** as a result of the base-promoted elimination of acetic acid in addition to the amide formation.[14]

The synthesis of the *N*-isopropyl derivative **14** was carried out with the purpose of preparing an amide more hindered than **10** (Scheme 2). The synthesis of *p*-bromo-*N*-isopropylaniline **13** was achieved by the palladium(0)/BINAP-catalyzed aryl amination of 1,4-dibromobenzene **12**.[15] Amine **13** was coupled to carboxylic acid **7** using DCC to produce **14**.

The preparation of amides which have the azide group at the anomeric position was undertaken (Schemes 3 and 4).[12] Acid **7** was used to produce **15** via the reaction of its acid chloride with allyl alcohol in the presence of pyridine. The reaction of **15** with azidotrimethylsilane in the presence of tin(IV) chloride[16] produced the β-azide **16**. The allyl ester was removed using $Pd(Ph_3P)_4$ in the presence of pyrrolidine in acetonitrile, by a modification of a previously described procedure, to produce the β-acid **17**.[17] Acid **17** can also be prepared from azide **18**[18] by the saponification of all esters and the subsequent acetylation for 6 days in the presence of acetic anhyride and sodium acetate. Acid **17** can be converted into an amide by direct coupling with aniline or *N*-methylaniline or via the acid chloride **19** to produce **20** or **21**.[19]

Mixtures (78:22) of α-azide **23** and β-azide **17** were obtained from the reaction of the 6,1-lactone **22** with

SCHEME 3



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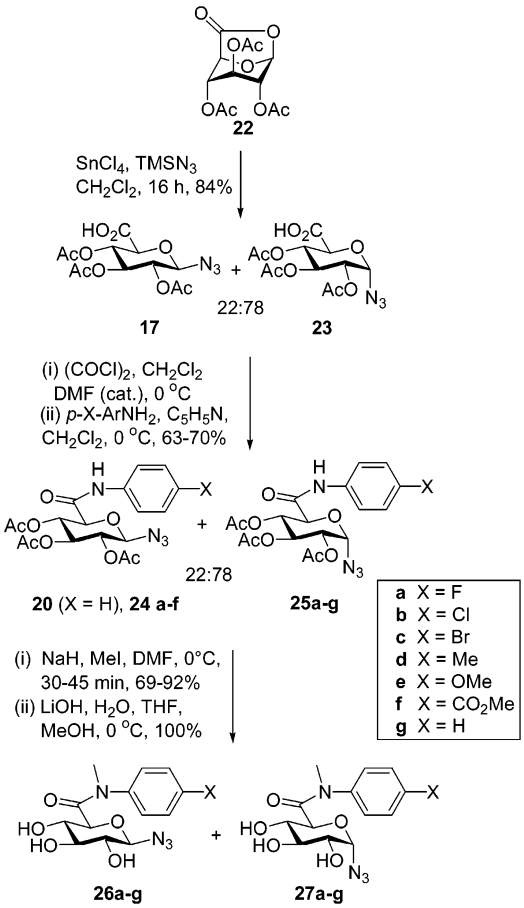

$TMSN_3$ and $SnCl_4$ (Scheme 4).[20] These mixtures were converted into amides **20**, **24a**−**f**, and **25a**−**g** via the acid

(13) BeMiller, J. N.; Yadav, M. P. *Carbohydr. Res.* **1990**, *200*, 111.
(14) It is known that formation of $\Delta^{4,5}$-glucuronides can occur from acetylated D-glucuronic acid derivatives in the presence of base; evidence for an E1cB mechanism has been presented. See: Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rep.* **1998**, 173.
(15) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.
(16) Peto, C.; Batta, G.; Györgydeák, Z.; Sztaricskai, F. *Liebigs Ann. Chem.* **1991**, 505.
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SCHEME 5

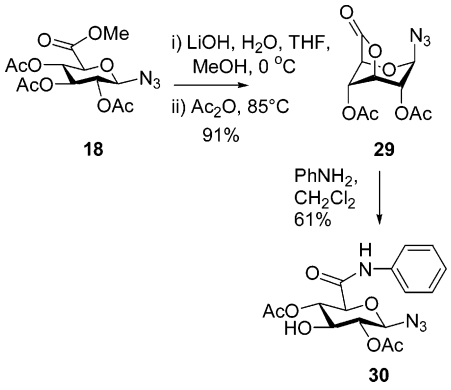
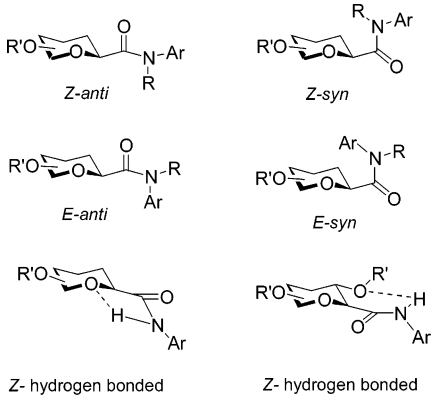


CHART 2. Amide Structure and Nomenclature



chlorides. Alkylation of **20**, **24a**–**f**, and **25a**–**g** with methyl iodide and sodium hydride in DMF at 0 °C and the subsequent deprotection produced **26a**–**g** and **27a**–**g**. In some cases, the α- and *β*-anomers of **26** and **27** were separated by reverse-phase HPLC.

Amide **30** was prepared via the 6,3-lactone derivative **29**, which was prepared in two steps from ester **18**. This 6,3-lactone is reactive toward nucleophiles and can be readily ring-opened in the presence of aniline to produce **30** (Scheme 5).

2.2. X-ray Structural Analysis of Amides. The amide structures that were considered are defined in Chart 2.[21] They were *Z*-syn and *Z*-anti with no hydrogen bonding, two *Z*-anti hydrogen-bonded structures (hydrogen bonding between NH and the pyranose oxygen and between NH and O-4), and *E*-anti and *E*-syn. Single crystals suitable for X-ray-based structure determination were obtained for the secondary amides **20** and **25c**. Amide **20** (Figure 1) had the *Z* configuration, and an intramolecular hydrogen bond between NH and the pyranose oxygen was observed in the solid state; a dihedral angle of 5.55° was defined by $O_5-C_5-C_6-N$[22]

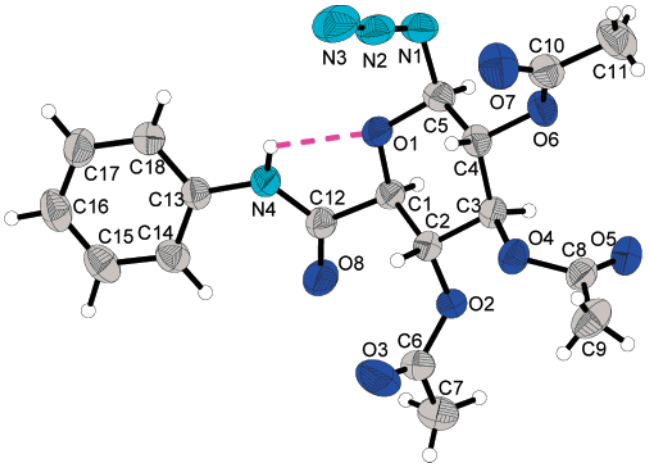


FIGURE 1. Molecular diagram and atomic labeling scheme for **20**. The atomic displacement parameters are at the 50% level. An intramolecular hydrogen bond is shown between NH and the pyranose oxygen atom.

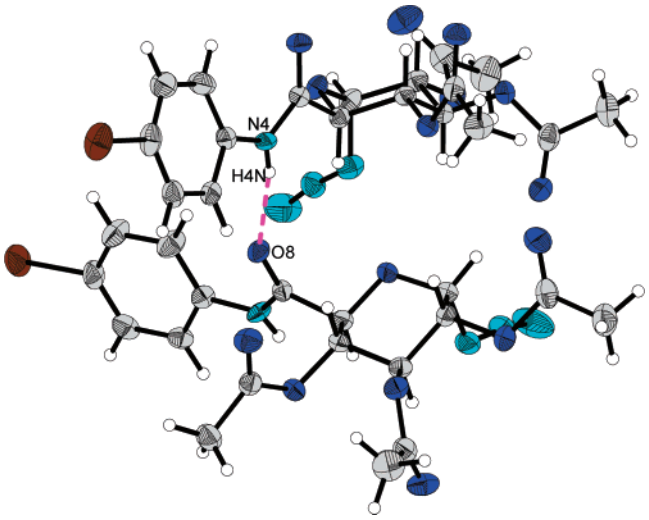


FIGURE 2. Molecular diagram and atomic labeling scheme for **25c**. The atomic displacement parameters are at the 50% level. An intermolecular hydrogen bond is shown between NH and the amide carbonyl.

revealing a five-membered-ring arrangement.[23] The aromatic group was coplanar with the amide group, and the distances between the hydrogen atom of the NH group and H-5 and H-4 in the crystal structure were 3.02 and 3.60 Å, respectively. The *Z*-anti structure and intermolecular hydrogen bonding were observed for the 4-Br derivative **25c**; this involved the NH group and the amide carbonyl group of an adjacent molecule in the packed structure (Figure 2). Intramolecular hydrogen bonding was not observed in this case.

2.3 Structural Analysis by Computational Methods. The coordinates from the crystal structure of **20** formed the basis for building of models of the anilides, and they were used in the subsequent structural analysis using Macromodel 8.5.[24] The dihedral angle

(19) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529.

(20) Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2518.

(21) The *E* and *Z* nomenclature refers to the amide configuration. For the *Z* isomer, the two groups of highest priority according to the Cahn Ingold Prelog rules (i.e., the aromatic group and oxygen atom) are on same side of the bond with double bond character (amide bond); for the *E* isomer these same two groups are on opposite sides of the amide bond. The syn and anti nomenclature refers to the torsion angle defined by $H_5-C_5-C_6-O$. For the anti isomer, this angle is 180 ± 90°; for the syn isomer, this angle is 0 ± 90°.

(22) The nomenclature refers to the pyranose numbering system.

(23) This geometrical arrangement has been observed but is not common. See: (a) Kroon, J.; Kanters, J. A.; van Duijnevelt-van De Rijdt, J. G. C. M.; van Duijnevelt, F. B.; Vliegenthart, J. A. *J. Mol. Struct.* **1975**, *24*, 109. (b) Taylor, R.; Kennard, O.; Wersischel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761.

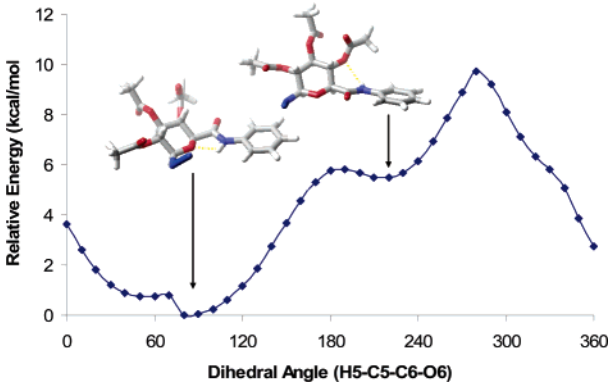


FIGURE 3. Energy (Merck Molecular Force Field, no solvent) plotted as a function of the dihedral angle $H_5-C_5-C_6-O_6$ using the crystal structure of **20** as the starting structure. The isomer ($H_5-C_5-C_6-O_6 = 90°$) with intramolecular hydrogen bonding between NH and the pyranose oxygen is lowest in energy. An isomer ($H_5-C_5-C_6-O_6 = 225°$) with a hydrogen bond between NH and O-4 was also a local minimum.

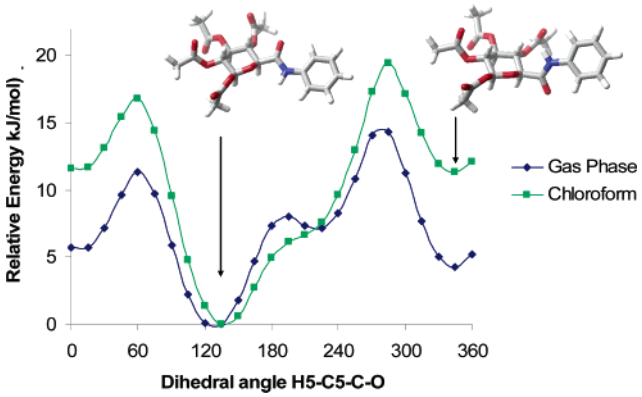


FIGURE 4. Energy (OPLSAA) plotted as a function of the dihedral angle $H_5-C_5-C_6-O_6$ using the model structure built for **9**. An anti conformation ($H_5-C_5-C_6-O_6 = 135°$) is calculated to be lower in energy than the conformations where hydrogen bonding to pyranose oxygen ($H_5-C_5-C_6-O_6 = 90°$) and O-4 ($H_5-C_5-C_6-O_6 = 225°$) would occur (shown in Figure 5) and lower in energy than a syn isomer where a dihedral angle defined by $H_5-C_5-C_6-O_6 = 345°$ corresponds to a local minimum. The distance between H-5 and NH for the lowest-energy *Z*-anti isomer is 2.33 Å. The distance between H-4 and NH for the syn local minimum isomer is 1.99 Å.

$H_5-C_5-C_6-O_6$ was varied by 15° increments, and the energy was calculated after minimization at each incremental stage; then the relationship was plotted as shown in Figures 3 and 4. The profiles obtained were force field dependent. The calculations with the Merck Molecular Force Field (Figure 3) predicted that the conformation with the intramolecular hydrogen bond between NH and the pyranose oxygen was a local minimum and the lowest-energy isomer; another local minimum was located for an isomer with a hydrogen bond between NH and the pyranose O-4. Similar energy profiles were obtained: (i) if these calculations were repeated for structural isomers where the anomeric azide group was replaced with a hydrogen atom, (ii) for **9**, and (iii) if the

(24) (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.

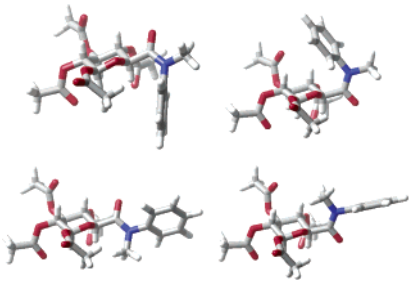


FIGURE 5. Local minima for *E*-anti (top left), *E*-syn (top right), *Z*-anti (bottom left), and *Z*-syn (bottom right) for **10** obtained using conformational searching techniques with the OPLSAA force field in Macromodel.

TABLE 1. Computed Relative Energy (kJ/mol) for Structural Isomers of 10[a]

solvent	force field	*E*-anti	*E*-syn	*Z*-anti	*Z*-syn
no solvent	OPLSAA	0.0	14.2	15.5	35.0
		(0.0)	(16.6)	(12.0)	(35.5)
no solvent	MMFFs	0.0	17.1	8.3	9.6
$CHCl_3$	OPLSAA	0.0	15.0	11.0	31.6
		(0.0)	(18.5)	(10.3)	(33.9)
$CHCl_3$	MMFFs	0.0	17.2	4.0	7.9

[a] Energies were minimized and calculated using Macromodel 8.1 in the gas phase (no solvent) and using the GBSA solvent continuum for chloroform. Structures used for the energy calculations were local minima generated using conformational searching techniques. Values in parentheses are for the corresponding analogue where H replaced the 1-OAc group.

GB/SA solvent continuum for $CHCl_3$ available in Macromodel was used. In contrast, the use of the OPLSAA Force Field (Figure 4) predicted that a *Z*-anti structure ($H_5-C_5-C_6-O_6 = 135°$) where no intramolecular hydrogen bonding occurs is a local minimum and the lowest-energy energy isomer and that a *Z*-syn structure ($H_5-C_5-C_6-O_6 = 345°$) is also a local minimum. The distance, in the calculated structure, between H-5 and NH for the lowest-energy *Z*-anti structure is 2.33 Å; the distance between H-4 and NH for the *Z*-syn local minimum structure is 1.99 Å. The anti isomer was 12 kJ/mol lower in energy than the syn isomer when the GB/SA solvent continuum for chloroform was applied in the calculation.

Conformational searching techniques and dihedral angle analysis were used to generate four local minima structures for the tertiary amide **10**, and they were *E*-anti, *E*-syn, *Z*-anti, and *Z*-syn (Figure 5). The energies were calculated using both the OPLSAA force field and the Merck Molecular force field in Macromodel 8.1 for the gas phase, and the effect of the solvent was also considered in the calculations by using the GBSA solvent continuum for chloroform. The *E*-anti isomer was calculated to be 4−18.5 kJ/mol more stable than the *E*-syn or *Z*-anti isomer and 7.9−35.5 kJ/mol more stable than the *Z*-syn isomer using these methods (Table 1).

2.4. NMR Spectroscopic Analysis of Amides. One set of signals was generally observed for the secondary amides in the ^1H and ^{13}C NMR spectra; this is consistent with the presence of one configurational isomer, the *Z* isomer. The distances observed between the NH and H-4 and H-5 in the crystal structure of **20** are within the range (<4.0 Å) where the NOE cross-peaks would be expected to be observed if the hydrogen-bonded structure,

TABLE 2. Dihedral Angles (deg) for Structural Isomers of 10[a]

	force field	*E*-anti	*E*-syn	*Z*-anti	*Z*-syn
Ψ ($H_5-C_5-C_6-O_6$)	OPLSAA	153.4	−0.8	152.9	1.2
φ ($O_6-C_6-N-C_{Me}$)	OPLSAA	1.4	3.0	−179.9	−176.4
Ψ ($H_5-C_5-C_6-O_6$)	MMFFs	153.4	4.0	136.1	20.1
φ ($O_6-C_6-N-C_{Me}$)	MMFFs	1.4	1.4	−170.7	−172.9

[a] The structural isomers correspond to the local minima in Table 1.

TABLE 3. Selected NMR Data for Anilides and the *Z*/*E* Ratios for Tertiary Amides

	δ (^{1}H NMR[a])					
compd	H-1 ($J_{1,2}$) Z	H-1 ($J_{1,2}$) E	H-5 ($J_{4,5}$) Z	H-5 ($J_{4,5}$) E	NH	*Z*/*E*
8	5.75 (8.0)	–	4.02 (9.7)	–	6.10	*Z*
9	5.85 (7.3)	–	4.24 (9.3)	–	7.94	*Z*
10	5.74 (8.1)	5.30 (8.0)	4.54 (10.0)	4.04 (9.8)	–	1:14.5
14	5.70	5.21 (8.4)	4.51	3.78 (9.6)	–	<1:10
20	4.85 (8.9)	–	4.15 (9.1)	–	8.03	*Z*
21	4.76 (8.2)	4.04 (8.0)	4.52 (10.2)	3.97 (9.5)	–	1:10
24a	4.85 (8.9)	–	4.13 (9.9)	–	8.01	*Z*
24b	4.86 (8.7)	–	4.14 (9.5)	–	8.07	*Z*
24c	4.85 (9.0)	–	4.13 (9.5)	–	8.01	*Z*
24d	4.85 (8.9)	–	4.13 (9.4)	–	8.02	*Z*
24e	4.85 (8.9)	–	4.13 (9.5)	–	7.98	*Z*
24f	4.88 (8.7)	–	4.17 (9.5)	–	8.21	*Z*
25a	5.76 (4.2)	–	4.49 (10.3)	–	7.97	*Z*
25b	5.70 (4.2)	–	4.49 (10.1)	–	8.04	*Z*
25c	5.76 (4.2)	–	4.49 (10.2)	–	7.98	*Z*
25d	5.75 (4.2)	–	4.48 (10.1)	–	7.97	*Z*
25e	5.75 (4.2)	–	4.49 (10.1)	–	7.94	*Z*
25f	5.78 (4.1)	–	4.52 (10.2)	–	8.17	*Z*
26c	4.91 (8.8)	4.40 (8.5)	nd	3.88 (9.6)	–	1:5.5
26f	4.92 (9.5)	4.49 (8.4)	nd	nd	–	1:5.5
26g	4.93 (8.8)	4.39 (8.4)	nd	3.89 (9.6)	–	1:5.7
27a	5.60	5.43 (4.4)	nd	4.16 (9.8)	–	1:11.8
27b	5.60	5.43 (4.4)	nd	4.17 (9.9)	–	1:11.3
27c	5.60	5.43 (4.2)	nd	4.17 (9.7)	–	1:8.4
27d	5.60	5.42 (4.4)	nd	4.20 (9.8)	–	1:7.6
27e	5.59	5.40 (4.2)	nd	4.17 (9.6)	–	1:11.7
27f	5.60	5.42 (4.4)	nd	4.16 (9.6)	–	1:9.4
27g	5.60	5.43 (4.4)	nd	4.19 (9.7)	–	1:11.1
30	4.77 (8.8)	–	–	–	8.06	*Z*

[a] NMR data for **8**−**21** and **30** recorded in $CDCl_3$; 300 MHz for **26** and **27** in D_2O.

observed in the solid state, was predominant in solution; a stronger NOE enhancement would be expected between the signals for H-5 and the NH. Such NOE enhancements would also be observed if either the *Z*-anti or *Z*-syn structures were populated and in dynamic equilibrium. The 2D-NOESY spectra of the phenyl derivatives **9** and **20** showed strong NOEs of similar intensity between the NH proton and both H-5 and H-4; this suggests an equilibrium between the *Z*-anti and *Z*-syn isomers in solution, hydrogen bonding between NH and the pyranose oxygen, or both. Population of the *Z*-syn isomer, even to a minor extent, could lead to the observation of a significant NOE cross-peak between H-4 and NH; because the distance between NH and H-4 in this isomer would be only 1.99 Å and the distance between the NH and H-5 is 2.33 Å, it is, therefore, not possible to conclude that *Z*-syn is significantly populated on the basis of the observation of a strong NOE. No NOE cross-peak was observed for the isopropyl derivative **8** between NH and H-4. The chemical shift for the NH of both **9** (δ 7.94) and **20** (δ 8.03) indicated that the amide protons of both

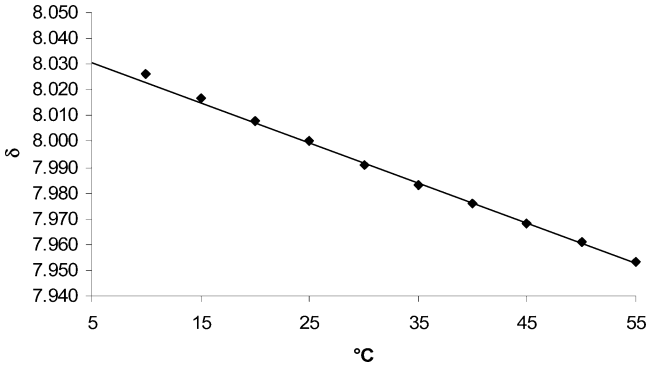


FIGURE 6. Effect of temperature on chemical shift (N*H* shift) of **20** in $CDCl_3$.

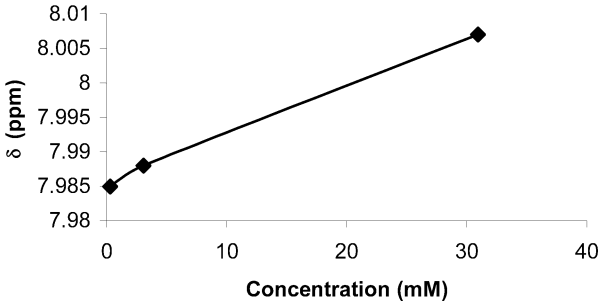


FIGURE 7. Effect of the concentration of **20** on the NH chemical shift.

compounds are in similar environments, and this is the case for all the secondary anilides (Table 3). The dependence of the chemical shift (δ) of the NH on temperature was investigated in $CDCl_3$ for **20** (and **25c**) and was plotted as a function of temperature (Figure 6); δ decreased with increasing temperature, and the temperature coefficient, $\Delta\delta/\Delta T$, for **20** was −1.6 ppb/K. In addition, the concentration of **9**, **20**, or **25c** had little impact on δ_{NH} (Figure 7). These observations are consistent with a free or intramolecular hydrogen-bonded NH but not an intermolecular hydrogen-bonded NH.[25]

There were two signal sets present in the NMR spectra for tertiary amides, corresponding to the two structural isomers, *E* and *Z*, consistent with those observed for tertiary glycosylamide derivatives such as **1**.[26] Evidence for the interconversion of the *E* and *Z* amide structural isomers was obtained by 1D-NOESY experiments. For example, for **10** there were signals of the opposite sign from that of the NOE enhancements; they were between H-5, H-1, and the *N*-methyl group of the major signal set (at δ 5.38, 4.04, and 3.30, respectively) and H-5, H-1, and the *N*-methyl group of the minor set (δ 5.75, 4.54, and 3.45, respectively). Qualitative NOE studies supported the assignment of *E*-anti as the major solution structural isomer. Irradiation of the H-5 at δ 4.04 led to strong positive enhancement of the signals for H-1 and H-3, as would be expected, and to medium enhancements for H-4 and the aromatic protons as well as to the

(25) (a) Vasella, A.; Witzig, C. *Helv. Chim. Acta* **1995**, *78*, 1971. (b) Fowler, P.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 269. (c) Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.

(26) Avalos, M.; Babiano, R.; Carretero, M. J.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron* **1998**, *54*, 615.

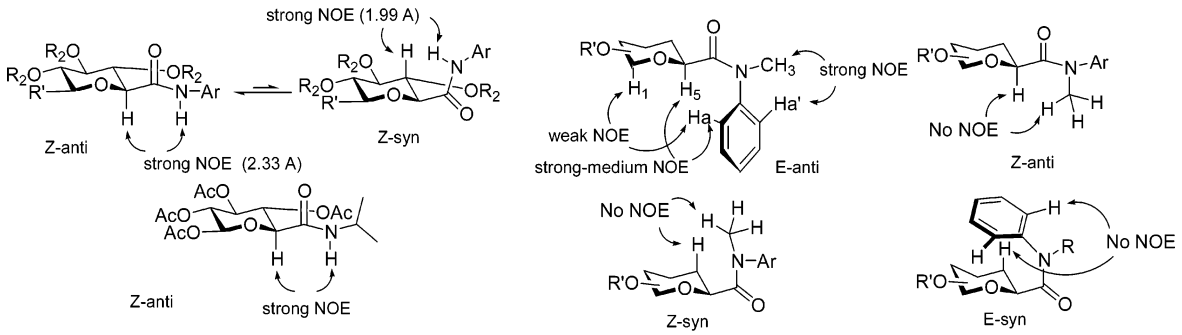
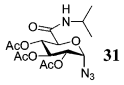
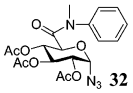


FIGURE 8. Summary of NOEs observed for secondary and tertiary amides.

negative NOE described above.[27] There were no enhancements of the H-5 or H-4 proton signals upon the irradiation of the *N*-methyl signals as would have been expected if *Z*-anti or *Z*-syn were significantly populated in solution. Similarly, there were no NOE correlations between the aromatic protons and H-4 which would have supported *E*-syn as a major structural isomer. A summary of the NOE studies is provided in Figure 8. The minor set of signals observed in the ^{1}H NMR spectra were thus assigned to the *Z*-configurational isomers. Integration of the signal sets in the ^{1}H NMR spectra enabled the determination of the *E*/*Z* ratios (Table 3); for **10** the *E*/*Z* ratio was 93:7 at 5 °C. Some trends are evident: the *E*/*Z* ratio increases when the anomeric substituent is OAc rather than azide, and the *E*/*Z* ratio for α-azides is greater than that for *β*-azides. There was no correlation between Hammet σ values for the substituents on the aromatic ring and the *E*/*Z* ratio. Some trends from ^{1}H NMR chemical shifts are as follows: (i) the chemical shift for the anomeric proton (δ_{H-1}) has a lower value for the *E* isomer than it has for the *Z* isomer, and (ii) the chemical shift for H-5 (δ_{H-5}) has a lower value for the *E* isomer than it has for the *Z* isomer. The chemical shifts of the protons, which are in proximity to the aromatic ring, appear at a higher field, presumably, because there is greater shielding of these protons compared to that of the *Z*-anti isomer.[28]

2.5. Infrared Spectroscopic Analysis of Amides. Infrared spectroscopy has commonly been used to study hydrogen bonding.[29] The IR spectra have been recorded for a range of amides both in the solid state (diffuse reflectance IR spectroscopy) and in solution (solutions in $CHCl_3$, $CDCl_3$, or CCl_4), and the results are summarized in Table 4. A single band corresponding to an NH stretch at <3350 cm^{-1} was generally observed for secondary amides in the solid state, consistent with the hydrogen bonding that was observed in the two crystal structures described above. Evidence for hydrogen bonding in solution was obtained only for compound **20** in CCl_4; a weak band was observed at 3348.1 cm^{-1} (hydrogen-bonded NH), similar to the band at 3349.7 cm^{-1} observed in the solid state. Also, there was a stronger band at 3419.3 cm^{-1} which was assigned to a free or non-hydrogen-bonded NH. For all of other compounds that were studied, the NH stretch was found to occur from 3410.8 to 3426.7 cm^{-1}; these observations are consistent with a free NH.[30] The carbonyl stretches for secondary amides appear at a higher frequency (1681.9−1705.9 cm^{-1}) than they do for tertiary amides (1670.0−1677.2 cm^{-1}). The asymmetric azide stretch showed less variation (2119.9−2124.8 cm^{-1}).

TABLE 4. Infrared Spectroscopic Data

Compd.		IR (cm^{-1})		
		NH	-N_3 asymm.	amide C=O
8	$CDCl_3$	3425.9	-	1681.9
 **31**	Solid state	3261.1	2124.5	1689.8
	$CDCl_3$	3426.7	2121.9	1681.3
9	Solid state	3374.9		1682.2
	$CHCl_3$	3411.9		1697.5
	$CDCl_3$	3411.6		1697.5
	CCl_4	3418.3		1705.9
10	Solid state	-	-	1673.0
11	$CDCl_3$	3412.0		1696.3
20	Solid state	3349.7	2122.4	1697.7
	$CHCl_3$	3412.1	2122.4	1696.7
	$CDCl_3$	3412.3	2122.4	1697.1
	CCl_4	3419.3 (s), 3348.1 (w)	2119.9	1704.6
25g	Solid state	3347.1	2124.8	1693.0
	$CHCl_3$	3410.8	2122.3	1695.6
	$CDCl_3$	3410.9	2122.1	1694.6
	CCl_4	3418.0	2120.0	1702.2
 **32**	Solid state	-	2122.2	1677.2
	$CDCl_3$	-	2121.2	1670.0

2.6. Summary and Conclusions. The results provide evidence that *Z* amides are preferred for secondary anilides derived from glucuronic acid, whereas *E*-configured amides are preferred by the tertiary anilides. The X-ray crystallographic and IR data support the intramolecular and intermolecular hydrogen bonding of secondary amides in the solid state. One of the crystal structures shows that the amide has a *Z*-anti structure, and there is no intramolecular hydrogen bond. Molecular mechanics calculations using the OPLSAA force field suggest that the *Z*-anti structure is preferred for secondary anilides with *Z*-syn being a higher-energy structure. Infrared spectroscopic analysis in solution indicates, in all but one case studied, that the amide NH is not strongly hydrogen bonded. The NOE data for secondary amides can be

(27) No similar enhancement of aromatic proton signals was observed upon the irradiation of H-5 of the secondary amides.

(28) NOE experiments for tertiary amides were generally carried out at 5 °C if broadening of the signals occurred at room temperature.

(29) For a selected example, see: Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228.

(30) Interaction with solvent cannot be ruled out.

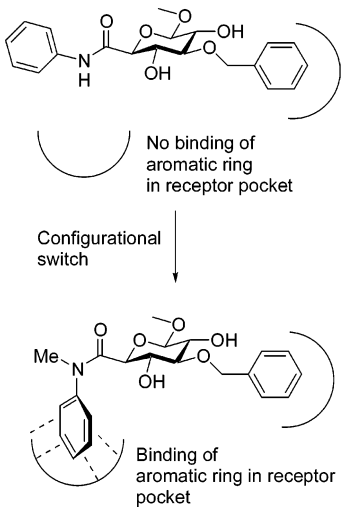


FIGURE 9. A potential application of the configurational switching of anilides. For the secondary anilide, the aromatic group is not oriented in the direction of the binding pocket. After the configurational switch, the aromatic group can bind.

interpreted as being a result of the dynamic equilibrium between the syn and anti non-hydrogen-bonded isomers, where the *Z*-anti isomer is more populated. The hydrogen-bonding interactions observed in the crystals are possibly a result of the crystal packing. Qualitative NOE studies and molecular mechanics calculations (both OPLSAA and Merck Molecular Force Field) support the proposal that the *E*-anti structure is preferred for tertiary anilides. The explanations for this are as follows: (i) the greater steric interaction of the pyranose groups with the alkyl group destabilizes the *Z*-anti structure, (ii) the steric interaction of the alkyl group with H-4 destabilizes the *Z*-syn structure, and (iii) the steric interaction of the aromatic group with H-4 destabilizes the *E*-syn structure. The *Z*-configured amide, presumably *Z*-anti, is detected by ^{1}H NMR in solution (<15%) for the tertiary anilides, and the possibility that *E*-syn is also populated to a minor degree cannot be ruled out. Thus, alkylation of secondary anilides to produce tertiary anilides induces a configurational switch that alters the orientation of the aromatic group with respect to the pyranose ring. The aromatic group is projected in a different orientation from the pyranose scaffold in a manner dependent on the structure of the amide. This could have implications for bioactive molecule discovery or development using saccharide scaffolds, and a possible application is shown in Figure 9. The presentation of the carbohydrate units in related bivalent compounds also diverges depending on the anilide structure; this is discussed in the subsequent paper in which further evidence to support the conclusions described herein is detailed.

3. Experimental Section

1,2,3-Tri-*O*-acetyl-$\Delta^{4,5}$-β-D-glucopyranuronic Acid, Phenylamide 11. Triethylamine (0.20 mL, 1.435 mmol) and ethyl chloroformate (0.12 mL, 1.255 mmol) were added to a stirred solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronic acid **7** (0.500 g, 1.380 mmol) in dry dichloromethane (6 mL) cooled to −14 °C. After 15 min, aniline (0.11 mL, 1.207 mmol) was added, and the mixture was allowed to stir for a further 1 h; the temperature was allowed to rise to −5 °C. The organic solution was then washed with diluted HCl (0.25 M, 6 mL), deionized water (6 mL), saturated $NaHCO_3$ (6 mL), and deionized water again (6 mL), dried ($MgSO_4$), and filtered. The solvent was removed, and the residue (0.514 g) purified by chromatography (1:4 EtOAc/petroleum ether) to produce **11** (0.219 g, 42%): R_f 0.54 (1:1 EtOAc/petroleum ether); mp 115−117 °C; $[\alpha]_D$ +31° (*c* 0.6, $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br s, 1H, N*H*), 7.57 (d, 2H, J = 8.0, Ar H), 7.30 (t, J = 7.5, 2H, Ar H), 7.10 (t, 1H, Ar H), 6.36 (d, 1H, $J_{1,2}$ = 2.9, H-1), 6.34 (dd, 1H, $J_{3,4}$ = 4.8, $J_{2,4}$ = 1.2, H-4), 5.28 (m, 1H, H-3), 5.15 (m, 1H, H-2), 2.11, 2.09, 2.06 (each s, each 3H, each COC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 169.8, 169.4, 169.0 (each s, each *C*OCH$_3$), 158.2 (s, *C*ONH), 144.6 (s, C-5), 137.1 (s, Ar C), 129.2, 125.1, 120.4 (each d, each Ar *C*H), 104.2 (d, C-4), 88.6 (d, C-1), 67.3, 63.8 (each d, C-2 and C-3), 20.9, 20.8, 20.8 (each q, each CO*C*H$_3$); FTIR (KBr) 3382, 3060, 2994, 2942, 1754, 1692, 1664, 1600, 1536, 1446, 1371, 1328, 1224, 1150, 1105, 1038, 925 cm^{-1}; CI-HRMS found 395.1454, required 395.1454 [M + NH_4]$^+$.

***p*-Bromo-*N*-isopropylaniline 13.** A Schlenk flask was charged with 1,4-dibromobenzene (2.00 g, 8.48 mmol), isopropylamine (0.85 mL, 9.98 mmol), sodium *tert*-butoxide (1.10 g, 11.45 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), and racemic BINAP (0.04 g, 0.06 mmol) in freshly distilled toluene (17 mL). The heterogeneous mixture was heated and vigorously stirred at 80 °C under a nitrogen atmosphere for 26 h, after which the reaction was judged completed by TLC (1:7 EtOAc/petroleum ether). The solution was cooled to room temperature, taken up in diethyl ether (30 mL), and filtered. The solvent was removed to produce the title compound as an orange-brown oil (1.44 g, 79%); it can be used directly without purification in the next step. Some of the residue was purified by Kugelrohr distillation to give a clear liquid that was used for analytical purposes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 2H, J = 8.9, Ar H), 6.46 (d, 2H, Ar H), 3.58 (heptet, 1H, $J_{CH(CH3)2}$ = 6.2, C*H*(CH$_3$)$_2$), 3.46 (br s, 1H, N*H*), 1.20 (d, 6H, $J_{CH(CH3)2}$ = 6.2, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ 146.8 (s, Ar C), 132.2, 115.0 (each d, each Ar *C*H), 108.6 (s, Ar C), 44.6 (d, *C*H(CH$_3$)$_2$), 23.1 (two q overlapping, each CH(*C*H$_3$)$_2$); CI-HRMS found 214.0230, required 214.0231 [M + H]$^+$.

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranuronic Acid, *N*-Isopropyl-*p*-bromophenylamide 14. Acid **7** (0.5 g, 1.380 mmol) was dissolved in dry dichloromethane (5 mL) and cooled to 0 °C. DCC (1.0 M solution in dichloromethane, 1.38 mL, 1.380 mmol) was added, and the mixture was stirred for 10 min. Then **13** (0.301 g, 1.406 mmol) was added, and the mixture was stirred for an additional hour. The mixture was filtered and washed with aq saturated $NaHCO_3$ (20 mL) and aq HCl (1.0 M, 20 mL). The organic layer was dried ($MgSO_4$), and the mixture was filtered. Then, the solvent was removed, and the residue was purified by chromatography (1:4 EtOAc/petroleum ether) to produce the title compound as a white solid (0.302 g, 40%). Analytical data for the major structural isomer (*E*): ^{1}H NMR data (500 MHz, $CDCl_3$, 5 °C) δ 7.69 (dd, 1H, J = 2.0, 8.2, Ar H), 7.63 (dd, 1H, Ar H), 7.09 (dd, 1H, Ar H), 6.98 (dd, 1H, Ar H), 5.58 (t, 1H, $J_{3,4}$ = 9.6, H-4), 5.21 (d, 1H, $J_{1,2}$ = 8.4, H-1), 5.16 (t, 1H, $J_{2,3}$ = 9.2, H-2), 5.06 (t, 1H, H-3), 4.93 (heptet, 1H, C*H*(CH$_3$)$_2$), 3.78 (d, 1H, $J_{4,5}$ = 9.7, H-5), 2.13, 2.02, 2.01, 2.00 (each s, each 3H, each COC*H*$_3$), 1.13 (d, 3H, J = 6.7, CH(C*H*$_3$)$_2$), 1.01 (d, 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 5 °C) δ 170.9, 169.4, 169.2, 169.0 (each s, each *C*OCH$_3$), 164.0 (s, *C*ONH), 136.0 (s, Ar C), 133.5, 132.9, 132.7, 131.0 (each d, each Ar *C*H), 123.4 (s, Ar C), 91.8 (d, C-1), 72.8, 71.3, 69.9, 69.5 (each d, C-2−C-5), 47.6 (d, *C*H(CH$_3$)$_2$), 21.5, 21.2 (each q, each CH(*C*H$_3$)$_2$), 21.0, 20.9, 20.9, 20.6 (each q, each CO*C*H$_3$); selected ^{1}H NMR signals for the minor structural isomer (*Z*, 300 MHz, $CDCl_3$, 25 °C) δ 5.70 (d, 1H, H-1), 4.51 (d, 1H, H-5); ES-LRMS 580.0 [M + Na]$^+$, 498.0 [M + H − HOAc]$^+$; CI-HRMS found 498.0765, required 498.0764 [M + H − HOAc]$^+$.

1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranosiduronic Acid, Allyl Ester 15. 1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranuronic

acid **7** (1.55 g, 4.28 mmol) was dissolved in dry dichloromethane (40 mL) and cooled to 0 °C under an N_2 atmosphere; oxalyl chloride (0.37 mL, 4.28 mmol) was added as well as DMF (0.15 mL). This solution was stirred for 30 min on ice and for 1.5 h at room temperature. In a separate flask, a solution of allyl alcohol (0.30 mL, 4.41 mmol) and dry pyridine (0.71 mL, 8.78 mmol) in dichloromethane (5 mL) was stirred in the presence of 4 Å molecular sieves. The solution containing the acid chloride was cooled to 0 °C, and the solution containing the alcohol and pyridine was slowly added to it; the mixture was allowed to stir for 30 min at 0 °C and for a further 1.5 h at room temperature. The mixture was then transferred to a separatory funnel and was washed with aq $NaHCO_3$ (40 mL). The organic layer was washed with aq HCl (0.1 M, 40 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was triturated in hot petroleum ether to give the title compound (1.33 g, 77%) as a white solid: mp 95−97 °C; $[\alpha]_D$ +17° (*c* 0.4, $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H, C*H*=CH_2), 5.79 (d, 1H, $J_{1,2}$ = 7.7, H-1), 5.30 (m, 4H, CH=C*H*$_2$, H-3 and H-4 overlapping), 5.15 (dd, 1H, $J_{2,3}$ = 8.7, H-2), 4.61 (m, 2H, OC*H*$_2$CH=CH_2), 4.20 (d, 1H, $J_{4,5}$ = 9.4, H-5), 2.12, 2.04, 2.03, 2.02 (each s, each 3H, each COC*H*$_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.1, 170.0, 169.5, 169.1 (each s, each *C*OCH_3), 166.3 (s, *C*OOAll), 131.2 (d, *C*H=CH_2), 119.8 (t, CH=*C*H_2), 91.6 (d, C-1), 73.2, 72.1, 70.4, 69.1 (each d, C-2−5), 67.0 (t, O*C*H_2CH=CH_2), 21.0 (q, CO*C*H_3), 20.7 (3 q, overlapping, each CO*C*H_3); FTIR (KBr) 2941, 2857, 1755, 1697, 1673, 1514, 1378, 1222, 1087, 1040 cm^{-1}; CI-HRMS found 420.1508, required 420.1506 $[M + NH_4]^+$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-*β*-D-glucopyranuronic Acid, Allyl Ester 16. Azidotrimethylsilane (1.09 mL, 8.29 mmol) and tin(IV) chloride (0.19 mL, 1.62 mmol) were added to a solution of **15** (1.33 g, 3.31 mmol) in dichloromethane (35 mL) under N_2, and the mixture was stirred for 4 h. The reaction mixture was then diluted with dichloromethane and washed with saturated $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed; a yellow oil was obtained (1.08 g). This was crystallized from hot ethanol to give **16** as a white solid (0.85 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H, C*H*=CH_2), 5.31 (m, 4H, CH=C*H*$_2$, H-3 and H-4 overlapping), 4.97 (m, 1H, $J_{2,3}$ = 9.4, $J_{1,2}$ = 8.6, H-2), 4.71 (d, 1H, H-1), 4.63 (m, 2H, OC*H*$_2$CH=CH_2), 4.14 (m, 1H, $J_{4,5}$ = 9.8, H-5), 2.08, 2.02, 2.01 (each s, each 3H, each COC*H*$_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.2, 169.4, 169.3 (each s, each *C*OCH_3), 166.0 (s, *C*OOAll), 131.2 (d, *C*H=CH_2), 119.8 (t, CH=*C*H_2), 88.3 (d, C-1), 74.6, 72.2, 70.7, 69.3 (each d, C-2−5), 67.0 (t, O*C*H_2CH=CH_2), 20.7 (3 q, each CO*C*H_3); CI-HRMS found 403.1465, required 403.1465 $[M + NH_4]^+$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-*β*-D-glucopyranuronic Acid 17.[31] Allyl ester **16** (508 mg, 1.32 mmol) was dissolved in dry acetonitrile (7 mL) and cooled to 0 °C, and $Pd(Ph_3)_4$ (155 mg, 0.134 mmol) and pyrrolidine (0.12 mL, 1.438 mmol) were added and stirred for 20 min. The mixture was filtered through Celite, and the solvent was removed; the residue was dissolved in EtOAc and washed with water. The aq layer was acidified to pH 2 using Amberlite IR-120 and, after filtration, was extracted with EtOAc, dried (Na_2SO_4), and filtered. The solvent was removed to give **17** as a white solid (423 mg, 93%): $[\alpha]_D$ +7.5° (*c* 0.6, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 5.36 (t, 1H, $J_{3,4}$ = 9.4, H-3), 5.19 (t, 1H, H-4), 5.02 (d, 1H, $J_{1,2}$ = 8.8, H-1), 4.91 (t, 1H, $J_{2,3}$ = 9.3, H-2), 4.33 (d, 1H, $J_{4,5}$ = 10.0, H-5), 2.07, 2.02, 2.01 (each s, each 3H, each COC*H*$_3$); ^{13}C NMR (D_2O) δ 173.2 (s, *C*OOH), 172.8, 172.7, 172.5 (each s, each *C*OCH_3), 87.5 (d, C-1), 74.7, 72.9, 71.2, 69.9 (each d, C-2−C-5), 20.4, 20.3, 20.2 (each q, each CO*C*H_3); FTIR (KBr) 3498, 2955, 2129, 1746, 1619, 1429, 1376, 1232, 1046, 901, 794, 601 cm^{-1}; CI-LRMS 344 $[M - H]^-$, 302 $[M - H - N_3]^-$, 284 $[M - H - HOAc]^-$.

(31) Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Fluorophenylamide 25a/24a. α-Anomer **25a** and *β*-anomer **24a**: ^{1}H NMR data for the α-anomer (300 MHz, $CDCl_3$) δ 7.97 (s, 1H, NH), 7.44 (d, 1H, *J* = 4.7, Ar H), 7.42 (d, 1H, *J* = 4.9, Ar H), 7.02 (m, 2H, Ar H), 5.76 (d, 1H, $J_{1,2}$ = 4.2, H-1), 5.49 (t, 1H, $J_{2,3}$ = 10.1, $J_{3,4}$ = 9.8, H-3), 5.20 (t, 1H, $J_{3,4}$ = 9.8, $J_{4,5}$ = 10.3, H-4), 4.94 (dd, 1H, H-2), 4.49 (d, 1H, H-5), 2.12, 2.09, 2.03 (each s, each 3H, each $COCH_3$); selected ^{1}H NMR data for the *β*-anomer δ 8.01 (s, 1H, NH), 4.85 (d, 1H, $J_{1,2}$ = 8.9, H-1), 4.13 (d, 1H, $J_{4,5}$ = 9.9, H-5);^{13}C NMR for the α-anomer (125 MHz, $CDCl_3$) δ 170.3, 170.0, 169.8 (each s, each *C*OCH_3), 164.65 (s, CONH), 161.1, 159.1 (each s, each Ar C, *J* = 244.3), 132.6, 132.6 (each s, each Ar C, *J* = 3.1), 126.7, 122.7 (each d, each Ar C, *J* = 7.7), 116.1, 115.9 (each d, each Ar C, *J* = 22.6), 86.36 (d, C-1), 70.5, 70.3, 69.4, 68.8 (each d, C2−5,), 20.9, 20.8, 20.7 (each s, each CO*C*H_3); selected ^{13}C NMR for the *β*-anomer 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 164.0 (s, CONH), 161.2, 159.26 (each s, each Ar C, *J* = 244.8),-132.5, 132.4(each s, each Ar C, *J* = 3.3), 123.0, 122.9 (each d, each Ar C, *J* = 8.2), 116.1, 115.9 (each d, each Ar C, *J* = 23.1), 88.4 (d, C-1), 74.8, 71.9, 70.7, 69.3 (each d, C2−5), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution on NaCl plates) 3342, 2962, 2123, 1755, 1691, 1536, 1510, 1370, 1220, 1047, 1001 cm^{-1}; ES-HRMS found 437.1093, required 437.1109 $[M - H]^-$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Chlorophenylamide 25b/24b. α-Anomer **25b** and *β*-anomer **24b**: ^{1}H NMR data for the α-anomer (300 MHz, $CDCl_3$): δ 8.04 (s, 1H, NH), 7.43 (d, 2H, *J* = 8.9, Ar H), 7.29 (d, 2H, *J* = 8.9, Ar H), 5.70 (d, 1H, $J_{1,2}$ = 4.2, H-1), 5.49 (t, 1H, $J_{2,3}$ = 10.1, $J_{3,4}$ = 9.7, H-3), 5.19 (t, 1H, $J_{3,4}$ = 9.7, $J_{4,5}$ = 10.1, H-4), 4.90 (dd, 1H, H-2), 4.49 (d, 1H, H-5), 2.12, 2.09, 2.03 (each s, each 3H, each $COCH_3$); selected ^{1}H NMR data for the *β*-anomer δ 8.07 (s, 1H, NH), 4.86 (d, 1H, $J_{1,2}$ = 8.7, H-1), 4.14 (d, 1H, $J_{4,5}$ = 9.5, H-5); ^{13}C NMR for α-anomer (125 MHz, $CDCl_3$) δ 170.3, 169.9, 169.8 (each s, each *C*OCH_3), 164.6 (s, CONH), 135.2, 130.4 (each s, each Ar C), 129.3, 121.9 (each d, Ar C), 86.3 (d, C-1), 70.4, 70.3, 69.3, 68.8 (each d, C2−5), 20.9, 20.8, 20.7 (each s, each CO*C*H_3); selected ^{13}C NMR for the *β*-anomer 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 164.0 (s, CONH), 135.1, 130.4(each s, each Ar C), 122.1 (d, Ar C), 88.4 (d, C-1), 74.8, 71.9, 70.7, 69.3 (each d, C2−5), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution) 3337, 2961, 2123, 1754, 1695, 1596, 1533, 1493, 1370, 1306, 1221, 1047, cm^{-1}; ES-HRMS found 453.0815, required 453.0813 $[M - H]^-$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Bromophenylamide 25c/24c. α-Anomer **25c** and *β*-anomer **24c**: ^{1}H NMR data for the α-anomer (300 MHz, $CDCl_3$) δ 7.98 (s, 1H, NH), 7.44 (d, 2H, *J* = 9.0, Ar H), 7.37 (d, 2H, *J* = 8.9, Ar H), 5.76 (d, 1H, $J_{1,2}$ = 4.2, H-1), 5.49 (t, 1H, $J_{2,3}$ = 9.9, $J_{3,4}$ = 9.7, H-3), 5.19 (t, 1H, $J_{3,4}$ = 9.7, $J_{4,5}$ = 10.2, H-4), 4.94 (dd, 1H, H-2), 4.49 (d, 1H, H-5), 2.12, 2.09, 2.03 (each s, each 3H, each $COCH_3$); selected ^{1}H NMR data for the *β*-anomer δ 8.01 (s, 1H, NH), 4.85 (d, 1H, $J_{1,2}$ = 9.0, H-1), 4.13 (d, 1H, $J_{4,5}$ = 9.5, H-5); ^{13}C NMR for the α-anomer (125 MHz, $CDCl_3$) δ 170.3, 169.9, 169.8 (each s, each *C*OCH_3), 164.6 (s, CONH), 135.8 (s, Ar C), 132.3, 122.2 (each d, Ar C), 118.0 (s, Ar C), 86.3 (d, C-1), 70.4, 70.3, 69.3, 68.8 (each d, C2−5), 20.9, 20.8, 20.7 (each q, each CO*C*H_3); selected ^{13}C NMR for the *β*-anomer δ 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 164.0 (s, CONH), 135.6 (s, Ar C), 122.4 (d, Ar C), 118.27 (s, Ar C), 88.4 (d, C-1), 74.8, 71.8, 70.7, 69.3 (each d, C2−5), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution) 3340, 2962, 2122, 1754, 1695, 1593, 1530, 1490, 1369, 1220, 1072, 1047, cm^{-1}; ES-HRMS found 497.0328, required 497.0308 $[M - H]^-$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Methylphenylamide 25d/24d. α-Anomer **25d** and *β*-anomer **24d**: ^{1}H NMR data for the α-anomer (300 MHz, $CDCl_3$) δ 7.97 (s, 1H, N*H*), 7.35 (d, 2H, *J* = 8.5, Ar *H*), 7.12 (d, 2H, *J* = 8.2, Ar *H*), 5.75 (d, 1H, $J_{1,2}$ = 4.2, H-1), 5.48 (t, 1H, $J_{2,3}$ = 10.1, $J_{3,4}$ = 9.7, H-3), 5.20 (t, 1H, $J_{3,4}$ = 9.7, $J_{4,5}$ = 10.1, H-4), 4.95 (dd, 1H, H-2), 4.48 (d, 1H, H-5), 2.31(s, 3H, CH_3),

2.11, 2.08, 2.03 (each s, each 3H, each $COCH_3$); selected ^1H NMR data for the β-anomer δ 8.02 (s, 1H, N*H*), 4.85 (d, 1H, $J_{1,2} = 8.9$, H-1), 4.13 (d, 1H, $J_{4,5} = 9.4$, H-5); ^{13}C NMR for the α-anomer (125 MHz, $CDCl_3$) δ 170.3, 169.9, 169.8 (each s, each *C*OCH_3), 164.4 (s, CONH), 135.0, 134.1 (each s, each Ar C), 129.8, 120.8 (each d, each Ar C), 86.3 (d, C-1), 70.5, 70.3, 69.4, 69.0 (each d, C2−5), 21.1 (q, CH_3) 20.9, 20.8, 20.7(each q, each CO*C*H_3); selected ^{13}C NMR for the β-anomer: 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 163.8 (s, CONH), 135.2, 133.9 (each s, each Ar C), 121.0 (d, Ar C), 88.3 (d, C-1), 74.8, 72.0, 70.8, 69.4 (each d, C2−5), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution) 3322, 2959, 2122, 1755, 1689, 1604, 1533, 1370, 1221, 1047, cm^{-1}; ES-HRMS found 433.1364, required 433.1359 $[M - H]^-$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Methoxyphenylamide 25e/24e. α-Anomer **25e** and β-anomer **24e**: ^1H NMR data for the α-anomer (300 MHz, $CDCl_3$) δ 7.94 (s, 1H, N*H*), 7.36 (d, 2H, $J = 8.9$, Ar *H*), 6.80(d, 2H, $J = 9.1$, Ar H), 5.75 (d, 1H, $J_{1,2} = 4.2$, H-1), 5.48 (t, 1H, $J_{2,3} = 10.1$, $J_{3,4} = 9.5$, H-3), 5.20 (t, 1H, $J_{3,4} = 9.5$, $J_{4,5} = 10.1$, H-4), 4.94 (dd, 1H, H-2), 4.49 (d, 1H, H-5), 3.78 (s, 3H, OCH_3), 2.11, 2.08, 2.03 (each s, each 3H, each $COCH_3$); selected ^1H NMR data for the β-anomer δ 7.98 (s, 1H, NH), 4.85 (d, 1H, $J_{1,2} = 8.9$, H-1), 4.13 (d, 1H, $J_{4,5} = 9.5$, H-5); ^{13}C NMR for the α-anomer (125 MHz, $CDCl_3$) δ 170.3, 169.9, 169.88 (each s, each *C*OCH_3), 164.4 (s, CONH), 157.2 (s, Ar C), 129.6 (s, Ar C), 122.7, 114.5 (each d, each Ar C), 86.3 (d, C-1), 70.5, 70.3, 69.5, 68.9 (each d, C2−5), 55.7 (s, O*C*H_3), 20.9, 20.8, 20.7 (each s, each CO*C*H_3); selected ^{13}C NMR for the β-anomer δ 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 163.9 (s, CONH, β), 157.4 (s, Ar C), 129.5 (s, Ar C), 122.9 (d, Ar C), 88.3 (d, C-1), 74.8, 72.0, 70.8, 69.4 (each d, C2−5, β), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution) 3332, 2959,2838, 2121, 1756, 1689, 1513, 1467, 1370, 1236, 1046, cm^{-1}; ES-HRMS found 449.1295, required 449.1309 $[M - H]^-$.

2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/b-D-glucopyranuronic Acid, *p*-Methoxycarbonylphenylamide 25f/24f. α-Anomer **25f** and β-anomer **24f**: ^1H NMR data for the α-anomer (300 MHz, $CDCl_3$) δ 8.17 (s, 1H, NH), 8.01 (d, 2H, $J = 8.7$, Ar H), 7.57 (d, 2H, $J = 8.7$, Ar H), 5.78 (d, 1H, $J_{1,2} = 4.1$, H-1), 5.50 (t, 1H, $J_{2,3} = 10.0$, $J_{3,4} = 9.8$, H-3), 5.21 (t, 1H, $J_{3,4} = 9.8$, $J_{4,5} = 10.2$, H-4), 4.96 (dd, 1H, H-2), 4.52 (d, 1H, H-5), 3.90 (s, 3H, $COOCH_3$), 2.12, 2.10, 2.04 (each s, each 3H, each $COCH_3$); selected ^1H NMR data for the β-anomer δ 8.21 (s, 1H, NH), 4.88 (d, 1H, $J_{1,2} = 8.7$, H-1), 4.17 (d, 1H, $J_{4,5} = 9.5$, H-5); ^{13}C NMR for the α-anomer (125 MHz, $CDCl_3$) δ 170.2, 169.9, 169.8 (each s, each *C*OCH_3), 166.6 (s, *C*$OOCH_3$), 164.7 (s, CONH), 140.9 (s, Ar C), 131.0 (d, Ar C), 126.7 (s, Ar C), 119.7 (d, Ar C), 88.4 (d, C-1), 70.4, 70.2, 69.3, 68.8 (each d, C2−5), 52.2 (s, COO*C*H_3), 20.8, 20.8, 20.7 (each s, each CO*C*H_3); selected ^{13}C NMR for the β-anomer δ 170.0, 169.8, 169.4 (each s, each *C*OCH_3), 166.6 (s, *C*$OOCH_3$) 164.1 (s, CONH), 140.7 (s, Ar C), 126.8 (s, Ar C), 119.9 (d, Ar C), 86.3 (d, C-1), 74.8, 71.9, 70.7, 69.2 (each d, C2−5), 20.8, 20.7, 20.7 (each q, each CO*C*H_3); FTIR (CH_2Cl_2 solution on NaCl plates) 3341, 2957, 2122, 1754, 1719, 1603, 1531, 1436, 1410, 1370, 1283, 1047, cm^{-1}; ES-HRMS found 477.1264, required 477.1258 $[M - H]^-$.

1-Azido-1-deoxy-α/b-D-glucopyranuronic Acid, *N*-Methyl-*p*-fluorophenylamide 27a/26a. α-Anomer **27a** and β-anomer **26a**: ^1H NMR data for the α-anomer (300 MHz, D_2O) δ 7.4−7.2 (m, 4H, Ar H), 5.43 (d, 1H, $J_{1,2} = 4.4$, H-1), 4.16 (d, 1H, $J_{4,5} = 9.8$, H-5), 3.67 (t, 1H, $J_{3,4} = 9.4$, $J_{4,5} = 9.8$, H-4), 3.58 (dd, 1H, $J_{2,3} = 9.7$, H-2), 3.29 (t, 1H, H-3), 3.25 (s, 3H, N−CH_3); selected ^1H NMR data for the β-anomer δ 4.41 (d, 1H, $J_{1,2} = 8.5$, H-1), 3.89 (d, 1H, $J_{4,5} = 9.6$, H-5); ^{13}C NMR for the α-anomer (75 MHz, D_2O) δ 170.0 (s, *C*$ONCH_3$), 164.6 (s, Ar C), 140.2, 140.2 (each d, each Ar C, $J = 7.0$), 130.9, 130.8 (each d, each Ar C, $J = 8.7$), 117.6, 117.4 (each d, each Ar C, $J = 23.1$), 92.5 (d, C-1), 74.1, 72.6, 72.5, 71.0 (each d, C2−5), 38.2 (N CH_3); ^{13}C NMR data for the β-anomer δ 169.0 (s, *C*$ONCH_3$), 162.6 (s, Ar C), 130.8 (d, Ar C), 77.3, 75.2, 74.2, 72.1 (each d, C2−5), 38.2 (N CH_3); ES-HRMS found 325.0945, required 325.0948 $[M - H]^-$.

1-Azido-1-deoxy-α/b-D-glucopyranuronic Acid, *N*-Methyl-*p*-chlorophenylamide 27b/26b. α-Anomer **27b** and β-anomer **26b**: ^1H NMR data for the α-anomer (300 MHz, D_2O) δ 7.53 (d, 2H, $J = 8.8$, Ar H), 7.30 (d, 2H, $J = 8.8$, Ar H), 5.43 (d, 1H, $J_{1,2} = 4.4$, H-1), 4.17 (d, 1H, $J_{4,5} = 9.7$, H-5), 3.67 (t, 1H, $J_{3,4} = 9.5$, $J_{4,5} = 9.7$, H-4), 3.58 (dd, 1H, $J_{2,3} = 9.7$, H-2), 3.29 (t, 1H, H-3), 3.25 (s, 3H, N C*H*$_3$); selected ^1H NMR data for the β-anomer δ 4.41 (d, 1H, $J_{1,2} = 8.3$, H-1), 3.88 (d, 1H, $J_{4,5} = 9.7$, H-5); ^{13}C NMR for the α-anomer (75 MHz, MeOH-d_4) δ 170.0 (s, *C*$ONCH_3$), 142.8 (s, Ar C), 135.4 (s, Ar C), 131.1 (d, Ar C), 130.5 (d, Ar C), 92.6 (d, C-1), 74.2, 72.7, 72.6, 71.2 (each d, C2−5), 38.3 (N CH_3); ^{13}C NMR data for the β-anomer δ 169.1 (s, *C*$ONCH_3$), 130.7 (s, Ar C), 130.5 (d, Ar C), 92.5 (d, C-1), 77.4, 75.4, 74.4, 72.3 (each d, C2−5), 38.3 (N CH_3); ES-HRMS found 341.0666, required 341.0653 $[M - H]^-$.

1-Azido-1-deoxy-β-D-glucopyranuronic Acid, *N*-Methyl-*p*-bromophenylamide 26c. Compound **26c**: ^1H NMR data (300 MHz, D_2O) δ 7.66 (d, 2H, $J = 8.5$, Ar H), 7.23 (d, 2H, $J = 8.6$, Ar H), 4.40 (d, 1H, $J_{1,2} = 8.5$, H-1), 3.88 (d, 1H, $J_{4,5} = 9.6$, H-5), 3.70 (t, 1H, $J_{3,4} = 9.2$, $J_{4,5} = 9.6$, H-4), 3.25 (s, 3H, N C*H*$_3$), 3.23 (m, 2H, H-2 and H-3); ^{13}C NMR (75 MHz, D_2O) δ 169.2 (s, *C*$ONCH_3$), 141.1 (s, Ar C), 133.3 (d, Ar C), 129.2 (d, Ar C), 122.4 (s, Ar C), 90.2 (d, C-1), 72.1, 71.1, 70.4, 69.5 (each d, C2−5), 37.8 (NCH_3); ES-HRMS found 385.0139, required 385.0148 $[M - H]^-$.

1-Azido-1-deoxy-α-D-glucopyranuronic Acid, *N*-Methyl-*p*-bromophenylamide 27c. Compound **27c**: ^1H NMR data (300 MHz, D_2O) δ 7.69 (d, 2H, $J = 8.8$, Ar H), 7.24 (d, 2H, $J = 8.8$, Ar H), 5.43 (d, 1H, $J_{1,2} = 4.2$, H-1), 4.17 (d, 1H, $J_{4,5} = 9.7$, H-5), 3.66 (t, 1H, $J_{3,4} = 9.4$, $J_{4,5} = 9.7$, H-4), 3.58 (dd, 1H, $J_{2,3} = 9.67$, H-2), 3.29 (t, 1H, H-3), 3.25 (s, 3H, N C*H*$_3$); ^{13}C NMR (75 MHz, D_2O) δ 168.4 (s, *C*$ONCH_3$), 133.3 (d, Ar C), 90.6 (d, C-1), 75.0, 73.5, 72.5, 70.9 (each d, C2−5), 37.9 (N CH_3); ES-HRMS found 385.0139, required 385.0148 $[M - H]^-$.

1-Azido-1-deoxy-α/b-D-glucopyranuronic Acid, *N*-Methyl-*p*-methylphenylamide 27d/26d. α-Anomer **27d** and β-anomer **26d** (*E* isomer): ^1H NMR data for the α-anomer (300 MHz, D_2O, *E* isomer) δ 7.34 (d, 2H, $J = 8.2$. Ar H), 7.18 (d, 2H, $J = 8.4$, Ar H), 5.42 (d, 1H, $J_{1,2} = 4.4$, H-1), 4.20 (d, 1H, $J_{4,5} = 9.8$, H-5), 3.65 (t, 1H, $J_{3,4} = 9.5$, $J_{4,5} = 9.8$, H-4), 3.57 (dd, 1H, $J_{2,3} = 9.7$, H-2), 3.26 (t, 1H, H-3), 3.25 (s, 3H, N C*H*$_3$), 2.33 (s, 3H, CH_3); selected ^1H NMR data for the β-anomer δ 4.38 (d, 1H, $J_{1,2} = 8.3$, H-1), 3.88 (d, 1H, $J_{4,5} = 9.7$, H-5); ^{13}C NMR for the α-anomer (75 MHz, MeOH-d_4) δ 168.7 (s, *C*$ONCH_3$), 140.0 (s, Ar C), 138.2 (s, Ar C), 129.9 (d, Ar C), 126.9 (d, Ar C), 91.0 (d, C-1), 72.6, 71.1, 71.0, 69.6 (each d, C2−5), 36.8 (NCH_3), 19.7 (Ar CH_3); ES-HRMS found 321.1184, required 321.1199 $[M - H]^-$.

1-Azido-1-deoxy-α/b-D-glucopyranuronic Acid, *N*-Methyl-*p*-methoxyphenylamide 27e/26e. α-Anomer **27e** and β-anomer **26e** (*E* isomer): ^1H NMR data for the α-anomer (300 MHz, D_2O, *E* isomer) δ 7.24 (d, 2H, $J = 8.9$, Ar H), 7.05 (d, 2H, $J = 9.0$, Ar H), 5.40 (d, 1H, $J_{1,2} = 4.2$, H-1), 4.16 (d, 1H, $J_{4,5} = 9.7$, H-5), 3.80 (s, 3H, OCH_3), 3.67 (t, 1H, $J_{3,4} = 9.7$, $J_{4,5} = 9.7$, H-4), 3.57 (dd, 1H, $J_{2,3} = 9.7$, H-2), 3.28 (t, 1H, H-3), 3.23 (s, 3H, N C*H*$_3$); selected ^1H NMR data for the β-anomer δ 4.37 (d, 1H, $J_{1,2} = 8.4$, H-1), 3.88 (d, 1H, $J_{4,5} = 9.6$, H-5); ^{13}C NMR for the α-anomer (75 MHz, MeOH-d_4) δ 171.6 (s, *C*$ONCH_3$), 162.2 (s, Ar C), 137.9 (s, Ar C), 131.0 (d, Ar C), 117.2 (d, Ar C), 93.8 (d, C-1), 75.3, 73.8, 73.7, 72.2 (each d, C2−5), 57.3 (O CH_3), 39.5 (N CH_3); ^{13}C NMR data for the β-anomer δ 173.0 (s, *C*$ONCH_3$), 170.5 (s, Ar C), 137.8 (s, Ar C), 132.1 (d, Ar C), 118.7 (d, Ar C), 94.0 (d, C-1), 78.6, 76.5, 75.5, 73.3 (each d, C2−5); ES-HRMS found 337.1162, required 337.1148 $[M - H]^-$.

1-Azido-1-deoxy-β-D-glucopyranuronic Acid, *N*-Methyl-*p*-methoxycarbonylphenylamide 26f. Compound **26f**: ^1H NMR (300 MHz, D_2O) δ 4.39 (d, 1H, $J_{1,2} = 8.5$, H-1), 3.90 (s, 3H, $COOCH_3$), 3.88 (d, 1H, $J_{4,5} = 9.5$, H-5), 3.71 (t, 1H, $J_{3,4} = 9.1$, $J_{4,5} = 9.5$, H-4), 3.29 (s, 3H, N C*H*$_3$), 3.22 (m, 2H, H-2

and H-3); ^{13}C NMR (75 MHz, D_2O) δ 130.7 (s, Ar C), 129.9 (d, Ar C), 127.1 (s, Ar C), 90.6 (d, C-1), 75.0, 73.7, 72.5, 70.9 (each d, C2−5), 37.8 (N CH_3); ES-HRMS found 365.1115, required 365.1097 $[M + H]^-$.

1-Azido-1-deoxy-α-D-glucopyranuronic Acid, *N*-Methyl-*p*-methoxycarbonylphenylamide 27f. Compound **27f**: ^{1}H NMR (300 MHz, D_2O) δ 8.12 (d, 2H, J = 8.6, Ar H), 7.45 (d, 2H, J = 8.6, Ar H), 5.42 (d, 1H, $J_{1,2}$ = 4.4, H-1), 4.16 (d, 1H, $J_{4,5}$ = 9.6, H-5), 3.89 (s, 3H, COOCH_3), 3.68 (t, 1H, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.6, H-4), 3.58 (dd, 1H, $J_{2,3}$ = 9.7, H-2), 3.29 (s, 3H, N CH_3), 3.27(t, 1H, H-3); ^{13}C NMR (75 MHz, D_2O) δ 169.1 (s, *C*ONCH$_3$), 168.6 (s, *C*OOCH$_3$), 146.3 (d, Ar C), 131.4 (s, Ar C), 130.0 (d, Ar C), 127.7 (s, Ar C), 91.7 (d, C-1), 86.0, 85.5, 84.7, 83.2 (each d, C2−5), 53.1 (O CH_3), 37.7 (N CH_3); ES-HRMS found 365.1115, required 365.1097 $[M - H]^-$.

1-Azido-1-deoxy-β-D-glucopyranuronic Acid, *N*-Methylphenylamide 26g. Compound **26g**: ^{1}H NMR (300 MHz, D_2O, *E* isomer) δ 7.55−7.30 (m, 5H, Ar H), 4.39 (d, 1H, $J_{1,2}$ = 8.4, H-1), 3.89 (d, 1H, $J_{4,5}$ = 9.6, H-5), 3.70 (t, 1H, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.6, H-4), 3.27 (s, 3H, N CH_3), 3.25 (m, 2H, H-2 and H-3); ^{13}C NMR (75 MHz, D_2O) δ 168.6 (s, *C*ONCH$_3$), 141.9 (s, Ar C), 130.0 (s, Ar C), 129.1 (d, Ar C), 127.4 (d, Ar C), 90.5 (d, C-1), 75.0, 73.5, 72.6, 70.9 (each d, C2−5), 38.0 (N CH_3); ES-HRMS found 307.1046, required 307.1042 $[M - H]^-$.

1-Azido-1-deoxy-α-D-glucopyranuronic Acid, *N*-Methylphenylamide 27g. Compound **27g**: ^{1}H NMR data (300 MHz, D_2O) δ 7.55−7.33 (m, 5H, Ar H), 5.43 (d, 1H, $J_{1,2}$ = 4.4, H-1), 4.18 (d, 1H, $J_{4,5}$ = 9.7, H-5), 3.66 (t, 1H, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.7, H-4), 3.58 (dd, 1H, $J_{2,3}$ = 9.7, H-2), 3.27 (s, 3H, N CH_3), 3.26 (t, 1H, H-3); ^{13}C NMR (75 MHz, D_2O) δ 169.4 (s, *C*ONCH$_3$), 142.0 (s, Ar C), 130.3 (s, Ar C), 129.2 (d, Ar C), 127.3 (d, Ar C), 90.2 (d, C-1), 72.2, 71.2, 70.4, 69.5 (each d, C2−5), 37.9 (NCH$_3$); ES-HRMS found 307.1046, required 307.1042 $[M - H]^-$.

2,4-Di-*O*-acetyl-β-D-glucopyranuronosyl Azide-3,6-lactone 29. Methyl ester **18** (3.94 g, 10.97 mmol) was suspended in 0.3 M LiOH (in 5:4:1 MeOH/water/THF, 220 mL) at 0 °C and stirred for 3 h until it was completely dissolved. The mixture was then diluted with water, and the pH was adjusted to 2 using Amberlite IR-120. Filtration and evaporation of the solvents produced 1-azido-1-deoxy-β-D-glucopyranuronic acid (2.21 g). This material was then suspended in acetic anhydride (100 mL) and heated at 85 °C for 2 h, after which the starting material was completely consumed as determined by TLC analysis (1:1 EtOAc/petroleum ether). The solvent was evaporated in vacuo followed by evaporation of toluene from the residue (×5) to produce **29** (2.83 g, 91% over two steps) as a yellow solid: R_f 0.51 (1:1 EtOAc/petroleum ether); $[\alpha]_D$ −23° (*c* 0.7, $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (s, 1H, H-1), 5.08 (t, 1H, $J_{2,3}$ = 3.5, $J_{3,4}$ = 5.0, H-3), 4.94 (t, 1H, H-2, overlapping with H-4), 4.93 (t, 1H, H-4, overlapping with H-2), 4.37 (d, 1H, $J_{4,5}$ = 3.4, H-5), 2.20, 2.11 (each s, each 3H, each COCH_3); ^{13}C NMR ($CDCl_3$) δ 170.2 (s, *C*OO), 169.0, 168.9 (each s, each *C*OCH$_3$), 88.5 (d, C-1), 71.5, 68.9, 68.6, 67.6 (each d, C-2−C-5), 20.7, 20.7 (each q, each CO*C*H$_3$); FTIR (KBr) 3031, 2967, 2119, 1816, 1754, 1395, 1371, 1265, 1231, 1067, 1047, 896, 743 cm^{-1}; CI-HRMS found 303.0940, required 303.0941 $[M + NH_4]^+$.

2,4-Di-*O*-acetyl-1-azido-1-deoxy-β-D-glucopyranuronic Acid, Phenylamide 30. A solution of 3,6-lactone **29** (0.047 g, 0.165 mmol) and aniline (0.02 mL, 0.219 mmol) in anhydrous dichloromethane (25 mL) was stirred at room temperature under a N_2 atmosphere for 18 h. The crude mixture was washed with 1.0 M HCl (3 mL) and dried ($MgSO_4$), and then the solvent was removed to produce a yellow residue (0.046 g). Recrystallization from dichloromethane/petroleum ether produced **30** as a pale yellow solid (0.038 g, 61%): R_f 0.20 (1:1 EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H, N*H*), 7.47 (d, 2H, J = 8.0, Ar H), 7.33 (t, 2H, J = 7.5, Ar H), 7.14 (t, 1H, Ar H), δ 5.15 (t, 1H, $J_{3,4}$ = 9.5, H-4), 4.92 (t, 1H, $J_{2,3}$ = 9.0, H-2), 4.77 (d, 1H, $J_{1,2}$ = 8.8, H-1), 4.07 (d, 1H, $J_{4,5}$ = 10.0, H-5), 3.89 (t, 1H, H-3), 3.20 (br s, 1H, O*H*), 2.16, 2.15 (each s, each 3H, each COCH_3); ^{13}C NMR ($CDCl_3$) δ 170.3, 169.2 (each s, each *C*OCH$_3$), 164.3 (s, *C*ONH), 136.4 (s, Ar C), 129.1, 125.3, 120.8 (each d, each Ar *C*H), 88.1 (d, C-1), 74.9, 72.9, 72.7, 71.6 (each d, C-2−5), 20.9, 20.8 (each q, each CO*C*H$_3$); FTIR (KBr) 3446, 2921, 2123, 1752, 1691, 1601, 1542, 1447, 1375, 1231, 1081, 1039 cm^{-1}; CI-HRMS found 379.1252, required 379.1254 $[M + NH_4]^+$.

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Supporting Information Available: Additional experimental procedures, ^{1}H NMR, selected additional spectra, molecular modeling coordinates, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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