JOC Article

Development of Carbohydrate-Based Scaffolds for Restricted Presentation of Recognition Groups. Extension to Divalent Ligands and Implications for the Structure of Dimerized Receptors

Paul V. Murphy,* Helena Bradley, Manuela Tosin, Nigel Pitt, Geraldine M. Fitzpatrick, and W. Kenneth Glass

Chemistry Department, Centre for Synthesis and Chemical Biology, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland

paul.v.murphy@ucd.ie

Received March 13, 2003

The solution structure of glycosyl amides has been studied by using NMR. A strong preference is displayed by tertiary aromatic glycosyl amides for *E-anti* structures in contrast with secondary aromatic glycosyl amides where *Z-anti* structures predominate. The structural diversity displayed by these classes of molecules would seem to be important as the directional properties of the aromatic ring, or groups attached to the aromatic ring, would be determined by choosing to have either a secondary or tertiary amide at the anomeric center and could be considered when designing bioactive molecules with carbohydrate scaffolds. The structural analysis was also carried out for related divalent secondary and tertiary glycosyl amides and these compounds display preferences similar to that of the monovalent compounds. The constrained divalent compounds have potential for promoting formation of clusters that will have restricted structure and thus have potential for novel studies of mechanisms of action of multivalent ligands. Possible applications of such compounds would be as scaffolds for the design and synthesis of ligands that will facilitate protein−protein or other receptor−receptor interactions. The affinity of restricted divalent (or higher order) ligands, designed to bind to proteins that recognize carbohydrates which would facilitate clustering and concomitantly promote protein−protein interactions, may be significantly higher than monovalent counterparts or multivalent ligands without these properties. This may be useful as a new approach in the development of therapeutics based on carbohydrates.

1. Introduction

Pharmacophore group presentation is important in medicinal chemistry. Researchers working in this area often introduce conformational restriction to obtain a precise presentation of groups important for recognition at the receptor. The benefits of synthesizing compounds with restricted structures are that they can be more potent, display higher selectivity, and have increased metabolic stability and better bioavailability.[1] They can also provide information regarding the desired bioactive conformation and exclude presentations of the binding groups that have different and perhaps unwanted activities.

Multivalency[2,3] has attracted attention from researchers in diverse fields including those interested in drug development. For example, the recognition of carbohydrate clusters by receptors is believed to be important for generating high affinity interactions between two cells, thus mediating cell−cell recognition, adhesion, and modulation of signal transduction pathways. Multivalent carbohydrate ligands have advantages over their monovalent counterparts, which generally bind their receptors weakly (mM). The development of low molecular weight compounds that bind strongly to carbohydrate receptors has therefore been difficult and this has greatly hindered the development of therapeutics based on carbohydrates.[4] There has been interest in the development of multivalent ligands as high affinity antagonists of receptors of interest for the development of agents for the treatment of inflammation[5] and infection[6] and for xenotransplantation[7] and anti-cancer vaccines.[8] Synthetic multi-

(1) For examples relating to peptides and peptidomimetics see: Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389.

(2) Lee, Y. V.; Townsend, R. R.; Hardy, M. R.; Lönngren, J.; Arnarp, J.; Haraldsson, M.; Lönn, H. *J. Biol. Chem.* **1983**, *258*, 199.

(3) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2754.

(4) Wong, C. H. *Acc. Chem. Res.* **1999**, *32*, 376.

(5) (a) Simanek, E. E.; McGarvey, G. J.; Jablonski J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833 and references cited therein. (b) Hanessian, S.; Mascitti, V.; Rogel, O. *J. Org. Chem.* **2002**, *67*, 3346 and references cited therein. (c) Murphy, P. V.; Hubbard, R. E.; Manallack, D. T.; Wills, R. E.; Montana, J. G.; Taylor, R. J. K. *Bioorg. Med. Chem.* **1998**, *6*, 2421.

(6) (a) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M. *Nature* **1993**, *363*, 418. (b) Kamitakahara, H.; Suzuki, T.; Nishigori, N.; Suzuki, Y.; Kanie, O.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 1524. (c) Kitov, P. I.; Sadowska, J. M.; Mulvey, G.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669.

(7) Liu, B.; Roy, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 773.

10.1021/jo034336d CCC: $25.00
Published on Web 06/18/2003

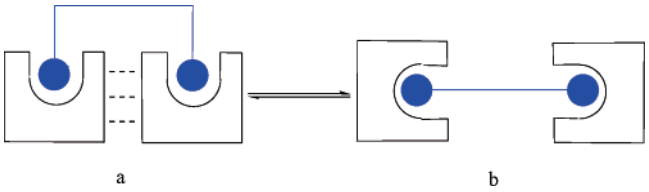


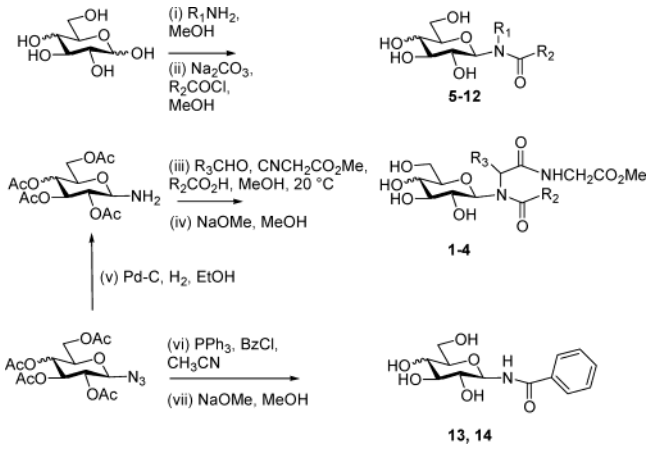
FIGURE 1. (a) The divalent ligand that promotes clustering of receptors and receptor−receptor interactions. (b) The divalent ligand that promotes clustering of receptors but not receptor−receptor interactions.

valent ligands can also effect or promote biological processes.[9] The cross-linking of multivalent carbohydrates with lectins can lead to formation of supramolecular assemblies that have roles in signal transduction.[10]

The mechanisms by which cells exploit multivalent interactions to bind with increased affinity and specificity and how cell-surface receptor organization influences signaling and the cellular responses that result have been reviewed[11] and can be influenced by the ligand architecture.[12] An explanation often offered is that increases in binding affinity are due to the chelate effect. Toone and co-workers have provided evidence that observed enhancements in the apparent binding affinity of multivalent ligands appear, in some cases at least, to be the result of entropically driven aggregation and precipitation.[13] On the other hand Burke, Kiessling, and co-workers have described a trivalent ligand that promotes synergistic formation of soluble lectin clusters; in this case the chelate effect cannot operate and precipitation of the ligand does not occur at concentrations where the clusters are soluble.[14] Other thermodynamic analyses of multivalent ligand binding have been carried out by Brewer and co-workers.[15]

Enhancements in binding affinity and perhaps specificity, observed for multivalent ligands, could also be explained if receptor−receptor interactions were promoted as a result of clustering (Figure 1). Synthetic ligands, which would promote such interactions, may show higher affinities. The determination of whether such mechanisms for generating high-affinity interactions operate could be investigated by synthesizing multivalent ligands that are structurally restricted; the

SCHEME 1



presentation of the groups required for recognition could be organized in a manner such that a particular ligand would promote clustering and receptor−receptor interactions whereas another ligand would promote clustering but not receptor−receptor interactions; there should be significant differences in binding affinities, perhaps also in specificity, and there may be consequences for biological function. To investigate these issues it is necessary to develop scaffolds that facilitate the presentation of multiple binding groups into precise and well-defined orientations. The study of these processes with use of these tools will aid in understanding the mechanism of action of multivalent ligands in greater detail and perhaps provide new strategies that can be considered in drug development.

Our initial interest is in the generation of a diverse range of structurally restricted divalent ligands so that they can be used for homo- and heterodimerization of receptors and that diverse clustering mechanisms and functional consequences can be investigated in detail. Dimerization is the simplest form of receptor clustering and its role as a regulatory mechanism in signal transduction has been reviewed; it can be promoted by small molecules that have been referred to as "chemical inducers of dimerization".[16] Dimeric compounds often show improved activity; it has been shown for example that dimerization of an inactive fragment of a natural product can produce a compound with twice the potency of the natural product.[17] In this paper we describe monovalent aromatic glycosyl amides that have potential as scaffolds for restricted presentation of binding groups for targeting receptors. This work has been extended to the synthesis of structurally related divalent glycosyl amides[18] that have well-defined structures with potential for use in structurally restricted receptor clustering.

2. Results and Discussion

2.1. Syntheses of Monovalent Glycosylamides. A series of secondary and tertiary amides (Table 1, Scheme 1) were first prepared for structural evaluation. The

(8) (a) Liebe B.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 618. (b) Keil, S.; Claus, C.; Dippold, W.; Kunz, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 366 and references cited therein. (c) Deshpande, P.; Danishefsky, S. J. *Nature* **1997**, *387*, 167. (d) Hummel, G.; Schmidt, R. R. *Tetrahedron Lett.* **1997**, *38*, 1173. (e) For a multivalent vaccine see: Ragupathi, G.; Coltart, D. M.; Williams, L. J.; Koide, F.; Kagan, E.; Allen, J.; Harris, C.; Glunz, P. W.; Livingston P. O.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. (U.S.A.)* **2002**, *99*, 13699.

(9) Gestwicki, J. E.; Strong, L. E.; Kiessling, L. L. *Chem. Biol.* **2000**, *7*, 583.

(10) Sacchettini, J. C.; Baum, L. G.; Brewer, C. F. *Biochemistry* **2001**, *40*, 3009.

(11) Kiessling, L. L.; Gestwicki, J. E.; Strong, L. E. *Curr. Opin. Chem. Biol.* **2000**, *4*, 696.

(12) Comparisons were made between low molecular weight compounds, dendrimers, globular proteins, linear polymers, and polydisperse polymers. Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, 124, 14922.

(13) Corbell, J. B.; Lundquist, J. L.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 95.

(14) Burke S. D.; Zhao, Q.; Schuster, M. C.; Kiessling, L. L. *J. Am. Chem. Soc.* **2000**, *122*, 4518.

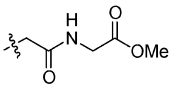
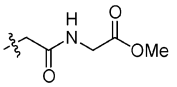
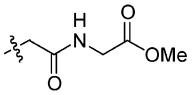
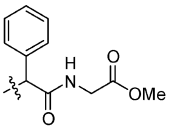
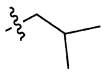
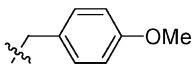
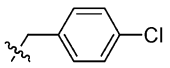
(15) Dam, T. K.; Roy, R.; Das, S. K.; Oscarson, S.; Brewer, C. F. *J. Biol. Chem.* **2000**, *275*, 14223.

(16) Klemm, J. D.; Schreiber, S. L.; Crabtree, G. R. *Annu. Rev. Immunol.* **1998**, *21*, 418−422.

(17) Carlier, P. R.; Du, D.-M.; Han, Y.-F.; Liu, J.; Perola, E.; Williams, I. D.; Pang, Y.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 1775.

(18) A preliminary account of the work described herein has been published previously. Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 2629.

TABLE 1. Structure of Monovalent Glycosyl Amides

Comp.	Saccharide	R_1	R_2	*Z anti* : *E anti*	δ (ppm)[a] H-1 ($J_{1,2}$ Hz)	
					Z anti	*E anti*
1	Glucose		Ph	8:92	5.94	4.92 (8.9)
2	Galactose		Ph	10:90	5.77	4.86 (9.0)
3	Galactose		Me	1:3	5.65 (9.1)	5.12 (8.2)
4	Galactose		Me	1:1	5.60	5.11
5	Galactose	Me	Ph	15:85	5.63 (9.4)	4.93 (9.2)
6	Galactose	Et	Ph	7:93	5.42	4.57 (9.0)
7	Galactose		Ph	7:93	5.21	4.54 (9.0)
8	Galactose	CH_2Ph	Ph	<1:9	5.70	5.01
9	Galactose	CH_2Ph	Me	1:2	5.66 (8.3)	4.72 (8.5)
10	Galactose	Me	Me	47:53	5.51 (9.0)	4.98 (8.8)
11	Galactose		Ph	6:94	5.45	4.68 (8.8)
12	Galactose		Ph	7:93	5.44	4.68 (9.0)
13	Galactose	H	Ph	100:0	5.22 (8.3)	-
14	Glucose	H	Ph	100:0	5.27 (9.3)	-

[a] Spectra were recorded in D_2O at 10−40 °C with HOD (δ 4.80) as the internal reference.

reaction of D-glucose or D-galactose with an amine gives a glycosylamine, which is acylated selectively at nitrogen by treatment with an acid chloride in methanol in the presence of sodium carbonate; this protocol was used to prepare compounds **5**−**12**.[19] The four-component Ugi condensation of the 2,3,4,6-tetra-*O*-acetylated-*β*-D-glycopyranosylamine with formaldehyde, isocyanide, and carboxylic acid and subsequent removal of the acetate protecting groups was also used to synthesize tertiary amides; this conveniently provided the neoglycopeptides **1**−**4**. A variation of the Staudinger reaction was used for synthesis of secondary amides; activation of the appropriate 2,3,4,6-tetra-*O*-acetylated-*β*-D-glycopyranosyl azide by triphenylphosphine in the presence of benzoyl chloride gives a protected glycosylamide from which the protecting groups were removed to give **13** and **14**.

2.2. Structure of Monovalent Glycosylamides. Structural analyses of some *β*-glycosyl amide derivatives (Figure 2) have been reported previously.[20,21] Previous research has indicated that an antiperiplanar (*anti*) rather than synperiplanar (*syn*) conformation is often

(19) Tertiary amides have been prepared previously. See: (a) Lockhoff, O.; Sadler, P. *Carbohydr. Res.*, **1998**, *314*, 13. (b) Retailleau, L.; Laplace, A.; Fensterbank, H.; Larpent, C. *J. Org. Chem.*, **1998**, *63*, 608.

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

(21) The α-glycosides have not been reported. Conventions for describing the configurations and conformations of the *β*-derivatives have been described previously, see: Avalos, M.; Babiano, R.; Durán, C. J.; Jiménez, J. L.; Palacios, J. C. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2205 and references cited therein.

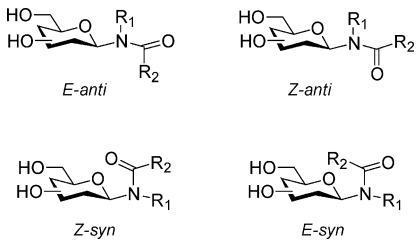


FIGURE 2. Nomenclature of glycosyl amides.

preferred for such amides. The ^{1}H and ^{13}C NMR spectra for most of the known tertiary amide derivatives ($R_1 \neq$ H) show two signal sets and this has been attributed to the presence of *Z-anti* and *E-anti* isomers of the β-glycosyl amide. The previous workers have found correlation of the major preferred solution structure with that observed in the solid state.[22] A set of rules was established, based on ^{1}H and ^{13}C chemical shifts, that are used to assign the *Z* or *E* configuration. For example, for glycosyl amides the chemical shift for the anomeric proton of the *Z-anti* isomer will be greater than that of the *E-anti* isomer due to deshielding caused by the carbonyl group; the chemical shift of the signal observed for the anomeric carbon of the *Z*-isomer is usually less than that of the *E*-isomer. A range of novel unprotected galactose and glucose derivatives **1**−**14**, synthesized as outlined in Scheme 1, have been studied and the results are summarized in Table 1. In general *E-anti* structures predominate for the tertiary aromatic amides (**1**, **2**, **5**−**8**, **11**, **12**) whereas for secondary aromatic amides (**13**, **14**) *Z-anti* structures are favored. In the NMR spectra the tertiary amides **1**−**12** showed two clear signal sets whereas the secondary amides **13** and **14** showed only one signal set. The resonances for the anomeric protons for all the glycosyl amides were generally doublets and had coupling constants consistent with the β-configuration; the NMR data and NOE enhancements observed for the remaining pyranose ring protons confirmed that the $^4C_1$ conformations are always favored, as expected. The NOE data also supported the structures proposed for the secondary and tertiary amide derivatives (Figures 3 and 4). For example, strong enhancements of the signal for the anomeric proton and a significantly weaker enhancement for the methyl signal were observed in the 1D NOE spectrum of **5** obtained by irradiating the aromatic signal; this is consistent with a predominant *E-anti* structure. Tertiary aromatic amides, in contrast with secondary aromatic amides, are generally not planar and the observed dihedral angle depends on the extent of steric interactions; angles of up to 90 ° between the carbonyl and aromatic group have been observed.[23] Interestingly a weak enhancement of the signal for H-5 but not for H-3 was observed after irradiating the aromatic signal of **5**, suggesting that the aromatic ring may be rotated toward the H-5 proton in the *E-anti* structure. The 1D and 2D NOE spectra in general showed evidence for exchange between the *Z* and *E* isomers, providing further support for the proposed structures for the tertiary amides. The 1D NOE spectrum for galactose derivative **13** obtained

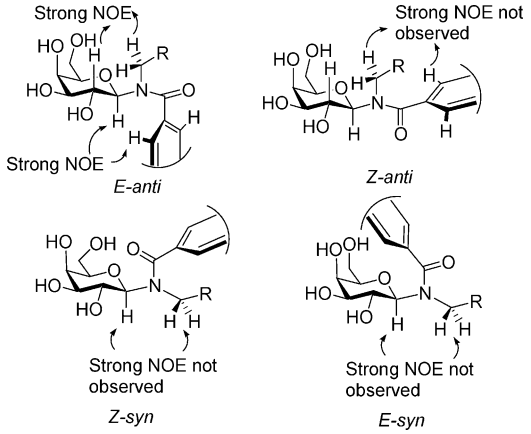


FIGURE 3. Summary of NOE data for tertiary amides. There were strong NOE enhancements between the aromatic protons and H-1 and also between H-2 and the methylene group (or methyl group) bonded to the nitrogen atom. Strong NOEs were not observed between the methylene group (or methyl group) and H-1 as would have been expected for *syn* conformations.

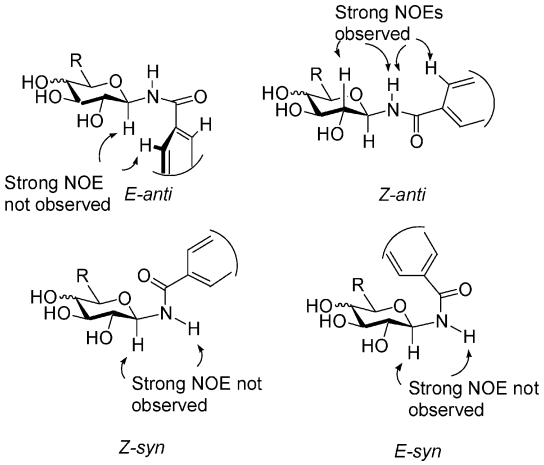


FIGURE 4. Summary of NOE data for aromatic secondary amides. There were strong NOE enhancements between NH and H-2 and between NH and aromatic protons. Strong NOEs were not observed between the NH and H-1 as would have been expected for syn conformations (spectra were recorded in D_2O:H_2O 10:90 so that NH could be observed). Strong NOEs were not observed between aromatic protons and H-1 as would be expected for *E-anti*.

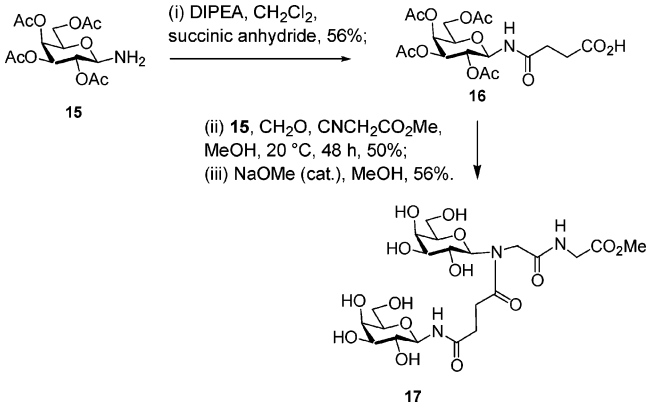
in D_2O after the irradiation of signal for the anomeric proton showed only a very weak enhancement of the signal for the aromatic protons when compared to the enhancement observed for H-3 and H-5; a strong enhancement would have been expected for significant population of the *E-anti* structure. The spectrum of **13** was also recorded in 10:90 D_2O:H_2O; the coupling constant that was observed between H-1 and the NH was 9.0 Hz; the 1D-NOE spectrum of **13** in this solvent mixture showed a strong enhancement of the signals for aromatic protons and H-2 on irradiation of the signal for the NH; these data further support the *Z-anti* structural assignment for the secondary amides, which is consistent with that found by other workers. Some other trends are evident. The tendency to adopt the *E-anti* structure for the tertiary amides was greater for aromatic derivatives (**1**, **2**, **5**−**8**, **11**, **12**) than for aliphatic derivatives (**3**, **4**, **9**,

(22) Avalos, M.; Babiano, R.; Carretero, M. J.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron* **1998**, *54*, 615.
(23) Bragg, R. A.; Clayden J.; Morris, G. A.; Pink, J. H. *Chem. Eur. J.* **2002**, *8*, 1279 and references cited therein.

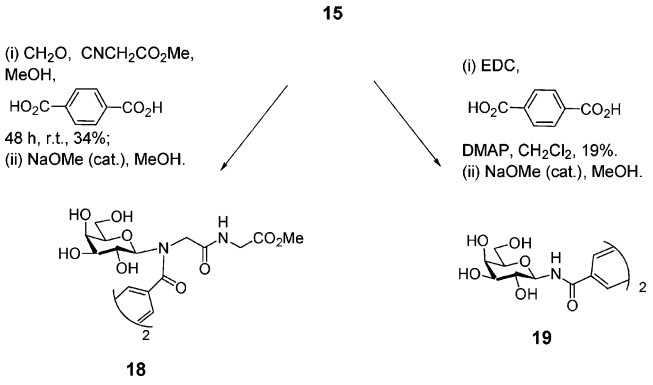
10), and increasing the substitution on the carbon adjacent to the nitrogen (R_1 substituent) showed an increase in the *E*/*Z* ratio (compare **2**, **5**−**8**, **11**, **12**). For the benzyl derivatives (**8**, **11**, **12**) no major changes in the *E*/*Z* ratio were observed on variation of the substituent on the aromatic ring. The structural preference displayed by tertiary aromatic amides may be due to a simple steric effect between the ortho aromatic protons and the R_1 substituent; as the size of the R_1 substituent increases the greater the steric interaction and thus there is an increase in preference for the *E-anti* structure. This effect is not as pronounced when the R_2 substituent is methyl. We anticipate on the basis of the above results that the *E*/*Z* ratio might be higher (>93:7) for *N*-glycosyl-*N*-isopropyl aromatic amides. These predictions have been supported by molecular mechanics calculations of such derivatives but we have not been able to prepare these derivatives as yet using the synthetic routes described herein; work is currently in progress to investigate the synthesis of these compounds.

2.3. Potential of Monovalent Aromatic Glycosyl Amides as Scaffolds. The use of carbohydrates as scaffolds in peptidomimetic and other research related to drug development has recently been explored by Hirschmann, Nicolaou, Smith, and co-workers[24] and other researchers.[25] The low bioavailability of peptide drugs has led to investigations of placing pharmacophoric groups on a nonpeptide scaffold; the scaffold can orient these groups in the direction of their respective binding subsites. The results obtained indicate that evaluation of compounds based on monosaccharide and even disaccharide[26] scaffolds holds great promise for being universally useful as a drug discovery platform. Also some workers have been exploring the synthesis and evaluation of carbohydrate mimetics and "*carbohybrids*"[27] with a view to developing compounds that will bind with high affinities to carbohydrate receptors. In these contexts the structural diversity (i.e. *E-anti* for tertiary amides, *Z-anti* for secondary amides) displayed by amides **1**−**14**, in particular for the aromatic amides, would seem to be important. The directional properties of the aromatic ring or groups attached to the aromatic ring would be determined by choosing to have either a secondary or tertiary amide at the anomeric center and this could be taken into consideration in the design of bioactive molecules based on carbohydrate templates.

SCHEME 2



SCHEME 3



2.4. Synthesis of Divalent Glycosyl Amides. Having observed the strong preferences for *E-anti* structure for tertiary aromatic glycosyl amides, it seemed appropriate to prepare structurally related divalent compounds and thus the synthesis of **17**−**20** was carried out. Reaction of the amine **15** with succinic acid in the presence of diisopropylethylamine gives **16**. The Ugi reaction of **16** with **15**, formaldehyde, and methyl isocyanoacetate and subsequent removal of the protecting groups gave **17** (Scheme 2). A double Ugi reaction of terephthalic acid with **15**, formaldehyde, and methyl isocyanoacetate followed by deacetylation was used to synthesize **18**. The secondary amide **19** was prepared via the EDC-promoted coupling of **15** with terephthalic acid (Scheme 3) followed by deprotection. The synthesis of **20** (Scheme 4) was carried out by coupling of an amine derived from glucuronic acid with terephthalic acid, using a mixture of DCC, HOBT, and DMAP in THF and subsequent deprotection.

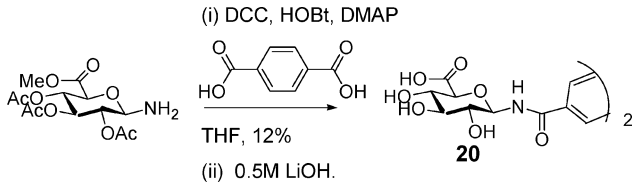
(24) (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In *Peptides−Chemistry, Structure, and Biology: Proceedings of the 11th American Peptide Symposium*; Rivier, J. E., Marshall, G. R., Eds.; ESCOM: Leiden, The Netherlands, 1990; pp 881−884. (c) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B. H.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. A.; Strader, C. D. *J. Am. Chem.* Soc. **1993**, *115*, 12550. (d) Hirschmann, R.; Hynes, J., Jr.; Cichy-Knight, M. A.; van Rijn, R. D.; Sprengeler, P. A.; Spoors, P. G.; Shakespeare, W. C.; Pietranico-Cole, S.; Barbosa, J.; Liu, J.; Yao, W.; Rohrer, S.; Smith, A. B., III *J. Med. Chem.* **1998**, *41*, 1382−1391.

(25) (a) Ghosh, M.; Dulina, R. G.; Kakarla, R.; Sofia, M. J. *J. Org. Chem.* **2000**, *65*, 8387. (b) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503. (c) Boer, J.; Gottschling; Schuster; Holzmann, B.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3870. (d) Wessel, H. P.; Banner, D.; Gubernator, K.; Hilpert, K.; Myller, K.; Tschopp, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 751. (e) Moitessier, N.; Dufour, S.; Chrétien, F.; Thiery, J. P.; Maigret, B.; Chapleur, Y. *Bioorg. Med. Chem.* **2001**, *9*, 511. (f) Zuccarello, G.; Bouzide, A.; Kvarnstrom, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karlen, A.; Hallberg, A.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1998**, *63*, 4898. (g) Hanessian, S.; Huynh, H. K. *Synlett* **1999**, *1*, 102. (h) Xuereb, H.; Maletic, M.; Gildersleeve, J.; Pelczer, I.; Kahne, D. *J. Am. Chem. Soc.* **2000**, *122*, 1883. (i) Kawato, H. C.; Nakayama, K.; Inagaki, H.; Ohta, T. *Org. Lett.* **2001**, 3, 3451. (j) Liao, Y.; Li, Z. M.; Wong, H. N. C. *Chin. J. Chem.* 2001, 19, 1119. (k) Murphy, P. V.; O'Brien, J. L.; Gorey-Feret, L.; Smith, A. B., III *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1763−66. (l) The Versatile Assembly on Sugar Templates (VAST) program initiated by Alchemia Corporation, see: Schliebs, D. *Mod. Drug Discov.* **2001**, *4*, 61.

(26) For an example of a disaccharide scaffold see: Baizman, E. R.; Branstrom, A. A.; Longley, C. B.; Allanson, N.; Sofia, M. J.; Gange, D.; Goldman, R. C. *Microbiology-UK* **2000**, *146*, 3129−3140.

(27) For a review see: Schweizer, F.; Hindsgaul, O. *Curr. Opin. Chem. Biol.* **1999**, 3, 291−298;

SCHEME 4



2.5. Structure of Divalent Glycosyl Amides. The structural preferences displayed by the divalent glycosyl amides **17**−**20** were consistent with that observed for the related monovalent compounds. The *Z-anti*:*E-anti* ratio was 27:73 for the divalent galactose derivative **17**; this is a more flexible compound than the other divalent compounds prepared due to the presence of succinic acid linker. This contrasts with the remainder of divalent structures **18**−**20**, which are more rigid. A series of 1D NOE, 2D NOESY, and 2D ROESY experiments for **18** showed strong NOE enhancements for the major isomer (87%) consistent with the amides adopting *E-anti* conformations; there were strong enhancements observed between the methylene protons adjacent to the nitrogen atom at C-1 with H-2 and between H-1 and the aromatic protons. Also the chemical shift for the anomeric proton of the major isomer at δ 4.98 is consistent with that observed for *E-anti* structures in the monovalent series. The presence of a minor isomer (13%, **18c** and **18d**), where one amide is *E-anti* and the other *Z-anti* (Figure 5), can be detected from the NMR data as there are two anomeric signals (^{1}H NMR, δ 5.90 and δ 4.90, 40 °C)[28] that show clear cross-peaks with the anomeric signal at δ 4.98 in the 2D NOESY and ROESY spectra; these cross-peaks had opposite sign to the NOE enhancements, indicating that exchange between the isomers occurs further supporting the structural assignment.[29] The NMR spectra for this compound were also obtained in CD_3OD and the *E-anti* isomer also predominated in this solvent. Interpretation of the data obtained suggests that the major structural isomer adopted by **18** is either **18a** or **18b** (Figure 5). Both of these isomers contain a *C-2* symmetry axis; for **18a** the carbohydrates are in a cis arrangement, for **18b** they are trans. The aromatic signal for **18** in D_2O or CD_3OD appears as a singlet; however, at −85 °C in CD_3OD the aromatic signal appeared as two broad signals (∼1:2 ratio) supporting the most likely possibility that there is dynamic equilibrium between the cis and trans isomers. Computational methods (Monte Carlo conformational searches)[30] would indicate that **18a** and **18b** are both low-energy structures although a significantly higher number of structures with trans geometries (Figure 6) were found within 3 kcal mol^{-1} of the global minimum. The NMR spectra for the secondary amide derivatives **19** and **20** were similar to those observed for the related monovalent compounds **13** and **14**. A single set of signals was evident in the ^{1}H and ^{13}C NMR spectra. The signal for the anomeric proton of **19** appeared at δ 5.24 ($J_{1,2}$ = 8.9 Hz) and for that of **20** at δ 5.33 ($J_{1,2}$ = 8.7 Hz) in the ^{1}H spectrum. The 1D NOE spectrum for **20** was obtained where the anomeric signal

(28) At 10 °C the signals are doublets at δ 5.58 and δ 4.60.
(29) Exchange between *Z-* and *E-anti* conformations has been observed also for other tertiary amides described herein by NOE. See the Supporting Information for selected spectra.
(30) Calculations were carried out with Macromodel 6.0.

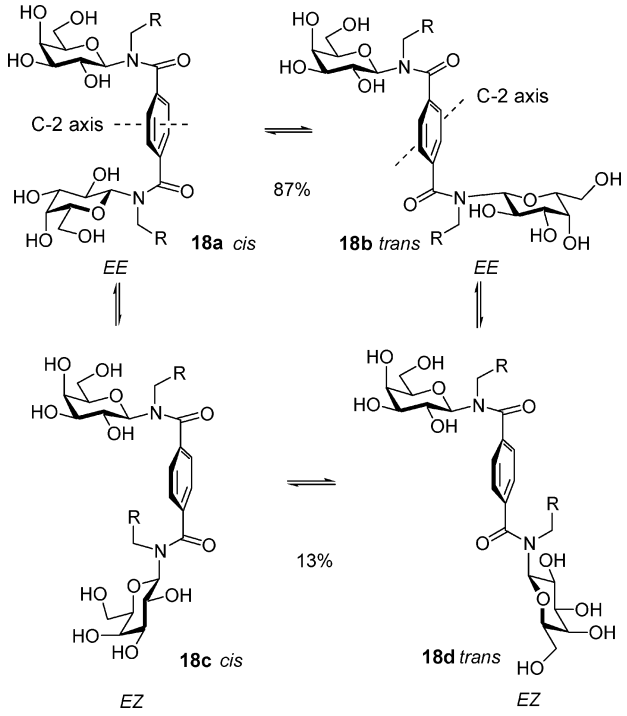


FIGURE 5. Structure of **18**.

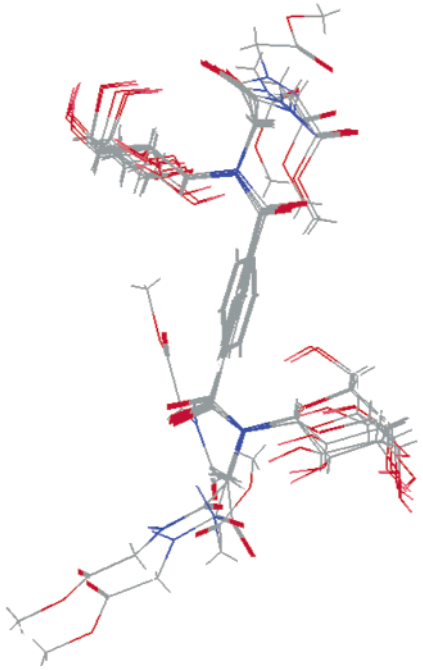


FIGURE 6. Lowest energy structures for **18b**.

was irradiated and strong NOE enhancements were observed for H-2, H-3, and H-5 but only a very minor enhancement was observed for the aromatic protons; this is again consistent with the *Z-anti* structure being preferred for these amides. This suggests that the major isomers adopted by **19** are **19a** and **19b** (Figure 7, 8) and that those of **20** are **20a** and **20b**. For **19a** and **20a** the carbohydrates can again be considered to be cis, whereas for **19b** and **20b** they are trans. Calculations with Monte

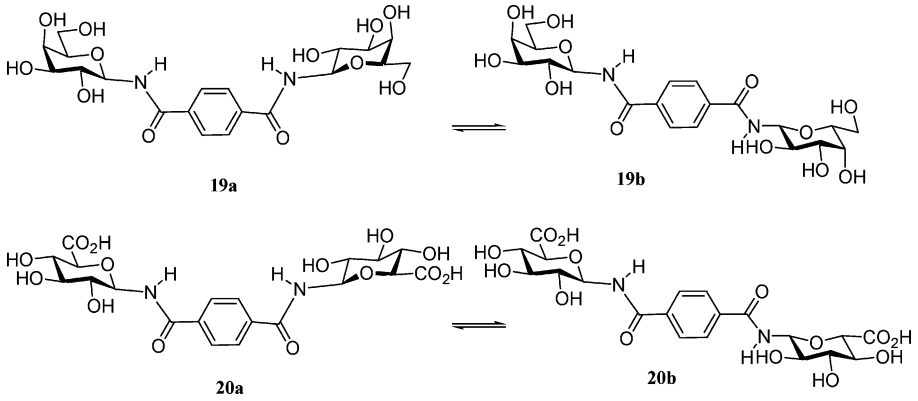


FIGURE 7. Structure of **19** and **20**.

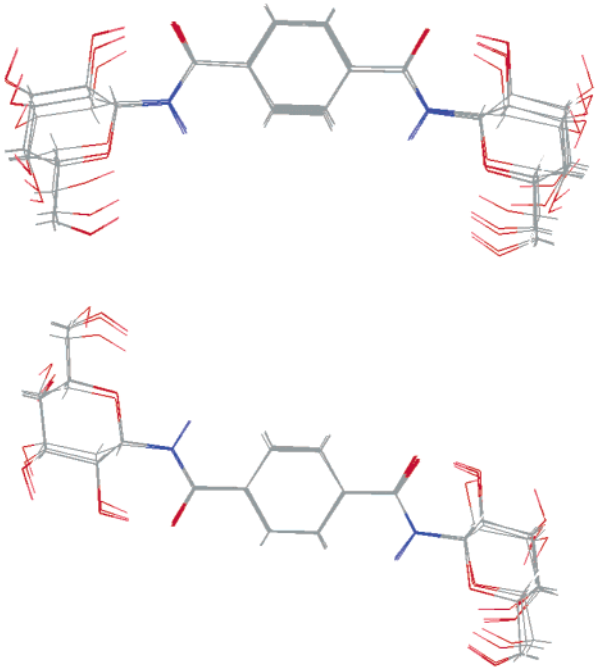


FIGURE 8. Lowest energy structures for **19a** (top) and **19b** (bottom) obtained by a Monte Carlo conformational search.

Carlo conformational searching techniques indicate that both **19a** and **19b** are low-energy structures (Figure 8).

2.6. Potential Applications of Restricted Divalent Ligands. It is clear that the structural space occupied by cis and trans isomers of **18** and **19** (Figure 9) differs considerably and as a consequence the structural space occupied by receptors that would be clustered by binding to the two saccharide units, or to any bioactive group attached to the saccharide unit, will also differ considerably. This provides a basis for generating structural diversity combined with an ability to present the structure of the binding groups in well-defined orientations. Furthermore, the various hydroxyl groups on the saccharide units can be used for attachment of bioactive groups or molecular recognition components, in a fashion similar to that adopted by those interested in using carbohydrate-based scaffolds in medicinal chemistry; this approach would facilitate the generation of a library of divalent compounds where the recognition components belonging to each member of the library would occupy

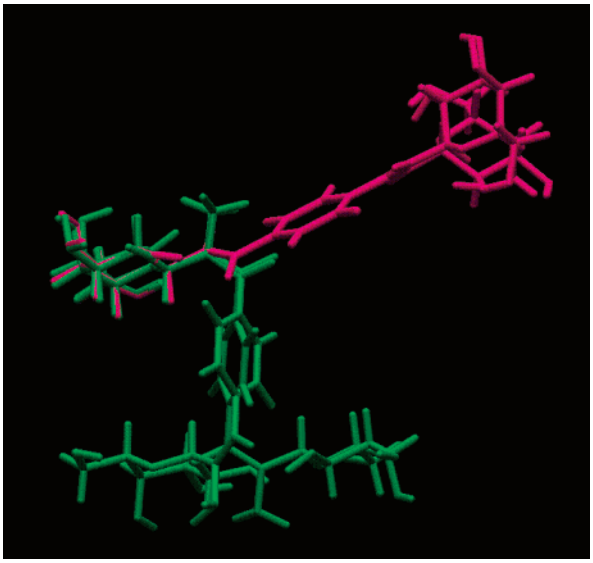


FIGURE 9. Atoms (the ring O, C-1, C-2, C-3, C-4, C-5) of one of the galactose residues (shown top left) of the lowest energy structures of the divalent ligands **18a**, **18b** (green), **19a**, and **19b** (red) were superimposed. The peptide chains of **18** have been removed for clarity.

their own structural space. This structural diversity would be increased by using a range of monosaccharides (D and L) or by using higher order saccharides (oligosaccharides).

3. Summary and Conclusions

The structure of unprotected glycosyl amides in water has been investigated. The structural preferences for the secondary amides are clearly different from those observed for the tertiary glycosyl amides and there are strong preferences for *E-anti* structures for the aromatic tertiary amides. Monovalent and divalent compounds based on aromatic glycosyl amides have potential as scaffolds to present binding groups in well-defined orientation. The results have implications for the structures of clusters that will form on binding of divalent ligands to receptors. Preliminary molecular modeling studies[31] we have carried out indicate that **18**−**20** and related scaffolds can, at least in principle, be used as a basis for

(31) These studies will be discussed in a subsequent publication.

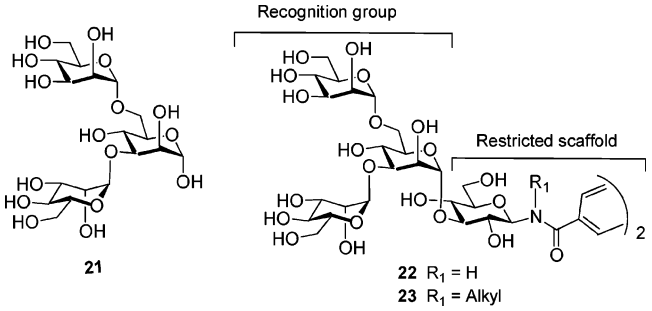


FIGURE 10. Structures of **21**−**23**.

the design of ligands suitable for clustering proteins and the modeling indicates it might be possible to present recognition groups in such a way that a restricted divalent ligand could promote receptor−receptor interactions. For example, divalent compound **22** (Figure 10) bearing the trimannoside **21**, a ligand for Concanavalin A, can bring the two monomeric proteins within a distance where protein−protein interactions may occur; this is unlikely for the related tertiary amides **23**. Synthesis and biological evaluation of these ligands is underway and the results will be reported in due course. Irrespective of the results that these studies will generate it seems worthwhile to further explore the synthesis of restricted divalent ligands for applications in biological and medicinal chemistry.

4. Experimental Section

[2-(Benzoyl-(β-D-glucopyranosyl)-amino)-acetylamino]-acetic Acid, Methyl Ester (1). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamine (0.3 g, 0.86 mmol), benzoic acid (0.11 g, 0.86 mmol), formaldehyde (0.06 mL, 0.86 mmol), and methyl isocyanoacetate (0.08 mL, 0.86 mmol) were suspended in methanol (5 mL). The reaction mixture was allowed to stir at room temperature. Analysis by TLC (EtOAc) showed that the reaction was complete after 24 h. Excess solvent was removed and the residue was purified by chromatography (EtOAc: petroleum ether, 2:1) to yield [2-(benzoyl-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-amino)-acetylamino]-acetic acid, methyl ester as a yellow syrup (0.24 g, 49%); R_f 0.27 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (br s, 5H, aromatic H), 6.91 (br s, 1H, N*H*), 5.04−5.17 (broad overlapping signals, H-1−4), 4.01−4.21 (br signals, 6H, H-6a, H-6b, 2 × CH_2), 3.75 (s, 3H, OCH_3), 3.60−3.75 (br signal, 1H, H-5), 2.10, 2.04, 2.01, 1.99 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$) δ 170.7, 170.5, 170.3, 169.4, 168.6 (each s, each C═O), 134.5 (s, aromatic C), 131.1, 129.1, 127.0 (each d, aromatic C), 74.6, 73.4, 68.6, 68.1 (each d), 61.9 (t, C-6), 52.5 (q, OCH_3), 41.5 (t, CH_2), 20.9, 20.7 (each q, each OAc); ν_{max} (KBr) 3400, 2977, 2544, 1763, 1671, 1541, 1439, 1370, 1220, 1051 cm^{-1}. HRMS-CI: found 581.1987 $[M + H]^+$, required 581.1983. This intermediate (0.13 g, 0.22 mmol) was suspended in MeOH (20 mL), sodium methoxide (0.1 mL of a 0.25 M solution) was added, and the reaction mixture was allowed to stir at room temperature. TLC analysis (MeOH:EtOAc, 1:4) showed that the reaction was complete after 3 h. Amberlite (H^+) was added and after 5 min the reaction mixture was filtered and the solvent removed to yield **1** as a yellow solid (0.08 g, 98%); R_f 0.5 (MeOH:EtOAc, 1:4); $[\alpha]_D$ +25.0 (*c* 0.04, H_2O); mp 70−74 °C; ^{1}H NMR (300 MHz, D_2O; *Z*:*E*, 8:92) δ 7.65 (s, 5H, aromatic H), 5.94 (br s, 1H, H-1, *Z*-isomer), 4.92 (d, 1H, $J_{1,2}$ = 8.9 Hz, H-1, *E*- isomer), 4.42 (AB d, 2H, *J* = 17.0 Hz, CH_2), 4.19 (AB d, 2H, *J* = 17.0 Hz, CH_2), 3.86 (dd, 1H, $J_{6a,5}$ = 1.9 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 3.85 (s, 3H, OCH_3), 3.80 (dd, 1H, $J_{6b,5}$ = 5.5 Hz, $J_{6b,6a}$ = 12.4 Hz, H-6b), 3.67 (apt t, $J_{2,1} = J_{2,3}$ = 8.9 Hz, H-2), 3.37−3.52 (overlapping signals, 3H, H-3, H-4, H-5); ^{13}C NMR (D_2O, *E*-isomer) δ 175.7 (s, CO_2Me), 172.4, 172.2 (each s, each C═O), 133.7 (s, aromatic C), 131.4, 129.3, 127.2 (each d, aromatic C), 87.8 (d, C-1), 78.2, 75.8, 70.4, 69.4 (each d), 61.0 (t, C-6), 53.1 (q, OCH_3), 45.2 (t, CH_2), 41.6 (t, CH_2); ν_{max} (KBr) 3445, 2954, 2881, 1910, 1745, 1648, 1556, 1448, 1371, 1222, 1080 cm^{-1}. HRMS-FAB: found 435.1378 $[M + Na]^+$, required 435.1380. Analytical HPLC (C-4; 5:95; CH_3CN:H_2O) indicated >95% purity.

[2-(Benzoyl-(β-D-galactopyranosyl)-amino)-acetylamino]-acetic Acid, Methyl Ester (2). 2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosylamine[32] (**15**; 0.5 g, 1.44 mmol), benzoic acid (0.18 g, 1.44 mmol), and formaldehyde (0.11 mL, 1.44 mmol) were suspended in methanol (5 mL) and stirred at room temperature for 1 h. Methyl isocyanoacetate (0.13 mL, 1.44 mmol) was then added and the reaction mixture was allowed to stir at room temperature. TLC analysis (EtOAc) showed that the reaction was complete after 48 h. The solvent was removed and the residue purified by chromatography (EtOAc:petroleum ether, 1:1) to give [2-(benzoyl-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-amino)-acetylamino]-acetic acid, methyl ester as a white foam (0.6 g, 73%); R_f 0.32 (EtOAc); $[\alpha]_D$ +33.3 (*c* 0.02, MeOH); mp 25−29 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.17 (br s, 1H, N*H*), 7.25−7.51 (overlapping signals, 5H, aromatic H), 5.10−5.24 (overlapping signals, 4H, H-1−4), 3.63−4.19 (overlapping signals, 7H, H-5, H-6a, H-6b, 2 × CH_2), 3.64 (s, 3H, OMe), 1.95−2.05 (overlapping signals, 12H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 169.9 (each s, each C═O), 135.2, 134.5 (each s, aromatic C), 130.9 (s, aromatic C), 128.9, 128.8, 127.1, 126.8, 126.5 (each d, aromatic C), 90.1 (br signal, d, C-1), 73.3, 68.6, 67.0, 66.0 (each d), 61.4 (t, C-6), 52.3 (q, OCH_3), 41.3, 41.2 (each t, each CH_2), 20.7 (2 signals), 20.6, 20.5 (each q, each OAc); ν_{max} (KBr) 3400, 2977, 2544, 1763, 1671, 1541, 1439, 1370, 1220, 1051 cm^{-1}. HRMS-CI: found 581.1983 $[M + H]^+$, required 581.1987. This intermediate (0.37 g, 0.65 mmol) was suspended in methanol (10 mL) and NaOMe (0.2 mL of a 0.25 M solution) was added. The reaction mixture was allowed to stir at room temperature. TLC analysis (MeOH: EtOAc, 1:4) showed that the reaction was complete after 2.5 h. Amberlite (H^+) was added and after 5 min the reaction mixture was filtered and the solvent removed. The residue was purified by chromatography (MeOH) to yield **2** as an off-white foam (0.16 g, 59%); R_f 0.5 (MeOH:EtOAc, 1:4); $[\alpha]_D$ +40.0 (*c* 0.04, MeOH); mp 58−60 °C; ^{1}H NMR (300 MHz, D_2O; *Z*:*E*, 10:90) δ 7.65 (s, 5H, aromatic H), 5.77 (br s, H-1, *Z*-isomer), 4.86 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1, *E*-isomer), 4.46 (s, 2H, CH_2), 4.21 (s, 2H, CH_2), 3.97 (d, 1H, $J_{4,3}$ = 3.0 Hz, H-4), 3.81−3.92 (overlapping signals, 6H, H-2, H-6a, H-6b, OCH_3), 3.64 (dd, 1H, $J_{5,6a}$ = 4.0 Hz, $J_{5,6b}$ = 7.6 Hz, H-5), 3.59 (dd, 2H, $J_{3,4}$ = 3.0 Hz, $J_{3,2}$ = 9.5Hz, H-3); ^{13}C NMR (D_2O) δ 175.9 (s, CO_2Me, *Z*-isomer), 175.7 (s, CO_2Me, *E*-isomer), 172.4, 172.2 (each s, each C═O, *E*-isomer), 171.5 (s, C═O, *Z*-isomer), 133.7 (s, aromatic C, *E*-isomer), 131.4, 129.2, 127.1, 126.5 (each d, aromatic C, *E*-isomer), 131.0, 129.9 (2 signals), 129.0 (each d, each aromatic C, *Z*-isomer), 88.4 (d, C-1, *E*-isomer), 77.6, 72.9, 68.8, 68.0 (each d, *E*-isomer), 75.4, 73.1, 73.0, 69.0 (each d, *Z*-isomer), 61.4 (t, *Z*-isomer), 61.3 (t, C-6, *E*-isomer), 53.1 (q, OCH_3), 45.3, 43.7 (each t, each CH_2, *Z*-isomer), 45.1, 41.6 (each t, each CH_2, *E*-isomer); ν_{max} (KBr) 3413, 2938, 1744, 1654, 1555, 1449, 1369, 1225, 1096 cm^{-1}. HRMS-FAB: found 435.1374 $[M + Na]^+$, required 435.1380. Analytical HPLC (C-4; 5:95 CH_3CN:H_2O) indicated >90% purity.

[2-(Acetyl-(β-D-galactopyranosyl)-amino)-acetylamino]-acetic Acid, Methyl Ester (3). The amine **15** (0.5 g, 1.44 mmol) was suspended in dry THF (30 mL). To this solution was added formaldehyde (0.11 mL, 1.44 mmol), acetic acid (0.15 mL, 2.0 mmol), methyl isocyanoacetate (0.15 mL, 1.73 mmol), and zinc chloride (0.5 M solution in THF, 0.2 mL, 1.44 mmol), and the mixture was allowed to stir at −25 to −40 °C.

(32) Bertho, A.; Maier, J. *Justus Liebigs Ann. Chem.* **1932**, *498*, 50, 55.

TLC analysis (EtOAc) showed that the reaction was complete after 24 h. The solvent was removed and the residue purified by chromatography (EtOAc) to give [2-(acetyl-(tetra-*O*-acetyl-β-D-galactopyranosyl)-amino)-acetylamino]-acetic acid, methyl ester[33] as a white foam (0.08 g, 11%); R_f 0.27 (EtOAc); $[\alpha]_D$ +43.75 (*c* 0.02, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27 (br s, 1H, N*H*), 6.00 (d, 1H, H-1), 5.17−5.47 (overlapping signals, H-2−4), 3.99−4.22 (overlapping signals, H-5, H-6a, H-6b, 2 × CH_2), 3.74 (s, 3H, OCH_3), 2.00−2.20 (overlapping signals, 4 × OAc, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.7, 170.5, 170.4, 170.2, 170.0, 169.8, 169.2 (each s, each C═O), 80.5 (d, C-1), 74.0, 71.1, 67.4, 66.5 (each d), 61.9 (t, C-6), 52.5 (q, OCH_3), 48.6 (t, CH_2), 41.3 (t, CH_2), 22.2 (q, CH_3), 20.8, 20.7 (2 signals) (each q, each OAc); ν_{max} (film) 2884, 2086, 1741, 1447, 1374, 1241 cm^{-1}. HRMS-CI: found 519.1828 $[M + H]^+$, required 519.1826. This intermediate (0.02 g, 0.04 mmol) was suspended in MeOH (5 mL), sodium methoxide (0.1 mL of a 0.25 M solution) was added, and the reaction mixture was allowed to stir at room temperature. After 40 min another 0.1 mL of NaOMe was added to the reaction mixture. After a further 2 h of reaction an additional 0.1 mL of NaOMe was added. TLC analysis (MeOH:EtOAc, 1:4) showed that the reaction was complete after a total of 3.5 h. Amberlite (H^+) was added and after 5 min the reaction mixture was filtered and the solvent removed to give the title compound as a clear oil (0.01 g, 71%); R_f 0.17 (MeOH:EtOAc, 1:4); ^{1}H NMR (300 MHz, D_2O; *Z*:*E*, 1:3) δ 5.65 (d, 1H, $J_{1,2}$ = 9.1 Hz, H-1, *Z*-isomer), 5.12 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1, *E*-isomer), 3.80−4.25 (overlapping signals, 13H, H-2−6, 2 × CH_2, OCH_3), 2.37 (s, 3H, NAc).

[2-(Acetyl-(β-D-galactopyranosyl)-amino)-2-phenylacetylamino]-acetic Acid, Methyl Ester (4). The amine **15** (0.3 g, 0.86 mmol) was suspended in dry THF (20 mL). To this solution was added benzaldehyde (0.10 mL, 0.95 mmol), acetic acid (0.07 mL, 1.2 mmol), and methyl isocyanoacetate (0.10 mL, 0.32 mmol). The reaction mixture was cooled to −25 °C, zinc chloride (0.5 M solution in THF, 0.12 mL, 0.86 mmol) was added, and the mixture was allowed to stir at −25 to −40 °C. After 3 h at this temperature the reaction was complete and the reaction mixture was allowed to stir at room temperature. TLC analysis showed that the reaction was complete after 48 h. The solvent was removed and the product purified by chromatography (EtOAc) to give [2-(acetyl-(tetra-*O*-acetyl-β-D-galactopyranosyl)-amino)-2-phenylacetylamino]-acetic acid, methyl ester (0.18 g, 35%); R_f 0.18 (EtOAc); $[\alpha]_D$ −58.75 (*c* 0.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.48 (m, 5H, aromatic H), 4.85−5.59 (overlapping signals, 4H, H-1−4), 3.73−4.03 (br signals, 9H, H-5, H-6a, H-6b, C*H*Ph, CH_2, OCH_3), 2.16 (s, 3H, NAc), 2.04, 2.03, 2.01, 1.97 (each s, each OAc); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.4 (2 signals), 170.2, 169.7, 169.4 (each s, each C═O), 129.0, 128.9, 128.7, 128.4 (each d, aromatic C), 73.0, 72.2, 67.4, 63.0, 60.6 (each d), 61.3 (t, C-6), 52.4 (q, OCH_3), 41.7 (t, CH_2), 31.0 (d, *C*HPh), 20.9, 20.8 (2 signals), 20.7 (each q, each OAc); ν_{max} (KBr) 3432, 2973, 2858, 1754, 1672, 1540, 1439, 1370, 1228, 1052 cm^{-1}. HRMS-FAB: found 617.1960 $[M + Na]^+$, required 617.1959. This intermediate (0.09 g, 0.15 mmol) was suspended in MeOH (10 mL), sodium methoxide (0.1 mL of a 0.25 M solution) was added, and the reaction mixture was allowed to stir at room temperature. After 6 and 15 h additional portions of NaOMe solution (each 0.1 mL) were added to the reaction mixture. After a n additional 15 h of reaction another 0.1 mL of NaOMe was added. TLC analysis (MeOH:EtOAc, 1:4) showed that the reaction was complete after a total of 24 h. Amberlite (H^+) was added and after 5 min the reaction mixture was filtered and the solvent removed. The residue was purified by chromatography (MeOH:EtOAc, 1:40) to yield the title compound **4** as an off-white foam (0.03 g, 45%); R_f 0.17 (MeOH:EtOAc, 1:4); $[\alpha]_D$ +45.0 (*c* 0.04, H_2O); ^{1}H NMR (300 MHz, D_2O; *Z*:*E*, 1:1) δ 7.64 (br s, 2H, aromatic H), 7.50 (br s, 3H, aromatic H), 5.60 (br s, 1H, H-1, *Z*-isomer), 5.11 (br s, 1H, H-1, *E*-isomer), 4.03−4.21 (overlapping signals, 4H, H-2, H-4, CH_2), 3.70−3.92 (overlapping signals, C*H*Ph, H-3, H-5, H-6a, H-6b, OCH_3), 2.25 (s, 3H, NAc); ^{13}C NMR (D_2O) δ 174.8, 173.1, 172.2 (each s, each C═O), 134.9 (s, aromatic C), 130.2, 128.9, 128.8, 128.5 (each d, aromatic C), 88.2 (d, C-1), 77.9, 73.1, 69.0, 68.5 (each d), 61.2 (t, C-6), 53.1 (q, OCH_3), 41.9 (t, CH_2), 22.3 (q, CH_3); ν_{max} (KBr) 3428, 2925, 2839, 1743, 1646, 1539, 1442, 1374, 1223, 1083 cm^{-1}. HRMS-FAB: found 449.1537 $[M + Na]^+$, required 449.1536. Analytical HPLC (C-4; 2:98 CH_3CN:H_2O) indicated >85% purity.

***N*-Methyl-D-galactopyranosylamine.** To a solution of methylamine in methanol (5.4 mL, 11.2 mmol) was added D-galactose (2.0 g, 11.2 mmol). The reaction mixture was heated to 60−65 °C for 30 min. The reaction mixture was then allowed stir at room temperature. After 9 h of reaction the solvent was removed and the residue recrystallized from ethanol to give the title compound as an off-white solid (1.76 g, 82%); $[\alpha]_D$ −11.67 (*c* 0.02, MeOH); mp 118−120 °C; ^{1}H NMR (300 MHz, D_2O; 1:2 mixture of α:β anomers) δ 5.32 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1, α-anomer), 4.65 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1, β-anomer), 3.48−4.05 (overlapping signals, 12H, H-2−6), 2.38, 2.32 (each s, each 3H, each CH_3); ^{13}C NMR (D_2O, β-anomer) δ 98.5 (d, C-1, α-anomer), 91.4 (d, C-1, β-anomer), 76.2, 74.0, 70.6, 69.3 (each d, β-anomer), 75.3, 73.1, 72.4, 69.1 (each d, α-anomer), 61.5 (t), 61.3 (t), 31.1 (q, CH_3); ν_{max} (KBr) 3312, 2966, 2860, 1654, 1503, 1452, 1357, 1240, 1142, 1058, 987 cm^{-1}. HRMS-FAB: found 194.1030 $[M + H]^+$, required 194.1028.

***N*-Methyl-*N*-(β-D-galactopyranosyl)-benzamide (5).** Sodium carbonate (0.17 g, 1.6 mmol) was added to a solution of *N*-(methyl)-D-galactopyranosylamine (0.12 g, 0.6 mmol) in methanol (15 mL). The resulting solution was cooled to 0 °C and benzoyl chloride (0.14 mL, 1.2 mmol) was added dropwise over 5 min. The ice bath was then removed and the reaction mixture was allowed to stir at room temperature. TLC analysis (MeOH:EtOAc, 1:3) showed the reaction was complete after 20 min. The solvent was removed and the residue purified by chromatography (2×, MeOH:EtOAc, 1:30 to 1:10) to yield the title compound as a clear oil (0.05 g, 27%); R_f 0.34 (MeOH:EtOAc, 1:3); $[\alpha]_D$ +40.0 (*c* 0.02, H_2O); mp 78−80 °C; ^{1}H NMR (300 MHz, D_2O; *Z*:*E*, 15:85) δ 7.58−7.66 (m, 5H, aromatic H), 5.63 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1, *Z*-isomer), 4.69 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1, *E*-isomer), 4.01 (apt t, 1H, $J_{2,3}$ = $J_{2,1}$ = 9.2 Hz, H-2), 3.94 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.86 (dd, 2H, $J_{6a,5}$ = 7.8 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.79 (dd, 1H, $J_{6b,5}$ = 4.5 Hz, $J_{6b,6a}$ = 12.0 Hz, H-6b), 3.54 (br signal, 1H, H-5), 3.39 (dd, 1H, $J_{4,3}$ = 3.4 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.09 (s, 3H, OCH_3); ^{13}C NMR δ (D_2O) 176.0 (s, C═O), 134.5 (s, aromatic C), 131.1, 129.2, 127.1 (each d, aromatic C), 88.5 (d, C-1, *E*-isomer), 82.7 (d, C-1, *Z*-isomer), 77.3, 73.5, 68.9, 67.4 (each d), 61.2 (t), 28.0 (q, CH_3); ν_{max} (KBr) 3409, 2909, 1502, 1447, 1367, 1279, 1055 cm^{-1}. HRMS-FAB: found 320.1118 $[M + Na]^+$, required 320.1110.

***N*-Ethyl-D-galactopyranosylamine.** The reaction of D-galactose (2.5 g, 13.46 mmol) and ethylamine (13.5 mL, 2.0 M solution in MeOH, 27 mmol) in MeOH (35 mL) as described above gave *N*-methyl-D-galactopyranosylamine as a white solid (1.06 g, 68%); ^{1}H NMR (300 MHz, D_2O) δ 5.16 (br d, 1H, H-1 for α-anomer), 4.50−4.47 (br d, 1H, H-1 for β-anomer), 4.00−3.25 (m, 7H, H-2−H-6 for both anomers), 2.90−2.75 (m, 2H, CH_2CH$_3$ for α-anomer), 2.70−2.50 (m, 2H, CH_2CH$_3$ for β-anomer), 0.99 (t, 3H, CH$_2$CH_3 for both anomers); ^{13}C NMR (300 MHz, D_2O) for β-anomer δ 90.0 (d, C-1), 76.1, 74.0, 70.8, 69.3 (each d), 61.4 (t, C-6), 39.5 (t, *C*H$_2$CH$_3$), 14.1 (q, CH$_2$*C*H$_3$), for α-anomer 97.2 (d, C-1), 75.3, 73.1, 72.4, 69.1 (C-2−C-5, each d), 61.2 (t, C-6), 35.4 (t, *C*H$_2$CH$_3$), 16.3 (q, CH$_2$*C*H$_3$).

***N*-Ethyl-*N*-(β-D-galactopyranosyl)-benzamide (6).** The reaction of *N*-ethyl-D-galactopyranosylamine (0.99 g, 4.78 mmol) with benzoyl chloride (1.1 mL, 9.6 mmol) as described for **5** gave a mixture (1.32 g, 89%) that contained the title compound. An analytical sample of the title compound (0.210 g, 14%) was obtained after two chromatographic separations (MeOH:EtOAc gradient elution). ^{1}H NMR (300 MHz, D_2O) δ

(33) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651.

7.50−7.40 (m, 5H, aromatic H), 5.42 (br s, H-1 for Z-isomer), 4.57 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1 for E-isomer), 4.00−3.28 (m, 9H, H-2−H-7 and CH_2CH$_3$), 1.25 (t, 3H, CH$_2$CH_3 for *E*-isomer), 1.12−0.96 (br t, 3H, CH$_2$CH_3 for Z-isomer); ^{13}C NMR (300 MHz, D$_2$O) δ 175.7 (s, C=O), 135.1 (s, aromatic C), 130.8 (d, aromatic CH), 129.1 (d, aromatic CH), 126.8 (d, aromatic CH), 88.9 (d, C-1), 77.3, 73.8, 68.9, 67.7 (C-2−C-5, each d), 61.3 (t, C-6), 37.4 (t, *C*H$_2$CH$_3$), 13.8 (q, CH$_2$*C*H$_3$); ν_{max} (KBr) 3393, 2976, 2937, 1623, 1577, 1497, 1446, 1395, 1330, 1234, 1076 cm^{-1}. CI-HRMS: found 312.1447, required 312.1451 [M + H]$^+$.

***N*-Isobutyl-β-D-galactopyranosylamine.** The reaction of D-galactose (2.0 g, 10.77 mmol) and isobutylamine (2.1 mL, 21.54 mmol) in methanol as described for *N*-isobutyl-β-D-galactopyranosylamine gave the title compound as a white solid (2.45 g, 97%); R_f 0.24 (in 1:4 MeOH/EtOAc); ^{1}H NMR (300 MHz, D$_2$O) δ 3.90−3.30 (7H, H-1−H-7), 3.90−3.80 (m, 2H), 3.70−3.60 (m, 2H), 3.60−3.50 (m, 2H), 3.45−3.30 (apt t, 1H), 2.65−2.58 (m, 1H, C*H*(H)CH(CH$_3$)$_2$), 2.46−2.41 (m, 1H, CH$_a$*H$_b$*-CH(CH$_3$)$_2$), 1.75−1.55 (m, 1H, CH$_a$H$_b$C*H*(CH$_3$)$_2$), 0.83 (d, 6H, CH$_a$H$_b$CH(C*H$_3$*)$_2$). CI-HRMS: found 236.1502, required 236.1498 [M + H]$^+$.

***N*-Isobutyl-*N*-(β-D-galactopyranosyl)-benzamide (7).** The reaction of *N*-isobutyl-β-D-galactopyranosylamine (1.11 g, 4.62 mmol) with benzoyl chloride as described for **5** gave a white solid (1.30 g, 83%) containing the title compound; an extra chromatographic separation was necessary to obtain an analytical sample (0.200 g, 13%, R_f 0.59 in 1:4 MeOH/EtOAc); ^{1}H NMR (300 MHz, D$_2$O) δ 7.92 (m, ArH for *Z*-isomer), 7.60−7.40 (m, 5H, ArH for both conformers), 5.21 (br d, 1H, H-1 for *Z*-isomer), 4.54 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1 for *E*-isomer), 4.00−3.10 (m, 9H, H-2−H-7 and CH_2CH(CH$_3$)$_2$), 2.20−2.10 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 0.93 (d, 6H, CH$_2$CH(C*H$_3$*)$_2$ for *E*-isomer), 0.65 (br t, 6H, CH$_2$CH(C*H$_3$*)$_2$ for *Z*-isomer); ^{13}C NMR (300 MHz, D$_2$O) δ 175.8 (s, C=O), 135.1 (s, aromatic C), 131.0 (d), 129.1 (d), 127.1 (each d, each aromatic C), 89.0 (d, C-1), 77.3, 73.9, 69.0, 67.6 (C-2−C-5, each d), 61.5 (t, C-6), 49.1 (t, *C*H$_2$CH-(CH$_3$)$_2$), 27.8 (d, CH$_2$*C*H(CH$_3$)$_2$), 20.0, 19.9 (each q, each CH$_2$-CH(*C*H$_3$)$_2$); ν_{max} (KBr) 3381, 2958, 2871, 1625, 1448, 1384, 1231, 1075 cm^{-1}. CI-HRMS: found 340.1759, required 340.1760 [M + H]$^+$.

***N*-(Benzyl)-β-D-galactopyranosylamine.** The reaction of benzylamine (1.22 mL, 11.2 mmol) and D-galactose (2.0 g, 11.2 mmol) as described for *N*-methyl-β-D-galactopyranosylamine gave the title compound as an off-white solid (0.28 g, 10%); R_f 0.31 (MeOH:EtOAc, 1:3); [α]$_D$ −18.33 (*c* 0.02, MeOH); mp 72−75 °C; ^{1}H NMR (300 MHz, D$_2$O, 2:3 mixture of α:β anomers) δ 7.49 (s, 5H, aromatic H), 5.34 (br s, 1H, H-1, α-isomer), 4.65 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1, β-isomer), 3.51−4.15 (overlapping signals, 8H, H-2−6, CH_2Ph); ^{13}C NMR (D$_2$O) δ 139.5 (s, aromatic C), 129.0, 128.9, 127.8 (each d, aromatic C), 89.3 (d, C-1), 76.1, 73.9, 70.9, 69.2 (each d), 61.4 (t, C-6), 48.7 (t, CH$_2$-Ph); ν_{max} (KBr) 3276, 2894, 1645, 1452, 1356, 1055 cm^{-1}. HRMS-FAB: found 270.1341 [M + H]$^+$, required 270.1341.

***N*-(Benzyl)-*N*-(β-D-galactopyranosyl)-benzamide (8).** The reaction of *N*-(benzyl)-β-D-galactopyranosylamine (0.5 g, 1.96 mmol) with benzoyl chloride (0.5 mL, 3.92 mmol) as described for **5** gave the title compound as a white foam (0.5 g, 71%); [α]$_D$ +30.0 (*c* 0.02, H$_2$O); ^{1}H NMR δ (500 MHz, D$_2$O, 40 °C; *Z*:*E* >10:90) 7.52−7.77 (overlapping signals, 10H, aromatic H), 5.70 (br s, 1H, H-1, *Z*-isomer), 5.01 (br s, 1H, H-1, *E*-isomer), 4.07−4.10 (br signals, 5H, H-2−4, CH$_2$Ph), 3.99 (dd, 1H, $J_{6a,5}$ = 7.4 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 3.92 (dd, 1H, $J_{6b,5}$ = 4.2 Hz, $J_{6b,6a}$ = 11.8 Hz, H-6b), 3.61−3.90 (br signal, 1H, H-5); ^{13}C NMR (D$_2$O) δ 176.0 (s, C=O), 138.2 (s, aromatic C), 135.0 (s, aromatic C), 129.5, 128.9, 126.5, 126.3, 126.1 (each d, each aromatic C), 89.0 (d, C-1), 77.0, 74.3, 69.5, 68.0 (each d), 61.0 (t, C-6), 45.2 (t, CH$_2$Ph); ν_{max} (film) 3412, 2930, 2866, 2102, 1888, 1622, 1428, 1281, 1070 cm^{-1}.

***N*-(Benzyl)-*N*-(β-D-galactopyranosyl)-acetamide (9).** The reaction of *N*-(benzyl)-β-D-galactopyranosylamine (0.5 g, 1.96 mmol) and acetyl chloride (0.28 mL) as described for **5** gave the title compound as a white foam (0.03 g, 5%); R_f 0.22 (MeOH:EtOAc, 1:4); ^{1}H NMR (300 MHz, D$_2$O; *Z*:*E*, 33:67) δ 7.39−7.55 (m's, 5H, aromatic H), 5.66 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1, *Z*-isomer), 4.72 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1, *E*-isomer), 3.42−4.07 (overlapping signals, 8H, H-2−6, CH_2Ph), 2.39, 2.31, 2.30, 2.11 (each s, each CH$_3$, *Z*- and *E*-isomers); ^{13}C NMR (D$_2$O) δ 177.3, 175.7 (each s, each C=O, *E*- and *Z*-isomers), 138.2, 138.0 (each s, aromatic C), 129.0, 128.9, 128.7, 127.6, 127.3 (2 signals), 126.9 (each d, aromatic C), 88.1 (d, C-1, *E*-isomer), 83.6 (d, C-1, *Z*-isomer), 77.4, 74.1, 73.9, 69.0, 68.9, 68.4, 67.9 (each d), 61.3, 61.2 (each t, each C-6), 47.7, 45.4 (each t, CH$_2$-Ph), 22.3, 21.6 (q, CH$_3$). HRMS-FAB: found 334.1270 [M + Na]$^+$, required 334.1267.

***N*-Methyl-*N*-(β-D-galactopyranosyl)-acetamide (10).** The reaction of *N*-(methyl)-D-galactopyranosylamine (0.12 g, 0.6 mmol) and acetyl chloride (0.1 mL, 1.2 mmol) as described for **5** gave the title compound as a white solid (0.12 g, 80%); ^{1}H NMR (300 MHz, D$_2$O; *Z*:*E*, 47:53) δ 5.51 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1, *Z*-isomer), 4.98 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1, *E*-isomer), 3.77−4.05 (overlapping signals, 12H, H-2−6, *E*- and *Z*- isomers), 3.11 (s, 3H,COC*H$_3$*, *Z*-isomer), 2.97 (s, 3H, COC*H$_3$*, *E*-isomer), 2.29 (s, 3H, CH$_3$, *Z*-isomer), 2.25 (s, 3H, CH$_3$, *E*-isomer); ^{13}C NMR (D$_2$O) δ 176.6 (s, C=O, *E*-isomer), 175.7 (s, C=O, *Z*-isomer), 87.5 (d, C-1, *E*-isomer), 82.5 (d, C-1, *Z*-isomer), 77.4 (2 signals), 73.8, 73.5, 69.0, 68.9, 67.6, 67.1 (each d, *Z*- and *E*-isomers), 61.1 (2 signals) (each t, *Z*- and *E*-isomers), 30.2, 27.4 (q, CO*C*H$_3$, *Z*- and *E*-isomers), 21.9, 21.1 (q, *C*H$_3$, *Z*- and *E*-isomers); ν_{max} (film) 3437, 2115, 1640, 1414, 1261, 1077 cm^{-1}. LRMS-ES: found 258.0 [M + Na]$^+$, required 258.1.

***N*-(4-Methoxybenzyl)-β-D-galactopyranosylamine.**[34] The reaction of 4-methoxybenzylamine (1.45 mL, 11 mmol) and D-galactose (2.0 g, 11 mmol) as described for *N*-(4-methyl)-β-D-galactopyranosylamine gave the title compound as a white solid (0.92 g, 28%); R_f 0.52 (MeOH:EtOAc, 2:1); [α]$_D$ −18.33 (*c* 0.02, MeOH); mp 96−102 °C; ^{1}H NMR δ (300 MHz, D$_2$O) 7.42 (d, 2H, *J* = 8.2 Hz, aromatic H), 7.06 (d, 2H, *J* = 8.4 Hz, aromatic H), 3.50−4.09 (overlapping signals, 12H, H-1−6, OCH$_3$, CH_2Ar); ^{13}C NMR (D$_2$O) δ 160.8 (s, aromatic C), 134.7 (s, aromatic C), 133.0, 132.0 (each d, each aromatic C), 117.1, 116.9 (each d, each aromatic C), 91.7 (d, C-1), 78.7, 76.5, 74.7, 73.5 (each d), 64.0 (t, C-6), 58.3 (q, OCH$_3$), 46.5 (t, CH$_2$); ν_{max} (KBr) 3356, 2921, 2836, 1636, 1508, 1432, 1300, 1248, 1100, 1042 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-(β-D-galactopyranosyl)-benzamide (11).** The reaction of *N*-(4-methoxybenzyl)-β-D-galactopyranosylamine (0.5 g, 1.67 mmol) and benzoyl chloride (0.39 mL, 3.34 mmol) as described for **5** gave the title compound as a yellow foam (0.13 g, 19%); R_f 0.27 (MeOH:EtOAc, 1:8); [α]$_D$ −5.0 (*c* 0.02, MeOH); ^{1}H NMR (500 MHz, D$_2$O, 10 °C; *Z*:*E*, 6:94) δ 7.24−7.42 (overlapping signals, aromatic H), 5.45 (br s, H-1, *Z*-isomer), 4.68 (d, 1H, $J_{1,2}$ = 8.8 Hz, H-1, *E*-isomer), 4.62 (AB d, 2H, *J* = 15.5 Hz, CH_2Ar), 3.62−3.73 (overlapping signals, 6H, H-2, H-4, H-6a, OCH$_3$), 3.59 (dd, 1H, $J_{6b,6a}$ = 12.0 Hz, $J_{6b,5}$ = 4.3 Hz, H-6b), 3.40 (dd, 1H, $J_{5,6a}$ = 8.0 Hz, $J_{5,6b}$ = 4.2 Hz, H-5), 3.28 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{3,2}$ = 9.5 Hz, H-3); ^{13}C NMR (D$_2$O) δ 176.0 (s, C=O), 172.0 (s, aromatic C), 158.0 (s, aromatic C), 133.2, 131.1, 130.6, 129.6, 129.3, 129.1, 128.8, 127.0, 114.2 (each d, aromatic C), 89.0 (d, C-1), 77.3, 73.7, 68.9, 68.0 (each d), 61.3 (t, C-6), 55.7 (q, OCH$_3$), 45.0 (t, CH$_2$Ph); ν_{max} (film) 3457, 3055, 2930, 1697, 1629, 1513, 1451, 1265, 1177, 1036 cm^{-1}. HRMS-FAB: found 426.1527 [M + Na]$^+$, required 426.1529.

***N*-(4-Chlorobenzyl)-β-D-galactopyranosylamine.** Reaction of 4-chlorobenzylamine (1.33 mL, 11 mmol) and D-galactose (2.0 g, 11 mmol) as described for *N*-(methyl)-β-D-galactopyranosylamine gave the title compound as white crystals (1.84 g, 55%); R_f 0.3 (EtOAc:petroleum ether, 1:4); [α]$_D$ −23.3 (*c* 0.02, MeOH); mp 144−146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43−7.31 (m, 4H, aromatic H), 4.61 (d, 1H, *J*

(34) (a) Retailleau, L.; Laplace, A.; Fensterbank, H.; Larpent, C. *J. Org. Chem.* **1998**, *63*, 608. (b) Pigman, W.; Cleaveland, E. A.; Couch, D. H.; Cleaveland, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 1967.

4.2, OH), 4.52 (t, 2H, $J_{6,5}$ = 5.6 Hz, H-6a, H-6b), 4.46 (d, 1H, $J_{4,3}$ = 3.1 Hz, H-4), 4.23 (d, 1H, J = 4.5 Hz, H-1), 3.26−3.65 (overlapping signals, 3H, H-2, H-3, H-5), 3.86 (AB d, 2H, J = 14.2 Hz, CH_2Ar); ^{13}C NMR (DMSO-d_6) δ 140.8, 131.6 (each s, each aromatic C), 130.4, 128.6 (each d, each aromatic C), 90.5 (d, C-1), 76.6, 74.8, 71.6, 69.2 (each d), 61.3 (t, C-6), 48.5 (t, CH_2); ν_{max} (KBr) 3435, 2963, 2895, 2845, 1762, 1491, 1426, 1196, 1078, 928 cm^{-1}. HRMS-FAB: found 326.0771 [M + Na]$^+$, required 326.0771.

***N*-(4-Chlorobenzyl)-*N*-β-D-galactopyranosylbenzamide (12).** Reaction of *N*-(4-chlorobenzyl)-β-D-galactopyranosylamine (0.5 g, 1.65 mmol) and benzoyl chloride (0.38 mL, 3.3 mmol) as described for **5** gave the title compound as an off-white solid (0.12 g, 17%); R_f 0.44 (MeOH:EtOAc, 1:20 × 2); [α]$_D$ +10.0 (*c* 0.04, MeOH); ^{1}H NMR (500 MHz, D_2O, 10 °C; *Z*:*E*, 7:93) δ 7.42 (d, 2H, J = 7.3 Hz, aromatic H), 7.38 (d, 2H, J = 6.8 Hz, aromatic H), 7.35 (d, 2H, J = 8.3 Hz, aromatic H), 7.25 (d, 2H, J = 8.3 Hz, aromatic H), 5.44 (br s, 1H, H-1, *Z*-isomer), 4.68 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1, *E*-isomer), 4.61 (AB d, 2H, J = 15.5 Hz, CH_2Ar), 3.64−3.73 (overlapping signals, 3H, H-2, H-4, H-6a), 3.57 (dd, 1H, $J_{6b,5}$ = 4.0 Hz, $J_{6b,6a}$ = 11.8 Hz, H-6b), 3.40 (dd, 1H, $J_{5,6a}$ = 7.3 Hz, $J_{5,6b}$ = 3.9 Hz, H-5), 3.28 (dd, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 2.9 Hz, H-3); ^{13}C NMR (D_2O) δ 175.8 (s, C=O), 136.6 (s, aromatic *C*-CO), 134.7 (s, aromatic *C*Cl), 132.4 (s, aromatic C), 131.2, 129.3 (2 signals), 129.2, 129.0, 128.6, 128.5, 127.1 (each d, each aromatic C), 88.9 (d, C-1), 77.4, 73.7, 68.9, 68.0 (each d), 61.4 (t, C-6), 45.2 (t, CH_2-Ar); ν_{max} (KBr) 3409, 2929, 2869, 1653, 1493, 1410, 1340, 1086 cm^{-1}. HRMS-FAB: found 430.1035 [M + Na]$^+$, required 430.1033.

***N*-(β-D-Galactopyranosyl)benzamide (13).** Benzoyl chloride (0.19 mL, 1.6 mmol) and 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl azide[35] (0.3 g, 0.8 mmol) were suspended in dry CH_3CN (10 mL). Triphenylphosphine (0.43 g, 1.04 mmol) was dissolved in dry dichloromethane (1 mL), which was then added to the reaction mixture,[36] and the solution was left stirring at room temperature. TLC analysis (EtOAc:petroleum ether, 1:1) showed the reaction was complete after 24 h at room temperature. The reaction mixture was washed with sodium bicarbonate (3 × 50 mL) and water (3 × 50 mL), extracted with dichloromethane (3 × 50 mL), dried ($MgSO_4$), and filtered and excess solvent was removed. The residue was purified by chromatography (EtOAc:petroleum ether, 1:6) to yield *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)benzamide as an off-white foam (0.01 g, 28%); R_f 0.57 (EtOAc:petroleum ether, 1:1); [α]$_D$ −12.5 (*c* 0.04, $CHCl_3$); mp 40−44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, 2H, J = 5.0, 1.3 Hz, aromatic H), 7.41−7.59 (m, 3H, aromatic H), 7.13 (d, 1H, $J_{NH,H-1}$ = 9.1 Hz, N*H*), 5.49 (d, 1H, J = 2.6 Hz, H-4), 5.46 (apt t, 1H, $J_{1,2}$ = $J_{NH,\ H-1}$ = 9.1 Hz, H-1), 5.21−5.30 (overlapping signals, 2H, H-2, H-3), 4.10−4.18 (overlapping signals, 3H, H-5, H-6a, H-6b), 2.16, 2.05, 2.04, 2.02 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$) δ 171.9, 170.6, 170.3, 170.0, 167.3 (each s, each C=O), 133.5 (s, aromatic C), 132.6, 128.9, 127.5 (each d, aromatic C), 84.0 (d, C-1), 72.6, 71.1, 68.9, 67.5 (each d), 61.4 (t), 20.9, 20.8 (2 signals), 20.7 (each q, each OAc); ν_{max} (film) 3410, 2357, 1745, 1669, 1528, 1371, 1243, 1082, 910 cm^{-1}. HRMS-CI: found 452.1557 [M + H]$^+$, required 452.1556. This intermediate (0.13 g, 0.29 mmol) was suspended in MeOH (20 mL) and NaOMe (0.1 mL of a 0.25 M solution in MeOH) was added. TLC analysis (MeOH) showed that the reaction was complete after 1 h. Amberlite (H$^+$) was added and after 5 min the reaction mixture was filtered and the solvent removed to give the title compound as an off-white solid (0.08 g, 99%); R_f 0.55 (MeOH); [α]$_D$ +95.0 (*c* 0.04, H_2O) (lit.[37] [α]$_D$ +25.0 (*c* 0.02, H_2O)); mp 114−118 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.91 (dd. 2H, J = 1.5, 8.5 Hz, aromatic H), 7.69−7.74 (apt t, 1H, J = 8.5 Hz, aromatic H), 7.58−7.63 (apt t, 2H, J = 8.5 Hz, aromatic H), 5.22 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.09 (d, 1H, J = 3.0 Hz, H-3), 3.80−3.95 (overlapping signals, 5H, H-2, H-4−6); ^{13}C NMR (D_2O) δ 172.3 (s, C=O), 133.1 (s, aromatic C), 133.0, 129.1, 127.8 (each d, each aromatic C), 80.7 (d, C-1), 77.1, 73.8, 69.6, 69.0 (each d), 61.2 (t); ν_{max} (KBr) 3400, 1665, 1558, 1109, 1098 cm^{-1}. HRMS-FAB: found 306.0954 [M + Na]$^+$, required 306.0954. Analytical HPLC (C-4 column; 5:95 CH_3CN:H_2O) indicated >90% purity.

***N*-(β-D-Glucopyranosyl)-benzamide (14).** Benzoyl chloride (0.19 mL, 1.6 mmol) and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide (0.3 g, 0.8 mmol) were suspended in dry CH_3CN (10 mL). Triphenylphosphine (0.43 g, 1.04 mmol) was dissolved in dry dichloromethane (1 mL) and this solution was then added to the reaction mixture, which was allowed to stir at room temperature. TLC analysis (EtOAc) showed the reaction was complete after an additional 24 h. The solvent was removed and the residue washed with sodium bicarbonate (3 × 50 mL) and water (3 × 50 mL), extracted with dichloromethane (3 × 50 mL), and dried ($MgSO_4$) and excess solvent was removed. The residue was purified by chromatography (EtOAc:petroleum ether 1:1) to give *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)benzamide as a white foam (0.17 g, 47%); R_f 0.54 (EtOAc). ^{1}H NMR[38] (300 MHz, $CDCl_3$) δ 7.76 (dd, 2H, J = 1.6, 7.0 Hz, aromatic H), 7.42−7.54 (m, 3H, aromatic H), 7.06 (d, 1H, $J_{NH,H-1}$ = 9.1 Hz, N*H*), 5.50 (apt t, 1H, $J_{1,2}$ = $J_{NH,H-1}$ = 9.1 Hz, H-1), 5.39 (apt t, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.4 Hz, H-3), 5.13 (2 × overlapping apt t, 2H, J = 9.5 Hz, H-2, H-4), 4.32 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{6a,5}$ = 4.4 Hz, H-6a), 4.11 (dd, 1H, $J_{6b,6a}$ = 12.4 Hz, $J_{6b,5}$ = 2.0 Hz, H-6b), 3.91 (ddd, 1H, $J_{5,6b}$ = 2.0 Hz, $J_{5,6a}$ = 4.4 Hz, $J_{5,4}$ = 10.1 Hz, H-5), 2.01, 2.04 (2 signals), 2.03 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$) δ 171.5, 170.8, 170.1, 169.8, 167.5 (each s, each C=O), 133.1 (s, aromatic C), 132.4, 132.3, 128.9, 128.7 (each d, aromatic C), 79.1, 73.9, 73.0, 71.1, 68.2 (each d), 62.0 (t), 20.9 (2 signals), 20.8 (2 signals) (each q, each OAc); ν_{max} (KBr) 3057, 2928, 1760, 1577, 1537, 1439, 1369, 1223, 1043 cm^{-1}. HRMS-CI: found 452.1559 [M + H]$^+$, required 452.1557. This intermediate (0.07 g, 0.14 mmol) was suspended in MeOH (10 mL). NaOMe (0.1 mL of a 0.25 M solution) was added. The reaction was not complete after 2 h so another 0.1 mL of NaOMe was added to the reaction mixture and TLC analysis (MeOH:EtOAc, 1:4) after a total of 3.5 h showed that the reaction was complete. Amberlite (H$^+$) was then added and after 5 min the reaction mixture was filtered and the solvent removed to give the title compound as a white solid (0.04 g, 100%); R_f 0.18 (MeOH:EtOAc, 1:4); [α]$_D$ −45.0 (*c* 0.04, H_2O) (lit. [α]$_D$ −11.6 (*c* 0.6, H_2O)); mp 218−220 °C (lit. mp 230−232 °C);[39] ^{1}H NMR[40] (300 MHz, D_2O) δ 7.91 (d, 2H, J = 7.2 Hz, aromatic H), 7.73 (apt t, 1H, J = 7.2 Hz, aromatic H), 7.62 (apt t, 2H, J = 7.2 Hz, aromatic H), 5.27 (d, 1H, $J_{1,2}$ = 9.3 Hz, H-1), 3.98 (dd, 1H, $J_{6a,5}$ = 2.2 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 3.84 (dd, 1H, $J_{6b,5}$ = 5.1 Hz, $J_{6b,6a}$ = 12.3 Hz, H-6b), 3.65−3.73 (overlapping signals, 3H, H-3−5), 3.57 (apt t, 1H, $J_{2,1}$ = $J_{2,3}$ = 9.3 Hz, H-2); ^{13}C NMR (D_2O) δ 172.2 (s, C=O), 133.1 (s, aromatic C), 133.0, 129.1, 127.7 (each d, aromatic C), 80.2 (d, C-1), 77.9, 76.8, 72.0, 69.5 (each d), 60.8 (t); ν_{max} (KBr) 3400, 2856, 1663, 1526, 1291, 1090 cm^{-1}. HRMS-FAB: found 306.0952 [M + Na]$^+$, required 306.0955. Analytical HPLC (C-4; 5:95 CH_3CN:H_2O) indicated >95% purity.

***N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-succinamic Acid (16).** The amine **15** (2.0 g, 5.76 mmol) and succinic anhydride (5.76 g, 57.6 mmol) were suspended in CH_2Cl_2 (50 mL), DIPEA (1.0 mL, 5.76 mmol) was added, and the reaction was allowed to stir at room temperature under an

(35) Tropper, F. D.; Andersson, F. O.; Braun, S.; Roy, R. *Synthesis* **1992**, 618.

(36) Boullanger, P.; Maunier, V.; Lafont, D. *Carbohydr. Res.* **2000**, *324*, 97.

(37) Savel'ev, A. N.; Ibatyllin, T. M.; Eneyskaya, E. V.; Kachurin, A. M.; Neustroev, K. N. *Carbohydr. Res.* **1996**, *296*, 261.

(38) Kovacs, L.; Osz, E.; Domokos, V.; Holzer, W.; Györgydeák, Z. *Tetrahedron* **2001**, *57*, 4609.

(39) Cerezo, A. S.; Sproviero, J. F.; Deulofeu, V.; Delpy, S. *Carbohydr. Res.* **1968**, *7*, 395.

(40) Sriram, D.; Stinivasan, S.; Priya, K.; Aruna, V.; Loganathan, D. *Acta Crystallogr.* **1998**, *C54*, 1670.

inert atmosphere. More DIPEA (2.0 mL, 11.52 mmol) was added after 48 h and analysis by TLC (MeOH:EtOAc, 1:4) indicated that the reaction was complete after stirring for a further 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with HCl (1.0 M solution, 2 × 100 mL), and dried ($MgSO_4$), excess solvent was removed, and the residue was purified by chromatography (EtOAc:petroleum ether, 2:1) to give the title compound as an off-white solid (1.45 g, 56%); R_f 0.37 (EtOAc); $[\alpha]_D$ +28.0 (*c* 0.5, $CHCl_3$); mp 57−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (br s, 1H, CO_2H), 6.71 (d, 1H, $J_{NH,H-1}$ = 9.0 Hz, N*H*), 5.44 (d, 1H, $J_{4,3}$ = 3.0 Hz, H-4), 5.28 (apt t, 1H, $J_{H-1,NH} = J_{1,2}$ = 9.0 Hz, H-1), 5.16 (dd, 1H, $J_{3,4}$ = 3.0 Hz, $J_{3,2}$ = 9.0 Hz, H-3), 5.11 (apt t, 1H, $J_{2,1} = J_{2,3}$ = 9.0 Hz, H-2), 4.04−4.16 (overlapping signals, 3H, H-5, H-6a, H-6b), 2.36−2.80 (m, 4H, CH_2CH_2), 2.06, 2.05, 2.04, 2.00 (each s, each 3H, each CH_3); ^{13}C NMR ($CDCl_3$) δ 176.6 (s, COOH), 172.3, 171.5, 170.7, 170.2, 170.0 (each s, each C═O), 78.4 (d, C-1), 72.3, 70.9, 68.3, 67.2 (each d), 61.2 (t, C-6), 30.6, 28.6 (each t, CH_2CH_2), 20.7, 20.6 (each q, each 2 signals, each CH_3); ν_{max} (KBr) 3051, 2981, 1787, 1666, 1599, 1538, 1371, 1227 cm^{-1}. HRMS-ESI: found 470.1274 [M + Na]$^+$, required 470.1274.

{2-[β-D-Galactopyranosyl-(3-β-D-galactopyranosylcarbamoylpropionyl)-amino]-acetylamino}-acetic Acid, Methyl Ester (17). The amine **15** (0.78 g, 2.2 mmol), the acid **16** (0.5 g, 1.12 mmol), and formaldehyde (0.15 mL, 2.2 mmol) were suspended in methanol (25 mL) and the reaction mixture was stirred at room temperature for 1 h. Methyl isocyanoacetate (0.2 mL, 2.2 mmol) was then added and the reaction mixture was allowed to stir at room temperature. Analysis by TLC (EtOAc) showed the reaction was complete after 24 h. Excess solvent was removed and the product was purified by chromatography (EtOAc) to give {2-[tetra-*O*-acetyl-β-D-galactopyranosyl-(3-tetra-*O*-acetyl-β-D-galactopyranosyl carbamoylpropionyl)-amino]-acetylamino}-acetic acid, methyl ester as a white foam (0.5 g, 50%); R_f 0.075 (EtOAc); $[\alpha]_D$ +16.0 (*c* 0.5, $CHCl_3$); mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, 1H, *J* = 6.0 Hz, N*H*-CH_2), 6.69 (d, 1H, *J* = 9.5 Hz, N*H*-CH), 5.90 (d, 1H, *J* = 9.0 Hz, C*H*-NH), 5.46 (d, 1H, *J* = 1.5 Hz, H-4), 5.42 (d, 1H, *J* = 3.0 Hz, H-4′), 5.25 (t, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.95−5.19 (overlapping signals, 4H, H-2, 2′, H-3, 3′), 3.71−4.27 (overlapping signals, 10H, H-5, 5′, H-6a, 6a′, H-6b, 6b′, NHCH_2CO, NHCOCH_2N), 3.76 (s, 3H, OCH_3), 2.49−2.67 (m's, 4H, CH_2CH_2CO), 2.18, 2.13, 2.04, 2.03, 2.02, 2.00, 1.99, 1.98 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$) δ 173.0, 171.8, 171.6, 170.5 (2 signals), 170.4, 170.3, 170.0 (2 signals), 169.8, 169.7 (each s, each C═O), 80.4, 78.1 (each d, C-1, C-1′), 73.6, 72.4, 72.3, 70.9, 70.7, 68.1, 67.2, 67.1 (each d), 61.6, 61.3 (each t, C-6, C-6′), 52.6 (q, OCH_3), 47.5, 41.0, 31.0, 28.5 (each t, each CH_2), 21.0, 20.7, 20.6, 20.5 (each q, each *C*H_3); ν_{max} (KBr) 3381, 2951, 2855, 1752, 1676, 1541, 1439, 1371, 1229, 1050 cm^{-1}. HRMS-ESI: found 928.2811 [M + Na]$^+$, required 928.2811. This intermediate (0.15 g, 0.17 mmol) was suspended in methanol (5 mL). NaOMe (0.1 mL of a 0.25 M solution) was added and the reaction mixture was stirred at room temperature. Analysis by TLC (MeOH) showed that the reaction was complete after 40 h. Amberlite (H$^+$) was added and after 5 min the reaction mixture was filtered and the solvent removed to give a yellow oil (0.09 g, 97%) that was further purified by using chromatography (MeOH:EtOAc, 1:1) and preparative HPLC (C-18, CH_3CN:H_2O gradient eluant, 1:99 to 100:0 over 40 min) to give **17** as an off-white solid; R_f 0.31 (MeOH); $[\alpha]_D$ −25.0 (*c* 0.02, MeOH); ^{1}H NMR (600 MHz, D_2O, 20 °C; *Z*:*E*, 27:73) δ 5.45 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1, *Z*-isomer), 5.19 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1, *E*-isomer), 4.97 (d, 1H, $J_{1',2'}$ = 9.0 Hz, H-1′, *E*- and *Z*-isomer), 3.70 (s, 3H, OCH_3), 3.50−4.40 (m's, 16H, H-2−6, H-2′−6′, CH_2CONH, CH_2NHCO), 2.89 (m's, 2H, CH_2CH_2CONH), 2.60 (m's, 2H, C$H_2$$CH_2$CONH); ^{13}C NMR ($D_2O$) δ 174.7, 175.3, 178.2, 178.9 (each s, each *C*═O), 89.0 (d, C-1, *E*-isomer), 85.3 (d, C-1, *Z*-isomer), 82.5 (d, C-1′), 80.2, 79.4, 76.1, 75.4, 72.1, 71.4, 70.7 (each d), 63.8, 63.7 (each t, C-6, C-6′), 55.6 (q, OCH_3), 47.4, 43.9, 32.9, 30.8 (t, CH_2-CO); ν_{max}(film) 3512, 2661, 1633, 1426, 1270, 1185 cm^{-1}. HRMS-ES: found 592.1966 [M + Na]$^+$, required 592.1966.

***N,N′*-Di-(β-D-galactopyranosyl)-terephthalamide (19).** Terephthalic acid (0.17 g, 1.0 mmol), EDC (0.38 g, 2.0 mmol), and DMAP (catalytic) were suspended in dry dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 30 min, and then the amine **15** (0.7 g, 2.0 mmol) was added. The reaction was allowed to stir at room temperature. TLC analysis (EtOAc) showed the reaction was complete after 72 h. Excess solvent was removed and the residue purified by chromatography (EtOAc:petroleum ether, 3:1) to yield *N*,*N*′-di(tetra-*O*-acetyl-β-D-galactopyranosyl)terephthalamide as a white foam (0.31 g, 19%); R_f 0.54 (EtOAc:petroleum ether, 3:1); $[\alpha]_D$ +50.0 (*c* 0.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 4H, aromatic H), 7.23 (d, 1H, $J_{NH,H1}$ = 9.0 Hz, N*H*), 5.20−5.54 (overlapping signals, H-1−4), 4.09−4.17 (overlapping signals, H-5, H-6a, H-6b), 2.04−2.20 (overlapping signals, OAc); ^{13}C NMR ($CDCl_3$) δ 172.1, 170.6, 170.2, 170.0 (each s, each C═O), 166.3 (s, aromatic C═O), 136.5 (s, aromatic C), 127.9, (d, aromatic C), 79.5, 72.7, 70.9, 68.9, 67.5 (each d), 61.4 (t), 21.0, 20.9, 20.8 (each q, each OAc); ν_{max} (KBr) 2972, 2933, 2356, 2336, 1752, 1673, 1547, 1501, 1368, 1229 cm^{-1}. HRMS-FAB: found 847.2385 [M + Na]$^+$, required 847.2398. This intermediate (0.1 g, 0.12 mmol) was suspended in MeOH (10 mL). Sodium methoxide (0.1 mL of a 0.25 M solution) was added and the reaction mixture was allowed to stir at room temperature. TLC analysis (MeOH) after 3 h showed that the reaction was complete. Amberlite (H$^+$) was added and after 5 min the reaction mixture was filtered and the solvent removed. The residue was purified by chromatography (MeOH:EtOAc, 1:1) to give the title compound **17** as a white solid (0.04 g, 67%, mixture of anomers); R_f 0.21 (MeOH); $[\alpha]_D$ +65.0 (*c* 0.04, H_2O); mp 60−64 °C; ^{1}H NMR (300 MHz, D_2O) δ 8.02 (s, 4H, aromatic H), 5.24 (d, 1H, $J_{1,2}$ = 8.9 Hz, H-1), 3.76−4.11 (overlapping signals, 6H, H-2−6); ^{13}C NMR (D_2O) δ 173.9 (s, C═O), 139.4 (s, aromatic C), 130.7 (d, aromatic CH), 83.2 (d, C-1), 79.8, 76.3, 72.2, 71.6 (each d), 63.8 (t); ν_{max} (KBr) 3410, 2931, 1660, 1550, 1424, 1299, 1086 cm^{-1}. LRMS-FAB: found 511.0 [M + Na]$^+$, required 511.2. The compound was further purified by preparative HPLC (C-4 column; 5:95 CH_3CN:H_2O) indicating 99% purity.

N,N′-Di(β-D-galactopyranosyl)-*N*,*N*′-di[methoxycarbonylmethylcarbamoylmethyl]-terephthalamide (18). Terephthalic acid (0.2 g, 1.2 mmol), amine **15** (0.84 g, 2.4 mmol), and formaldehyde (0.17 mL, 2.4 mmol) were suspended in methanol (20 mL) and stirred at room temperature for 1 h. Methyl isocyanoacetate (0.22 mL, 2.4 mmol) was then added and the reaction mixture was allowed to stir at room temperature. TLC analysis (EtOAc) showed that the reaction was complete after 48 h. The solvent was removed and the residue purified by chromatography (EtOAc) to give *N*,*N*′-di(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-*N*,*N*′-di[methoxycarbonylmethylcarbamoylmethyl]terephthalamide as an off-white foam (0.45 g, 34%); R_f 0.21 (EtOAc); mp 115−118 °C; $[\alpha]_D$ +15.0 (*c* 0.02, $CHCl_3$); ^{1}H NMR (270 MHz, C_5D_5N, 100 °C) δ 8.16 (t, 2H, *J* = 3.0 Hz, N*H*CH_2), 7.96 (s, 4H, aromatic H), 5.80−5.87 (overlapping signals, 6H, H-1, H-2, H-4), 6.05 (dd, 2H, *J* = 3.5, 9.0 Hz, H-3), 3.90−4.60 (m's, 14H, H-5, H-6a, H-6b, methylenes), 3.72 (s, 6H, OMe), 2.16, 2.14, 2.09, 2.05 (each s, each 6H, OAc); ^{13}C NMR (C_5D_5N, 100 °C) δ 171.8, 170.3, 169.9, 169.6, 169.4, 168.5 (each s, each C═O), 137.6 (s, aromatic C), 127.6 (d, aromatic C), 73.6, 71.9, 68.1, 67.4 (each d), 61.8 (t, C-6), 51.5 (q, OCH_3), 41.5 (t, CH_2), 20.1, 20.0, 19.9, 19.6 (each q, each OAc); ν_{max} (film) 3058, 1749, 1667, 1536, 1439, 1371, 1224, 1055 cm^{-1}. LRMS-ES: found 1105.4 [M + Na]$^+$, required 1105.3. This intermediate (0.07 g, 0.067 mmol) was suspended in MeOH (5 mL) and NaOMe (0.1 mL of a 0.25 M solution) was then added. TLC analysis (MeOH) showed that the reaction was complete after 1 h. Amberlite (H$^+$) was added and after 5 min, the reaction mixture was filtered and excess solvent removed to give and the residue, which was purified by preparative HPLC (C-18, CH_3CN:H_2O, 1:99 to 5:95

gradient elution over 1 h) and gave the title compound as a white solid; R_f 0.48 (MeOH); $[\alpha]_D$ +262.5 (*c* 0.008, MeOH); ^{1}H NMR (500 MHz, D_2O, 10 °C; *EE:EZ*, 83:17) δ 7.40−7.60 (m's, 4H, aromatic H), 5.58 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1 (*EZ* isomer)), 4.61 (d, 2H, $J_{1,2}$ = 9.0 Hz, H-1 (*EE* isomer)), 4.60 (d, 1H, $J_{1,2}$ = 9.0 Hz, H-1 (*EZ* isomer)), 4.22 (AB d, 4H, *J* = 16.5 Hz, NCH_2-$CONHCH_2$), 3.92 (AB d, 4H, *J* = 17.5 Hz, $NCH_2CONHCH_2$), 3.92 (d, 2H, $J_{4,3}$ = 3.0 Hz, H-4), 3.69 (apt t, 2H, $J_{2,3}$ = $J_{2,1}$ = 9.0 Hz, H-2), 3.51−3.71 (overlapping signals, 10H, H-6a, 6b, OCH_3), 3.42 (dd, 2H, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 3.5 Hz, H-5), 3.39 (dd, 2H, $J_{3,4}$ = 3.0 Hz, $J_{3,2}$ = 9.0 Hz, H-3); ^{13}C NMR (D_2O, 40 °C) δ 174.6, 172.3 (each s, 2 signals, each C═O), 136.4 (s, aromatic C), 128.0 (d, aromatic C), 88.5 (d, C-1, *EE*-isomer), 83.5 (d, C-1, *ZE*-isomer), 77.8, 73.0, 69.0, 68.1 (each d), 61.5 (t, C-6), 53.2 (q, OCH_3), 45.3, 41.8 (t, each CH_2); ν_{max} (film) 3383, 3045, 1620, 1421, 1255, 1109, 725 cm^{-1}. HRMS-ES: found 769.2392 $[M + Na]^+$, required 769.2392.

***N,N′*-Di(*β*-D-glucopyranuronosyl)-terephthalamide (20).** 2,3,4-Tri-*O*-acetyl-*β*-D-glucopyranosylamine uronic acid methyl ester[41] (0.8 g, 2.4 mmol), HOBt (0.72 g, 3.0 mmol), and terephthalic acid (0.44 g, 2.67 mmol) were suspended in dry THF (15 mL) at 0 °C. DCC (5.3 mL of a 1.0 M solution in CH_2Cl_2, 5.3 mmol) and DMAP (catalytic) were then added and the reaction mixture was allowed to stir at room temperature. TLC analysis (EtOAc) showed the reaction was complete after 26 h. The solvent was removed, the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (2 × 20 mL) and sodium bicarbonate (2 × 20 mL), dried ($MgSO_4$), filtered, and the solvent was removed. The residue was purified by chromatography (EtOAc:petroleum ether, 2:1) to give a white solid that was further purified by recrystallization (petroleum ether/EtOAc mixture) (0.13 g, 12%); R_f 0.49 (EtOAc); $[\alpha]_D$ −15.0 (*c* 0.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H, aromatic H), 7.38 (d, 1H, $J_{NH,H-1}$ = 9.5 Hz, N*H*), 5.49 (apt t, 1H, $J_{1,2}$ = $J_{NH,H1}$ = 9.5 Hz, H-1), 5.46 (apt t, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.5 Hz, H-3), 5.15 (apt t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H-4), 5.09 (apt t, 1H, $J_{2,3}$ = $J_{2,1}$ = 9.5 Hz, H-2), 4.25 (d, 1H, $J_{5,4}$ = 9.5 Hz, H-5), 3.73 (s, 3H, OCH_3), 2.06, 2.05 (2 signals) (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$) δ 171.6, 170.0, 169.8, 167.3, 166.6 (each s, each C═O), 136.4 (s, aromatic C), 128.0 (d, aromatic C), 78.9, 74.2, 72.0, 70.8, 70.0 (each d), 53.2 (q, OCH_3), 20.9, 20.8, 20.7 (each q, each OAc); ν_{max} (KBr) 3485, 3339, 3059, 3026, 2956, 2853, 1751, 1667, 1538, 1502, 1376, 1089 cm^{-1}. HRMS-FAB: found 819.2072 $[M + Na]^+$, required 819.2073. This intermediate (0.08 g, 0.10 mmol) was suspended in LiOH solution (2.5 mL of 0.5 M, 1.24 mmol) and the reaction mixture was allowed to stir at room temperature. TLC analysis (MeOH) showed that the reaction was complete after 2 h. The mixture was diluted with water (10 mL), neutralized with Amberlite (H^+), and filtered and the solvent was removed to give the title compound as an off-white solid (0.05 g, quantitative); this residue was further purified by preparative HPLC (C-4; 5:95 $CH_3CN:H_2O$); R_f 0.69 (MeOH); $[\alpha]_D$ +15.0 (*c* 0.04, H_2O); mp 130−132 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.99 (s, 2H, aromatic H), 5.33 (d, 1H, $J_{1,2}$ = 8.7 Hz, H-1), 4.10 (d, 1H, *J* = 9.2 Hz, H-5), 3.59−3.77 (m, 3H, H-2−4); ^{13}C NMR (D_2O) δ 174.2 (s, COOH), 171.0 (s, C═O, amide), 136.7 (s, aromatic C), 128.2 (d, aromatic C), 80.1, 77.4, 76.5, 71.8, 71.7 (each d); ν_{max} (KBr) 3437, 2929, 1792, 1645, 1550, 1442, 1234, 1063 cm^{-1}. LRMS-ES (negative): found 515.0 $[M - H]^-$, required 515.1.

Molecular Modeling Procedures. Monte Carlo conformational searching techniques and minimization of structures with Macromodel 6.0 were used to generate low-energy structures for **18** and **19**. The SUMM method, GB/SA solvation model for water, and AMBER (all atom) force field were employed. Each structure generated was minimized with the PRCG method. Structures with energy values 3 kcal/mol above the global minimum structure were rejected for both **18** and **19**. For calculations of **18** the distance between the ortho aromatic protons and anomeric proton were constrained to within 4 Å; 5000 structures were generated for minimization; the amide torsion angle was allowed to have values ranging from 0 to 180 deg. Distance constraints were not used for calculations of **19**; 1000 structures were generated for minimization. The Macromodel command files and coordinate input and output files are provided in the Supporting Information.

Acknowledgment. The authors thank Enterprise Ireland and Pfizer Pharmaceuticals Inc., Ringaskiddy, Co. Cork for an Irish American Partnership award to H.B.; Enterprise Ireland for a Basic Research Award (SC2002/225) and DAAD for a travel grant for H.B.; the Health Research Board (Ireland) and the Wellcome Trust for an equipment grant; Dublin Coorporation and IRCSET for scholarships to M.T.; Professor Horst Kunz for discussions and for hosting a research visit from H.B.; and the referees for their useful comments regarding the structural preferences exhibited by the tertiary amides.

Supporting Information Available: ^{1}H and ^{13}C NMR and selected 1D- and 2D-NOE spectra, synthetic procedures and analytical data for known compounds, and molecular modeling procedures and coordinate files. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034336D

(41) (a) Györgydeák, Z.; Thiem, J. *Carbohydr. Res.* **1995,** *268*, 85. (b) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156.