Stereospecific Synthesis of the α- and β-D-Glucopyranosyl Ureas

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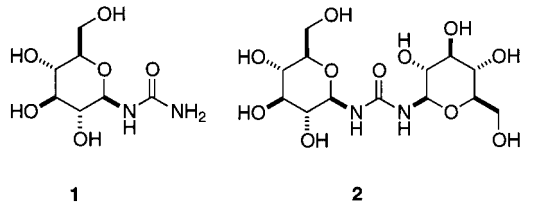
A new, one-pot, two-stage procedure for the preparation of the α- and β-D-glucopyranosyl ureas has been developed. Oxidation of glucopyranosyl isocyanides provides glucopyranosyl isocyanates, which can be trapped in situ with amines to afford good yields of glucopyranosyl ureas. Application of this method establishes the successful synthesis of the hitherto unknown *N*,*N*′-di-α,α- and α,β-D-glucopyranosyl ureas.

Introduction

The first synthesis of glucopyranosyl ureas dates back to the report from 1903 by Schoorl, who employed the acid-catalyzed condensation of D-glucose with urea in water.[1] Further improvement of this method by Benn established the synthesis of the *N*-β-D-glucopyranosyl urea **1** and the *N*,*N*′-di-β,β-D-glucopyranosyl urea **2** (Figure 1).[2] Fisher reported another method for the preparation of **1** as shown in Scheme 1.[3] In Fisher's method, reaction of the tetraacetylbromoglucose **3** with silver cyanate in xylene provided the glucopyranosyl isocyanate **4** which was treated with aqueous ammonia to afford **1**. Subsequent work by Johnson and Bergman demonstrated that Fisher's preliminary experiments for the synthesis of glucopyranosyl isocyanate **4** were not stereospecific. Two types of glucopyranosyl isocyanates were isolated, but their stereochemistry has never been determined.[4] More recently, the synthesis of sugar ureas by employing the sugar phosphinimines have been reported.[5] Although many methods for the synthesis of the β-D-glucopyranosyl ureas have been documented, they are all limited in scope because no method for the preparation of the α-D-glucopyranosyl urea is available.

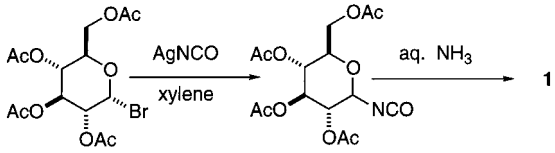
In the course of our research to explore a new type of the glycopeptide mimic, we examined the synthesis of glucopyranosyl isocyanates and their reactions with amines for stereospecific synthesis of the α- and β-D-glucopyranosyl ureas. Although synthesis of the α- and β-D-glucopyranosyl isothiocyanates has been extensively studied,[6] no general method for the synthesis of the α- and β-D-glucopyranosyl isocyanates has been reported. Under this circumstance, we set out to develop a new method for the synthesis of glucopyranosyl isocyanates and ureas. In this report, we will discuss the details and further efforts on the synthesis of glucopyranosyl isocyanates and ureas, where initial experimental reports focused on the preparation of the glucopyranosyl isocyanates.[7]



1 **2**

Figure 1.

Scheme 1



3 **4**

Results and Discussion

Initial Approach to the Synthesis of Glucopyranosyl Isocyanates. Our initial plan for the synthesis of the glucopyranosyl isocyanates relied upon the reaction of glucopyranosylamines with phosgen equivalent (COX_2), because a similar reaction of the glucopyranosylamines with thiophosgene for the preparation of the glucopyranosyl isothiocyanates has been well studied.[8] In addition, we planned to prepare both the α- and β-D-glucopyranosylamines by reducing the α- and β-D-glucopyranosyl azides. Scheme 2 shows our approach of this plan.

Catalytic hydrogenation of the β-azide **5** in the presence of triethylamine gave the β-amine **6** as crystals.[9] A solution of **6** in dichloromethane was treated with triphosgene and aqueous sodium hydrogencarbonate.[10] After

(1) Schoorl, M. N. *Rec. Trav. Chim.* **1903**, *22*, 31.
(2) Benn, M. H.; Jones, A. S. *J. Chem. Soc.* **1960**, 3837.
(3) Fisher, E. *Ber.* **1914**, *47*, 1377.
(4) Johnson, T. B.; Bergmann, W. *J. Am. Chem. Soc.* **1932**, *54*, 3360.
(5) (a) Bannister, B. *J. Antibio.* **1972**, *25*, 377. (b) Pinter, I.; Kovacs; J.; Toth, G. *Carbohydr. Res.* **1995**, *273*, 99.
(6) (a) M. J.; Fernandez-Resa, P.; Garcia-Lopez. M. T.; Heras, F. G.; Mendez-Castrillon, P. P.; Felix, A. S. *Synthesis* **1984**, 509. (b) Lindhorst, T. K.; Kieburg, C. *Synthesis* **1995**, 1228. (c) Benito, J. M.; Mellet, C. O.; Sadalapure, K.; Lindhorst, T. K.; Defaye, J.; Garcua Fernandez, J. M. *Carbohydr. Res.* **1999**, *320*, 37.
(7) For a preliminary account of this work, see: Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, 1253.
(8) Babiano Caballero, R.; Fuentes Mota, J.; Galbis Perez, J. A. *Carbohydr. Res.* **1986**, *154*, 280.
(9) Ogawa reported that the use of less polar solvent and the addition of triethylamine prevents anomerization during catalytic hydrogenation of the glucopyranosyl azide. See: Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47 (29)*, 281.

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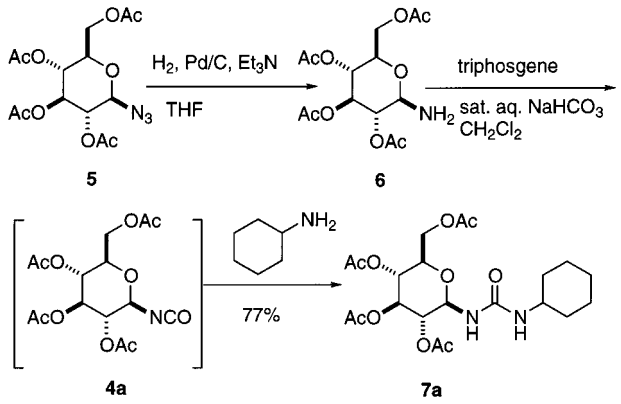
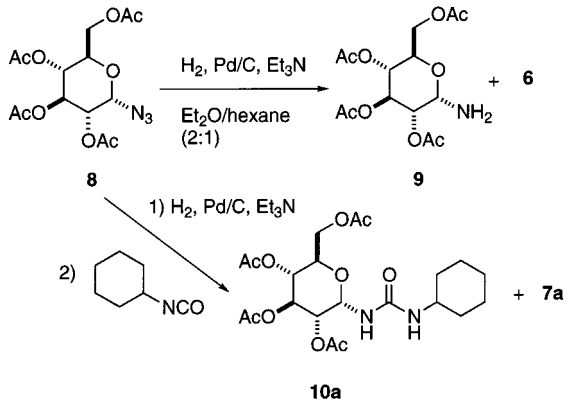
Scheme 2



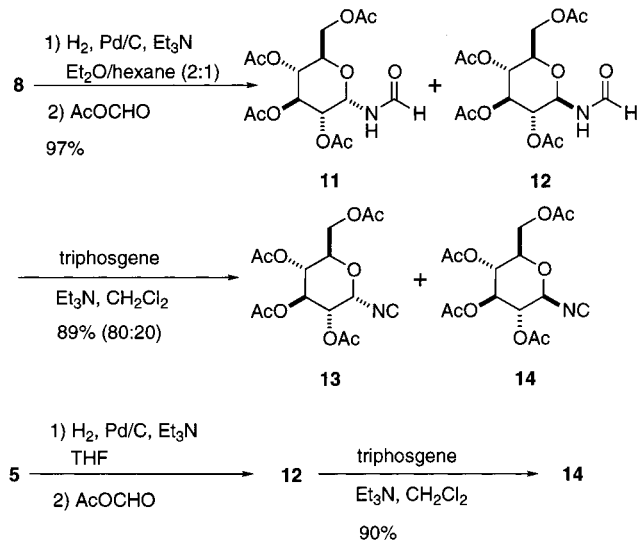
Scheme 3



30 min of vigorous stirring of the two-phase mixture, the organic layer was separated, dried (Na_2SO_4), and then treated with cyclohexylamine. After workup and purification by chromatography, the β-D-glucopyranosyl urea **7a** was isolated in 77% yield. In this reaction sequence, it should be noted that the reaction period of **6** with triphosgene was crucial, since prolonged reaction periods, for example, 120 min, yielded **7a** in a decreased, 65%, yield. In addition, we avoided isolating the β-isocyanate **4a**, because we were concerned that the isolation procedure would decrease the yield because of the high reactivity associated with the isocyanate function. Attempts to isolate the reactive isocyanate **4a** were carried out by rapid concentration of the reaction mixture before addition of cyclohexylamine. The resulting crude product showed the isocyanate IR absorption at 2220 cm^{-1} and the ^{13}C NMR peak at 127.0 ppm which characterized the structure of **4a**. However, it proved to be extremely difficult to purify **4a**, because **4a** easily solidified on standing due to the pronounced oligomerization reaction of the isocyanate.[11,12]

Encouraged by the successful synthesis of **7a**, we also investigated the catalytic hydrogenation of the α-azide **8** for the preparation of the α-amine **9** (Scheme 3). Many attempts at catalytic hydrogenation, under a variety of conditions, afforded a mixture of **9** and **6**. Furthermore, α-amine **9** rapidly isomerized into the thermodynamically stable β-amine **6** during isolation.[13] We also attempted

Scheme 4



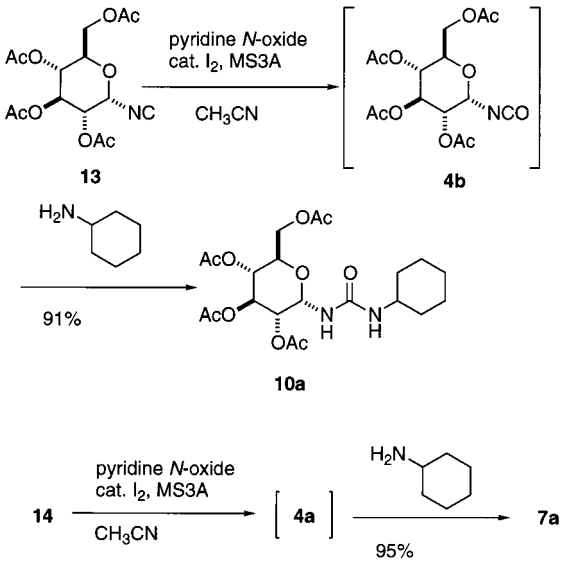
to trap the unstable α-amine **9** in situ. Accordingly, the reaction mixture was immediately treated with cyclohexyl isocyanate after catalytic hydrogenation of **8**; however, the mixture we isolated consisted of ureas **10a** and **7a** that were difficult to separate. Since α-amine **9** is so pronounced to isomerize into the β-amine **6**, we have concluded that a more stable precursor for the preparation of the α-D-glucopyranosyl isocyanate should be selected.

Synthesis of the Glucopyranosyl Ureas Starting from the Glucopyranosyl Isocyanides. Martin-Lomas reported that the reaction of the tetraacetyl-α-D-gluopyranosyl bromide with silver cyanide in boiling xylene afforded a mixture of the α- and β-D-glucopyranosyl isocyanides in 10 and 12% yield.[14] Separation of this mixture by silica gel chromatograghpy gave each isocyanide as stable crystals. Lead tetracetate oxidation of the β-ribofuranosyl isocyanide into the corresponding β-isocyanate has been reported by Zbiral.[15] On the basis of these two precedents, we planned to oxidize glucopyranosyl isocyanides for the preparation of glucopyranosyl isocyanates. In this plan, we have focused on the four problems: (i) the synthesis of the β-D-glucopyranosyl isocyanide has been well-known for some time,[16] but there appears to be no practical method for the preparation of the α-D-glucopyranosyl isocyanide; (ii) a toxic, hazardous oxidizing reagent which, after use, must then be disposed of, is not desirable; (iii) an anomerization problem during oxidation of the α-D-glucopyranosyl isocyanide; (iv) α-D-glucopyranosyl isocyanate has an unknown stability. We initially focused on the synthesis of the α-D-glucopyranosyl isocyanide as shown in Scheme 4.

Catalytic hydrogenation of the α-azide **8** and successive treatment of the reaction mixture with acetic formic anhydride afforded a mixture of the formamides **11** and **12**. Dehydration of the reaction mixture by employing triphosgene and triethylamine and separation of the reaction mixture by silica gel chromatography furnished

(10) Eckert, H.; Forster, B. *Angew. Chem.* **1987**, *99*, 922.
(11) Ulrich, H. *Chemistry and Technology of Isocyanates*, John Wiley & Sons: 1996.
(12) Studies are currently in progress to fully purify the glucopyranosyl isocyanate and to determine the structure of the Fisher's isocyanates A and B. For Fisher's isocyanates A and B, see ref 4.
(13) Takeda, T.; Sugiura, Y.; Ogihara, Y.; Shibata. S. *Can. J. Chem.* **1980**, *58*, 2600. See also ref 9.
(14) Martin-Lomas, M.; Chacon-Fuertes, E. *Carbohydr. Res.* **1977**, *59*, 604.
(15) Hiebl, J.; Zbiral, E. *Liebigs Ann. Chem.* **1988**, 765.
(16) Witczak, Z. J. *J. Carbohydr. Chem.* **1984**, *3(3)*, 359.

Scheme 5



an 89% yield of the isocyanides **13** and **14**, with the ratio of 80:20. In this dehydration reaction, triphosgene appears to be a more convenient reagent than the one we previously reported (PPh_3, CBr_4, Et_3N),[7] because the latter reagent gave off a considerable amount of triphenylphosphine oxide. Using the same sequence of reactions, the β-isocyanide **14** was also obtained starting from the β-azide **5** in 90% overall yield.[17]

With the α- and β-isocyanides in hand, the development of the oxidation of these isocyanides was undertaken. Since we had hoped to employ a one-pot process in order to convert the in-situ-generated isocyanates into the corresponding ureas to avoid the isolation of the reactive isocyanates, it was necessary to find a mild and neutral oxidizing condition. After screening a number of different oxidizing reagents and solvents, we finally realized that pyridine *N*-oxide (3.0 equiv) and a catalytic amount of iodine (0.07 equiv) in acetonitrile were the most satisfactory oxidation conditions.[18] A typical example from the synthesis of the α-glucopyranosyl urea **10a** has been shown in Scheme 5. An acetonitrile solution of the α-isocyanide **13** and pyridine *N*-oxide in the presence of powdered molecular sieves 3 Å was treated with iodine. Oxidation reaction was performed at room temperature for 30 min, and silica gel TLC analysis of the reaction mixture showed the consumption of the isocyanide **13**. Subsequent treatment of the resulting reaction mixture with cyclohexylamine converted the in-situ-generated isocyanate **4b** into the stable urea **10a**.[19] After workup, we were very pleased to find that examination of the crude reaction mixture by ^{1}H NMR did not show β-urea formation. This result confirmed that oxidation of the α-isocyanide **13** proceeded with retention of the configuration at the anomeric position, and that the resulting α-isocyanate **4b** was configurationally stable enough to react with cyclohexylamine to provide the α-urea **10a**. Finally, purification of the crude reaction mixture by chromatography yielded the α-urea **10a** as crystals in 91% yield. In this transformation, it should be noted that higher and reproducible yields were obtained by employing molecular sieves 3 Å to scavenge water, and that the hygroscopic solid, pyridine *N*-oxide, was purified by distillation before use. Similar results were also observed in the transformation of the β-isocynide **14** into the β-urea **7a** in 95% yield. The structure of the glucopyranosyl ureas prepared in this study are shown in Figure 2, and the yields are summarized in Table 1. Entries 4 and 10 clearly showed that even sterically hindered diisopropylamine reacted to give the corresponding ureas **7d** and **10d** in good yield. The ureas **7e** and **10e** (entries 5 and 11) represented the assembly of monosaccharides through the urea glycosidic linkage. Replacement of the glycosidic oxygen atom by other

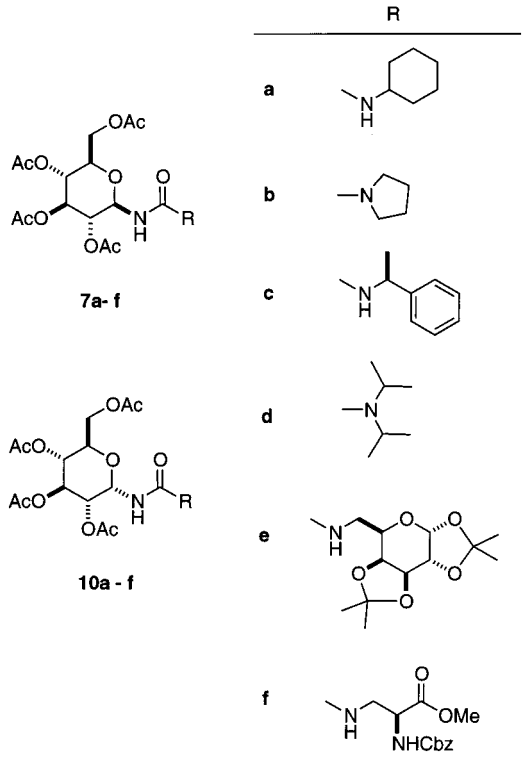


Figure 2.

Table 1. Synthesis of the Glucopyranosyl Ureas from the Glucopyranosyl Isocyanides

entry	glucopyranosy isocyanide	product	yield[a] (%)
1	**12**	**7a**	95[b]
2	**12**	**7b**	95[b]
3	**12**	**7c**	93[b]
4	**12**	**7d**	92[b]
5	**12**	**7e**	95[c]
6	**12**	**7f**	87[d]
7	**13**	**10a**	91[b]
8	**13**	**10b**	89[b]
9	**13**	**10c**	91[b]
10	**13**	**10d**	91[b]
11	**13**	**10e**	84[c]
12	**13**	**10f**	86[d]

[a] Yield of isolated product. [b] Glucopyranosyl isocyanide (1 equiv) and amine (3 equiv) were employed. [c] Glucopyranosyl isocyanide (1 equiv) and amine (1.4 equiv) were employed. [d] Glucopyranosyl isocyanide (2 equiv) and amine (1 equiv) were employed.

(17) Transformation of **12** into **14** by employing diphosgene as the dehydrating reagent has been reported. See: Ziegler, T.; Kaisers, H.-J.; Schlomer, R.; Koch, C. *Tetrahedron* **1999**, *55*, 8397. Diphosgene is not commercially available in Japan.

(18) Johnson, H. W.; Krutzsch, H. *J. Org. Chem.* **1967**, *32*, 1939. While a few oxidizing reagents (lead tetraacetate,[15] iodobenzene bis(trifluoroacetate), and 2,4,6-trimethylbenzonitrile oxide[7]) were found to be effective in oxidizing the glucopyranosyl isocyanides, pyridine *N*-oxide in the presence of iodine was chosen because it is safe, commercially available, inexpensive, and a nonhazardous waste.

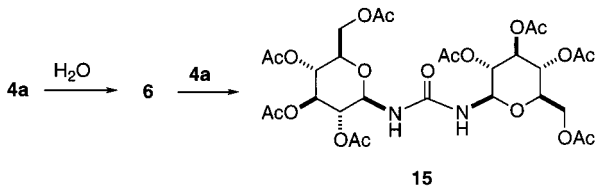
(19) Since the isocyanate **4b** could not be observed by TLC analysis, we employed 3 equiv of cyclohexylamine to optimize the yield.

Table 2. Diagnostic NMR Data

substance	anomeric config	δ H1	$J_{H1,H2}$ (Hz)	δ C1
7a	β	5.14[a]	9.5	80.2[a]
7b	β	5.20[a]	9.5	80.2[a]
7c	β	5.14[a]	9.5[a]	80.0[a]
7d	β	5.18−5.26[a,c]	9.5	80.4[a]
7e	β	5.16	9.5[a]	80.1[a]
7f	β	5.06−5.14[a,c]	10[a]	80.1[a]
10a	α	5.39[a]	5	77.5[a]
10b	α	5.82	5	75.7[a]
10c	α	5.43[a]	5	76.9[a]
10d	α	5.84[a]	6	76.1[a]
10e	α	5.44−5.52[a,c]	5	76.6[b]
10f	α	5.68[b]	5.5	76.7[b]

[a] Measured in $CDCl_3$. [b] Measured in MeOH-d_4. [c] Overlapped.

Scheme 6

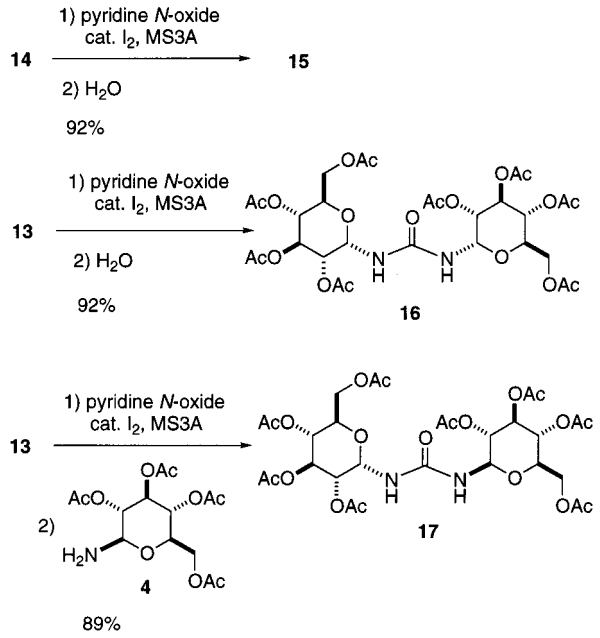


functional groups such as ureas appears to be an attractive approach to the development of potential glycosidase inhibitors. The ureas **7f** and **10f** (entries 6 and 12) present our approach to the synthesis of the glycopeptide mimics in which *O*- and *N*-glycosyl linkages are replaced by urea-glycosyl bonds.

^{1}H and ^{13}C NMR Analysis of the Glucopyranosyl Ureas. Assignment of the anomeric stereochemistry of the glucopyranosyl ureas can be confirmed by comparing the $J_{H1,H2}$ coupling constants as represented in Table 2. The large coupling constants of **7a**−**f** around 9 Hz indicate that the axial−axial relationship between these two protons determined the β-stereochemistry, and the small $J_{H1,H2}$ value around 5 Hz in the case of **10a**−**f** was consistent with the α-linkage. Moreover, the interesting stereoregular patterns of the ^{1}H and ^{13}C NMR chemical shift at anomeric positions can be observed. Thus, the ^{1}H NMR of β-ureas **7a**−**f** show anomeric protons at ca. 5.1−5.2 ppm, and anomeric carbons in the region of 80−81 ppm. In the case of α-ureas **10a**−**f**, the ^{1}H NMR chemical shift of anomeric protons appears in the region of 5.4−5.8 ppm, and the ^{13}C NMR chemical shift of the ureido glycosidic carbon appears around 75−78 ppm.

Stereospecific Synthesis of the Three Isomers of *N*,*N*′-Di-D-glucopyranosyl Ureas. During our initial studies of oxidation of the β-isocyanide **14** in the absence of molecular sieves 3 Å, we isolated octaacetyl *N*,*N*′-di-β,β-D-glucopyranosyl urea **15** as a byproduct (Scheme 6). This urea may be formed by the hydrolysis of the moisture sensitive β-isocyanate **4a** to give the amine **6** which successively reacted with **4a** to afford **15**. The structure of **15** was confirmed by an independent synthesis of **15** starting from D-glucose and the urea under acidic condition and acetylation.[2] Based on this observation, a method for the stereospecific synthesis of bis-glucopyranosyl ureas has been designated and is shown in Scheme 7. Thus, oxidation of the β-isocyanide **14** was carried out according to the procedure described before. After completion of oxidation, water was added to the reaction mixture. After stirring at room temperature for 20 min, TLC analysis showed the formation of **15**, which was isolated in a 92% yield.

Scheme 7



We were interested in the synthesis of the *N*,*N*′-di-α,α-D-glucopyranosyl urea, because such a urea glycoside seems to mimic α,α-trehalose with the urea−glycosidic bond. Moreover, such an α,α-isomer cannot be prepared by the thermodynamically controlled acid-catalyzed condensation of D-glucose with urea. Following the same sequence of reactions as before, the α-isocyanide **13** was converted into the α,α-urea **16** in a 92% yield. The C_2-symmetric structure of **16** can be confirmed by the 2-fold simplification of the ^{1}H and ^{13}C NMR spectra, and its α-configuration was confirmed by a $J_{H1,H2}$ coupling constant of 6 Hz. In addition, the glucosidic carbon of **16** had a shift of 75.5 ppm, which is consistent with the α-ureas **10a**−**f**. Finally, oxidation of the α-isocyanide **13** and successive treatment of the reaction mixture with the β−amine **4** afforded the *N*,*N*′-di-α,β-D-glucopyranosyl urea **17** in a 89% yield, establishing stereospecific synthesis of the three isomers of *N*,*N*′-di-D-glucopyranosyl ureas.

Conclusion

We have developed an efficient means of stereospecific synthesis of the glucopyranosyl ureas. Pyridine *N*-oxide oxidation of the glucopyranosyl isocyanides catalyzed by iodine afford the glucopyranosyl isocyanates which can be successively treated with a variety of amines in a one-pot process to afford the glucopyranosyl ureas in good yields. Our method seems to be useful for the preparation of a combinatorial library of the glucopyranosyl urea derivatives which may find widespread use in pharmaceutical industries.

Experimental Section

General Procedures. Melting points were recorded on a Yanaco MP−S3 melting point apparatus and are not corrected. Infrared spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Gemini-2000 spectrometers. Optical rotations were measured on a JASCO DIP-370 digital polarimeter.

For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm) were used. Column chromatography was performed on silica gel (Silica gel 60) supplied by E. Merck. Preparative TLC separation was made on plates prepared with a 2 mm layer of silica gel (Silica gel PF_{254}) obtained from E. Merck. Reactions were run under atmosphere of nitrogen when the reactions were sensitive to moisture or oxygen. Dichloromethane and acetonitrile were stored over molecular sieves 3 Å. Pyridine *N*-oxide was purified by distillation before use.[20]

Preparation of 2,3,4,6-Tetra-*O*-acetyl-α-D-glycopyranosyl Isocyanide (13). A solution of **8** (3.00 g, 8.04 mmol), triethylamine (3.4 mL, 24.1 mmol) and palladium on activated carbon (2%, 450 mg) in a mixture of ether and hexane (135 mL, 2:1) was stirred vigorously under hydrogen atmosphere for 30 min. To the resulting solution was added acetic formic anhydride (3.0 mL, 40.2 mmol) at room temperature, and stirring continued for 20 min. The mixture was filtered on Super Cell, and concentration of the filtrate gave a mixture of formamides **11** and **12** (2.85 g) which was used for the next reaction without further purification.

To a solution of formamides **11** and **12** (2.85 g, 7.60 mmol) and triethylamine (3.19 mL, 22.8 mmol) dissolved in dichloromethane (70 mL) cooled to 0 °C was added triphosgene (1.80 g, 6.08 mmol). After stirring at 0 °C for 55 min, additional triethylamine (1.60 mL, 11.4 mmol) and triphosgene (0.90 g, 3.03 mmol) were added. The cooling bath was removed, and the stirring was continued for 25 min. The reaction mixture was poured into aqueous sodium bicarbonate solution, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. Concentration and purification by silica gel chromatography (ethyl acetate:hexane, 1:5) gave the α-glucopyranosyl isocyanide **13** (1.82 g), a mixture of **13** and **14** (298 mg, 2:3) and **14** (298 mg). The combined yield of **13** and **14** was 89% in the ratio of 80:20.

General Method for the Preparation of the Glucopyranosyl Urea. To a solution of β-glucopyranosyl isocyanide **14** (100 mg, 0.28 mmol) and powdered molecular sieves 3 Å (200 mg) in acetonitrile (2.0 mL) was added a solution of pyridine *N*-oxide (80 mg, 0.84 mmol, dissolved in 0.5 mL of acetonitrile) and iodine (5 mg, 0.02 mmol, dissolved in 0.5 mL of acetonitrile) under nitrogen atmosphere. After stirring at room temperature for 25 min, cyclohexylamine (96 μL, 0.84 mmol) was added. After stirring for 25 min, a saturated aqueous solution of sodium hydrogensulfite was added. Aqueous layer was extracted with ethyl acetate, and combined organic layers were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting crude residue (131 mg) was purified by silica gel chromatography (AcOEt:hexane, 1:3 and 1:2) to afford β-glucopyranosyl urea **7a** (126 mg, 95%).

2,3,4,6-Tetra-*O*-acetyl-*N*-(cyclohexylaminocarbonyl)-β-D-glucopyranosylamine (7a): mp 83 °C; $[\alpha]^{27}_D = -0.80$ (*c* 0.98, MeOH); IR (KBr) ν_{max} 3363, 1753, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.0−1.9 (10H), 1.98 (3H, s), 1.99 (3H, s, OAc), 2.02 (3H, s), 2.05 (3H, s), 3.38−3.54 (1H, br), 3.80 (1H, ddd, *J* = 10, 4.5, 2), 4.05 (1H, dd, *J* = 12.5, 2), 4.31 (1H, dd, *J* = 12.5, 4.5), 4.78 (1H, d, *J* = 8), 4.88 (1H, t, *J* = 9.5), 5.04 (1H, dd, *J* = 10.0, 9.5), 5.14 (1H, t, *J* = 9.5), 5.28 (1H, t, *J* = 9.5), 5.42 (1H, d, *J* = 9.5); ^{13}C NMR ($CDCl_3$,75 MHz), δ 20.4, 20.6, 24.7, 25.3, 33.5, 49.1, 61.8, 68.3, 70.5, 72.9, 73.1, 80.2, 155.6, 169.7, 170.0, 170.7, 171.1. Anal. Calcd for $C_{21}H_{32}N_2O_{10}$: C, 53.38; H, 6.83; N, 5.93. Found: C, 53.38; H, 6.82; N, 5.90.

2,3,4,6-Tetra-*O*-acetyl-*N*-(pyrrolidinocarbonyl)-β-D-glucopyranosylamine (7b): mp 182 °C; $[\alpha]^{27}_D = -3.83$ (*c* 0.97, $CHCl_3$); $[\alpha]^{20}_D = -13.7$ (*c* 0.66, CH_3OH); IR (KBr) ν_{max} 3396, 1753, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.86−1.96 (4H), 2.03 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.08 (3H, s), 3.2−3.4 (4H), 3.84 (1H, ddd, *J* = 10, 4, 2), 4.09 (1H, dd, *J* = 12.5, 2), 4.34 (1H, dd, *J* = 12.5, 4), 4.93 (1H, t *J* = 9.5), 5.08 (1H, dd *J* = 10, 9.5), 5.20 (1H, t *J* = 9.5), 5.29 (1H, d, *J* = 9.5), 5.33 (1H, t, *J* = 9.5), ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.6, 20.7, 25.3, 45.4, 61.6, 68.2, 70.7, 72.7, 72.9, 80.2, 154.6, 169.7, 169.9, 170.7, 171.5. Anal. Calcd for $C_{19}H_{28}N_2O_{10}$: C, 51.35; H, 6.35; N, 6.30. Found: C, 51.33; H, 6.39; N, 6.24.

2,3,4,6-Tetra-*O*-acetyl-*N*-[(*S*)-(−)-β-methylbenzylaminocarbonyl]-β-D-glucopyranosylamine (7c): mp 75 °C; $[\alpha]^{27}_D = -22.5$ (*c* 1.17, $CHCl_3$); IR (KBr) ν_{max} 3368, 1753, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.44 (3H, d, *J* = 7), 1.97 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 2.06 (3H, s), 3.77 (1H, ddd, *J* = 10, 4.5, 2), 4.07 (1H, dd, *J* = 12.5, 2), 4.31 (1H, dd, *J* = 12.5, 4.5), 4.80−4.90 (1H), 4.86 (1H, t, *J* = 9.5), 5.04 (1H, t, *J* = 9.5), 5.14 (1H, t, *J* = 9.5), 5.20−5.28 (1H, br), 5.27 (1H, t, *J* = 9.5), 5.47 (1H, d, *J* = 9.5), 7.2−7.4 (5H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.5, 20.6, 22.7, 49.8, 61.8, 68.3, 70.5, 72.9, 73.1, 80.0, 125.9, 127.3, 128.6, 143.9, 155.8, 169.8, 170.0, 170.8, 171.0. Anal. Calcd for $C_{23}H_{30}N_2O_{10}$: C, 55.86; H, 6.12; N, 5.67. Found: C, 55.86; H, 6.19; N, 5.65.

2,3,4,6-Tetra-*O*-acetyl-*N*-(diisopropylaminocarbonyl)-β-D-glucopyranosylamine (7d): mp 147 °C; $[\alpha]^{30}_D = -12.6$ (*c* 1.02, MeOH); IR (KBr) ν_{max} 3429, 1754, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.24 (12H, d, *J* = 7), 2.02 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 3.72 (2H, sept, *J* = 7), 3.81 (1H, ddd, *J* = 10, 4, 2), 4.08 (1H, dd, *J* = 13, 2), 4.36 (1H, dd, *J* = 13, 4.5), 4.96 (1H, t, *J* = 9.5), 5.08 (1H, dd, *J* = 10, 9.5), 5.18−5.26 (2H, H-1), 5.32 (1H, t, *J* = 9.5); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.5, 20.56, 20.62, 20.9, 21.0, 45.8, 61.6, 68.3, 70.6, 72.8, 73.0, 80.4, 155.1, 169.7, 170.0, 170.7, 171.3. Anal. Calcd for $C_{21}H_{34}N_2O_{10}$: C, 53.16; H, 7.22; N, 5.90. Found: C, 53.13; H, 6.95; N, 5.83.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylureido)-α-D-galactopyranose (7e): mp 113 °C; $[\alpha]^{25}_D = -19.2$ (*c* 1.55, $CHCl_3$); IR (KBr) ν_{max} 3394, 1752, 1559 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.32 (3H, s), 1.34 (3H, s), 1.44 (3H, s), 1.50 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.19 (1H, ddd, *J* = 13, 9, 3), 3.54−3.66 (1H, br), 3.78−3.90 (2H), 4.07 (1H, dd, *J* = 12.5, 1.5), 4.20 (1H, dd, *J* = 8, 1.5), 4.30 (1H, dd, *J* = 12.5, 4), 4.31 (1H, dd, *J* = 5, 2.5), 4.60 (1H, dd, *J* = 8, 2.5), 4.91 (1H, t, *J* = 9.5), 5.06 (1H, t, *J* = 9.5), 5.16 (1H, t, *J* = 9.5), 5.30 (1H, t, *J* = 9.5), 5.44 (1H, dd, *J* = 8, 3), 5.52 (1H, d, *J* = 5), 5.76 (1H, d, *J* = 9.5); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.5, 24.1, 24.8, 25.75, 25.84, 40.6, 61.8, 67.1, 68.3, 70.5, 70.6, 71.4, 72.9, 73.1, 80.1, 96.1, 108.7, 109.3, 156.8, 169.6, 169.9, 170.66, 170.74. Anal. Calcd for $C_{27}H_{40}N_2O_{15}$: C, 51.26; H, 6.37; N, 4.43. Found: C, 51.17; H, 6.57; N, 4.46.

Methyl N^2-benzyloxycarbonyl-N^3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-aminocarbonyl)-2(*S*),3-diaminopropanoate (7f): mp 99 °C; $[\alpha]^{27}_D = +2.51$ (*c* 0.40, $CHCl_3$); IR (KBr) ν_{max} 3383, 1753, 1559 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 2.01 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 3.5−3.7 (2H), 3.74 (3H, s), 3.79 (1H, ddd, *J* = 10.5, 4.5, 2), 4.07 (1H, dd, *J* = 13, 2), 4.29 (1H, dd, *J* = 13, 4.5), 4.34−4.42 (1H, br), 4.89 (1H, t, *J* = 10), 5.05 (1H, t, *J* = 10), 5.06−5.14 (3H), 5.28 (1H, t, *J* = 10, H-3), 5.48 (1H, brt, *J* = 6), 5.68 (1H, brt, *J* = 9.5), 6.09 (1H, brd, *J* = 7), 7.3−7.4 (5H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.5, 20.6, 42.0, 52.7, 54.8, 61.8, 67.1, 68.2, 70.5, 72.9, 73.1, 80.1, 128.1, 128.3, 128.6, 136.2, 156.4, 157.1, 169.7, 170.0, 170.8, 171.1. Anal. Calcd for $C_{27}H_{35}N_3O_{14}$: C, 51.84; H, 5.64; N, 6.72. Found: C, 51.84; H, 5.67; N, 6.48.

2,3,4,6-Tetra-*O*-acetyl-*N*-(cyclohexylaminocarbonyl)-α-D-glucopyranosylamine (10a): mp 188 °C; IR (KBr) ν_{max} 3370, 1756, 1652 cm^{-1}; $[\alpha]^{26}_D = +105.9$ (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$300 MHz), δ 1.0−2.0 (10H), 2.02 (3H, s), 2.04 (3H, s, OAc), 2.08 (3H, s), 2.11 (3H, s), 3.58−3.72 (1H, br), 4.07−4.20 (2H), 4.24 (1H, dd, *J* = 12.5, 4.5), 5.01 (1H, brd, *J* = 3.0), 5.06 (1H, t, *J* = 9.5), 5.08 (1H, dd, *J* = 10, 5), 5.20 (1H, brd *J* = 8), 5.32 (1H, dd, *J* = 10, 9.5), 5.39 (1H, dd, *J* = 5, 3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.5, 20.6, 24.7, 25.4, 33.5, 48.8, 61.8, 67.0, 68.1, 68.9, 69.7, 77.5, 156.9, 169.3, 169.5, 170.0, 170.6. Anal. Calcd for $C_{21}H_{32}N_2O_{10}$: C, 53.38; H, 6.83; N, 5.93. Found: C, 53.37; H, 6.86; N, 5.79.

2,3,4,6-Tetra-*O*-acetyl-*N*-(pyrrolidinocarbonyl)-α-D-glucopyranosylamine (10b): mp 178 °C; IR (KBr) ν_{max} 3416, 1753, 1651 cm^{-1}; $[\alpha]^{29}_D = +77.9$ (*c* 1.13, $CHCl_3$); ^1H NMR

(20) Mosher, H. S.; Turner, L.; Carlsmith, A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 828.

($CDCl_3$, 300 MHz), δ 1.94−1.99 (4H), 2.03 (3H, s, OAc), 2.04 (6H, s, OAc), 2.09 (3H, s), 3.36−3.48 (4H), 4.02 (1H, ddd, *J* = 10, 3.5, 2.5), 4.09 (1H, dd, *J* = 12, 2.5), 4.35 (1H, dd, *J* = 12, 3.5), 4.94 (1H, d, *J* = 6.5), 5.03 (1H, dd, *J* = 10, 9), 5.18−5.32 (2H), 5.82 (1H, dd, *J* = 6.5, 5); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.5, 25.3, 45.6, 61.6, 67.0, 68.4, 68.5, 70.3, 75.7, 155.0, 168.9, 169.5, 170.3, 170.8. Anal. Calcd for $C_{19}H_{28}N_2O_{10}$: C, 51.35; H, 6.35; N, 6.30. Found: C, 51.34; H, 6.36; N, 6.26.

2,3,4,6-Tetra-*O*-acetyl-*N*-[(*S*)-(−)-α-methylbenzylaminocarbonyl]-α-D-glucopyranosylamine (10c): mp 206 °C; $[\alpha]^{26}_D$ = +93.3 (*c* 1.14, $CHCl_3$); IR (KBr) ν_{max} 3359, 1755, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.50 (3H, d, *J* = 7), 2.00 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 4.08−4.20 (2H), 4.25 (1H, *J* = 5), 4.93−5.04 (1H, br), 5.05 (1H, t, *J* = 10), 5.08 (1H, dd, *J* = 10, 5), 5.14 (1H, d, *J* = 3.5), 5.32 (1H, t, *J* = 10), 5.43 (1H, dd, *J* = 5, 3.5), 5.53−5.63 (1H, br), 7.2−7.4 (5H), ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.36, 20.42, 20.6, 22.7, 49.6, 61.8, 67.0, 68.2, 68.7, 69.9, 76.9, 125.9, 127.3, 128.7, 143.6, 156.9, 169.2, 169.5, 170.1, 170.7. Anal. Calcd for $C_{23}H_{30}N_2O_{10}$: C, 55.86; H, 6.12; N, 5.67. Found: C, 55.87; H, 6.25; N, 5.63.

2,3,4,6-Tetra-*O*-acetyl-*N*-(diisopropylaminocarbonyl)-α-D-glucopyranosylamine (10d): mp 90 °C; $[\alpha]^{26}_D$ = +60.0 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max} 3418, 1751, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.29 (6H, d, *J* = 7, Me), 1.30 (6H, d, *J* = 7), 2.02 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.98 (1H, ddd, *J* = 10, 4.5, 2.5), 4.03 (2H, sept, *J* = 7), 4.12 (1H, dd, *J* = 13, 2.5), 4.34 (1H, dd, *J* = 13, 4.5), 4.98 (1H, d *J* = 6), 5.04−5.14 (1H, m), 5.20−5.30 (2H), 5.84 (1H, brt, *J* = 6); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.3, 20.48, 20.50, 20.6, 21.2, 44.9, 61.7, 67.5, 68.3, 68.7, 70.6, 76.1, 155.7, 168.7, 169.4, 170.4, 170.8. Anal. Calcd for $C_{21}H_{34}N_2O_{10}$: C, 53.16; H, 7.22; N, 5.90. Found: C, 53.17; H, 7.18; N, 5.78.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylureido)-α-D-galactopyranose (10e): mp 124 °C; $[\alpha]^{24}_D$ = +48.7 (*c* 0.56, $CHCl_3$); IR (KBr) ν_{max} 3394, 1753, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.30 (3H, s), 1.34 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 2.02 (6H, s), 2.67 (3H, s), 2.10 (3H, s), 3.10−3.26 (1H, br), 3.56−3.70 (1H, br), 3.94 (1H, brd, *J* = 9), 4.08−4.18 (3H), 4.22 (1H, dd, *J* = 8, 1), 4.30 (1H, dd, *J* = 4.5, 2,), 4.39 (1H, dd, *J* = 13, 3), 4.60 (1H, dd, *J* = 8, 2), 5.11 (1H, dd, *J* = 10, 5), 5.30 (1H, t, *J* = 9.5), 5.14 (1H, t, *J* = 10), 5.34 (1H, t, *J* = 10), 5.44−5.52 (1H), 5.51 (1H, d, *J* = 4.5), 5.7−5.8 (1H, br); ^{13}C NMR (CD_3OD, 75 MHz), δ 20.6, 20.7, 24.5, 25.2, 26.3, 41.5, 63.2, 68.0, 68.4, 69.9, 70.5, 71.7, 71.8, 72.0, 72.7, 76.6, 97.7, 110.1, 110.7, 159.9, 171.6, 171.8, 172.2, 173.0. Anal. Calcd for $C_{27}H_{40}N_2O_{15}$: C, 51.26; H, 6.37; N, 4.43. Found: C, 51.26; H, 6.38; N, 4.25.

Methyl N^2-benzyloxycarbonyl-N^3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-aminocarbonyl)-2(*S*),3-diaminopropanoate (10f): mp 74 °C; $[\alpha]^{27}_D$ = +86.9 (*c* 0.47, $CHCl_3$); IR (KBr) ν_{max} 3380, 1752, 1559 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz), δ 1.99 (3H, s), 2.00 (6H, s), 2.02 (3H, s), 3.43 (1H, dd, *J* = 14, 7), 3.62 (1H, dd, *J* = 14, 5), 3.72 (3H, s), 3.90 (1H, ddd, *J* = 10, 4, 2), 4.04 (1H, dd, *J* = 12, 2), 4.27 (1H, dd, *J* = 12, 4), 4.32 (1H, dd, *J* = 7, 5), 5.00 (1H, dd, *J* = 10, 5.5), 5.05 (1H, dd, *J* = 10, 9.5), 5.09 (2H, s), 5.43 (1H, dd, *J* = 10, 9.5), 5.68 (1H, d, *J* = 5.5), 7.3−7.4 (5H); ^{13}C NMR (CD_3OD, 75 MHz), δ 20.4, 20.57, 20.63, 41.9, 53.0, 55.9, 63.2, 67.9, 68.8, 70.0, 70.6, 71.7, 76.7, 129.0, 129.2, 129.6, 138.1, 158.6, 159.7, 171.4, 171.5, 171.9, 172.7, 172.8. Anal. Calcd for $C_{27}H_{35}N_3O_{14}$: C, 51.84; H, 5.64; N, 6.72. Found: C, 51.85; H, 5.68; N, 6.61.

***N,N′*-Di-β,β−2,3,4,6-octa-*O*-acetyl-D-glucopyranosylulea (15).** To a solution of β-glucopyranosyl isocyanide **14** (150 mg, 0.42 mmol) and powdered molecular sieves 3 Å (200 mg) in acetonitrile (2.0 mL) was added a solution of pyridine *N*-oxide (120 mg, 1.26 mmol, dissolved in 1.0 mL of acetonitrile) and iodine (10 mg, 0.04 mmol, dissolved in 0.5 mL of acetonitrile) under nitrogen atmosphere. After stirring at room temperature for 25 min, water (200 μL, 11.1 mmol) was added and the stirring continued for 20 min. Saturated aqueous solution of sodium hydrogensulfite was added to the resulting reaction mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated. The resulting crude residue was purified by silica gel chromatography (AcOEt:hexane, 3:2) to afford *N,N′*-di-β,β-D-glucopyranosyl urea **15** (142 mg, 94%): mp 153 °C; $[\alpha]^{25}_D$ = +0.46 (*c* 1.09, $CHCl_3$); IR (KBr) ν_{max} 3386, 1752, 1559 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.02 (6H, s), 2.04 (6H, s), 2.06 (6H, s), 2.08 (6H, s), 3.84 (2H, ddd, *J* = 10, 4.5, 2), 4.11 (2H, dd, *J* = 12.5, 2), 4.31 (2H, dd, *J* = 12.5, 4.5), 4.88 (2H, t, *J* = 9.5), 5.04 (2H, t, *J* = 9.5), 5.31 (2H, t, *J* = 9.5), 5.04−5.16 (2H), 5.89 (2H, d, *J* = 9. 5); ^{1}H NMR (CD_3OD, 300 MHz), δ 1.97 (6H, s), 2.01 (12H, s), 2.02 (6H, s), 3.91 (2H, ddd, *J* = 10, 4.5, 2), 4.10 (2H, dd, *J* = 12.5, 2), 4.26 (2H, dd, *J* = 12.5, 4.5), 4.93 (2H, t, *J* = 9.5), 5.01 (2H, dd, *J* = 10, 9.5), 5.15 (2H, d, *J* = 9.5), 5.32 (2H, t, *J* = 9.5); ^{13}C NMR ($CDCl_3$, 75 MHz), δ. 20.5, 20.6, 61.7, 68.2, 70.5, 72.8, 73.2, 80.0, 155.5, 169.8, 170.0, 170.7, 171.2. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$: C, 48.33; H, 5.59; N, 3.89. Found: C, 48.33; H, 5.82; N, 3.89.

***N,N′*-Di-α,α−2,3,4,6-octa-*O*-acetyl-D-glucopyranosylulea (16):** mp 114 °C; $[\alpha]^{25}_D$ = +107.6 (*c* 0.86, $CHCl_3$); IR (KBr) ν_{max} 3393, 1753, 1553 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.04 (12H, s), 2.07 (6H, s), 2.11 (6H, s), 4.06 (2H, ddd, *J* = 9.5, 4.5, 2.5), 4.16 (2H, dd, *J* = 12.5, 2.5), 4.32 (2H, dd, *J* = 12.5, 4.5), 5.08 (2H, t, *J* = 9.5), 5.12 (2H, dd, *J* = 9.5, 5), 5.32 (2H, t, *J* = 9.5), 5.65 (2H, t, *J* = 5), 5.98 (2H, brd, *J* = 5); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.4, 20.5, 61.7, 68.0, 68.6, 69.6, 76.1, 156.5, 169.2, 169.4, 170.1, 170.7. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$: C, 48.33; H, 5.59; N, 3.89. Found: C, 48.24; H, 5.80; N, 3.89.

***N,N′*-Di-α,β−2,3,4,6-octa-*O*-acetyl-D-glucopyranosylulea (17):** mp 192 °C; $[\alpha]^{25}_D$ = +60.2 (*c* 1.24, $CHCl_3$); IR (KBr) ν_{max} 3393, 1751, 1559 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.02 (3H, s), 2.03 (3H, s), 2.035 (3H, s), 2.04 (3H, s), 2.045 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.11 (3H, s), 3.82 (1H, ddd, *J* = 10, 4, 2), 4.00 (1H, dt, *J* = 9.5, 2.5), 4.10 (1H, dd, *J* = 12.5, 2), 4.21 (1H, dd, *J* = 12.5, 2.5), 4.30 (1H, dd, *J* = 12.5, 4), 4.41 (1H, dd, *J* = 12.5, 2.5), 4.92 (1H, t, *J* = 9.5), 5.06 (1H, t, *J* = 9.5), 5.14 (1H, t, *J* = 9.5), 5.14 (1H, dd, *J* = 10, 5.5), 5.23 (1H, t, *J* = 9.5), 5.30 (1H, dd, *J* = 10, 9. 5), 5.32 (1H, t, *J* = 10), 5.56 (1H, t, *J* = 5.5), 5.78 (1H, br), 5.98 (1H, d, *J* = 9.5); ^{13}C NMR (CD_3OD, 75 MHz), δ 20.5, 20.6, 20.7, 63.1, 69.0, 69.6, 69.8, 70.5, 71.7, 71.9, 74.2, 74.6, 76.4, 80.5, 158.6, 171.6, 171.8, 171.9, 172.1, 172.3, 172.97, 173.03. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$: C, 48.33; H, 5.59; N, 3.89. Found: C, 48.33; H, 5.55; N, 3.54.

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Supporting Information Available: Experimental details for Scheme 2; ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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