Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 2621–2627
Tetrahedron

Stereospecific synthesis of urea-tethered neoglycoconjugates starting from glucopyranosyl carbamates

Yoshiyasu Ichikawa,* Taihei Nishiyama and Minoru Isobe

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

Received 26 September 2003; accepted 9 January 2004

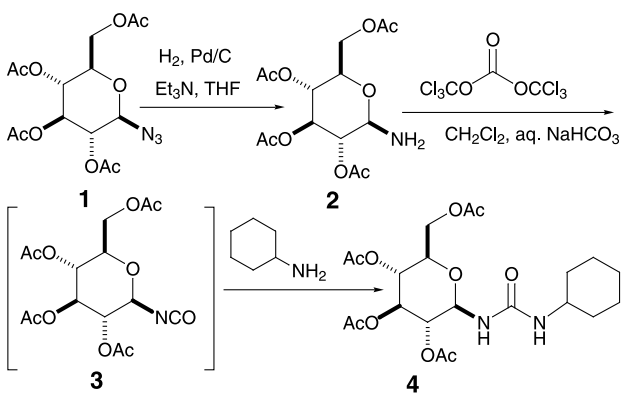
Abstract—Silyl-assisted elimination reaction of glucopyranosyl carbamates has been established for the synthesis of α- and β-D-glucopyranosyl isocyanates and ureas. This method proved to be useful for the synthesis of urea-tethered neoglycoconjugates.

1. Introduction

The importance of carbohydrates linked to the peptide backbone of protein (glycopeptides) has become increasingly appreciated in the bioorganic and/or medicinal research work due to their involvement in various biological events such as cellular recognition and adhesion.[1] Glycopeptides have two main classes of glycosidic linkage which involve either oxygen atom in the side chain of serine and threonine, or nitrogen atom in the side chain of asparagine.[2] Although synthetic chemists continue to explore the synthesis of accurately sequenced glycopeptides for biological and structural studies, total synthesis of the native glycopeptides still remain time-consuming and challenging tasks. In parallel, there are also much efforts toward the design and synthesis of glycopeptide mimetics which will supply homogeneous, stable and readily accessible glycopeptide analogues for biological studies and applications as potential therapeutic agents.[3] For example, *O*-glycosidic linkage is replaced by carbon–carbon,[4] carbon–sulfur[5] and carbon–aminooxy units.[6] With glycopeptide mimetics for *N*-glycosidic linkage, the amide group in *N*-glycosides was replaced by a retoamide subunit,[7] and alanine–hydroxylamine and alanine–hydrazine was employed as asparagine surrogates.[8] In addition to this rich area of glycopeptide mimetics, multivalent glycoconjugates such as glycoclusters and glycodendrimers have emerged as a new class of compounds which bear a structural resemblance to polysaccharides.[9] Such multivalent glycoconjugates are synthetically available and have exactly defined structure, which may be useful to explore the cluster effect of glycosides. Recently, we proposed a new approach to glycopeptide mimetics, which proposed urea glycosyl bond as the carbohydrate–peptide linkage.[10] The synthesis of urea glycosyl bond was planned to be constructed by the reaction of glycopyranosyl isocyanates with amines.[11]

During this research endeavor, a new synthetic method for the preparation of β-D-glucopyranosyl isocyanate **3** was established as represented in Scheme 1. Following the procedure reported by Ogawa,[12] catalytic hydrogenation of β-azide **1** gave β-amine **2**, treatment of which with triphosgene under Schotten–Baumann conditions afforded a solution of β-isocyanate **3**. Since isolation of pure **3** was unsuccessful due to the highly reactive nature of the isocyanate group,[13] the resulting reaction mixture was successively treated with cyclohexylamine to afford the stable and easily isolable urea glucoside **4** as crystals.

While β-urea **4** was obtained with this simple method, many attempts to prepare α-isomer using similar reaction sequence failed. In fact, hydrogenation of α-azide **5** gave

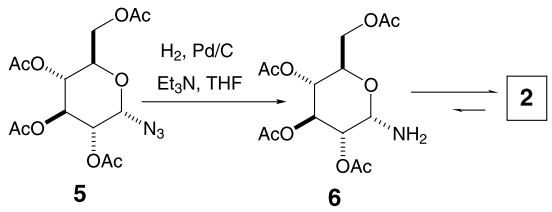


Scheme 1. Synthesis of β-glucopyranosyl isocyanate and urea by the reaction of β-glucopyranosyl amine with triphosgene.

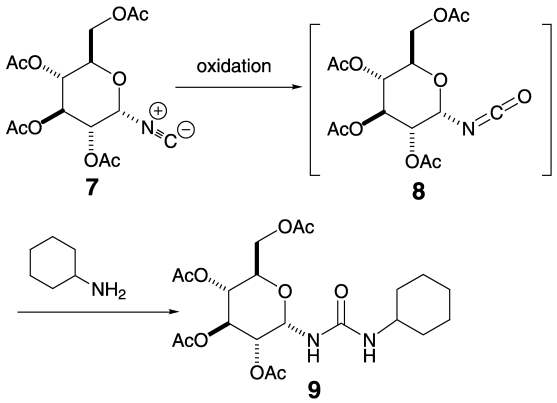
Keywords: Carbamate; Carbohydrates; Neoglycoconjugates; Urea; Synthetic methods.
* Corresponding author. Tel.: +81-5-2789-4115; fax: +81-5-2789-4100; e-mail address: ichikawa@agr.nagoya-u.ac.jp

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.01.055

α-amine **6**, which rapidly isomerized into the thermodynamically more stable β-isomer **2** during work-up (Scheme 2). To avoid such an anomerization problem, we developed a method utilizing the oxidation of glucopyranosyl isonitrile **7** for the preparation of α-glucopyranosyl urea **9** (Scheme 3).



Scheme 2. A rapid anomerization of α-glucopyranosyl amine.

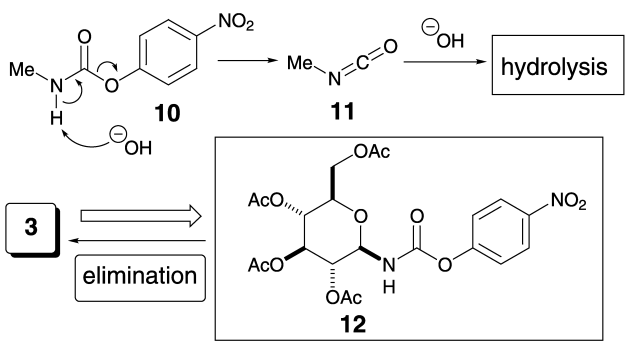


Scheme 3. Synthesis of α-glucopyranosyl isocyanate and urea starting from α-glucopyranosyl isonitrile.

While this protocol established a stereospecific synthesis of α- and β-D-glucopyranosyl isocyanates and ureas, we felt that more convenient method uncovered. Herein, we report the full detail of our second-generation synthesis of glucopyranosyl isocyanates and ureas starting from glucopyranosyl carbamates.[14]

2. Results and discussion

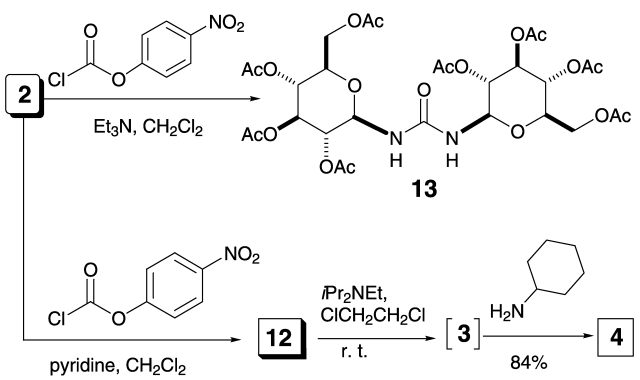
Bender proposed that *p*-nitrophenyl *N*-methylcarbamate **10** undergoes alkaline hydrolysis via elimination–addition mechanism, which involves methyl isocyanate **11** as an intermediate[15] (Scheme 4). This report inspired us to set



Scheme 4. Elimination–addition mechanism of carbamate hydrolysis and evolution of a new synthetic plan for glucopyranosyl isocyanate starting from glucopyranosyl carbamate.

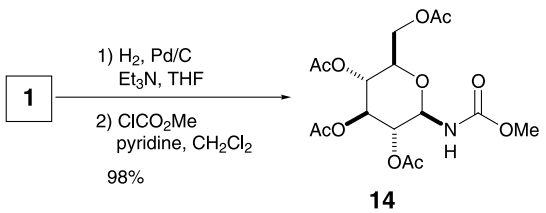
p-nitrophenyl β-*N*-glucopyranosyl carbamate **12** as a precursor to β-glucopyranosyl isocyanate **3**.

Initial attempts to synthesize **12** by the reaction of β-amine **2** with *p*-nitrophenyl chloroformate in the presence of triethylamine were unsuccessful; only bis-urea **13** was isolated (Scheme 5). We reasoned that use of triethylamine caused elimination of the initially formed *p*-nitrophenyl carbamate **12** to afford isocyanate **3**, which spontaneously reacted with the remaining amine **2**. This rationalization led us to employ a weaker base; the combination of *p*-nitrophenyl chloroformate and pyridine successfully suppress the elimination to furnish **12** as pale yellow crystals. As expected, base-catalyzed elimination of *p*-nitrophenyl carbamate **12** occurred quite readily; reaction of **12** in dichloroethane with diisopropylethylamine (iPr$_2$NEt) at room temperature spontaneously afforded an yellow solution containing β-isocyanate **3**, which was successively treated with cyclohexylamine to yield urea glucoside **4** in 84% yield for two steps. Although we were delighted with these results, we found the problem associated with **12**, which slowly decomposed even in a refrigerator. Moreover, purification of **12** by silica-gel chromatography was accompanied with partial formation of **13** to result in the decreased recovery of **12**.



Scheme 5. Synthesis of *p*-nitrophenyl glucopyranosyl carbamate and its use for the preparation of glucopyranosyl urea.

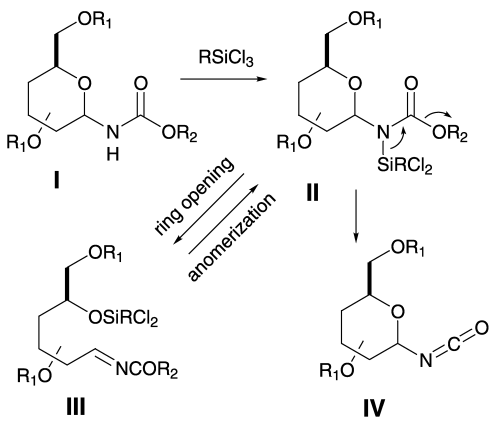
We next turned our attention to the more stable methyl carbamate **14**, which was prepared from **1** in 98% yield (Scheme 6).



Scheme 6. Synthesis of methyl glucopyranosyl carbamate.

Although **14** was sufficiently stable to be stored at room temperature for several weeks, the base-catalyzed elimination of methyl carbamate **14** (iPr$_2$NEt, 1,2-dichloroethane, reflux temperature, overnight) did not occur. To solve this problem, we explored the silyl-promoted elimination reaction of carbamates.[16] Although such elimination of carbamates are well-established transformations, no example of this reaction with α-alkoxy carbamate is

known. Accordingly, we were concerned about the behavior of the plausible intermediate, *N*-silylated species such as **II** (Scheme 7), which is critical to the origin of the stereoselectivity in this elimination reaction. If intermediate **II** is configurationally stable and undergoes the elimination reaction, complete retention of the anomeric stereochemistry in the starting material **I** will be observed. On the other hand, if equilibrium between **II** and *N*-carbamoylimine intermediate **III** occurs via reversible ring-opening reaction, then the product distribution will be determined by the relative stability of the α- and β-anomers **II** and/or the rates of their elimination and equilibration. In this sense, we were especially worried about the fate of **II** having α-anomer configuration, because α-*N*-glycosides are expected to be less stable than β-isomers.

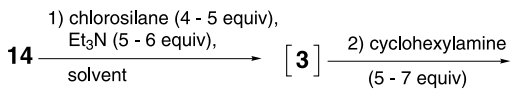


Scheme 7. A plausible reaction mechanism for the silyl-promoted elimination of glucopyranosyl carbamates.

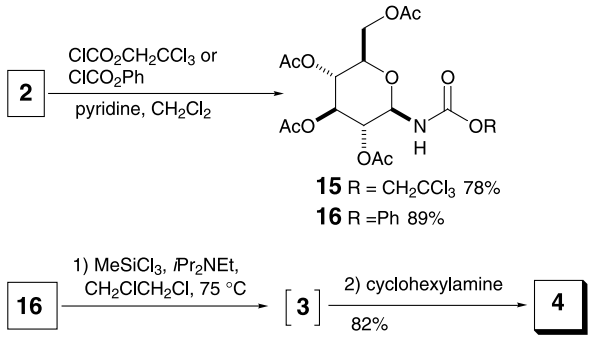
After screening several chlorosilanes and solvents, we have finally found that trichloromethylsilane (CH_3SiCl_3) and trichlorophenylsilane ($PhSiCl_3$) in 1,2-dichloroethane or acetonitrile are effective for this transformation as represented in Table 1. However, we soon realized a serious drawback; a large excess of cyclohexylamine (5 to 7 equiv.) was necessary to obtain a good yield of urea glucoside **4**. For example, when only 2 equiv. of cyclohexylamine was employed, the yield of isolated urea glucoside **4** dropped appreciably (ca. 30%). Since this problem appeared to arise from excess chlorosilane used which would interfere with the reaction of glucopyranosyl isocyanate **3** with cyclohexylamine, we turned our attention to the more reactive glucopyranosyl carbamates with moderate stability.

Since it is expected that the extent and rate of elimination depend on pK_a values of the leaving alkoxy substituents in the carbamates, we have prepared trichloroethyl (Troc) and phenyl carbamates **15** and **16** by treatment of **2** with 2,2,2-trichloroethyl chloroformate and phenyl chloroformate in 78 and 89% yields, respectively (Scheme 8). While elimination of the Troc carbamate **15** was sluggish and excess reagents were necessary, phenyl carbamate **16** underwent smooth elimination (1.5 equiv. of $MeSiCl_3$, 4.0–5.0 equiv. of iPr_2NEt, 1,2-dichloroethane, 75 °C, 5 h) to afford glucopyranosyl isocyanate **3**. Successive treatment of the reaction mixture containing **3** with cyclohexylamine (2.0 equiv.) afforded β-urea glucoside **4** in 82% yield after chromatographic purification.[17]

Table 1. Silyl-promoted elimination of β-methyl glucopyranosyl carbamate **14**

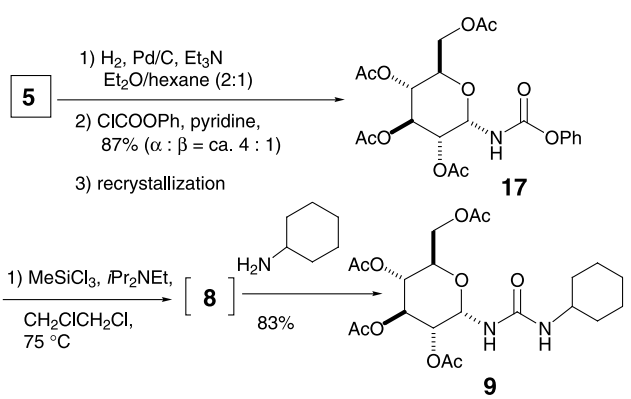


Entry	Chlorosilane	Solvent	Conditions	Yield (%)
A	$MeSiCl_3$	CH_2ClCH_2Cl	80 °C/4 h	90
B	$PhSiCl_3$	CH_3CN	45 °C/3 h	85
C	$MeSiCl_3$	CH_2ClCH_2Cl	80 °C/5 h	90
D	$PhSiCl_3$	CH_3CN	50 °C/6 h	89



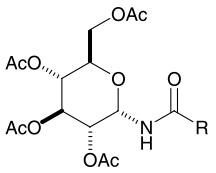
Scheme 8. Synthesis of Troc and phenyl glucopyranosyl carbamates and their use for the synthesis of β-urea glucoside.

Encouraged by this result, α-phenyl carbamate **17** was also prepared from α-azide **5** (Scheme 9). Catalytic hydrogenation of α-azide **5** followed by immediate treatment of the reaction mixture with phenyl chloroformate and pyridine afforded a 4:1 mixture of phenyl carbamates with the desired α-isomer **17** predominating in 87% yield. Although a mixture of these anomers could be separated by careful silica-gel chromatography, α-isomer **17** was much more conveniently purified by recrystallization.[18] Using a procedure similar to that given in Scheme 8, silyl-promoted elimination of α-carbamate **17** was carried out, and the corresponding α-urea glucoside **9** was isolated in 83% yield. According to ^1H NMR analysis of the crude reaction products, any β-isomer **4** has never been detected, which clearly showed that elimination of α-carbamate **17** proceeded stereospecifically without anomerization. It should be noted that while our previous method using glucopyranosyl isonitriles gave slightly better yields (Scheme 3) than the present procedure, both glucopyranosyl carbamates **16**

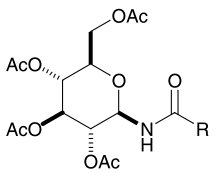


Scheme 9. Synthesis of α-phenyl glucopyranosyl carbamate and urea glucoside.

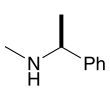
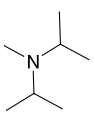
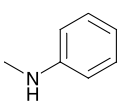
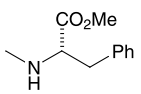
Table 2. Synthesis of urea-tethered neoglycoconjugates



18a-e



19a-e

Entry	A	B	C	D	E
R					
α-Urea glucosides (yield, %)[a]	**18a** (89%)[b]	**18b** (80%)[b]	**18c** (84%)[b]	**18d** (80%)[b]	**18e** (93%)[c]
β-Urea glucosides (yield, %)[a]	**19a** (82%)[b]	**19b** (78%)[b]	**19c** (82%)[b]	**19d** (81%)[b]	**19e** (94%)[c]

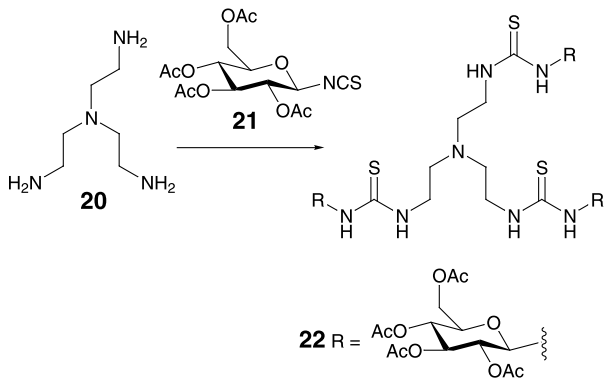
[a] Isolated yield after chromatographic purification.
[b] Glucopyranosyl carbamate (1.0 equiv.) and amine (2.0 equiv.) were employed. Yield based on glucopyranosyl carbamate.
[c] Glucopyranosyl carbamate (1.5 equiv.) and amine (1.0 equiv.) were used. Yield calculated based upon L-phenylalanine methyl ester hydrochloride.

and **17** can be readily prepared from glucopyranosyl azides in two steps using commercially available reagents. Moreover, a practical merit for the purification of α-phenyl glucopyranosyl carbamate **17** is noticed in its easy crystallinity.

With a new route to glucopyranosyl ureas established, we undertook to examine the utility of glucopyranosyl carbamates as glycosyl donors for the synthesis of urea-tethered neoglycoconjugates. The results are summarized in Table 2, in which a variety of urea-glucosides are prepared by the reaction with five different amines. It is notable that even sterically hindered amine, such as diisopropylamine (entry C), as well as low nucleophilic amine, such as aniline (entry D), gave satisfactory yields (>80%).

The first synthesis of both glucopyranosyl isocyanate **3** and isothiocyanate **21** was announced in 1914 by Fischer.[19] Although many syntheses of neoglycoconjugates using glucopyranosyl isothiocyanate has been reported,[20] little attention has been paid to glucopyranosyl isocyanate **3**. This miserable situation for **3** may be due to the difficulties associated with the preparation of the more reactive glucopyranosyl isocyanate **3**. Since a reliable synthetic method for the preparation of both α- and β-D-glucopyranosyl isocyanates has been established, we turned our attention upon comparing glucopyranosyl isocyanate with isothiocyanate counterpart in the context with the neoglycoconjugates synthesis. In this sense, we were interested in the report of Lindhorst,[21] who synthesized thio-bridged cluster of β-glucoside **22** by the reaction of tris(2-aminoethyl)amine **20** with β-glucopyranosyl isothiocyanate **21** (Scheme 10). In this case, the base-catalyzed O→N migration of acyl groups from the acetyl-protected glucosyl isothiocyanates onto the amino termini of the trivalent amine proved to be troublesome. To avoid this problem, reaction conditions using diluted solution and reflux temperature (CH_2Cl_2) were carefully employed.

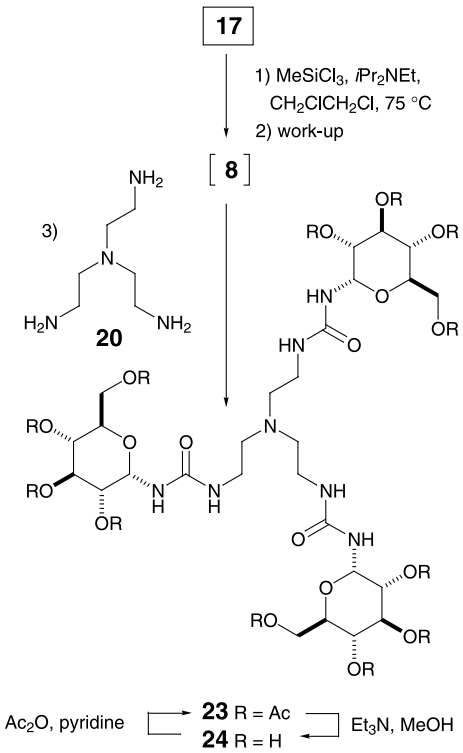
This report led us to examine the reaction of glucopyranosyl isocyanate with trivalent amine, which would offer an



Scheme 10. Lindhorst synthesis of thio-bridged cluster of β-glucoside.

opportunity to compare glucopyranosyl isocyanate with isothiocyanate counterpart. Furthermore, we expected that the synthesis of α-urea-bridged glucopyranosyl cluster appeared to be more appealing than the β-isomer synthesis, because the corresponding α-thiourea analogue is difficult to be synthesized.[22] Scheme 11 summarizes our approach to the urea-tethered α-glucopyranosyl cluster.

Using a procedure similar to that in Scheme 9, α-carbamate **17** was transformed into α-isocyanate **8**. Subsequent treatment of the resulting reaction mixture containing **8** with tris(2-aminoethyl)amine **20** resulted in low yields of product. After some experimentation, it was finally found that aqueous work-up was necessary. In fact, after silyl-promoted elimination of **17**, rapid and careful work-up gave the crude isocyanate **8**,[23] which was immediately dissolved in dichloroethane. Treatment of the resulting solution with **20** furnished the multivalent glucoside **23** in 89% yield.[24] It should be noted that any migration of acetyl group in **8** was not observed, which appears to reflect the more reactive nature of glucopyranosyl isocyanate. Further deprotection of **23** with a mixture of triethylamine and methanol gave water-soluble glucodendrimer **24**. Any anomerization of urea-glucoside linkage did not occur during hydrolysis of acetates in **23**, which was confirmed by acetylation of **24** to afford **23**.[25]



Scheme 11. Synthesis of urea-tethered cluster of glucoside with α-anomeric stereochemistry.

3. Conclusion

We have demonstrated that glucopyranosyl carbamates are valuable synthons for the preparation of urea-tethered neoglycoconjugates. The present method is especially useful for the synthesis of urea glycosides with α-stereochemistry. Studies to prepare mannopyranosyl and galactopyranosyl isocyanates and their use for the neoglycoconjugate synthesis is now in progress.

4. Experimental

4.1. General procedures

Melting points were recorded with a micro melting point apparatus and are not corrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded with a JASCO FT/IR-8300 spectrophotometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Varian Gemini-2000 spectrometers. ^1H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, δ=0.00 in $CDCl_3$), CHD_2OH (δ=3.31 in CD_3OH), and *t*-BuOH (δ=1.24 in D_2O) as internal standards. Data are reported as follows; chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sext=sextet, br=broadened, m=multiplet), coupling constants (*J*, given in Hz). ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ=77.0), CD_3OD (δ=49.0), *t*-BuOH (δ=30.29, in D_2O) as internal standards. High-resolution mass spectra (HRMS) are reported in *m/z*. Elemental analysis was performed by Analytical Laboratory at Graduate School of Bioagricultural Sciences, Nagoya University. 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 (CH_2Cl_2) was dried with molecular sieves 3 Å. Pyridine and triethylamine (Et_3N) were stored over anhydrous KOH. All other commercially available reagents were used as received.

4.1.1. Synthesis of *p*-nitrophenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl carbamate 12 and its use for the preparation of glucopyranosyl urea. A solution of glucopyranosyl azide **1** (1.50 g, 4.02 mmol) and palladium on activated carbon (2%, 350 mg) in THF (100 mL) was vigorously stirred under hydrogen atmosphere for 3 h. The mixture was filtered through Celite and concentrated under reduced pressure. The resulting amine **2** (1.50 g) was dissolved in a mixture of pyridine (1.30 mL, 16.1 mmol) and CH_2Cl_2 (30.0 mL), and then treated with *p*-nitrophenyl chloroformate (1.62 g, 8.04 mmol) at room temperature. After being stirred for 30 min, the mixture was poured into aqueous saturated ammonium chloride solution, and the separating aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4) and then concentrated. The resulting residue was passed through a short column of silica-gel (AcOEt–hexane, 2:1) to afford *p*-nitrophenyl glucopyranosyl carbamate **12** (1.97 g, 96%) as pale yellow solids. Since we have not succeeded in purifying **12**, the crude material was successively employed for the next reaction. IR (KBr) ν_{max}=3358, 1753, 1527, 1225; $\delta_H(CDCl_3)$; 2.05 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 3.87 (1H, ddd, *J*=10, 4.5, 2 Hz), 4.14 (1H, dd, *J*=12.5, 2 Hz), 4.35 (1H, dd, *J*=12.5, 4.5 Hz), 5.02 (1H, t, *J*=10, 9 Hz), 5.08 (1H, t, *J*=9 Hz), 5.12 (1H, t, *J*=10 Hz), 5.36 (1H, t, *J*=10 Hz), 6.26 (1H, d, *J*=9 Hz), 7.32–7.36 (2H), 8.24–8.27 (2H); $\delta_C(CDCl_3)$; 20.4, 20.5, 61.5, 67.9, 70.2, 72.5, 73.5, 80.8, 121.9, 125.2, 145.2, 152.5, 155.1, 169.6, 169.9, 170.6, 170.9.

To a solution of *p*-nitrophenyl glucopyranosyl carbamate **12** (100 mg, 0.20 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was added diisopropylethylamine (175 μL, 0.98 mmol) at room temperature. The starting material disappeared immediately (TLC check), and the resulting yellow solution was treated with cyclohexylamine (30 μL, 0.26 mmol). After stirring for 10 min, the solution was poured into aqueous saturated ammonium chloride solution, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. Purification of the resulting residue by silica-gel column chromatography (AcOEt–hexane, 2:1) gave β-urea **4** (79 mg, 87%).

4.1.2. Methyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl carbamate 14. A solution of **1** (500 mg, 1.34 mmol), Et_3N (0.19 mL, 1.40 mmol) and palladium on activated carbon

(2%, 0.20 g) in THF (20 mL) was stirred vigorously under hydrogen atmosphere for 90 min. The resulting solution was then filtered on Super Cell, and the filtrate was concentrated under reduced pressure until half volume. The resulting solution containing amine **2** was diluted with CH_2Cl_2 (10 mL), and then treated with pyridine (0.54 mL, 6.70 mmol) and methyl chloroformate (0.26 mL, 3.35 mmol) at room temperature. After stirring for 15 min, the mixture was poured into aqueous saturated sodium hydrogencarbonate solution, and aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. Purification of the resulting residue by silica-gel column chromatography (AcOEt–hexane, 1:1) afforded β-methyl carbamate **14** (535 mg, 98%); mp 104 °C; $[\alpha]_D^{22}$=+3.84 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=1753, 1541, 1370, 1237; $\delta_H(CDCl_3)$; 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.71 (3H, s), 3.76–3.84 (1H, m), 4.10 (1H, dd, *J*=12.5, 2 Hz), 4.31 (1H, dd, *J*=12.5, 4.5 Hz), 4.92 (1H, t, *J*=9.5 Hz), 5.03 (1H, bdt, *J*=9.5 Hz), 5.07 (1H, t, *J*=9.5 Hz), 5.30 (1H, t, *J*=9.5 Hz), 5.53 (1H, bd, *J*=9.5 Hz); $\delta_C(CDCl_3)$; 20.4, 20.5, 20.6, 52.6, 61.6, 68.1, 70.2, 72.8, 73.2, 80.8, 156.1, 169.6, 170.0, 170.7. Anal. Calcd for $C_{16}H_{23}NO_{11}$: C, 47.41; H, 5.72; N, 3.46. Found: C, 47.40; H, 5.54; N, 3.43.

4.2. General procedure for the preparation of glucopyranosyl urea

To a solution of **16** (120 mg, 0.26 mmol) and diisopropylethylamine (220 μL, 1.28 mmol) dissolved in 1,2-dichloroethane (6.0 mL) was added trichloromethylsilane (45 μL, 0.39 mmol). The reaction flask was sealed under nitrogen and then heated at 75 °C for 5 h. The resulting brown solution was treated with cyclohexylamine (58 μL, 0.51 mmol) at room temperature for 20 min. Usual work-up and purification by silica-gel chromatography (AcOEt–hexane, 2:3) afforded urea **4** (99 mg, 82%).

4.2.1. 2,3,4,6-Tetra-*O*-acetyl-*N*-(benzenaminocarbonyl)-α-D-glucopyranosylamine 18d. Mp 87 °C; $[\alpha]_D^{24}$=+135.2 (*c* 1.06, $CHCl_3$); IR (KBr) ν_{max}=3368, 1753, 1671, 1559, 1232,; $\delta_H(CDCl_3)$; 1.99 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 4.10–4.20 (2H), 4.24 (1H, dd, *J*=12, 5.5 Hz), 5.08 (1H, t, *J*=10 Hz), 5.17 (1H, dd, *J*=10, 5 Hz), 5.48 (1H, t, *J*=10 Hz), 5.76 (1H, t, *J*=5 Hz), 6.29 (1H, brd, *J*=4 Hz), 7.00–7.50 (5H); $\delta_C(CDCl_3)$; 20.43, 20.48, 61.8, 67.4, 68.3, 68.8, 69.9 76.7, 120.1, 123.9, 129.1, 137.9, 155.3, 169.3, 169.5, 170.3, 170.8. Anal. Calcd for $C_{21}H_{26}N_2O_{10}$: C, 54.07; H, 5.62; N, 6.01. Found: C, 54.31; H, 5.55; N, 5.99.

4.2.2. Methyl *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-aminocarbonyl)-2(*S*)-phenylalanine 18e. A solution of **17** (200 mg, 0.43 mmol), trichloromethylsilane (75 μL, 0.64 mmol) and diisopropylethylamine (225 μL, 1.28 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was sealed under nitrogen and then heated at 75 °C for 6.5 h. The resulting brown solution was treated with a solution of L-phenylalanine methyl ester hydrochloride (64 mg, 0.28 mmol) and diisopropylethylamine (65 μL, 0.36 mmol) in 1,2-dichloroethane (2.0 mL) at room temperature for 30 min. Usual work-up and purification by silica-gel chromatography (AcOEt–hexane, 1:3) afforded urea **18e** (143 mg, 93%). Mp 144 °C; $[\alpha]_D^{21}$=+112.3 (*c* 1.43, $CHCl_3$); IR (KBr) ν_{max}=3386, 1752, 1654, 1559, 1228; $\delta_H(CDCl_3)$; 2.01 (6H, s), 2.04 (3H, s), 2.06 (3H, s), 3.06 (1H, dd, *J*=14, 6.5 Hz), 3.26 (1H, dd, *J*=14, 6.5 Hz), 3.64 (1H, brdd, *J*=12.5, 1.5 Hz), 3.76 (3H, s), 3.93 (1H, dt, *J*=10, 1.5 Hz), 4.20 (1H, dd, *J*=12.5, 3.5 Hz), 4.77 (1H, q, *J*=6.5 Hz), 5.07 (1H, t, *J*=10 Hz), 5.10 (1H, dd, *J*=10, 5 Hz), 5.32 (1H, t, *J*=10 Hz), 5.50 (1H, t, *J*=5 Hz), 5.57 (1H, d, *J*=4 Hz), 5.73 (1H, d, *J*=7 Hz), 7.10–7.34 (5H); $\delta_C(CDCl_3)$; 20.37, 20.40, 20.43, 20.5, 37.8, 52.3, 53.8, 61.2, 67.1, 67.8, 68.6, 69.9, 76.7, 127.2, 128.6, 129.2, 135.9, 156.6, 169.2, 169.4, 170.3, 170.7, 172.7. Anal. Calcd for $C_{25}H_{32}N_2O_{12}$: C, 54.34; H, 5.84; N, 5.07. Found: C, 54.35; H, 5.85; N, 5.11.

4.2.3. Tris[2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)urea-ethyl]amine (23). A solution of **17** (200 mg, 0.43 mmol), trichloromethylsilane (75 μL, 0.64 mmol) and diisopropylethylamine (260 μL, 1.46 mmol) dissolved in 1,2-dichloroethane (10.0 mL) was heated at 75 °C for 5 h. The resulting solution was diluted with CH_2Cl_2 (40 mL) and then carefully poured into water containing cracked ice. The resulting precipitate was quickly filtered on glass filter, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting residue was immediately dissolved in 1,2-dichloroethane (10.0 mL) and then treated with a solution of tris(2-aminoethyl)amine (12 mg, 0.082 mmol) in 1,2-dichloroethane (1.5 mL). After stirring at room for 30 min, usual work-up and purification by silica-gel chromatography (AcOEt–2–PrOH, 10:1) afforded the multivalent glucoside **23** (92 mg, 89%); mp 134 °C; $[\alpha]_D^{21}$=+128.7 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3377, 1752, 1663, 1236; $\delta_H(CD_3OD)$; 1.99 (9H, s), 2.01 (9H, s), 2.02 (9H, s), 2.05 (9H, s), 2.48–2.68 (6H), 3.12–3.28 (6H), 3.93–4.04 (6H), 4.26 (3H, dd, *J*=12, 5 Hz), 5.03 (3H, t, *J*=10 Hz), 5.09 (3H, dd, *J*=10, 5.5 Hz), 5.52 (3H, t, *J*=10 Hz), 5.80 (3H, d, *J*=5.5 Hz); $\delta_C(CDCl_3)$; 20.47, 20.56, 20.69, 20.7, 39.6, 55.5, 63.7, 68.3, 70.2, 70.4, 71.8, 76.8, 156.0, 171.4, 171.6, 171.8, 172.5. Anal. Calcd for $C_{51}H_{75}N_7O_{30}$: C, 48.38; H, 5.97; N, 7.74. Found: C, 48.38; H, 5.65; N, 7.45. HRMS (FAB) calcd for $C_{51}H_{76}N_7O_{30}$ $[M+H]^+$ 1266.4637, found 1266.4659.

4.2.4. Tris[2-(α-D-glucopyranosyl)urea-ethyl]amine 24. A solution of **23** (253 mg, 0.20 mmol) and Et_3N (2.0 mL) in methanol (12.0 mL) was stirred at room temperature overnight, and the reaction mixture was concentrated under reduced pressure. The resulting residue was washed with methanol to give **24** (151 mg, quantitatively) as a white amorphous solid; $[\alpha]_D^{23}$=+106.0 (*c* 0.57, H_2O); IR (KBr) ν_{max}=3352, 1652, 1560; $\delta_H(D_2O)$; 2.66 (6H, brt, *J*=6 Hz), 3.23 (6H, brt, *J*=6 Hz), 3.41 (3H, t, *J*=10 Hz), 3.53 (3H, ddd, *J*=10, 4, 2 Hz), 3.62 (3H, t, *J*=10 Hz), 3.68–3.84 (9H), 5.46 (3H, d, *J*=5.5 Hz); $\delta_C(D_2O)$; 38.4, 49.6, 54.3, 61.3, 70.2, 72.5, 73.9, 78.7 160.7. HRMS (FAB) calcd for $C_{27}H_{52}N_7O_{18}$ $[M+H]^+$ 762.3369, found 726.3339.

Acknowledgements

This research was financially supported by a Grant-In-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture.

References and notes

1. (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (b) Varki, A. *Glycobiology* **1993**, *3*, 97.
2. (a) Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* **1999**, *5*, 1384. (b) Kunz, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 294.
3. (a) Taylor, C. M. *Tetrahedron* **1998**, 11317. (b) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579.
4. (a) Burkhart, F.; Hoffmann, H.; Kessler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1191. (b) Dondoni, A.; Mara, A. *Chem. Rev.* **2000**, *100*, 4395. (c) McGravey, G. J.; Benedum, T. E.; Schmidimann, F. W. *Org. Lett.* **2002**, *4*, 3591.
5. (a) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1991**, *32*, 6793. (b) Jobron, L.; Hummel, G. *Org. Lett.* **2000**, *2*, 2265. (c) Knapp, S.; Myers, D. S. *J. Org. Chem.* **2001**, *66*, 3636. (d) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405. (e) Zhu, X.; Pachamuthu, K.; Schmidt, R. R. *J. Org. Chem.* **2003**, *68*, 5641, and references therein.
6. Rodriguez, E. C.; Marcaurelle, L. A.; Bertozzi, C. R. J. *J. Org. Chem.* **1998**, *63*, 7134.
7. Hoffmann, M.; Burkhart, F.; Hessler, G.; Kessler, H. *Helv. Chim. Acta* **1996**, *79*, 1519.
8. Peluso, D.; Imperiali, B. *Tetrahedron Lett.* **2001**, *42*, 2085.
9. (a) Lindhorst, T. K. *Nachr. Chem. Tech. Lab.* **1966**, *44*, 1073. (b) Jayaraman, N.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Eur. J.* **1997**, *3*, 1193.
10. The idea of glycopeptide mimetics with urea glycosyl bond came from an amino sugar antibiotic, LL-BM γ1. For LL-BM γ1, see the reference: Ellestad, G. A.; Cosulich, D. B.; Broschard, R. W.; Martin, J. H.; Kunstmann, M. P.; Morton, G. O.; Lancaster, J. E.; Fulmor, W.; Lovell, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 2515.
11. (a) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, 1253. (b) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *J. Org. Chem.* **2001**, *66*, 4200.
12. Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47*(29), 281.
13. Recently, we have succeded in establishing a simple procedure for isolating glucopyranosyl isocyanate **1** as crystals. See the reference: Ichikawa, Y.; Matsukawa, Y.; Nishiyama, T.; Isobe, M. *Eur. J. Org. Chem.* **2004**, 586.
14. For a preliminary work, see the reference: Nishiyama, T.; Ichikawa, Y.; Isobe, M. *Synlett* **2003**, 47.
15. Bender, M. L.; Homer, R. B. *J. Am. Chem. Soc.* **1965**, 3975.
16. (a) Mironov, V. F.; Seludjakov, V. D.; Kozjukov, V. P.; Chatuncev, G. D. *Dokl. Akad. Nauk. SSSR* **1968**, *181*, 115. (b) Greber, G.; Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 941. (c) Gastaldi, S.; Weinreb, S. M.; Stien, D. *J. Org. Chem.* **2000**, *65*, 3239. (d) Yeung, B. K. S.; Adamski-Werner, S. L.; Bernard, J. B.; Poulenat, G.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 3135.
17. Since glucopyranosyl isocyanate cannot be detected by silica-gel TLC analysis, 2 equiv. of amine for the transformation into urea has been employed.
18. For the synthesis of carbamates **16** and **17** and their characterization, see Ref. 14.
19. Fischer, E. *Ber.* **1914**, *47*, 1377.
20. Witczak, Z. J. *Adv. Carbohydr. Chem. Biochem.* **1986**, *44*, 91.
21. Lindhorst, T. K.; Kieburg, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1953.
22. Although the corresponding β-isomer of **23** was also prepared from the β-carbamate **16** using the similar procedure to Scheme 11 in 88% yield, a more simple synthesis using crystalline β-glucopyranosyl isocyante **3** was realized recently in our laboratory. See Ref. 13.
23. This procedure appeared to remove the by-products derived from the silicon reagent which may interfere with the reaction of **8** with **20**.
24. While the conformational properties of α-cluster **23** resulted in line broadening of the ^{1}H NMR peaks measured in $CDCl_3$, only one set of moderately sharp signals for the sugar moieties due to the C_3-symmetric nature in **23** was detected with CD_3OD as solvent.
25. This hydrolysis of acetate contrasts with the Zemplen deacetylation of mannopyranosyl thioureido derivatives. See the reference: Benito, J. M.; Mellet, C. O.; Sadalapure, K.; Lindhorst, T. K.; Defaye, J.; Fernandez, J. M. G. *Carbohydr. Res.* **1999**, *320*, 37.