Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Protecting Group Free Synthesis of Urea-linked Glycoconjugates: Efficient Synthesis of β-Urea glycosides in Aqueous Solution

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A method for the protecting group free synthesis of β-urea-linked glycoconjugates has been developed. The one step process, involving reaction between urea and D-glucose, *N*-acetyl-D-glucosamine or D-xylose in acidic aqueous solution, furnishes the corresponding β-urea glycoside in modest yield. This simple and efficient procedure is applicable to the synthesis of β-urea tethered amino acid-carbohydrate conjugates.

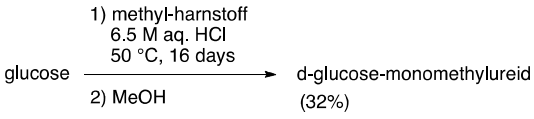
Introduction

The urea glycosyl linkage has been known in Nature as a unique and important structural motif found in members of the glycocinnamolyspermidine amino-sugar antibiotic family. In these natural products, two amino sugars are connected via a urea glycosyl bond. Moreover, the synthesis of neoglycoconjugates, in which native and enzymatically labile glycosidic bonds are replaced by robust non-native linkers, have received considerable recent attention due to the increasing need to develop a new type of molecular tools in glycobiology and potential therapeutic agents.[2]

Replacement of naturally occurring *O*- and *N*-glycosyl linkages with urea-glycosyl bonds is one strategy used to design new neoglycoconjugates.[3] Although a number of new synthetic methods to access urea glycosides have been devised by us[4] and other groups,[5] all methods require the use of protected carbohydrates as intermediates. As a result, the reported synthetic routes to urea glycosides are often lengthy as a consequence of the need for protection/deprotection steps.[6]

The shortcomings of routes to urea glycosides that rely on the use of protected carbohydrates have directed our attention to a classical method involving acid-catalyzed condensation reaction of glucose with urea in water.[7] Although well documented, the applications of this process to reactions of *N*-substituted urea derivatives are both rare and questionable.

In 1926, Helferich, a former student of Emile Fischer, reported the reaction of glucose with methyl-harnstoff (N-methylurea) in aqueous 6.5 M HCl to obtain 'd-glucose-monomethyureid' (eq. 1).[8]



(eq.1)

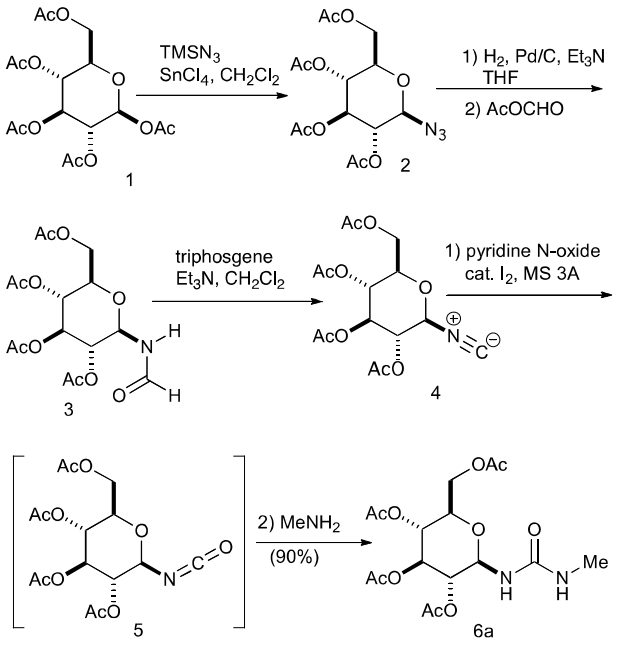
In 1953, Erickson investigated the reaction of long-chain octadecylurea with D-glucose.[9]

The observations made in these two precedents suggest that direct coupling of *N*-substituted ureas with unprotected carbohydrates could serve as a general method for the preparation of urea glycosides. However, the reliability of the two reports was questionable owing to the fact that both Helferich and Erickson characterized the reaction products only by using melting point, elemental analysis and optical rotation data. Furthermore, the yields in the reported reactions were exceedingly low and the stereochemistry at the anomeric position of the products was not determined. As a result of these issues, we have carried out an investigation of the one-step, acid promoted reactions of N-substituted ureas with carbohydrates. This effort has led to the development of a unique and efficient protecting group free method for the synthesis of urea-linked glycoconjugates.[10]

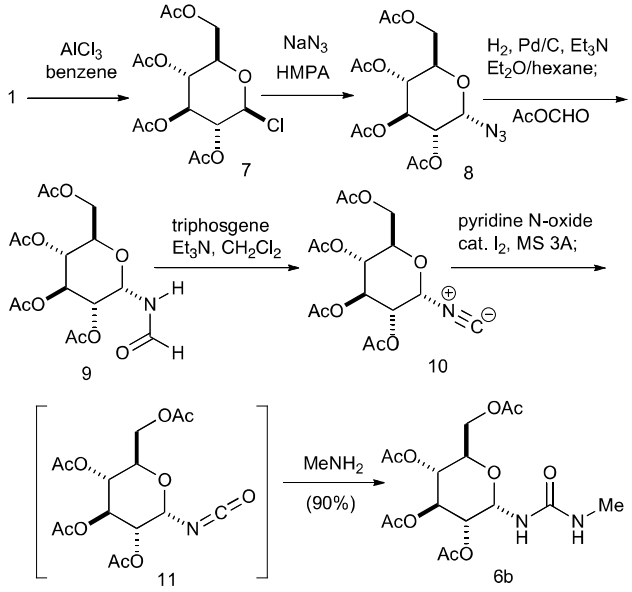
Results and discussion

In the initial phase of this study, we aimed at characterization of the product (d-glucose-monomethyureid) formed in the reaction between glucose and N-methylurea reported by Helferich. For this purpose, we prepared the anomeric pair of 1-methyl-3-glucosylurea by employing our previously established "isocyanide method" (Scheme 1).[11] Starting with commercially available pentaacetyl-β-D-glucose (**1**), β-glucosyl isocyanide **4** was prepared in a three step sequence involving (i) azide glucosylation of **1**, (ii) catalytic hydrogenation of azide **2** followed by formylation of the produced glucosyl amine, and (iii)

dehydration of glucosyl formamide **3** with triphosgene and triethylamine. Oxidation of β-glucosyl isocyanide **4** with pyridine N-oxide in the presence of a catalytic amount of iodine and MS 3A (anhydrous conditions) generated the highly reactive glucosyl isocyanate **5**, which, without isolation, was treated with methylamine. This process formed β-1-methyl-3-glucosylurea **6a** in 90% yield. A similar set of transformations starting with α-glucosyl isocyanide **10**, prepared from **1** in four steps, afforded α-1-methyl-3-glucosylurea **6b** in 90% yield (Scheme 2).



Scheme 1 Synthesis of β-1-methyl-3-glucosylureas from β-glucosyl isocyanide

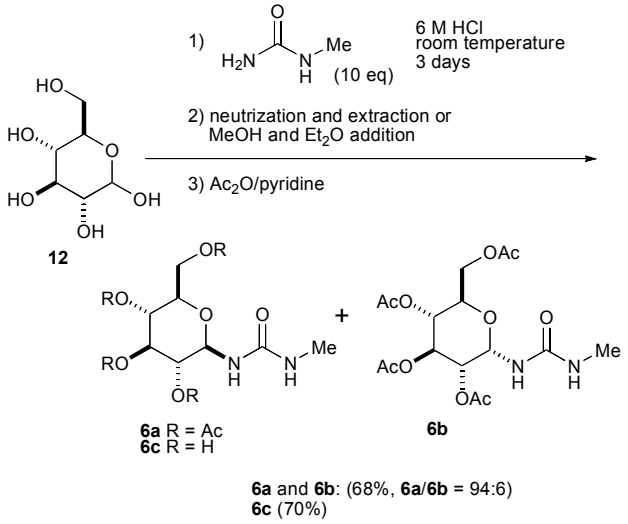


Scheme 2 Synthesis of α-1-methyl-3-glucosylurea from α-glucosyl isocyanide

With tetraacetyl derivatives of the two anomeric 1-methyl-3-glucosylureas in hand, we next explored the acid-catalyzed condensation reaction of D-glucose (**12**) with N-methylurea in water as described by Helferich (Scheme 3). In initial experiments using the reported conditions (2.4 equivalents of N-methylurea, aqueous 5.5 M HCl at 50 °C for 16 d) the product gave only trace amounts of products. After some experiments varying acid catalysts (HCl, H_2SO_4, acidic resins), amount of N-methylurea, a range of temperature and time, we found that this reaction, using 6 M HCl, ten equivalent excess N-methylurea, room temperature and a three-day time period, resulted in higher product yields. Specifically, neutralization of the crude reaction mixture with sodium bicarbonate followed by concentration in vacuo afforded a solid residue, which when treated with Ac_2O and pyridine followed by chromatography produced a mixture of tetraacetyl β- and α-1-methyl-3-glucosylurea (**6a** and **6b**) in a 94:6 ratio and a 68% yield. The products of this process were found to be identical to the independently synthesized glucosyl ureas (Scheme 1 and 2).

In order to demonstrate that our approach is truly 'protecting free', we further examined the work-up procedure to obtain a non-acylated N-methylurea glucoside. After some experiments, it was found that simply treating the reaction mixture with methanol and ether led to crystallization of the product. As a result, non-acylated N-methylurea glucoside **6c** was isolated as crystals in 70% yield. .

The high β-selectivity in this process is presumably the consequence of the fact that the reaction most likely proceeds under thermodynamically controlled conditions and that the urea group displays only a small anomeric effect.[12] The product distribution dominating the formation of β-anomer **6a** over α-isomer **6b** seems to reflect the sterically driven preference for the bulky urea substituents at the pyranose anomeric position to occupy the equatorial position.

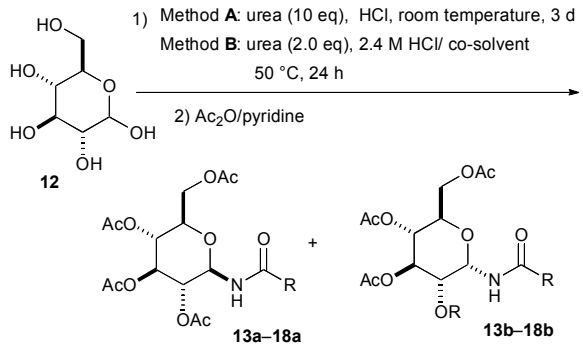


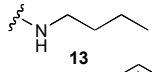
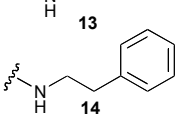
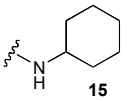
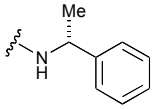
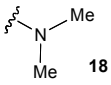
Scheme 3 Synthesis of 1-methyl-3-glucosylurea

In order to explore the scope of the process in Scheme 3, we examined the synthesis of a number of urea glucosides (Table 1, Method **A**: 10 equivalents of urea, 6 M HCl, room temperature and three-day reaction time). The results show that reactions employing *n*-butyl and β–phenethyl urea generated the corresponding urea glucosides **13** and **14** in reasonable yields (entries A and B, 67% and 56%, respectively) and high β-selectivities (**13a**/**13b** = 93:7 and **14a**/**14b** = 93:7).[13] To our disappointment, cyclohexylurea and (*R*)-α-methylbenzylurea, both of which possess α-alkyl branching, reduced the yield considerably (Method **A**, entry C and D, 26% and 24%). Also, reactions with pyrrolidineurea and N,N-dimethylurea took place in low yields (Method **A**, entry E and F, 10% and 6%, respectively). In addition to the low yields, we sometimes encountered problems in purification steps to remove excess amount of urea.

In order to increase the yield and to reduce the amount of loading urea, we further investigated the conditions, which led to the observation that employing 2.4 M HCl, co-solvents such as ethyl acetate or acetonitrile, two equivalents of each urea, and a shorter reaction time (ca. 24 h) brought about much more efficient glucosyl urea formation (Method **B**). In the case of *n*-butylurea and phenetylurea (Method **B**, entries A and B), two equivalents of urea were enough to produce the products in comparable yields with those of Method **A**. Glucosylation of cyclohexylurea and (*R*)-α-methylbenzylurea employing Method **B** raised the yields considerably (entries C and D; 68 and 72%). Although yields in the case of ureas derived from secondary amines were still low even using Method **B** (entries E and F, 27 and 30%), increases in the amounts of the ureas (10 equiv) cause a significant improvement in the yields (Method **B**, entries E and F, 40 and 51%). It should be noted that all reactions using Method **B** generated products with high degree of β-selectivity (>90:10). Moreover, due to the high crystalline nature of β-urea glucosides, the minor α-anomers were easily removed by recrystallization.

Table 1 protecting group free synthesis of N-Substituted urea glucosides



entry[a]	urea glucoside (R =)	Method **A** 6 M HCl yield[b] (ratio = β/α)[c]	Method **B** 2.4 M HCl/solvent (ratio) yield (ratio = β/α)
A	 **13**	67% (93:7)	2.4 M HCl/CH_3CN (1:4) 65% (92:8)
B	 **14**	56% (93:7)	2.4 M HCl/CH_3CN (1:4) 63% (90:10)
C	 **15**	26% (92:8)	2.4 M HCl/AcOEt (1:6) 68% (>98:2)
D	 **16**	24% (>98:2)	2.4 M HCl/CH_3CN (1:6) 72% (>98:2)
E	 **17**	10% (97:3)	2.4 M HCl/AcOEt (1:6) 27% (97:3) 2.4 M HCl/AcOEt (1:1) 40%[b] (95:5)
F	 **18**	6% (97:3)	2.4 M HCl/AcOEt (1:2) 30% (97:3) 2.4 M HCl/AcOEt (1:1) 51%[b] (97:3)

[a]The reaction was carried out on 300-mg scale of D-glucose (**12**).

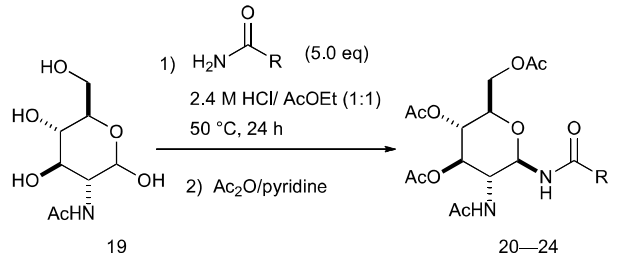
[b]Yields obtained empolying 10 equiv of urea.

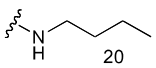
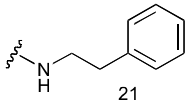
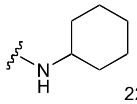
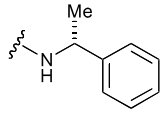
[c]The ratio was determined by ^{1}H NMR analysis of the crude products after acetylation.

The potential generality of the protecting group free synthesis of urea glycosides was explored by using *N*-acetyl-D-glucosamine (**19**) as a substrate and Method **B** conditions (Table 2). Preliminary experiments, which revealed that acetonitrile is a poor co-solvent to solubilize *N*-acetyl-D-glucosamine (**19**), suggested that ethyl acetate be used as the co-solvent. In addition, five equivalents of urea were necessary to obtain reasonable yields. By using modified Method **B**, we obtained the corresponding urea glucosamides **20**–**23** (entries A to D) in comparable yields to those observed for reactions of D-glucose (Table 1, entries A to D). Unfortunately, in the case of pyrrolidine urea (entry E), a low yield (5%) of the urea glucosaminde **24** was obtained. In each case, the β-anomer was

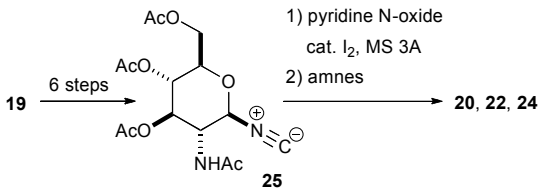
formed exclusively. The structures of **21, 22** and **24** were unambiguously confirmed by comparison with previously reported samples prepared from **19** in 6 steps using the isocyanide method (eq. 2).[3] Protecting group free synthesis of urea glucosamides shows that this method is a convenient short step syntheses of β-urea glucosamides in which urea moieties are derived from primary amines.

Table 2 Synthesis of β-urea glucosamides starting from *N*-acetyl-D-glucosamine (**19**)



entry[a]	urea glucoside (R =)	yield (%)
A	 20	49
B	 21	45
C	 22	57
D	 23	48
E	 24	5

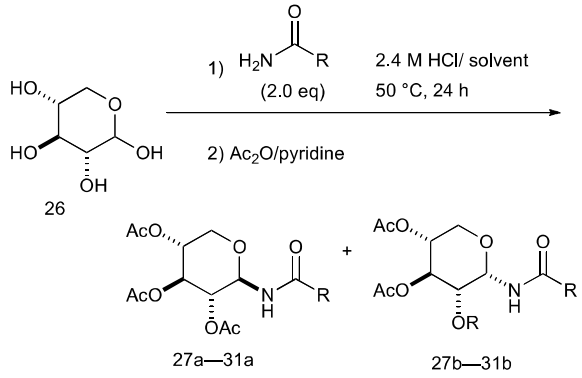
[a]The reaction was carried out on 300-mg scale of *N*-acetyl-D-glucosamine (**19**).

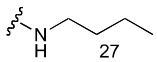
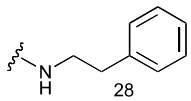
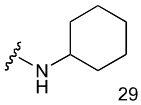
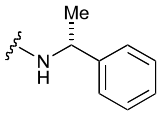


(eq. 2)

Further studies aimed at broadening the substrate scope of the process led us to explore the urea forming reaction of D-xylose (**26**) using Method **B** (Table 3). We are delighted to find that D-xylose (**26**) is a better substrate than hexsoes, giving good yields of urea xylosides **27**–**30** (entries A to D, 71–89%) with high degree of β-selectivity (≥ 98:2). Even in the reaction with pyrrolidineurea (entry E), the corresponding urea xyloside **31** was obtained in modest (41%) yield. The structures and β/α-selectivity of the products (**27**–**31**) were unambiguously determined by comparison with authentic samples synthesized by using the isocyanide method (Scheme 4).[14]

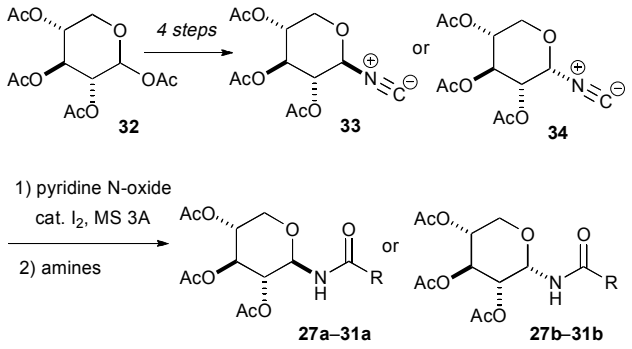
Table 3 Protecting group free urea glycosylation of D-xylose (**26**)



entry[a]	urea glucoside (R =)	2.4 M HCl/solvent (ratio)	yield[b] (%)	β/α[b]
A	 27	2.4 M HCl/CH_3CN (1:4)	73	98:2
B	 28	2.4 M HCl/CH_3CN (1:4)	71	>98:2
C	 29	2.4 M HCl/AcOEt (1:6)	89	>98:2
D	 30	2.4 M HCl/CH_3CN (1:6)	78	>98:2
E	 31	2.4 M HCl/AcOEt (1:6)	41	>98:2

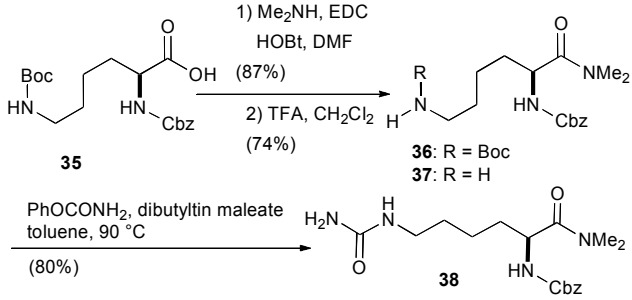
[a] The reaction was carried out on 300-mg scale of D-xylose (**26**).

[b] The ratio was determined by ^{1}H NMR analysis of the crude products after acetylation.



Scheme 4 Independent synthesis of urea xylosides

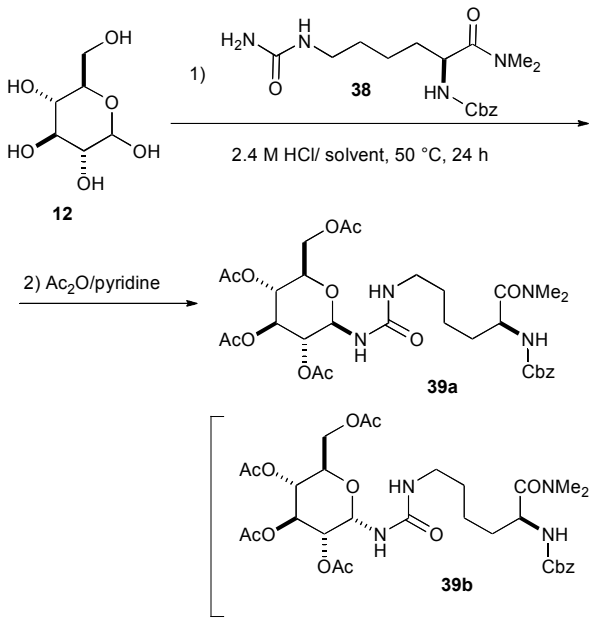
Having developed an efficient method for the synthesis of β-urea glycosides starting with unprotected carbohydrates, our attention next focused on its application to the synthesis of urea-tethered amino acid-carbohydrate conjugates. For this purpose, we examined to install a urea group on a lysine derivative **35** (Scheme 5). Amide formation of **35** with dimethylamine using EDC in the presence of HOBt and deprotection of N-Boc group in **36** with TFA produce the amine **37**. Transcarbamoylation of phenyl carbamate with **37** in the presence of the catalyst dibutyltin maleate furnished urea **38** in 80% yield.[15]



Scheme 5 Setting up a urea group on lysine derivative **35**

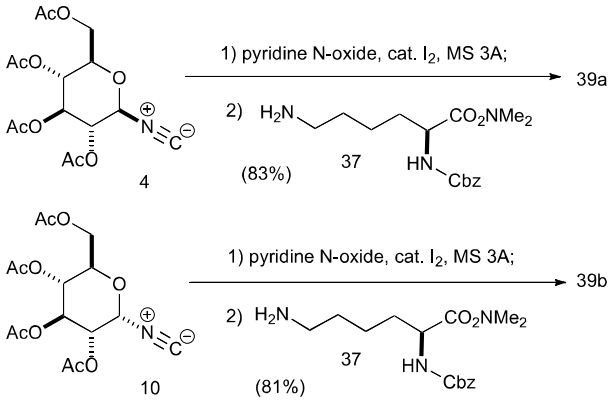
Reactions of urea **38** (2 equiv) with D-glucose **12** in 2.4 M HCl and co-solvents were examined (Table 4). Although we could obtain the desired amino acid-glucose conjugate **39** with high β-selectivity, the yields were low in each co-solvent, acetonitrile (entry A, 9%, β/α = 91:9) and ethyl acetate (entry B, 19%, β/α = 96:4). Although raising the stoichiometry of urea **38** to 5 equivalents and use of acetonitrile as a co-solvent gave the product in only 20% yield (entry C), employing ethyl acetate as a co-solvent improved the yield to an acceptable level (entry D, 51%, β/α = 95:5). The presence of the α-isomer **39b** and the determination of the β/α-selectivities of the reactions were made possible by the availability of authentic samples of **39a** and **39b**, prepared by using the isocyanide method starting with isocyanides **4** and **10** (Scheme 6).

Table 4 Synthesis of urea-tethered amino acid-carbohydrate conjugate



entry	urea (eq)	2.4 M HCl/solvent (ratio)	yield (%)	β/α[a]
A	2.0	2.4 M HCl/CH_3CN (1:4)	9	91:9
B	2.0	2.4 M HCl/AcOEt (1:6)	19	96:4
C	5.0	2.4 M HCl/CH_3CN (1:4)	20	92:8
D	5.0	2.4 M HCl/AcOEt (1:6)	51	95:5

[a] The ratio was determined by ^{1}H NMR analysis of the crude products after acetylation.



Scheme 6 Independent synthesis of urea-tethered amino acid-carbohydrate conjugates **39a** and **39b**

Conclusion

An investigation of the reaction of glucose with N-substituted urea is revisited over 100 years later sine the report by Helferich, which led to a protecting group free method for the synthesis of urea glycosides. The established process is a good and simple method for the preparation of β-urea glycosides in which urea moieties contain primary amines. While the yields are only moderate, the reactions are both scabable and highly β-selective. This protecting group free method is complementary to one developed earlier based on reactions of glycosyl isocyanide intermediates.

Experimental

Synthesis of *N'*-methyl-*N*-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl urea (6a) employing Method A

A solution of D-glucose **12** (500 mg, 2.78 mmol) and 1-methylurea (2.10 g, 27.8 mmol) in 6 N HCl (2.0 ml) was stirred at room temperature for 3 days. The reaction mixture was neutralized with solid $NaHCO_3$ and washed with CH_2Cl_2 to remove excess 1-methylurea. The aqueous layer was concentrated under reduced pressure to give crude urea glucoside as solids (2.68 g), which was dissolved in a mixture of pyridine (12 ml) and Ac_2O (6.0 ml). The solution was stirred at 50 °C for 3 hours, and the resulting reaction mixture was treated with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried (Na_2SO_4) and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (2:1 AcOEt/hexane) to afford a mixture of 1-methyl-3-glucosylurea **6** (764 mg, 68%, **6a**:**6b** = 94:6): Mp 195–196 ˚C (recrystallized from AcOEt/hexane); $[\alpha]_D^{27}$ = +2.87 (*c* 1.00, $CHCl_3$) IR (KBr) ν_{max} 3323, 2939, 2355, 1755, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.01 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.76 (d, *J* = 4.5 Hz, 3H), 3.83 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H), 4.09 (dd, *J* = 12.0, 2.5 Hz, 1H), 4.30 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.83 (q, *J* = 4.5 Hz, 1H), 4.90 (t, *J* = 9.5 Hz, 1H), 5.06 (t, *J* = 9.5 Hz, 1H), 5.17 (t, *J* = 9.5 Hz, 1H), 5.31 (t, *J* = 9.5 Hz, 1H), 5.49 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.35, 20.38, 20.5, 26.6, 61.8, 68.2, 70.2, 72.8, 72.9, 79.8, 157.4, 169.5, 169.7, 170.41, 170.46. Anal. Calcd for $C_{16}H_{24}N_2O_{10}$: C, 47.52; H, 5.98; N, 6.93. Found: C, 47.72; H, 6.03; N, 6.94.

Synthesis and isolation of *N'*-methyl-*N*-β-D-glucopyranosyl urea (6c).

To a solution of D-glucose **12** (1.0 g, 5.74 mmol) and *N*-methyl urea (2.0 g 24.4 mmol) in water (1.0 ml) was added conc. HCl (1.0 ml). After being stirred at room temperature for 3 days, MeOH (20 ml) and Et_2O (35 mL) were added. After standing the mixture at 0 °C for 2 days, the crystals formed are collected, washed with MeOH (5.0 ml) and Et_2O (5.0 ml), and air-dried to furnish 1-methyl-3-glucosylurea **6c** (946 mg, 70 %) as colorless crystals; Mp 208–209 °C (recrystallized from methanol and ether); $[\alpha]_D^{25}$ –29.9 (*c* 1.00, H_2O); IR (KBr) ν_{max} 3449, 3336, 2918, 2869, 1672, 1574, 1514, 1301, 1084 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 2.72 (s, 3H), 3.35 (brt, *J* = 9.5 Hz, 1H), 3.39 (t, *J* = 9.5 Hz, 1H), 3.48–3.57 (m, 1H), 3.54 (t, *J* = 9.5 Hz, 1H), 3.71 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.88 (dd, *J* = 12.0, 5.5 Hz, 1H), 4.84 (brd, *J* = 9.5 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 26.8, 61.3, 67.2, 70.0, 72.5, 77.2, 77.6, 81.7, 160.8. HRMS(ESI): m/z calcd for $C_8H_{17}N_2O_6$ $[M+H]^+$ 237.1087, found 237.1081; m/z calcd for $C_8H_{16}N_2O_6Na$ $[M+Na]^+$ 259.0906, found 259.0917.

General method for the synthesis of N-Substituted urea glucosides using Method B

***N'*-butyl-*N*-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl urea (13a).** A solution of D-glucose **12** (300 mg, 1.67 mmol) and *n*-butylurea (387 mg, 3.33 mmol) dissolved in a mixture of CH_3CN (1.0 mL) and 2.4 N HCl (0.25 mL) was stirred at 50 °C for 1 day, and then was neutralized with solid $NaHCO_3$. The resulting reaction mixture was diluted with H_2O (ca. 2.0 mL) and washed with CH_2Cl_2. The separated aqueous layer was extracted with *n*-BuOH, and the combined organic extracts were concentrated under reduced pressure to afford the solids.

The resulting crude product was dissolved in a mixture of pyridine (10 mL) and Ac_2O (5.0 mL). The solution was stirred at 50 °C for 3 hours, and diluted with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (2:1 AcOEt/hexane) to afford *n*-butylurea glucoside **13a** as a white solid (485 mg, 65%, β:α = 92:8): Mp 97–98 ˚C (recrystallized from AcOEt/hexane); $[\alpha]_D^{26}$ = +1.46 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3369, 2960, 2875, 2359, 2342, 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.32 (sept, *J* = 7.0 Hz, 2H), 1.45 (quint, *J* = 7.0 Hz, 2H), 2.01 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 3.10–3.17 (m, 2H), 3.82 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H), 4.09 (dd, *J* = 12.5, 2.5 Hz, 1H), 4.32 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.72 (t, *J* = 5.5, 1H), 4.90 (t, *J* = 9.5 Hz, 1H), 5.06 (t, *J* = 9.5 Hz, 1H), 5.16 (t, *J* = 9.5 Hz, 1H), 5.30 (t, *J* = 9.5 Hz, 1H), 5.36 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 20.0, 20.5, 20.6, 20.7, 32.0, 40.0, 61.8, 68.3, 70.5, 72.9, 73.0, 80.1, 156.3, 169.6, 169.8, 170.6, 170.9; HRMS(ESI): m/z calcd for $C_{19}H_{31}N_2O_{10}$ $[M+H]^+$ 447.1979, found 447.1989.

Acknowledgments

Financial support for this study, provided by the Kochi University President's Discretionary Grant, is greatly appreciated.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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13. For β-urea glucosides **13a**, **14a**, **15a** and **17a** and α-urea glucosides **15b** and **17b**, their structures and stereoselectivities (β/α) were determined by comparing with authentic samples reported in ref. 11 and 4f. Authentic samples of α-urea glucosides **13b**, **14b**, **16b** and **18b** were prepared by the isocyanide method. For their syntheses, see ESI.

14. For the synthesis of an anomeric pair of pyrrolidine urea xyloside **31a** and **31b**, see the reference 12. Other urea xylosdies **27**—**30** were prepared by the isocyanide method starting with isocyanides **33** and **34**.

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