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Hexafluoroacetone as a Protecting and Activating Reagent. *N*- and *O*-Glycosylation of Isoserine and Isocysteine*

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Summary. Starting from *HFA*-protected malic and thiomalic acid a series of *O*- and *N*-glycoconjugates suitable for peptide and depsipeptide modification has been synthesized.

Keywords. Malic acid; Thiomalic acid; Hexafluoroacetone; Isocyanates; Glycosylamines; Glycoconjugates.

Introduction

O- and *N*-Glycosylation are important co- and post-translational modifications of proteins [1–3]. Glycoconjugates play a key role in various biological recognition processes, including cell to cell communication and adhesion of bacteria or of viruses to cell-surface proteins [4]. Glycosylation improves certain properties of peptides and proteins, *i.a.* solubility, thermal and proteolytical stability [5]. Furthermore, glycosylation influences conformation and folding [6]. This suggests an enormous potential of glycoconjugates in drug design [7].

In glycoconjugates the carbohydrate and peptide part are linked together by glycosidic bonds, which are potentially acid-sensitive and in some cases labile even under moderate basic conditions [8]. In general, glycoconjugates isolated from biological sources or produced by gentechnological methods are microheterogenous. Therefore, the development of new methodologies for the assembly of

* Dedicated to Prof. Dr. *K. Schulze* on the occasion of his 70th birthday
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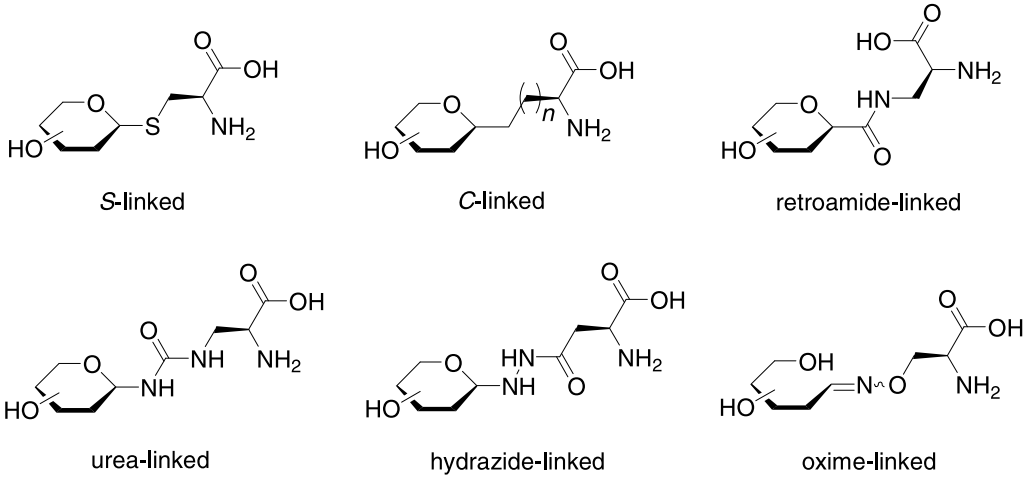


Scheme 1. Non-natural linkages in glycoconjugates

homogeneous and more robust glycopeptide mimetics by chemoselective ligation is of current interest.

Multivalency [9] has attracted attention not only of chemists interested in drug design. Multivalent carbohydrate ligands have advantages over their monovalent counterparts, which generally bind their receptors weakly. The development of low molecular weight compounds that bind strongly to carbohydrate receptors is a challenge to medicinal chemists [10]. Cross-linking of multivalent carbohydrates to proteins can lead to supramolecular assemblies. To study the factors governing the strength of these cluster effects, new methodologies have to be developed for the synthesis of oligosaccharide and glycoconjugate mimetics [11].

In this context, glycoconjugates have been synthesized where *O*- and *N*-glycosidic linkages are replaced by non-natural linkages, like carbon–carbon [12], carbon–sulfur [13], and carbon–aminooxy units [14] (Scheme 1). Alternative concepts proposed by *H. Kessler et al.* are the replacement of the amide group of *N*-glycosylated species by a retroamide subunit [15] or an ethylene isoster [16], and by *B. Imperiali et al.* are the incorporation of alanine-β-hydroxylamine and alanine-β-hydrazide [17] as asparagine surrogates. Recently, a new approach to glycopeptide mimetics was disclosed by *Y. Ichikawa et al.* [18]. They replaced *O*- and *N*-glycosidic linkages by urea-glycosyl bonds. Urea-glycosyl bonds can be constructed from glycosyl isocyanates and the corresponding amines and *vice versa* from glycosylamines and amino acid moieties with an isocyanate group in the side chain. An alternative approach *via* glycosyl phosphinimines, obtained from glycosyl azides and triphenylphosphine was described by *I. Pinter et al.* [19].

The β-amino-α-hydroxycarboxylate unit can be found in many naturally occurring, biologically active compounds, like GABOB [20], carnitin [21], and statin [22]. Isoserine was found as a constituent of antibiotics like edeine [23] and tatumin [24] produced by *bacillus brevis Vm*^{4} strains. Biological activity of antibiotics, *e.g.* butirosin [25] and gentamycin [26], was improved by incorporation of isoserine into strategical positions of the molecule.

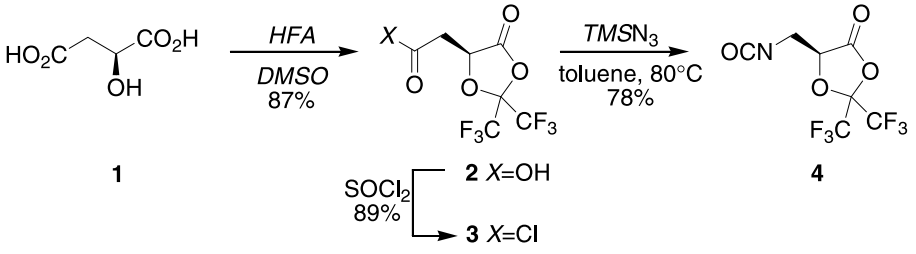
In the case of glycopeptides, even low molecular oligomers have been documented to have significant activities [27]. In addition, some isosters exhibit increased stability [28]. Like α-peptides, β-peptides fold into helices, sheets, and turns which are the main structural elements of proteins. In some instances β-peptides exhibited higher biological activity than their parent α-peptides [29]. Furthermore, β-peptides show improved resistance to peptidases and proteases. Consequently, conjugates comprised of a carbohydrate and a β-amino acid unit are valuable building blocks for drug design [30].

Results and Discussion

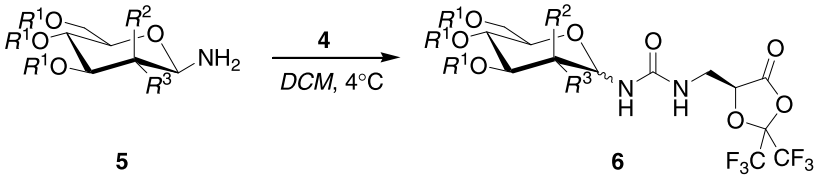
N-Glycosylation of Isoserine

Based on *Ichikawa*'s results, we developed a new route for constructing urea-glycosyl bonds *via* reaction of glycosylamines with isocyanate **4**, using hexafluoroacetone (*HFA*) as protecting and activating reagent.

Isocyanates of type **4** are readily obtained from *HFA*-protected malic, citramalic, and thiomalic acid in a two step procedure [31] (Scheme 2). Compounds **3** and **4** belong to a new class of preparatively highly interesting dielectrophiles where the lactone moiety plays a double role. In the first step of the reaction sequence the lactone acts as protective group for the α-hydroxy as well as for the α-carboxy group. In the second step it acts as an activated ester. The isocyanate and the acid chloride are considerably more reactive than the lactone moiety. At 4°C they react



Scheme 2



5

a R^1=*Ac*, R^2=H, R^3=O*Ac*
b R^1=*Ac*, R^2=O*Ac*, R^3=H
c R^1=*Ac*, R^2=H, R^3=NH*Ac*
d R^1=*Bzl*, R^2=H, R^3=O*Bzl*
e R^1=*Bzl*, R^2=O*Bzl*, R^3=H
f R^1=*Bzl*, R^2=H, R^3=NH*Ac*

6

a 64% (β:α=12:1)
b 64% (β:α=12:1)
c 64% (β:α>20:1)
d 62% (β:α=3:1)
e 68% (β:α=10:1)
f 75% (β:α>20:1)

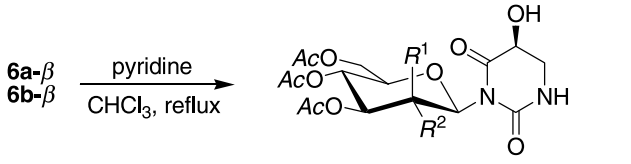
Scheme 3

readily with weak nucleophiles, like glycosylamines **5**, in a site-specific way to give the *N*-glycosylated isoserine derivatives **6** (Scheme 3). During this transformation the lactone remains unaffected. Compounds **6** are obtained as anomeric mixtures, with the β-anomers being the main products (anomeric ratios see Scheme 3), while in the case of *Glc*N*Ac* derivatives **6c** and **6f** the pure β-anomers crystallize from the reaction mixture.

β-Anomers **6a-*β***, **6d-*β***, and **6e-*β*** have been isolated from the crude reaction mixtures by flash chromatography. However, experiments to separate the anomeric pair **6b-*β*/6b-α** failed so far.

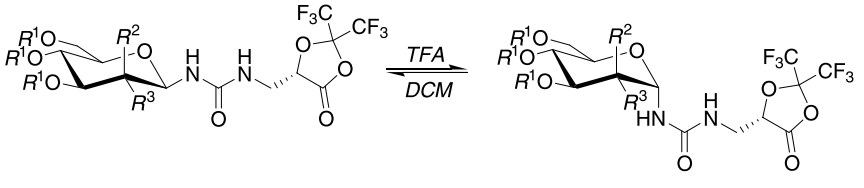
On heating a solution of **6a-*β*** in chloroform in the presence of pyridine an intramolecular cylcocondensation reaction takes place to form 3-glycosylated 5-hydroxy-2,4-dioxo-5,6-dihydropyrimidine **7a** (Scheme 4). A similar type of ring closure was observed when *N*-glycosylated *HFA*-protected malic acid derivatives were treated under the same conditions [32]. While the transformation of the glucose derivative **6a** gives acceptable yields of **7a**, the mannose derivative **6b** decomposed on prolonged heating.

When a solution of **6-*β*** in dichloromethane (*DCM*) was stirred with trifluoroacetic acid (*TFA*, 2 equiv) a slow anomerization process was initiated. Equilibrium ratios were taken from ^{1}H and ^{19}F NMR spectra after 36 h (Scheme 5).



7a R^1=H, R^2=O*Ac*, 42%
7b R^1=O*Ac*, R^2=H, 0%

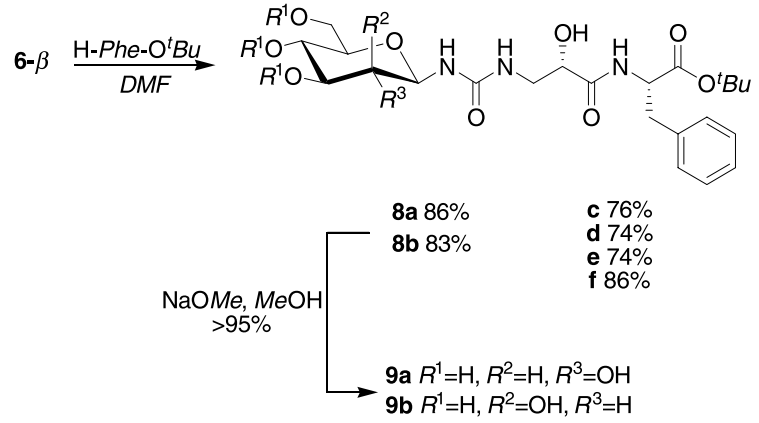
Scheme 4



6-*β* **6-*α***

No.	Equilibrium ratio [**6-*α***] : [**6-*β***]
6a	1:4
6b	1:4
6d	3:1
6e	2:3

Scheme 5

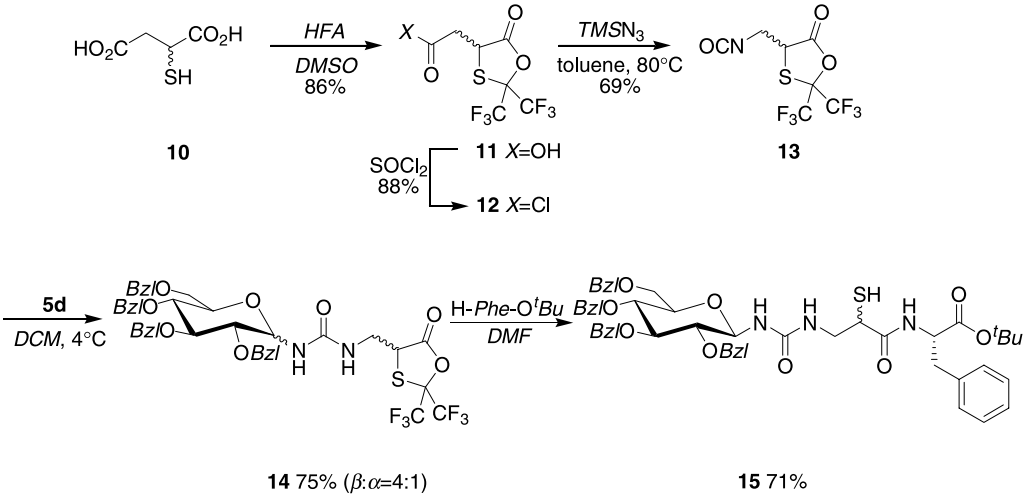


Scheme 6

Compounds **6** are α-carboxy-activated species. Therefore, they can be directly submitted to reactions with nucleophiles (Scheme 6). Cleavage of the lactone ring is always coupled with a simultaneous deprotection of the α-hydroxy group, which can be functionalized afterwards. Compounds **6** represent versatile building blocks suitable for the construction of libraries of *N*-glycosylated peptide hybrides and depsipeptides. Deprotection of the hydroxy groups of the carbohydrate moiety can be achieved without anomerization applying *Zemplén* conditions (**8a**/**b** → **9a**/**b**) [33].

N-Glycosylation of Isocysteine

Analogously, *HFA*-protected thiomalic acid **11** can be transformed into a doubly activated isocysteine synthone **13** *via Curtius* rearrangement (Scheme 7). The isocyanate **13** provides access to a series of new mercapto acid derivatives. At 4°C



Scheme 7

glycosylamines **5** add selectively across the isocyanate group. Since the reaction sequence was started with racemic thiomalic acid, mixtures of diastereomers were formed.

Reactivity of *N*-glycosylated 2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones **14** is similar to that of *N*-glycosylated 2,2-bis(trifluoromethyl)-1,3-dioxolan-4-ones **6** providing ready access to new types of peptide and depsipeptide hybrids (**14** → **15**).

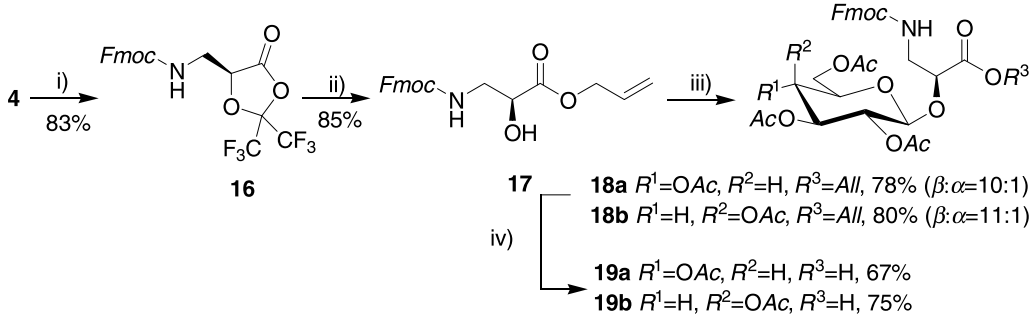
O-Glycosylation of Isoserine

Isoserine represents an α-functionalized β-amino acid. Therefore, *O*-glycosylated isoserine derivatives represent new interesting building blocks for the construction of glycosylated β-peptides [34].

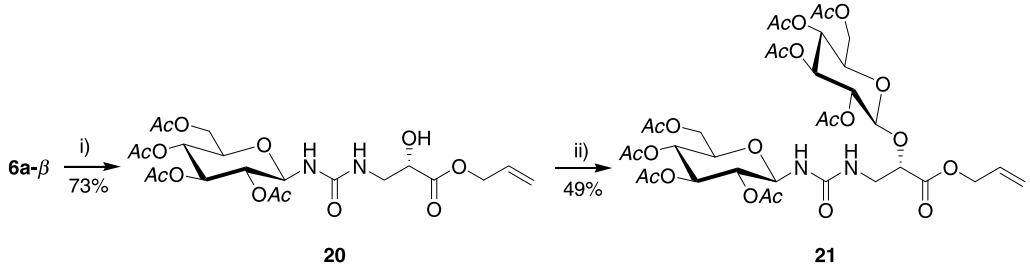
9-Fluorenylmethanol adds regioselectively across the isocyanate function of compound **4** when heated in chloroform to give fully protected, carboxy group activated isoserine derivative **16**, which on treatment with an excess of allyl alcohol readily reacts to give the corresponding allyl ester **17** (Scheme 8). Concomitantly, the hydroxy group is deblocked, and can be glycosylated in a consecutive step, *e.g.* by *R. R. Schmidt*'s imidate strategy [35]. Compounds **18** are *O*-glycosylated orthogonally protected β-alanine derivatives. Deblocking of the carboxyl moiety can be achieved by applying the protocol of *Kunz* and *Waldmann* [36] to obtain *O*-glycosylated *N-Fmoc*-protected isoserine derivatives **19**. *Via* a slightly modified procedure compound **4** can be transformed into *N*- and *C*-protected di- and tripeptides *Fmoc-Ise-Xaa*-O*Me* and *Fmoc-Xaa-Ise-Yaa*-O*Me*, respectively [31a], which were transformed into *O*-glycosides. However, even on application of the imidate method the yields of the glycosylation step are low (20–30%) [37].

N-, O-Diglycosylated Isoserines

Another new type of building block, namely *N*-,*O*-diglycosylated isoserine derivative **21**, is obtained on *O*-glycosylation of **20** (Scheme 9). Since the aminolytic ring cleavage can also be performed with β-amino acid esters diglycosylated β-dipeptides become readily available by this route.



Scheme 8. i) 9-Fluorenylmethanol, $CHCl_3$, reflux; ii) allyl alcohol, $CHCl_3$, reflux; iii) α-*D*-Ac_4-*Glc*{*Gal*}-O-C(=NH)CCl_3, cat. *TMSOTf*, MS 4 Å, *DCM*; iv) $(Ph_3P)_4Pd$, *N*-methyl-aniline, *THF*



Scheme 9. i) Allyl alcohol, $CHCl_3$, reflux; ii) α-*D*-Ac_4-*Glc*-O-C(=NH)CCl_3, cat. *TMSOTf*, MS 4 Å, *DCM*

Conclusion

Starting from *HFA*-protected malic and thiomalic acid a series of new glycosylated and diglycosylated monomers suitable for α-peptide, β-peptide, and depsipeptide modification has been described.

Experimental

NMR spectra were recorded on Varian Gemini 300 or Bruker DRX 600 spectrometers. ^{1}H chemical shifts are referenced to residual protic solvent ($CDCl_3$, $\delta_H = 7.26$ ppm; *DMSO*-d_6, $\delta_H = 2.49$ ppm). ^{13}C chemical shifts were referenced to the solvent signals ($CDCl_3$, $\delta_C = 77.16$; *DMSO*-d_6, $\delta_C = 39.50$ ppm) and ^{19}F chemical shifts to CF_3COOH (external, $\delta_F = 0.00$ ppm). IR spectra were obtained with a FT-IR spectrometer (Genesis ATI Mattson/Unicam). Mass spectra were recorded on a Finnigan ZAB-HSQ spectrometer (matrix: 3-*NBA*). Melting points (uncorrected) were determined on a Boëtius heating table. Optical rotation indices were measured with a Schmidt & Haensch Polartronic-D polarimeter. Solvents were purified and dried prior to use. Reagents were used as purchased. Isocyanates **4** and **13** were prepared according to known procedures [31]. Glycosylamines **5a–5c** were obtained by hydrogenation of the corresponding glycosylazide in the presence of 10% Pd/C in ethyl acetate. Glycosylamines **5d–5f** were prepared starting from the peracetylated glycosylazides by *Zemplén*-deacetylation, benzylation, and careful hydrogenation in the presence of 10% Pd/C in methanol [38]. TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by UV light or phosphomolybdic acid/ceric sulphate in 5% aqueous sulfuric acid followed by heating. Flash chromatography was performed using silica gel (32–63 μm) with solvent systems given in the text. Elemental analyses were performed with a CHNO-S-Rapid apparatus (Fa. Heraeus); their results agreed favourably with the calculated values.

Synthesis of N-Glycosylated Isoserine Derivatives

Protocol 1: A solution of isocyanate **4** (1.05 equiv) in dry *DCM* (5 cm^3 per 1 mmol) was cooled to 0°C. After addition of the corresponding β-*D*-glycosylamine **5** (1.00 equiv) the reaction mixture was kept for 18 h in a fridge at 4°C. Then the solvent was evaporated *in vacuo* and the remaining foamy solid was purified by flash chromatography.

Protocol 2: A solution of the *HFA*-protected isoserine derivative **6** (1.0 equiv) in dry *DCM* (20 cm^3 per 1 mmol) was stirred for 36 h at room temperature after addition of *TFA* (2.0 equiv). Then *DCM* (40 cm^3 per 1 mmol) was added and the organic layer was washed with sat. $NaHCO_3$ solution and sat. NaCl solution (15 cm^3 per mmol). After drying the organic layer with $MgSO_4$, the solvent was removed *in vacuo* and the anomers were separated by flash chromatography or crystallization.

Protocol 3: To a solution of an amino acid *tert*-butylester hydrochloride (1.2 equiv) and *N*-ethylmorpholine (*NEM*) (1.2 equiv) in dimethylformamide (*DMF*) (5 cm^3 per 1 mmol) compound **6** (1.0 equiv) was added. The mixture was stirred at room temperature until TLC-analysis showed complete consumption of the starting material (2–3 d). Then the solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate (50 cm^3 per 1 mmol). The organic layer was washed with citric acid (10%), water, and brine (10 cm^3 per 1 mmol). After drying with $MgSO_4$, the organic solvent was removed and the residue purified by column chromatography.

Protocol 4: Under an atmosphere of argon a solution of compound **7** (1.0 equiv) in dry methanol (5 cm^3 per 0.3 mmol) was stirred with NaO*Me* (0.1 equiv per *O*-acetyl group) for 3 h at room temperature. After neutralization with Dowex 50X8 and filtration, the solvent was evaporated and the residue dried *in vacuo*.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (**6a-β**, $C_{21}H_{24}F_6N_2O_{13}$)

Ac$_4$-*β-D-Glc*-NH_2 (**5a**, 1.20 g, 3.46 mmol) was reacted with isocyanate **4** (1.02 g, 3.64 mmol) due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum ether = 1:1, $R_f(\beta) = 0.28$, $R_f(\alpha) = 0.22$) provides 1.04 g (48%) **6a-β** and 351 mg (16%) of a diastereomeric mixture of **6a-β** and **6a-α** (ratio 3:1) as foamy solids.

6a-β $[\alpha]_D = -4° \, cm^3 \, g^{-1} \, dm^{-1}$ ($c = 1.3$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 2.01$ (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H) (OAc), 3.64 (dt, 1H, $J = 5.7$, 14.8 Hz, CH_2^{Ise}), 3.80–3.90 (m, 2H, CH_2^{Ise}, 5-H), 4.07 (dd, 1H, $J = 1.8$, 12.6 Hz, 6-H_a), 4.30 (dd, 1H, $J = 4.5$, 12.6 Hz, 6-H_b), 4.79 (t, 1H, $J = 5.7$ Hz, CH^{Ise}), 4.89 (dd, 1H, $J = 9.6$, 9.6 Hz, 2-H), 5.05 (dd, 1H, $J = 9.6$, 9.9 Hz, 4-H), 5.11 (dd, 1H, $J = 9.3$, 9.6 Hz, 1-H), 5.30 (dd, 1H, $J = 9.6$, 9.6 Hz, 3-H), 5.61 (t, 1H, $J = 6.3$ Hz, NH^{Ise}), 5.88 (d, 1H, $J = 9.0$ Hz, 1-NH) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.18$ (m, 3F), -2.84 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.86$ (2C), 20.93, 20.98 (OAc), 40.48 (CH_2^{Ise}), 62.36 (6-CH_2), 68.86 (4-CH), 70.97 (2-CH), 73.37 (3-CH), 73.68 (5-CH), 74.81 (CH^{Ise}), 80.42 (1-CH), 98.00 (sept, $J = 36$ Hz), 119.22 (q, $J = 287$ Hz), 119.97 (q, $J = 289$ Hz), 157.05, 167.25, 170.46, 170.55, 171.45, 171.55 ppm; IR (KBr): $\bar{\nu} = 1850$, 1751, 1667, 1565 cm^{-1}; MS (FAB): $m/z = 649.1$ $[M + Na]^+$, 627.1 $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-acetyl-D-mannopyranosyl)urea (**6b-β**, $C_{21}H_{24}F_6N_2O_{13}$)

Ac$_4$-*β-D-Man*-NH_2 (**5b**, 993 mg, 2.86 mmol) was reacted with isocyanate **4** (840 mg, 3.01 mmol) due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum ether = 3:2, $R_f(\beta) = R_f(\alpha) = 0.35$) provides 1.15 g (64%) of a diastereomeric mixture of **6b-β** and **6b-α** (ratio 15:1) as foamy solid.

6b-β: $[\alpha]_D = -20° \, cm^3 \, g^{-1} \, dm^{-1}$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.90$ (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.18 (s, 3H) (OAc), 3.49 (dt, 1H, $J = 4.8$, 15.0 Hz, CH_2^{Ise}), 3.83 (m, 1H, 5-H), 3.92–3.98 (m, 2H, CH_2^{Ise}, 6-H_a), 4.10 (dd, 1H, $J = 5.4$, 12.6 Hz, 6-H_b), 4.98 (dd, 1H, $J = 9.9$, 10.2 Hz, 4-H), 5.12 (dd, 1H, $J = 1.2$, 3.3 Hz, 2-H), 5.31–5.36 (m, 2H, CH^{Ise}, 3-H), 5.55 (dd, 1H, $J = 1.2$, 9.9 Hz, 1-H), 6.48 (t, 1H, $J = 5.7$ Hz, NH^{Ise}), 6.81 (d, 1H, $J = 9.9$ Hz, 1-NH) ppm; ^{19}F NMR (*DMSO*-d_6, 282 MHz): $\delta = -2.16$ (m, 3F), -1.72 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.69$, 20.86 (2C), 20.93 (OAc), 40.27 (CH_2^{Ise}), 62.56 (6-CH_2), 65.61 (4-CH), 70.20 (2-CH), 71.65 (3-CH), 73.81 (5-CH), 74.39 (CH^{Ise}), 77.90 (1-CH), 98.31 (sept, $J = 37$ Hz), 118.87 (q, $J = 287$ Hz), 119.62 (q, $J = 290$ Hz), 156.36, 166.93, 170.16, 170.34, 170.62, 171.15 ppm; IR (KBr): $\bar{\nu} = 1851$, 1751, 1668, 1556 cm^{-1}; MS (FAB): $m/z = 649.0$ $[M + Na]^+$, 627.1 $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)urea (**6c-β**, $C_{21}H_{25}F_6N_3O_{12}$)

Ac$_3$-*β-D-Glc*N*Ac*-NH_2 (**5c**, 955 mg, 2.76 mmol) was reacted with isocyanate **4** (818 mg, 2.93 mmol) due to protocol 1. The analytically pure β-anomer crystallizes from the reaction mixture. After filtration and careful trituration with cold *DCM* 1.11 g (64%) of **6c-β** were obtained as colorless crystals. Mp 224°C (dec); $[\alpha]_D = +5^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.3$, *DMF*); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.77$ (s, 3H, NHAc), 1.93 (s, 3H), 1.98 (s, 3H), 2.02 (s, 3H) (OAc), 3.42 (dt, $J = 4.2$, 15.3 Hz, CH_2^{Ise}), 3.79 (5-H), 3.85–3.97 (m, 3H, CH_2^{Ise}, 2-H, 6-H_a), 4.19 (dd, 1H, $J = 4.2$, 12.3 Hz, 6-H_b), 4.83 (dd, 1H, $J = 9.6$, 9.9 Hz, 4-H), 5.00 (dd, 1H, $J = 9.6$, 9.6 Hz, 1-H), 5.09 (dd, 1H, $J = 9.9$, 9.9 Hz, 3-H), 5.36 (t, 1H, $J = 4.2$ Hz, CH^{Ise}), 6.69–6.72 (m, 2H, 1-NH, NH^{Ise}), 8.05 (d, 1H, $J =$ 9.3 Hz, 2-NH) ppm; ^{19}F NMR (*DMSO*-d_6, 282 MHz): $\delta = -2.18$ (q, 3F, $J = 9.0$ Hz), -1.57 (q, 3F, $J = 9.0$ Hz) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 20.98$, 21.05, 21.15 (OAc), 23.04 (NHAc), 39.40 (CH_2^{Ise}), 52.47 (2-CH), 62.65 (6-CH_2), 69.36 (4-CH), 72.43 (5-CH), 74.02 (3-CH), 76.11 (CH^{Ise}), 80.60 (1-CH), 97.22 (sept, $J = 36$ Hz), 119.23 (q, $J = 286$ Hz), 120.09 (q, $J = 289$ Hz), 157.48, 167.44, 170.01, 170.21, 170.75, 171.14 ppm; IR (KBr): $\bar{\nu} = 1849$, 1745, 1659, 1566 cm^{-1}; MS (FAB): $m/z = 626.1$ $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)urea (**6d-β**, $C_{41}H_{40}F_6N_2O_9$)

Bzl$_4$-*β-D-Glc*-NH_2 (**5d**, 1.01 g, 1.87 mmol) was reacted with isocyanate **4** (550 mg, 1.97 mmol) due to protocol 1. Purification by flash chromatography (ethyl acetate:$CHCl_3 = 1{:}4$, $R_f(\alpha) =$ 0.55, $R_f(\beta) = 0.30$) provides 234 mg (16%) of **6d-α** and 714 mg (46%) of **6d-β** as crystalline solids.

6d-β: Mp 164–166°C; $[\alpha]_D = -21^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 3.32$ (dd, 1H, $J = 9.0$, 9.0 Hz, 2-H), 3.40 (dt, 1H, $J = 5.7$, 14.4 Hz, CH_2^{Ise}), 3.50–3.64 (m, 4H, 4,5-H, CH_2^{Ise}, 6-H_a), 3.68 (dd, 1H, $J = 1.8$, 10.4 Hz, 6-H_b), 3.77 (dd, 1H, $J = 8.7$, 9.0 Hz, 3-H), 4.44 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.50 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.70 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.75 (t, 1H, $J = 5.7$ Hz, CH^{Ise}), 4.84 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.85 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.90–4.94 (m, 3H, CH_2Ph, 1-H), 5.05 (d, 1H, $J = 8.4$ Hz, 1-NH), 5.10 (br.s, 1H, NH^{Ise}), 7.13–7.41 (m, 20H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.17$ (q, 3F, $J = 9.0$ Hz), -2.89 (q, 3F, $J = 9.0$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR, APT): $\delta = 40.64$ (CH_2^{Ise}), 68.96 (6-CH_2), 73.61 (CH_2Ph), 74.20 (CH^{Ise}), 74.79 (CH_2Ph), 75.08 (CH_2Ph), 75.88 (CH_2Ph), 76.04 (5-CH), 78.18 (4-CH), 81.00 (2-CH), 81.50 (1-CH), 85.70 (3-CH), 97.71 (sept, $J = 36$ Hz), 118.98 (q, $J = 286$ Hz), 119.70 (q, $J = 288$ Hz), 127.9–128.7, 137.39, 137.97 (2C), 138.41, 157.05, 166.48 ppm; IR (KBr): $\bar{\nu} = 1847$, 1651, 1574 cm^{-1}; MS (FAB): $m/z = 841.3$ $[M + Na]^+$, 819.3 $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)urea (**6d-α**, $C_{41}H_{40}F_6N_2O_9$)

6d-β (500 mg, 0.61 mmol) was subjected to acid catalyzed anomerization due to protocol 2. **6d-α** was separated from the anomeric mixture by flash chromatography (ethyl acetate:$CHCl_3 = 1{:}4$). Yield 262 mg (52%) **6d-α**, crystalline solid, mp 160–162°C; $[\alpha]_D = +55^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 3.30$ (dt, 1H, $J = 6.3$, 14.6 Hz, CH_2^{Ise}), 3.59 (m, 1H, 4-H), 3.67 (dd, 1H, $J = 5.1$, 10.4 Hz, 6-H_a), 3.71–3.81 (m, 4H, 2,3-H, 6-H_b, CH_2^{Ise}), 3.93 (ddd, $J = 2.2$, 5.1, 9.9 Hz, 5-H), 4.47 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.53 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.60 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.66 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.71 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.78 (t, 1H, $J = 5.8$ Hz, CH^{Ise}), 4.84 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.86 (d, 1H, $J = 11.0$ Hz, CH_2Ph),

4.94 (d, 1H, $J = 10.7$ Hz, CH_2Ph), 5.13 (br.s, 1H, 1-H), 5.42 (d, 1H, $J = 1.7$ Hz, 1-NH), 6.07 (t, 1H, $J = 6.1$ Hz, NH^{Ise}), 7.15–7.32 (m, 20H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.13$ (q, 3F, $J = 9.0$ Hz), -2.90 (q, 3F, $J = 9.0$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR, APT): $\delta = 40.46$ (CH_2^{Ise}), 68.59 (6-CH_2), 70.01 (5-CH), 73.22 (CH_2Ph), 73.67 (CH^{Ise}), 73.70 (CH_2Ph), 75.09 (CH_2Ph), 75.96 (CH_2Ph), 77.34 (4-CH), 78.04 (2-CH), 78.17 (1-CH), 81.95 (3-CH), 97.61 (sept, $J = 36$ Hz), 118.89 (q, $J = 286$ Hz), 119.64 (q, $J = 288$ Hz), 127.8–128.7, 137.07, 137.7, 138.08, 138.33, 158.44, 166.52 ppm; IR (KBr): $\bar{\nu} = 1849$, 1681, 1554 cm^{-1}; MS (FAB): $m/z = 841.3$ $[M + Na]^+$, 819.3 $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)urea (**6e-β**, $C_{41}H_{40}F_6N_2O_9$)

Bzl$_4$-*β-D-Man*-NH_2 (**5e**, 943 mg, 1.65 mmol) was reacted with isocyanate **4** (485 mg, 1.74 mmol) due to protocol 1. Purification by flash chromatography (ethyl acetate:petroleum ether = 1:2, $R_f(\alpha) = 0.26$, $R_f(\beta) = 0.21$) provides 163 mg (12%) of a mixture of **6e-α** and **6e-β** (ratio 1:1) and 778 mg (56%) of **6e-β** as foamy solids.

6e-β: $[\alpha]_D = +5^\circ$ cm^3 g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 3.21$ (dt, 1H, $J = 6.0$, 14.4 Hz, CH_2^{Ise}), 3.40–3.47 (m, 2H, CH_2^{Ise}, 6-H_a), 3.54 (m, 1H, 5-H), 3.60 (dd, 1H, $J = 1.8$, 12.0 Hz, 6-H_b), 3.66 (dd, 1H, $J = 2.7$, 9.6 Hz, 3-H), 3.76 (dd, 1H, $J = 1.5$, 2.7 Hz, 2-H), 3.77 (dd, 1H, $J = 9.3$, 9.6 Hz, 4-H), 4.40 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 4.42 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.48 (d, 1H, $J = 11.4$ Hz, CH_2Ph), 4.56 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.67 (t, 1H, $J = 6.0$ Hz, CH^{Ise}), 4.75 (s, 2H, CH_2Ph), 4.83 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 5.03 (d, 1H, $J = 9.6$ Hz, 1-H), 5.08 (br.t, 1H, NH^{Ise}), 5.15 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 5.49 (d, 1H, $J = 9.3$ Hz, 1-NH), 7.12–7.40 (m, 20H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.24$ (m, 3F), -3.03 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR, APT): $\delta = 40.28$ (CH_2^{Ise}), 69.83 (6-CH_2), 73.20 (CH_2Ph), 73.75 (CH_2Ph), 74.15 (CH^{Ise}), 74.83 (CH_2Ph), 75.31 (4-CH), 75.46 (CH_2Ph), 76.24 (5-CH), 77.14 (2-CH), 78.81 (1-CH), 83.93 (3-CH), 97.50 (sept, $J = 36$ Hz), 118.92 (q, $J = 287$ Hz), 119.62 (q, $J = 289$ Hz), 127.9–128.8, 137.47, 138.22, 138.34, 139.02, 156.46, 167.21 ppm; IR (KBr): $\bar{\nu} = 1847$, 1649, 1568 cm^{-1}; MS (FAB): $m/z = 841.3$ $[M + Na]^+$, 819.3 $[M + H]^+$.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)urea (**6e-α**, $C_{41}H_{40}F_6N_2O_9$)

6e-β (500 mg, 0.61 mmol) was subjected to acid catalyzed anomerization due to protocol 2. **6e-α** was separated from the anomeric mixture by crystallization (*DCM*/petroleum ether, -28°C). Yield 131 mg (26%) **6e-α**, colorless needles, mp 170–171°C; $[\alpha]_D = +20^\circ$ cm^3 g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz, COSY): $\delta = 3.08$ (dt, 1H, $J = 6.0$, 14.6 Hz, CH_2^{Ise}), 3.67 (dt, 1H, $J = 6.0$, 14.6 Hz, CH_2^{Ise}), 3.69 (dd, 1H, $J = 2.4$, 10.5 Hz, 6-H_a), 3.72 (t, 1H, $J = 2.9$ Hz, 2-H), 3.75 (dd, 1H, $J = 4.8$, 10.5 Hz, 6-H_b), 3.80 (dd, 1H, $J = 2.9$, 8.1 Hz, 3-H), 3.85 (dd, 1H, $J = 8.4$, 8.4 Hz, 4-H), 3.91 (m, 1H, 5-H), 4.45 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.51 (d, 1H, $J = 11.2$ Hz, CH_2Ph), 4.54 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.58 (d, 1H, $J = 2.0$ Hz, CH_2Ph), 4.59 (m, 1H, CH^{Ise}), 4.61 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.66 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.68 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.79 (d, 1H, $J = 11.2$ Hz, CH_2Ph), 5.14 (t, 1H, $J = 3.0$ Hz, 1-H), 5.78 (br.s, 1H, 1-NH), 6.12 (br.t, 1H, NH^{Ise}), 7.12–7.30 (m, 20H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.12$ (m, 3F), -2.94 (m, 3F) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, HMQC): $\delta = 40.49$ (CH_2^{Ise}), 68.91 (6-CH_2), 72.06 (5-CH), 72.62 (CH_2Ph), 72.75 (CH_2Ph), 73.58 (CH_2Ph), 74.06 (CH^{Ise}), 74.49 (2-CH), 74.69 (CH_2Ph), 74.84 (4-CH), 78.80 (3-CH), 78.96 (1-CH), 97.58 (sept, $J = 36$ Hz), 118.78 (q, $J = 286$ Hz), 119.56 (q, $J = 288$ Hz), 127.7–128.6, 137.67, 138.07, 138.15, 138.27, 158.56, 166.30 ppm; IR (KBr): $\bar{\nu} = 1850$, 1675, 1558 cm^{-1}.

1-[(5S)-4-Oxo-2,2-bis(trifluoromethyl)-1,3-dioxolan-5-ylmethyl]-3-(3,4,6-tri-O-benzyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)urea (**6f-β**, $C_{36}H_{37}F_6N_3O_9$)

Bzl$_3$-β-*D-Glc*N*Ac*-NH_2 (**5f**, 900 mg, 1.83 mmol) was reacted with isocyanate **4** (538 mg, 1.93 mmol) due to protocol 1. The product precipitates from the reaction mixture. After filtration and careful trituration with ethyl acetate 1.06 g (75%) of **6f-β** were obtained as colorless crystals. Mp 218–219°C; $[\alpha]_D = +1^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.2$, *DMF*); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.82$ (s, 3H, NHAc), 3.36–3.50 (m, 3H, 4,5-H, CH_2^{Ise}), 3.60–3.64 (m, 3H, 3-H, 6-H_2), 3.78 (m, 1H, 2-H), 3.97 (ddd, 1H, $J = 3.9$, 7.5, 15.3 Hz, CH_2^{Ise}), 4.46–4.56 (m, 3H, CH_2Ph), 4.67–4.75 (m, 3H, CH_2Ph), 4.81 (dd, 1H, $J = 9.9$, 9.3 Hz, 1-H), 6.54 (d, 1H, $J = 9.6$ Hz, 1-NH), 6.77 (t, 1H, $J = 7.5$ Hz, NH^{Ise}), 7.18–7.36 (m, 15H, H^{arom}), 8.16 (d, 1H, $J = 9.3$ Hz, 2-NH) ppm; ^{19}F NMR (*DMSO*-d_6, 282 MHz): $\delta = -2.16$ (q, 3F, $J = 9.0$ Hz), −1.51 (q, 3F, $J = 9.0$ Hz) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 22.54$ (NHAc), 39.08 (CH_2^{Ise}), 53.24 (2-CH), 68.74 (6-CH_2), 72.30 (CH_2Ph), 73.91 (CH_2Ph), 74.08 (CH_2Ph), 75.26 (4/5-CH), 75.53 (CH^{Ise}), 77.93 (4/5-CH), 80.23 (1-CH), 83.12 (3-CH), 96.44 (sept, $J = 35$ Hz), 118.58 (q, $J = 286$ Hz), 119.43 (q, $J = 289$ Hz), 127.3–128.2, 138.08, 138.15, 138.57, 156.96, 166.75, 169.22 ppm; IR (KBr): $\bar{\nu} = 1844$, 1653, 1568 cm^{-1}; MS (FAB): $m/z = 792.2$ $[M + Na]^+$, 770.2 $[M + H]^+$.

(5S)-5-Hydroxy-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5,6-dihydropyrimidin-2,4-dione (**7a**, $C_{18}H_{24}N_2O_{12}$)

6a-β (626 mg, 1.00 mmol) and pyridine (1.98 g, 25.0 mmol) were heated under reflux for 24 h in dry $CHCl_3$ (10 cm^3). After removal of the volatiles, the residue was redissolved in $CHCl_3$. The organic layer was washed twice with 0.5 *M* HCl, sat. NaCl solution and dried with $MgSO_4$. After removal of the solvent the product was purified by flash chromatography (ethyl acetate, $R_f = 0.26$). Yield 192 mg (42%) **7a**, colorless foam; $[\alpha]_D = -15^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 2.03$ (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H) (OAc), 3.26 (m, 1H, CH_2^{Ise}), 3.63 (m, 1H, CH_2^{Ise}), 3.85 (m, 1H, 5-H), 4.20–4.25 (m, 2H, 6-H_2), 4.31 (m, 1H, CH^{Ise}), 5.24 (dd, 1H, $J = 9.3$, 9.6 Hz, 4-H), 5.31 (dd, 1H, $J = 9.6$, 9.3 Hz, 3-H), 5.70 (d, 1H, $J = 9.0$ Hz, 1-H), 5.96 (br.s, 1H, NH), 6.05 (dd, 1H, $J = 9.0$, 9.3 Hz, 2-H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 20.69$ (2C), 20.72, 20.95 (OAc), 41.49 (CH_2^{Ise}), 61.97 (6-CH_2), 65.56 (CH^{Ise}), 68.05 (4-CH), 69.12 (2-CH), 73.57 (3-CH), 74.66 (5-CH), 81.02 (1-CH), 153.05, 169.58, 169.85, 170.24, 170.83, 171.43 ppm; IR (KBr): $\bar{\nu} = 3400$, 1752, 1700, 1640 cm^{-1}; MS (FAB): $m/z = 461.1$ $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-ureido]propyl}phenylalaninate (**8a**, $C_{31}H_{43}N_3O_{14}$)

6a-β (626 mg, 1.00 mmol) was reacted with HCl ∗ H-*Phe*-O^t*Bu* (309 mg, 1.20 mmol) due to protocol 3. Purification by flash chromatography (ethyl acetate, $R_f = 0.27$). Yield 586 mg (86%) **8a**, colorless needles from acetone, mp 116–117°C; $[\alpha]_D = +1^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.1$, *THF*); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.36$ (s, 9H, CH_3^{tBu}), 1.96 (s, 3H), 1.99 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H) (OAc), 2.93 (m, 1H, CH_2^{Ise}), 2.99–3.05 (m, 2H, β-CH_2^{Phe}), 3.38 (m, 1H, CH_2^{Ise}), 3.87 (m, 1H, CH^{Ise}), 3.95 (dd, 1H, $J = 2.1$, 12.0 Hz, 6-H_a), 4.03 (m, 1H, 5H), 4.14 (dd, 1H, $J = 4.5$, 12.0 Hz, 6-H_b), 4.45 (m, 1H, α-CH^{Phe}), 4.78 (dd, 1H, $J = 9.6$, 9.6 Hz, 2-H), 4.90 (dd, 1H, $J = 9.6$, 9.9 Hz, 4-H), 5.24 (dd, 1H, $J = 9.9$, 9.6 Hz, 1-H), 5.35 (dd, 1H, $J = 9.6$, 9.6 Hz, 3-H), 5.97 (d, 1H, $J = 5.7$ Hz, OH), 6.28 (t, 1H, $J = 5.7$ Hz, NH^{Ise}), 6.94 (d, 1H, $J = 9.9$ Hz, 1-NH), 7.20–7.34 (m, 5H, H^{arom}), 7.82 (d, 1H, $J = 8.1$ Hz, NH^{Phe}) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 21.01$, 21.10, 21.14, 21.22 (OAc), 28.25 (CH_3^{tBu}), 37.67 (β-CH_2^{Phe}), 44.11 (CH_2^{Ise}), 53.92 (α-CH^{Phe}), 62.56 (6-CH_2), 68.85 (4-CH), 71.15 (2-CH), 71.57 (CH^{Ise}), 72.29 (5-CH), 73.62 (3-CH), 79.46 (1-CH), 81.81 (C^{tBu}), 127.26, 128.89, 130.00, 137.62, 157.51, 170.05, 170.19, 170.73, 170.95, 172.60 ppm; IR (KBr): $\bar{\nu} = 3400$, 1749, 1660, 1560, 1531 cm^{-1}; MS (FAB): $m/z = 682.3$ $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(2,3,4,6-tetra-O-acetyl-β-D-mannopyranosyl)-ureido]propyl}phenylalaninate (**8b**, $C_{31}H_{43}N_3O_{16}$)

6b-β (626 mg, 1.00 mmol) was reacted with HCl ∗ H-*Phe*-O*t*Bu (309 mg, 1.20 mmol) due to protocol 3. Purification by flash chromatography (ethyl acetate, $R_f = 0.29$). Yield 565 mg (83%) **8b**, colorless foam; $[\alpha]_D = -26^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.3$, $CHCl_3$); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta =$ 1.36 (s, 9H, $CH_3{}^{tBu}$), 1.92 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.20 (s, 3H) (OAc), 2.92 (m, 1H, $CH_2{}^{Ise}$), 2.99–3.05 (m, 2H, β-$CH_2{}^{Phe}$), 3.39 (m, 1H, $CH_2{}^{Ise}$), 3.86–3.97 (m, 3H, CH^{Ise}, 5-H, 6-H_a), 4.11 (dd, 1H, $J = 5.4$, 12.6 Hz, 6-H_b), 4.45 (m, 1H, α-CH^{Phe}), 5.00 (dd, 1H, $J = 9.9$, 9.9 Hz, 4-H), 5.16 (d, 1H, $J = 3.3$ Hz, 2-H), 5.33 (dd, 1H, $J = 3.3$, 9.9 Hz, 3-H), 5.53 (d, 1H, $J = 9.9$ Hz, 1-H), 6.04 (d, 1H, $J = 5.7$ Hz, OH), 6.29 (br.t, 1H, NH^{Ise}), 6.84 (d, 1H, $J = 9.9$ Hz, 1-NH), 7.19–7.32 (m, 5H, H^{arom}), 7.83 (d, 1H, $J = 7.8$ Hz, NH^{Phe}) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 21.05$, 21.23, 21.27, 21.50 (OAc), 28.24 ($CH_3{}^{tBu}$), 37.55 (β-$CH_2{}^{Phe}$), 43.94 ($CH_2{}^{Ise}$), 53.90 (α-CH^{Phe}), 62.94 (6-CH_2), 66.13 (4-CH), 70.82 (2-CH), 71.43 (CH^{Ise}), 71.65 (3-CH), 72.56 (5-CH), 77.46 (1-CH), 81.80 (C^{tBu}), 127.26, 128.89, 130.01, 137.59, 156.82, 170.14, 170.30, 170.77, 170.84, 170.97, 172.59 ppm; IR (KBr): $\bar{\nu} = 3400$, 1747, 1655, 1554, 1533 cm^{-1}; MS (FAB): $m/z = 704.3$ $[M + Na]^+$, 682.3 $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)ureido]propyl}phenylalaninate (**8c**, $C_{31}H_{44}N_4O_{13}$)

6c-β (624 mg, 1.00 mmol) was reacted with HCl ∗ H-*Phe*-O*t*Bu (309 mg, 1.20 mmol) due to protocol 3. Purification by flash chromatography (*DCM*:*i*PrOH = 10:1, $R_f = 0.20$). Yield 516 mg (76%) **8c**, crystalline solid, mp 213–214°C; $[\alpha]_D = +12^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.3$, *DMF*); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.37$ (s, 9H, $CH_3{}^{tBu}$), 1.79 (s, 3H, NHAc), 1.93 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H) (OAc), 2.89 (m, 1H, $CH_2{}^{Ise}$), 3.00–3.04 (m, 2H, β-$CH_2{}^{Phe}$), 3.38 (m, 1H, $CH_2{}^{Ise}$), 3.78 (m, 1H, 5-H), 3.84–3.96 (2-H, 6-H_a, CH^{Ise}), 4.17 (dd, 1H, $J = 3.9$, 12.6 Hz, 6-H_b), 4.46 (m, 1H, α-CH^{Phe}), 4.83 (dd, 1H, $J = 9.6$, 9.6 Hz, 4-H), 5.00 (dd, 1H, $J = 9.6$, 9.9 Hz, 1-H), 5.08 (dd, 1H, $J = 9.9$, 9.9 Hz, 3-H), 5.98 (d, 1H, $J = 5.4$ Hz, OH), 6.37 (t, 1H, $J = 5.7$ Hz, NH^{Ise}), 6.81 (d, 1H, $J = 9.6$ Hz, 1-NH), 7.20–7.33 (m, 5H, H^{arom}), 7.81 (d, 1H, $J = 7.8$ Hz, NH^{Phe}), 8.02 (d, 1H, $J = 9.6$ Hz, 2-NH) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 20.33$, 20.40, 20.50 (OAc), 22.67 (NHAc), 27.53 ($CH_3{}^{tBu}$), 36.96 (β-$CH_2{}^{Phe}$), 43.37 ($CH_2{}^{Ise}$), 51.89 (2-CH), 53.17 (α-CH^{Phe}), 61.92 (6-CH_2), 68.56 (4-CH), 71.04 (CH^{Ise}), 71.67 (5-CH), 73.56 (3-CH), 79.96 (1-CH), 81.07 (C^{tBu}), 126.53, 128.16, 129.28, 136.89, 157.02, 169.30, 169.38, 169.55, 170.03, 170.23, 171.86 ppm; IR (KBr): $\bar{\nu} = 3400$, 1740, 1655, 1564, 1535 cm^{-1}; MS (FAB): $m/z = 681.3$ $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-ureido]propyl}phenylalaninate (**8d**, $C_{51}H_{59}N_3O_{10}$)

6d-β (409 mg, 0.50 mmol) was reacted with HCl ∗ H-*Phe*-O*t*Bu (155 mg, 0.60 mmol) due to protocol 3. Purification by flash chromatography (ethyl acetate:$CHCl_3$ = 5:4, $R_f = 0.20$). Yield 323 mg (74%) **6d-β**, crystalline solid, mp 150–151°C; $[\alpha]_D = -25^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.37$ (s, 9H, $CH_3{}^{tBu}$), 2.99–3.04 (m, 2H, β-$CH_2{}^{Phe}$), 3.08 (m, 1H, $CH_2{}^{Ise}$), 3.32 (dd, 1H, $J = 9.0$, 9.6 Hz, 2-H), 3.40–3.52 (m, 3H, 4,5-H, $CH_2{}^{Ise}$), 3.63–3.66 (m, 2H, 6-H_2), 3.70 (dd, 1H, $J = 9.0$, 9.0 Hz, 3-H), 3.94 (m, 1H, CH^{Ise}), 4.45–4.56 (m, 4H, α-CH^{Phe}, CH_2Ph), 4.66–4.85 (m, 5H, CH_2Ph), 4.91 (dd, 1H, $J = 9.0$, 9.6 Hz, 1-H), 6.01 (d, 1H, $J = 5.4$ Hz, OH), 6.18 (t, 1H, $J = 5.7$ Hz, NH^{Ise}), 7.16–7.36 (m, 26H, 1-NH, H^{arom}), 7.85 (d, 1H, $J = 7.5$ Hz, NH^{Phe}) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 27.53$ ($CH_3{}^{tBu}$), 36.94 (β-$CH_2{}^{Phe}$), 43.58 ($CH_2{}^{Ise}$), 53.21 (α-CH^{Phe}), 68.70 (6-CH_2), 71.09 (CH^{Ise}), 72.33 (CH_2Ph), 73.83 (CH_2Ph), 73.91 (CH_2Ph), 74.50 (CH_2Ph), 75.02, 77.79 (4,5-CH), 80.50 (1-CH), 81.03 (C^{tBu}), 81.40 (2-CH), 84.74 (3-CH), 126.4–129.3, 136.86, 138.18, 138.20, 138.45, 138.65, 157.09, 170.17, 171.94 ppm; IR (KBr): $\bar{\nu} = 3400$, 1732, 1651, 1570, 1525 cm^{-1}; MS (FAB): $m/z = 896.4$ $[M + Na]^+$, 874.4 $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)-ureido]propyl}phenylalaninate (**8e**, $C_{51}H_{59}N_3O_{10}$)

6e-*β* (409 mg, 0.50 mmol) was reacted with HCl ∗ H-*Phe*-O*t Bu* (155 mg, 0.60 mmol) due to protocol 3. Purification by flash chromatography (ethyl acetate:petrolether = 4:1, $R_f = 0.40$). Yield 319 mg (74%) **8e**, foamy solid; $[\alpha]_D = -9^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 2.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.39$ (s, 9H, $CH_3{}^{tBu}$), 2.99–3.13 (m, 2H, β-$CH_2{}^{Phe}$), 3.32–3.36 (m, 2H, $CH_2{}^{Ise}$), 3.42–3.48 (m, 2H, 5-H, 6-H_a), 3.62–3.67 (m, 2H, 3-H, 6-H_b), 3.75 (m, 1H, 2-H), 3.86 (dd, 1H, $J = 9.3$, 9.3 Hz, 4-H), 4.01 (m, 1H, CH^{Ise}), 4.40 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.46 (d, 1H, $J = 11.1$ Hz, CH_2Ph), 4.53 (d, 2H, $J = 11.7$ Hz, CH_2Ph), 4.73 (s, 2H, CH_2Ph), 4.74 (m, 1H, α-CH^{Phe}), 4.84 (d, 1H, $J = 10.5$ Hz, CH_2Ph), 5.05 (d, 1H, $J = 9.9$ Hz, 1-H), 5.12 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 5.62 (br.t, 1H, NH^{Ise}), 5.82 (d, 1H, $J = 9.9$ Hz, 1-NH), 5.85 (br.s, 1H, OH), 7.14–7.37 (m, 25 H, H^{arom}), 7.58 (d, 1H, $J = 8.7$ Hz, NH^{Phe}) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 28.17$ ($CH_3{}^{tBu}$), 38.89 (β-$CH_2{}^{Phe}$), 45.01 ($CH_2{}^{Ise}$), 53.55 (α-CH^{Phe}), 69.27 (6-CH_2), 72.94 (CH^{Ise}), 73.07 (CH_2Ph), 73.55 (CH_2Ph), 74.96 (CH_2Ph), 75.11 (4-CH), 75.34 (CH_2Ph), 76.45 (5-CH), 77.09 (2-CH), 78.97 (1-CH), 82.39 (C^{tBu}), 84.06 (3-CH), 127.2–129.8, 136.44, 137.82, 138.27, 138.47, 138.82, 159.11, 170.27, 172.32 ppm; IR (KBr): $\bar{\nu} = 3400$, 1732, 1651, 1562, 1520 cm^{-1}; MS (FAB): $m/z = 896.3$ $[M + Na]^+$, 874.4 $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(3,4,6-tri-O-benzyl-2-acetamido-2-deoxy-β-D-glucopyranosyl)ureido]propyl}phenylalaninate (**8f**, $C_{46}H_{56}N_4O_{10}$)

6f-*β* (384 mg, 0.5 mmol) was treated with HCl ∗ H-*Phe*-O*t Bu* (155 mg, 0.60 mmol) due to protocol 3. Purification by flash chromatography ($CHCl_3$:*Me*OH = 10:1, $R_f = 0.26$). Yield 355 mg (86%) **8f**, colorless crystals, mp 208–209°C; $[\alpha]_D = -4^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.1$, *DMF*); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.37$ (s, 9H, $CH_3{}^{tBu}$), 1.83 (s, 3H, NHAc), 2.89 (m, 1H, $CH_2{}^{Ise}$), 3.00–3.05 (m, 2H, β-$CH_2{}^{Phe}$), 3.36–3.50 (m, 3H, 4,5-H, $CH_2{}^{Ise}$), 3.58–3.64 (m, 3H, 3-H, 6-H_2), 3.77 (m, 1H, 2-H), 3.87 (m, 1H, CH^{Ise}), 4.43–4.54 (m, 4H, α-CH^{Phe}, CH_2Ph), 4.66–4.75 (m, 3H, CH_2Ph), 4.82 (dd, 1H, $J = 9.6$, 9.6 Hz, 1-H), 5.99 (d, 1H, $J = 5.7$ Hz, OH), 6.43 (t, 1H, $J = 5.1$ Hz, NH^{Ise}), 6.64 (d, 1H, $J = 9.6$ Hz, 1-NH), 7.18–7.36 (m, 20H, H^{arom}), 7.82 (d, 1H, $J = 7.8$ Hz, NH^{Phe}), 8.10 (d, 1H, $J = 9.3$ Hz, 2-NH) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 22.54$ (NHAc), 27.51 ($CH_3{}^{tBu}$), 36.98 (β-$CH_2{}^{Phe}$), 43.45 ($CH_2{}^{Ise}$), 53.16 (α-CH^{Phe}), 53.43 (2-CH), 68.76 (6-CH_2), 71.20 (CH^{Ise}), 72.29, 73.90, 74.09 (3×CH_2Ph), 75.29, 77.97 (4,5-CH), 80.37 (1-CH), 81.04 (C^{tBu}), 83.43 (3-CH), 126.5–129.3, 136.87, 138.14, 138.21, 138.62, 157.43, 169.30, 170.22, 171.87 ppm; IR (KBr): $\bar{\nu} = 1731$, 1651, 1568, 1531 cm^{-1}; MS (FAB): $m/z = 825.4$ $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(β-D-glucopyranosyl)ureido]propyl}phenylalaninate (**9a**, $C_{23}H_{35}N_3O_{10}$)

8a (205 mg, 0.30 mmol) was treated with NaO*Me* (6.5 mg, 0.12 mmol) due to protocol 4. Yield 150 mg (>95%) **9a**, foam; $[\alpha]_D = -17^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.0$, *Me*OH); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.38$ (s, 9H, $CH_3{}^{tBu}$), 2.83–2.96 (m, 2H, $CH_2{}^{Ise}$, 2-H), 3.02–3.10 (m, 4H, β-$CH_2{}^{Phe}$, 4,5-H), 3.18 (m, 1H, 3-H), 3.37–3.44 (m, 2H, $CH_2{}^{Ise}$, 6-H_a), 3.63 (m, 1H, 6-H_b), 3.88 (m, 1H, CH^{Ise}), 4.46 (m, 1H, α-CH^{Phe}), 4.50 (t, 1H, $J = 6.0$ Hz, 6-OH), 4.60 (dd, 1H, $J = 9.3$, 9.3 Hz, 1-H), 4.88 (d, 1H, $J = 4.8$ Hz, 4-OH), 4.91 (d, 1H, $J = 5.4$ Hz, 2-OH), 4.99 (d, 1H, $J = 4.5$ Hz, 3-OH), 6.05 (d, 1H, $J = 5.4$ Hz, OH^{Ise}), 6.12 (br.t, 1H, NH^{Ise}), 6.77 (d, 1H, $J = 9.3$ Hz, 1-NH), 7.20–7.34 (m, 5H, H^{arom}), 7.85 (d, 1H, $J = 8.1$ Hz, NH^{Phe}) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 28.27$ ($CH_3{}^{tBu}$), 37.61 (β-$CH_2{}^{Phe}$), 44.18 ($CH_2{}^{Ise}$), 53.89 (α-CH^{Phe}), 61.62 (6-CH_2), 70.71 (4-CH), 71.96 (CH^{Ise}), 73.67 (2-CH), 78.44 (3-CH), 78.68 (5-CH), 81.79 (1-CH, C^{tBu}), 127.03, 128.92, 130.03, 137.63, 158.21, 170.99, 172.74 ppm; IR (KBr): $\bar{\nu} = 3400$, 1728, 1660, 1561, 1527 cm^{-1}; MS (FAB): $m/z = 552.2$ $[M + K]^+$, 536.2 $[M + Na]^+$, 514.2 $[M + H]^+$.

tert-Butyl N-{(2S)-2-Hydroxy-1-oxo-3-[3-(β-D-mannopyranosyl)-ureido]propyl}phenylalaninate (**9b**, $C_{23}H_{35}N_3O_{10}$)

8b (205 mg, 0.30 mmol) was treated with NaO*Me* (6.5 mg, 0.12 mmol) due to protocol 4. Yield 150 mg (>95%) **9b**, foam; $[\alpha]_D = -10° \text{ cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 1.0$, *Me*OH); ^{1}H NMR (*DMSO*-d_6, 300 MHz, COSY): $\delta = 1.37$ (s, 9H, CH_3^{tBu}), 2.82 (m, 1H, CH_2^{Ise}), 3.00–3.07 (m, 3H, β-CH_2^{Phe}, 5-H), 3.29–3.48 (m, 4H, CH_2^{Ise}, 3,4-H, 6-H_a), 3.54 (m, 1H, 2-H), 3.65 (m, 1H, 6-H_b), 3.87 (m, 1H, CH^{Ise}), 4.43–4.48 (m, 2H, 6-OH, α-CH^{Phe}), 4.71 (d, 1H, $J = 4.8$ Hz, 4-OH), 4.82 (d, 1H, $J = 4.8$ Hz, 3-OH), 4.86 (d, 1H, $J = 4.8$ Hz, 2-OH), 4.91 (d, 1H, $J = 9.9$ Hz, 1-H), 6.03 (d, 1H, $J = 6.0$ Hz, OH^{Ise}), 6.66 (t, 1H, $J = 5.7$ Hz, NH^{Ise}), 6.73 (d, 1H, $J = 9.9$ Hz, 1-NH), 7.20–7.34 (m, 5H, H^{arom}), 7.80 (d, 1H, $J = 8.1$ Hz, NH^{Phe}) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz, HETCOR): $\delta = 28.27$ (CH_3^{tBu}), 37.63 (β-CH_2^{Phe}), 44.20 (CH_2^{Ise}), 53.81 (α-CH^{Phe}), 62.02 (6-CH_2), 67.50 (4-CH), 71.88 (2-CH), 72.13 (CH^{Ise}), 75.05 (3-CH), 79.05 (5-CH), 79.18 (1-CH), 81.85 (C^{tBu}), 127.30, 128.90, 130.03, 137.59, 157.85, 170.97, 172.66 ppm; IR (KBr): $\bar{\nu} = 3400$, 1727, 1650, 1561, 1529 cm^{-1}; MS (FAB): $m/z = 552.2$ $[M + K]^+$, 536.2 $[M + Na]^+$, 514.2 $[M + H]^+$.

Synthesis of N-Glycosylated Isocysteine Derivatives

1-[5-Oxo-2,2-bis(trifluoromethyl)-1,3-oxathiolan-4-ylmethyl]-3-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)urea (**14**, $C_{41}H_{40}F_6N_2O_8S$)

Bzl$_4$-β-*D-Glc*-NH_2 (**5d**, 866 mg, 1.61 mmol) was reacted with isocyanate **13** (502 mg, 1.70 mmol) due to protocol 1. Purification by flash chromatography (ethyl acetate:$CHCl_3 = 1:5$, $R_f(\alpha) = 0.43$, $R_f(\beta) = 0.18$) provides 201 mg (15%) of **14-α** and 809 mg (60%) of **14-β** as foamy solids.

14-α: Diastereomeric mixture (ratio 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.29$–3.39 (m, 2H, CH_2^{Icy}), 3.50–3.81 (m, 12 H, CH_2^{Icy}, 2,3,4-CH, 6-CH_2), 3.89–3.94 (m, 2H, 5-H), 4.35 (t, 1H, $J = 6.0$ Hz, CH^{Icy}), 4.40 (t, 1H, $J = 6.0$ Hz, CH^{Icy}), 4.42–4.70 (m, 10H, CH_2Ph), 4.80 (d, 2H, $J = 11.1$ Hz, CH_2Ph), 4.82 (dd, 2H, $J = 10.5$ Hz, CH_2Ph), 4.90 (d, 2H, $J = 11.1$ Hz, CH_2Ph), 5.09 (br.s, 2H, 1-H), 5.39 (d, 1H, $J = 2.1$ Hz, 1-NH), 5.40 (d, 1H, $J = 2.1$ Hz, 1-NH), 6.19 (br.t, 1H, $J = 5.7$ Hz, NH^{Icy}), 6.24 (br.t, 1H, $J = 5.7$ Hz, NH^{Icy}), 7.18–7.40 (m, 40H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 0.76$–0.88 (m, 6F), 1.95–2.13 (m, 6F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT): $\delta = 41.73$, 41.89 (CH_2^{Icy}), 46.24, 46.32 (CH^{Icy}), 68.61, 68.68 (6-CH_2), 69.96, 69.99 (5-CH), 73.14, 73.23, 73.64, 73.71, 75.11, 75.92 (CH_2Ph), 77.35 (4-CH), 78.02, 78.08, 78.18 (1,2-CH), 81.87, 81.90 (3-CH), 83.31 (sept, $J = 36$ Hz), 120.82 (q, $J = 288$ Hz), 121.41 (q, $J = 284$ Hz), 128.0–128.9, 137.06, 137.09, 137.63, 137.94, 138.30, 158.47, 158.63, 169.43, 169.67 ppm; IR (KBr): $\bar{\nu} = 1813$, 1666, 1554 cm^{-1}; MS (FAB): $m/z = 857.2$ $[M + Na]^+$, 835.2 $[M + H]^+$.

14-β: Diastereomeric mixture (ratio 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.33$ (dd, 1H, $J = 9.0$, 9.0 Hz, 2-H), 3.34 (dd, 1H, $J = 9.0$, 9.0 Hz, 2-H), 3.42–3.79 (m, 14H, CH_2^{Icy}, 3,4,5-H, 6-H_2), 4.21 (t, 1H, $J = 6.3$ Hz, CH^{Icy}), 4.37 (t, 1H, $J = 6.0$ Hz, CH^{Icy}), 4.38–4.53 (m, 6H, CH_2Ph), 4.66–4.93 (m, 12H, 1-H, CH_2Ph), 5.30 (d, 2H, $J = 9.0$ Hz, 1-NH), 5.56 (m, 2H, NHI^{cy}), 7.12–7.35 (m, 40 H, H^{arom}) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = 0.81$–0.93 (m, 6F), 1.91–2.07 (m, 6F) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT): $\delta = 41.85$, 42.77 (CH_2^{Icy}), 46.29 (CH^{Icy}), 68.85, 68.96 (6-CH_2), 73.55, 74.66, 75.09, 77.81 (CH_2Ph), 75.85 (5-CH), 77.99 (4-CH), 81.00, 81.05, 81.35, 81.42 (1,2-CH), 83.36 (sept, $J = 36$ Hz), 85.47, 85.54 (3-CH), 120.81 (q, $J = 284$ Hz), 121.39 (q, $J = 285$ Hz), 127.9–128.8, 137.16, 137.24, 137.75, 137.78, 137.80, 137.84, 138.26, 138.27, 157.11, 157.18, 169.83, 169.96 ppm; IR (KBr): $\bar{\nu} = 1811$, 1645, 1572 cm^{-1}; MS (FAB): $m/z = 857.2$ $[M + Na]^+$, 835.2 $[M + H]^+$.

tert-Butyl N-{2-Mercapto-1-oxo-3-[3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)ureido]-propyl}phenylalaninate (**15**, $C_{51}H_{59}N_3O_9S$)

14-β (236 mg, 0.28 mmol) was reacted with HCl ∗ H-*Phe*-O^t*Bu* (87 mg, 0.34 mmol) due to protocol 3. The reaction mixture was flushed with argon for 30 min. Purification by flash chromatography (ethyl

acetate:petrolether = 1:1, $R_f = 0.29$, $R_f = 0.25$). Yield 181 mg (71%) **15**, foam, diastereomeric mixture (ratio 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.42$ (s, 9H, $CH_3{}^{tBu}$), 1.45 (s, 9H, $CH_3{}^{tBu}$), 2.03 (br.s, 2H, SH), 3.06–3.14 (m, 4H, β-$CH_2{}^{Phe}$), 3.31–3.82 (m, 18H, 2,3,4,5-H, 6-H_2, CH^{Icy}, $CH_2{}^{Icy}$), 4.43–4.65 (m, 10H, CH_2Ph, α-CH^{Phe}), 4.71–5.03 (m, 11H, CH_2Ph, 1-H, 1-NH), 5.14 (d, 1H, $J = 9.0$ Hz, 1-NH), 5.43 (m, 2H, NH^{Icy}), 6.91 (d, 1H, $J = 7.2$ Hz, NH^{Phe}), 7.03 (d, 1H, $J = 6.6$ Hz, NH^{Phe}), 7.17–7.36 (m, 50H, H^{arom}) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT, HETCOR): $\delta = 28.06$ ($CH_3{}^{tBu}$), 37.67, 37.84 (β-$CH_2{}^{Phe}$), 41.89, 42.76 (CH^{Icy}), 44.85, 45.43 ($CH_2{}^{Icy}$), 54.37, 54.62 (α-CH^{Phe}), 68.52, 68.65 (6-CH_2), 73.49, 73.58, 74.77, 74.99, 75.82 (CH_2Ph), 76.02 (5-CH), 77.92, 78.01 (4-CH), 80.86, 81.04 (2-CH), 81.40, 81.53 (1-CH), 82.75 (C^{tBu}), 85.88, 85.93 (3-CH), 127.9–129.6, 136.1–138.5 (arom), 157.23, 170.56, 171.06, 171.16, 171.59 ppm; MS (FAB): $m/z = 890.3$ $[M + H]^+$.

Synthesis of O-Glycosylated Isoserine Derivatives

Protocol 5: To a solution of the glycosyl donor (1.2 equiv) and the glycosyl acceptor (1.0 equiv) in dry *DCM* (10 cm^3 per mmol) 0.5 g of activated molecular sieves (4 Å) were added. After stirring for 2 h, trimethylsilyl triflate (*TMSOTf*, 0.1 equiv) was added and stirring was continued until complete consumption of the glycosyl donor was judged by TLC (1–2 h). The mixture was diluted with *DCM* (40 cm^3 per mmol) and extracted with sat. $NaHCO_3$ solution (10 cm^3 per mmol) and water (10 cm^3 per mmol). After drying with $MgSO_4$ the organic solvent was removed *in vacuo* and the residue purified by column chromatography.

Protocol 6: To a solution of the allyl ester (1.0 equiv) and $(Ph_3P)_4Pd$ (0.1 equiv) in dry *THF* (25 cm^3 per mmol) *N*-methylaniline (10 equiv) was added within 3 min. The mixture was stirred until complete consumption of the starting material (TLC, 30 min). After addition of chloroform (50 cm^3 per mmol) and extraction with 1.5 *M* HCl the organic layer was dried and evaporated *in vacuo*. The remaining residue was purified by column chromatography.

5-(5S)-[(9-Fluorenylmethoxycarbonyl)amino]methyl-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (**16**)

9-Fluorenylmethanol (2.47 g, 12.6 mmol) and **4** (4.05 g, 14.5 mmol) were heated in dry chloroform (50 cm^3) for 40 h under reflux. The reaction mixture was concentrated under reduced pressure to 10 cm^3. After addition of petroleum ether (90 cm^3) the product crystallized to give colorless, fine needles. Yield 4.95 g (83%) **16**, mp 116–117°C; $R_f = 0.59$ (ethyl actate:petroleum ether = 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.71$ (m, 1H, $CH_2{}^{Ise}$), 3.81 (m, 1H, $CH_2{}^{Ise}$), 4.26 (t, 1H, $J = 6.6$ Hz, CH^{Fmoc}), 4.45–4.55 (m, 2H, $CH_2{}^{Fmoc}$), 4.82 (m, 1H, CH^{Ise}), 5.14 (br.t, 1H, NH^{Ise}), 7.36 (t, 2H, $J = 7.5$ Hz), 7.45 (t, 2H, $J = 7.5$ Hz), 7.61 (d, 2H, $J = 7.5$ Hz), 7.81 (d, 2H, $J = 7.5$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -3.0$ (m, 3F, CF_3), -2.80 (m, 3F, CF_3); for further data see Ref. [31a].

Allyl N-(9-Fluorenylmethoxycarbonyl)isoserinate (**17**, $C_{21}H_{21}NO_5$)

A solution of **16** (1.19 g, 2.50 mmol) and allyl alcohol (7.5 cm^3) in chloroform (15 cm^3) was heated under reflux for 2 d. The volatiles were distilled off under reduced pressure and the residue was purified by column chromatography (ethyl acetate:petroleuum ether = 1:1, $R_f = 0.34$). Yield 779 mg (85%) **17**, crystalline solid, mp 119–121°C; $[\alpha]_D = +3°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.6$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.57$–3.71 (m, 2H, $CH_2{}^{Ise}$), 4.26 (t, 1H, $J = 6.9$ Hz, CH^{Fmoc}), 4.32 (m, 1H, CH^{Ise}), 4.38 (d, 2H, $J = 6.9$ Hz, $CH_2{}^{Fmoc}$), 4.68 (d, 2 H, $J = 4.5$ Hz, $OCH_2{}^{All}$), 5.22 (br.t, 1H, NH^{Ise}), 5.26 (m, 1H, $^3J_{cis} = 10.5$ Hz, $=CH_2{}^{All}$), 5.34 (m, 1H, $^3J_{trans} = 17.1$ Hz, $=CH_2{}^{All}$), 5.91 (m, 1H, $=CH\text{-}^{All}$), 7.32 (t, 2H, $J = 7.5$ Hz), 7.40 (m, 2H), 7.58 (d, 2H, $J = 7.5$ Hz), 7.76 (d, 2H, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 44.33$ ($CH_2{}^{Ise}$), 47.25 (CH^{Fmoc}), 66.74, 67.14 ($OCH_2{}^{All}$, $CH_2{}^{Fmoc}$), 70.20 (CH^{Ise}), 119.47 ($=CH_2{}^{All}$), 120.05, 125.10, 127.11, 127.76, 131.22 ($=CH\text{-}^{All}$), 141.33, 143.84, 156.66, 172.66 ppm; IR (KBr): $\bar{\nu} = 3400$, 1740, 1697, 1541 cm; MS (FAB): $m/z = 368.2$ $[M + H]^+$.

Allyl 3-[(9-Fluorenylmethoxycarbonyl)amino]-2-(2S)-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)oxy]propionate (**18a-β**, $C_{35}H_{39}NO_{14}$)

17 (250 mg, 0.68 mmol) and 2,3,4,6-tetra-O-acetyl-α-*D*-glucopyranosyl trichloroacetimidate (402 mg, 0.82 mmol) were reacted due to protocol 5. Purification by flash chromatography ($CHCl_3$: acetone = 10:1, $R_f(\alpha) = 0.26$, $R_f(\beta) = 0.22$). Yield 62 mg (13%) of a 1:1 mixture of **18a-α** and **18a-β** and 310 mg (65%) **18a-β**, foam; $[\alpha]_D = -21^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.5$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 2.05$ (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H) (OAc), 3.54–3.66 (m, 2H, CH_2^{Ise}, 5-H), 3.73 (m, 1H, CH_2^{Ise}), 4.11 (dd, 1H, $J = 1.8$, 12.0 Hz, 6-H_a), 4.17 (dd, 1H, $J = 4.8$, 12.0 Hz, 6-H_b), 4.24 (t, 1H, $J = 6.9$ Hz, CH^{Fmoc}), 4.38–4.48 (m, 3H, CH_2^{Fmoc}, CH^{Ise}), 4.56 (d, 1H, $J = 8.1$ Hz, 1-H), 4.67 (d, 2H, $J = 5.7$ Hz, OCH_2^{All}), 5.07 (dd, 1H, $J = 8.1$, 9.6 Hz, 2-H), 5.08 (dd, 1H, $J = 9.6$, 9.6 Hz, 4-H), 5.25–5.40 (m, 4H, 3-H, NH^{Ise}, $=CH_2^{All}$), 5.95 (m, 1H, $=CH\text{-}^{All}$), 7.33–7.48 (m, 4H), 7.62–7.66 (m, 2H), 7.78–7.81 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, HETCOR): $\delta = 20.89$ (2C), 21.02 (2C) (OAc), 43.25 (CH_2^{Ise}), 47.51 (CH^{Fmoc}), 61.98 (6-CH_2), 66.42 (OCH_2^{All}), 66.97 (CH_2^{Fmoc}), 68.60, 71.27 (4/2-CH), 72.18 (5-CH), 72.49 (3-CH), 76.23 (CH^{Ise}), 100.40 (1-CH), 119.53 ($=CH_2^{All}$), 120.25, 125.36, 127.36, 128.01, 131.62 ($=CH\text{-}^{All}$), 141.56, 144.14, 156.57, 168.88, 169.89, 170.13, 170.42, 170.82 ppm; IR (KBr): $\bar{\nu} = 1753$, 1634, 1523 cm^{-1}; MS (FAB): $m/z = 736.2$ $[M + K]^+$, 720.2 $[M + Na]^+$, 698.2 $[M + H]^+$.

Allyl 3-[(9-Fluorenylmethoxycarbonyl)amino]-2-(2S)-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxy]propionate (**18b-β**, $C_{35}H_{39}NO_{14}$)

17 (231 mg, 0.63 mmol) and 2,3,4,6-tetra-O-acetyl-α-*D*-galactopyranosyl trichloroacetimidate (373 mg, 0.76 mmol) were reacted due to protocol 5. Purification by flash chromatography ($CHCl_3$:acetone = 9:1, $R_f(\alpha) = 0.32$, $R_f(\beta) = 0.28$). Yield 43 mg (9%) of a 1:1 mixture of **18b-α** and **18b-β** and 312 mg (71%) **18b-β**, foam; $[\alpha]_D = -12^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 1.97$ (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H) (OAc), 3.57 (m, 1H, CH_2^{Ise}), 3.68–3.78 (m, 3H, CH_2^{Ise}, 5-H), 4.05–4.09 (m, 2H, 6-H_2), 4.25 (t, 1H, $J = 6.6$ Hz, CH^{Fmoc}), 4.42 (m, 1H, CH^{Ise}), 4.46–4.55 (m, 3H, 1-H, CH_2^{Fmoc}), 4.65–4.70 (m, 2H, OCH_2^{All}), 5.07 (dd, 1H, $J = 3.3$, 10.2 Hz, 3-H), 5.25 (dd, 1H, $J = 7.8$, 10.2 Hz, 2-H), 5.29–5.41 (m, 3H, 4-H, $=CH_2^{All}$), 5.45 (br.t, 1H, NH^{Ise}), 7.32–7.46 (m, 4H), 7.64–7.67 (m, 2H), 7.81 (d, 2H, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.76$, 20.87, 20.91, 21.15 (OAc), 43.36 (CH_2^{Ise}), 47.51 (CH^{Fmoc}), 61.58 (6-CH_2), 66.43 (OCH_2^{All}), 66.78 (CH_2^{Fmoc}), 67.13 (4-CH), 68.83 (2-CH), 70.68 (3-CH), 71.08 (5-CH), 76.42 (CH^{Ise}), 101.00 (1-CH), 119.56 ($=CH_2^{All}$), 120.27, 125.29, 127.39, 128.02, 131.61 ($=CH\text{-}^{All}$), 141.63, 144.15, 156.63, 168.88, 170.40 (2C), 170.49, 170.62 ppm; IR (KBr): $\bar{\nu} = 1745$–1717, 1523 cm^{-1}; MS (FAB): $m/z = 720.2$ $[M + Na]^+$, 698.2 $[M + H]^+$.

3-[9-Fluorenylmethoxycarbonyl)amino]-2-(2S)-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)oxy]propionic acid (**19a**, $C_{32}H_{35}NO_{14}$)

18a-β (140 mg, 0.20 mmol) was deprotected due to protocol 6. Purification by flash chromatography (eluent 1: $CHCl_3$:*Me*OH:*Ac*OH = 100:5:1, $R_f = 0.25$; eluent 2: $CHCl_3$:acetone:*Ac*OH = 20:20:1, $R_f = 0.34$). Yield 88 mg (67%), foamy solid; $[\alpha]_D = -14^\circ\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.6$, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.89$ (s, 3H), 2.02 (s, 6H), 2.06 (s, 3H) (OAc), 3.52–3.68 (m, 3H, CH_2^{Ise}, 5-H), 4.04 (dd, 1H, $J = 1.8$, 12.0 Hz, 6-H_a), 4.11 (dd, 1H, $J = 4.5$, 12.0 Hz, 6-H_b), 4.18 (t, 1H, $J = 6.6$ Hz, CH^{Fmoc}), 4.39 (d, 2H, $J = 6.6$ Hz, CH_2^{Fmoc}), 4.50 (d, 1H, $J = 7.8$ Hz, 1-H), 4.98–5.05 (m, 2H, 2,4-H), 5.25 (dd, 1H, $J = 9.6$, 9.6 Hz, 3-H), 5.47 (t, $J = 5.5$ Hz, NH^{Ise}), 7.28–7.42 (m, 4H), 7.58–7.61 (m, 2H), 7.74–7.77 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.70$ (2C), 20.73, 20.81 (OAc), 43.17 (CH_2^{Ise}), 47.27 (CH^{Fmoc}), 61.79 (6-CH_2), 66.91 (CH_2^{Fmoc}), 68.38, 71.21, 71.89, 72.29 (2,3,4,5-CH), 76.21 (CH^{Ise}), 100.31 (1-CH), 120.10, 125.24, 127.22, 127.89, 141.38, 143.89, 156.82,

169.56, 170.25, 170.34, 170.73, 171.69 ppm; IR (KBr): $\bar{\nu} = 1751$, 1630, 1522 cm^{-1}; MS (FAB): $m/z = 696.2$ $[M + K]^+$, 680.2 $[M + Na]^+$, 658.2 $[M + H]^+$.

3-[9-Fluorenylmethoxycarbonyl)amino]-2-(2S)-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxy]propionic acid (**19b**, $C_{32}H_{35}NO_{14}$)

18b-β (140 mg, 0.20 mmol) was deprotected due to protocol 6. Purification by flash chromatography ($CHCl_3$:*Me*OH:*Ac*OH = 100:5:1, $R_f = 0.26$). Yield 99 mg (75%), foamy solid; $[\alpha]_D = -10° \, cm^3 \, g^{-1} \, dm^{-1}$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.89$ (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 2.13 (s, 3H) (OAc), 3.52–3.68 (m, 3H, CH_2^{Ise}, 5-H), 3.96–4.00 (m, 2H, 6-H_2), 4.18 (t, 1H, $J = 6.6$ Hz, CH^{Fmoc}), 4.29 (m, 1H, CH^{Ise}), 4.37 (d, 1H, $J = 7.8$ Hz, 1-H), 4.39–4.48 (m, 2H, CH_2^{Fmoc}), 5.01 (dd, 1H, $J = 3.3$, 10.2 Hz, 3-H), 5.17 (dd, 1H, $J = 7.8$, 10.2 Hz, 2-H), 5.32 (d, 1H, $J = 3.3$ Hz, 4-H), 5.57 (br.t, 1H, NH^{Ise}), 7.28–7.42 (m, 4H), 7.58–7.61 (m, 2H), 7.75 (d, 2H, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.52$, 20.70 (2C), 20.92 (OAc), 43.38 (CH_2^{Ise}), 47.24 (CH^{Fmoc}), 61.46 (6-CH_2), 66.74, 66.97, 68.85, 70.36, 70.81 (CH_2^{Fmoc}, 2,3,4,5-CH); 76.61 (CH^{Ise}), 100.89 (1-CH), 120.11, 125.20, 127.25, 127.89, 141.38, 143.85, 156.94, 170.25, 170.34, 170.49, 170.59, 172.34 ppm; IR (KBr): $\bar{\nu} = 1747$, 1628, 1531 cm^{-1}; MS (FAB): $m/z = 696.1$ $[M + K]^+$, 680.2 $[M + Na]^+$, 658.2 $[M + H]^+$.

Allyl 2-(2S)-Hydroxy-3-[3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)ureido]propanoate (**20**, $C_{21}H_{30}N_2O_{13}$)

A mixture of **6a-β** (507 mg, 0.81 mmol) and allyl alcohol (3 cm^3) in dry chloroform (3 cm^3) was heated under reflux for 2 d. After removal of the volatiles under reduced pressure, the residue was purified by flash chromatography (ethyl acetate, $R_f = 0.36$). Yield 306 mg (73%), colorless foam, which was contaminated by 5–10% of the α-anomer; $[\alpha]_D = -4° \, cm^3 \, g^{-1} \, dm^{-1}$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.00$ (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H) (OAc), 3.52–3.66 (m, 2H, CH_2^{Ise}), 3.82 (ddd, 1H, $J = 2.1$, 4.8, 9.9 Hz, 5-H), 4.08 (dd, 1H, $J = 1.8$, 12.3 Hz, 6-H_a), 4.30 (dd, 1H, $J = 4.8$, 12.3 Hz, 6-H_b), 4.33 (m, 1H, CH^{Ise}), 4.68 (d, 2H, $J = 5.7$ Hz, OCH_2^{All}), 4.91 (dd, 1H, $J = 9.6$, 9.6 Hz), 5.05 (dd, 1H, $J = 9.9$, 9.3 Hz), 5.13 (dd, 1H, $J = 9.3$, 9.6 Hz) (4,2,1-H), 5.25–5.37 (m, 3H, $=CH_2^{All}$, 3-H), 5.43 (t, 1H, $J = 6.0$ Hz, NH^{Ise}), 5.78 (d, 1H, $J = 9.3$ Hz, 1-NH), 5.91 (m, 1H, $=CH\text{-}^{All}$) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT): $\delta = 20.83$, 20.86, 21.00 (2C) (OAc), 43.88 (CH_2^{Ise}), 62.18 (6-CH_2), 66.71 (OCH_2^{All}), 68.57, 70.79, 70.90, 73.34 (2C) (2,3,4,5-CH, CH^{Ise}), 80.13 (1-CH), 119.49 ($=CH_2^{All}$), 131.64 ($=CH\text{-}^{All}$), 157.57, 169.98, 170.22, 171.05, 171.32, 173.10 ppm; IR (KBr): $\bar{\nu} = 3400$, 1700, 1684, 1635, 1542 cm^{-1}; MS (FAB): $m/z = 519.2$ $[M + H]^+$.

Allyl 2-(2S)-[(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)oxy]-3-[3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)ureido]propanoate (**21**, $C_{35}H_{48}N_2O_{22}$)

20 (160 mg, 0.31 mmol) and 2,3,4,6-tetra-O-acetyl-α-*D*-glucopyranosyl trichloroacetimidate (183 mg, 0.37 mmol) were reacted due to protocol 5. Purification by flash chromatography (gradient elution, $CHCl_3$:acetone = 5:1 → 3:1, $R_f = 0.28$). Yield 130 mg (49%), foamy solid, $[\alpha]_D = +1° \, cm^3 \, g^{-1} \, dm^{-1}$ ($c = 1.0$, DCM); ^{1}H NMR($CDCl_3$, 300 MHz, COSY): $\delta = 1.99$–2.14 (several s, OAc), 3.46–3.54 (m, 1H, CH_2^{Ise}), 3.64–3.74 (m, 2H, CH_2^{Ise}, 5- or 5′-H), 3.81 (ddd, 1H, $J = 2.1$, 4.2, 10.2 Hz, 5- or 5′-H), 4.07 (dd, 2H, $J = 2.1$, 12.3 Hz, 6-H_a, 6′-H_b), 4.23–4.31 (m, 2H, CH^{Ise}, 6-H_b or 6′-H_b), 4.52 (d, 1H, $J = 8.1$ Hz, 1′-H), 4.50 (dd, 1H, $J = 2.1$, 12.6 Hz, 6-H_b or 6′-H_b), 4.52 (d, 1H, $J = 8.1$ Hz, 1′-H), 4.60 (d, 2H, $J = 5.7$ Hz, OCH_2^{All}), 5.90 (dd, 1H, $J = 9.3$, 9.6 Hz, 2-H), 4.98 (dd, 1H, $J = 8.1$, 9.3 Hz, 2′-H), 5.02–5.31 (m, 8H, 4,4′,1,3,3′-H, NH^{Ise}, $=CH_2^{All}$), 5.88 (m, 1H, $=CH\text{-}^{All}$), 6.03 (d, 1H, $J = 9.6$ Hz, 1-NH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, APT, HECTCOR): $\delta = 20.86$ (4C), 20,99 (2C), 21.09, 21.15 (OAc), 42.32 (CH_2^{Ise}), 61.34, 62.12 (6,6′-CH_2), 66.43 (OCH_2^{All}), 68.22, 68.49 (4,4′-CH), 70.79, 71.18

(2-,2′-H), 72.35 (3- or 3′-H), 77.47 (CH_2^{Ise}), 72.44, 73.19 (5, 5′-H), 73.52 (3-, 3′-H), 77.47 (CH^{Ise}), 80.17 (1-CH), 100.89 (1′-H), 119.49 (=CH_2^{All}), 131.61 (=CH-^{All}), 156.70, 168.82, 169.60, 169.88, 170.22, 170.40, 170.45, 170.60. 170.91, 171.73 ppm; IR (KBr): $\bar{\nu} = 1751$, 1697–1633, 1558 cm^{-1}; MS (FAB): $m/z = 871.3$ $[M + Na]^+$, 849.3 $[M + H]^+$.

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