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New synthetic approaches to sugar ureas. Access to ureido-β-cyclodextrins

Óscar López, Susana Maza, Inés Maya, José Fuentes and José G. Fernández-Bolaños*

Departamento Química Orgánica, Facultad Química, Universidad Sevilla, Apartado 553, E-41071 Seville, Spain

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Abstract—An efficient method for the preparation of urea-bridged cyclodextrins using triphosgene in the isocyanation step in an aqueous two-phase system is reported. Per-*O*-acetylated glycopyranosylamines and 2-amino-2-deoxy-α and β-D-glucose were also transformed into the corresponding isocyanates using either an aqueous two-phase or an anhydrous dichloromethane medium, and converted in situ into ureas. An alternative method for the preparation of sugar-derived ureas consisting of desulfurization of sugar thioureas with mercury oxide is also presented.

1. Introduction

Urea functionality is a structural feature present in many biologically active compounds, such as anti-mycobacterial[1] and anti-trypanosomal[2] agents, plant and insect growth regulators,[3,4] and as antagonists of natural receptors.[5,6] Several ureido derivatives have also proved to be anti-tumor agents,[7–9] and to inhibit HIV protease[10–15] and glycine transporter GlyT-2.[16]

In the carbohydrate field, pseudooligosaccharides incorporating a urea bridge have been found in glycocinnamoyl spermidine antibiotics.[17] Synthetic *N*-nitrosoureas derived from aminosugars have shown to be useful as antitumorals[18] and naturally-occuring streptozotocin,[19] a *N*-nitrosourea derived from 2-amino-2-deoxy-D-glucose, is widely used to induce diabetes mellitus in experimental animals.[20] Furthermore, some ureido glycuronate derivatives have shown to be α-glucosidase inhibitors[21] and *N*-acyl-*N*′-β-D-glucopyranosyl ureas exhibit strong inhibition against glycogen phosphorylase,[22] and so they could act as antidiabetic agents.[23]

Cyclodextrins are cyclic oligosaccharides that possess practical applications in medicinal[24] and supramolecular chemistry.[25] For instance, they are able to form complexes, improving solubilization and bioavailability of lipophilic drugs,[26,27] and they have also been used in the design of artificial enzymes[28,29] and for separation of enantiomers.[30] Much effort has been devoted to the preparation of cyclodextrin dimers[31] in order to improve the binding properties of the parent structure.[28] For this purpose, many different linkages have been introduced[32] in the preparation of dimers, among which we can find the urea tether.[33]

Sugar ureas have often been obtained by reaction of glycosylamines or amino sugars with alkyl or aryl isocyanates[34,35] in anhydrous solvents. The synthesis of fully *O*-protected sugar isocyanates has also been reported by Jochims[36] by reaction of *O*-protected amino sugars and toxic phosgene in anhydrous toluene.

To avoid handling hazardous phosgene, other methods to afford sugar ureas have been developed. These methods involve the use of aryl carbamates derived from amino sugars,[37] the use of phosphinimines[38] or carbodiimides[39] as intermediates, or the oxidation of glycosyl isocyanides with pyridine *N*-oxide proposed by Ichikawa et al.[40] By the last procedure, Prosperi et al. have described the synthesis of nonsymmetrical urea-linked disaccharides in which two glycopyranoside units are bound at the 1→2, 1→4, and 1→6 positions.[41]

Recently, we have communicated[42] our preliminary results on the one-pot two-phase preparation of sugar-derived ureas, including cyclodextrin derivatives. Ureas were obtained starting from sugar amines and glycopyranosylamines by using triphosgene[43] in the isocyanation step. Herein we report the full details of this procedure and our results of a different approach to access sugar ureas, based

Keywords: Cyclodextrin; Triphosgene; Sugar isocyanates; Ureas; Mercury oxide; Two-phase system.
* Corresponding author. Tel.: +34 95 4557151; fax: +34 95 4624960; e-mail: bolanos@us.es

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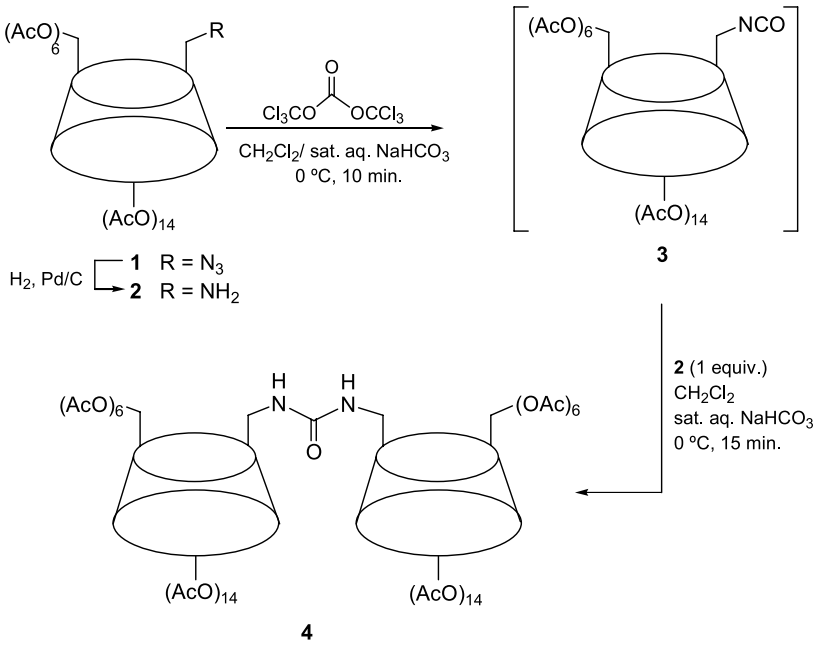


Scheme 1.

on desulfurization of sugar thioureas through non-isolated carbodiimides. Fischer's per-*O*-acetylated β-D-glucopyranosyl isocyanate **20**,[44] which we use without isolation in the synthesis of β-D-glucopyranosyl ureas, has been recently prepared as a crystalline form from the *O*-protected β-D-glucopyranosylamine with triphosgene under Schotten-Baumann conditions.[45]

2. Results and discussion

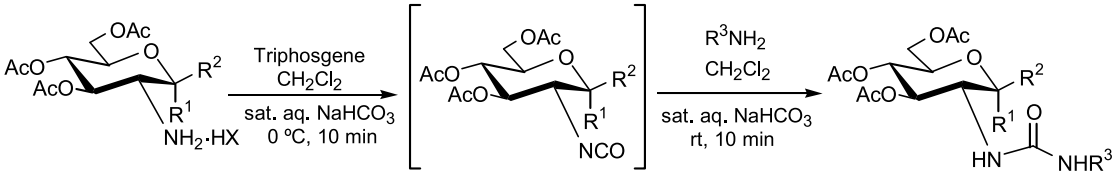
We have carried out the synthesis of β-cyclodextrin dimer **4** starting from per-*O*-acetylated 6^A-azido-6^A-deoxy-β-cyclodextrin **1**,[46] which was prepared in three steps from β-cyclodextrin: monotosylation with 1-(*p*-toluenesulfonyl)-imidazole,[47] acetylation and displacement of the tosyloxy group with sodium azide (Scheme 1).

Compound **1** was hydrogenated in the presence of palladium over charcoal to afford monoamino derivative **2**, which was used without further purification for the isocyanation step; thus, crude **2** was dissolved in a vigorously stirred 1:1 CH_2Cl_2–saturated aqueous $NaHCO_3$ mixture at 0 °C, to which solid triphosgene was added. After 15 min of stirring at 0 °C, another equivalent of monoamino **2** was added to afford β-cyclodextrin dimer **4** in a 49% yield for the three steps (hydrogenation, isocyanation of the amine and coupling with the same amine). The overall yield for the preparation of **4** is comparable to a recently described procedure[48] involving a polymer-bound triphenylphosphine, carbon dioxide and azide **1**.

The same method was applied to the preparation of per-*O*-acetylated 6-monodeoxy-6-mono[3-(β-D-glucopyranos-2-yl)ureido]-β-cyclodextrin **15** starting from readily available hydrochloride **6**[49] (Scheme 2). Treatment of compound **6** with triphosgene under the conditions described above led to isocyanate **8** which was used in situ for coupling with amine **2** to give β-cyclodextrin-derived urea **15** in a 46% yield, calculated from azide **1**.

Similarly, 2-ureido-α and β-D-glucopyranoses **9**, **10**, **12** and **13** and urea-linked symmetrical pseudo-disaccharides **11** and **14** were obtained (Scheme 2) in good yields (63–86%) starting from 2-amino-2-deoxy-D-glucopyranose hydrohalides of α- and β-configurations **5**[50] and **6**, and using alkyl and arylamines or the same hydrohalide for the coupling reaction with the non-isolated isocyanates **7** and **8** (Table 1, Method A).

Isocyanates **7** and **8** were obtained as syrups in quantitative yields by extraction with dichloromethane after the isocyanation step. NMR spectra of crude **7** and **8** showed no impurities; however, column chromatography of these



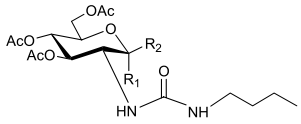
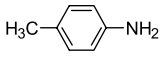
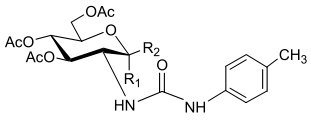
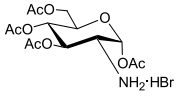
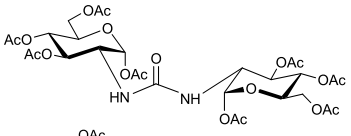
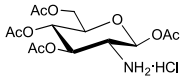
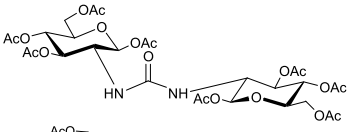
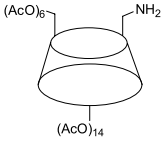
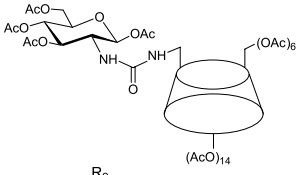
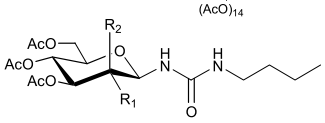
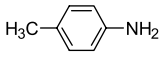
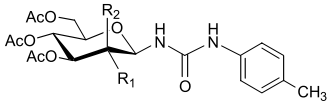
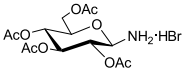
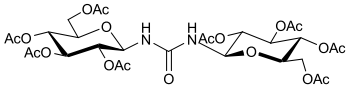
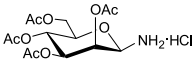
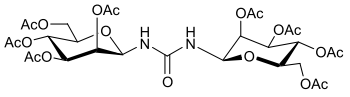
5 R^1=OAc, R^2=H, X=Br
6 R^1=H, R^2=OAc, X=Cl

7 R^1=OAc, R^2=H
8 R^1=H, R^2=OAc

9-11 R^1=OAc, R^2=H
12-15 R^1=H, R^2=OAc

Scheme 2.

Table 1. Synthesis of ureas **9–15** and **22–27**

Entry	Amines	Products	Ureas	Method	
				A[a]	B[b]
1	$CH_3(CH_2)_3NH_2$		**9** **12**	73[c] 86	58[c] —
2			**10** **13**	63 86	66 —
3			**11**	82	62
4			**14**	78	—
5			**15**	46	—
6	$CH_3(CH_2)_3NH_2$		**22** **25**	63 71	65 —
7			**23** **26**	66 58	64 —
8			**24**	99	54
9			**27**	69	—

[a] Biphasic CH_2Cl_2/water reaction conditions.
[b] Monophasic anhydrous CH_2Cl_2 reaction conditions.
[c] Isolated yields.

isocyanates led to extensive decomposition. Resonances at 125.9 and 126.7 ppm, for compounds **7** and **8** in ^{13}C NMR (Table 2), together with strong IR absorbtions at 2261 and 2253 cm^{-1}, respectively, confirm the presence of a –NCO moiety. These data are in agreement to those found for Fischer's isocyanate **20**,[44] studied spectroscopically by Ichikawa.[45]

Following the same one-pot biphasic procedure we have also carried out the preparation of per-*O*-acetylated glycopyranosyl ureas of D-*gluco* and D-*manno* configuration (Scheme 3). Crystalline hydrobromide **18**[51] was prepared from compound **16** after removal of the enamino group by oxidation with bromine in moist dichloromethane. Compound **18** was treated subsequently with triphosgene and with several amines in the biphasic medium to afford ureas **22–24**, via the non-isolated isocyanate **20**, in a 63–99% yield calculated from **18** (Table 1, Method A).

As hydrohalide **19**[52,53] could not be obtained as a crystalline product, the enamino group of compound **17** was removed by adding aliquots of a saturated solution of Cl_2 in moist CH_2Cl_2 at 0 °C over a 2 h period, until disappearance of the starting material by TLC. After solvent removal, crude hydrohalide **19** was directly used for the next two steps (isocyanation and coupling of isocyanate **21** with amines) to afford mannopyranosyl ureas **25–27** (Scheme 3) in a 58–71% overall yield for the three steps (Table 1, Method A). By-products formed in chlorolysis of enamine-derived **17** did not interfere with the following two steps. ^1H and ^{13}C NMR spectra of crude isocyanates **20**[45] and the hitherto unknown **21** (Table 2), obtained after the

Table 2. Selected data for isocyanates **7**, **8** and **21**

Compound	^{1}H and ^{13}C NMR data[a] (δ, ppm; J, Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
7	6.25	3.80	5.39	5.07	4.08	4.29	4.04
8	5.59	3.78	5.14	5.01	3.83	4.29	4.07
21	4.77	5.39	5.05	5.22	3.71	4.23	4.17
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
7	3.6	10.4	9.7	9.9	3.9	2.3	12.3
8	8.6	10.2	9.4	9.7	4.6	2.1	12.6
21	1.2	3.2	10.0	10.0	5.0	2.5	12.5
	C-1	C-2	C-3	C-4	C-5	C-6	NCO
7	89.9	55.6	71.9	67.3	69.8	61.3	125.9
8	92.4	56.8	73.3	67.5	72.9	61.3	126.7
21	81.7	69.4	70.8	65.2	74.5	62.3	129.6

[a] In $CDCl_3$.

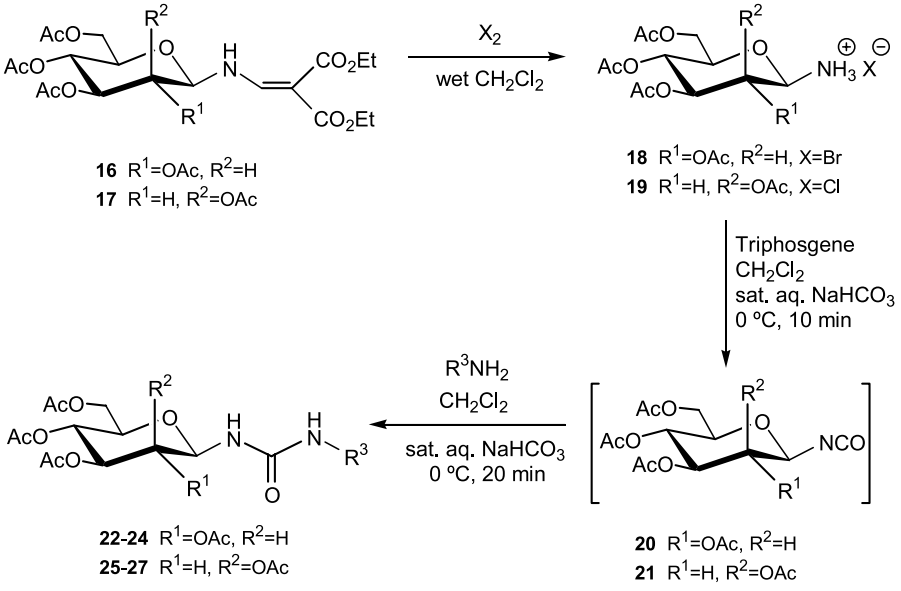
isocyanation step, showed these isocyanates to be the main products.

For the preparation of ureas **9**–**11**, and **22**–**24**, we also carried out the two steps (isocyanation and coupling with amines) in an anhydrous monophasic system. Thus, hydrohalides **5** and **18** were dissolved in dry dichloromethane containing 4 Å molecular sieves and diisopropylethylamine, and to the corresponding solutions at rt was dropwise added a solution of triphosgene in dry dichloromethane to give isocyanates **7** and **20**, respectively. These isocyanates were converted in situ into ureas **9**–**11** and **22**–**24** by addition of the corresponding amines in a 54–66% yield (Table 1, Method B). However, this procedure proved to be sensitive to moisture, and the use of molecular sieves proved to be essential for the yield of the reaction. Furthermore, the yields obtained by using anhydrous dichloromethane were in some examples lower than those obtained by the biphasic procedure (Table 1, Method A), despite moisture sensitivity associated to triphosgene and isocyanates.[54,55]

Finally, we have considered a third procedure for obtaining sugar ureas from the corresponding thioureas. They have been more extensively studied than the ureas counterparts due to easier preparation of sugar isothiocyanates[56] as compared to sugar isocyanates. This third procedure is based on the desulfurization of sugar thioureas by treatment with yellow mercury (II) oxide; these results contrast with the desulfurization of *O*-unprotected glucopyanosyl thioureas to afford trans-fused bicyclic isoureas.[57]

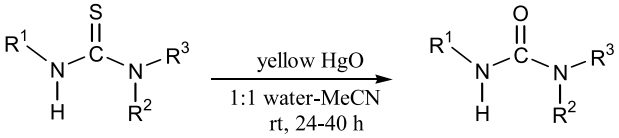
Treatment of thioureas **28**–**30** in aqueous acetonitrile with mercury oxide at rt for 1 h led to the corresponding carbodiimides, detected by TLC as a faster-moving compound; carbodiimides reacted slowly (24 h) at rt with water to give ureas **10**, **23** and **24** in a 67–74% yield (Table 3). For *N*,*N*-diethyl thiourea **31**, no carbodiimide was detected by TLC and a slower transformation (40 h) of thiourea into urea **32** took place in a 72% yield.

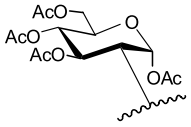
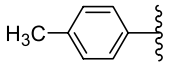
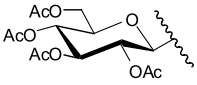
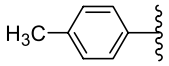
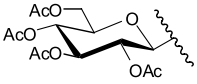
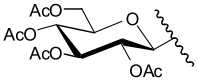
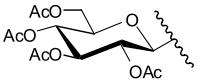
Per-*O*-acetylated thiourea **29** was prepared starting from thiourea **33**, easily available in a one-pot fashion from β-D-glucopyranosylamine.[57] Conventional acetylation of **33** at rt led regiospecifically to the new penta acetyl derivative **34** in



Scheme 3.

Table 3. Synthesis of ureas by desulfurization of thioureas **28–31**

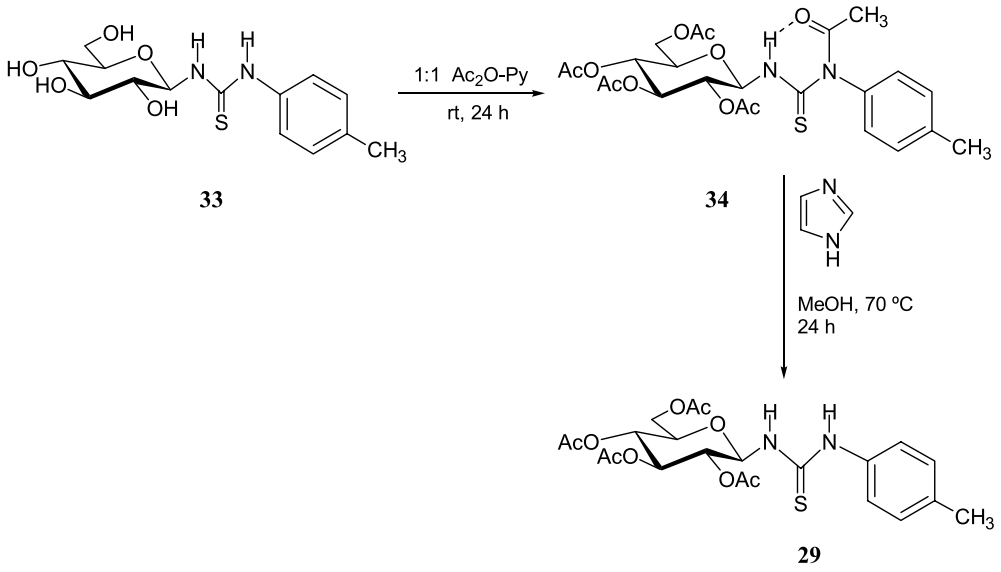


Entry	Thiourea	R^1	R^2	R^3	Urea	Yield (%)
1	**28**		H		**10**	67
2	**29**		H		**23**	74
3	**30**		H		**24**	68
4	**31**		CH_3CH_2–	CH_3CH_2–	**32**	72

a 73% yield (Scheme 4); probably due to steric hindrance no acetylation took place on the nitrogen attached to the sugar moiety. The strong deshielding exhibited by the NH proton in ^{1}H NMR of **34** (12.01 ppm) indicated the presence of an intramolecular hydrogen bonding with the carbonyl group of the vicinal *N*-acetyl moiety. Li et al. have recently reported[58] the use of imidazole as a mild base for the selective anomeric *O*-deacetylation of carbohydrates; using the same procedure we have carried out the selective *N*-deacetylation of **34** to give tetra-*O*-acetylated **29** in a 86% yield (Scheme 4).

Tetra-*O*-acetyl thioureas **28**, **31** and known **30**[51] were prepared by coupling reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocianato-α-D-glucopyranose[59] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate[51] with the corresponding amines in EtOAc at rt.

In conclusion, we report a practical one-pot two-step synthesis in an aqueous two-phase system of urea-tethered cyclodextrin dimer **4** and of 6-monodeoxy-6-mono(*N*′-glucopyranos-2-ylureido)-β-cyclodextrin **15** through non-isolated sugar isocyanates. This procedure was also successfully applied to the preparation of other symmetrical and unsymmetrical *N*,*N*′-disubstituted sugar ureas including pseudodisaccharides with a (1→1) or (2→2) urea linkage. An anhydrous monophasic system was also used for the two-step synthesis, although the yields were generally lower. We also report the desulfurization of *O*-protected sugar thioureas with yellow mercury (II) oxide in aqueous



33 **34** **29**

Scheme 4.

acetonitrile as an alternative pathway for the preparation of sugar ureas.

3. Experimental

3.1. General procedures

Melting points were recorded on an Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter, and IR spectra (KBr disks) were obtained with an FT-IR Bomem MB-120 spectrophotometer. ^{1}H (300 and 500 MHz) and ^{13}C (75.5 and 125.7 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers. The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. Mass spectra (EI, CI and FAB) were recorded on Kratos MS80-RFA and Micromass AutoSpec-Q mass spectrometers with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using thioglycerol as matrix and NaI as salt. MALDI spectra were recorded with a TOFSPEC spectrometer. TLC was performed on aluminium pre-coated sheets (E. Merck Silica Gel 60 F_{254}); spots were visualized by UV light, by charring with 10% H_2SO_4 in EtOH. Column chromatography was performed using E. Merck Silica Gel 60 (40–63 μm).

3.2. *N*,*N*′-Bis[icosa-*O*-acetyl-6^{A}-deoxy-β-cyclodextrin-6^{A}-yl]urea (4)

A solution of 6^{A}-azido-6^{A}-deoxy-β-cyclodextrin **1** (260 mg, 0.13 mmol) in methanol (10 mL) was hydrogenated at atmospheric pressure by stirring with 10% Pd(C) catalyst for 2.5 h at rt. After filtration of the mixture through a Celite pad, the filtrate was concentrated to dryness to afford the crude amine **2** and divided into two equal portions. One portion was dissolved in an 1:1 CH_2Cl_2–saturated aqueous $NaHCO_3$ mixture (12 mL), cooled to 0 °C in an ice bath and treated with triphosgene (6.5 mg, 0.022 mmol). After 15 min of vigorous stirring the other portion of amine **2** was added and the stirring was maintained at rt for 15 min. Conventional work-up and column chromatography ($CH_2Cl_2 \rightarrow$40:1 CH_2Cl_2–MeOH) afforded cyclodextrin dimer **4** (127 mg, 49%) as a white amorphous powder, mp 172–178 °C; $[\alpha]_D^{26}$ +117 (*c* 1.1, CH_2Cl_2); lit.[33] $[\alpha]_D^{25}$ +121 (*c* 1.0, $CHCl_3$); IR ν_{max} 3300, 1748, 1541, 1433, 1371, 1233, 1042 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32–5.25 (m, 7H, H-3$^{A–G}$), 5.17 (d, 1H, $J_{1,2}$=3.5 Hz, H-1^{A}), 5.14–5.11 (m, 1H, NH), 5.10–5.05 (m, 6H, H-1$^{B–G}$), 4.87–4.71 (m, 7H, H-2$^{A–G}$), 4.58–4.49 (m, 6H, H-6a$^{B–G}$), 4.31–4.23 (m, 6H, H-6b$^{B–G}$), 4.18–4.11 (m, 6H, H-5$^{B–G}$), 3.98–3.94 (m, 1H, H-5^{A}), 3.88–3.82 (m, 1H, H-6a^{A}), 3.76–3.64 (m, 7H, H-4$^{A–G}$), 3.46–3.41 (m, 1H, H-6b^{A}), 2.14–2.03 (20 s, 60H, 20Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6–170.3, 169.6–169.3 (CH_3CO), 158.2 (CO urea), 96.9–96.7 (C-1), 77.8–76.5 (C-4$^{A–G}$), 71.2–69.4 (C-2$^{A–G}$, C-3$^{A–G}$, C-5$^{A–G}$), 62.9–62.4 (C-6$^{B–G}$), 40.4 (C-6^{A}), 20.8–20.6 (CH_3CO); MALDITOF-MS *m*/*z* 3980 $[M+H]^+$. Anal. Calcd for $C_{165}H_{220}N_2O_{109}$ $4H_2O$: C, 48.96; H, 5.68; N, 0.96, found: C, 48.72; H, 5.35; N, 0.89.

3.3. General methods for the synthesis of ureas 9–15, 22–27 and 32.

Method A. To a vigorously stirred solution of the hydrohalides **5**, **6** or **18** (0.6 mmol) in an 1:1 mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (12 mL) at 0 °C in an ice bath was added triphosgene (0.22 mmol); after 10 min of stirring, butylamine, *p*-toluidine, or the hydrohalides **5**, **6** or **18** (0.66 mmol) were added. For the preparation of D-glucosamine derived ureas **9–14** the coupling with the amines was performed at rt for 10 min; for the preparation of glycopyranosyl ureas **22–24** the coupling of the isocyanate with the amines was carried out at 0 °C for 20 min. Conventional work-up and column chromatography afforded ureas **9–14** and **22–24**. For the preparation of **15**, this procedure was carried out starting from hydrochloride **6** (0.13 mmol). Azide **1** (260 mg, 0.13 mmol) was hydrogenated as described in Section 3.2 to give amino cyclodextrin derivative **2**, which was added to the crude isocyanate **8** and the coupling reaction took place at rt for 15 min.

In the case of ureas **25–27**, to a solution of enamine **17** (0.6 mmol) in wet CH_2Cl_2 (10 mL) at 0 °C were added small portions of a saturated solution of Cl_2 in CH_2Cl_2 until disappearance of the starting material by TLC. Then the mixture was concentrated to dryness and the residue containing hydrochloride **19** was treated as described above to give ureas **25–27**.

Method B. To a stirred mixture of hydrohalides **5** or **18** (0.6 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.8 mmol) in CH_2Cl_2 (6 mL) containing 4 Å molecular sieves under Ar at rt was dropwise added a solution of triphosgene (0.2 mmol) in dry CH_2Cl_2 (3 mL) over 30 min. After a further 10 min of stirring a solution of butylamine or *p*-toluidine (0.6 mmol) in dry CH_2Cl_2 (3 mL) was added in one portion. In the case of adding the hydrohalides **5** or **18** (0.6 mmol), their solutions in CH_2Cl_2 (3 mL) had an extra portion of DIEA (1.2 mmol). The reaction mixture was stirred at rt for 10 min. Conventional work-up and column chromatography afforded ureas **9–11** and **22–24**.

Method C. To a solution of thioureas **28–31** (0.44 mmol) in 1:1 water–acetonitrile (20 mL) was added yellow mercury (II) oxide (572 mg, 2.64 mmol). The mixture was stirred at rt in the darkness for 24–40 h and then it was filtered through a Celite pad. The filtrate was concentrated to dryness and purified by column chromatography.

3.3.1. *N*-Butyl-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (9). *Method A*. Column chromatography ($CH_2Cl_2 \rightarrow$40:1 CH_2Cl_2–MeOH) gave **9**: 196 mg, 73% as a syrup.

Method B. Column chromatography gave **9**: 150 mg, 58%. R_f=0.33 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{25}$ +62 (*c* 0.5, CH_2Cl_2); IR ν_{max} 3322, 2920, 1750, 1642, 1561, 1370, 1221, 1125, 1007 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, 1H, $J_{2,NH}$=9.2 Hz, NH′), 6.16 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 5.19–5.17 (m, 2H, H-3, H-4), 4.43 (t, 1H, J_{NH,CH_2}=5.5 Hz, NH), 4.31 (m, 1H, H-2), 4.22 (dd, 1H, $J_{5,6a}$=4.2 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.03 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b),

3.95 (m, 1H, H-5), 3.08 (m, 2H, $CH_2\alpha$), 2.14, 2.06, 2.02, 2.01 (4s, 12H, 4Ac), 1.40 (m, 2H, $CH_2\beta$), 1.29 (m, 2H, $CH_2\gamma$), 0.88 (t, 3H, $J=7.4$ Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.8, 170.7, 169.1, 168.6 (4 CO), 156.7 (CO urea), 91.5 (C-1), 71.2 (C-3), 69.7 (C-5), 67.6 (C-4), 61.7 (C-6), 52.0 (C-2), 40.3 ($CH_2\alpha$), 32.1 ($CH_2\beta$), 20.9, 20.8, 20.7, 20.5 (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 469 ([M+Na]$^+$, 100%), 915 ([2M+Na]$^+$, 10%); EI-MS *m/z* 446 ([M]$^+$, 1%); HREI-MS *m/z* calcd for [M]$^+$$C_{19}H_{30}N_2O_{10}$: 446.1900, found: 446.1897.

3.3.2. *N*-(*p*-Methylphenyl)-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (10). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **10** as a white solid: 182 mg, 63%.

Method B. Column chromatography gave **10**: 191 mg, 66%.

Method C. The mixture was stirred for 24 h and purified by column chromatography to give **10**: 128 mg, 67%; mp 184–188 °C; R_f 0.30 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ +103 (*c* 1.2, CH_2Cl_2); IR ν_{max} 3345, 1753, 1659, 1603, 1533, 1514, 1370, 1223, 1132, 926 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (m, 4H, Ar–H), 6.97 (s, 1H, NH), 6.23 (d, 1H, $J_{1,2}=$ 3.4 Hz, H-1), 5.19 (m, 2H, H-3, H-4), 4.41 (t, 1H, $J_{2,NH}=$ 8.1 Hz, NH′), 4.24 (m, 1H, H-2), 4.24 (dd, 1H, $J_{5,6a}=$ 4.0 Hz, $J_{6a,6b}=$12.4 Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}=$2.2 Hz, H-6b), 3.97 (m, 1H, H-5), 2.29 (s, 3H, CH_3), 2.08, 2.07, 2.03, 2.01 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.5, 170.8, 169.1, 168.7 (4CO), 155.2 (CO urea), 135.1, 134.3, 129.8, 121.7 (Ar), 91.2 (C-1), 70.9 (C-3), 69.7 (C-5), 67.6 (C-4), 61.6 (C-6), 51.7 (C-2), 20.7, 20.7, 20.7, 20.5 (*C*H_3Ar, 4Ac); FAB-MS *m/z* 503 ([M+Na]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$$C_{22}H_{28}N_2O_{10}$: 480.1744, found: 480.1740.

3.3.3. *N*,*N*′-Bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (11). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **11** as a white solid: 177 mg, 82%.

Method B. Column chromatography gave **11**: 134 mg, 62%; mp 193–194 °C; R_f 0.12 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{18}$ +115° (*c* 1.0, CH_2Cl_2); IR ν_{max} 3366, 2963, 1753, 1562, 1373, 1227, 1040, 926 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, $J_{1,2}=$3.6 Hz, H-1), 5.16 (t, 1H, $J_{3,4}=$10.0 Hz, $J_{4,5}=$9.8 Hz, H-4), 5.09 (t, 1H, $J_{2,3}=$10.5 Hz, H-3), 4.66 (d, 1H, $J_{2,NH}=$9.4 Hz, NH), 4.28 (ddd, 1H, H-2), 4.20 (dd, 1H, $J_{5,6a}=$4.1 Hz, $J_{6a,6b}=$12.5 Hz, H-6a), 4.02 (dd, 1H, $J_{5,6b}=$ 2.1 Hz, H-6b), 3.94 (ddd, 1H, H-5), 2.14, 2.06, 2.00 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.0, 170.7, 169.0, 168.6 (4CO), 155.5 (CO urea), 91.2 (C-1), 70.9 (C-3), 69.7 (C-5), 67.5 (C-4), 61.6 (C-6), 51.9 (C-2), 20.8, 20.7, 20.6, 20.5 (4Ac); FAB-MS *m/z* 743 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$$C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2296. Anal. Calcd for $C_{29}H_{40}N_2O$: C, 48.33; H, 5.59; N, 3.89, found: C, 48.13; H, 5.54; N, 3.96.

3.3.4. *N*-Butyl-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (12). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **12** as a syrup: 230 mg, 86%. R_f 0.33 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ +33 (*c* 0.8, CH_2Cl_2); IR ν_{max} 3356, 2926, 2870, 1769, 1665, 1582, 1370, 1044, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (d, 1H, $J_{1,2}=$8.5 Hz, H-1), 5.14–5.10 (m, 2H, H-3, H-4), 4.57 (d, 1H, $J_{2,NH}=$9.5 Hz, NH′), 4.55 (t, 1H, $J_{NH,CH_2}=$5.5 Hz, NH), 4.27 (dd, 1H, $J_{5,6a}=$5.0 Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}=$2.0 Hz, H-6b), 4.08 (m, 1H, H-2), 3.81 (m, 1H, H-5), 3.12 (m, 2H, $CH_2\alpha$), 2.12, 2.09, 2.05, 2.03 (4s, 12H, 4Ac), 1.43 (m, 2H, $CH_2\beta$), 1.31 (m, 2H, $CH_2\gamma$), 0.90 (t, 3H, $J=$7.1 Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.3, 170.7, 169.6, 169.3 (4CO), 157.0 (CO urea), 93.3 (C-1), 73.1, 72.9 (C-3, C-5), 67.9 (C-4), 61.8 (C-6), 54.2 (C-2), 40.2 ($CH_2\alpha$), 32.2 ($CH_2\beta$), 20.9, 20.7, 20.6, (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 469 ([M+Na]$^+$, 92%), 915 ([2M+Na]$^+$, 10%); HRCI-MS *m/z* calcd for [M+H]$^+$$C_{19}H_{31}N_2O_{10}$: 447.1978, found: 447.1981.

3.3.5. *N*-(*p*-Methylphenyl)-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (13). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **13**: 248 mg, 86% as a white solid; mp 184–186 °C; $[\alpha]_D^{18}$ +32 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3304, 2918, 1748, 1636, 1570, 1454, 1377, 1084, 1040, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.00 (m, 5H, Ar–H, NH), 5.78 (d, 1H, $J_{1,2}=$8.7 Hz, H-1), 5.27 (t, 1H, $J_{2,3}=$9.0 Hz, $J_{3,4}=$ 9.5 Hz, H-3), 5.25 (d, 1H, NH′), 5.10 (t, 1H, $J_{4,5}=$9.6 Hz, H-4), 4.25 (dd, 1H, $J_{5,6a}=$4.6 Hz, $J_{6a,6b}=$12.3 Hz, H-6a), 4.10 (dd, 1H, $J_{5,6b}=$1.5 Hz, H-6b), 4.05 (m, 1H, H-2), 3.82 (m, 1H, H-5), 2.27 (s, 3H, Me), 2.08, 2.06, 2.02 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.7, 169.5, 169.4 (4CO), 155.4 (CO urea), 135.4, 133.9, 129.8, 121.4 (Ar), 92.8 (C-1), 72.7 (C-3), 72.6 (C-5), 68.1 (C-4), 61.8 (C-6), 54.0 (C-2), 20.9, 20.8, 20.6 (*C*H_3Ar, 4Ac); FAB-MS *m/z* 480 ([M]$^+$, 22%), 503 ([M+Na]$^+$, 60%), 983 ([2M+Na]$^+$, 11%); HRFAB-MS *m/z* calcd for [M]$^+$$C_{22}H_{28}N_2O_{10}$: 480.1744, found: 480.1739. Anal. Calcd for $C_{22}H_{28}N_2O_{10}$: C, 55.00; H, 5.87; N, 5.83, found: C, 55.09; H, 5.90; N, 5.93.

3.3.6. *N*,*N*′-Bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (14). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **14** as a white solid: 169 mg, 78%. R_f 0.18 (40:1 CH_2Cl_2–MeOH); mp 218–220 °C; $[\alpha]_D^{22}$ +25 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3331, 2940, 1750, 1659, 1599, 1433, 1371, 1227, 1040, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, 1H, $J_{1,2}=$8.7 Hz, H-1), 5.22 (d, 1H, $J_{2,NH}=$8.9 Hz, NH), 5.18 (t, 1H, $J_{2,3}=$ 8.7 Hz, $J_{3,4}=$9.5 Hz, H-3), 5.10 (t, 1H, $J_{4,5}=$9.5 Hz, H-4), 4.26 (dd, 1H, $J_{5,6a}=$5.0 Hz, $J_{6a,6b}=$12.4 Hz, H-6a), 4.10 (q, 1H, H-2), 4.10 (dd, 1H, $J_{5,6b}=$1.5 Hz, H-6b), 3.83 (ddd, 1H, H-5), 2.08, 2.06. 2.03 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3, 170.6, 169.7, 169.4 (4CO), 156.2 (CO urea), 93.3 (C-1), 72.7 (C-3), 72.6 (C-5), 68.1 (C-4), 61.9 (C-6), 54.2 (C-2), 20.8, 20.7, 20.6 (4Ac); FAB-MS *m/z* 743 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$$C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2286. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$: C, 48.33; H, 5.59; N, 3.89, found: C, 48.37; H, 5.58; N, 3.93.

3.3.7. Icosa-*O*-acetyl-6^A-deoxy-6^A-[3-(1′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranos-2′-yl)ureido)]-β-cyclodextrin (15). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **15**: 140 mg, 46%, as a white solid; mp 146–152 °C; R_f 0.31 (40:1 CH_2Cl_2–MeOH, 2 elutions); $[\alpha]_D^{26}$ +101 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3295, 1746, 1520,

1456, 1366, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, 1H, $J_{1,2}=8.9$ Hz, H-1′), 5.35–5.21 (m, 8H, H-3^{A-G}, H-3′), 5.14 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 5.15–5.12 (m, 1H, NH), 5.10 (t, 1H, $J_{3',4'}=10.0$ Hz, H-4′), 5.09–5.06 (m, 5H, H-1^{B-F}), 4.98 (d, 1H, $J_{1,2}=3.0$ Hz, H-1), 4.94–4.91 (m, 1H, N*H*–CH_2), 4.89 (dd, 1H, $J_{1,2}=4.5$ Hz, $J_{2,3}=8.5$ Hz, H-2), 4.84 (dd, 1H, $J_{1,2}=4.0$ Hz, $J_{2,3}=9.7$ Hz, H-2), 4.81 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.0$ Hz, H-2), 4.80 (dd, 1H, $J_{1,2}=$ 3.5 Hz, $J_{2,3}=9.5$ Hz, H-2), 4.77 (dd, 1H, $J_{1,2}=4.1$ Hz, $J_{2,3}=9.5$ Hz, H-2), 4.75 (dd, 1H, $J_{1,2}=3.6$ Hz, $J_{2,3}=$ 9.5 Hz, H-2), 4.67 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.0$ Hz, H-2), 4.65–4.47 (m, 6H, H-$6a^{B-G}$), 4.33–4.22 (m, 7H, H-$6b^{B-G}$, H-6a′), 4.18–4.07 (m, 8H, H-5^{B-G}, H-2′, H-6b′), 4.01–3.97 (m, 1H, H-5^{A}), 3.94–3.89 (m, 1H, H-5′), 3.76–3.59 (m, 8H, H-4^{A-G}, H-$6a^{A}$), 3.47–3.42 (m, 1H, H-$6b^{A}$), 2.16–1.99 (24s, 72H, 24Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.5, 170.9–170.3, 169.6–169.3 (24CO), 157.7 (CO urea), 97.4, 97.0, 96.9, 96.9, 96.8, 96.5, 96.5 (C-1^{A-G}), 92.8 (C-1′), 78.4 (C-4^{A}), 77.2–76.1 (C-4^{B-G}), 72.8 (C-5′), 72.4 (C-3′), 71.5–69.0 (C-2^{A-G}, C-3^{A-G}, C-5^{A-G}), 68.1 (C-4′), 63.0, 62.8, 62.8, 62.5, 62.4, 62.2 (C-6^{B-G}), 61.8 (C-6′), 54.0 (C-2′), 40.9 (C-6^{A}), 20.9–20.6 (24Ac); FAB-MS *m/z* 2370 ($[M+Na]^+$, 29%). Anal. Calcd for $C_{97}H_{130}N_2O_{64}$ $2H_2O$: C, 48.87; H, 5.67; N, 1.18, found: C, 48.50; H, 5.24; N, 1.31.

3.3.8. *N*-Butyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (22). *Method A*. Column chromatography (hexane→1:1 hexane–EtOAc) yielded **22** as a syrup: 169 mg, 63%.

Method B. Column chromatography yielded **22**: 174 mg, 65%. R_f 0.24 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{22}$ 0 (*c* 0.7, CH_2Cl_2); IR ν_{max} 3329, 2957, 1753, 1657, 1562, 1433, 1368, 1227, 1101, 1036, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.28 (m, 2H, $J_{1,NH'}=9.3$ Hz, $J_{2,3}=9.5$ Hz, $J_{3,4}=$ 9.5 Hz, NH′, H-3), 5.14 (t, 1H, $J_{1,2}=9.4$ Hz, H-1), 5.04 (t, 1H, $J_{4,5}=9.7$ Hz, H-4), 4.87 (t, 1H, H-2), 4.62 (t, 1H, $J_{NH,CH_2}=6.5$ Hz, NH), 4.30 (dd, 1H, $J_{5,6a}=4.3$ Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b}=1.8$ Hz, H-6b), 3.79 (ddd, 1H, H-5), 2.05, 2.03, 2.00, 1.99 (4s, 12H, 4Ac), 3.12 (q, 2H, $CH_2\alpha$), 1.43 (m, 2H, $CH_2\beta$), 1.29 (m, 2H, $CH_2\gamma$), 0.89 (t, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.7, 169.9, 169.6 (4 CO), 156.2 (CO urea), 80.2 (C-1), 73.1 (C-5), 72.9 (C-3), 70.6 (C-2), 68.3 (C-4), 61.8 (C-6), 40.2 ($CH_2\alpha$), 32.0 ($CH_2\beta$), 20.7, 20.6 (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 447 ($[M+H]^+$, 40%), 469 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1971.

3.3.9. *N*-(*p*-Methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (23). *Method A*. Column chromatography (hexane→1:1 hexane–EtOAc) yielded **23** as a white solid, 190 mg, 66%.

Method B. Column yielded **23**, 184 mg, 64%.

Method C. The mixture was stirred for 24 h and purified by column chromatography (hexane→1:1 hexane–EtOAc) to give **23**: 143 mg, 74%. R_f 0.22 (40:1 CH_2Cl_2–MeOH); mp 93–96 °C; $[\alpha]_D^{18}$ −17 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3189, 1746, 1645, 1575, 1393, 1092, 1034, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14–7.06 (m, 4H, Ar–H), 6.87 (s, 1H, NH), 5.74 (d, 1H, $J_{1,NH'}=9.3$ Hz, NH′), 5.29 (t, 1H, $J_{2,3}=9.6$ Hz, $J_{3,4}=9.5$ Hz, H-3), 5.21 (t, 1H, $J_{1,2}=9.4$ Hz, H-1), 5.03 (t, 1H, $J_{4,5}=10.0$ Hz, H-4), 4.89 (t, 1H, H-2), 4.29 (dd, 1H, $J_{5,6a}=4.5$ Hz, $J_{6a,6b}=12.5$ Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}=1.9$ Hz, H-6b), 3.79 (ddd, 1H, H-5), 2.28 (s, 3H, Me), 2.05, 2.02, 2.01, 1.99 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 170.7, 169.9, 169.6 (4CO), 154.4 (CO urea), 134.8, 129.8, 121.5 (Ar), 80.0 (C-1), 73.3 (C-5), 72.9 (C-3), 70.4 (C-2), 68.3 (C-4), 61.8 (C-6), 20.8, 20.7, 20.6 (*C*H_3Ar, 4*C*H_3CO); FAB-MS *m/z* 481 ($[M+H]^+$, 80%), 503 ($[M+Na]^+$, 45%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_{10}$: 481.1822, found: 481.1813. Anal. Calcd for $C_{22}H_{28}N_2O_{10}$ H_2O: C, 53.01; H, 6.07; N, 5.62, found: C, 53.33; H, 5.78; N, 5.37.

3.3.10. *N*,*N*′-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (24). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) yielded **24** as a white solid: 214 mg, 99%.

Method B. Column chromatography yielded **24**: 117 mg, 54%.

Method C. The mixture was stirred for 24 h and purified by column chromatography to give **24**: 197 mg, 68%. R_f 0.19 (40:1 CH_2Cl_2–MeOH); mp: 152–155 °C. $[\alpha]_D^{18}$ −5 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3362, 1750, 1543, 1435, 1370, 1229, 1036, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, 1H, $J_{1,NH}=9.1$ Hz, NH), 5.28 (t, 1H, $J_{1,2}=9.4$ Hz, $J_{2,3}=$ 9.5 Hz, H-2), 5.02 (m, 2H, $J_{3,4}=9.5$ Hz, $J_{4,5}=10.0$ Hz, H-1, H-4), 4.85 (t, 1H, H-3), 4.29 (dd, 1H, $J_{5,6a}=4.5$ Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}=2.0$ Hz, H-6b), 3.81 (ddd, 1H, H-5), 2.05, 2.04, 2.01, 1.99 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 170.6, 169.9, 169.6 (4CO), 155.3 (CO urea), 80.0 (C-1), 73.2 (C-5), 72.8 (C-2), 70.5 (C-3), 68.2 (C-4), 61.7 (C-6), 20.7, 20.6 (4*C*H_3CO); CI-MS *m/z* 721 ($[M+H]^+$, 9%); HRCI-MS *m/z* calcd for $[M+H]^+C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2290. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$ H_2O: C, 47.16; H, 5.73; N, 3.79, found: C, 47.10; H, 5.74; N, 3.55.

3.3.11. *N*-Butyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)urea (25). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) yielded **25** as a syrup: 190 mg, 71%. R_f 0.22 (1:1 hexane–EtOAc); $[\alpha]_D^{21}$ −19 (*c* 0.8, CH_2Cl_2); IR ν_{max} 3314, 2932, 1748, 1663, 1370, 1225, 1053, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (dd, 1H, $J_{1,2}=1.2$ Hz, $J_{1,NH'}=9.6$ Hz, H-1), 5.35 (dd, 1H, $J_{2,3}=$ 3.3 Hz, H-2), 5.26 (d, 1H, NH′), 5.20 (t, 1H, $J_{3,4}=10.0$ Hz, $J_{4,5}=9.8$ Hz, H-4), 5.08 (dd, 1H, H-3), 4.60 (t, 1H, $J_{NH,CH_2}=$ 6.6 Hz, NH), 4.30 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=12.4$ Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b}=2.3$ Hz, H-6b), 3.75 (ddd, 1H, H-5), 3.15 (q, 2H, $J=6.6$ Hz, $CH_2\alpha$), 2.18, 2.06, 2.02, 1.95 (4s, 12H, 4Ac), 1.44 (m, 2H, $CH_2\beta$), 1.30 (m, 2H, $CH_2\gamma$), 0.89 (t, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.4, 169.8, 169.7 (4CO), 155.9 (CO urea), 77.9 (C-1), 73.7 (C-5), 71.8 (C-3), 70.5 (C-2), 65.3 (C-4), 62.3 (C-6), 40.2 ($CH_2\alpha$), 30.0 ($CH_2\beta$), 20.9, 20.8, 20.7, 20.5 (4*C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); CI-MS *m/z* 447 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1980.

3.3.12. *N*-(*p*-Methylphenyl)-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)urea (26). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) gave **26** as a white solid: 167 mg, 58%. R_f 0.25 (1:1 hexane–EtOAc); mp 80–88 °C; $[\alpha]_D^{18}$ −21 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3291, 2922, 1767, 1555, 1096, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (m, 4H, Ar–H), 6.89 (s, 1H, NH), 5.92 (d, 1H, $J_{1,NH'}$=9.5 Hz, NH′), 5.45 (dd, 1H, $J_{1,2}$=0.9 Hz, H-1), 5.39 (d, 1H, $J_{2,3}$=3.1 Hz, H-2), 5.17 (t, 1H, $J_{3,4}$=10.0 Hz, $J_{4,5}$=9.9 Hz, H-4), 5.08 (dd, 1H, H-3), 4.25 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.01 (dd, 1H, $J_{5,6b}$=2.0 Hz, H6b), 3.75 (ddd, 1H, H-5), 2.27 (s, 3H, Me), 2.08, 2.01, 1.95 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.2, 169.8, 169.7 (4CO), 154.3 (CO urea), 134.7, 129.8, 122.0 (Ar), 77.6 (C-1), 73.8 (C-5), 71.6 (C-3), 70.3 (C-2), 64.3 (C-4), 62.3 (C-6), 20.8, 20.7, 20.6, 20.4 (*C*H_3Ar, 4*C*H_3CO); FAB-MS *m/z* 481 ($[M+H]^+$, 28%), 503 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_{10}$: 481.1822, found: 481.1814.

3.3.13. *N,N′*-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-manopyranosyl)urea (27). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) gave **27** as a white solid: 149 mg, 69%. R_f 0.12 (1:1 hexane–EtOAc); mp 154–156 °C (from EtOH); $[\alpha]_D^{25}$ −24 (*c* 0.3, CH_2Cl_2); IR ν_{max} 3352, 2917, 1746, 1647, 1537, 1370, 1227, 1092, 1051, 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (dd, 1H, $J_{1,2}$=0.9 Hz, H-1), 5.45 (d, 1H, $J_{1,NH}$=9.6 Hz, NH), 5.37 (dd, 1H, $J_{2,3}$=3.3 Hz, H-2), 5.20 (t, 1H, $J_{3,4}$=10.0 Hz, $J_{4,5}$=10.0 Hz, H-4), 5.11 (dd, 1H, H-3), 4.29 (dd, 1H, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.77 (ddd, 1H, H-5), 2.21, 2.09, 2.04, 1.97 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.8, 170.2, 169.8, 169.7 (4CO), 153.8 (CO urea), 77.4 (C-1), 73.8 (C-5), 71.6 (C-3), 70.3 (C-2), 65.1 (C-4), 62.2 (C-6), 20.9, 20.8, 20.7, 20.5 (4*C*H_3CO); FAB-MS *m/z* 721 ($[M+H]^+$, 36%), 743 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{29}H_{41}N_2O_{19}$: 721.2304, found: 721.2294. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$ H_2O: C, 47.16; H, 5.73; N, 3.79, found: C, 47.26; H, 5.61; N, 3.83.

3.3.14. *N,N*-Diethyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (32). *Method C*. The mixture was stirred for 40 h and purified by column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) to give **32**, as an amorphous solid: 94 mg, 72%; mp 39–42 °C; $[\alpha]_D^{20}$ +19 (*c* 0.9, CH_2Cl_2); IR ν_{max} 3320, 2936, 1753, 1379, 1225, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, 1H, $J_{1,NH}$=9.3 Hz, NH′), 5.31 (t, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=9.4 Hz, H-3), 5.20 (t, 1H, $J_{1,2}$=9.3 Hz, H-1), 5.06 (t, 1H, $J_{4,5}$=9.6 Hz, H-4), 4.93 (t, 1H, H-2), 4.33 (dd, 1H, $J_{5,6a}$=4.0 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b), 3.80 (ddd, 1H, H-5), 3.18 (m, 4H, 2CH_2), 2.07, 2.03, 2.01, 2.0 (4s, 12H, 4Ac), 1.11 (t, 6H, $J_{H,H}$=7.2 Hz, 2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.4, 170.7, 169.98, 169.7 (4CO), 155.4 (CO urea), 80.8 (C-1), 73.2 (C-5), 73.0 (C-3), 70.8 (C-2), 68.5 (C-4), 61.8 (C-6), 41.3 (2*C*H_2), 20.8, 20.8, 20.7, 20.6 (4*C*H_3CO); 13.7 (2*C*H_3); CI-MS *m/z* 447 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1955.

3.4. Method for the preparation of isocyanates 7 and 8

To a vigorously stirred solution of the hydrohalides **5** or **6** (0.6 mmol) in a 1:1 mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (12 mL) at 0 °C was added triphosgene (0.22 mmol) in a single portion. After 10 min of stirring, the organic layer was separated, dried ($MgSO_4$), filtered and concentrated to dryness to give pure **7** or **8**.

3.4.1. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isocyanato-α-D-glucopyranose (7). Yield: 224 mg, quantitative, as a syrup. R_f 0.32 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +126 (*c* 1.3, CH_2Cl_2); IR ν_{max} 2963, 2261, 1765, 1371, 1217, 1026, 936 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 and δ 2.22, 2.11, 2.07, 2.04 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.5, 170.2, 169.4, 168.6 (4CO), 20.8, 20.6, 20.5 (4*C*H_3CO). Anal. Calcd for $C_{15}H_{19}NO_{10}\cdot 1/3H_2O$: C, 47.50; H, 5.23; N, 3.69, found: C, 47.55; H, 5.30; N, 3.69.

3.4.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isocyanato-β-D-glucopyranose (8). Yield: 224 mg, quantitative, as a syrup. R_f 0.21 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{25}$ +32 (*c* 1.0, CH_2Cl_2); IR ν_{max} 2959, 2253, 1765, 1371, 1215, 1090, 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 and δ 2.18, 2.09, 2.07, 2.02 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.5, 169.8, 169.5, 168.6 (4CO), 20.7, 20.6, 20.5 (4*C*H_3CO). Anal. Calcd for $C_{15}H_{19}NO_{10}$: C, 48.26; H, 5.13; N, 3.75, found: C, 48.17; H, 5.20; N, 3.79.

3.5. *N*-(*p*-Methylphenyl)-*N′*-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)thiourea (28)

A mixture of hydrobromide **18** (250 mg, 0.58 mmol), thiophosgene (0.07 mL, 0.88 mmol) and calcium carbonate (176 mg, 1.76 mmol) in 1:1 water–CH_2Cl_2 (20 mL) was vigorously stirred at rt for 2 h. Then the mixture was filtered off and the organic layer containing known 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-D-glucopyranose[59] was separated and concentrated to dryness. To a solution of crude isothiocyanate in EtOAc (10 mL) was added *p*-toluidine (62 mg, 0.58 mmol). The solution was kept at rt for 5 h and then it was concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2→ 80:1 CH_2Cl_2–MeOH) to give **28** as a white solid: 295 mg (93%). R_f 0.5 (40:1 CH_2Cl_2–MeOH); mp 140–142 °C; $[\alpha]_D^{25}$ +96 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3332, 1750, 1532, 1370, 1223, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H, NH), 7.24–6.99 (m, 4H, Ar–H), 6.31 (d, 1H, $J_{1,2}$=6.3 Hz, H-1), 5.80 (d, 1H, $J_{2,NH}$=8.3 Hz, NH′), 5.21 (m, 1H, H-4), 5.16 (m, 1H, H-3), 5.13 (m, 1H, H-2), 4.23 (dd, 1H, $J_{5,6a}$=4.1 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.03 (dd, 1H, $J_{5,6b}$=2.3 Hz, H-6b), 3.91 (ddd, 1H, $J_{4,5}$=9.5 Hz, H-5), 2.37 (s, 3H, CH_3), 2.08, 2.07, 2.00 1.94 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.6 (CS), 171.5, 170.8, 169.1, 168.3 (4CO), 138.6, 132.7, 130.9, 126.2 (Ar), 90.5 (C-1), 70.9 (C-3), 69.9 (C-5), 67.5 (C-4), 61.6 (C-6), 56.3 (C-2), 21.2 (*C*H_3Ar), 20.9, 20.8, 20.7, 20.6 (4*C*H_3CO); CI-MS *m/z* 497 ($[M+H]^+$, 35%); HRCI-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_9S$: 497.1594, found: 497.1570.

3.6. *N*-(*p*-Methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (29)

To a solution of *N*-acetyl-*N*-(*p*-methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea **34** (22 mg, 0.04 mmol) in MeOH (10 mL) was added imidazole (2.8 mg, 0.04 mmol). The solution was heated at 40 °C for 24 h and then it was concentrated to dryness and the residue was purified by column chromatography ($CH_2Cl_2 \rightarrow$80:1 CH_2Cl_2–MeOH) to give **29** as a syrup: 18 mg (86%). $[\alpha]_D^{23}$ −11 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3329, 1751, 1535, 1370, 1229, 1040, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, NH), 7.25–7.03 (m, 4H, Ar–H), 6.52 (d, 1H, $J_{1,NH}$=8.7 Hz, NH′), 5.82 (t, 1H, $J_{1,2}$=9.0 Hz, H-1), 5.33 (t, 1H, $J_{2,3}$=9.3 Hz, $J_{3,4}$=9.6 Hz, H-3), 5.01 (t, 1H, $J_{4,5}$=9.9 Hz, H-4), 4.88 (t, 1H, H-2), 4.30 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.3 Hz, H-6a), 4.08 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.84 (ddd, 1H, H-5), 2.37 (s, 3H, Me), 2.06, 2.05, 2.01, 1.98 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3 (CS), 170.7, 170.6, 169.8, 169.5 (4CO), 138.3, 132.3, 130.7, 125.6 (Ar), 83.2 (C-1), 73.6 (C-5), 72.7 (C-3), 70.5 (C-2), 68.2 (C-4), 61.6 (C-6), 21.1 (CH_3Ar), 20.7, 20.6, 20.5, 20.5 (4CH_3CO); FAB-MS *m*/*z* 497 ($[M+H]^+$, 100%); HRFAB-MS *m*/*z* calcd for $[M+H]^+C_{22}H_{29}N_2O_9S$: 497.1594, found: 497.1625. Anal. Calcd for $C_{22}H_{28}N_2O_9S$: C, 53.22; H, 5.68; N, 5.64; S, 6.46, found: C, 53.35; H, 5.73; N, 5.55; S, 6.07.

3.7. *N*,*N*-Diethyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (31)

A mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl hydrobromide **18** (400 mg, 0.94 mmol), thiophosgene (0.104 mL, 1.36 mmol) and calcium carbonate (280 mg, 2.8 mmol) in 1:1 water–CH_2Cl_2 (20 mL) was vigorously stirred at rt for 2 h. Then the mixture was filtered off and the organic layer, containing known 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate[51] was separated and concentrated to dryness. Crude isothiocyanate was dissolved in EtOAc (5 mL) and to the solution was added *N*,*N*-diethylamine (0.100 mL, 0.94 mmol). The solution was kept at rt for 1 h and then it was concentrated to dryness and the residue was purified by column chromatography ($CH_2Cl_2 \rightarrow$80:1 CH_2Cl_2–MeOH) to give **31** as a white solid: 299 mg (69%); mp. 140–142 °C; R_f 0.54 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +14 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3378, 1750, 1362, 1225, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, 1H, $J_{1,NH}$=8.2 Hz, NH), 5.84 (t, 1H, $J_{1,2}$=9.6 Hz, H-1), 5.37 (t, 1H, $J_{2,3}$=9.6 Hz, $J_{3,4}$=9.7 Hz, H-3), 5.07 (t, 1H, $J_{4,5}$=10.1 Hz, H-4), 5.01 (t, 1H, H-2), 4.33 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.11 (dd, 1H, $J_{5,6b}$=2.1 Hz, H-6b), 3.86 (ddd, 1H, H-5), 3.61 (m, 4H, 2CH_2), 2.07, 2.05, 2.02, 2.02 (4s, 12H, 4Ac), 1.20 (t, 6H, $J_{H,H}$=7.2 Hz, 2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1 (CS), 172.1, 170.7, 169.8, 169.7 (4CO), 83.8 (C-1), 73.3 (C-5), 72.9 (C-3), 71.2 (C-2), 68.7 (C-4), 61.8 (C-6), 45.6 (2CH_2), 20.8, 20.7, 20.7, 20.7 (4CH_3CO), 12.4 (2CH_3); CI-MS *m*/*z* 463 ($[M+H]^+$, 68%); HRCI-MS *m*/*z* calcd for $[M+H]^+C_{19}H_{31}N_2O_9S$: 463.1750, found: 463.1769.

3.8. *N*-Acetyl-*N*-(*p*-methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (34)

To a solution of *N*-(β-D-glucopyranosyl)-*N*′-(*p*-methylphenyl) thiourea **33**[42] (2.22 g, 6.76 mmol) in pyridine (15 mL) at 0 °C was added acetic anhydride (15 mL). The solution was kept at rt for 24 h and then it was co-concentrated with toluene and ethanol to dryness and the residue was crystallized from ethanol to give **34**: 2.66 g, 73%. Mp 140–144 °C; $[\alpha]_D^{25}$ +15 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3318, 2922, 1753, 1682, 1370, 1225, 1044, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.01 (d, 1H, $J_{1,NH'}$=8.8 Hz, NH′), 7.26–7.05 (m, 4H, Ar–H), 5.79 (dd, 1H, $J_{1,2}$=9.3 Hz, H-1), 5.34 (t, 1H, $J_{2,3}$=9.3 Hz, $J_{3,4}$=9.3 Hz, H-3), 5.21 (t, 1H, H-2), 5.11 (t, 1H, $J_{4,5}$=10.0 Hz, H-4), 4.28 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}$=2.1 Hz, H-6b), 3.82 (ddd, 1H, H-5), 2.39 (s, 3H, Me), 2.08, 2.07, 2.02, 1.92 (4s, 15H, 5Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 186.8 (CS), 175.1, 170.8, 170.1, 169.6 (5CO), 139.6, 139.3, 130.3, 129.2 (Ar), 83.4 (C-1), 73.8 (C-5), 73.2 (C-3), 70.5 (C-2), 68.4 (C-4), 61.7 (C-6), 28.0 (NAc), 21.4 (CH_3Ar), 20.9, 20.7, 20.7, 20.7 (4CH_3CO); FAB-MS *m*/*z* 561 ($[M+Na]^+$, 28%); HRFAB-MS *m*/*z* calcd for $[M+H]^+C_{24}H_{31}N_2O_{10}S$: 539.1699, found: 539.1676. Anal. Calcd for $C_{24}H_{30}N_2O_{10}S$: C, 53.52; H, 5.61; N, 5.20; S, 5.95, found: C, 53.76; H, 5.77; N, 4.95; S, 5.43.

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