New synthetic approach to per-*O*-acetyl-isocyanates, isothiocyanates and thioureas in the disaccharide and cyclodextrin series

Stephane Menuel,[a] Stanislaw Porwanski[b] and Alain Marsura*[a]

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An efficient method for the preparation of per-*O*-acetyl disaccharides and cyclodextrin isocyanates or isothiocyanates by the phosphine imide strategy is reported. Successful one-pot, high yield syntheses of cellobiose, lactose and sucrose isocyanates or/and isothiocyanates pure β-anomers have been completed starting from their corresponding monoazido-per-*O*-acetyl derivatives. Transformation of the $^{\mathrm{ACE}}$tris-6-azido-per-*O*-methylated and the $^{\mathrm{ACE}}$tris-6-azido-per-*O*-acetylated-α-cyclodextrins or of the 6$^{\mathrm{A}}$-azido-6$^{\mathrm{A}}$-deoxy-per-*O*-acetyl-β-cyclodextrin into the corresponding isocyanates and/or isothiocyanates is also presented. Finally the conversion of the cyclodextrin isothiocyanates by nucleophilic addition of primary and secondary amines into a large panel of original thioureido-cyclodextrins derivatives is described.

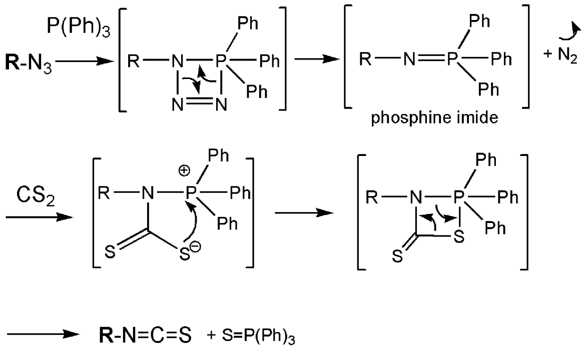
Introduction

It is well known that compounds containing the urea or thiourea functionality are of extended biological interest in several classes of drugs.[1a–g] In the carbohydrate field, glycosylureas have been shown also to be useful antidiabetic agents.[2a,b] As a powerful easy access to urea functionality and other main quadrivalent functions of chemistry as *e.g.* isocyanate, carbodiimide, thiourea… notably in the cyclodextrin series, we earlier reported and demonstrated the high safety, efficiency and versatility of the phosphine imide reaction.[3a–c] The latter was proposed as a general method for symmetrical or unsymmetrical urea synthesis, either from azides,[4] or amines,[5] using CO_2 or sCO_2 (supercritical CO_2)[6] as solvent and/or reagent in the presence of free,[3a–c] or polymer-supported triphenylphosphine.[7]

Applied to the cyclodextrin series (CDs), the phosphine imide reaction afforded for the first time, from the native or peracetylated azido-Cds, a direct and very easy access to the non-acetylated or peracetylated urea bridged CD-dimers, respectively, in high yields, (91 to 94%)[3a–c] presently unmatched by other methods.[8a,b] In the same way, sophisticated supramolecular hosts such as dimers, trimers and tetramers of ureido-CD-cyclams or aza-crown ether,[3,9a,b] were obtained by this method. More recently, we introduced the URFT-cyclodextrins (**U**pper **R**im **F**ully **T**ethered)-CDs and $^{\mathrm{ACE}}$tris-ureido-α-CD, new classes of tritopic podands which have been designed to afford original mononuclear or dinuclear lanthanides and/or transition-metal complexes exhibiting interesting luminescence, redox and amphiphilic properties.[10a–e] The reaction was also further applied by another group, in the field of analytical chemistry, to obtain grafted cyclodextrin chromatographic phases.[11] In comparison, the recent literature reports two other procedures for urea synthesis. A first one, using triphosgene,[8a,b] giving the peracetylated urea bridged β-CD-dimer in medium yield (49%) and a scope-limited second one, using a metal–carbonyl reagent as carbon monoxide source.[12]

Results and discussion

Continuing our research on the scope and limitations of the phosphine imide reaction and considering results previously obtained with CO_2, we performed the reaction with CS_2 expecting that CDs-isothiocyanates and/or other isothiocyanates, could be interestingly prepared in this way in pure form and in high yields. Considering the mechanism hypothesis of Scheme 1, based on our previous theoretical results with CO_2,[13a,b] and despite that our early attempts to obtain isothiocyanates instead of isocyanates failed,[14] we report here, the first successful synthesis of the 6-monoisothiocyanato-per-*O*-acetyl-β-cyclodextrin **3** and the $^{\mathrm{ACE}}$tris-6-isothiocyanato-per-*O*-acetyl-α-cyclodextrin **4** (Scheme 2) through the "thiophosphine imide reaction" (so named by analogy with the initial phosphine imide reaction with CO_2) by the action of



Scheme 1

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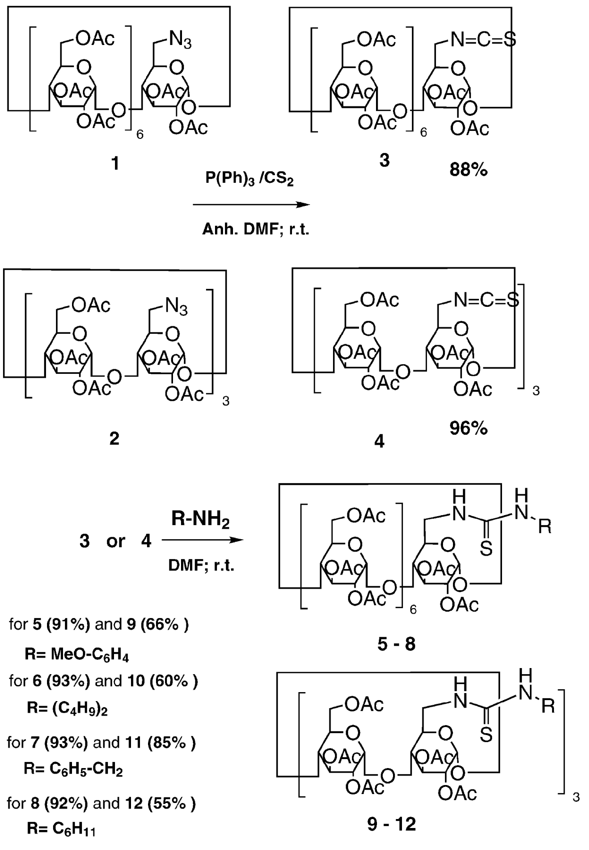
[a] GEVSM SRSMC, UMR 7565 CNRS-Université Henri Poincaré-Nancy-1, Faculté de Pharmacie, 5 rue A. Lebrun, B.P. 80403, 54001 Nancy Cedex, France. E-mail: Alain.Marsura@pharma.uhp-nancy.fr; Fax: +33 (0) 3 83682345; Tel: +33 (0) 3 83682324
[b] Department of Organic Chemistry, University of Lodz, ul. Naturowicza 68, 90-136 Lodz, Poland. E-mail: porwany@chemul.uni.lodz.pl; Fax: +48 42 678 16 09; Tel: +48 42 636 42 61



Scheme 2

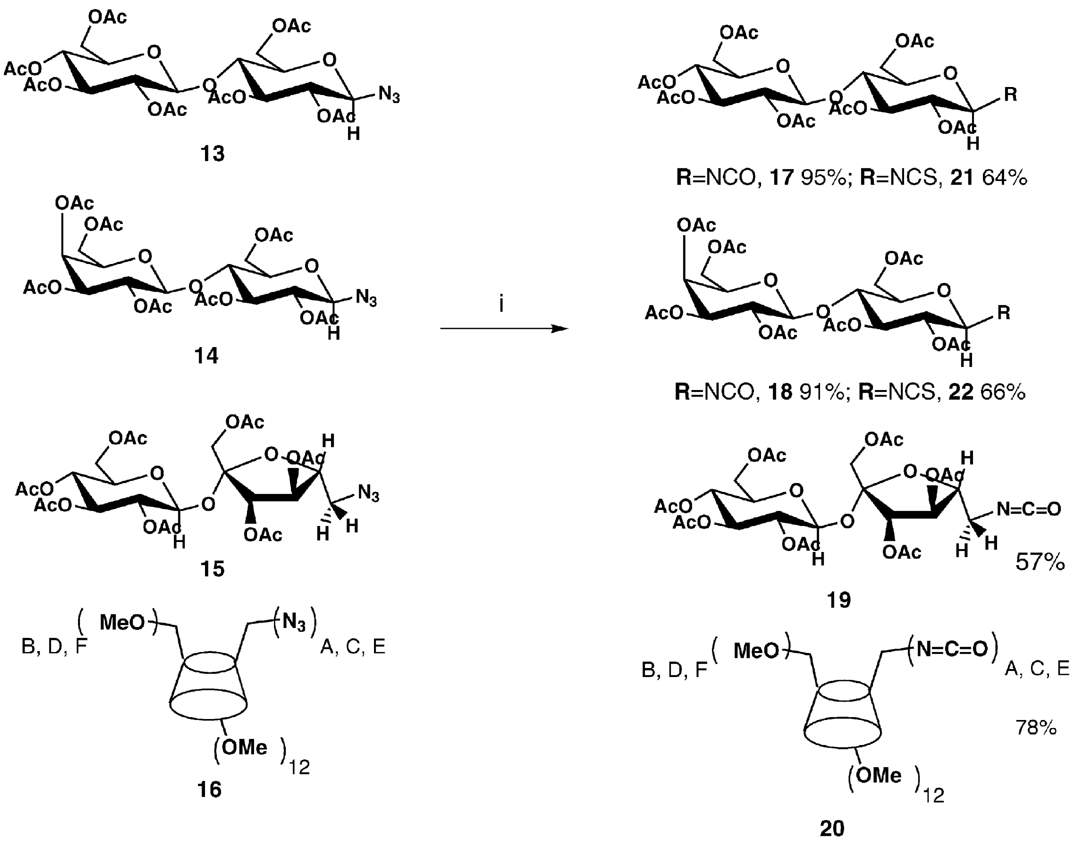
carbon disulfide on the 6^A-azido-6^A-deoxy-per-*O*-acetyl-β-cyclodextrin **1** or the ^{ACE}tris-6-azido-per-*O*-acetyl-α-cyclodextrin **2**. In a separate second step, we described their straightforward conversion into the corresponding thiourea derivatives **5** to **12** by addition of primary and secondary nucleophilic amines (Scheme 2). All the synthesised products were obtained in fairly good yields, 88 and 96% (β- and α-CDs isothiocyanates) and 55 to 93% (CDs thioureas), respectively. The purification step is easy, limited to a simple precipitation with cyclohexane, followed by a rapid flash chromatography filtration on silica gel to discard triphenylphosphine oxide. The reaction conditions are found to be close to those of the phosphine imide reaction with CO$_2$ except that a careful control of anhydrous conditions must especially be respected, with regards to the stronger sensitivity of the isothiocyanates *vs.* the corresponding isocyanates. The reaction time to complete formation of the isothiocyanates is 60 h, instead of the shorter time (6 h) necessary for the conversion at rt into thiourea derivatives from the latter. The reaction works well with aliphatic or aromatic primary amines and also with secondary amines. Analyses of **3** to **12** by FTIR and NMR spectroscopy and elemental analyses are in total agreement with the proposed structures. For the isothiocyanates **3** and **4**, the FTIR spectra show the presence of a weak absorption band at 2100 cm^{-1}, characteristic of the N=C=S vibration, also confirmed by the ^{13}C-NMR corresponding signal at 162–163 ppm. Concerning the thiourea compounds **5** to **12**, the FTIR spectra show a characteristic absorption between 1648 and 1654 cm^{-1} and a quaternary carbon ^{13}C-NMR signal between 180 and 182 ppm, characteristic of the C=S double bond of the thiourea function. To our knowledge, only one example of a multistep synthesis of an α-CD isothiocyanate was reported in the patent literature,[15] but other CDs-isothiocyanates have not been obtained before.

Usually, the preparation of monosaccharidyl and disaccharidyl isocyanates or isothiocyanates is achieved by isocyanation or isothiocyanation with phosgene or thiophosgene,[16a,b] hazardous reagent (CSCl$_2$). In the following, we report the first synthesis of pure monoisocyanates and monoisothiocyanates of three popular disaccharides, cellobiose, lactose and sucrose along the original ^{ACE}tris-6-isocyanato-per-*O*-methyl-α-cyclodextrin host using the phosphine imide reaction in anhydrous conditions and without use of phosgene or thiophosgene (Scheme 3). For the preparation of the azido peracetylated disaccharide starting materials **13–14** we followed the sequence: peracetylation, bromination, azidation, by using known literature procedures,[17] and for the 6-monoazido-6-deoxy-sucrose heptaacetate **15** another literature method was used.[18] Finally, concerning the case of ^{ACE}tris-6-azido-per-*O*-methylated-α-cyclodextrin **16** we followed our original published synthesis.[19]

Isocyanates **17–19**, isothiocyanates **21–22** and ^{ACE}tris-6-isocyanato-per-*O*-methylated-α-cyclodextrin **20** were prepared using CO$_2$ or CS$_2$ in the presence of triphenylphosphine in anhydrous toluol and were obtained as pure white microcrystalline powders after a simple precipitation with cyclohexane. No further purification was needed. The isothiocyanate of sucrose cannot be isolated in a pure form and is not reported here. Analytical and spectroscopic data of the compounds are in perfect agreement with the proposed structures. Strong IR absorptions at 2192–2155 cm^{-1} together with ^{13}C-NMR resonances at 137.9 and 144.5 ppm confirm the presence of the N=C=O and N=C=S moieties, respectively. ^{1}H- and ^{13}C-NMR spectra of the disaccharidyl derivatives show that the sole β-anomer was obtained in the reaction.

To our knowledge, this practical one-pot preparation is the first example reported, of a direct and scale-up preparation of isocyanates and isothiocyanates of oligosaccharides at the anomeric position from their corresponding azides. In comparison rare examples of oligosaccharidyl isothiocyanate synthesis at the 6-primary alcohol position have been reported earlier, from amines by reaction with thiophosgene,[20] and two other monosaccharidyl-isocyanates have been recently claimed to be formed, but not isolated, using triphosgene in a biphasic water–CH$_2$Cl$_2$ medium.[8a,b]

Elsewhere, considering details of the mechanism proposed earlier for this reaction, our calculations[13a,b] clearly predicted the *in situ* formation of an isocyanate as the key intermediate and its evolution to a urea by a nucleophilic attack of a primary or a secondary amine. Our previous experimental work confirms this prediction and earlier allowed us to isolate the 6-monoisocyanato-per-*O*-acetyl-β-cyclodextrin in a high overall yield (92%),[3a] recently improved to 97%. It should be noted here, that in the mechanisms of analogous reactions, key intermediate isocyanates were often invoked in the urea formation pathways.[8a,b,12] Nevertheless, it should be pointed out that sometimes, in these reactions, isocyanates cannot be



Scheme 3 *Reagents and conditions:* i = P(Ph)$_3$, CO$_2$ (**17–20**) or CS$_2$ (**21**, **22**), toluol (anh.), rt.

isolated and as recently reported in literature,[21] their effective existence appeared controversial with *e.g.* correlative functional density calculations.

Conclusion

In summary, we find that the proposed phosphine imide reaction and its thio-variant, bring efficient high yielding, soft and safe (without hazardous phosgene or analogues) synthetic methodologies for CDs and disaccharide isothiocyanate and isocyanate scale-up preparation. This very practical method needs no fastidious protection/deprotection sequence or sophisticated separation procedures and will also be promising for further reactions with sensitive and/or sophisticated structures, with regards to the generally mild reaction conditions. We argued that the proposed methods could be considered as a valuable and interesting alternative to the sole usual phosgene/thiophosgene isocyanation/isothiocyanation. Further, some of the above described isocyanates and/or isothiocyanates, notably the preorganised original trisubstituted-CDs derivatives are reactive and truly precious starting materials for the rapid development of new designed supramolecular podands. Moreover, we demonstrate that the reaction offers the opportunity and versatility to obtain a large panel of monosubstituted and trisubstituted ureido- or thioureido-CDs derivatives in one step and high yields. Now, the study of the trisubstituted thioureido-CDs towards cation/anion complexation is underway.

Experimental

The structures of all compounds were assigned by ^{1}H and ^{13}C NMR spectroscopy on a Bruker-DRX 400 spectrometer; FTIR spectra were recorded on a Bruker-Vector 22 spectrometer. Mass spectra were recorded on an ESI-MS Platform Micromass Platform spectrometer. Elemental analyses were obtained with a Thermofinnigan Flash EA1112 analyser. The solvents were purified by standard methods.

Syntheses

The 6^{A}-azido-6^{A}-deoxy-per-*O*-acetyl-β-cyclodextrin **1** was synthesised by a known literature procedure.[3a]

^{ACE}Tris-6-azido-per-*O*-acetyl-α-cyclodextrin 2. ^{ACE}Tris-6-azido-α-cyclodextrin[19] (1 g) in solution in a mixture of pyridine–acetic anhydride (100 mL; 2 : 1 v/v) was stirred at 80 °C under argon for 15 h. After evaporation the resulting oily paste was dissolved in 150 mL of toluol and evaporated three times with the same amount of toluol to dryness. The same operation was carried out with methanol (150 mL) in order to eliminate all traces of pyridine and acetic anhydride from the residue. Finally 100 mL of water was added to give a solid which was filtered and washed with water over a glass sinter. A white pure powder of **2** was obtained (0.740 g, 46%). Found C 47.01, H 5.31, N 7.15; calc. for $C_{66}H_{87}N_9O_{42}$ (1678.43): C, 47.23; H, 5.22; N, 7.51%; FTIR KBr; υ_{max}/cm^{-1} 2105 (N$_3$), 1759 (CO); δ_H (400 MHz; CDCl$_3$) 5.54 (6H, t, *J* 9.8 Hz, 3-H), 5.04 (6H, d, *J* 3.53 Hz, 1-H), 4.55 (6H, dd, J_1 3.27 Hz, J_2 10.1

Hz, 2-H), 4.40 (12H, 2s, 6-H), 4.18 (6H, m, 3-H), 3.78 (6H, dd, J_1 8.8 Hz, J_2 8.9 Hz, 4-H), 2.12 (45H, m, CH_3); δ_C(100 MHz; $CDCl_3$) 171.2–169.5 (C═O), 96.9 (C-1), 77.6 (C-4), 71.3, 71.2, 69.8 (C62, C-3, C-5), 63.5 (C-6a), 51.12 (C-6b), 21.2 (CH_3); ES-MS *m*/*z*: 1797.31 ($M^+ + CHCl_3$), 1696.02 ($M^+ + HO^\bullet$).

6^A-Isothiocyanato-6^A-deoxy-6-(icosa-*O*-acetyl)-β-cyclodextrin 3. 6^A-Azido-6^A-deoxy-per-*O*-acetyl-β-cyclodextrin **1** (2.0 g, 1 mmol),[3] was added to a solution of triphenylphosphine (18.35 g, 70 equiv.) in an anhydrous CS_2–DMF (10 : 6) mixture under argon at rt. After 60 h, the solution was evaporated to dryness. The residue was dissolved in 2 cm^3 of anhydrous CH_2Cl_2 and anhydrous hexane was added. The resulting precipitate was filtered and washed on a glass sinter under argon (1.77 g, 88%). Found: C, 49.91; H, 5.35; N, 0.59; S, 1.38; calc. for $C_{83}H_{109}NO_{54}S$: C, 49.43; H, 5.45; N, 0.69; S, 1.59%; FTIR υ_{max}(KBr)/cm^{-1} 2100 (N═C═S), 1750 (C═O); δ_H (400 MHz; $CDCl_3$) 5.36–5.24 (7H, m, 3-H), 6.01 (7H, d, *J* 3.3 Hz, 1-H), 4.83–4.76 (7H, m, 2-H), 4.61–4.54 (12H, m, 6a-H), 4.35–4.24 (2H, m, 6b-H), 4.06–4.20 (7H, m, 5-H), 3.78–3.65 (7H, m, 4-H), 2.10 (60H, m, CH_3); δ_C(100 MHz; $CDCl_3$) 170.9, 170.7, 169.7 (C═O), 162.8 (N═C═S), 97.5, 97.3 (C-1), 78.0–77.1 (C-4), 70.9–69.9 (C-2, C-3, C-5), 62.8 (C-6a), 46.3 (C-6b), 21.1 (CH_3).

6^A,6^C,6^E-Tris-isothiocyanato-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-acetyl-hexakis(2,3-di-*O*-acetyl) cyclomaltohexaose 4. ^{ACE}Tris-azido-per-*O*-acetyl-α-cyclodextrin **2** (1 g, 0.67 mmol) was added to a solution of triphenylphosphine (12.25 g, 70 equiv.) in an anhydrous CS_2–DMF (1 : 1) mixture under argon at rt. After 60 h, the solution was evaporated to dryness. The residue was dissolved in 2 cm^3 of anhydrous CH_2Cl_2 and anhydrous hexane was added. The resulting precipitate was filtered and washed with anhydrous hexane under argon (1.11 g, 96%). Found: C, 48.04; H, 5.05; N, 2.38 S, 5.18; calc. for $C_{69}H_{87}N_3O_{42}S_3$: C, 47.99; H, 5.04; N, 2.43; S, 5.56%; FTIR υ_{max}(KBr)/cm^{-1} 2092 (N═C═S), 1749 (C═O); δ_H (400 MHz; $CDCl_3$) 5.56 (6H, dd, J_1 8.5 Hz, J_2 8.6 Hz, 3-H), 5.06 (6H, d, *J* 3.2 Hz, 1-H), 4.77 (6H, dd, J_1 3.2 Hz, J_2 10.1 Hz, 2-H), 4.39 (6H, m, 6a-H), 4.23–4.14 (12H, m, 6b-H, 5-H), 3.79 (6H, dd, *J* 8.9 Hz, 4-H), 2.12 (45H, m, CH_3); δ_C(100 MHz; $CDCl_3$) 171.0–169.5 (C═O), 162.9 (N═C═S), 96.9 (C-1), 77.6 (C-4), 71.3–71.2–69.8 (C-2, C-3, C-5), 63.5 (C-6a), 47.1 (C-6b), 21.2 (CH_3).

Thioureas 5–12 general procedure. The desired amine was added to a solution of isothiocyanate **3** or **4** in anhydrous CH_2Cl_2 under argon at room temperature. After 6 h, the solution was evaporated to dryness. The residue was dissolved into 2 cm^3 of CH_2Cl_2 and hexane was added. The resulting precipitate was filtered, washed three times with hexane and purified by flash chromatography on a silica gel column (CH_2Cl_2–MeOH, 9 : 1).

***N*-[Icosa-*O*-acetyl-6^A-deoxy-β-cyclodextrin-6^A-yl]-*N*′-[*p*-anisidinyl]-thiourea 5.** *p*-Anisidine (0.012 g, 2 equiv.), isothiocyanate **3** (0.10 g, 0.05 mmol); (0.097 g, 91%). Found: C, 50.75; H, 5.55; N, 1.16; S, 1.38; calc. for $C_{90}H_{118}N_2O_{55}S$: C, 50.50; H, 5.51; N, 1.31; S, 1.49%; FTIR υ_{max}(KBr)/cm^{-1} 1748 (C═O), 1649 (C═S); δ_H (400 MHz; $CDCl_3$) 6.63 (2H, d, *J* 8.8 Hz, H_{arom}), 6.55 (2H, d, *J* 8.8 Hz, H_{arom}), 5.33–5.26 (7H, m, 3-H), 5.24–5.15 (7H, m, 1-H), 5.08–4.98 (7H, m, 2-H), 4.81–4.64 (12H, m, 6a-H), 4.53–4.29 (9H, m, 6b-H, 5-H), 4.23–3.98 (7H, m, 4-H), 3.51 (3H, s, OCH_3), 2.08 (70H, *several* s, CH_3–C═O); δ_C(100 MHz; $CDCl_3$) 182.0 (C═S), 171.2–169.8 (C═O), 134.2, 132.7, 129.3, 127.2 (C_{arom}), 97.2 (C-1), 77.1 (C-4), 72.0, 71.0, 70.0 (C-2, C-3, C-5), 63.3 (C-1a), 56.1 (OCH_3), 21.2 (CH_3–CO).

***N*-[Icosa-*O*-acetyl-6^A-deoxy-β-cyclodextrin-6^A-yl]-*N*′-[dibutyl]-thiourea 6.** Di-*N*-butylamine (0.014 g, 1.1 equiv.), isothiocyanate **3** (0.20 g, 0.099 mmol); (0.197 g, 93%). Found: C, 50.97; H, 5.88; N, 1.13; S, 1.42; calc. for $C_{91}H_{128}N_2O_{54}S$: C, 50.91; H, 5.96; N, 1.30; S, 1.49%; FTIR υ_{max}(KBr)/cm^{-1} 1756 (C═O), 1649 (C═S); δ_H (400 MHz; $CDCl_3$) 5.40–5.28 (7H, m, 3-H), 5.18–5.08 (7H, m, 1-H), 4.86–4.78 (7H, m, 2-H), 4.62 4.56 (12H, m, 6a-H), 4.38–4.19 (9H, m, 6b-H, 5-H), 3.80–3.70 (7H, m, 4-H), 2.65 (4H, t, *J* 7.4 Hz, $CH_2\alpha$), 2.12 (70H, *several* s, CH_3–C═O), 1.54 (4H, m, $CH_2\beta$), 1.38 (4H, m, $CH_2\gamma$), 0.94 (6H, t, *J* 7.3 Hz, CH_3 chain); δ_C(100 MHz; $CDCl_3$) 181.7 (C═S), 171.0–169.6 (C═O), 97.2 (C-1), 76.5 (C-4), 71.3–70.0 (C-2, C-3, C-5), 63.0 (C-6a), 53.8 (C-6b), 49.8 ($CH_2\alpha$), 32.1 ($CH_2\beta$), 21.1 (CH_3–CO), 20.8 ($CH_2\gamma$), 14.2 (CH_3 chain).

***N*-[Icosa-*O*-acetyl-6^A-deoxy-β-cyclodextrin-6^A-yl]-*N*′-[benzyl]-thiourea 7.** Benzylamine (0.016 g, 1.5 equiv.), isothiocyanate **3** (0.20 g, 0.099 mmol); (0.195 g, 93%). Found: C, 50.80; H, 5.42; N, 1.21; S, 1.41; calc. for $C_{90}H_{118}N_2O_{54}S$: C, 50.88; H, 5.56; N, 1.32; S, 1.50%; FTIR υ_{max}(KBr)/cm^{-1} 1759 (C═O), 1652 (C═S); δ_H (400 MHz; $CDCl_3$) 7.41–7.26 (5H, m, H_{arom}), 5.34–5.19 (7H, m, 3-H), 5.17–5.01 (7H, m, 1-H), 4.88–4.68 (7H, m, 2-H), 4.62–4.40 (6H, m, 6a-H), 4.36–3.96 (10H, m, 5-H, 6b-H, CH_2benzyl), 3.81–3.62 (7H, m, 4-H), 2.10 (45H, m, CH_3); δ_C(100 MHz; $CDCl_3$) 171.1–170.9–169.7 (C═O), 129.0–128.3–127.9 (C_{arom}), 97.3 (C-1), 77.3 (C-4), 71.3–69.2 (C-2, C-3, C-5), 62.9 (C-6), 21.1 (CH_3).

***N*-[Icosa-*O*-acetyl-6^A-deoxy-β-cyclodextrin-6^A-yl]-*N*′-[cyclohexyl]-thiourea 8.** Cyclohexylamine (0.007 g, 1.5 equiv.), isothiocyanate **3** (0.1 g, 0.05 mmol); (0.097 g, 92%). Found: C, 50.47; H, 5.71; N, 1.25; S, 1.38; calc. for $C_{89}H_{122}N_2O_{54}S$: C, 50.50; H, 5.76; N, 1.32; S, 1.51%; FTIR υ_{max}(KBr)/cm^{-1} 1757 (C═O), 1654 (C═S); δ_C(100 MHz; $CDCl_3$) 182.3 (C═S), 171.4–169.9 (C═O), 97.3 (C-1), 76.5 (C-4), 71.8–70.1–69.7 (C-2, C-3, C-5), 63.0 (C-6a), 50.8 (C-6b), 33.2–30.7–25.9–25.2 (cyclohexyl), 21.2 (CH_3CO).

6^A,6^C,6^E-Tris[*p*-anisidinyl-thioureido]-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-acetyl-hexakis(2,3-di-*O*-acetyl) cyclomaltohexaose 9. *p*-Anisidine (0.096 g, 6.0 equiv.), isothiocyanate **4** (0.2 g, 0.129 mmol); (0.178 g, 66%). Found: C, 51.46; H, 5.41; N, 3.87; S, 4.48; calc. for $C_{90}H_{114}N_6O_{45}S_3$: C, 51.56; H, 5.44; N, 4.01; S, 4.58%; FTIR υ_{max}(KBr)/cm^{-1} 1749 (C═O), 1648 (C═S); δ_H (400 MHz; $CDCl_3$) 6.72 (2H, d, *J* 8.8 Hz, H_{arom}), 6.61 (2H, d, *J* 8.8 Hz, H_{arom}), 5.59–5.49 (6H, m, 3-H), 5.08 (6H, d, *J* 3.3 Hz, 1-H), 7.74 (6H, dd, J_1 3.5 Hz, J_2 10.3 Hz, 2-H), 4.4 (6H, s, 6a-H), 4.13–4.22 (12H, m, 6b-H, 5-H), 3.78–3.82 (6H, m, 4-H), 3.71 (9H, s, OCH_3), 2.04 (45H, *several* s, CH_3–C═O); δ_C(100 MHz; $CDCl_3$) 179.6 (C═S), 168.9–167.6 (C═O), 130.4, 130.3, 126.9, 126.7 (C_{arom}), 94.7

(C-1), 75.3 (C-4), 69.1–67.7 (C-2, C-3, C-5), 61.4 (C-1a), 53.7 (OCH_3), 46.5 (C-6b), 19.1 (CH_3–CO).

6^A,6^C,6^E-Tris[di-*N*-butyl-thioureido]-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-acetyl-hexakis(2,3-di-*O*-acetyl) cyclomaltohexaose 10. Di-*N*-butylamine (0.075 g, 4.5 equiv.), isothiocyanate **4** (0.20 g, 0.129 mmol); (0.164 g, 60%). Found: C, 53.92; H, 6.89; N, 3.79; S, 4.45; calc. for $C_{95}H_{146}N_6O_{41}S_3$: C, 54.00; H, 6.91; N, 3.98; S, 4.54%; FTIR υ_{max}(KBr)/cm^{-1} 1749 (C═O), 1648 (C═S); δ_H (400 MHz; $CDCl_3$) 5.55 (6H, dd, J_1 8.8 Hz, J_2 10.1 Hz, 3-H), 5.04 (6H, d, *J* 3.5 Hz, 1-H), 4.78 (6H, dd, J_1 3.5 Hz, J_2 10.3 Hz, 2-H), 4.23 (6H, d, *J* 2.8 Hz, 6a-H), 4.21–4.15 (12H, m, 6b-H, 5-H), 3.78 (6H, dd, J_1 8.9 Hz, J_2 10.0 Hz, 4-H), 2.92 (12H, m, $CH_2\alpha$), 2.08 (45H, m, CH_3–C═O), 1.9 (12H, m, $CH_2\beta$), 1.41 (12H, m, $CH_2\gamma$), 0.96 (18H, t, *J* 7.3 Hz, CH_3 chain); δ_C(100 MHz; $CDCl_3$) 181.3 (C═S), 171.0, 169.7 (C═O), 96.8 (C-1), 77.5 (C-4), 71.2, 71.1, 69.8 (C-2, C-3, C-5), 63.5 (C-6a), 48.4 (C-6b), 30.0 ($CH_2\alpha$), 29.1 ($CH_2\beta$), 21.2 (CH_3–CO), 20.6 ($CH_2\gamma$), 14.0 (CH_3 chain).

6^A,6^C,6^E-Tris[benzyl-thioureido]-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-acetyl-hexakis(2,3-di-*O*-acetyl) cyclomaltohexaose 11. Benzylamine (0.062 g, 4.5 equiv.), isothiocyanate **4** (0.20 g, 0.129 mmol); (0.224 g, 85%). Found: C, 52.69; H, 5.52; N, 3.97; S, 4.29; calc. for $C_{90}H_{114}N_6O_{42}S_3$: C, 52.77; H, 5.57; N, 4.10; S, 4.69%; FTIR υ_{max}(KBr)/cm^{-1} 1749 (C═O), 1654 (C═S); δ_H (400 MHz; $CDCl_3$) 7.45–7.23 (15H, 1m, H_{arom}), 5.59 (6H, dd, J_1 9.3 Hz, J_2 9.2 Hz, 3-H), 5.06 (6H, d, *J* 3.2 Hz, 1-H), 4.79 (6H, dd, J_1 3.5 Hz, J_2 10.3 Hz, 2-H), 4.42 (12H, m, CH_2 benzyl), 4.18 (12H, m, 6b-H, 5-H), 3.81 (12H, m, H_{6b}, H_5), 3.81 (dd, J_1 = 9.1 Hz, J_2 = 9.2 Hz, H_4), 2.10 (45H, m, CH_3–C═O); δ_C(100 MHz; $CDCl_3$) 171.0–169.7 (C═O), 132.4, 129.1, 128.2, 127.8 (C_{arom}), 96.8 (C-1), 77.3 (C-4), 71.2–69.8 (C-2, C-3, C-5), 63.5 (C-6a), 44.8 (CH_2 benzyl) 21.2 (CH_3–CO).

6^A,6^C,6^E-Tris[cyclohexyl-thioureido]-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-acetyl-hexakis(2,3-di-*O*-acetyl) cyclomaltohexaose 12. Cyclohexylamine (0.058 g, 4.5 equiv.), **4** (0.20 g, 0.129 mmol); (0.143 g, 55%). Found: C, 51.57; H, 6.25; N, 4.03; S, 4.61; calc. for $C_{87}H_{126}N_6O_{42}S_3$: C, 51.61; H, 6.23; N, 4.15; S, 4.74%; FTIR υ_{max}(KBr)/cm^{-1} 1757 (C═O), 1654 (C═S); δ_C(100 MHz; $CDCl_3$) 181.8 (C═S), 171.0–169.5 (C═O), 96.9 (C-1), 77.6 (C-4), 71.2–69.7 (C-2, C-3, C-5), 63.5 (C-6a), 50.7 (C-6b), 33.0, 25.8, 25.1, 24.7 (cyclohexyl), 21.2 (CH_3CO).

Isocyanates 17–19 general procedure. The hepta-*O*-acetyl monoazido disaccharide (0.5 mmol) and triphenylphosphine (0.655 g, 2.5 mmol) were dissolved in anhydrous toluol (10 mL). The resulting solution was stirred for 2 h at rt; and then 24 h under anhydrous CO_2 bubbling. Cyclohexane (40 mL) was then added to the solution, a white solid powder precipitated and was filtered on a glass sinter, washed several times with small quantities of cyclohexane and dried under vacuum to give the pure white isocyanate powder.

2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-isocyanato-β-D-cellobiose 17. (0.312 g, 95%). TLC (EtOAc–hexane; 7 : 3): R_f = 0.43; found C, 49.09; H, 5.37; N, 2.22; calc. for $C_{27}H_{35}NO_{18}$: C, 49.02; H, 5.33; N, 2.12%; FTIR υ_{max}(KBr)/cm^{-1} 2190 (N═C═O), 1751 (C═O), 1229, 1043. δ_H (400 MHz; $CDCl_3$) 5.16 (2H, t *large*, *J* 9.6 Hz, 3-H, 3′-H), 5.09 (1H, t, $J^{4'-5'}$ 9.6 Hz, $J^{4'-3'}$ 9.6 Hz, 4′-H), 4.94 (1H, t, $J^{2'-3'}$ 9.0 Hz, $J^{2'-1'}$ 8.3 Hz, 2′-H), 4.87 (1H, t, J^{2-3} 9.3 Hz, J^{2-1} 8.8 Hz, 2-H), 4.73 (1H, d, J^{1-2} 8.8 Hz, 1-H), 4.54 (1H, d, J^{6b-6a} 12.0 Hz, 6b-H), 4.53 (1H, d, $J^{1'-2'}$ 8.3 Hz, 1′-H), 4.39 (1H, dd, $J^{6'b-6'a}$ 12.6 Hz, $J^{6'b-5'}$ 4.04 Hz, 6′b-H), 4.14 (1H, dd, J^{6a-6b} 12.08 Hz, J^{6a-5} 5.0 Hz, 6a-H4), 4.05 (1H, d, $J^{6'a-6'b}$ 12.6 Hz, 6′a-H), 3.81 (1H, t, J^{4-3} 9.6 Hz, J^{4-5} 9.3 Hz, 4-H), 3.69–3.65 (2H, m, 5-H, 5′-H), 2.16, 2.14, 2.06, 2.05, 2.03, 2.03, 2.00 (21H, 7s, CH_3, Ac); δ_C(100 MHz; $CDCl_3$) 170.9, 170.7, 170.6, 170.1, 169.8, 169.7, 169.4 (7*C*O, Ac), 137.9 (*C*O, N═*C*═O), 101.2 (C-1′), 84.3 (C-1), 76.5 (C-4), 75.2 (C-5), 73.3 (C-3), 73.0, 72.9 (C-2, C-5′), 72.4 (C-3′), 72.0 (C-2′), 68.1 (C-4′), 62.0, 61.9 (C-6, C-6′), 21.26, 21.05, 20.98, 20.93, 20.92, 20.91, 20.87 (*several* s, 7CH_3, Ac); ES-MS *m*/*z*: 662.12 $[M + H]^+$.

2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-isocyanato-β-D-lactose 18. (0.301 g, 91%). TLC (EtOAc–hexane; 7 : 3): R_f = 0.48; found C, 48.98; H, 5.39; N, 2.24; calc. for $C_{27}H_{35}NO_{18}$ C, 49.02; H, 5.33; N, 2.12%; FTIR υ_{max}(KBr)/cm^{-1} 2192 (N═C═O), 1752 (C═O), 1226, 1069; δ_H (400 MHz; $CDCl_3$) 5.33 (1H, dd, $J^{4'-3'}$ 3.2 Hz, $J^{4'-5'}$ 1.5 Hz, 4′-H), 5.15 (1H, t, J^{3-2} 9.3 Hz, J^{3-4} 9.3 Hz, 3-H), 5.08 (1H, dd, $J^{2'-3'}$ 10.0 Hz, $J^{2'-1'}$ 8.0 Hz, 2′-H), 4.94 (1H, t, $J^{3'-4'}$ 3.2 Hz, $J^{3'-2'}$ 10.0 Hz, 3′-H), 4.83 (1H, t, J^{2-3} 9.0 Hz, J^{2-1} 9.0 Hz, 2-H), 4.70 (1H, d, J^{1-2} 9.0 Hz, 1-H), 4.51 (1H, d, $J^{1'-2'}$ 8.0 Hz, 1′-H), 4.50 (1H, d, J^{6b-6a} 12.0 Hz, 6b-H), 4.13–4.03 (3H, m, 6′b-H, 6′a-H, 6b-H), 3.88–3.85 (1H, m, 5′-H), 3.80 (1H, t, J^{4-3} 9.6 Hz, J^{4-5} 9.6 Hz, 4-H), 3.66–3.63 (1H, m, 5-H), 2.13, 2.12, 2.04, 2.02, 2.02, 2.02, 1.94 (21H, 7s, CH_3, Ac); δ_C(100 MHz; $CDCl_3$) 170.7, 170.6, 170.5, 170.4, 170.1, 169.8, 169.4 (7*C*O, Ac), 137.9 (N═*C*═O), 101.5 (C-1′), 84.2 (C-1), 76.3 (C-4), 75.1 (C-5), 73.3, (C-3), 73.1 (C-2), 71.3 (C-3′), 71.1 (C-5′), 69.5 (C-2′), 67.0 (C-4′), 62.1 (C-6), 61.1 (C-6′), 21.2, 21.1, 21.0, 20.9 (*several* s, 7CH_3, Ac); ES-MS *m*/*z*: 662.24 $[M + H]^+$.

2,3,4,1′,3′,4′,6-Hepta-*O*-acetyl-6′-isocyanato-6′deoxy sucrose 19. (0.189 g, 57%). TLC (EtOAc–hexane; 7 : 3): R_f = 0.43; FTIR υ_{max}(KBr)/cm^{-1} 2140 (N═C═O), 1748, (C═O), 1225, 1040; δ_H (400 MHz; $CDCl_3$) 5.66 (1H, d, J^{1-2} 3.5 Hz, 1-H), 5.47 (1H, d, $J^{3'-4'}$ 7.0 Hz, 3′-H), 5.44 (1H, t, J^{3-2} 10.6 Hz, J^{3-4} 9.8 Hz, 3-H), 5.32 (1H, dd, $J^{4'-3'}$ 7.0 Hz, $J^{4'-5'}$ 4.8 Hz, 4′-H), 5.09 (1H, t, J^{4-3} 9.8 Hz, J^{4-5} 9.8 Hz, 4-H), 4.90 (1H, dd, J^{2-1} 3.5 Hz, J^{2-3} 10.6 Hz, 2-H), 4.11–4.08 (6H, m, 1′a-H, 1′b-H, 6a-H, 6b-H, 5-H, 5′-H), 3.68 (1H, dd, $J^{6'a-6'b}$ 13.1 Hz, $J^{6'a-5'}$ 7.3 Hz, 6′a-H), 3.55 (1H, dd, $J^{6'b-6'a}$ 13.1 Hz, $J^{6'b-5'}$ 4.8 Hz, 6′b-H), 2.19, 2.12, 2.12, 2.10, 2.10, 2.07, 2.02, (21H, 7s, CH_3, Ac); δ_C(100 MHz; $CDCl_3$) 171.1, 170.8, 170.7, 170.3, 170.2, 169.9, 169.8 (7*C*O, Ac), 139.4 (N═*C*═O), 104.0 (C-2′), 90.2 (C-1), 80.9 (C-5′), 77.4 (C-3′), 76.0 (C-4′), 70.3 (C-2), 69.7 (C-3), 69.5 (C-4), 68.4 (C-5), 63.6 (C-6′), 63.0 (C-1′), 62.0 (C-6), 21.5–20.9 (*several* s, 7CH_3, Ac).

6^A,6^C, 6^E-Tris-isocyanato-6^A,6^C, 6^E-trideoxy-6^B,6^D,6^F-tri-*O*-methyl-hexakis(2,3-di-*O*-methyl) cyclomaltohexaose 20. Anhydrous DMF (50 mL), ^{ACE}tris-6-azido-per-*O*-methylated-α-cyclodextrin,[19] **16**, (0.2 g, 0.108 mmol) polystyrene bound triphenylphosphine resin (2.0 g, 6 mmol) are placed in a solid phase peptide synthesis reactor. The resulting mixture was then stirred for 24 h at room temperature under anhydrous CO_2 bubbling. The mixture was filtered and evaporated until dryness. The residue was treated with anhydrous DMF (2 mL) and precipitated with cyclohexane (100 mL). The pure product was obtained as a white powder (0.156 g, 78%). FTIR υ_{max}(KBr)/cm^{-1} 2261 (N=C=O), δ_H (400 MHz; CDCl$_3$) 4.96 (6H, m, 1-H^{A-F}), 3.76 (12H, m, 2-H^{A-F}, 3-H^{A-F}), 3.68 (6H, m, 4-H^{A-F}), 3.57 (18H, s, O–CH_3), 3.49 (6H, m, 5-H^{A-F}), 3.43 (18H, s, O–CH_3), 3.33 (9H, s, O–CH_3), 3.09 (12H, m, 6-H$^{ACE+BDF}$); δ_C(100 MHz; CDCl$_3$) 127.8 (N=C=O^{B,D,F}), 100.6 (C-1^{A-F}), 83.8 (C-4^{A-F}), 82.7 (C-2 $^{A-F}$), 81.6 (C-3 $^{A-F}$), 71.6 (C-5 $^{A-F}$), 62.2 (C-6 $^{A-F}$), 59.5 (O–CH$_3$), 58.4 (O–CH$_3$).

Isothiocyanates 21–22 general procedure. The hepta-*O*-acetyl monoazido disaccharide (0.5 mmol) and triphenylphosphine (0.655 g, 2.5 mmol) were dissolved in anhydrous toluol (10 mL). The resulting solution was stirred for 2 h at rt, then CS$_2$ (1.90 g, 25 mmol) was added to the solution and the resulting mixture was stirred for a further 48 h under argon. Cyclohexane (40 mL) was then added to the solution, a white solid powder precipitated and was filtered on a glass sinter, washed several times with small quantities of cyclohexane and dried under vacuum to give the pure white isothiocyanate powder.

2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-isothiocyanato-β-D-cellobiose 21. (0.211 g, 64%). FTIR υ_{max}(KBr)/cm^{-1} 2157 (N=C=S), 1752 (C=O); TLC (EtOAc–hexane; 7 : 3): R_f = 0.3; δ_H (400 MHz; CDCl$_3$) 5.16 (2H, t *large*, $J^{3'-4'}$ 9.6 Hz, J^{3-2} 9.3 Hz, 3-H, 3′-H), 5.09 (1H, t, $J^{4'-3'}$ 9.6 Hz, $J^{4'-5'}$ 9.6 Hz, 4′-H), 4.92 (1H, t, $J^{2'-3'}$ 9.0 Hz, $J^{2'-1'}$ 8.3 Hz, 2′-H), 4.87 (1H, t, J^{2-3} 9.3 Hz, J^{2-1} 8.8 Hz, 2-H), 4.72 (1H, d, J^{1-2} 8.8 Hz, 1-H), 4.53 (1H, d, $J^{1'-2'}$ 8.3 Hz, 1′-H), 4.52 (1H, d, J^{6b-6a} 12.0 Hz, 6b-H), 4.38 (1H, dd, $J^{6'b-6'a}$ 12.6 Hz, $J^{6'b-5'}$ 4.04 Hz, 6′b-H), 4.14 (1H, dd, J^{6a-6b} 12.08 Hz, J^{6a-5} 5.04 Hz, 6a-H), 4.05 (1H, dd, $J^{6'a-6'b}$ 12.6 Hz, $J^{6'a-5}$ 2.0 Hz, 6′a-H), 3.81 (1H, t, J^{4-3} 9.6 Hz, J^{4-5} 9.3 Hz, 4-H), 3.68–3.66 (2H, m, 5-H, 5′-H), 2.15, 2.10, 2.06, 2.05, 2.03, 2.03, 2.00 (21H, 7s, CH$_3$, Ac); δ_C(100 MHz; CDCl$_3$) 170.8, 170.6, 170.5, 170.1, 170.0, 169.7, 169.4 (7CO, Ac), 144.5 (N=C=S), 101.2 (C-1′), 84.3 (C-1), 76.2 (C-4), 75.3 (C-5), 73.2 (C-3), 72.5, 72.4 (C-2, C-5′), 72.0 (C-3′), 71.9 (C-2′), 68.1 (C-4′), 62.0, 61.9 (C-6, C-6′), 21.3, 21.2, 21.1, 21.0, 20.9, 20.8 (*several* s, 7CH$_3$, Ac); ES-MS m/z: 700 [M + Na]$^+$.

2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-isothiocyanato-β-D-lactose 22. (0.223 g, 66%). TLC (EtOAc–hexane; 7 : 3): R_f = 0.40; FTIR υ_{max}(KBr)/cm^{-1} 2153 (N=C=S), 1751 (C=O), 1232, 1050; δ_H (400 MHz; CDCl$_3$) 5.37 (1H, d *large*, $J^{4'-3'}$ 3.2 Hz, $J^{4'-5'}$ 1.0 Hz, 4′-H), 5.19 (1H, t, J^{3-2} 9.1 Hz, J^{3-4} 9.4 Hz, 3-H), 5.12 (1H, t, $J^{2'-3'}$ 10.0 Hz, $J^{2'-1'}$ 8.0 Hz, 2′-H), 4.97 (1H, t, $J^{3'-4'}$ 3.3 Hz, $J^{3'-2'}$ 10.0 Hz, 3′-H), 4.87 (1H, d, J^{2-3} 9.1 Hz, J^{2-1} 9.0 Hz, 2-H), 4.66 (1H, d, J^{1-2} 9.0 Hz, 1-H), 4.51 (1H, d, $J^{1'-2'}$ 8.3 Hz, 1′-H), 4.50 (1H, d, J^{6b-6a} 12.0 Hz, 6b-H), 4.16–4.07 (3H, m, 6b-H, 6′a-H, 6b-H), 3.90–3.86 (1H, m, 5′-H), 3.84 (1H, dd, J^{4-3} 9.4 Hz, J^{4-5} 9.6 Hz, 4-H), 3.70–3.67 (1H, m, 5-H), 2.17, 2.15, 2.08, 2.07, 2.06, 2.05, 1.98 (21H, 7s, CH$_3$, Ac); δ_C(100 MHz; CDCl$_3$) 170.7, 170.6, 170.5, 170.4, 170.1, 169.9, 169.4 (7CO, Ac), 144.5 (N=C=S), 101.5 (C-1′), 84.3 (C-1), 76.3 (C-4), 75.1 (C-5), 73.3, (C-3), 73.1 (C-2), 71.3, 71.1 (C-5, C-3′), 69.5 (C-2′), 67.0 (C-4′), 62.2, 61.1 (C-6, C-6′), 21.3, 21.2, 21.1, 21.03, 21.02, 21.01, 20.9 (*several* s, 7 CH$_3$, Ac).

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