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An efficient synthesis of L-idose and L-iduronic acid thioglycosides and their use for the synthesis of heparin oligosaccharides☆

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Abstract—Efficient preparations of thioglycoside derivatives of L-idose and L-iduronic acid are described. The method avoids the tedious chromatographic separations of furanose and pyranose anomeric mixtures, and affords the thioglycosides in a stereoselective manner. The L-idose and L-iduronic acid thioglycosides having combinations of different protecting groups proved to be efficient glycosyl donors in the synthesis of heparin disaccharides.

Keywords: Heparin; L-Iduronic acid; Thioglycosides; Glycosylation; Oligosaccharide synthesis

1. Introduction

The structurally related heparin (HP) and heparan sulfate (HS), members of the glycosaminoglycan family of polysaccharides, interact with a large number of proteins of diverse biological functions.[1,2] Heparin–protein interactions modulate the biological activities of these proteins and affect a series of physiological processes. It is commonly assumed, though not rigorously proven, that specific oligosaccharide structures within the heterogeneous polysaccharide chains are responsible for the binding to individual proteins.[3,4]

Identification of oligosaccharide ligands of individual heparin-binding proteins would be most conveniently done by screening the proteins against libraries of homogeneous HP/HS oligosaccharides. These oligosaccharides are, however, accessible only with extreme difficulties by degradations of the natural polysaccharides. Chemical synthesis is a viable option to provide well-defined HP/HS oligosaccharide sequences for reviews on the syntheses of heparin oligosaccharides.[5–12] Whereas earlier synthetic approaches targeted a single heparin oligosaccharide in each synthesis,[5] more recently synthetic strategies are being developed with the aim of generating a series of heparin oligosaccharides.[13–20] We have developed[21,22] a new synthesis strategy based on orthogonal protection of the positions, which are optionally sulfated in the target compounds. In this way, from a single protected oligosaccharide, a large number of differently sulfated derivatives could be synthesized.

Heparin and heparan sulfate are built up of alternating D-glucosamine and hexuronic acid units, the latter being either D-glucuronic acid or L-iduronic acid. Whereas building blocks of D-glucosamine and D-glucuronic

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acid for oligosaccharide synthesis are accessible with relative ease, the synthesis of L-iduronic acid derivatives is more problematic. Neither L-idose and L-iduronic acid nor their derivatives are available commercially. Most of the synthetic methods for their preparation start from some D-glucose or D-glucuronic acid derivative and involve C-5 epimerization either on the hexose[23–27] or on the hexuronic acid[28–34] stage, though stereoselective procedures using chain-elongation of pentose derivatives have also been developed.[35] For the appropriately protected derivatives required for oligosaccharide synthesis, the introduction of the protecting groups is normally done partly at the D-*gluco* and partly at the L-*ido* stage. The use of D-glucofuranose derivatives not only offers easy access to C-5 for inversion by different methods but also allows the ready introduction of some of the required protecting groups. The furanose→pyranose switch, however, is troublesome in these syntheses as high proportions of the furanose anomers are formed both with L-idose and L-iduronic acid derivatives, and the separation of the different tautomers requires tedious chromatographic separations and prevents large scale synthesis. Although significant improvement has been made[36] by optimization of the reaction conditions for the formation of a pyranose anomer on a particular iduronic acid derivative, the generality of these conditions for the preparation of other derivatives remains to be seen.

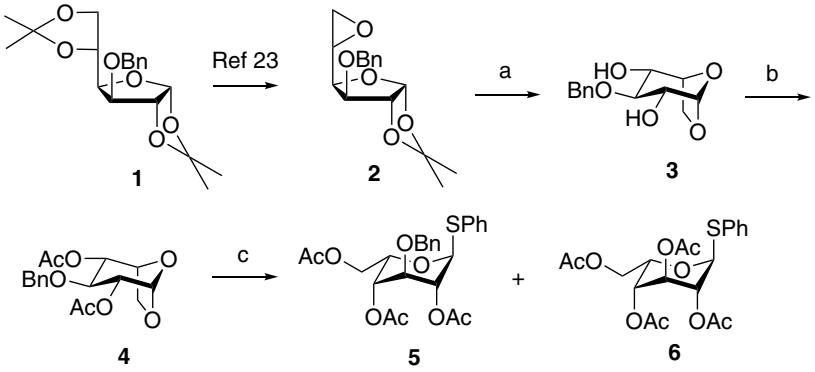
Until very recently[21,22,37] almost invariably only trichloroacetimidate derivatives of L-idose and L-iduronic acid have been used as glycosyl donors in the synthesis of heparin oligosaccharides. Attempted use of thioglycosides was reported to be discouraging,[38] due to difficulties in their preparation and inferior results in glycosylations. Thioglycosides, in general, can be advantageously used in oligosaccharide syntheses,[39–42] as they can be used both as glycosyl donors and glycosyl acceptors, and as the thioglycoside function remains intact under most protecting group manipulations. Both the dual donor–acceptor property of thioglycosides, which reduces the number of monomers required for the synthesis of higher oligosaccharides, and the well-known stability of thioglycosides in protecting group transformations made this type of compound attractive for our synthesis strategy, which relies heavily on protecting group manipulations.

For these reasons, we have developed a stereoselective synthesis method for the preparation of phenyl 3-*O*-benzyl-1-thio-α-L-idopyranoside, a key synthon in our synthesis strategy, and prepared various L-idose and L-iduronic acid derivatives from it. We also report on the use of these compounds as glycosyl donors for the synthesis of various protected heparin oligosaccharide derivatives.

2. Results and discussion

The commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) was converted into L-*ido* epoxide (**2**) by the method of van Boeckel,[23] which can readily be performed on a 100 g scale (Scheme 1). Treatment of the epoxide (**2**) with 1 M H_2SO_4 in dioxane at reflux temperature afforded the 1,6-anhydro-β-L-idopyranose derivative (**3**) in a single step via epoxide opening, isopropylidene hydrolysis and intramolecular glycosylation. In compound **3**, the ring is fixed in the pyranose form, and as the reaction product was readily isolated by crystallization in 65% yield, the synthesis of this intermediate eliminates the need for the tedious chromatographic separation of the furanose and pyranose tautomers needed in other synthetic routes. Formation of 1,6-anhydro-β-L-idopyranose from 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose under strongly acidic conditions has been observed before[43] and after presenting our results[21,22] a similar synthesis of **3** has been reported[44] independently.

For the conversion of **3** into a thioglycoside, the compound was first acetylated to give the crystalline diacetate (**4**). Thiolysis of compound **4** with



Scheme 1. Synthesis of phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-thio-α-L-idopyranoside. Reagents and conditions: (a) 1 M H_2SO_4, dioxane, 65%; (b) Ac_2O, pyridine, 93%; (c) (i) $PhSSi(CH_3)_3$, ZnI_2, CH_2Cl_2, (ii) Ac_2O, pyridine, 76%.

trimethyl(phenylthio)silane in the presence of ZnI_2[45,46] afforded the thioglycoside. As partial acetyl migration was observed in the crude thiolysis product, the thioglycoside was isolated after acetylation in the form of its triacetate (**5**) in 76% yield. The thiolysis reaction was accompanied by partial debenzylation, which resulted in the formation of the tetra-*O*-acetyl derivative (**6**) as by-product isolated in 8% yield. The anomeric configuration of **5** proved to be α, which was ascertained by the $^1J_{C\text{-}1,H\text{-}1}$ value of 168 Hz, and no β thioglycoside could be detected. The stereoselectivity of this thioglycosidation is noteworthy, as the reaction of 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-L-idopyranose with thiols in the presence of $BF_3{\cdot}Et_2O$ gave anomeric mixtures of thioglycosides (details not given). Non-stereoselective formation of thioglycosides from 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-L-idopyranose has also been reported by others recently.[37,47,48] The preparative ease of the furanose→pyranose transformation via **3** and the stereoselectivity of the thiolysis of **4** allowed the preparation of large quantities of **5**, which was the key compound for further transformations.

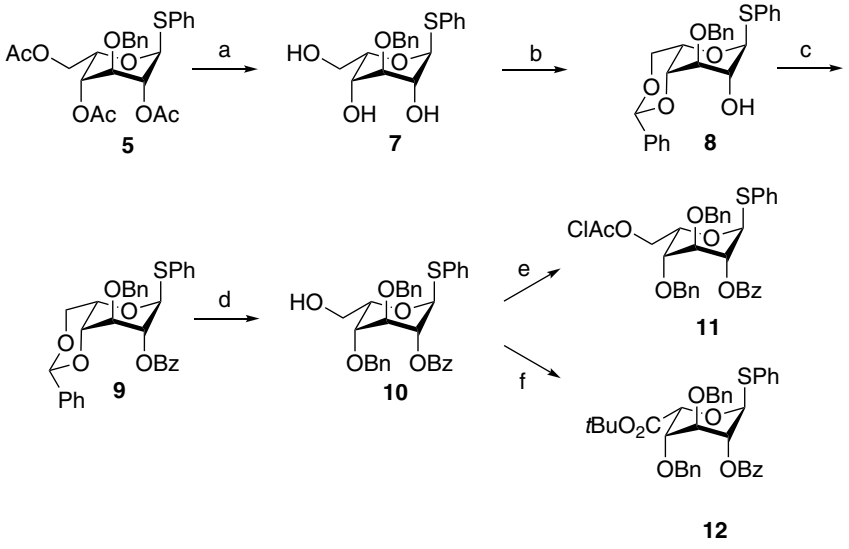
To convert **5** to building blocks to be used in heparin oligosaccharide synthesis, the compound was first subjected to Zemplén deacetylation to give the triol (**7**) (Scheme 2). Benzylidenation of **7** with benzaldehyde dimethyl acetal in the presence of camphorsulfonic acid in DMF afforded the crystalline acetal (**8**), which was benzoylated to give **9**. Compounds **7**–**9** were obtained in crystalline form and had more negative optical rotations than those published.[38] Reductive opening of the 4,6-*O*-benzylidene acetal with $BH_3{\cdot}NMe_3$–$AlCl_3$[49] in ether–dichloromethane[50] afforded the primary alcohol **10**. Chloroacetylation of **10** gave the thioglycoside L-idopyranosyl glycosyl donor (**11**) having a temporary protecting group at O-6 allowing later conversion to the uronic acid. For the synthesis of an L-iduronosyl donor, **10** was oxidized with pyridinium dichromate in the presence of acetic anhydride and *tert*-butanol[51] to give the *tert*-butyl ester **12**. In this reaction, the oxidation of the sulfur to the corresponding sulfoxide and sulfone could almost completely be avoided.

For the synthesis of higher oligosaccharides, L-iduronic acid derivatives having a temporary protecting group at O-4 are required. We have previously proposed[52] the use of the (1-naphthyl)methyl (^{1}NAP) group as a less expensive alternative of the (2-naphthyl)methyl[53,54] regioisomer. (1-Naphthyl)methyl ethers are readily prepared by, among others, reductive cleavage of (1-naphthyl)methylidene acetals, and the selective removal of the (1-naphthyl)methyl group with ceric ammonium nitrate can be accomplished in the presence of benzyl groups.[52] We have, therefore, synthesized 4-*O*-(1-naphthyl)methylated L-iduronic acid thioglycosides, which will allow chain elongation toward the nonreducing terminus.

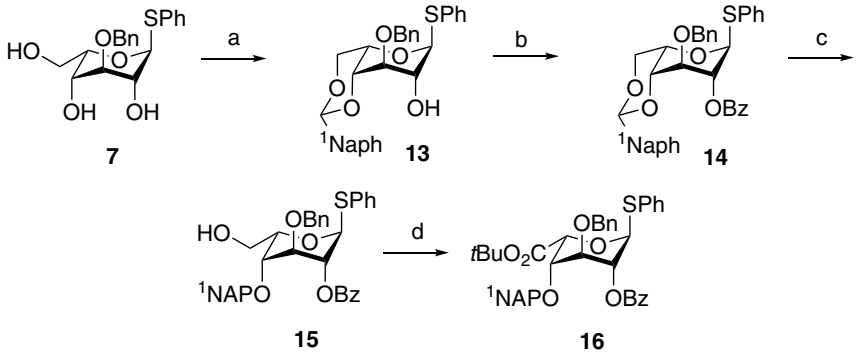
The triol **7** was treated with 1-naphthaldehyde dimethyl acetal to give the (1-naphthyl)methylidene derivative **13** (Scheme 3). After benzoylation, regioselective reductive opening of the 4,6-*O*-(1-naphthyl)methylidene acetal in **14** was carried out by our recently developed method[55] using $BH_3{\cdot}THF$ and TMSOTf to give the 4-*O*-(1-naphthyl)methyl ether (**15**) in 92% yield. Oxidation of **15**, as for **12**, gave the *tert*-butyl L-iduronate thioglycoside **16**.

The preparations of both the 4-*O*-benzylated and 4-*O*-(1-naphthyl)methylated L-idose and L-iduronic acid thioglycosides were readily performed on a 10 g scale.

The glycosylating capability of the L-idose and L-iduronic acid thioglycosides was tested using D-glucosamine



Scheme 2. Synthesis of L-*ido* thioglycoside donors. Reagents and conditions: (a) NaOMe, MeOH, 99%; (b) $PhCH(OMe)_2$, CSA, DMF, 88%; (c) BzCl, pyridine, CH_2Cl_2, 85%; (d) $BH_3{\cdot}NMe_3$, $AlCl_3$, CH_2Cl_2, Et_2O, 71%; (e) $ClCH_2C(O)Cl$, pyridine, CH_2Cl_2, 76%; (f) PDC, Ac_2O, *t*BuOH, CH_2Cl_2, 62%.



Scheme 3. Synthesis of *tert*-butyl (phenyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)methyl-1-thio-α-L-idopyranoside)uronate. Reagents and conditions: (a) ^{1}NaphCH(OMe)$_2$, CSA, DMF, 98%; (b) BzCl, pyridine, CH_2Cl_2, 98%; (c) BH_3·THF, TMSOTf, CH_2Cl_2, 92%; (d) PDC, Ac_2O, *t*BuOH, CH_2Cl_2, (74%).

derivatives **17**,[56] **20**[57] and **23**[25] having O-4 free and differing in their substituents at O-6 (Scheme 4). Reaction of the L-idose thioglycoside **11** with **17** promoted by DMTST[58] proceeded smoothly and afforded disaccharide **18** in 71% yield. The 1-naphthylmethylidene acetal (**14**) could also be used as glycosyl donor. Its reaction with **17** was performed using our recently developed powerful promoter system[59] of dimethyl disulfide–triflic anhydride. The reaction proceeded at −40 °C within 10 min and gave disaccharide **19** in 90% yield.

Glycosylations of acceptors **20** and **17** with the L-iduronic acid thioglycoside **12** were performed at room temperature in the presence of DMTST, and afforded disaccharides **21** and **22** in excellent yields (86% and 88%, respectively). Moreover, the 6-*O*-chloroacetylated acceptor **23** was coupled with thioglycoside **16** under the same conditions to give the disaccharide **24** in 71% yield. The anomeric configuration of the interglycosidic linkages was proved to be α by the $^{1}J_{C\text{-}1,H\text{-}1} = 171$ Hz coupling constant. It is noteworthy that while uronic acids, in general, tend to be poorer glycosyl donors than the corresponding neutral sugars, no such difference could be observed in the above cases. Our results clearly show that thioglycosides of both L-idose and L-iduronic acid can be used efficiently as glycosyl donors.

The above disaccharides are important intermediates in our syntheses of various heparin oligosaccharides.

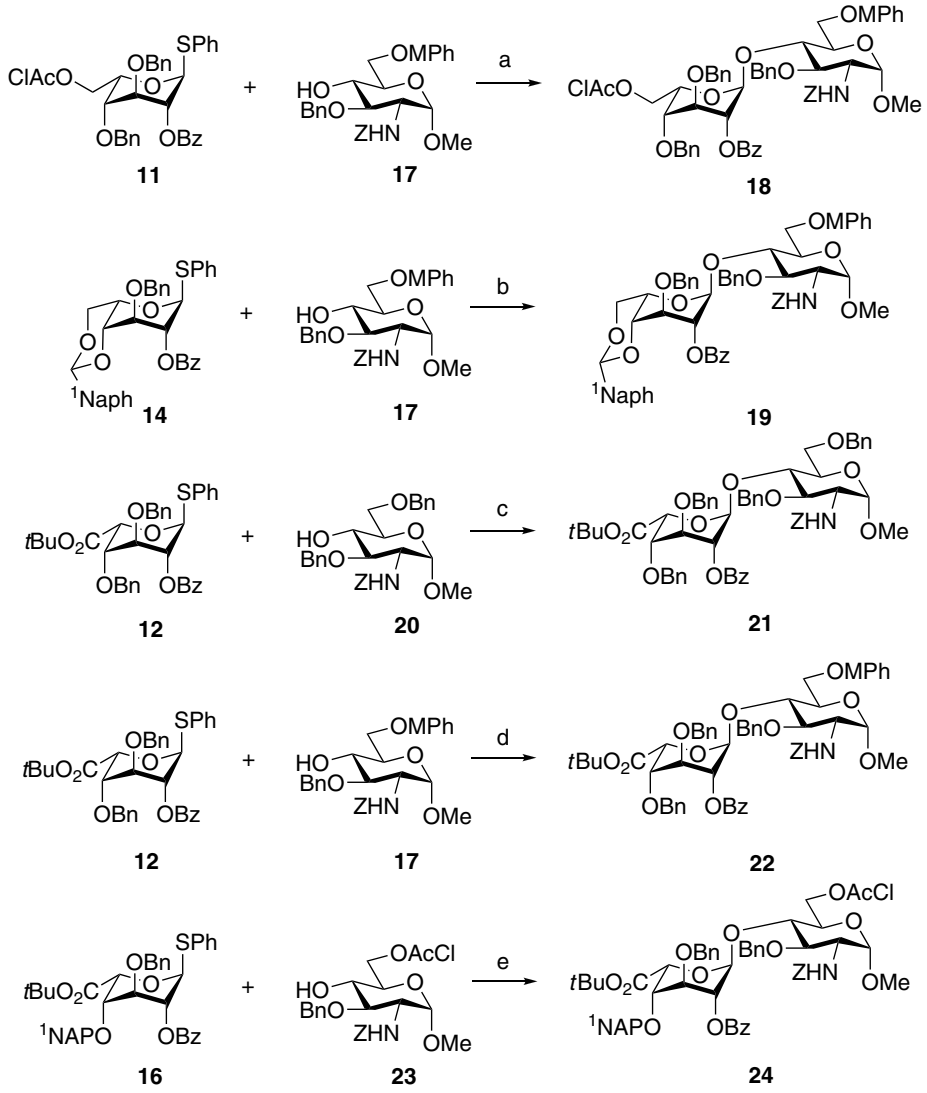
3. Experimental

3.1. General methods

Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure at 40 °C. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (E. Merck, Darmstadt), the compounds were detected under UV light and by spraying the plates with a 0.02 M solution of resorcinol in 20% methanolic H_2SO_4 solution followed by heating. For column chromatography, Silica Gel 60 (0.040–0.063 mm) (E. Merck) was employed. Melting points were determined in capillary tubes on a Griffin melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C with an Optical Activity AA-10R polarimeter. The NMR spectra were recorded on Varian Gemini 2000 (^{1}H: 200 MHz; ^{13}C: 50 MHz), Varian Gemini 3000 (^{1}H: 300 MHz; ^{13}C: 75 MHz), and Varian Unity-Inova (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers at ambient temperature in $CDCl_3$. The chemical shifts were referenced to TMS (0.00 ppm for ^{1}H) and to the central line of $CDCl_3$ (77.16 ppm for ^{13}C) as internal standards. Elemental analyses were performed with an Elementar Vario EL III instrument at the Analytical Department of the Chemical Research Center, Hungarian Academy of Sciences.

3.2. 1,6-Anhydro-3-*O*-benzyl-β-L-idopyranose (3)

A solution of **2** (33.4 g, 114 mmol) in 2 M aq H_2SO_4 (70 mL) and dioxane (70 mL) was heated under reflux overnight. The mixture was cooled to room temperature, neutralized with aq $Ba(OH)_2$, the solid was removed by filtration and was washed with EtOAc. The filtrate was extracted with EtOAc (3 × 500 mL), the organic layers were combined and it was washed with water, dried and concentrated. The residue was crystallized from EtOH to afford **3** as a white solid (18.6 g, 65%); mp 155–156 °C, lit.[60] 158–159 °C; $[\alpha]_D$ +66 (*c* 0.4, MeOH), lit.[60] +69 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.26 (m, 5H, aromatic), 5.27 (d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 4.95 and 4.73 (2d, 2H, *J* 11.7 Hz, $PhCH_2$), 4.42 (t, 1H, $J_{4,5}\sim J_{5,6a}$ 4.8 Hz, H-5), 4.04 (d, 1H, $J_{6a,6b}$ 7.7 Hz, H-6a), 3.87 (ddd, 1H, H-4), 3.72 (dd, 1H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.65 (dt, 1H, H-2), 3.39 (t, 1H, $J_{2,3}\sim J_{3,4}$ 8.0 Hz, H-3), 2.20 (d, 1H, $J_{4,OH\text{-}4}$ 3.3 Hz, OH-4), 2.05 (d, 1H, $J_{2,OH\text{-}2}$ 8.8 Hz, OH-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 127.9, 127.6, 127.3 (aromatic), 101.8 (C-1), 83.3 (C-3), 75.4, 74.6 (C-2, C-4), 74.5 ($PhCH_2$), 70.8 (C-5), 64.5 (C-6).



Scheme 4. Synthesis of heparin related disaccharides. Reagents and conditions: (a) DMTST, CH_2Cl_2, 71%; (b) Me_2S_2–Tf_2O, DTBMP, CH_2Cl_2, 90%; (c) DMTST, CH_2Cl_2, 86%; (d) DMTST, CH_2Cl_2, 88%; (e) DMTST, CH_2Cl_2, 71%.

3.3. 2,4-Di-*O*-acetyl-1,6-anhydro-3-*O*-benzyl-β-L-idopyranose (4)

To a solution of **3** (13.5 g, 53.5 mmol) in dry pyridine (90 mL), acetic anhydride (50 mL) was added at 0 °C. The mixture was stirred at room temperature overnight, after which the reaction was quenched with water. The mixture was diluted with CH_2Cl_2 (500 mL), washed with aq 2 M HCl, saturated aq $NaHCO_3$, and water. The organic phase was dried and concentrated. The residue was crystallized from EtOAc–hexanes to afford **4** (16.7 g, 93%); mp 78–80 °C; $[\alpha]_D$ +50 (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.41–7.23 (m, 5H, aromatic), 5.45 (d, 1H, $J_{1,2}$ 1.5 Hz, H-1), 5.05 (ddd, 1H, $J_{3,4}$ 8.8 Hz, $J_{4,5}$ 4.4 Hz, $J_{4,6b}$ 1.1 Hz, H-4), 4.84 (dd, 1H, $J_{2,3}$ 8.4 Hz, H-2), 4.65 (s, 2H, $PhCH_2$), 4.61 (dd, 1H, $J_{5,6a}$ 4.8 Hz, H-5), 4.03 (d, 1H, $J_{6a,6b}$ 7.7 Hz, H-6a), 3.86 (t, 1H, H-3), 3.73 (ddd, 1H, $J_{5,6b}$ 4.8 Hz, H-6b), 2.06 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.2 (O*C*(O)CH_3), 169.8 (O*C*(O)-CH_3), 138.2, 128.6, 127.9, 127.7 (aromatic), 99.4 (C-1), 77.2 (C-3), 76.3 (C-2), 74.6 ($PhCH_2$), 72.8 (2C, C-4, C-5), 65.7 (C-6), 21.02 (CH_3), 20.97 (CH_3). Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.68, H, 5.98.

3.4. Phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-thio-α-L-idopyranoside (5)

To a solution of **4** (13.5 g, 40.1 mmol) in dry CH_2Cl_2 (150 mL), trimethyl(phenylthio)silane (22.7 mL, 121 mmol) and ZnI_2 (25.6 g, 80.2 mmol) were added. The mixture was stirred at room temperature overnight, filtered through a pad of Celite. The filtrate was diluted with CH_2Cl_2 (400 mL), after which a solution of HCl in dioxane (18 mL) and water (10 mL) were added.

The mixture was stirred at room temperature for 10 min, the organic layer was washed with aq 2 M HCl, saturated aq $NaHCO_3$, and water, filtered and concentrated. To the solution of the residue in dry pyridine (50 mL), acetic anhydride (19 mL) was added at 0 °C. The mixture was stirred at room temperature overnight, after which the reaction was quenched with water. The mixture was diluted with CH_2Cl_2, washed with aq 2 M HCl, saturated aq $NaHCO_3$, and water. The organic layer was dried and concentrated. The residue was purified by column chromatography using 5:1 hexane–acetone as eluent to give first **5** as a syrup (14.8 g, 76%); $[\alpha]_D$ −105 (*c* 0.4, $CHCl_3$), lit.[38] −91 (*c* 0.56, $CHCl_3$), lit.[47] −95 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.59–7.24 (m, 10H, aromatic), 5.50 (d, 1H, $J_{1,2}$ 1.3 Hz, H-1), 5.17 (dd, 1H, $J_{2,3}$ 2.6 Hz, H-2), 5.02 (ddd, 1H, $J_{5,6a}$ 7.5 Hz, $J_{5,6b}$ 5.3 Hz, H-5), 4.89 (dd, 1H, $J_{4,5}$ 2.0 Hz, H-4), 4.85 and 4.69 (2d, 2H, *J* 11.0 Hz, $PhCH_2$), 4.28 (dd, 1H, $J_{6a,6b}$ 11.5 Hz, H-6a), 4.18 (dd, 1H, H-6b), 3.79 (ddd, 1H, $J_{3,4}$ 2.8 Hz, $J_{1,3}$ 1.1 Hz, H-3), 2.09 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.02 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7 (O*C*(O)CH_3), 170.2 (O*C*(O)CH_3), 169.6 (O*C*(O)-CH_3), 137.2, 135.9, 131.5, 129.0, 128.6, 128.1, 127.8, 127.6 (aromatic), 86.0 (C-1, $J_{C\text{-}1,H\text{-}1}$ 168 Hz), 72.8 ($PhCH_2$), 71.6, 68.9, 67.2, 64.7 (C-2, C-3, C-4, C-5), 62.9 (C-6), 21.1 (CH_3), 20.9 (CH_3), 20.8 (CH_3).

Second eluted one was **6** (1.43 g, 8%), syrup; $[\alpha]_D$ −135 (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.55–7.50 (m, 2H, aromatic), 7.34–7.26 (m, 3H, aromatic), 5.48 (d, 1H, $J_{1,2}$ 1.1 Hz, H-1), 5.06 (dd, 1H, $J_{2,3}$ 3.3 Hz, H-2), 5.04–4.87 (m, 3H, H-3, H-4, H-5), 4.28 (dd, 1H, $J_{5,6a}$ 6.6 Hz, $J_{6a,6b}$ 11.5 Hz, H-6a), 4.21 (dd, 1H, $J_{5,6b}$ 5.5 Hz, H-6b), 2.20 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.6 (O*C*(O)CH_3), 169.8 (O*C*(O)CH_3), 169.3 (O*C*(O)CH_3), 168.7 (O*C*(O)CH_3), 134.7, 131.8, 129.1, 127.9 (aromatic), 85.5 (C-1), 68.4, 66.5, 66.4, 65.4 (C-2, C-3, C-4, C-5), 62.4 (C-6), 20.9 (2C, $2CH_3$), 20.8 (CH_3), 20.7 (CH_3). Anal. Calcd for $C_{25}H_{28}O_8S$: C, 61.46; H, 5.78; S, 6.56. Found: C, 61.51, H, 5.73; S, 6.61.

3.5. Phenyl 3-*O*-benzyl-1-thio-α-L-idopyranoside (7)

To a solution of **5** (18.9 g, 38.7 mmol) in dry MeOH (200 mL), a catalytic amount of NaOMe was added. The mixture was stirred overnight at room temperature, neutralized with Amberlite IR 120 (H^+) resin, filtered, and concentrated to give **7** (13.9 g, 99%), mp 110–111 °C (from EtOAc–hexanes); $[\alpha]_D$ −191 (*c* 0.6, $CHCl_3$) lit.[47] −151 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.20 (m, 10H, aromatic), 5.57 (t, 1H, $J_{1,2}\sim J_{1,3}$ 1.3 Hz, H-1), 4.79 and 4.57 (2d, 2H, *J* 11.2 Hz, $PhCH_2$), 4.56 (d, 1H, $J_{4,OH}$ 2.0 Hz, OH-4), 4.52 (ddd, 1H, $J_{4,5}$ 1.0 Hz, $J_{5,6a}$ 3.0 Hz, $J_{5,6b}$ 2.8 Hz, H-5), 4.42 (d, 1H, $J_{2,OH}$ 9.7 Hz, OH-2), 4.12 (m, 1H, $J_{2,3}$ 2.9 Hz, $J_{2,4}$ 1.5 Hz, H-2), 4.07 (ddd, 1H, H-4), 4.04 (m, 1H, H-6a), 3.99 (m, 1H, H-6b), 3.74 (ddd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 2.55 (dd, 1H, $J_{6,OH}$ 7.0 and 5.0 Hz, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.8, 131.1, 129.0, 128.5, 127.9, 127.7, 127.1 (aromatic), 90.1 (C-1), 74.3 (C-3), 72.3 ($PhCH_2$), 71.0 (C-4), 68.8 (C-2), 66.3 (C-5), 65.5 (C-6).

3.6. Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-L-idopyranoside (8)

To a solution of **7** (15.2 g, 41.9 mmol) in dry DMF (150 mL), benzaldehyde dimethyl acetal (9.5 mL, 62.9 mmol) and (±)-camphor-10-sulfonic acid (1.5 g, 6.5 mmol) were added. The mixture was stirred at 50 °C under diminished pressure (40 kPa) for 3 h, neutralized with saturated aq $NaHCO_3$ and concentrated. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with water, then the organic phase was dried and concentrated. The residue was purified by column chromatography (99:1 toluene–acetone) to give **8** (16.5 g, 88%); mp 118–119 °C (from EtOAc–hexanes); $[\alpha]_D$ −140 (*c* 0.3, $CHCl_3$), lit.[38] −91 (*c* 0.56, $CHCl_3$), lit.[47] −145 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.56–7.14 (m, 15H, aromatic), 5.68 (br s, 1H, H-1), 5.54 (s, 1H, PhCH), 4.85 and 4.60 (2d, 2H, *J* 11.7 Hz, $PhCH_2$), 4.45 (br s, 1H, H-5), 4.34 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.17–4.07 (m, 3H, H-2, H-4, H-6b), 3.85 (d, 1H, $J_{2,OH}$ 11.9 Hz, OH), 3.82 (m, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.4, 137.33, 137.29, 130.3, 129.4, 129.2, 129.0, 128.7, 128.5, 128.2, 127.9, 126.9, 126.1 (aromatic), 101.7 (PhCH), 89.1 (C-1), 74.5, 73.8 (C-3, C-4), 72.5 ($PhCH_2$), 70.2 (C-6), 67.8 (C-2), 60.8 (C-5).

3.7. Phenyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-L-idopyranoside (9)

Benzoyl chloride (6.4 mL, 57.8 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a solution of **8** (16.4 g, 36.5 mmol) in dry CH_2Cl_2 (75 mL) and dry pyridine (25 mL) at 0 °C. The mixture was stirred at room temperature overnight, after which the reaction was quenched with water. The mixture was diluted with CH_2Cl_2 (500 mL), washed with 2 M aq HCl, saturated aq $NaHCO_3$ and water, dried and concentrated. The residue was purified by column chromatography (99:1 toluene–acetone) to give **9** (17.2 g, 85%); mp 136–137 °C (from EtOAc–hexanes), lit.[38] 137–138 °C; $[\alpha]_D$ −89 (*c* 0.2, $CHCl_3$), lit.[38] −80 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.02–7.95 (m, 2H, aromatic), 7.62–7.18 (m, 18H, aromatic), 5.82 (d, 1H, $J_{1,2}$ 1.3 Hz, H-1), 5.59 (s, 1H, PhCH), 5.53 (ddd, 1H, $J_{2,3}$ 2.5 Hz, $J_{2,4}$ 1.0 Hz, H-2), 4.98 and 4.71 (2d, 2H, *J* 11.7 Hz, $PhCH_2$), 4.52 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{5,6b}$

2.0 Hz, H-5), 4.38 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.20 (dd, 1H, H-6b), 4.12 (ddd, 1H, $J_{4,5}$ 1.6 Hz, H-4), 3.93 (dd, 1H, $J_{3,4}$ 2.6 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (O*C*(O)Ph), 137.9, 137.3, 136.6, 133.1, 130.5, 130.1, 129.6, 129.0, 128.9, 128.6, 128.2, 128.1, 127.9, 127.0, 126.4 (aromatic), 101.1 (PhCH), 86.0 (C-1), 73.3 (C-4), 73.2 (C-3), 72.5 ($PhCH_2$), 70.0 (C-6), 67.9 (C-2), 60.7 (C-5).

3.8. Phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-L-idopyranoside (10)

A solution of **9** (9.9 g, 17.9 mmol) and $Me_3N{\cdot}BH_3$ (13.0 g, 179.0 mmol) in dry CH_2Cl_2 (90 mL) was stirred in the presence of 4 Å molecular sieves (4 g). After 30 min, a solution of aluminum chloride (9.6 g, 71.5 mmol) in dry ether (35 mL) was added dropwise at 0 °C. After 3 h, the mixture was filtered through a pad of Celite. The filtrate was diluted with CH_2Cl_2 (500 mL) and stirred with 2 M aq HCl (90 mL) for 1 h. The organic layer was washed with saturated aq $NaHCO_3$ and water, dried and concentrated. The residue was purified by column chromatography (95:5 toluene–acetone) to give **10** as a syrup (7.1 g, 71%); $[\alpha]_D$ −98 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.10 (m, 20H, aromatic), 5.65 (dd, 1H, $J_{1,2}$ 1.6 Hz, $J_{1,4}$ 0.6 Hz, H-1), 5.49 (ddd, 1H, $J_{2,3}$ 3.0 Hz, $J_{2,4}$ 1.2 Hz, H-2), 4.92 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.72 (m, 1H, $J_{5,6a}$ 6.6 Hz, $J_{5,6b}$ 4.3 Hz, H-5), 4.65 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.49 (d, 1H, *J* 11.3 Hz, $PhCH_2$), 4.32 (d, 1H, *J* 11.3 Hz, $PhCH_2$), 4.01 (dd, 1H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.99 (ddd, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.78 (dd, 1H, H-6b), 3.57 (m, 1H, $J_{4,5}$ 2.3 Hz, H-4), 2.04 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (O*C*(O)Ph), 137.3, 137.2, 135.7, 133.3, 131.7, 130.0, 129.5, 129.0, 128.5, 128.4, 128.3, 128.2, 128.04, 127.97, 127.4 (aromatic), 86.0 (C-1), 74.5 (C-4), 72.5 ($PhCH_2$), 72.2 ($PhCH_2$), 70.7 (C-3), 69.3 (C-2), 68.4 (C-5), 62.8 (C-6). Anal. Calcd for $C_{33}H_{32}O_6S$: C, 71.20; H, 5.79; S, 5.76. Found: C, 71.31; H, 5.75; S, 5.82.

3.9. Phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-chloroacetyl-1-thio-α-L-idopyranoside (11)

Chloroacetyl chloride (0.31 mL, 3.96 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise to a stirred solution of **10** (1.10 g, 1.98 mmol) in dry CH_2Cl_2 (75 mL) and dry pyridine (3.0 mL) at −20 °C. After 30 min, the reaction was quenched with water, and stirred for 20 min. The mixture was diluted with CH_2Cl_2 (300 mL), washed with 2 M aq HCl, saturated aq $NaHCO_3$ and water, dried and concentrated. The residue was purified by column chromatography (98:2 toluene–acetone) to give **11** (0.95 g, 76%) as a syrup; $[\alpha]_D$ −97 (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20–7.95 (m, 2H, aromatic), 7.58–7.08 (m, 18H, aromatic), 5.63 (dd, 1H, $J_{1,2}$ 2.5 Hz, $J_{1,3}$ 1.0 Hz, H-1), 5.47 (ddd, 1H, $J_{2,3}$ 2.8 Hz, $J_{2,4}$ 0.8 Hz, H-2), 4.94 (d, 1H, *J* 11.7 Hz, $PhCH_2$), 4.93 (m, 1H, H-5), 4.63 (d, 1H, *J* 11.7 Hz, $PhCH_2$), 4.56 (dd, 1H, $J_{5,6a}$ 7.3 Hz, $J_{6a,6b}$ 10.8 Hz, H-6a), 4.49 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.36 (dd, 1H, $J_{5,6b}$ 4.4 Hz, H-6b), 4.28 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 3.99 (ddd, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.92 (m, 2H, CH_2Cl), 3.49 (ddd, 1H, $J_{4,5}$ 2.3 Hz, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.1 (O*C*(O)CH_2Cl), 165.8 (O*C*(O)Ph), 137.34, 137.27, 135.9, 133.4, 131.5, 130.1, 129.6, 129.2, 128.7, 128.51, 128.48, 128.4, 128.2, 128.11, 128.08, 127.5 (aromatic), 85.8 (C-1), 73.3 (C-4), 72.6 ($PhCH_2$), 72.2 ($PhCH_2$), 70.4, (C-3), 69.1 (C-2), 66.3, 65.4 (C-5, C-6), 40.8 (CH_2Cl). Anal. Calcd for $C_{35}H_{33}ClO_7S$: C, 66.39; H, 5.25; S, 5.06. Found: C, 66.32; H, 5.28; S, 5.09.

3.10. *tert*-Butyl (phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-1-thio-α-L-idopyranoside)uronate (12)

To a solution of **10** (6.0 g, 10.8 mmol) in CH_2Cl_2 (135 mL), pyridinium dichromate (8.1 g, 21.6 mmol), Ac_2O (10.2 mL, 108 mmol) and *tert*-butyl alcohol (20 mL, 216 mmol) were added. The mixture was stirred for 2 h at room temperature and it was then applied on the top of a silica gel column in EtOAc, with a 10 cm layer of EtOAc on top of the gel. The chromium compounds were allowed to precipitate in the presence of EtOAc and after 30 min the product was eluted with EtOAc. After evaporating the solvent, the residue was purified by column chromatography (98:2 toluene–acetone) to give **12** (4.2 g, 62%); mp 90–93 °C (from EtOAc–hexanes); $[\alpha]_D$ −84 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.88 (m, 2H, aromatic), 7.59–7.10 (m, 18H, aromatic), 5.77 (dd, 1H, $J_{1,2}$ 2.7 Hz, $J_{1,3}$ 1.0 Hz, H-1), 5.41 (ddd, 1H, $J_{2,3}$ 3.5 Hz, $J_{2,4}$ 1.0 Hz, H-2), 5.11 (d, 1H, H-5), 4.89 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.65 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.54 (d, 1H, *J* 11.4 Hz, $PhCH_2$), 4.51 (d, 1H, *J* 11.4 Hz, $PhCH_2$), 3.99 (ddd, 1H, $J_{3,4}$ 3.7 Hz, H-3), 3.95 (dd, 1H, $J_{4,5}$ 2.8 Hz, H-4), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C-6), 165.6 (O*C*(O)Ph), 137.6, 137.4, 135.8, 133.1, 131.1, 130.1, 129.4, 129.0, 128.6, 128.3, 128.14, 128.09, 127.7, 127.6, 127.3 (aromatic), 85.7 (C-1), 82.0 (*C*$(CH_3)_3$), 75.1 (C-4), 72.9 (2C, $2PhCH_2$), 72.3 (C-3), 69.4 (C-5), 69.1 (C-2), 28.2 (C(*C*$H_3)_3$). Anal. Calcd for $C_{37}H_{38}O_7S$: C, 70.90; H, 6.11; S, 5.12. Found: C, 70.85; H, 6.11; S, 5.08.

3.11. Phenyl 3-*O*-benzyl-4,6-*O*-(1-naphthyl)methylidene-1-thio-α-L-idopyranoside (13)

To a solution of **7** (13.9 g, 38.4 mmol) in dry DMF (100 mL), 1-naphthaldehyde dimethyl acetal (12.1 mL, 57.3 mmol) and (±)-camphor-10-sulfonic acid (1.6 g, 7.0 mmol) were added. The mixture was stirred at 50 °C under diminished pressure (40 kPa) for 3 h,

neutralized with saturated aq $NaHCO_3$ and concentrated. The residue was dissolved in CH_2Cl_2 (500 mL), washed with water, the organic layer was dried and concentrated. The residue was purified by column chromatography (99:1 toluene–acetone) to give **13** (18.8 g, 98%) as a white foam; $[\alpha]_D$ −121 (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (d, 1H, aromatic), 7.89–7.80 (m, 2H, aromatic), 7.66–7.13 (m, 14H, aromatic), 5.99 (s, 1H, ^{1}NaphCH), 5.75 (d, 1H, $J_{1,2}$ 1.5 Hz, H-1), 4.85 and 4.59 (2d, 2H, *J* 11.7 Hz, $PhCH_2$), 4.54 (br s, 1H, H-5), 4.42 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.26–4.17 (m, 2H, H-4, H-6b), 4.12 (ddd, 1H, $J_{2,3}$ 2.9 Hz, H-2), 3.81 (d, 1H, $J_{2,OH}$ 11.7 Hz, OH), 3.79 (m, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.5, 137.2, 134.1, 132.6, 130.8, 130.6, 130.3, 129.1, 128.8, 128.7, 128.4, 128.2, 128.0, 127.1, 126.8, 126.0, 125.4, 125.2, 125.0, 124.4 (aromatic), 102.6 (^{1}NaphCH), 89.5 (C-1), 74.9, 74.1, 72.6 (C-3, C-4, $PhCH_2$), 70.5 (C-6), 68.0 (C-2), 60.9 (C-5). Anal. Calcd for $C_{30}H_{28}O_5S$: C, 71.98; H, 5.64; S, 6.41. Found: C, 72.02; H, 5.61; S, 6.44.

3.12. Phenyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-(1-naphthyl)-methylidene-1-thio-α-L-idopyranoside (14)

Compound **13** (18.8 g, 37.6 mmol) was benzoylated as described for compound **9**. The product was purified by column chromatography (98:2 toluene–EtOAc) to give **14** (22.3 g, 98%); mp 135–136 °C (from EtOAc–hexanes); $[\alpha]_D$ −108 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33–7.01 (m, 22H, aromatic), 6.12 (s, 1H, ^{1}NaphCH), 5.88 (t, 1H, $J_{1,2}\sim J_{1,3}$ 1.2 Hz, H-1), 5.55 (ddd, 1H, $J_{2,3}$ 2.5 Hz, $J_{2,4}$ 1.0 Hz, H-2), 5.00 and 4.72 (2d, 2H, *J* 11.8 Hz, $PhCH_2$), 4.60 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{5,6b}$ 2.0 Hz, H-5), 4.44 (dd, 1H, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.31 (dd, 1H, H-6b), 4.22 (m, 1H, $J_{4,5}$ 1.0 Hz, H-4), 3.92 (ddd, 1H, $J_{3,4}$ 2.6 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (O*C*(O)Ph), 137.3, 136.4, 133.8, 133.2, 133.0, 130.9, 130.6, 130.1, 129.7, 129.4, 129.1, 129.0, 128.6, 128.4, 128.10, 128.08, 127.96, 127.2, 126.4, 125.6, 124.9, 124.6 (aromatic), 100.8 (^{1}NaphCH), 86.2 (C-1), 73.7 (C-4), 73.6 (C-3), 72.6 ($PhCH_2$), 70.1 (C-6), 68.1 (C-2), 60.8 (C-5). Anal. Calcd for $C_{37}H_{32}O_6S$: C, 73.49; H, 5.33; S, 5.30. Found: C, 73.32; H, 5.38; S, 5.39.

3.13. Phenyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)-methyl-1-thio-α-L-idopyranoside (15)

To a solution of **14** (18.0 g, 29.8 mmol) in dry CH_2Cl_2 (100 mL), 1 M BH_3·THF in THF (58.7 mL, 58.7 mmol) and TMSOTf (0.54 mL, 2.98 mmol) were added. The mixture was stirred for 2 h at room temperature, cooled to 0 °C, and quenched with triethylamine (20 mL) and MeOH (100 mL). The solution was concentrated in vacuo and co-evaporated three times with MeOH. The residue was purified by column chromatography (98:2→9:1 toluene–acetone) to give **15** (16.6 g, 92%) as a syrup; $[\alpha]_D$ −113 (*c* 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03–7.92 (m, 3H, aromatic), 7.85–7.73 (m, 2H, aromatic), 7.55–7.10 (m, 17H, aromatic), 5.65 (s, 1H, H-1), 5.49 (dd, 1H, $J_{1,2}$ 1.2 Hz, $J_{2,3}$ 3.3 Hz, H-2), 4.95 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.89 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.73 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.72 (m, 1H, H-5), 4.61 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.02 (dd, $J_{3,4}$ 2.6 Hz, H-3), 3.92 (ddd, 1H, $J_{5,6a}$ 6.9 Hz, $J_{6a,6b}$ 11.4 Hz, $J_{6a,OH}$ 3.3 Hz, H-6a), 3.64 (dd, $J_{5,6b}$ 4.7 Hz, H-6b), 3.59 (dd, 1H, $J_{4,5}$ 2.0 Hz, H-4), 1.74 (dd, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.8 (O*C*(O)Ph), 137.5, 135.9, 133.8, 133.4, 132.8, 131.8, 131.7, 130.1, 129.7, 129.16, 129.12, 128.8, 128.7, 128.5, 128.4, 128.2, 127.5, 127.2, 126.5, 126.1, 125.4, 125.1, 123.8 (aromatic), 86.1 (C-1), 73.8 (C-4), 72.6 ($ArCH_2$), 70.8 (C-3), 70.5 ($ArCH_2$), 69.6 (C-2), 68.8 (C-5), 62.6 (C-6). Anal. Calcd for $C_{37}H_{34}O_6S$: C, 73.24; H, 5.65; S, 5.28. Found: C, 73.18; H, 5.67; S, 5.32.

3.14. *tert*-Butyl (phenyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)methyl-1-thio-α-L-idopyranoside)uronate (16)

Compound **15** (8.3 g, 13.7 mmol) was oxidized as described for compound **12**. The product was purified by column chromatography (98:2 toluene–acetone) to give **16** (6.9 g, 74%); $[\alpha]_D$ −88 (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93–7.70 (m, 5H, aromatic), 7.59–7.52 (m, 2H, aromatic), 7.45–7.07 (m, 15H, aromatic), 5.77 (d, 1H, $J_{1,2}$ 2.2 Hz, H-1), 5.39 (dd, 1H, $J_{2,3}$ 2.9 Hz, H-2), 5.16 (d, 1H, H-5), 5.02 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.91 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.83 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.57 (d, 1H, *J* 11.7 Hz, $ArCH_2$), 4.08 (t, 1H, $J_{4,5}$ 2.8 Hz, H-4), 3.97 (t, 1H, $J_{3,4}$ 3.0 Hz, H-3), 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2 (C-6), 165.6 (O*C*(O)Ph), 137.5, 135.7, 133.6, 133.2, 133.1, 131.4, 131.3, 130.1, 129.5, 129.1, 129.0, 128.6, 128.3, 128.2, 128.11, 128.08, 127.4, 126.3, 125.8, 125.4, 125.2, 123.8 (aromatic), 86.0 (C-1), 82.2 ($C(CH_3)_3$), 75.2 (C-4), 73.0 ($ArCH_2$), 72.9 (C-3), 71.2 ($ArCH_2$), 69.6, 69.4 (C-2, C-5), 28.2 ($C(CH_3)_3$). Anal. Calcd for $C_{41}H_{40}O_7S$: C, 72.76; H, 5.96; S, 4.74. Found: C, 72.68; H, 5.93; S, 4.81.

3.15. Methyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-chloroacetyl-α-L-idopyranosyl)-(1→4)-3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-(4-methoxy)phenyl-α-D-glucopyranoside (18)

A mixture of **11** (0.84 g, 1.32 mmol), **17** (0.55 g, 1.06 mmol), and 4 Å molecular sieves (1.00 g) was stirred in dry CH_2Cl_2 (10 mL) at 0 °C under argon for 30 min, then DMTST (1.37 g, 5.28 mmol) was added. After 1 h, the reaction was quenched with triethylamine (1 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (250 mL)

and washed with 2 M aq HCl, saturated aq $NaHCO_3$ and water, dried, and concentrated. The residue was purified by column chromatography (9:1 toluene–EtOAc) to give **18** (0.78 g, 71%) mp 145–146 °C (from EtOAc–hexanes); $[\alpha]_D$ +33 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.82–7.78 (m, 2H, aromatic), 7.50 (m, 1H, aromatic), 7.37–7.08 (m, 22H, aromatic), 6.85–6.76 (m, 2H, aromatic), 6.65–6.56 (m, 2H, aromatic), 5.18 (ddd, 1H, $J_{2',3'}$ 3.3 Hz, $J_{2',4'}$ 0.7 Hz, H-2′), 5.06 (d, 1H, *J* 12.0 Hz, $PhCH_2$), 5.04 (d, 1H, $J_{1',2'}$ 2.2 Hz, H-1′), 5.01 (d, 1H, *J* 12.0 Hz, $PhCH_2$), 4.77 (d, 1H, *J* 11.6 Hz, $PhCH_2$), 4.71 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.68 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.64 (d, 1H, $J_{2,NH}$ 10.0 Hz, NH), 4.61 (d, 1H, *J* 11.6 Hz, $PhCH_2$), 4.52 (d, 1H, *J* 11.3 Hz, $PhCH_2$), 4.48 (ddd, 1H, $J_{5',6a'}$ 7.5 Hz, $J_{5',6b'}$ 4.8 Hz, H-5′), 4.48 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.31 (d, 1H, *J* 11.3 Hz, $PhCH_2$), 4.23 (dd, 1H, $J_{6a',6b'}$ 11.4 Hz, H-6a′), 4.16 (dd, 1H, H-6b′), 4.14 (dd, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.14 (dd, 1H, $J_{6a,6b}$ 11.0 Hz, H-6a), 4.12 (dd, 1H, H-6b), 4.01 (ddd, 1H, $J_{2,3}$ 10.3 Hz, H-2), 3.98 and 3.92 (2d, 2H, *J* 14.8 Hz, CH_2Cl), 3.88 (dd, 1H, $J_{3',4'}$ 3.8 Hz, H-3′), 3.87 (ddd, 1H, $J_{5,6a}$ 2.7 Hz, $J_{5,6b}$ 3.3 Hz, H-5), 3.60 (s, 3H, $ArOCH_3$), 3.55 (dd, 1H, $J_{3,4}$ 9.2 Hz, H-3), 3.45 (ddd, 1H, $J_{4',5'}$ 2.5 Hz, H-4′), 3.33 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (O*C*(O)CH_2Cl), 165.7 (O*C*(O)Ph), 155.8 (NH*C*(O)OCH_2Ph), 154.0, 152.2, 138.2, 137.5, 137.4, 136.4, 133.2, 129.9, 128.50, 128.48, 128.41, 128.3, 128.23, 128.15, 128.11, 128.06, 128.02, 127.95, 127.4, 115.8, 114.4 (aromatic), 99.2 (C-1), 97.2 (C-1′), 78.7 (C-3), 75.3 ($PhCH_2$), 74.3 (C-4), 73.2 (C-4′), 72.6 ($PhCH_2$), 72.3 (C-3′), 72.2 ($PhCH_2$), 70.4 (C-5), 68.4 (C-2′), 67.0 (NHC(O)O*C*H_2Ph), 66.9 (C-6), 65.8 (C-5′), 64.8 (C-6′), 55.5 ($ArOCH_3$), 55.2 (OCH_3), 55.0 (C-2), 41.1 (CH_2Cl). Anal. Calcd for $C_{58}H_{60}ClNO_{15}$: C, 66.56; H, 5.78; N, 1.34. Found: C, 66.51; H, 5.82; N, 1.30.

3.16. Methyl [2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-(1-naphthyl)methylidene-α-L-idopyranosyl]-(1→4)-3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-(4-methoxy)-phenyl-α-D-glucopyranoside (19)

A mixture of **14** (0.36 g, 0.60 mmol), **17** (0.26 g, 0.50 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.10 g, 0.50 mmol), and 4 Å molecular sieves (0.50 g) was stirred in dry CH_2Cl_2 (10 mL) at −40 °C under argon for 30 min, then a 1 M solution of a mixture of Me_2S_2 and Tf_2O in CH_2Cl_2 (0.90 mL, 0.90 mmol) was added. After 10 min, the reaction was quenched with triethylamine (1 mL). The mixture was filtered through a pad of Celite, the filtrate was diluted with CH_2Cl_2 (250 mL) and washed with 2 M aq HCl, saturated aq $NaHCO_3$ and water, dried, and concentrated. The residue was purified by column chromatography (98:2 CH_2Cl_2–EtOAc) to give **19** (0.46 g, 90%); mp 209–210 °C (from EtOAc–hexanes); $[\alpha]_D$ −17 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.42–6.60 (m, 31H, aromatic), 5.80 (s, 1H, ^{1}NaphCH), 5.24 (d, 1H, $J_{2',3'}$ 1.5 Hz, H-2′), 5.13 (s, 1H, H-1′), 5.07–4.98 (m, 3H, $PhCH_2$, NH), 4.81 (d, 1H, *J* 11.7 Hz, $PhCH_2$), 4.77 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 4.66 (s, 2H, $PhCH_2$), 4.65 (d, 1H, *J* 11.7 Hz, $PhCH_2$), 4.30–4.14 (m, 4H, H-2, H-4, H-6a, H-6b), 4.06 (s, 1H, H-5′), 4.00–3.90 (m, 3H, H-5, H-4′, H-6a′), 3.76 (t, 1H, $J_{2',3'}$ 2.2 Hz, H-3′), 3.63 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 3.60 (s, 3H, $ArOCH_3$), 3.42 (s, 3H, OCH_3), 3.19 (d, 1H, $J_{6a',6b'}$ 12.4 Hz, H-6b′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8 (O*C*(O)Ph), 155.9 (NH*C*(O)OCH_2Ph), 154.0, 152.2, 138.4, 137.8, 136.3, 133.9, 133.5, 132.9, 130.6, 130.0, 129.7, 129.1, 128.5, 128.4, 128.3, 128.1, 127.99, 127.95, 127.9, 127.4, 127.3, 126.3, 125.6, 125.3, 125.1, 124.7, 115.8, 114.5 (aromatic), 101.4 (^{1}NaphCH), 99.1 (C-1′), 98.0 (C-1), 79.7 (C-3), 75.0 (C-3′), 74.9 ($PhCH_2$), 73.8, 73.6 (C-4, C-5), 72.2 (2C, $2PhCH_2$), 70.4 (C-4′), 69.3 (C-6′), 67.0, 66.9, 66.8 (C-2′, C-6, NHC(O)O*C*H_2Ph), 59.8 (C-5′), 55.5, 55.4 ($ArOCH_3$, OCH_3), 55.3 (C-2). Anal. Calcd for $C_{60}H_{59}NO_{14}$: C, 70.78; H, 5.84; N, 1.38. Found: C, 70.53; H, 5.87; N, 1.39.

3.17. Methyl [*tert*-butyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-idopyranosyl)uronate]-(1→4)-3,6-di-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (21)

A mixture of **12** (1.54 g, 2.46 mmol), **20** (1.00 g, 1.97 mmol), and 4 Å molecular sieves (1.00 g) was stirred in dry CH_2Cl_2 (18 mL) at 0 °C under argon for 30 min, then DMTST (2.91 g, 11.4 mmol) was added. The mixture was allowed to attain room temperature and after stirring overnight triethylamine (2 mL) was added. The mixture was filtered through a pad of Celite, diluted with CH_2Cl_2 (500 mL) and washed with 2 M aq HCl, saturated aq $NaHCO_3$ and water, dried, and concentrated. The residue was purified by column chromatography (9:1 toluene–EtOAc) to give **21** (1.73 g, 86%); $[\alpha]_D$ +21.7 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.80 (m, 1H, aromatic), 7.55–7.45 (m, 1H, aromatic), 7.40–7.10 (m, 28H, aromatic), 5.53 (d, 1H, $J_{1',2'}$ 4.6 Hz, H-1′), 5.18 (ddd, $J_{2',3'}$ 4.9 Hz, $J_{2',4'}$ 0.8 Hz, H-2′), 5.01 (s, 2H, $PhCH_2$), 4.87 (d, 1H, *J* 11.4 Hz, $PhCH_2$), 4.76 (d, 1H, $J_{2,NH}$ 10.4 Hz, NH), 4.75 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.68 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.67 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.64 (d, 1H, H-5′), 4.58 (d, 1H, *J* 11.4 Hz, $PhCH_2$), 4.54 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.53 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.50 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.49 (d, 1H, *J* 11.5 Hz, $PhCH_2$), 4.08 (dd, 1H, $J_{4,5}$ 10.0 Hz, H-4), 4.02 (dd, 1H, $J_{3',4'}$ 5.6 Hz, H-3′), 4.00 (ddd, 1H, $J_{2,3}$ 10.6 Hz, H-2), 3.89 (ddd, 1H, $J_{4',5'}$ 4.5 Hz, H-4′), 3.70 (dd, 1H, $J_{6a,6b}$ 10.8 Hz, H-6a), 3.63 (ddd, 1H, $J_{5,6a}$ 4.5 Hz, $J_{5,6b}$ 2.0 Hz, H-5), 3.56 (dd, 1H, $J_{3,4}$ 8.8 Hz, H-3), 3.55 (dd, 1H, H-6b), 3.26 (s, 3H, OCH_3), 1.36 (s, 9H, $C(CH_3)_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C-6′), 165.5 (O*C*(O)Ph), 155.8 (NH*C*(O)OCH_2Ph), 138.8, 138.2, 137.9, 137.8, 137.7, 133.2, 130.0, 129.6, 129.1, 128.6, 128.4, 128.3, 128.2, 127.85, 127.79, 127.7, 127.6, 127.2, 125.3 (aromatic), 98.8 (C-1), 97.9 ($J_{C\text{-}1',H\text{-}1'}$ 171 Hz, C-1′), 81.8 (*C*$(CH_3)_3$), 78.9 (C-3), 76.3 (C-4′), 75.7 (C-4), 75.0 (C-3′), 74.1 (PhCH_2), 73.5 (PhCH_2), 73.3 (PhCH_2), 73.0 (PhCH_2), 70.89 (C-5′), 70.85 (C-2′), 70.8 (C-5), 68.3 (C-6), 66.8 (NHC(O)O*C*H_2Ph), 55.1 (OCH_3), 54.3 (C-2), 28.0 (C(*C*$H_3)_3$). Anal. Calcd for $C_{60}H_{65}NO_{14}$: C, 70.36; H, 6.40; N, 1.37. Found: C, 70.24; H, 6.42; N, 1.38.

3.18. Methyl [*tert*-butyl (2-*O*-benzoyl-3,4-di-*O*-benzyl-α-L-idopyranosyl)uronate]-(1→4)-3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-(4-methoxy)phenyl-α-D-glucopyranoside (22)

Compound **17** (1.2 g, 2.3 mmol) was glycosylated with **12** (1.8 g, 2.9 mmol), as described for the preparation of **21**. After workup, the product was purified by column chromatography (9:1 toluene–EtOAc) to give syrupy **22** (2.1 g, 88%); $[\alpha]_D$ +25 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–6.62 (m, 29H, aromatic), 5.45 (d, 1H, $J_{1',2'}$ 4.4 Hz, H-1′), 5.16 (ddd, 1H, $J_{2',3'}$ 4.1 Hz, $J_{2',4'}$ 0.8 Hz, H-2′), 5.02 (s, 2H, PhCH_2), 4.90 (d, 1H, *J* 11.3 Hz, PhCH_2), 4.79 (d, 1H, $J_{2,NH}$ 9.7 Hz, NH), 4.74 (d, 1H, *J* 11.5 Hz, PhCH_2), 4.71 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.66 (d, 1H, H-5′), 4.63 (d, 1H, *J* 11.5 Hz, PhCH_2), 4.55 (d, 1H, *J* 11.3 Hz, PhCH_2), 4.52 (d, 1H, *J* 11.5 Hz, PhCH_2), 4.47 (d, 1H, *J* 11.5 Hz, PhCH_2), 4.20 (dd, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.13 (dd, $J_{6a,6b}$ 10.5 Hz, 1H, H-6a), 4.11 (dd, 1H, H-6b), 4.05 (ddd, 1H, $J_{2,3}$ 10.5 Hz, H-2), 3.89 (dd, 1H, $J_{3',4'}$ 4.8 Hz, H-3′), 3.87 (dd, 1H, $J_{4',5'}$ 3.8 Hz, H-4′), 3.84 (ddd, 1H, $J_{5,6a}$ 3.8 Hz, $J_{5,6b}$ 3.0 Hz, H-5), 3.68 (s, 3H, ArOCH_3), 3.61 (dd, 1H, $J_{3,4}$ 8.9 Hz, H-3), 3.31 (s, 3H, OCH_3), 1.37 (s, 9H, C(C$H_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C-6′), 165.5 (O*C*(O)Ph), 155.8 (NH*C*(O)OCH_2Ph), 154.0, 152.6, 138.8, 137.8, 137.6, 136.5, 133.1, 130.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.79, 127.7, 127.6, 127.2, 116.1, 114.4 (aromatic), 98.9 (C-1), 97.9 (C-1′), 81.8 (*C*$(CH_3)_3$), 79.0 (C-3), 75.8 (C-4′), 75.7 (C-4), 74.6 (C-3′), 74.3 (PhCH_2), 73.0 (PhCH_2), 72.9 (PhCH_2), 70.7 (2C, C-5′, C-2′), 70.0 (C-5), 67.1 (C-6), 66.9 (NHC(O)O*C*H_2Ph), 55.6 (ArOCH_3), 55.2 (OCH_3), 54.4 (C-2), 28.1 (C(*C*$H_3)_3$). Anal. Calcd for $C_{60}H_{65}NO_{15}$: C, 69.28; H, 6.30; N, 1.35. Found: C, 69.32; H, 6.27; N, 1.33.

3.19. Methyl {*tert*-butyl [2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(1-naphthyl)methyl-α-L-idopyranosyl]uronate}-(1→4)-3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-*O*-chloroacetyl-α-D-glucopyranoside (24)

Compound **23** (0.20 g, 0.41 mmol) was glycosylated with **16** (0.42 g, 0.62 mmol) as described for the preparation of **21**. After workup, the product was purified by column chromatography (9:1 toluene–EtOAc) to give **24** (0.31 g, 71%); $[\alpha]_D$ +9 (*c* 0.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05–7.72 (m, 5H, aromatic), 7.58–7.10 (m, 22H, aromatic), 5.56 (d, 1H, $J_{1',2'}$ 5.5 Hz, H-1′), 5.16 (d, 1H, $J_{2',3'}$ 5.1 Hz, H-2), 5.12 (d, 1H, *J* 11.7 Hz, PhCH_2), 5.09 (d, 1H, *J* 11.7 Hz, PhCH_2), 5.05 (d, 1H, $J_{4',5'}$ 2.9 Hz, H-5′), 4.98 (d, 1H, *J* 11.7 Hz, PhCH_2), 4.94 (d, 1H, *J* 11.4 Hz, PhCH_2), 4.75 (d, 1H, $J_{2,NH}$ 9.9 Hz, NH), 4.64 (d, 1H, *J* 11.4 Hz, PhCH_2), 4.64 (d, 1H, $J_{1,2}$ 2.9 Hz, H-1), 4.62 (d, 1H, *J* 11.0 Hz, PhCH_2), 4.61 (d, 1H, *J* 11.0 Hz, PhCH_2), 4.57 (d, 1H, *J* 11.4 Hz, PhCH_2), 4.47 (dd, 1H, $J_{5,6a}$ 12.1 Hz, $J_{6a,6b}$ 3.3 Hz, H-6a), 4.29 (dd, 1H, $J_{5,6b}$ 1.5 Hz, H-6b), 4.28 and 4.09 (2d, 2H, *J* 18.3 Hz, CH_2Cl), 4.10–3.87 (m, 4H, H-2, H-4, H-3′, H-4′), 3.68 (m, 1H, H-5), 3.55 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 9.9 Hz, H-3), 3.25 (s, 3H, OCH_3), 1.39 (s, 9H, C(C$H_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.3, 167.4 (C-6′, O*C*(O)CH_2Cl), 165.4 (O*C*(O)Ph), 156.0 (NH*C*(O)OCH_2Ph), 138.7, 137.8, 136.5, 133.7, 133.4, 133.0, 131.4, 130.1, 129.4, 128.8, 128.64, 128.58, 128.5, 128.33, 128.28, 128.2, 128.0, 127.8, 127.4, 126.4, 125.9, 125.3, 123.7 (aromatic), 99.0 (C-1), 98.0 (C-1′), 82.3 (*C*$(CH_3)_3$), 78.6 (C-3), 76.3, 76.2, 76.1 (C-4, C-3′, C-4′), 74.8 (ArCH_2), 73.8 (ArCH_2), 72.0 (C-5), 71.8 (C-5′), 71.3 (ArCH_2), 68.8 (C-2′), 67.0 (NHC(O)-O*C*H_2Ph), 64.0 (C-6), 55.4 (OCH_3), 54.5 (C-2), 40.9 (OC(O)*C*H_2Cl), 28.2 (C(*C*$H_3)_3$). Anal. Calcd for $C_{59}H_{62}ClNO_{15}$: C, 66.82; H, 5.89; N, 1.32. Found: C, 66.87; H, 5.84; N, 1.36.

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Supplementary data

NMR spectra of compounds (**5**, **11**, **12**, **16**, **18**, **19**, **21**, **22**, **24**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.12.015.

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