Regioselective Synthesis of L-Idopyranuronic Acid Derivatives: Intermolecular Aglycon Transfer of Dithioacetal Under Standard Glycosylation Conditions

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REGIOSELECTIVE SYNTHESIS OF L-IDOPYRANURONIC ACID DERIVATIVES: INTERMOLECULAR AGLYCON TRANSFER OF DITHIOACETAL UNDER STANDARD GLYCOSYLATION CONDITIONS

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ABSTRACT

C-1-thioacetalization of L-idofuranurono-6,3-lactone followed by regioselective *p*-methoxybenzylidenation at C-2 and C-4 gave the hydroxylactones **4** and **19**, which were protected at C-5 with TBDMS. Lactone ring opening with methylamine followed by regioselective reductive cleavage of the 1,3-dioxane furnished acceptors **9** and **24**. Intermolecular ethyl and phenyl thio group transfers were observed during the attempted preparation of disaccharide **35** through coupling reactions of either **9** or **24** with trichloroacetimidate donor **33**, leading to the formation of thioglycoside of donor **33** and the thioglycoside of acceptors **9** or **24** in the furanose form. This intermolecular aglycon transfer was investigated under various glycosylation conditions. Finally, the free 4-hydroxyl groups in acceptors **9** and **24** were acetylated. Desilylation at C-5 followed by ring closure with mercuric salts afforded, in both cases, the IdopA donor and/or acceptor precursor **16**.

INTRODUCTION

Glycosaminoglycans are involved in a number of biological events by interacting with a diverse group of proteins.[1] Binding is mediated mainly by interactions between sulfate and carboxyl groups of the glycosaminoglycan and basic amino acid residues of the protein.[2] The biological properties of glycosaminoglycans were long believed to involve large fragments of these complex polysaccharides, but it is now well documented that unique sequences exist in rather short domains that are responsible for the protein binding associated with biological preperties.[3] Only chemical synthesis can afford the great variety of pure oligosaccharides needed to explored the structure-activity relationships or to mimic the biological properties of these domains. A key constituent of all these biologically active oligosaccharides is α-L-idopyranuronic acid.[4] Synthetic studies on the antithrombin III binding sequence of heparin, an α-L-idopyranuronic acid containing pentasaccharide, has afforded valuable information at the molecular level on sugar-protein interactions.[5]

We have devised an approach for the synthesis of universal α-L-IdopA-glycosyl donor and/or acceptor because: (1) α-L-IdopA and its derivatives are not commercially available; (2) multistep procedures in previous reports[6] provide low yields and/or poor stereocontrol combined with multiple chromatographic purifications; and (3) commonly used uronic esters donors are often unreactive due to the destabilization of the intermediate oxocarbenium cation by their carboxylate group. We propose to reduce this destabilization by using uronamide donors which can later be chemoselectively converted to a free carboxylic acid or ester.[7]
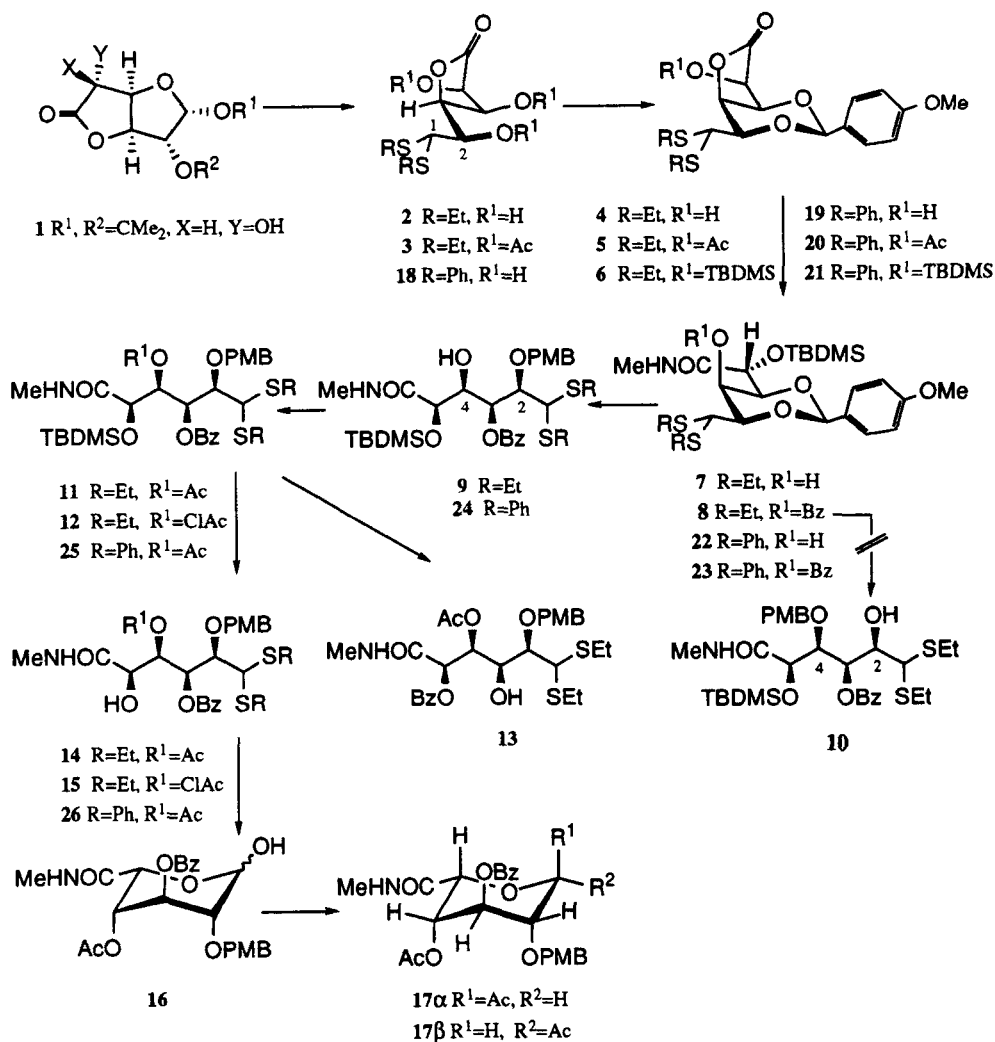
To simplify the synthesis of α-L-IdopA containing oligosaccharides, coupling reactions between glycosyl donor and iduronamide diethyl(phenyl)dithioacetals were investigated. To our best knowledge, this represents the first exploration of the use of dithioacetal as a glycosyl acceptor in carbohydrate chemistry. The advantage of this strategy is that ring closure generates either IdopA thioglycoside,[8] which can act as a donor in a subsequent coupling reaction,[9] or IdopA with a free anomeric OH group, which can be converted into trichloroacetimidate donor in a single step.[10] Alkyl and aryl 1-thioglycosides are powerful intermediates in the oligosaccharide synthesis although a number of undesirable transformations such as glycal formation, alkyl thio group transfer and decomposition were reported when using thioglycoside as glycosyl donor or acceptor.[11]

In a previous communication,[12] we reported a facile method for the synthesis of a potential universal L-IdopA-glycosyl-donor and/or-acceptor. Here we give a full account of a modified synthesis of idopyranuronic acid derivatives and also report the first observation about intermolecular aglycon transfer of diethyl(phenyl)dithioacetals under Lewis acid catalyzed glycosylation conditions.

RESULTS AND DISCUSSION

In the course of our synthetic studies on heparin oligosaccharides, we have focused on the preparation of suitably protected Glcp2N₃→IdopA disaccharide building blocks. Our major challenge has been the synthesis of IdopA derivatives as glycosyl acceptors/donors (Scheme 1). The 1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone[13] (1) was first converted into idurono-6,3-lactone diethyl dithioacetal (2) by a procedure similar to that described by Wolfrom.[14] The structure of 2 was characterized through its fully acetylated derivative, 2,4,5-tri-O-acetyl-idurono-6,3-lactone (3). Treatment of 2 with excess p-anisaldehyde in the presence of drierite and a catalytic amount of p-toluenesulfonic acid (TsOH·H₂O) resulted in the regioselective formation of the 2,4-O-(p-methoxy-benzylidene)-idurono-6,3-lactone diethyl dithioacetal (4). The structure of 4 was confirmed directly from its ¹H NMR spectrum (δ H-2 = 4.00, H-4 = 4.55, H-5 = 4.30 ppm) as well as by that of the corresponding 5-O-acetyl derivative (5) (δ H-2 = 4.00, H-4 = 4.56, H-5 = 5.20 ppm). Attempts to open the lactone ring in 4 by methanolysis failed because of the sensitivity of the corresponding methyl ester and its easy reversion to the starting lactone. The amide was made to overcome this problem, 4 was first transformed into 5-O-(tert- butyldimethylsilyl) -2,4-O-(p-methoxybenzylidene)- idurono -6,3-lactone diethyl dithioacetal (6) by treating with tert-butyldimethylsilyl chloride (TBDMSCl) in N,N-dimethylformamide (DMF) in the presence of imidazole. The lactone ring was opened with methylamine in tetrahydrofuran (THF) to afford the iduronamide 7 and then 3-O-benzoylated to give the fully protected amide 8. Reductive cleavage of the 2,4-O-(p-methoxybenzylidene) acetal of 8 with sodium cyanoborohydride-trimethylsilyl chloride[15] gave methyl [3-O-benzoyl-5-O-(tert-butyl-dimethylsilyl)-2-O-(p-methoxybenzyl)]-iduron-amide diethyl dithioacetal (9) with complete regioselectivity and in nearly quantitative yield. The structure of 9 was unequivocally established by a single frequency decoupling experiment (δ H-1 = 4.11, H-2 = 4.26, H-3 = 5.90, H-4 = 4.13, H-5 = 4.30 ppm) and the observation of a strong NOE between the protons at C-2 and at the thioacetal portions. The unusual regioselectivity of this reaction can be explained by the functionality surrounding the acetal O-atoms in 8. The C-4-oxygen in 8 has both a β-carbonyl and a β-oxygen withdrawing electron density, thus, it is insufficiently basic to form the intermediate p-methoxybenzilium ion. The C-2-oxygen with two β-sulfur atoms should have no trouble donating a lone electron pair to stabilize the intermediate oxonium ion.

With compound 9 in hand, we investigated the acceptor properties of this diethyl dithioacetal, as we believed that coupling at this step would significantly simplify the total synthesis of our target oligosaccharides. Problems that can arise from the use of thioglycosides as acceptors, such as the formation of the thioglycoside of the donor, have

1 R^1, R^2=CMe$_2$, X=H, Y=OH

2 R=Et, R^1=H
3 R=Et, R^1=Ac
18 R=Ph, R^1=H

4 R=Et, R^1=H
5 R=Et, R^1=Ac
6 R=Et, R^1=TBDMS

19 R=Ph, R^1=H
20 R=Ph, R^1=Ac
21 R=Ph, R^1=TBDMS

11 R=Et, R^1=Ac
12 R=Et, R^1=ClAc
25 R=Ph, R^1=Ac

9 R=Et
24 R=Ph

7 R=Et, R^1=H
8 R=Et, R^1=Bz
22 R=Ph, R^1=H
23 R=Ph, R^1=Bz

14 R=Et, R^1=Ac
15 R=Et, R^1=ClAc
26 R=Ph, R^1=Ac

13

10

16

17α R^1=Ac, R^2=H
17β R^1=H, R^2=Ac

Scheme 1

been reported.[16] However, the use of glycosyl trichloroacetimidates as donors with thioglycosides as acceptors has given promising results.[17] Thus, 4-O-allyl-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl trichloroacetimidate (33) was prepared (Scheme 2). Tert-butyldimethylsilyl 2-azido- 4,6-O-benzylidene-2- deoxy -β-D- glucopyranoside (27)[18] was benzylated with benzyl bromide and sodium hydride in DMF to give a 73% yield of tert - butyldimethylsilyl 2- azido - 3 -O -benzyl- 4,6-O -benzylidene- 2 -deoxy- β -D-glucopyranoside (28). Benzylation yield could be improved to 82% by using benzyl bromide
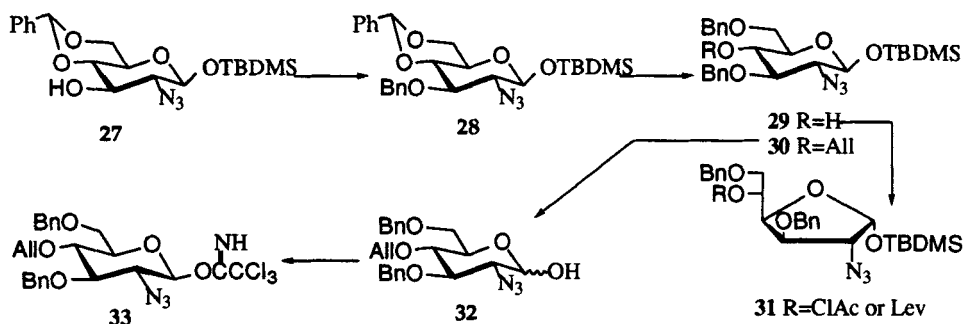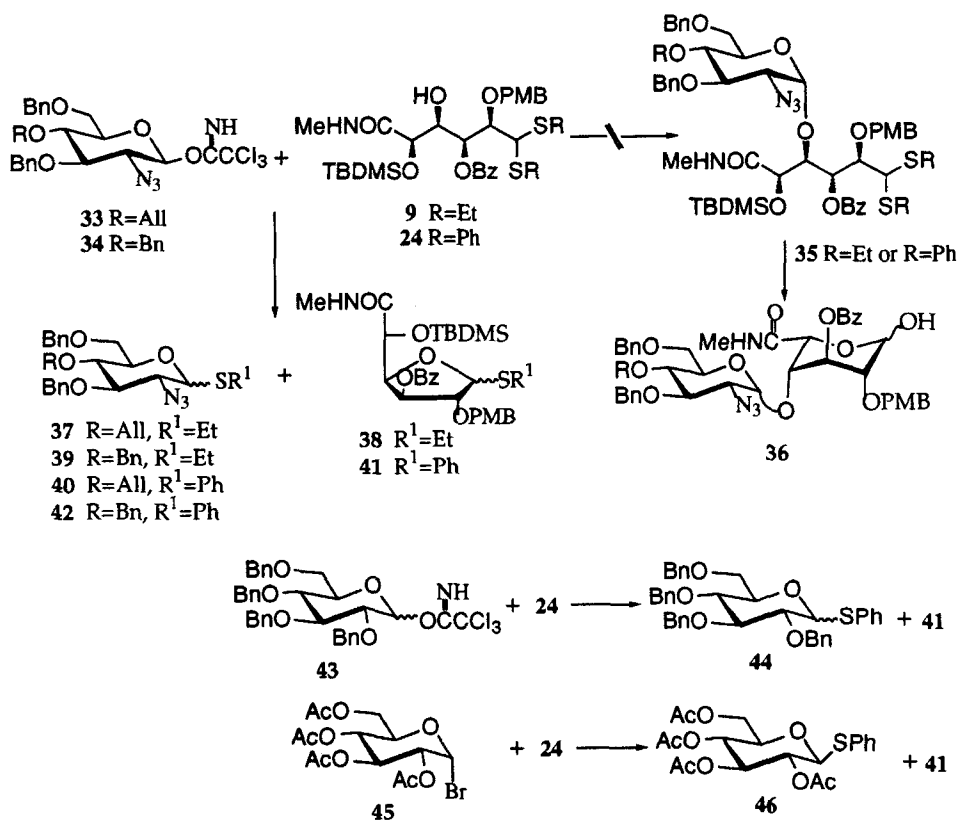
Scheme 2

and freshly prepared silver oxide. Regioselective reductive ring-opening of benzylidene acetal in **28** with NaBH₄(CN) and HCl(g) in ether gave *tert*-butyldimethylsilyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**29**) in 86% yield. While acylation of the 4-hydroxyl group of compound **29** afforded ring contracted furanoside **31**,[19] treatment with allyl bromide and sodium hydride gave *tert*-butyldimethylsilyl 4-*O*-allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**30**) in good yield. Desilylation of **30** with tetrabutylammonium fluoride (TBAF)-acetic acid complex in tetrahydrofuran, followed by activation of anomeric center with trichloroacetonitrile in the presence of solid, anhydrous potassium carbonate, gave the desired *O*-(4-*O*-allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl) trichloroacetimidate (**33**) donor in high yield (90% from **30**).

Compound **33** was glycosylated with **9** in anhydrous methylene chloride using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter (Scheme 3). Surprisingly, no disaccharide was detectable in the product mixture. Instead, the reaction unexpectedly lead exclusively to the formation of an equimolar mixture of thioglycoside derivatives **37** and **38**. This coupling reaction was repeated under a variety of reaction conditions (see Table). The conditions examined included variation of promoter (TMSOTf, ZnCl₂, BF₃·Et₂O, AgOTf), solvent (CH₂Cl₂, CH₃CN), reaction time (30 min to 4 h) and temperature (-42 °C to rt). None of the conditions gave even trace amounts of target disaccharide with intermolecular ethylthio group transfer always representing the major pathway.

The use of "less-reactive" thioglycoside (*i.e.*, phenyl in place of ethyl) might overcome this undesired transfer reaction.[11] Using this strategy acceptor **24** was prepared (Scheme 1). The coupling reaction between donor **33** and acceptor **24** (Scheme 3) under the same conditions gave similar results as were observed in reaction of **33** with **9**. To

Scheme 3

Table   Intermolecular alkyl (aryl) thio transfer reaction.

Entry	Reactants	Promoter	Solvent	Products [a]	Yield (%)
1	33+9	TMSOTf	CH_2Cl_2	37	85 [b]
2	33+9	TMSOTf	CH_3CN	37	73
3	33+9	$ZnCl_2$	CH_2Cl_2	37	37
4	33+9	$BF_3 \cdot Et_2O$	CH_2Cl_2	37	86
5	33+9	AgOTf	CH_2Cl_2	37	79
6	34+9	TMSOTf	CH_3CN	39	53
7	34+9	TMSOTf	CH_2Cl_2	39	78
8	34+9 [c]	TMSOTf	CH_2Cl_2	39	81
9	34+24	TMSOTf	CH_2Cl_2	42	80
10	34+24	$BF_3 \cdot Et_2O$	CH_2Cl_2	42	72
11	43+24	TMSOTf	CH_2Cl_2	44	89
12	45+24	AgOTf	CH_2Cl_2	46	77

a. The same equivalent amount of **38** was produced for entry 1-8, **41** for entry 9-12.
b. The yield changed slightly for different reaction conditions (see text).
c. Reverse coupling reaction at room temperature.

gain a deeper insight into this chemistry, different donors such as imidates **34** [20], **43** [21] and bromide **45,** [22] were coupled with acceptor **24** (Scheme 3). Again, no significant change of product distribution was observed. The reverse coupling reaction was also investigated. Acceptor **9** was stirred with 0.05 equiv of TMSOTf in dry methylene chloride for 5 min at -20 °C with N_2 protection and donor **34** (0.8 equiv of **9**) was added to this mixture. The reaction mixture was stirred for 30 min at room temperature and then quenched with solid sodium bicarbonate. ^{1}H NMR showed that compound **38**, **39** and unreacted acceptor **9** were obtained. Thus, the aglycon transfer reaction was independent of the nature of the donor, the reaction conditions and the order of reagent addition.

This unexpected intermolecular aglycon transfer might be due in part to the relatively unreactive 4-hydroxyl groups of iduronic acid derivatives **9** and **24**.[23] Furthermore, thiolates are more nucleophilic than alcholates. Treatment of a glycosyl donor with a Lewis acid in the presence of a suitable thiol, would lead to an equilibrium where the S-glycoside is strongly preferred over the O-glycoside.

We next turned our attention to an alternative route for the synthesis of universal iduronic acid donor and /or acceptor **16** (Scheme 1). The 4-hydroxyl groups of **9** and **24** were acetylated with acetic anhydride in pyridine to give **11** and **25**. Attempts to protect the 4-hydroxyl group of **9** with chloroacetyl resulted in significant acyl migration in the process of pyranose ring closure. Desilylation of **11** with basic tetrabutylammonium fluoride in THF resulted in an O-3 to O-5 benzoyl migration affording methyl (4-O-acetyl-5-O-benzoyl-2-O-(p-methoxybenzyl))-iduronamide diethyl dithioacetal (**13**) (the major of three products). The same reaction in the presence of the nearly neutral $Et_3N \cdot 3HF$ resulted in desilylation affording **14** and **26** in high yield. Treatment of **14** and **26** with a mercuric chloride/mercuric oxide mixture in an acetone-water (10:1) solvent system at room temperature (for **14**) or under reflux (for **26**) gave the desired idopyranuronamide derivative **16** in good yield. The trichloroacetimidate of **16** was easily formed. Trichloroacetimidates have been shown to be effective iduronic acid glycosyl donors.[24] The structure of **16** was confirmed by its acetylated derivatives **17α** and **17β**. All the small ^3J values in **17α**, **17β** suggested that the iduronic acid derivatives are in the $^1C_4$ conformation. Remarkably, only six chromatographic purification steps were required throughout the entire reaction sequence described in Scheme 1.

CONCLUSION

In conclusion, an α-L-IdopA-synthon **16** was prepared in high overall yield and in a fully regio- and stereocontrolled manner with a minimum of chromatographic steps. This synthon should be easily incorporated in glycosaminoglycan fragments following: 1) O-1-

activation to a glycosyl donor; [24] 2) selective O-4-deacetylation to a glycosyl acceptor; [25] and 3) selective O-2-deprotection [15] and subsequent sulfation. [26] Intermolecular aglycon transfer products were observed when dithioacetals were used as glycosyl acceptors. It appears from this research that the sulfur atom in dithioacetals react not only with thiophilic reagents (*i.e.*, mercuric salts) but also with the eletrophilic center of glycosyl oxocarbenium ions.

EXPERIMENTAL

General methods. Melting points were determined with an electrothermal apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Thin-layer chromatography (TLC) was performed using Merck plates of silica gel 60 with fluorescent indicator. Visualization was effected by spraying plates with Von's Reagent followed by heating at 140 °C. Flash chromatography was conducted with silica gel (230-400 mesh, Merck). THF, Py, CH_2Cl_2 were anhydrous solvents available from Aldrich. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ on a Varian UNITY-500 spectrometer. Chemical shifts are recorded in ppm (δ) relative to tetramethylsilane as internal standard, the ^{1}H NMR spectra were fully assigned by the use of single frequency decoupling. FABMS spectra were obtained on ZAB-HF (VG Analytical Inc.) spectrometer. Combustion analyses were performed by Galbraith (Knoxville, TN).

Idurono-6,3-lactone diethyl dithioacetal (2). To a solution of 1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone[13] (12 g, 55.6 mmol) in ethanethiol (36 mL), concentrated hydrochloric acid (25 mL) was added with vigorous stirring in an ice-cold water bath. The mixture was stirred for 2 h at 4 °C, poured into ice-cold water (800 mL), carefully neutralized with powdered sodium bicarbonate, repeatedly extracted with ethyl acetate (5 × 100 mL) and the organic layer was dried over anhydrous magnesium sulfate and concentrated. The crude product (15 g) was used directly as starting material for the next reaction without further purification.

2,4,5-Tri-O-acetyl-idurono-6,3-lactone diethyl dithioacetal (3). Compound 2 (106 mg, 0.38 mmol) was acetylated with pyridine (0.5 mL) and acetic anhydride (0.4 mL) at room temperature for 6 h to give 3 (145 mg, 95%) as a syrup; $[\alpha]_D$ +14 °(*c* 3, $CHCl_3$); ^{1}H NMR: δ 1.20-1.35 (m, 6 H, 2 CH_3CH$_2$S), 2.13, 2.15, 2.17 (3 s, 3 × 3 H, 3 CH_3CO), 2.55-2.80 (m, 4 H, 2 CH$_3$CH_2S), 3.82 (d, 1 H, $J_{1,2}$=4.0 Hz, H-1), 5.09 (dd, 1 H, $J_{2,3}$=7.5, $J_{3,4}$=3.3 Hz, H-3), 5.59 (dd, 1 H, H-2), 5.72 (d, 1 H, $J_{4,5}$=5.1 Hz, H-5), 5.78 (dd, 1 H, H-4).

Anal. Calcd for $C_{16}H_{24}O_8S_2$ (408.5): C, 47.05; H, 5.92. Found: C, 47.06; H, 5.88.

2,4-O- (p -Methoxybenzylidene)- idurono -6,3-lactone diethyl dithioacetal (4). To a solution of **2** (7.5 g, 26.6 mmol) containing drierite (10 g) in anhydrous acetonitrile (105 mL) was added p-anisaldhyde (15 mL) and p-toluenesulfonic acid monohydrate (70 mg) under a nitrogen atmosphere. The mixture was vigorously stirred at room temperature for 4 h, then more drierite (3 g) was added. The mixture was stirred for another 2 h, after which time TLC (2.5 : 1 petroleum ether-EtOAc) indicated that the reaction was complete. After filtration, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (eluent hexanes-EtOAc 4 : 1) to afford compound **4** (8.6 g, 81%) as a crystal; mp 97-99 °C; $[\alpha]_D$: +3.7° (c 0.1, CHCl$_3$); ^{1}H NMR: δ 1.22, 1.35 (2 t, 2 × 3 H, 2 CH$_3$CH$_2$S), 2.65-2.90 (m, 4 H, 2 CH$_3$CH$_2$S), 3.80 (s, 3 H, CH$_3$O), 4.00 (dd, 1 H, $J_{1,2}$=10.4, $J_{2,3}$=1.7 Hz, H-2), 4.20 (d, 1 H, H-1), 4.30 (s, 1 H, H-5), 4.55 (d, 1 H, $J_{3,4}$=2.2 Hz, H-4), 5.08 (dd, 1 H, H-3), 5.54 (s, 1 H, MeOPhCH), 6.84, 7.40 (2 d, 4 H, J=8.7 Hz, Arom. H). FABMS m/z 423 (M+Na)$^+$.

Anal. Calcd for C$_{18}$H$_{24}$O$_6$S$_2$ (400.5): C, 53.98; H, 6.04. Found: C, 53.99; H, 6.37.

5-O-Acetyl- 2,4 -O-(p-methoxybenzylidene)- idurono - 6,3 -lactone diethyl dithioacetal (5). Acetylation of **4** with acetic anhydride in pyridine gave **5** in quantitative yield; ^{1}H NMR: δ 1.22, 1.35 (2 t, 2 × 3 H, 2 CH$_3$CH$_2$S), 2.20 (s, 3 H, CH$_3$CO), 2.65-2.90 (m, 4 H, 2 CH$_3$CH$_2$S), 3.80 (s, 3 H, CH$_3$O), 4.00 (dd, 1 H, $J_{1,2}$=10.5, $J_{2,3}$=1.7 Hz, H-2), 4.21 (d, 1 H, H-1), 4.56 (d, 1 H, $J_{3,4}$=2.5 Hz, H-4), 5.01 (br t, 1 H, H-3), 5.20 (s, 1 H, H-5), 5.54 (s, 1 H, MeOPhCH), 6.84, 7.40 (2 d, 4 H, J=8.5 Hz, Arom. H).

Anal. Calcd for C$_{20}$H$_{26}$O$_7$S$_2$ (442.5): C, 54.28; H, 5.92. Found: C, 54.26; H, 6.13.

5-O-(Tert-butyldimethylsilyl)-2,4-O-(p-methoxybenzylidene)-idurono-6,3-lactone diethyl dithioacetal (6). To a solution of **4** (6.2 g, 15.5 mmol) in anhydrous N,N'-dimethylformamide (35 mL) in an ice water bath, imidazole (4 g, 58.7 mmol) and tert-butyldimethylsilyl chloride (3.4 g, 22.6 mmol) were added. The mixture was stirred overnight at room temperature. When TLC (6 : 1 hexanes-EtOAc) indicated that the reaction was complete, the reaction mixture was poured into ice-cold water (200 mL) and extracted with diethyl ether (3 × 100 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$, then concentrated under reduced pressure, while traces of DMF were removed by coevaporation with heptane. The crude product (7.81 g) was used directly in the next reaction without further purification . A small amount of crude product was purified by a flash column chromatography (eluent hexanes-EtOAc 8 : 1) for ^{1}H NMR analysis; mp 103-105 °C; $[\alpha]_D$: +3.3 ° (c 0.4, CHCl$_3$); ^{1}H NMR: δ 0.18, 0.20 (2 s, 2 × 3 H, 2 SiMe), 0.95 (s, 9 H, t-Bu), 1.22, 1.35 (2 t, 2 × 3 H, 2 CH$_3$CH$_2$S), 2.60-2.90 (m, 4

H, 2 CH$_3$CH_2S), 3.80 (s, 3 H, OCH_3), 3.98 (dd, 1 H, $J_{1,2}$ =10.6, $J_{2,3}$=1.5 Hz, H-2), 4.20 (s, 1 H, H-5), 4.23 (d, 1 H, H-1), 4.37 (d, 1 H, $J_{3,4}$ =1.7 Hz, H-4), 5.02 (br t, 1 H, H-3), 5.53 (s, 1 H, MeOPhCH), 6.85 (d, 2 H, arom. H), 7.40 (d, 2 H, Arom. H). FABMS m/z 537 (M+Na)⁺.

Anal. Calcd for C$_{24}$H$_{38}$O$_6$SiS$_2$ (514.8): C, 56.00; H, 7.44. Found: C, 56.10; H, 7.70.

Methyl [3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2,4-O-(*p*-methoxy-benzylidene)]-iduronamide diethyl dithioacetal (8). To a stirred solution of 6 (5 g, 9.5 mmol) in tetrahydrofuran (10 mL) under nitrogen at 4 °C, methylamine (10 mL, 2 M solution in THF) was added in one portion. The mixture was stirred about 30 min until the starting material had completely disappeared as determined by TLC (3 : 1 hexanes-EtOAc). The crude mixture, concentrated under reduced pressure, gave 7 (5.24 g) which was used without further purification in the next reaction. Compound 7 was purified for ¹H NMR by flash column chromatography (eluent hexanes-EtOAc 4:1); [α]$_D$: -12 ° (*c* 0.5, CHCl$_3$); ¹H NMR: δ 0.05 (s, 6 H, 2 SiMe), 0.88 (s, 9 H, *t*-Bu), 1.21, 1.30 (2 t, 2 × 3 H, 2 CH_3CH$_2$S), 2.65-2.83 (m, 4 H, 2 CH$_3$CH_2S), 2.90 (d, 3 H, $J_{CH, NH}$ =5.0 Hz, CH_3NH), 3.71-3.75 (m, 2 H, H-3, H-5), 3.81 (s, 3 H, OCH_3), 3.95 (d, 1 H, $J_{1,2}$ =5.5 Hz, H-1), 4.09 (br d, 1 H, H-2), 4.30 (d, 1 H, $J_{4,5}$ =7.3 Hz, H-4), 4.50 (s, 1 H, $J_{3,OH}$ = 10.1 Hz, OH), 5.49 (s, 1 H, MeOPhCH), 6.83-6.87 (m, 3 H, NH and Arom. H), 7.42 (d, 2 H, Arom. H).

To a crude 7 (4.1 g, 7.36 mmol) in methylene chloride (60 mL) at 0 °C, BzCl (1.1 mL, 9.57 mmol), triethylamine (2 mL, 14.4 mmol) and 4-dimethylaminopyridine (DMAP, 10 mg) was added. The mixture was stirred at room temperature for 4 days at which time TLC (2.5 : 1, hexanes-EtOAc) confirmed the disappearance of starting material. The reaction mixture was concentrated under reduced pressure, poured into cold aqueous saturated NaHCO$_3$ (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography (3.5:1 hexanes-EtOAc) of the residue yielded 8 as a syrup (3.4 g, 73%); [α]$_D$ +19 ° (*c* 1, CHCl$_3$); ¹H NMR: δ 0.08 (s, 6 H, 2 SiMe), 0.90 (s, 9 H, *t*-Bu), 1.05, 1.22 (2 t, 2 × 3 H, 2 CH_3CH$_2$S), 2.60-2.85 (m, 7 H, $J_{CH, NH}$ =5.4 Hz, 2 CH$_3$CH_2S, CH_3NH), 3.89 (s, 3 H, OCH_3), 4.12 (d, 1 H, $J_{4,5}$ =8.3 Hz, H-4), 4.14 (d, 1 H, $J_{1,2}$ =6.4 Hz, H-2), 4.20 (d, 1 H, H-1), 4.41 (d, 1 H, H-5), 5.70 (s, 1 H, MeOPhCH), 5.82 (s, 1 H, H-3), 6.65 (br d, 1 H, NH), 7.00-8.20 (m, 9 H, Arom. H).

Anal. Calcd for C$_{32}$H$_{47}$NO$_7$SiS$_2$ (649.9): C, 59.14; H, 7.29. Found: C, 58.86; H, 6.92.

Methyl   [3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2-O-(*p*-methoxy-benzyl)]-iduronamide diethyl dithioacetal (9). To a stirred mixture of 8 (2.6 g,

4.11 mmol), sodium cyanoborohydride (1.58 g, 95%, 25 mmol) and 4 Å molecular sieves (3 g) in anhydrous acetonitrile (80 mL), trimethylchlorosilane-acetonitrile solution (3.2 mL, 25 mmol TMSCl in 25 mL CH_3CN) was added dropwise under nitrogen at 0 °C. The mixture was stirred for 2 h at 0 °C then filtered, concentrated, and purified by flash column chromatography (4:1, hexanes-EtOAc) to afford **9** (2.48 g, 95%) as a syrup; $[\alpha]_D$ -11 ° (*c* 0.9, $CHCl_3$); ^1H NMR: δ 0.09, 0.21 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, *t*-Bu), 1.21, 1.25 (2 t, 2 × 3 H, 2 CH_3CH_2S), 2.10 (d, 3 H, $J_{CH, NH}$=5.2 Hz, CH_3NH), 2.65-2.81 (m, 4 H, 2 CH_3CH_2S), 3.70 (s, 3 H, CH_3O), 4.11 (d, 1 H, $J_{1,2}$=3.3 Hz, H-1), 4.13 (dd, 1 H, $J_{3,4}$=1.4, $J_{4,5}$=6.4 Hz, H-4), 4.26 (dd, 1 H, $J_{2,3}$=8.3 Hz, H-2), 4.30 (d, 1 H, H-5), 4.39, 4.64 (2 d, 2 H, J=11.7 Hz, MeOPhCH_2), 5.90 (dd, 1 H, H-3), 6.47 (br d, 1 H, NH), 6.61-8.00 (m, 9 H, Arom. H). FABMS *m/z* 674 (M+Na)$^+$.

Anal. Calcd for $C_{32}H_{49}NO_7SiS_2$ (651.9): C, 58.95; H, 7.58. Found: C, 59.23; H, 7.89.

Methyl [4-O-acetyl-3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2-O-(*p*-methoxybenzyl)]-iduronamide diethyl dithioacetal (11). Acetylation of **9** (1.37 g, 2.16 mmol) in pyridine (6 mL) and acetic anhydride (5 mL) at room temperature for 16 h gave **11** in quantitative yield as a syrup; $[\alpha]_D$ -27 ° (*c* 0.1, $CHCl_3$); ^1H NMR: δ 0.11, 0.22 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, *t*-Bu), 1.23, 1.28 (2 t, 2 × 3 H, 2 CH_3CH_2S), 2.20 (s, 3 H, CH_3CO), 2.22 (d, 3 H, J=5.0 Hz, NHCH_3), 2.60-2.80 (m, 4 H, 2 CH_3CH_2S), 3.72 (s, 3 H, OCH_3), 3.85 (d, 1 H, $J_{1,2}$=3.7 Hz, H-1), 4.00 (dd, $J_{2,3}$=7.8 Hz, H-2), 4.43, 4.63 (2 d, 2 H, J=10.5 Hz, MeOPhCH_2), 4.46 (d, 1 H, $J_{4,5}$=6.2 Hz, H-5), 5.18 (dd, 1 H, $J_{3,4}$=2.3 Hz, H-4), 6.14 (dd, 1 H, H-3), 6.30 (q, 1 H, NHCH_3), 6.80-8.10 (m, 9 H, Arom. H).

Anal. Calcd for $C_{34}H_{51}NO_8SiS_2$ (694.0): C, 58.84; H, 7.41. Found: C, 58.99; H, 7.37.

Methyl [4-O-chloroacetyl-3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2-O-(*p*-methoxybenzyl)]-iduronamide diethyl dithioacetal (12). Chloro-acetylation of **9** (150 mg, 0.24 mmol) with chloroacetic anhydride (45 mg, 0.26 mmol) and triethylamine (0.02 mL) in CH_2Cl_2 (3 mL) at room temperature gave **12** (160 mg, 93%) as a syrup; ^1H NMR: δ 0.04, 0.09 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, *t*-Bu), 1.18, 1.21 (2 t, 2 × 3 H, 2 CH_3CH_2S), 2.00 (d, 3 H, $J_{CH,NH}$=5.0 Hz, CH_3NH), 2.65-2.80 (m, 4 H, 2 CH_3CH_2S), 3.75 (s, 3 H, CH_3O), 3.84 (d, 1 H, $J_{1,2}$=3.3 Hz, H-1), 4.13 (dd, 1 H, $J_{2,3}$=7.8 Hz, H-2), 4.06 (s, 2 H, ClCH_2CO), 4.28, 4.59 (2 d, 2 H, J=10.5 Hz, MeOPhCH_2), 4.60 (d, 1 H, $J_{4,5}$=6.5 Hz, H-5), 5.23 (d, 1 H, $J_{3,4}$=2.0 Hz, H-4), 6.12 (br d, 1 H, NH), 6.21 (dd, 1 H, H-3), 6.82-7.80 (m, 9 H, Arom. H). HRMS(FAB) Calcd for $C_{34}H_{50}ClNO_8SiS_2Na$ 751.4278. Found *m/z* 751.4269 (M+Na).

Methyl **[4-O-acetyl-3-O-benzoyl-2-O-(p-methoxybenzyl)]-iduron-amide diethyl dithioacetal (14).** To a solution of **11** (1.03 g, 1.49 mmol) in THF (10 mL) at 4 °C, triethylamine trihydrofluoride (4 mL) was added. The solution was stirred at room temperature for 48 h, when TLC (2.5 : 1 hexanes-EtOAc) confirmed the disappearance of starting material. The solution was concentrated under diminished pressure to a syrupy residue that was purified by flash column chromatography (3:1 petroleum ether- EtOAc) to give **14** as a syrup (80.1 mg, 93.2%); $[\alpha]_D$ -33 ° (c 0.1, CHCl$_3$); ^{1}H NMR: δ 1.15, 1.20 (2 t, 2 × 3 H, 2 CH_3CH$_2$S), 2.07 (s, 3 H, CH_3CO), 2.15 (d, 3 H, $J_{CH,NH}$=4.9 Hz, CH_3NH), 2.60-2.80 (m, 4 H, 2 CH$_3$CH_2S), 3.78 (s, 3 H, CH_3O), 3.94 (d, 1 H, $J_{1,2}$=3.0 Hz, H-1), 3.99 (dd, 1 H, $J_{2,3}$=7.1 Hz, H-2), 4.31 (dd, 1 H, $J_{4,5}$=5.8, $J_{5,OH}$=7.9 Hz, H-5), 4.45, 4.65 (2 d, 2 H, J=11.7 Hz, MeOPhCH_2), 5.10 (dd, 1 H, $J_{3,4}$=2.5 Hz, H-4), 5.90 (dd, 1 H, H-3), 6.21 (br d, 1 H, NH), 6.80-7.80 (m, 9 H, Arom. H).

Anal. Calcd for C$_{28}$H$_{37}$NO$_8$S$_2$ (579.7): C, 58.01; H, 6.43. Found: C, 58.03; H, 6.39.

Methyl **[1,4-di-O-acetyl-3-O-benzoyl-2-O-(p-methoxybenzyl)-α-L-idopyranuronamide] (17α)** and **Methyl** **[1,4-di-O-acetyl-3-O-benzoyl-2-O-(p-methoxybenzyl)-β-L-idopyranuronamide] (17β).** A mixture of **14** (50 mg, 0.087 mmol), mercuric chloride (35 mg), mercuric oxide (32 mg) and water (0.2 mL) in acetone (2 mL) was stirred for 6 h at room temperature. The mixture was diluted with acetone (20 mL), filtered, and concentrated under reduced pressure. Traces of water in the mixture were coevaporated with toluene for several times affording a syrupy residue. Acetylation of this residue *in situ* with acetic anhydride (0.3 mL) and pyridine (0.5 mL) gave a mixture of **17α** and **17β** as a syrup (35.3 mg , 79%) in the ratio of (5:1) which was separated by flash column chromatography (2.5:1 hexanes:EtOAc). For **17α**, $[\alpha]_D$ -69 °(c 0.2, CHCl$_3$); ^{1}H NMR: δ 1.95, 1.98 (2 s, 2 × 3 H, 2 CH_3CO), 2.88 (d, 3 H, $J_{CH,NH}$=5.5 Hz, CH_3NH), 3.64 (br s, 1 H, H-2), 3.80 (s, 3 H, CH_3O), 4.62, 4.70 (2 d, 2 H, J=12.1 Hz, MeOPhCH_2), 4.86 (d, 1 H, $J_{4,5}$=1.2 Hz, H-5), 5.40 (br s, 1 H, H-4), 5.56 (br s, 1 H, H-3), 6.20 (br s, 1 H, H-1), 6.78 (br d, 1 H, NH), 7.05-8.05 (m, 9 H, Arom. H). FABMS m/z 516 (M+H)$^+$. For **17β**, $[\alpha]_D$ +3 ° (c 0.1, CHCl$_3$); ^{1}H NMR: 2.03, 2.18 (2 s, 2 × 3 H, 2 CH_3CO), 2.85 (d, 3 H, $J_{CH,NH}$=5.3 Hz, CH_3NH), 3.67 (dd, 1 H, $J_{1,2}$=1.8, $J_{2,3}$=2.7 Hz, H-2), 3.80 (s, 3 H, CH_3O), 4.67, 4.75 (2 d, 2 H, J=12.1 Hz, MeOPhCH_2), 4.69 (br s, 1 H, $J_{4,5}$<1 Hz, H-5), 5.32 (br d, 1 H, $J_{3,4}$=2.7 Hz, H-4), 5.63 (t, 1 H, H-3), 5.87 (d, 1 H, H-1), 6.78 (br d, 1 H, NH), 7.05-8.05 (m, 9 H, Arom. H).

Anal. Calcd for C$_{26}$H$_{29}$NO$_{10}$ (515.5): C, 60.58; H, 5.67. Found: C, 60.87; H, 5.55.

The same procedure was used to prepare **16** starting from idurono-6,3-lactone diphenyldithioacetal (**18**).

Idurono-6,3-lactone diphenyl dithioacetal (18). Compound **18** was prepared by the same procedure used for **2**. The structure of **18** was confirmed by analyzing its triacetate derivative; $[\alpha]_D$ +14 ° (*c* 3, CHCl$_3$); ^{1}H NMR: δ 2.01, 2.02, 2.10 (3 s, 3 × 3 H, 3 CH_3CO), 4.66 (d, 1 H, $J_{1,2}$= 9.6 Hz, H-1), 5.18 (dd, 1 H, $J_{2,3}$= 1.5 Hz, H-2), 5.59 (t, 1 H, $J_{3,4}$= $J_{4,5}$= 8.4 Hz, H-4), 5.66 (d, 1 H, H-5), 5.74 (dd, 1 H, H-3), 7.20-7.45 (m, 10 H, Arom. *H*).

Anal. Calcd for C$_{24}$H$_{24}$O$_8$S$_2$ (504.6): C, 57.13; H, 4.79. Found: C, 57.46; H, 4.93.

2,4-*O*-(*p*-Methoxybenzylidene)-idurono-6,3-lactone diphenyl dithioacetal (19). Compound **19** was prepared from **18** by using the same procedure used for 4; $[\alpha]_D$ +4.8 ° (*c* 0.4, CHCl$_3$); ^{1}H NMR: δ 2.87 (d, 1 H, $J_{5,OH}$=3.5 Hz, O*H*), 3.80 (s, 3 H, CH_3O), 3.98 (dd, 1 H, $J_{1,2}$=10.4, $J_{2,3}$=1.7 Hz, H-2), 4.28 (d, 1 H, H-5), 4.54 (d, $J_{3,4}$=2.5 Hz, H-4), 4.80 (d, 1 H, H-1), 5.14 (dd, 1 H, H-3), 5.47 (s, 3 H, MeOPhC*H*), 6.82-7.58 (m, 14 H, Arom. *H*). FABMS *m/z* 519 (M+Na)$^+$.

Anal. Calcd for C$_{26}$H$_{24}$O$_6$S$_2$ (496.6): C, 62.89; H, 4.87. Found: C, 62.52; H, 5.03.

5-*O*- Acetyl -2,4-*O*-(*p*-methoxybenzylidene)- idurono -6,3- lactone diphenyl dithioacetal (20). Compound **20** was prepared by acetylation of **19**; ^{1}H NMR: δ 2.19 (s, 3 H, CH_3CO), 3.80 (s, 3 H, CH_3O), 3.97 (dd, 1 H, $J_{1,2}$=10.3, $J_{2,3}$=1.8 Hz, H-2), 4.56 (d, 1 H, $J_{3,4}$=2.4 Hz, H-4), 4.79 (d, 1 H, H-1), 5.07 (br t, 1 H, H-3), 5.19 (s, 1 H, H-5), 5.54 (s, 1 H, MeOPhC*H*), 6.84-7.55 (m, 14 H, Arom. *H*).

Anal. Calcd for C$_{28}$H$_{26}$O$_7$S$_2$ (538.6): C, 62.44; H, 4.87. Found: C, 62.79; H, 5.04.

5-*O*-(*tert*-Butyldimethylsilyl)-2,4-*O*-(*p*-methoxybenzylidene)-idurono-6,3-lactone diphenyl dithioacetal (21). Compound **21** was prepared by silylation of **19**; $[\alpha]_D$ +6 ° (*c* 3, CHCl$_3$); ^{1}H NMR: δ 3.81 (s, 3 H, CH_3O), 4.00 (dd, 1 H, $J_{1,2}$=9.5, $J_{2,3}$=3.0 Hz, H-2), 4.60 (s, 1 H, H-5), 4.74 (d, 1 H, $J_{3,4}$=4.1 Hz, H-4), 4.78 (d, 1 H, H-1), 5.10 (dd, 1 H, H-3), 5.56 (s, 1 H, MeOPhC*H*), 6.86-7.60 (m, 14 H, Arom. *H*).

Anal. Calcd for C$_{32}$H$_{38}$O$_6$SiS$_2$ (610.9): C, 62.92; H, 6.27. Found: C, 63.11; H, 6.65.

Methyl [5-*O*-(*tert*-butyldimethylsilyl)-2,4-*O*-(*p*-methoxybenzylidene)]-iduronamide diphenyl dithioacetal (22). Compound **22** was prepared from **21** by the same procedure used for 7; $[\alpha]_D$ +12 ° (*c* 0.5, CHCl$_3$); ^{1}H NMR: δ 0.01, 0.04 (2 s, 2 × 3 H, 2 SiMe), 0.88 (s, 9 H, *t*-Bu), 2.88 (d, 3 H, $J_{CH, NH}$=4.9 Hz, CH_3NH), 3.68 (d, 1 H, $J_{1,2}$=7.3 Hz, H-2), 3.72 (d, 1 H, $J_{4,5}$=10.2 Hz, H-4), 3.80 (s, 3 H, CH_3O), 3.88 (d, 1 H,

$J_{3,OH}$=5.4 Hz, OH), 4.16 (d, 1 H, H-3), 4.46 (d, 1 H, H-1), 4.92 (d, 1 H, H-5), 6.80 (br d, 1 H, NH), 6.82-7.50 (m, 14 H, Arom. H).

Anal. Calcd for $C_{33}H_{43}NO_6SiS_2$ (641.9): C, 61.75; H, 6.75. Found: C, 61.78; H, 6.71.

Methyl [3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2,4-O-(*p*-methoxy-benzylidene)]-iduronamide diphenyl dithioacetal (23). Compound **23** was prepared by benzoylation of **22**. [α]$_D$ -67 ° (*c* 1.4, CHCl$_3$); ^{1}H NMR: δ 0.01, 0.12 (2 s, 2 × 3 H, 2 SiMe), 0.92 (s, 9 H, *t*-Bu), 2.80 (d, 3 H, J=5.5 Hz, CH_3NH), 3.92 (s, 3 H, OCH_3), 4.10 (dd, 1 H, $J_{1,2}$=8.7 Hz, $J_{2,3}$=1.2 Hz, H-2), 4.28 (dd, 1 H, $J_{3,4}$=1.2, $J_{4,5}$=4.4 Hz, H-4), 4.45 (d, 1 H,H-1), 4.84 (d, 1 H, H-5), 5.67 (s, 1 H, MeOPhCH), 5.79 (t,1 H, H-3), 6.72 (br d, 1 H, NH), 7.00-8.24 (m, 19 H, Arom. H). FABMS *m/z* 768 (M+Na)$^+$.

Anal. Calcd for $C_{40}H_{47}NO_7SiS_2$ (746.0): C, 64.40; H, 4.35. Found: C, 64.43; H, 6.31.

Methyl [3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2-O-(*p*-methoxy-benzyl)]-iduronamide diphenyl dithioacetal (24). Compound **24** was prepared from **22** by the same procedure used for **9**; [α]$_D$ -4.1 ° (*c* 1.6, CHCl$_3$); ^{1}H NMR: δ 0.02, 0.08 (2 s, 6 H, 2 SiMe), 0.90 (s, 9 H, *t*-Bu), 2.10 (d, 3 H, $J_{CH, NH}$=4.7 Hz, CH_3NH), 3.75 (s, 3 H, CH_3O), 4.29 (br s, 2 H, H-4, H-5), 4.34 (dd, 1 H, $J_{1,2}$=1.8, $J_{2,3}$=7.3 Hz, H-2), 4.46, 4.76 (2 d, 2 H, ^3J=10.7 Hz, MeOPhCH_2), 4.97 (d, 1 H, H-1), 5.27-5.30 (m, 1 H, 4-OH), 5.82 (d, 1 H, H-3), 6.45 (br d, 1 H, NH), 6.65-7.95 (m, 19 H, Arom. H). HRMS(FAB) Calcd for $C_{40}H_{49}NO_7SiS_2Na$ 771.0343. Found *m/z* 771.0359 (M+Na).

Methyl [4-O-acetyl-3-O-benzoyl-5-O-(*tert*-butyldimethylsilyl)-2-O-(*p*-methoxybenzyl)]-iduronamide diphenyl dithioacetal (25). Compound **25** was prepared by acetylation of **24**. [α]$_D$: -57 ° (*c* 0.4, CHCl$_3$); ^{1}H NMR: δ 0.01, 0.1 (2 s, 2 × 3 H, 2 SiMe), 0.90 (s, 9 H, *t*-Bu), 1.80 (s, 3 H, CH_3CO), 2.18 (d, 3 H, $J_{CH, NH}$ =5.1 Hz, CH_3NH), 3.79 (s, 3 H, OCH_3), 4.17 (dd, 1 H, $J_{1,2}$ =1.7, $J_{2,3}$ =7.1 Hz, H-2), 4.42 (d, 1 H, $J_{4,5}$ =6.1 Hz, H-5), 4.58,4.89 (2 d, 2 H, J =10.7 Hz, MeOPhCH_2), 4.67 (d, 1 H, H-1), 5.23 (dd, 1 H, $J_{3,4}$=1.7 Hz, H-4), 6.06 (dd, 1 H, H-4), 6.24 (br d, 1 H, NH), 6.74-8.00 (m, 19 H, Arom. H).

Anal. Calcd for $C_{42}H_{51}NO_8SiS_2$ (790.1): C, 63.85; H, 6.51. Found: C, 63.66; H, 6.13.

***Tert*-butyldimethylsilyl 2-azido-3-O- benzyl- 4,6-O- benzylidene -2-deoxy-β-D-glucopyranoside (28).** Method A: To a mixture of compound **27** [18] (4.0 g, 9.83 mmol) and NaH (790 mg, 95%, 31 mmol) in anhydrous DMF (15 mL) at 4 °C, BnBr (2.9 g, 16.9 mmol) was added dropwise. The mixture was stirred at rt for 10 h, then poured into ice-water (120 mL) and extracted with EtOAc (3 x 80 mL). The organic phase

was combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification of the product by flash column chromatography (9:1 petroleum ether-EtOAc) gives **28** as a syrup (3.56 g, 73%). Method B: To a solution of 27 (1.0 g, 2.5 mmol) in anhydrous CH_2Cl_2 (15 mL) freshly prepared silver oxide (810 mg, 3.4 mmol), 4 Å molecular sieves (2 g), and BnBr (0.4 mL, 3.3 mmol) were added. The mixture was stirred at rt for 48 h when TLC (7:1 petroleum ether-EtOAc) indicated that the starting material disappeared. The mixture was filtered, the organic solvent evaporated and the residue purified by flash column chromatography (9:1 petroleum ether-EtOAc) to give **2 8** as a syrup (1 g, 82%); $[\alpha]_D$: -42 ° (c 1.7, CHCl$_3$); ^{1}H NMR: δ 0.17, 0.19 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, t-Bu), 3.35-3.42 (m, 2 H, H-2, H-5), 3.51 (dd, 1 H, $J_{2,3}$ =9.5, $J_{3,4}$ =9.1 Hz, H-3), 3.70 (t, 1 H, $J_{4,5}$=9.1 Hz, H-4), 3.80 (dd, 1 H, $J_{5,6a}$=10.1 Hz, $J_{6a,6b}$ =10.4 Hz, H-6a), 4.30 (dd, 1 H, $J_{5,6b}$=4.9 Hz, H-6b), 4.60 (d, 1 H, $J_{1,2}$=7.9 Hz, H-1), 4.80, 4.90 (2 d, 2 H, J=11.4 Hz, PhCH$_2$), 5.58 (s, 1 H, PhCH), 6.92-7.50 (m, 10 H, Arom. H).

Anal. Calcd for $C_{26}H_{35}N_3O_5Si$ (497.7): C, 62.75; H, 7.09. Found: C, 62.78; H, 7.08.

Tert-butyldimethylsilyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-gluco-pyranoside (29). Diethyl ether saturated with hydrogen chloride (gas) was added at 0 ℃ to **28** (4.0 g, 8.05 mmol) in tetrahydrofuran (20 mL) containing sodium cyanoborohydride (3.5 g) and 4 Å molecular sieves (4 g) until the evolution of gas ceased. TLC (5:1 petroleum ether-EtOAc) after 5 min indicated complete reaction. The mixture was diluted with ether (100 mL), filtered, washed with water and with saturated aqueous sodium bicarbonate. The organic layer was dried with anhydrous sodium sulfate and concentrated. The resulting syrup was applied to a column of silica gel which was eluted with petroleum ether-EtOAc (6:1) to yield **29** as a syrup (3.45 g, 86%); $[\alpha]_D$: -35 ° (c 1.1, CHCl$_3$). [Lit [27], $[\alpha]_D$: -34.2 ° (c 1, CHCl$_3$)].

Tert-butyldimethylsilyl 4-*O*-allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (30). To a solution of **29** (1.0 g, 2 mmol) in DMF (5 mL) at 0 °C, allyl bromide (0.3 mL, 2.6 mmol) and NaH (190 mg) were added under N$_2$ protection. The mixture was stirred at rt for 4 h, when TLC (5:1 petroleum ether-EtOAc) indicated the reaction complete. The mixture was poured into ice-water (30 mL) and then extracted with EtOAc (3 × 20 mL), the organic phase was combined, dried and concentrated to a residue that was purified by flash column chromatography (petroleum ether-EtOAc 6:1), to give **3 0** (735 mg, 68%) as a syrup; $[\alpha]_D$: -11 ° (c 0.7, CHCl$_3$); [Lit [27] $[\alpha]_D$: -3 ° (c 1, CHCl$_3$), but gave a slightly different ^{1}H NMR spectrum]; ^{1}H NMR: δ 0.18, 0.19 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, t-Bu), 3.28-3.33 (m, 2 H, H-2, H-3), 3.36 (d t, 1 H, $J_{4,5}$ =9.5 Hz, $J_{5,6a}$=$J_{5,6b}$=3.4 Hz, H-5), 3.45-3.50 (m, 1 H, H-4), 3.64 (br d, 2 H, H-6a, H-6b), 4.06

(dd, 1 H, J_{gem} =12.4, J_{vic} =5.6 Hz, CH$_2$=CH-CH_a-), 4.26 (dd, 1 H, CH$_2$=CH-CH_b-), 4.48 (d, 1 H, $J_{1,2}$ =7.7 Hz, H-1), 4.55, 4.62 (2 d, 2 H, J = 12.1 Hz, PhCH_2), 4.77, 4.84 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 5.10-5.22 (m, 2 H, CH_2=CH-), 5.80-5.88 (m, 1 H, CH$_2$=CH -CH$_2$-), 7.21-7.40 (m, 10 H, Arom. H). HRMS(FAB) Calcd for C$_{29}$H$_{41}$N$_3$O$_5$SiNa 562.7425. Found 562.7419 m/z (M+Na)$^+$.

O- (4-O-Allyl-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl) trichloroacetimidate (33). Compound 33 was prepared from 30 according to Schmidt's procedure;[27] $[\alpha]_D$ -3.6 ° (c 1, CHCl$_3$); ^{1}H NMR: δ 3.48 (dd, 1 H, $J_{2,3}$=9.6, $J_{3,4}$=9.0 Hz, H-3), 3.54 (d t, 1 H, $J_{4,5}$ =9.6, $J_{5,6a}$=$J_{5,6b}$=3.2 Hz, H-5), 3.62 (dd, 1 H, H-4), 3.65 (dd, 1 H, $J_{1,2}$ =8.5 Hz, H-2), 3.77 (br d, 2 H, H-6a, 6b), 4.08 (dd, 1 H, J_{gem}=12.3 Hz, J_{vic}=5.6 Hz, CH$_2$=CH-CH-), 4.26 (dd, 1 H, CH$_2$=CH-CH-), 4.54, 4.63 (2 d, 2 H, J =12.1 Hz, PhCH_2), 4.84, 4.87 (2 d, 2 H, J =10.7 Hz, PhCH_2), 5.11-5.20 (m, 2 H, CH_2=CH-), 5.60 (d, 1 H, H-1), 5.78-5.86 (m, 1 H, CH$_2$=CH-CH$_2$-), 7.24-7.40 (m, 10 H, Arom. H), 8.73 (s, 1 H, NH).

Anal. Calcd for C$_{25}$H$_{27}$N$_4$O$_5$Cl$_3$ (569.9): C, 52.69; H, 4.78. Found: C, 52.78; H, 4.90.

General procedure for the coupling reactions: A mixture of donor (1 equiv) and the dithioacetal acceptor (1.2 equiv) in anhydrous CH$_2$Cl$_2$ (8 mL/mmol carbohydrate) was treated under nitrogen with TMSOTf (0.05 equiv of glycosyl donor) at temperatures of -42 °C to rt. The reaction was stirred for 30 min to 4 h. After completion (monitored by TLC), the reaction was quenched with solid sodium bicarbonate. The mixture was filtered, then concentrated under reduced pressure furnishing a residue which was further purified by flash column chromatography on silica gel (eluent petroleum ether-EtOAc 4:1).

Ethyl 4-O-allyl-2-azido-3,6-di-O-benzyl-2-deoxy-1-thio-D-gluco-pyranoside (37). Compound 37 was afforded in the coupling of 33 and 9 and purified by flash chromatography. α:β=0.45:0.55; ^{1}H NMR: 1.28 (t, 3 × 0.45 H, CH_3CH$_2$ of α), 1.32 (t, 3 × 0.55 H, CH_3CH$_2$ of β), 2.55-2.65 (m, 2 × 0.45 H, CH$_3$CH_2 of α), 2.66-2.78 (m, 2 × 0.55 H, CH$_3$CH_2 of β), 3.38-3.81 (m, 6 H, H-2,3,4,5,6,6'), 4.00-4.22 (m, 2 H, CH$_2$=CH-CH_2), 4.24 (d, 1 × 0.55 H, J=10.0 Hz, H-1 of β), 4.50, 4.65 (2 d, 2 × 0.45 H, J=12.0 Hz, PhCH_2 of α), 4.55, 4.61 (2 d, 2 × 0.55 H, J=11.2 Hz, PhCH_2 of β), 4.82 (d, 2 × 0.55 H, PhCH_2 of β), 4.86 (d, 2 × 0.45 H, PhCH_2 of α), 5.09-5.14 (m, 2 × 0.55 H, CH_2=CH-CH$_2$ of β), 5.15-5.21 (m, 2 × 0.45 H, CH_2=CH-CH$_2$ of α), 5.40 (d, 1 × 0.45 H, J=5.3 Hz, H-1 of α), 5.73-5.88 (m, 1 H, CH$_2$=CH-CH$_2$), 7.24-7.40 (m, 10 H, Arom. H).

Anal. Calcd for C$_{25}$H$_{31}$N$_3$O$_4$S (469.6): C, 63.94; H, 6.65. Found: C, 63.87; H, 6.98.

Methyl [ethyl 3-O-benzoyl-2-O-(p-methoxybenzyl)-5-O-($tert$-butyl-dimethylsilyl)-1-thio-glucofuranuronamide] (**38**). Compound **38** (α predominant) was afforded in the coupling of **33** and **9** or **34** and **9**. ^{1}H NMR: δ 0.17, 0.18 (2 s, 2 × 3 H, 2 SiMe), 0.98 (s, 9 H, t-Bu), 1.24 (t, 3 H, J =7.5 Hz, CH_3CH$_2$S), 2.64-2.70 (m, 2 H, CH$_3$CH_2S), 2.78 (d, 3 H, $J_{CH,NH}$=4.1 Hz, CH_3NH), 3.80 (s, 3 H, OCH_3), 4.10 (br d, 1 H, H-2), 4.20 (dd, 1 H, $J_{3,4}$=5.1 Hz, $J_{4,5}$=9.1 Hz, H-4), 4.50-4.58 (m, 1 H, H-5), 4.64, 4.80 (2 d, 2 H, J=10.9 Hz, MeOPhCH_2), 5.77 (dd, 1 H, H-3), 6.05 (d, 1 H, $J_{1,2}$=4.7 Hz, H-1), 6.70 (br d, 1 H, NH), 6.85-8.05 (m, 9 H, Arom. H). FABMS m/z 612 (M+Na)$^+$.

Anal. Calcd for C$_{30}$H$_{43}$NO$_7$SiS (589.8): C, 61.09; H, 7.35. Found: C, 60.78; H, 7.16.

Methyl [phenyl 3-O-benzoyl-2-O-(p-methoxybenzyl)-5-O-($tert$-butyl-dimethylsilyl) -1- thio -glucofuranuronamide] (**41**). Compound **41** (α predominant) was afforded when **24** was used as acceptor in the *in situ* coupling reactions and purified by flash chromatography (3:1 petroleum ether-EtOAc); ^{1}H NMR: δ 0.21, 0.22 (2 s, 2 × 3 H, 2 SiMe), 0.95 (s, 9 H, t-Bu), 2.66 (d, 3 H, $J_{CH,NH}$=5.4 Hz, CH_3NH), 3.80 (s, 3 H, OCH_3), 4.20 (dd, 1 H, $J_{3,4}$=6.6 Hz, $J_{4,5}$=8.1 Hz, H-4), 4.26 (d, 1 H, $J_{1,2}$=2.5 Hz, H-2), 4.50-4.58 (m, 1 H, H-5), 4.66, 4.78 (2 d, 2 H, J=11.2 Hz, MeOPhCH_2), 5.55 (d, 1 H, $J_{1,2}$=6.0 H-1), 5.63 (d, 1 H, $J_{2,3}$=0 Hz, H-3), 6.81 (br d, 1 H, NH), 6.90-8.10 (m, 14 H, Arom. H).

Anal. Calcd for C$_{34}$H$_{43}$NO$_7$SiS (637.9): C, 64.02; H, 6.79. Found: C, 63.92; H, 7.01.

Phenyl 2,3,4,6-tetra-O-benzyl-1-thio-D-glucopyranoside (α major) (**44**). Compound **44** was afforded by the coupling of **43** and **24** and purified by flash chromatography (5:1 hexanes:EtOAc); ^{1}H NMR: δ 3.60 (dd, 1 H, $J_{6a,6b}$=10.7, $J_{5,6a}$=2.1 Hz, H-6a), 3.80 (dd, 1 H, $J_{5,6b}$=3.5 Hz, H-6b), 4.34 (ddd, 1 H, $J_{4,5}$=10 Hz, H-5), 4.55-4.95 (m, 11 H, 4 PhCH_2, H-2,3,4), 5.63 (d, 1 H, $J_{1,2}$= 4.5 Hz, H-1), 7.10-7.60 (m, 25 H, Arom. H).

Anal. Calcd for C$_{40}$H$_{40}$O$_5$S (632.8): C, 75.92; H, 6.37. Found: C, 75.92; H, 6.53.

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