# Synthetic Carbohydrate Derivatives as Low Sulfated Heparin Mimetics†

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*Received July 20, 1999*

The total synthesis of a new family of heparin mimetics containing an hexadeca- (**2**), an octadeca- (**3**), and an eicosasaccharide (**4**) is described. All three oligosaccharides contain a pentasaccharidic antithrombin binding domain (DEFGH: van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671−1690), extended at the nonreducing end by a thrombin binding domain composed of repeated 2,3-di-*O*-methyl-6-*O*-sodium sulfonato-α-D-glucosyl units. The targets were synthesized using a key dodecasaccharide imidate as glycosyl donor as well as di- and tetrasaccharide imidates, all derived from maltose. Condensation of these imidates with a tetrasaccharide precursor of the EFGH part of the antithrombin binding domain gave fully protected hexadeca-, octadeca-, and eicosasaccharide that were deprotected and sulfated to yield **2**, **3**, and **4**. All three displayed antithrombin-mediated antifactor Xa and antithrombin (factor IIa) activity. The most active compound, the eicosasaccharide, showed activity similar to that of low molecular weight heparin. Significantly, unlike heparin and its derivatives, the present heparin mimetics do not interact with platelet factor 4, an interaction that can cause severe side effects in heparin-treated patients. Thus, this new family of compounds contains interesting drug candidates for the prevention and treatment of thrombosis.

## Introduction

Heparin, a natural anionic polysaccharide, is used worldwide for the treatment of thromboembolic disorders. It is well established now that it displays antithrombotic and anticoagulant activities mainly by inhibiting, via antithrombin, two blood coagulation factors: factor Xa and thrombin.[1] Inhibition of factor Xa is due to a unique pentasaccharide sequence (antithrombin binding domain; A-domain, Chart 1) which has been chemically synthesized[2] and is currently being evaluated in clinical trials. Molecular modeling and chemical synthesis[3] suggested that in order to inhibit thrombin, the pentasaccharide must be extended at the nonreducing end by an anionic domain (thrombin binding domain; T-domain) to constitute a template required to form the thrombin-antithrombin complex.[4] In heparin, the T-domain is the so-called "regular region", i.e., the repetition of →4)-(2-*O*-sulfonato-α-L-idopyranosyluronate)-(1→4)-(*N*-sulfonato-6-*O*-sulfonato-α-D-glucosaminyl)-(1→ disaccharide units.[5]

In our program devoted to the synthesis of new antithrombotics, we synthesized heparin mimetics in which, for easier synthesis, the structure of the T-domain was dramatically simplified compared to that in native heparin.[6−10] Thus, in the most active series, it consisted of repeated 3-*O*-methyl-2,6-di-*O*-sodium sulfonato-D-glucose residues alternatively α- and β-linked.[7] The antithrombotic activities of the compounds thus obtained were similar to that of heparin, but also like heparin, these compounds were neutralized by platelet factor 4 (PF4). PF4 is a platelet protein able to form a complex with heparin that can induce thrombocytopenia, a side reaction occurring in ca. 3% of heparin treated patients. It has been stated that the interaction of heparin and PF4 is related to two parameters: the size and the charge density of the heparin fragments.[11] Since the pentadecasaccharide **1**,[7] which possesses the shortest size of an oligosaccharide able to display dual anti-Xa and antithrombin activities, still interacts with PF4, the only possibility we had left to avoid this interaction was to decrease the charge of the molecule. To this end, we first synthesized compounds where the A-domain and the T-domain were separated by a neutral domain composed of either a flexible polyethylene spacer[3] or by an array of permethylated glucose residues that may be viewed as a rigid spacer.[8] However, in both cases, the preparation of this uncharged domain required numerous syn-

† Dedicated to Professor Pierre Sinaÿ on the occasion of his 62th birthday.

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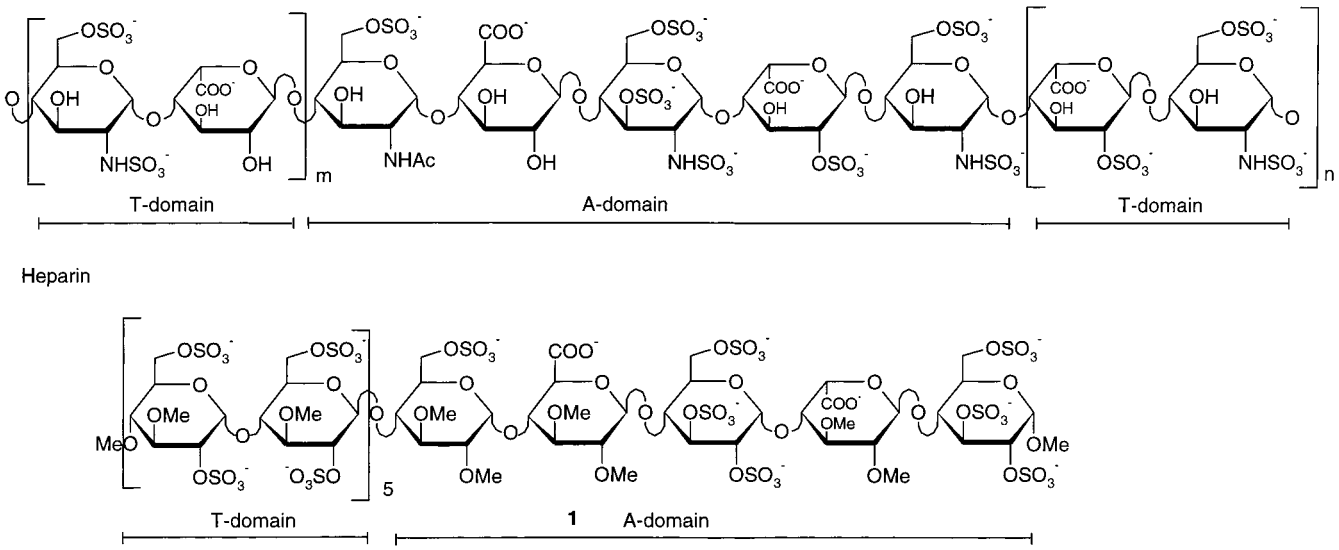
10.1021/jo991152j CCC: $18.00 
Published on Web 12/02/1999

**Chart 1**



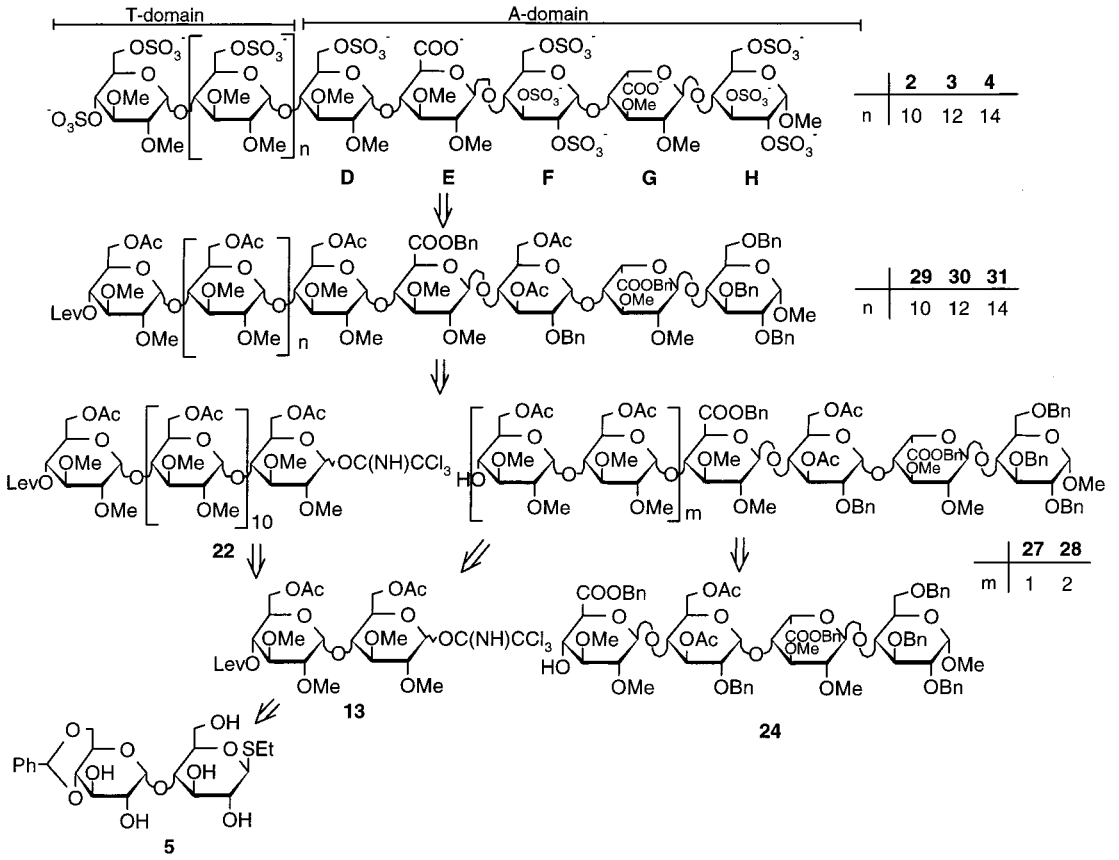

thetic steps, a matter of concern for the economic feasibility of the synthesis.

In the approach reported here, we have investigated the possibility of uniformly decreasing the charge density along the molecule by using a low sulfated sequence composed of a repetition of α-linked 2,3-di-*O*-methyl-6-*O*-sodium sulfonato-D-glucose residues as the T-domain. A high affinity pentasaccharide was used as A-domain. Biochemical studies show that with only one sulfate on each saccharide unit, the T-domain of these compounds contains enough charges to attract thrombin, but not enough to undergo neutralization by PF4. Thus, using a uniformly sulfated T-domain, heparin mimetics devoid of interaction with PF4 can be prepared in a very efficient way.

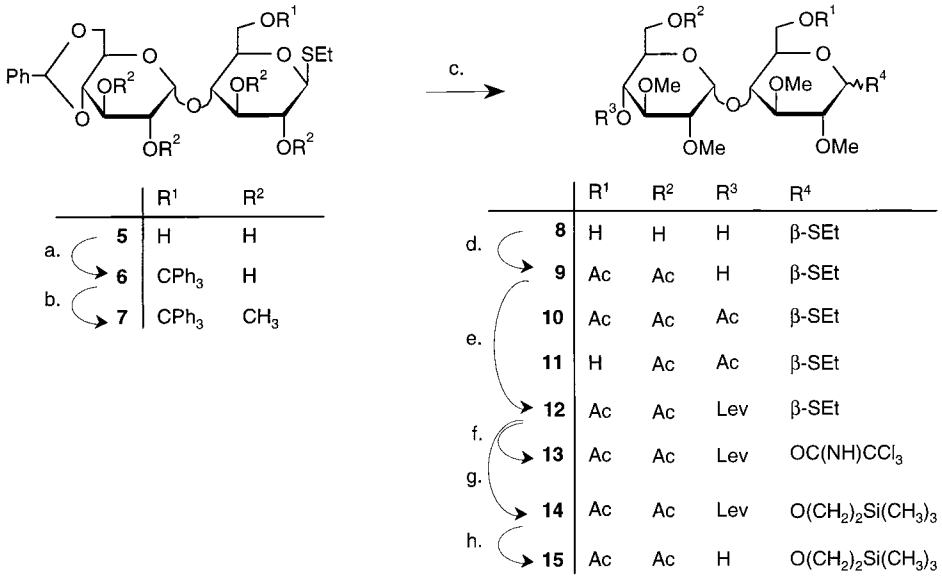
## Results and Discussion

**Synthetic Strategy.** As shown in Scheme 1, the three target compounds, hexadecasaccharide **2**, octadecasaccharide **3**, and eicosasaccharide **4**, are composed of two distinct domains: (i) an oligomer of α-linked 2,3-di-*O*-methyl-6-*O*-sodium sulfonato-D-glucose as a T-domain, and (ii) a pentasaccharide with high affinity for anti-

**Scheme 1. Retrosynthetic Analysis**



**Scheme 2**[a]




| | | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|
| | **5** | H | H | | |
| | **6** | $CPh_3$ | H | | |
| | **7** | $CPh_3$ | $CH_3$ | | |
| | **8** | H | H | H | β-SEt |
| | **9** | Ac | Ac | H | β-SEt |
| | **10** | Ac | Ac | Ac | β-SEt |
| | **11** | H | Ac | Ac | β-SEt |
| | **12** | Ac | Ac | Lev | β-SEt |
| | **13** | Ac | Ac | Lev | $OC(NH)CCl_3$ |
| | **14** | Ac | Ac | Lev | $O(CH_2)_2Si(CH_3)_3$ |
| | **15** | Ac | Ac | H | $O(CH_2)_2Si(CH_3)_3$ |

[a] Key: (a) $Ph_3CCl$, $Et_3N$, DMAP, $CH_2Cl_2$; (b) MeI, NaH, DMF; (c) 60% aqueous AcOH; (d) *N*-acetylimidazole, $(CH_2Cl)_2$; (e) levulinic acid, EDCI, DMAP, dioxane; (f) $H_2O$, NIS, AgOTf, $CH_2Cl_2/Et_2O$, then $CCl_3CN$, $Cs_2CO_3$, $CH_2Cl_2$; (g) $(CH_3)_3Si(CH_2)_2OH$, NIS, AgOTf, $CH_2Cl_2/Et_2O$; (h) $NH_2NH_2 \cdot HOAc$, toluene/EtOH.

thrombin as A-domain.[2] We needed a T-domain with a reduced number of sulfates, that could be obtained in a small number of steps from an inexpensive starting material. Because position six is an easy position to differentiate, we decided to localize the single sulfate at this position in the final compounds. As all the other hydroxyls are methylated, we opted for an α-linked oligomer because of the nonparticipating character of *O*-methyl groups in glycosylation reactions.

The retrosynthetic analysis for the preparation of hexadeca- to eicosamer (**2**−**4**) is depicted in Scheme 1. The sulfated compounds derive from the corresponding *O*-protected derivatives **29**−**31** themselves obtained by reaction of the key dodecasaccharide imidate **22** with the acceptors **24**, **27**, and **28**. Among the various possible strategies to synthesize imidate **22**, we chose to add twice a tetrasaccharide donor to the nonreducing end of a tetrasaccharide acceptor. Both tetrasaccharides could, in turn, be prepared from the same disaccharide (**13**). Consequently, **22** is obtained in a reduced number of steps compared to the strategy consisting of adding only one disaccharide at the time. Imidate **13** can be prepared from the known disaccharide **5**.[12]

The A-domain, also called DEFGH, is an analogue of the antithrombin binding sequence of heparin, in which the hydroxyls and *N*-sulfonates are replaced by methoxy groups and *O*-sulfonates, respectively.[2] The main advantages of these modifications are simpler chemistry and enhanced anti-factor Xa activity compared to the parent pentasaccharide fragment contained in heparin. Acceptors **27** and **28** were obtained by adding disaccharide **13** or its tetrasaccharide analogue to tetrasaccharide **24**, followed by delevulinylation. Because the T-domain and the D unit are composed of the same monomeric synthon, the lacking D unit of the pentasaccharide is automatically present as soon as **24** is elongated at the nonreducing end. The synthesis of the EFGH tetrasaccharide **24** has been previously described.[13]

**Preparation of the T-Domain**. For obvious reasons, we introduced the methyl groups at positions two and three of the glucose units at an early stage of the synthesis. To this end, the known ethyl (4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→4)-1-thio-*β*-D-glucopyranoside (**5**)[12] was considered as an appropriate starting material. It was first treated with trityl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine to give **6** (Scheme 2), and the remaining hydroxyls were methylated to furnish **7**. Hydrolysis of both the benzylidene and trityl groups was carried out on crude **7** using 60% aqueous acetic acid at 80 °C. Saponification was needed at this stage because some random acetylation of the free hydroxyls occurred during concentration of the acetic acid. Pure **8** was obtained after column chromatography (60% from **5**). The two primary hydroxyls (sulfonated in the final compounds) were acetylated using *N*-acetylimidazole in refluxing dichloro-1,2-ethane. Diacetate **9** was obtained in a moderate yield (57%), together with triacetate **10** (9%) and the unexpected diacetate **11** (8%). The structure of the latter has been unambiguously determined by mass spectroscopy and $^1H$ NMR (a shift of H-6a and H-6b from 3.70 to 4.32 ppm and 4.65 ppm was observed in the presence of trichloroacetyl isocyanate). Another fraction containing several unidentified byproducts was also obtained. The remaining hydroxyl of **9** was protected (95% yield) with levulinic acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and catalytic amounts of 4-(dimethylamino)pyridine to give **12**.

The synthesis of dodecasaccharide imidate **22** required the two tetrasaccharide building blocks **16** and **17**, which were prepared from **9** and **12**. The choice of the trimethylsilyl ethyl group to block the anomeric position in **17** deserves some comment: we needed a protecting group compatible with conditions of thioglycoside activation and

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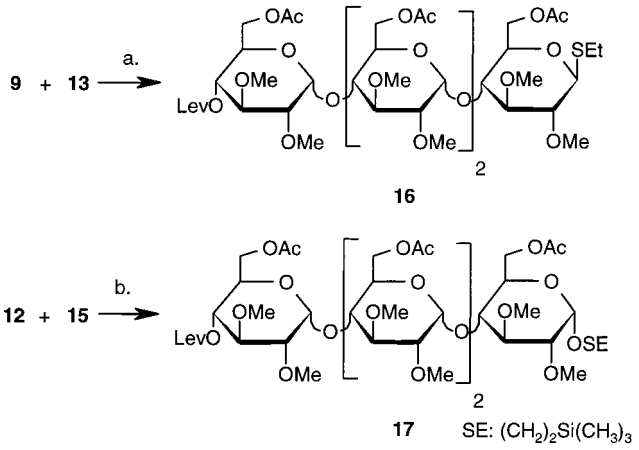
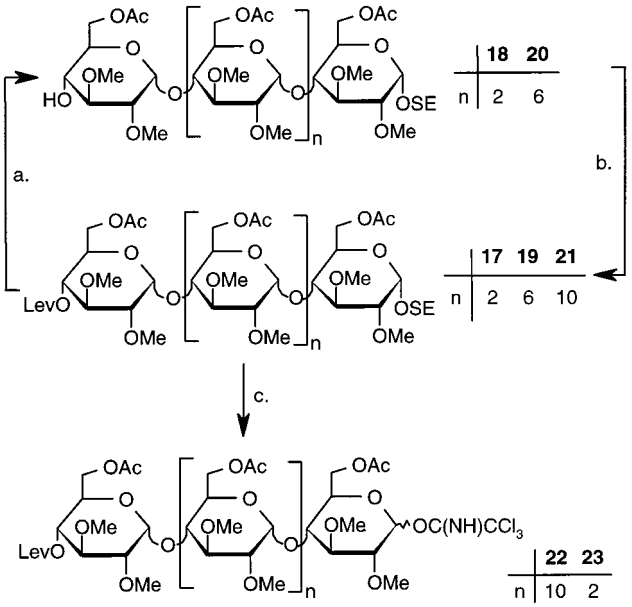
**Scheme 3**[a]




[a] Key: (a) *t*-BDMSOTf, $CH_2Cl_2/Et_2O$; (b) NIS, AgOTf, $CH_2Cl_2/Et_2O$.

levulinyl deprotection and that could be converted in a high yield into imidate **22**. In the present case, we might have used the intermediates with the anomeric thioethyl group as the glycosylating agent, which could have been condensed on acceptors **24**, **27**, and **28**. However, on some occasions, we observed a more favorable $\alpha/\beta$ ratio with 2-*O*-methoxyglycosyl donor trichloroacetimidates compared to the thioglycoside analogues. For this reason, a trimethylsilyl ethyl ether was chosen to block the anomeric position of the reducing unit, and conversion to a trichloroacetimidate was done at the dodecasaccharide level (the decision to use a trimethylsilyl ethyl ether was also motivated by other synthetic plans in which this building block was required). Hydrolysis of thioglycoside **12** using *N*-iodosuccinimide (NIS) and silver trifluoromethane sulfonate (AgOTf) led to the free anomeric hydroxyl, which was subsequently transformed into trichloroacetimidate **13** using trichloroacetonitrile, in the presence of cesium carbonate (89%, two steps). The trimethylsilyl ethyl glycoside **14** was synthesized from **12** using the same activator as above, with an excess (2 equiv) of trimethylsilylethanol. Because the use of diethyl ether generally enhances the thermodynamically more stable axial glycoside,[14] the coupling reaction was performed in a 2:1 mixture of diethyl ether/dichloromethane. Despite these precautions, an inseparable mixture of anomers **14** was obtained (85%; 65:35 $\alpha/\beta$), which was quantitatively delevulinylated to **15** with hydrazine acetate[15] in 2:1 ethanol/toluene. At this stage, the α-glycoside (60%) could be partially separated from the other anomer. Acceptor **9** and imidate **13** were coupled using *tert*-butyldimethylsilyl trifluoromethanesulfonate (*t*-BDMSOTf)[16] to yield tetrasaccharide **16** (71%; Scheme 3). Similarly to the synthesis of **14**, a 2:1 mixture of diethyl ether/dichloromethane was used to minimize the formation of the undesired $\beta$-anomer. The new α-D linkage was unambiguously determined, using high-field $^1$H NMR, by both the chemical shift ($\delta$ 5.39 ppm) and the coupling constant ($J_{1,2}$ 3.8 Hz) of the anomeric proton of the newly synthesized glycosidic bond. Thioglycoside **12** and acceptor **15** were coupled (NIS/AgOTf) to furnish tetrasaccharide **17** in 69% yield. Again, $^1$H NMR analysis ($\delta_{H\text{-}1}$ 5.43 ppm, $J_{1,2}$ 3.9 Hz) confirmed the α-D stereochemistry of the new glycosidic bond. For the synthesis of both **16** and **17**, no $\beta$-anomer could be isolated. Tetrasaccharide **17** was delevulinylated (Scheme 4) like **14** to give acceptor **18** (95%). The latter was coupled with thioglycoside **16** (NIS/AgOTf) to provide octasaccharide **19** (80%; $\delta_{H\text{-}1}$ ~5.43 ppm, $J_{1,2} \approx 3.8$ Hz), and delevulinylation yielded **20** in 85% yield. The acceptor thus obtained was coupled with **16** under the same conditions as above to give dodecasaccharide **21** (71%). Although the major product was the one expected ($\delta_{H\text{-}1}$ ~5.43 ppm, $J_{1,2} \approx 3.8$ Hz), for the first time during the chain elongation, a small amount of $\beta$-anomer (3%) was isolated and characterized by high-field NMR ($\delta_{H\text{-}1}$ 4.26 ppm, $J_{1,2} \approx 8$ Hz). Activation of **21** was realized first by deblocking[17] the trimethysilyl ether with the use of 2:1 trifluoroacetic acid/dichloromethane, and then treatment as described for the synthesis of **13** gave trichloroacetimidate **22** (86%, two steps).

**Scheme 4**[a]




[a] Key: (a) $NH_2NH_2$.HOAc, toluene/EtOH; (b) **16**, NIS, AgOTf, $CH_2Cl_2/Et_2O$; (c) TFA/$CH_2Cl_2$, then $CCl_3CN$, $Cs_2CO_3$, $CH_2Cl_2$.

**Elongation of the A-Domain**. To use the dodecasaccharide imidate **22** in the final step of the elongation process, the three glycosyl acceptors **24**, **27**, and **28** were required. Reaction (Scheme 5) of the tetrasaccharide **24** with the disaccharide imidate **13** gave **25** (60%; $\delta_{H\text{-}1}$ 5.50 ppm, $J_{1,2} = 3.7$ Hz), together with unreacted **24** (29%). The hexasaccharide **27** was obtained (89%) after delevulinylation. For the synthesis of **28**, the tetrasaccharide imidate **23** was synthesized first (77% yield from **17**) using the same route as for the synthesis of the imidate **22**. Reaction of **23** with **24** gave **26** (69%; $\delta_{H\text{-}1}$ 5.50 ppm, $J_{1,2} = 3.7$ Hz) together with unreacted **24** (14%). Finally, removal of the levulinyl group gave **28** (83%).

**Final Couplings**. The acceptors **24**, **27**, and **28** were reacted (Scheme 6) with trichloroacetimidate **22** in a

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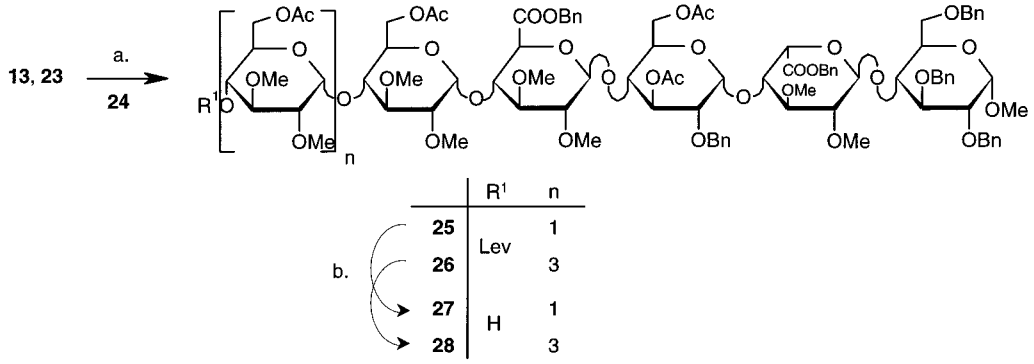
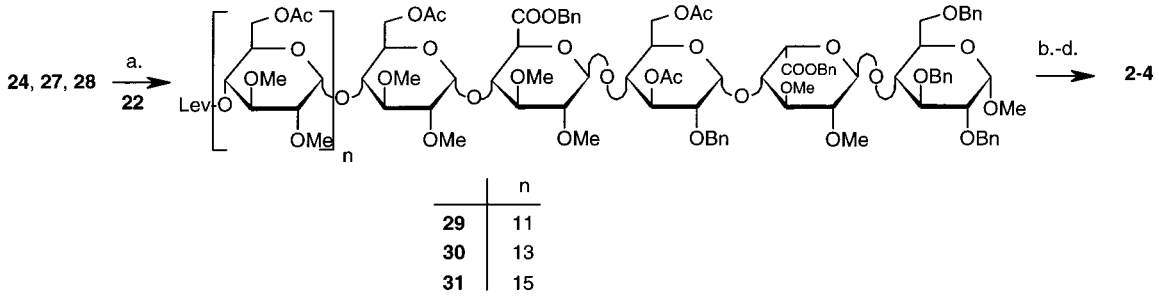
**Scheme 5**[a]




[a] Key: (a) *t*-BDMSOTf, $CH_2Cl_2/Et_2O$; (b) $NH_2NH_2$·HOAc, toluene/EtOH.

**Scheme 6**[a]




[a] Key: (a) *t*-BDMSOTf, $CH_2Cl_2/Et_2O$; (b) 5% Pd/C, $H_2$, AcOH; (c) aqueous NaOH, MeOH; (d) $Et_3N$·$SO_3$, DMF.

**Table 1. Comparison of the Biological Activity of Oligosaccharides 2−4 with that of Heparin and Low Molecular Weight Heparin**

| compd | **2** | **3** | **4** | heparin | low mol wt heparin |
|---|---|---|---|---|---|
| no. of saccharide units | 16 | 18 | 20 | ∼10−50 | ∼6−30 |
| molecular wt | 5030 | 5614 | 6199 | ∼15 000 | ∼4500 |
| $K_D$ antithrombin (nM) | 3.3 | 6 | 18 | 25 | 25 |
| factor Xa inhibition (units/mg) | 350 | 260 | 210 | 180 | 170 |
| thrombin inhibition−antithrombin-mediated ($IC_{50}$, ng/mL) | 490 | 360 | 88 | 3.3 | 27 |

mixture of diethyl ether and dichloromethane, using *t*-BDMSOTf as the activator to provide, respectively, hexadecasaccharide **29** (44%), octadecasaccharide **30** (48%), and eicosasaccharide **31** (51%). In each case, gel permeation chromatography followed by silica gel chromatography allowed easy purification of the product. As in the synthesis of **25** and **26**, some unreacted acceptor was isolated (45%, 39%, and 23%, respectively). Several byproducts were formed during the three coupling reactions, including likely some $\beta$-anomers. These complex mixtures were not characterized. Catalytic hydrogenation of the fully protected oligosaccharides **29**−**31**, followed by saponification of acyl groups with aqueous sodium hydroxide in methanol, and finally sulfonation of the hydroxyls using triethylamine sulfur trioxide complex yielded **2** (82% over the three steps), **3** (87%), and **4** (77%).

**Biological Assays**. The in vitro activities of compounds **2**−**4** were determined (Table 1) and compared to that of heparin and low molecular weight heparin. It appeared that for **2**−**4**, the affinity for antithrombin as well as inhibition of factor Xa are in the same range. None of the synthetic compounds was as potent as heparin in inhibiting thrombin. However, **4** displayed activities comparable to that of low molecular weight heparin. Particularly noteworthy is that none of the synthetic compounds **2**−**4** were neutralized by PF4 even at high protein concentrations (100 $\mu$g/mL, data not shown), indicating that this new family of synthetic compounds might constitute valuable alternatives to currently used standard heparin and low molecular weight heparin. Pharmacological evaluation of compounds **2**−**4** is currently being investigated.

## Experimental Section

**General Methods.** All compounds were homogeneous by TLC analysis and had spectral properties consistent with their assigned structures. Melting points are uncorrected. Optical rotations were measured at room temperature (22 ± 3 °C). Compound purity was checked by TLC on silica gel 60 $F_{254}$ (E. Merck) with detection by charring with sulfuric acid. Unless otherwise stated, column chromatography was performed on silica gel 60, 40−63, or 63−200 $\mu$m (E. Merck). $^1$H NMR spectra were recorded on Bruker AC 200, AM 250, AC 300, or AM 500 instruments, in $CDCl_3$ or $D_2O$. Before analysis in $D_2O$, samples were passed through a Chelex (Bio-Rad) ion-exchange column and lyophilized three times from $D_2O$. Chemical shifts are relative to external TMS ($CDCl_3$) or external TSP ($D_2O$). For NMR assignment purposes, the carbohydrate residues for products larger than monosaccharides have been designed starting from the reducing end (unit I).

**Crude Ethyl (4,6-*O*-Benzylidene-α-D-glucopyranosyl)-(1→4)-6-*O*-trityl-1-thio-β-D-glucopyranoside (6).** To a suspension of **5**[12] (50.0 g, 0.105 mol) in $CH_2Cl_2$ (620 mL) were added, under argon, triethylamine (35 mL, 0.252 mol), trityl chloride (29.3 g, 0.105 mol), and DMAP (1.28 g, 10 mmol). The mixture was refluxed, and after 2 h, the same quantity of trityl chloride was added. After an additional 2.5 h of reflux, starting material was no longer visible by TLC. After being cooled to room temperature, the solution was diluted with $CH_2Cl_2$, successively washed with cold 10% aqueous $KHSO_4$, $H_2O$, and

brine, dried ($Na_2SO_4$), and concentrated. Filtration over silica gel (2:1 then 1:1 toluene/acetone) gave crude **6**, which was sufficiently pure for use in the next step. An analytical sample was chromatographed: $[\alpha]_D$ +53° (*c* 0.74, $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$) $\delta$ 7.52−7.25 (m, 20H, 4Ph), 5.42 (s, CHPh), 4.97 (d, $J$ = 3.5 Hz, H-1 Glc$^{II}$), 4.40 (d, $J$ = 9.6 Hz, H-1 Glc$^{I}$), 3.82 (t, $J$ = 9.3 Hz, H-3 Glc$^{II}$), 3.70, 3.68 (m, 2H, H-3 Glc$^{I}$, H-4 Glc$^{I}$), 3.60 (dd, $J \approx$ 2.0, 11.0 Hz, H-6a Glc$^{I}$), 3.55 (td, $J$ = 5.2, 9.7, 9.7 Hz, H-5 Glc$^{II}$), 3.49−3.45 (m, 3H, H-2 Glc$^{I}$, H-2 Glc$^{II}$, H-5 Glc$^{I}$), 3.38 (dd, $J$ = 10.5 Hz, H-6a Glc$^{II}$), 3.33 (dd, H-6b Glc$^{II}$), 3.30−3.27 (m, 2H, H-4 Glc$^{II}$, H-6b Glc$^{I}$), 2.90−2.77 (m, 2 H, $SCH_2CH_3$), 1.40−1.37 (t, 3H, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 715 [(M − H)$^-$]. Anal. Calcd for $C_{40}H_{44}O_{10}S$: C, 67.02; H, 6.19; S, 4.47. Found: C, 66.83; H, 6.19; S, 4.19.

**Crude Ethyl (4,6-*O*-Benzylidene-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-methyl-6-*O*-trityl-1-thio-*β*-D-glucopyranoside (7).** MeI (34 mL, 0.536 mol) was added dropwise under argon to a solution of the preceding compound (64.1 g) in DMF (600 mL), and after the mixture was cooled in a water/ice mixture, NaH (13.5 g, 0.536 mol) was added portionwise. The suspension was stirred for 2 h at room temperature and then cooled to 0 °C, MeOH (35 mL) was added dropwise, and after 2 h of stirring, the mixture was diluted with EtOAc (500 mL) and $H_2O$ (600 mL). The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with $H_2O$, dried ($Na_2SO_4$), and concentrated to give a residue that was considered pure enough for the next step. An analytical sample was purified on silica gel (7:3 cyclohexane/acetone): $[\alpha]_D$ +45° (*c* 0.83, $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$) $\delta$ 7.52−7.19 (m, 20H, 4Ph), 5.51 (d, $J$ = 3.3 Hz, H-1 Glc$^{II}$), 5.43 (s, CHPh), 4.45 (d, $J$ = 9.8 Hz, H-1 Glc$^{I}$), 3.60, 3.59, 3.51, 3.49 (4s, 12H, 4OMe), 2.86 (q, 2H, $J$ = 7.5 Hz, $SCH_2CH_3$), 1.40 (t, 3H, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 795 [(M + Na)$^+$]. Anal. Calcd for $C_{44}H_{52}O_{10}S$: C, 68.37; H, 6.78; S, 4.15. Found: C, 68.28; H, 6.98; S, 4.09.

**Ethyl (2,3-Di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-methyl-1-thio-*β*-D-glucopyranoside (8).** A suspension of crude **7** (67.4 g) in 60% aqueous AcOH (470 mL) was heated at 80 °C for 2 h. The reaction mixture was cooled, filtered, and concentrated. The residue was treated with MeONa (940 mg) in MeOH (200 mL) for 1 h. The solution was then neutralized with Dowex 50 WX4 ($H^+$) resin, and after filtration, and concentration, column chromatography (3:2 toluene/acetone) gave **8** (27.9 g, 60% from **5**): $[\alpha]_D$ + 26° (*c* 1.07, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.62 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.35 (d, $J$ = 9.8 Hz, H-1 Glc$^{I}$), 3.64, 3.64, 3.59, 3.58 (4s, 12H, 4OMe), 1.29 (t, 3H, $J$ = 7.4 Hz, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 465 [(M + Na)$^+$]. Anal. Calcd for $C_{18}H_{34}O_{10}S\cdot H_2O$: C, 46.94; H, 7.87; S, 6.96. Found: C, 47.19; H, 7.72; S, 6.70.

**Ethyl (6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-1-thio-*β*-D-glucopyranoside (9), Ethyl (4,6-Di-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-1-thio-*β*-D-glucopyranoside (10), and Ethyl (4,6-Di-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-methyl-1-thio-*β*-D-glucopyranoside (11).** Triol **8** (5.86 g, 13.2 mmol) was refluxed overnight with *N*-acetylimidazole (3.21 g, 29.1 mmol) in $ClCH_2CH_2Cl$ (120 mL). Another portion of *N*-acetylimidazole (440 mg, 3.96 mmol) was added, and stirring was continued an additional 4 h. The reaction mixture was then allowed to reach room temperature, and MeOH (2 mL) was added. After 1 h of stirring, the mixture was diluted with $CH_2Cl_2$, successively washed with cold M HCl, $H_2O$, saturated aqueous $NaHCO_3$, and $H_2O$, dried ($Na_2SO_4$), and concentrated. Column chromatography (3.5:1 toluene/acetone) of the residue yielded diacetate **9** (3.97 g, 57%), triacetate **10** (652 mg, 9%), and diacetate **11** (539 mg, 8%). **9**: $[\alpha]_D$ +33° (*c* 1.90, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.51 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.34 (d, $J$ = 9.8 Hz, H-1 Glc$^{I}$), 3.64, 3.63, 3.59, 3.56 (4s, 12H, 4OMe), 2.11, 2.06 (2s, 6H, 2Ac), 1.31 (t, 3H, $J$ = 7.4 Hz, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 549 [(M + Na)$^+$]. Anal. Calcd for $C_{22}H_{38}O_{12}S$: C, 50.17; H, 7.27; S, 6.09. Found: C, 50.15; H, 7.49; S, 5.89. **10**: $[\alpha]_D$ +42° (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.55 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.33 (d, $J$ = 9.7 Hz, H-1 Glc$^{II}$), 3.63, 3.58, 3.57, 3.52 (4s, 12H, 4OMe), 2.08, 2.06 (2s, 9H, 3Ac), 1.30 (t, 3H, $J$ = 7.5 Hz, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 591 [(M + Na)$^+$]. Anal. Calcd for $C_{24}H_{40}O_{13}S$: C, 50.69; H, 7.09; S, 5.64. Found: C, 50.85; H, 7.29; S, 5.45. **11**: $[\alpha]_D$ + 36° (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.61 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.35 (d, $J$ = 9.7 Hz, H-1 Glc$^{I}$), 3.74, 3.62, 3.59, 3.57 (4s, 12H, 4OMe), 2.08, 2.06 (2s, 6H, 2Ac), 1.30 (t, 3H, $J$ = 7.5 Hz, $SCH_2CH_3$), 1.96 (t, $J$ = 7.0 Hz, OH); mass spectrum (ESI) *m*/*z* 549 [(M + Na)$^+$]. Anal. Calcd for $C_{22}H_{38}O_{12}S$: C, 50.17; H, 7.27; S, 6.09. Found: C, 50.28; H, 7.45; S, 5.89.

**Ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-1-thio-*β*-D-glucopyranoside (12).** To a solution of diacetate **9** (19.4 g, 36.7 mmol) in dioxane (400 mL) were added, under argon, levulinic acid (7.53 mL, 73.5 mmol), EDCI (14.1 g, 73.5 mmol), and DMAP (900 mg, 7.35 mmol). The mixture was stirred for 3.5 h, diluted with $CH_2Cl_2$, washed with $H_2O$, 10% aqueous $KHSO_4$, $H_2O$, 2% aqueous $NaHCO_3$, and $H_2O$, dried ($Na_2SO_4$), and concentrated. The residue was flash chromatographed (97:3 and then 79:21 $CH_2Cl_2$/acetone) to give **12** (21.8 g, 95%): $[\alpha]_D$ +40° (*c* 0.72, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.56 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.35 (d, $J$ = 9.8 Hz, H-1 Glc$^{I}$), 3.64, 3.60, 3.58, 3.55 (4s, 12H, 4OMe), 2.76−2.71 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); 2.19, 2.08, 2.07 (3s, 9H, 2Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 1.31 (t, 3H, $J$ = 7.4 Hz, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 647 [(M + Na)$^+$]. Anal. Calcd for $C_{27}H_{44}O_{14}S$: C, 51.91; H, 7.10; S, 5.13. Found: C, 51.88; H, 7.05; S, 4.96.

**(6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-1-trichloroacetimidoyl-D-glucopyranose (13).** To a solution of thioglycoside **12** (9.53 g, 15.3 mmol) in 1:1 $CH_2Cl_2$/$Et_2O$ (180 mL) were added $H_2O$ (1.4 mL, 76.3 mmol), NIS (6.84 g, 30.5 mmol), and AgOTf (0.51 g, 1.98 mmol). After 15 min, saturated aqueous $NaHCO_3$ (5 mL) was added, and the reaction mixture was diluted with $CH_2Cl_2$, washed with $H_2O$, M $Na_2S_2O_3$, 2% aqueous $NaHCO_3$, and $H_2O$. The organic layer was dried ($Na_2SO_4$) and concentrated, and the residue was purified over silica gel (2:1 then 1:0 EtOAc/cyclohexane) to give a solid that was engaged in the next step without characterization. A solution of the preceding compound (7.88 g, 13.59 mmol) in $CH_2Cl_2$ (120 mL) was treated, under argon, with $Cs_2CO_3$ (7.08 g, 21.74 mmol) and $CCl_3CN$ (6.81 mL, 67.93 mmol). After 40 min, the mixture was filtered, concentrated, and flash chromatographed (85:15 toluene/acetone) to give imidate **13** (9.16 g, 89%): $[\alpha]_D$ + 118° (*c* 1.00, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 8.66, 8.65 (2s, 1H, $\alpha$ and $\beta$ N:H), 6.52 (d, $J$ = 3.6 Hz, H-1$\alpha$ Glc$^{I}$), 5.70 (d, $J$ = 7.5 Hz, H-1$\beta$ Glc$^{I}$), 5.58 (d, $J$ = 3.7 Hz, H-1 Glc$^{II}$), 2.78−2.57 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.18, 2.07, 2.06 (3s, 9H, 2Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 746 [(M + Na)$^+$]. Anal. Calcd for $C_{27}H_{40}Cl_3NO_{15}\cdot 0.5H_2O$: C, 44.18; H, 5.63; N, 1.98. Found: C, 44.14; H, 5.61; N, 1.97.

**2-(Trimethylsilyl)ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-D-glucopyranoside (14).** A mixture of thioglycoside **12** (10.6 g, 16.9 mmol), 2-(trimethylsilyl)ethanol (4.8 mL, 33.9 mmol), and powdered molecular sieves (5.07 g, 4 Å) in 1:2 $CH_2Cl_2$/$Et_2O$ (105 mL) was stirred under argon for 1 h at 23 °C with protection from light, cooled to 0 °C, and treated with NIS (11.4 g, 50.82 mmol) and AgOTf (565 mg, 2.20 mmol). The reaction was quenched after 10 min with solid $NaHCO_3$ (250 mg), and after filtration (Celite), the reaction mixture was diluted with $CH_2Cl_2$ and successively washed with M $Na_2S_2O_3$, $H_2O$, 2% aqueous $NaHCO_3$, and $H_2O$. The organic phase was dried ($Na_2SO_4$) and concentrated, and the residue obtained was purified by chromatography (1:1 acetone/$CH_2Cl_2$) to give compound **14** (9.80 g, 85%) as an inseparable mixture of anomers ($\alpha$/$\beta$ 2:1): $^1$H NMR ($CDCl_3$) $\delta$ 5.58 (d, $J$ = 3.9 Hz, H-1 Glc$^{II}$), 4.94 (d, $J$ = 3.5 Hz, H-1$\alpha$ Glc$^{I}$), 4.26 (d, $J$ = 7.7 Hz, H-1$\beta$ Glc$^{I}$), 2.76−2.56 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.08, 2.05 (3s, 9H, 2Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 1.18−0.88 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.02 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 703 [(M + Na)$^+$]. Anal. Calcd for $C_{30}H_{52}O_{15}Si$: C, 52.92; H, 7.69. Found: C, 53.29; H, 7.75.

**2-(Trimethylsilyl)ethyl (6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-D-glucopyranoside (15).** Hydrazine acetate (12.7 g, 138.0

mmol) was added, under argon, to a solution of compound **14** (9.41 g, 13.8 mmol) in 1:2 toluene/EtOH (300 mL). After 15 min of stirring, the reaction mixture was concentrated, diluted with $CH_2Cl_2$, washed with $H_2O$, 2% aqueous $NaHCO_3$, and $H_2O$, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed (3:2 acetone/toluene) and afforded pure **15**α (4.81 g, 60%), together with a α/β mixture (3.06 g, 37%). **15**α: $[\alpha]_D$ +132° (*c* 0.61, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.55 (d, $J$ = 3.8 Hz, H-1 Glc$^{II}$), 4.95 (d, $J$ = 3.6 Hz, H-1 Glc$^{I}$), 2.10, 2.08 (2s, 6H, 2Ac), 1.16−0.89 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.02 (s, 9H, $OCH_2CH_2Si(CH_3)_3$; mass spectrum (ESI) *m*/*z* 621 [(M + K)$^+$]. Anal. Calcd for $C_{25}H_{46}O_{13}Si$: C, 51.53; H, 7.96. Found: C, 51.37; H, 8.06.

**Ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_2$-6-*O*-acetyl-2,3-di-*O*-methyl-1-thio-β-D-glucopyranoside (16).** A solution of imidate **13** (1.10 g, 1.52 mmol) and acceptor **9** (806 mg, 1.38 mmol) was stirred under argon for 1 h in 1:2 $CH_2Cl_2/Et_2O$ (22 mL) in the presence of finely grounded molecular sieves (1.10 g, 4 Å). After the solution was cooled to −20 °C, a solution of M *tert*-butyldimethysilyl trifluoromethanesulfonate (*t*-BDMSOTf) in $CH_2Cl_2$ (0.77 mL) was added, and the mixture was stirred for 30 min, diluted with $CH_2Cl_2$, and filtered (Celite). The organic phase was then washed with 2% aqueous $NaHCO_3$ and $H_2O$, dried ($Na_2SO_4$), concentrated, and purified by chromatography (2.5:1 then 3:1 EtOAc/cyclohexane) to yield pure **16** (1.12 g, 71%): $[\alpha]_D$ +95° (*c* 1.00, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.55 (d, $J$ = 3.9 Hz, H-1 Glc$^{IV}$), 5.39, 5.37 (2d, $J$ = 3.8, 3.9 Hz, H-1 Glc$^{II}$, H-1 Glc$^{III}$), 4.34 (d, $J$ = 9.7 Hz, H-1 Glc$^{I}$), 2.84−2.51 (m, 6H, $SCH_2CH_3$, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.17, 2.10, 2.09, 2.08, 2.04 (5s, 15H, 4Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 1.30 (t, 3H, $J$ = 7.4 Hz, $SCH_2CH_3$); mass spectrum (ESI) *m*/*z* 1111 [(M + Na)$^+$]. Anal. Calcd for $C_{47}H_{76}O_{26}S$: C, 51.83; H, 7.03; S, 2.94. Found: C, 51.66; H, 7.02; S, 2.94.

**2-(Trimethylsilyl)ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-]$_2$-6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside (17).** Thioglycoside **12** (4.21 g, 6.74 mmol) and glycosyl acceptor **15** (3.57 g, 6.13 mmol) were stirred in the dark for 45 min in 1:2 $CH_2Cl_2/Et_2O$ (105 mL), in the presence of powdered molecular sieves (3.57 g, 4 Å). NIS (4.53 g, 20.2 mmol) and AgOTf (225 mg, 0.13 equiv) were then added under argon atmosphere at 0 °C. After 10 min of stirring, the reaction mixture was filtered (Celite), diluted with $CH_2Cl_2$, washed with M $Na_2S_2O_3$, $H_2O$, 2% aqueous $NaHCO_3$, and $H_2O$, dried ($Na_2SO_4$), and concentrated. Purification of the residue by chromatography (3:1 then 9:1 acetone/cyclohexane) afforded **17** (4.81 g, 69%): $[\alpha]_D$ +143° (*c* 0.56, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.57 (d, $J$ = 3.9 Hz, H-1 Glc$^{IV}$), 5.44, 5.41 (2d, $J$ = 3.8 Hz, H-1 Glc$^{III}$, H-1 Glc$^{II}$), 4.96 (d, $J$ = 3.6 Hz, H-1 Glc$^{I}$), 2.78−2.58 (m, 4H, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.18, 2.12, 2.12, 2.09, 2.06 (5s, 15H, 4Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 1.21−0.97 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 1167 [(M + Na)$^+$]. Anal. Calcd for $C_{50}H_{84}O_{27}Si$: C, 52.44; H, 7.39. Found: C, 52.29; H, 7.46.

**2-(Trimethylsilyl)ethyl [(6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_3$-6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside (18).** Compound **17** (4.71 g, 4.11 mmol) was reacted like **14** with hydrazine acetate (3.79 g, 41.1 mmol) in 1:2 toluene/EtOH (90 mL) for 2 h. After workup, column chromatography (3:2 cyclohexane/acetone) yielded **18** (4.11 g, 95%): $[\alpha]_D$ +154° (*c* 0.63, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.46, 5.46, 5.41 (2d, 3H, $J$ = 3.9 Hz, H-1 Glc$^{II-IV}$), 4.95 (d, $J$ = 3.5 Hz, H-1 Glc$^{I}$), 2.81 (d, $J$ = 4.4 Hz, OH), 2.11, 2.09, 2.08 (3s, 12H, 4Ac), 1.19−0.97 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 1085 [(M + K)$^+$]. Anal. Calcd for $C_{45}H_{78}O_{25}Si$: C, 51.61; H, 7.51. Found: C, 51.39; H, 7.54.

**2-(Trimethylsilyl)ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_6$-6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside (19).** Thioglycoside **16** (3.86 g, 3.54 mmol) and glycosyl acceptor **18** (3.60 g, 3.44 mmol) were treated for 10 min under the conditions described for **17** with NIS (2.38 g, 10.58 mmol) and AgOTf (118 mg, 0.461 mmol) in 1:2 $CH_2Cl_2/Et_2O$ (60 mL) in the presence of molecular sieves (1.77 g, 4 Å). After workup and chromatography (7:2 then 2:1 $CH_2Cl_2$/acetone), pure **19** (5.71 g, 80%) was obtained: $[\alpha]_D$ +161° (*c* 0.65, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.54 (d, $J$ = 3.8 Hz, H-1 Glc$^{VIII}$), 5.47−5.40 (m, 6H, H-1 Glc$^{II-VII}$), 4.95 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 2.84−2.51 (m, 4H, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.17, 2.13, 2.12, 2.11, 2.11, 2.08, 2.05 (7s, 27H, 8Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 1.18−0.97 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 2112 [(M + K)$^+$]. Anal. Calcd for $C_{90}H_{148}O_{51}Si$: C, 52.12; H, 7.19. Found: C, 51.98; H, 7.25.

**2-(Trimethylsilyl)ethyl [(6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_7$-6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside (20).** Compound **19** (3.00 g, 1.45 mmol) was treated like **14** to give **20** (2.43 g, 85%): $[\alpha]_D$ +167° (*c* 0.57, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.47−5.40 (m, 7H, H-1 Glc$^{II-VIII}$), 4.95 (d, $J$ = 3.7, H-1 Glc$^{I}$), 2.80 (d, $J$ = 4.4 Hz, OH), 2.13, 2.11, 2.10, 2.08, 2.07 (5s, 24H, 8Ac), 1.18−0.97 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 2014 [(M + K)$^+$]. Anal. Calcd for $C_{85}H_{142}O_{49}Si$: C, 51.66; H, 7.24. Found: C, 51.32; H, 7.26.

**2-(Trimethylsilyl)ethyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_{10}$-6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranoside (21α).** Compounds **16** (1.35 g, 1.24 mmol) and **20** (2.38 g, 1.20 mmol) were treated for 10 min under the conditions described for the synthesis of **17**, with NIS (834 mg, 3.72 mmol) and AgOTf (41 mg, 0.160 mmol) in 1:2 $CH_2Cl_2/Et_2O$ (19 mL) in the presence of molecular sieves (620 mg, 4 Å). Treatment and column chromatography yielded **21**α (2.56 g, 71%) together with **21**β (116 mg, 3%). **21**α: $[\alpha]_D$ +166° (*c* 0.88, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.54 (d, $J$ = 3.8 Hz, H-1 Glc$^{XII}$), 5.47−5.40 (m, 10H, H-1 Glc$^{II-XI}$), 4.95 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 2.81−2.51 (m, 4H, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.17, 2.13, 2.12, 2.11, 2.11, 2.08, 2.05 (7s, 39H, 12Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 1.17−0.96 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9 H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 1525 [(M + 2Na)$^{2+}$/2]. Anal. Calcd for $C_{130}H_{212}O_{75}Si$: C, 51.99; H, 7.12. Found: C, 51.63; H, 7.12. **21**β: $[\alpha]_D$ +151° (*c* 0.93, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.56 (d, $J$ = 3.8 Hz, H-1 Glc$^{XII}$), 5.47−5.40 (m, 9H, H-1 Glc$^{II-VIII,X,XI}$), 4.95 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 4.26 (d, $J \sim 8$ Hz, H-1 Glc$^{IX}$), 2.81−2.51 (m, 4H, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.17, 2.13, 2.11, 2.10, 2.09, 2.09, 2.05 (7s, 39H, 12Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 1.17−0.96 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.03 (s, 9 H, $OCH_2CH_2Si(CH_3)_3$); mass spectrum (ESI) *m*/*z* 1525 [(M + 2Na)$^{2+}$/2].

**(6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_{10}$-6-*O*-acetyl-2,3-di-*O*-methyl-1-trichloroacetimidoyl-D-glucopyranose (22).** A solution of **21**α (400 mg, 0.133 mmol) in 2:1 TFA/$CH_2Cl_2$ (2 mL) was stirred for 1.5 h and then diluted with 2:1 toluene/*n*-PrOAc (12 mL), concentrated, and co-concentrated with toluene. Purification of the residue (4:3 acetone/cyclohexane) gave a solid (364 mg) that was dissolved in $CH_2Cl_2$ (2.5 mL). $Cs_2CO_3$ (65 mg, 0.200 mmol) and $CCl_3CN$ (63 mL, 0.620 mmol) were added to the mixture, which was stirred for 2.5 h and then filtered (Celite), concentrated, and purified on silica gel (50:50:0.1 cyclohexane/acetone/$Et_3N$) to give imidate **22** (348 mg, 86%): $[\alpha]_D$ +185° (*c* 0.91, $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$) $\delta$ 8.61, 8.58 (2s, 1H, α and β N:H), 6.35 (d, $J$ = 3.7 Hz, H-1α Glc$^{I}$), 5.59 (d, $J$ = 7.5 Hz, H-1β Glc$^{I}$), 5.38 (d, $J$ = 3.8 Hz, H-1 Glc$^{XII}$), 5.32−5.25 (m, 10H, H-1 Glc$^{II-XI}$), 2.64−2.40 (m, 4H, $O(C{=}O)CH_2CH_2(C{=}O)CH_3$), 2.02, 1.96, 1.95, 1.94, 1.93, 1.89 (6s, 39H, 12Ac and $O(C{=}O)CH_2CH_2(C{=}O)CH_3$); mass spectrum (ESI) *m*/*z* 1546 [(M + 2Na)$^{2+}$/2]. Anal. Calcd for $C_{127}H_{200}Cl_3NO_{25}$: C, 50.06; H, 6.61; N, 0.46. Found: C, 49.93; H, 6.52; N, 0.42.

**(6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-[(1→4)-(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)]$_2$-(1→4)-6-*O*-acetyl-2,3-di-*O*-methyl-1-trichloroacetimidoyl-D-glucopyranose (23).** A solution of **17** (200 mg, 0.174 mmol) in 2:1 TFA/$CH_2Cl_2$ (2.5 mL) was stirred for 3 h,

2:1 toluene/*n*-PrOAc (16 mL) was added, and the mixture was concentrated and co-concentrated with toluene. Column chromatography (3:2 toluene/acetone) of the residue yielded a solid (178 mg), which was dissolved in $CH_2Cl_2$ (5 mL) and was treated under argon with $Cs_2CO_3$ (140 mg, 0.40 mmol) and $CCl_3CN$ (75 $\mu$L, 0.749 mmol) for 2 h. The reaction mixture was then filtered, concentrated, and purified over silica gel (3:2 toluene/acetone) to yield **23** (230 mg, 77%): $[\alpha]_D$ +112° (*c* 0.99, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 8.66−8.64 (2s, 1 H, $\alpha$ and $\beta$ N:H), 6.51 (d, $J$ = 3.6 Hz, H-1$\alpha$ Glc$^I$), 5.71 (d, $J$ = 7.5 Hz, H-1$\beta$ Glc$^I$), 2.90−2.52 (m, 4 H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$, 2.17, 2.11, 2.11, 2.09, 2.05 (5s, 4Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 1226 [(M + K)$^+$].

**Methyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (25).** Imidate **13** (175 mg, 0.242 mmol) and acceptor **24** (306 mg, 0.220 mmol) were treated in 1:2 $CH_2Cl_2$/$Et_2O$ (6 mL) under the same conditions described for the synthesis of **16**, with molecular sieves (170 mg, 4 Å) and *t*-BDMSOTf (26 $\mu$L, 0.5 equiv), for 40 min. Neutralization was realized by adding solid $NaHCO_3$, the mixture was filtered, diluted with $CH_2Cl_2$, and processed as for **16**. Column chromatography (7:3 cyclohexane/acetone) yielded unreacted **24** (88 mg, 29%) and **25** (260 mg, 60%): $[\alpha]_D$ +76° (*c* 0.97, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.44−7.21 (m, 30H, 6Ph), 5.54 (d, $J$ = 3.8 Hz, H-1 Glc$^{VI}$), 5.50 (d, $J$ = 3.7 Hz, H-1 Glc$^V$), 5.29 (d, $J$ = 6.6 Hz, H-1 Glc$^{II}$), 5.18 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.56 (d, $J$ = 3.7 Hz, H-1 Glc$^I$), 4.08 (d, $J$ = 7.7 Hz, H-1 IdoUA$^{II}$), 2.80−2.60 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.13, 2.05, 2.00, 1.88 (5s, 15H, 4Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 1974 [(M + Na)$^+$]. Anal. Calcd for $C_{100}H_{126}O_{39}$: C, 61.53; H, 6.51. Found: C, 61.28; H, 6.59.

**Methyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-[(1→4)-(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)]$_3$-(1→4)-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (26).** A solution of **23** (73 mg, 0.061 mmol) and acceptor **24** (82 mg, 59 $\mu$mol) was treated for 30 min in 2:1 $Et_2O$/$CH_2Cl_2$ (1 mL) as for the synthesis of **16**. After workup, the compound was first purified using a Sephadex LH-20 chromatography column (1:1 $CH_2Cl_2$/EtOH) to remove unreacted **24** (20 mg, 14%) and then over a silica gel column to give pure **26** (98 mg, 69%): $[\alpha]_D$ +95° (*c* 1.01, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.43−7.20 (m, 30H, 6Ph), 5.55 (d, $J$ = 3.9 Hz, H-1 Glc$^{VIII}$), 5.50 (d, $J$ = 3.9 Hz, H-1 Glc$^V$), 5.44, 5.38 (2d, $J$ = 3.7, 3.9 Hz, H-1 Glc$^{VI}$, H-1 Glc$^{VII}$), 5.29 (d, $J$ = 6.8 Hz, H-1 IdoUA$^{II}$), 5.17 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.56 (d, $J$ = 3.7 Hz, H-1 Glc$^I$), 4.10 (d, $J$ = 7.9 Hz, H-1 GlcUA$^{IV}$), 2.81−2.50 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.15, 2.11, 2.09, 2.05, 2.00 (7s, 21H, 6Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 2456 [(M + K)$^+$]. Anal. Calcd for $C_{120}H_{158}O_{51}$: C, 59.63; H, 6.59. Found: C, 59.23; H, 6.58.

**Methyl [(6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_2$-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (27).** A solution of hexasaccharide **25** (149 mg, 76 $\mu$mol) in 1:2 toluene/EtOH (21 mL) was treated like **14** with hydrazine acetate (70 mg, 0.76 mmol), for 4 h. The reaction mixture was then concentrated, diluted in $CH_2Cl_2$, washed with 10% aqueous $KHSO_4$, $H_2O$, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. Chromatography (7:3 cyclohexane/acetone) of the residue gave **27** (126 mg, 89%): $[\alpha]_D$ +94° (*c* 0.77, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.42−7.23 (m, 30H, 6Ph), 5.50, 5.48 (2d, $J$ = 3.7 Hz, H-1 Glc$^V$, H-1 Glc$^{VI}$), 5.30 (d, $J$ = 6.8 Hz, H-1 IdoUA$^{II}$), 5.17 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.57 (d, $J$ = 3.6 Hz, H-1 Glc$^I$), 4.08 (d, $J$ = 8.1 Hz, H-1 GlcUA$^{IV}$), 2.12, 2.09, 2.00, 1.87 (4s, 12H, 4Ac); mass spectrum (ESI) *m*/*z* 1876 [(M + Na)$^+$]. Anal. Calcd for $C_{95}H_{120}O_{37}$: C, 61.54; H, 6.52. Found: C, 61.29; H, 6.51.

**Methyl [(6-*O*-Acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_4$-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (28).** Octasaccharide **26** (120 mg, 50 $\mu$mol) was reacted like **14** with hydrazine acetate (45 mg, 0.496 mmol) in 2:1 EtOH/toluene (22 mL) for 1.5 h. The reaction mixture was concentrated, diluted in $CH_2Cl_2$, washed with 10% aqueous $KHSO_4$, $H_2O$, saturated aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and concentrated. The residue was finally purified over silica gel (3:1 toluene/acetone) to give **28** (95 mg, 83%): $[\alpha]_D$ +80° (*c* 0.62, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.42−7.12 (m, 30H, 6Ph), 5.50, 5.46, 5.43, 5.40 (4d, $J$ = 3.9, 3.9, 3.7, 3.7 Hz, H-1 Glc$^{V-VIII}$), 2.14, 2.10, 2.09, 2.08, 2.00, 1.88 (6s, 18H, 6Ac); mass spectrum (ESI) *m*/*z* 2357 [(M + K)$^+$]. Anal. Calcd for $C_{115}H_{152}O_{49}$: C, 59.57; H, 6.60. Found: C, 59.49; H, 6.61.

**Methyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-(1→4)]$_{11}$-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (29).** Imidate **22** (75 mg, 24.6 $\mu$mol) and acceptor **24** (33 mg, 23.9 $\mu$mol) were reacted in the presence of powdered molecular sieves (18 mg, 4 Å) in 1:2 $CH_2Cl_2$/$Et_2O$ (0.75 mL) with a M solution of *t*-BDMSOTf (12.3 $\mu$L) in $CH_2Cl_2$, as described for the synthesis of **16**. After 1 h of stirring, the same amount of *t*-BDMSOTf was added, stirring was continued for 10 min, and the reaction mixture was neutralized with $NaHCO_3$. After filtration (Celite), the mixture was diluted with $CH_2Cl_2$, washed with 2% aqueous $NaHCO_3$ and $H_2O$, dried ($Na_2SO_4$), and filtered. The residue was first purified over a Toyopearl HW40 gel column using 1:1 $CH_2Cl_2$/EtOH as an eluant to remove unreacted **24** (15 mg, 45%) and then using silica gel to yield **29** (45 mg, 44%): $[\alpha]_D$ +135° (*c* 0.53, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 5.53 (d, $J$ = 3.8 Hz, H-1 Glc$^{XVI}$), 5.50−5.40 (m, 11H, H-1 Glc$^{V-XV}$), 5.28 (d, $J$ = 6.6 Hz, H-1 IdoUA$^{II}$), 5.17 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.58 (d, $J$ = 3.6 Hz, H-1 Glc$^I$), 4.11 (d, $J$ = 7.9 Hz, H-1 GlcUA$^{IV}$), 2.83−2.52 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.15, 2.12, 2.11, 2.08, 2.05, 1.99, 1.87 (8s, 45H, 14Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 4274 [(M + 2K)$^{2+}$]/2. Anal. Calcd for $C_{200}H_{286}O_{99}$: C, 56.20; H, 6.74. Found: C, 55.81; H, 6.58.

**Methyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-[(1→4)-(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)]$_{13}$-(1→4)-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (30).** A solution of **22** (144 mg, 47.3 $\mu$mol) and **27** (85 mg, 45.8 $\mu$mol) was reacted in 1:2 $CH_2Cl_2$/$Et_2O$ (2.5 mL) in the presence of molecular sieves (41 mg, 4 Å), with a M solution of *t*-BDMSOTf (23.6 $\mu$L) in $CH_2Cl_2$ under the conditions described for **16**. After 10 min of stirring, the reaction mixture was filtered (Celite), diluted with $CH_2Cl_2$, washed with 2% aqueous $NaHCO_3$ and $H_2O$, dried ($Na_2SO_4$), filtered, and concentrated. The residue was first purified over a Toyopearl HW50 gel column (1:1 $CH_2Cl_2$/EtOH) to separate unreacted **27** (33 mg, 39%) and then by silica gel chromatography (3:2 toluene/acetone) to yield pure octadecasaccharide **30** (103 mg, 48%): $[\alpha]_D$ +143° (*c* 0.57, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.34−7.25 (m, 30H, 6Ph), 5.54 (d, $J$ = 3.8 Hz, H-1 Glc$^{XVIII}$), 5.51−5.40 (m, 13H, H-1 Glc$^{V-XVII}$), 5.30 (d, $J$ = 6.6 Hz, H-1 IdoUA$^{II}$), 5.17 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.56 (d, $J$ = 3.6 Hz, H-1 Glc$^I$), 4.09 (d, $J$ = 7.9 Hz, H-1 GlcUA$^{IV}$), 2.82−2.51 (m, 4H, O(C=O)C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.16, 2.13, 2.11, 2.08, 2.05, 2.00, 1.88, 1.61 (9s, 51H, 16Ac and O(C=O)C$H_2$-C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 2408 [(M + 2K)$^{2+}$/2]. Anal. Calcd for $C_{220}H_{318}O_{111}$: C, 55.76; H, 6.76. Found: C, 55.29; H, 6.76.

**Methyl (6-*O*-Acetyl-4-*O*-levulinyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-[(1→4)-(6-*O*-acetyl-2,3-di-*O*-methyl-α-D-**

**glucopyranosyl)]$_{15}$-(1→4)-(benzyl 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-(benzyl 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (31).** Imidate **22** (84 mg, 27 μmol) was reacted with acceptor **28** (62 mg, 27 μmol) in 1:3 $CH_2Cl_2/Et_2O$ (4 mL) under the conditions described for **16**, using powdered molecular sieves (85 mg, 4 Å) and a M solution of *t*-BDMSOTf (14 μL) in $CH_2Cl_2$. After 1 h of stirring, the reaction mixture was diluted with $CH_2Cl_2$, filtered (Celite), washed with saturated aqueous $NaHCO_3$, dried ($Na_2SO_4$), filtered, and concentrated. The residue was first purified using a Toyopearl HW40 gel column to remove unreacted **28** (14 mg, 23%) and then on silica gel (1:1 acetone/cyclohexane) to yield pure **31** (71 mg, 51%): $[\alpha]_D$ +136° (*c* 0.95, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.42−7.18 (m, 30H, 6Ph), 5.54 (d, $J$ = 3.8 Hz, H-1 Glc$^{XX}$), 5.51−5.40 (m, 15H, H-1 Glc$^{V-XIX}$), 5.30 (d, $J$ = 6.8 Hz, H-1 IdoUA$^{II}$), 5.17 (d, $J$ = 3.5 Hz, H-1 Glc$^{III}$), 4.56 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 4.09 (d, $J$ = 7.9 Hz, H-1 GlcUA$^{IV}$), 2.85−2.53 (m, 4H, O(C=O)-C$H_2$C$H_2$(C=O)C$H_3$), 2.17, 2.16, 2.13, 2.11, 2.08, 2.05, 2.00, 1.88 (8s, 57H, 18Ac and O(C=O)C$H_2$C$H_2$(C=O)C$H_3$); mass spectrum (ESI) *m*/*z* 2641 [(M + 2K)$^{2+}$/2]. Anal. Calcd for $C_{240}H_{350}O_{123}\cdot 4H_2O$: C, 54.64; H, 6.84. Found: C, 54.51; H, 6.79.

**Methyl (2,3-Di-*O*-methyl-4,6-di-*O*-sodium sulfonato-α-D-glucopyranosyl)-[(1→4)-(2,3-di-*O*-methyl-6-*O*-sodium sulfonato-α-D-glucopyranosyl)]$_{11}$-(1→4)-(sodium 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranoside (2).** A solution of **29** (31 mg, 7.25 μmol) in AcOH (3 mL) was stirred for 4 h at 50 °C in the presence of 5% Pd/C (62 mg, 40 bar). The mixture was filtered (Celite), concentrated, and codistilled with $H_2O$. To a solution of the residue (27 mg) in MeOH (3 mL) was added, at 0 °C, 5 M aqueous NaOH (0.311 mL). After 4.5 h of stirring, the reaction mixture was diluted with $H_2O$ and loaded over a Sephadex G25 F gel column ($H_2O$). The residue (20 mg) obtained after concentration was acidified through a $H^+$ Dowex AG50WX4 (3 mL) column and concentrated. $Et_3N/SO_3$ complex (113 mg, 0.624 mmol) was added to a solution of the compound obtained in the preceding step in DMF (3 mL), and the mixture was heated at 55 °C for 20 h with protection from light. After cooling, the reaction mixture was diluted with 0.2 M aqueous NaCl (2 mL) and layered on top of a Sephadex G25 F gel column (0.2 M aqueous NaCl). The fractions were pooled, concentrated, and desalted on the same gel filtration column, equilibrated with $H_2O$. Lyophilization gave **2** (35 mg, 82% from **29**): $[\alpha]_D$ +119° (*c* 0.56, $H_2O$); $^1$H NMR ($D_2O$) $\delta$ 5.71−5.67 (m, 11H, H-1 Glc$^{VI-XVI}$), 5.48 (d, $J$ = 3.5 Hz, H-1 Glc$^{V}$), 5.43 (d, $J$ = 3.3 Hz, H-1 Glc$^{III}$), 5.16 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 5.11 (br s, H-1 IdoUA$^{II}$), 4.68 (d, $J$ = 7.5 Hz, H-1 GlcUA$^{IV}$); mass spectrum (ESI) *m*/*z* 815 [(M − 6Na)$^{6-}$]/6; CE 94% ($t_R$ = 15.07 min).

**Methyl (2,3-Di-*O*-methyl-4,6-di-*O*-sodium sulfonato-α-D-glucopyranosyl)-[(1→4)-(2,3-di-*O*-methyl-6-*O*-sodium sulfonato-α-D-glucopyranosyl)]$_{13}$-(1→4)-(sodium 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranoside (3).** Compound **30** (71 mg, 15 μmol) was hydrogenolyzed in AcOH (3 mL) with 5% Pd/C (140 mg, 40 bar) for 3.5 h at 50 °C. After filtration (Celite) and co-distillation with toluene and then with MeOH, the residue (62 mg) was dissolved in MeOH (6.5 mL), and 5 M aqueous NaOH (0.256 mL) was added at 0 °C. After 2 h of stirring, the reaction mixture was acidified (pH 3) with $H^+$ Dowex AG 50 WX4, concentrated, and loaded on a Toyopearl HW40 gel column ($H_2O$). The fractions were pooled and dried. The residue (42 mg) thus obtained was dissolved in DMF (3 mL), and $Et_3N/SO_3$ complex (111 mg, 0.613 mmol) was added. The reaction mixture was stirred in the dark at 55 °C for 21 h and then cooled and processed as for **2**. Lyophilization yielded **3** (29 mg, 87% from **30**): $[\alpha]_D$ +124° (*c* 1.25, $H_2O$); $^1$H NMR ($D_2O$) $\delta$ 5.71−5.67 (m, 13H, H-1 Glc$^{VI-XVIII}$), 5.48 (d, $J$ = 3.5 Hz, H-1 Glc$^{V}$), 5.42 (d, $J$ = 3.3 Hz, H-1 Glc$^{III}$), 5.17 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 5.11 (br s, H-1 IdoUA$^{II}$), 4.68 (d, $J$ = 7.5 Hz, H-1 GlcUA$^{IV}$); mass spectrum (ESI) *m*/*z* 779 [(M − 7Na)$^{7-}$]/7; CE 97% ($t_R$ = 15.16 min.).

**Methyl (2,3-Di-*O*-methyl-4,6-di-*O*-sodium sulfonato-α-D-glucopyranosyl)-[(1→4)-(2,3-di-*O*-methyl-6-*O*-sodium sulfonato-α-D-glucopyranosyl)]$_{15}$-(1→4)-(sodium 2,3-di-*O*-methyl-*β*-D-glucopyranosyluronate)-(1→4)-(2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-(2,3,6-tri-*O*-sodium sulfonato-α-D-glucopyranoside (4).** Compound **31** (55 mg, 10.5 μmol) was hydrogenolyzed in AcOH (3 mL) in the presence of Pd/C 5% (110 mg) with $H_2$ (40 bar) during 4 h. Charcoal was filtered off (Celite), volatiles were removed under vacuum, and co-distillation with $H_2O$ was realized. The residue (48 mg) was dissolved in MeOH (5 mL), and 5 M aqueous NaOH (0.193 mL) was slowly added. After 3 h of stirring, the reaction mixture was processed as described for **29**. Finally, the residue (34 mg) was dissolved in DMF (4 mL), reacted with $Et_3N/SO_3$ (186 mg, 1.03 mmol), and purified as for **2**. Freeze-drying gave **4** (50 mg, 77%): $[\alpha]_D$ +107° (*c* 0.52, $H_2O$); $^1$H NMR ($D_2O$) $\delta$ 5.71−5.67 (m, 15H, H-1 Glc$^{VI-XX}$), 5.48 (d, $J$ = 3.5 Hz, H-1 Glc$^{V}$), 5.43 (d, $J$ = 3.3 Hz, H-1 Glc$^{III}$), 5.17 (d, $J$ = 3.7 Hz, H-1 Glc$^{I}$), 5.10 (br s, H-1 IdoUA$^{II}$), 4.68 (d, $J$ = 7.5 Hz, H-1 GlcUA$^{IV}$); mass spectrum (ESI) *m*/*z* 596 [(M − 10Na)$^{10-}$/10]; CE 88% (15.27 min).

**Acknowledgment.** This work is part of a collaborative project between N.V. Organon (The Netherlands) and Sanofi (France) on antithrombotic oligosaccharides. The authors also wish to thank Dr. P. Sizun (high-field NMR experiments) and Dr. J.P. Hérault (biological assays).

JO991152J