Toluene was distilled from a Na/K alloy and degassed. $[Be\{N(SiMe_3)_2\}_2]$ was prepared according to a known procedure.[7] **Caution**: $[Be\{N(SiMe_3)_2\}_2]$ is a known carcinogen and should be handled only in a well-ventilated fume hood with proper precautions. Benzenethiol was dried over activated 4-Å molecular sieves. [18]Crown-6 was dissolved in hexane, and freshly cut potassium was added. The mixture was briefly heated to reflux, and the remaining potassium removed by filtration. The dried crown ether was isolated by crystallization from hexane.

1: HSPh (0.21 mL, 2.0 mmol) was added dropwise to $[Be\{N(SiMe_3)_2\}_2]$ (0.33 g, 1.0 mmol) and [18]crown-6 (0.26 g, 1.0 mmol) in toluene (20 mL) at room temperature. A heavy white precipitate formed after stirring for several minutes. Pyridine (0.1 mL, 1.2 mmol) was added dropwise, and a homogeneous light yellow solution was obtained. After the mixture had been stirred at room temperature for 30 min, it was filtered through a Celite-loaded frit and stored at 0 °C. Colorless plates gradually grew over several days, and 0.20 g (55 % yield) were collected from the first crystallization.[17] The white powder shrank slightly when heated above 80 °C and then irreversibly melted to a yellow oil in the range of 145 – 153 °C. ^{1}H NMR (300 MHz, 25 °C, [D$_8$]THF): $\delta = 8.54 - 6.71$ (broad overlapping signals, 40 H), 3.52 (s, 24 H), 2.31 (s, 6 H); IR (Nujol): $\tilde{\nu} = 3302$ m, 3197 m, 3043 w, 2926 s, 1643 m, 1610 m, 1576 s, 1463 s, 1377 m, 1352 m, 1317 s, 1286 m, 1216 m, 1137 m, 1105 s, 1070 m, 1050 m, 956 s, 837 m, 785 m, 743 s, 696 s, 648 w, 580 m, 478 cm^{-1} m.

Crystal structure data for **1**: $C_{60}H_{76}Be_2N_4O_6S_4$, $M_r = 1095.51$, triclinic, space group $P\bar{1}$, $a = 10.432(2)$, $b = 13.5950(3)$, $c = 22.0275(4)$ Å, $\alpha = 79.374(1)$, $\beta = 77.760(1)$, $\gamma = 87.160°$, $V = 3000.5(1)$ Å^3, $T = 150$ K, $Z = 2$, $\mu(Mo_{K\alpha}) = 0.210$, crystal dimensions $0.42 \times 0.20 \times 0.20$ mm. Of 12886 independent reflections collected ($2.56 \leq 2\theta \leq 56.00°$) on a Siemens SMART system with a three-circle goniometer and a CCD detector operating at -54 °C, 8176 were observed ($I > 2\sigma(I)$). Crystal decay was monitored by repeating a set of initial frames at the end of data collection and comparing the duplicate reflections; no decay was observed. An absorption correction was applied with the program SADABS.[18] The crystal structure was solved by direct methods with SHELXTL. Missing atoms were located in subsequent difference Fourier maps and included in the refinement. The structure of **1** was refined by full-matrix least-squares refinement on F^2.[19] Hydrogen atoms with the exception of the NH protons were placed geometrically and refined by using a riding model with U_{iso} constrained at 1.2 U_{eq} of the carrier C atom. All non-hydrogen atoms were refined anisotropically. NH_3 hydrogen atoms were located in difference maps and included in the refinement by using distance restraints. A center of symmetry, suspected in the center of the crown ether molecule could not be confirmed even after various symmetry checks and transformation of the suspected inversion center to the origin of the unit cell. The absence of significant correlations also confirms the correct symmetry. $R_1 = 0.0575$ for data with $I > 2\sigma(I)$, and $wR_2 = 0.1234$ for all data. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101292. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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First Synthetic Carbohydrates with the Full Anticoagulant Properties of Heparin**

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Heparin, a major drug for the prevention and treatment of cardiovascular diseases, exerts its activity through activation of the serine proteinase inhibitor antithrombin III (AT III), the main physiological inhibitor of blood coagulation.[1, 2] A unique pentasaccharide sequence[3] in the polysaccharide binds to the protein in a highly specific way, inducing a

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[**] This work is part of a collaborative project between N.V. Organon (The Netherlands) and Sanofi Recherche (France) on antithrombotic oligosaccharides.

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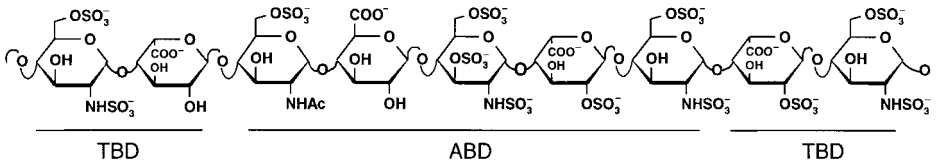


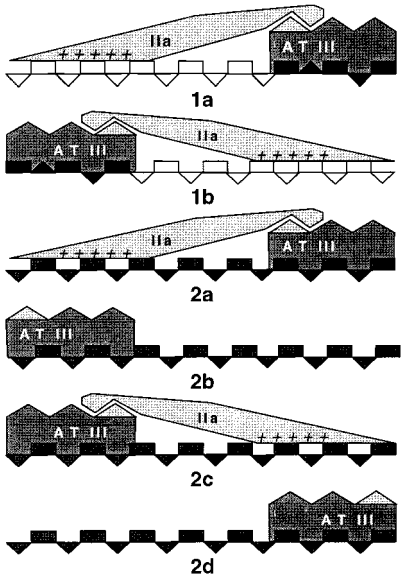
Scheme 1. An anticoagulant heparin molecule contains an antithrombin binding domain (ABD) prolonged at both ends by thrombin binding domains (TBDs). An ABD is a unique pentasaccharide sequence characterized by the presence of β-D-glucuronic acid linked to a *N*-sulfo-3,6-di-*O*-sulfo-α-D-glucosamine; TBDs mainly consist of repeated trisulfated disaccharides made of 2-*O*-sulfo-α-L-iduronic acid linked to *N*-sulfo-6-*O*-sulfo-α-D-glucosamine.

conformational change that allows adequate presentation of the inhibitory peptidic loop of AT III to the active sites of serine proteinases. The mere interaction with activated AT III is sufficient to inhibit coagulation factor Xa. This is at variance with thrombin inhibition, which requires the formation of a ternary complex involving heparin, AT III, and thrombin.[2] A longer heparin chain is then needed (Scheme 1) which contains the above-mentioned pentasaccharide that is prolonged at both ends by repeated trisulfated disaccharide units.[4] Thrombin is electrostatically attracted through its anion binding site exosite II,[5] and slides along the chain until it finally hooks itself on the inhibitory loop of activated AT III.

Thus, an oligosaccharide molecule containing both an AT III binding domain (ABD) and a thrombin binding domain (TBD) should be able to mimic the full anticoagulant activity of heparin. Various biochemical studies aimed at determining the size of such molecules pointed to tetradeca-, octadeca-, and eicosasaccharides.[6] It is noteworthy that when AT III is docked on its binding domain, thrombin, sliding along the heparin chain, must approach from the correct side to be inhibited. This implies that only one of the two possible ways of elongating the ABD with a TBD (reducing or nonreducing ends, Scheme 2) will allow thrombin inhibition.[7]

Synthesizing an oligosaccharide of this size, and reproducing the exact structure of the hypothetical heparin fragment, would be practically unfeasible.[9] In a first approach to overcome this difficulty, two saccharide molecules, an ABD and a TBD, were bridged by a non-carbohydrate linker.[8] The resulting conjugates displayed inhibition of thrombin and factor Xa, but in some assays the thrombin inhibitory potency was weaker than that of heparin. In the approach reported here we exploited the "non-glycosamino" glycan series of heparin analogues,[10] where *N*-sulfonato substituents are replaced by *O*-sulfonato groups and hydroxyl groups are alkylated. These structural modifications fully preserve the specific binding to AT III, yet they dramatically simplify the synthesis.

The structures of the target molecules stem from the following considerations: a) In contrast to the highly specific interaction between AT III and heparin, the interaction of thrombin with the polysaccharide merely results from an electrostatic attraction governed by the density of negative charges on the polysaccharide backbone.[4] Consequently the ABD, which contains at least six critical negative charges (Scheme 3), can also attract thrombin and serve as a TBD. b) A continuum of ABDs would necessarily display the correct relative position of ABD and TBD, since AT III can bind at either end of the molecule, and thrombin can be attracted by the rest of the chain (Scheme 2). c) For thrombin to efficiently compete with AT III for binding to a continuum of ABDs, the affinity of the AT III/ABD couple must preferably be in the same range of affinity as the thrombin/heparin couple—that is, in the micromolar range[11] and therefore two to three orders of magnitude lower than the highest affinity reached with some synthetic pentasaccharides. From this latter consideration it follows that we are, to a certain extent, allowed to adapt the structure of the ABD to our synthesis strategy (provided we preserve enough binding affinity). This is not a minor advantage for the synthesis of the targeted long saccharide fragments.



Scheme 2. Inhibition of thrombin by AT III and heparin. In an active anticoagulant molecule, AT III binds to heparin through the ABD pentasaccharide (see Scheme 1, symbolized in **1a**, **b** by black rectangles and triangles) and exposes its activated inhibitory loop (light grey triangle) to the catalytic site of thrombin (also called factor IIa). Thrombin, attracted by the negative charges of the TBD (white rectangles and triangles), slides along the chain until it hooks itself on the exposed loop of the inhibitor. Heparin and AT III dock themselves in a unique, unknown way (**1a** or **1b**), and thrombin apparently has to approach from the correct side to be inhibited. Among these two possible arrangements of ABD and TBD (both are present in a heparin molecule, see Scheme 1), the efficient one was unknown.[7] We therefore designed an hybrid molecule (dark grey rectangles and triangles) which is a continuum of ABDs. AT III can bind at either end of the molecule (**2a**–**d**), and, whatever the efficient arrangement (**2a** or **2b**), thrombin can be attracted and inhibited (**2a** or **IIc**) provided the saccharide chain is long enough to accommodate both proteins.

The structure of a pentasaccharide with high affinity for AT III[12] is shown in Scheme 3. The presence of two types of uronic acids having the D-*gluco* and the L-*ido* configurations is a structural features of high-affinity compounds. From this structure we reasoned that hexasaccharides consisting of a

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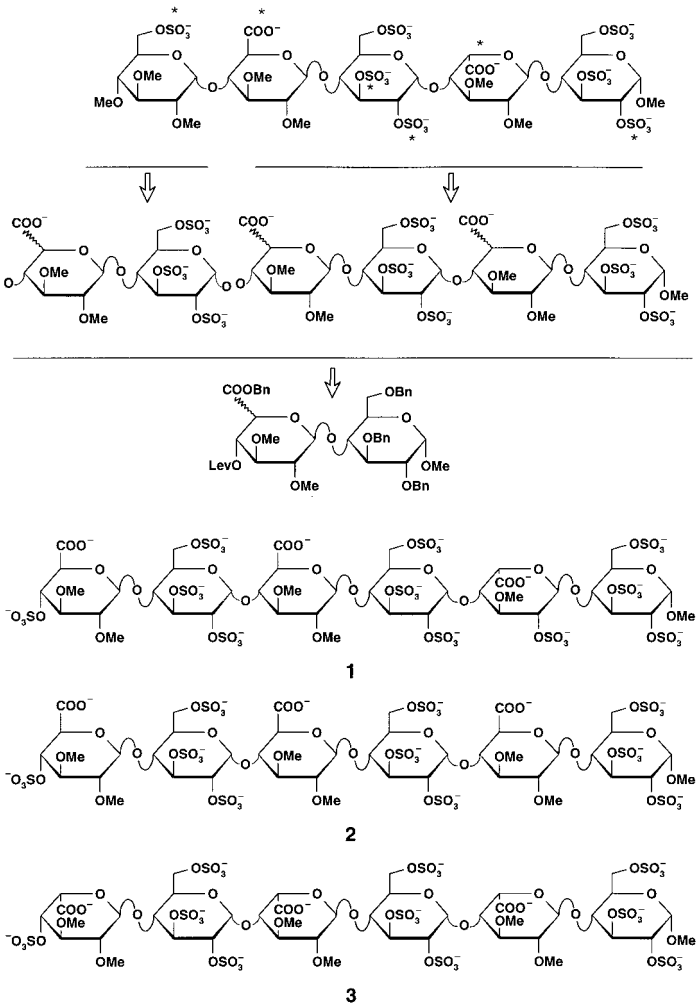
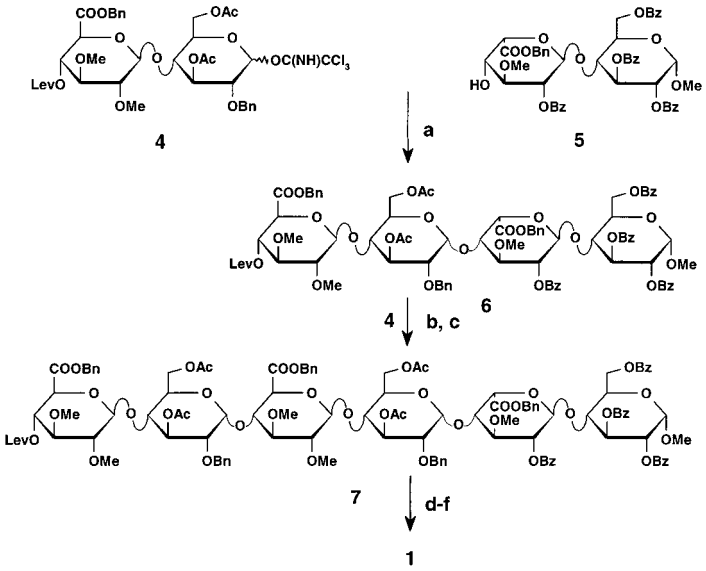


Scheme 3. Simplifying the structure of a high-affinity binding pentasaccharide sequence. The critical anionic groups involved in the interaction with AT III are labeled with an asterisk. The proposed changes (second line) introduce another sulfate group at position 3 of the third glucose unit and alter the configuration at C5 of the uronic acids. Such changes would allow synthesis from a single disaccharide building block (third line). Compounds **1**–**3** were synthesized to test these various possibilities: **1** contains a third trisulfated glucose residue, **2** contains only glucuronic acid, and **3** contains only iduronic acid (the latter was obtained from a single disaccharide building block).

single repeated disaccharide unit might display significant affinity for AT III, possibly in the desired micromolar range. Such hexasaccharides, obtainable from a single disaccharide synthon, meet our criteria for an easy synthesis of long fragments (the synthesis of the ultimate target longer saccharides would also be possible from the same basic synthon). To test this possibility we prepared the hexasaccharides **1**–**3** depicted in Scheme 3. Hexasaccharide **1** was synthesized to check the influence of adding one more trisulfated glucose unit, **2** to test whether the easily available D-glucuronic acid could substitute for L-iduronic acid, and **3** to obtain a compound in which L-iduronic acid is the only uronic acid present. The affinity of **1**–**3** for AT III was determined.

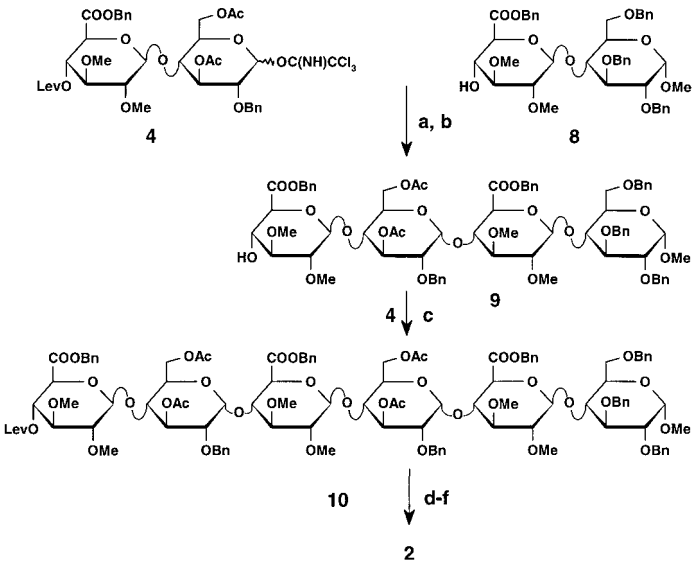
All three hexasaccharides were obtained using strategies (Scheme 4) where disaccharide building blocks were prepared first and then repeatedly condensed to each other by the imidate glycosylation procedure;[13] the final hexasaccharides



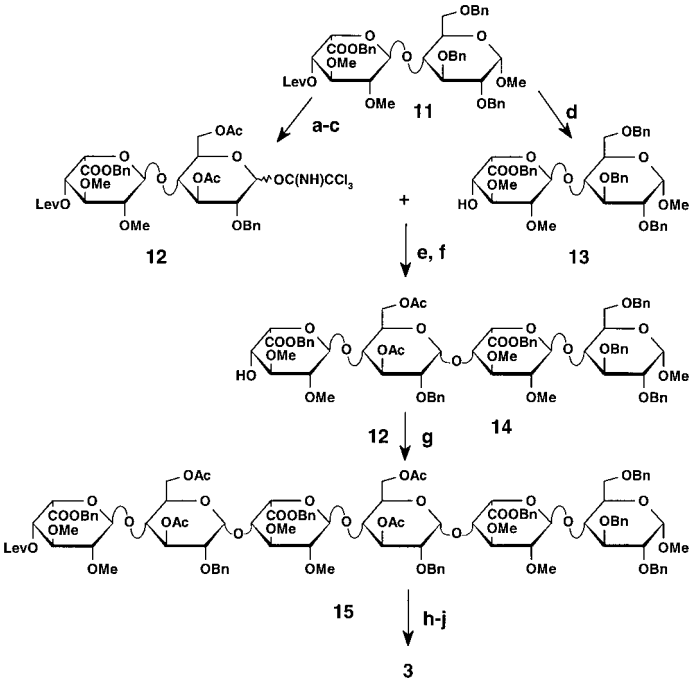
Scheme 4. a) $Me_3SiOSO_2CF_3$ (TMSOTf), toluene, 4-Å MS, $-20\,^{\circ}C$, 30 min, 62%; b) 1M NH_2NH_2/H_2O in pyridine/AcOH (3/2), 15 min, 87%; c) as for a), 48%; d) H_2, 10% Pd/C, MeOH, 24 h; e) 0.5M NaOH, 5 h (91% based on **7**); f) pyridine:SO_3, DMF, $55\,^{\circ}C$, 24 h, 98%.

were deprotected and sulfated. Thus, reaction of stoichiometric amounts of the known[14] glycosyl donor **4** and the acceptor **5** (prepared as reported for the methyl ester analogue[10a]) yielded the tetrasaccharide **6**[15] (62%, Scheme 4). Selective cleavage of the levulinic ester gave the corresponding glycosyl acceptor (87%), which was again condensed with **4** to afford the fully protected hexasaccharide **7** (a 5:1 mixture of the α and β anomers was formed, from which **7** was isolated in 39% yield after chromatography on silica gel). Catalytic hydrogenolysis of the benzyl groups was followed by saponification of the esters (91%). Complete removal of the protecting groups was monitored by high-field ^{1}H NMR spectroscopy. Subsequent sulfation and lyophilization gave **1** as a white powder (98%).[15] Compound **2**[15] was obtained in a similar manner (Scheme 5) from **4** and the acceptor **8**, which was prepared as reported for its methyl ester counterpart.[12] Finally, a similar series of reactions (Scheme 6) gave **3**.[15] The sequence started from **12** and **13**, which were both are derived from a common precursor, the disaccharide **11**, prepared as reported for its methyl ester counterpart.[12]

The affinity of **1**–**3** for AT III was determined by fluorescence spectroscopy[15] and compared to that of the pentasaccharide in Scheme 3 ($K_d = 1.4 \pm 0.2$ nM). The introduction of a third trisulfated glucose unit at the nonreducing end of the pentasaccharide sequence proved to be fully compatible with the recognition of AT III (K_d(**1**) $= 0.8 \pm 0.3$ nM). In contrast, substituting D-glucuronic acid for L-iduronic acid resulted in a dramatic loss of affinity (K_d(**2**) $= 3.4 \pm 0.3\,\mu$M). The opposite change (substituting L-iduronic acid for D-glucuronic acid), although it also decreased the affinity for AT III, nicely fitted our "relative affinity criterion" discussed above (c) since the affinity of **3** for AT III ($K_d = 0.35 \pm 0.01\,\mu$M) was very close to that reported[11] for thrombin and heparin (1 μM). We expected **3** (which like



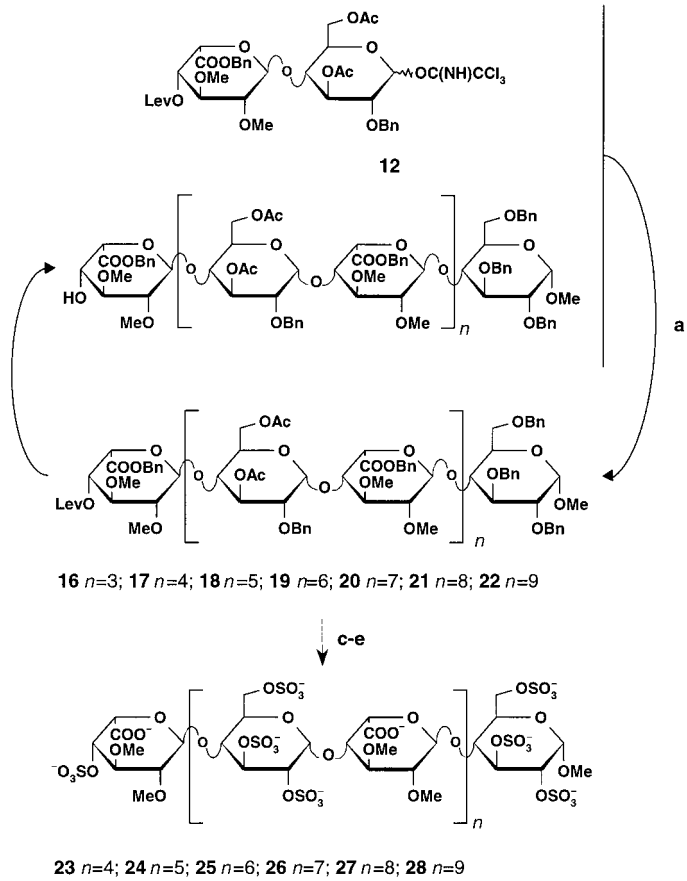
Scheme 5. a) TMSOTf, CH_2Cl_2, 4-Å MS, −20 °C, 30 min, 69 %; b) 1 M NH_2NH_2/H_2O in pyridine/AcOH (3/2), 15 min, 95 %; c) as for a), 63 %; d) H_2, 10 % Pd/C, MeOH, 24 h; e) 0.5 M NaOH, 5 h, 99 % (based on **10**); f) pyridine:SO_3, DMF, 55 °C, 24 h, 95 %.



Scheme 6. a) CF_3COOH/Ac_2O/AcOH, 60 °C, 4 h, 67 %; b) $HOCH_2$-CH_2NH_2, THF, RT, 74 %; c) CCl_3CN, K_2CO_3, CH_2Cl_2, RT, 1.5 h, 94 %; d) 1 M NH_2NH_2/H_2O in pyridine/AcOH (3/2), 15 min, 91 %; e) TBDM!SOTf, toluene, 4-Å MS, −20 °C, 30 min, 54 %; f) as for d), 99 %; g) as for e), 64 %; h) H_2, 10 % Pd/C, MeOH, 24 h; i) 0.5 M NaOH, 5 h; j) pyridine:SO_3, DMF, 55 °C, 24 h, 60 % (based on **15**).

heparin contains four negative charges per disaccharide unit) to have a similar affinity for thrombin. Interestingly, **3** also displays significant anti-factor Xa activity (325 units mg^{-1}). We were pleased that the synthesis of **3** involves repeated glycosylation at position 4 of a L-iduronic acid derivative, since in our experience such a glycosylation always afforded almost exclusively the desired α-coupled product when an imidate was used as the glycosyl donor.

Having identified an ABD that is easily obtainable from a single disaccharide building block (**11**), we attempted the synthesis of longer fragments consisting of a single repeating basic disaccharide unit. The strategy used to prepare **3** was further developed, as shown in Scheme 7. The imidate **12** was used as glycosyl donor to add disaccharide units to the new



Scheme 7. a) TMSOTf, toluene, 4-Å MS, −20 °C, 30 min; b) 1 M NH_2NH_2/H_2O in pyridine/AcOH (3/2), 15 min; c) H_2, 10 % Pd/C, MeOH, 24 h; d) 0.5 M NaOH, 5 h; e) pyridine:SO_3, DMF, 55 °C, 24 h.

glycosyl acceptor resulting from cleavage of the levulinoyl group of the oligosaccharide obtained at the preceding step.[17] The process was reiterated until an eicosamer was obtained. The structure of the fully protected intermediates (**16**–**22**) was ascertained by high-field ^1H NMR spectroscopy and mass spectrometry.[15] The yield of the successive coupling steps was about 60 % (not optimized), and no β-coupled product was detected. The large difference in size between the glycosyl donor disaccharide on the one hand, and the glycosyl acceptor and the product of the reaction on the other hand, made it very easy to recover, by gel permeation in dichloromethane/ethanol, a mixture containing exclusively the unchanged acceptor and the product. This mixture was occasionally submitted to another glycosylation reaction to improve the yield based on the expensive acceptors involved in the final steps of chain elongation. Deprotection and sulfation of the oligosaccharides (deca- to eicosamer) obtained at each step involved, as above for the preparation of hexasaccharides, hydrogenolysis, saponification, and sulfation. Complete re-

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Table 1. Properties of the sulfated iduronic acid containing oligosaccharides.

	3	**23**	**24**	**25**	**26**	**27**	**28**	heparin
saccharide units	6	10	12	14	16	18	20	10–50
molecular weight	2217	3606	4301	4995	5690	6384	7078	ca. 15000
factor Xa inhibition[a]	325 (±16)	405 (±32)	360 (±29)	310 (±16)	359 (±29)	270 (±23)	236 (±19)	180
thrombin inhibition[b]	>10	>10	>10	>10	130 (113–133)	23 (13–30)	6.7 (3–9)	3.3 (3–4)

[a] [units mg^{-1}] (standard deviation) ($n=3$). [b] IC_{50} [$ng\,mL^{-1}$] (95% confidence interval).

moval of the protecting groups was monitored before sulfation by high-field ^1H NMR spectroscopy. The desired sulfated oligomers **23**–**28** were obtained as white powders after lyophilization in yields of 49 to 86% over the three steps. Their purity was assessed by capillary electrophoresis, and their structure was clarified by ^1H NMR spectroscopy and electro spray ionization mass spectrometry (ESI-MS).[15]

These compounds were then submitted to biological tests to assess their ability to catalyze inhibition of factor Xa[18] and thrombin[19] by AT III (Table 1). All the compounds contain an ABD, which explains their ability to bind to AT III and their anti-factor Xa activity. The hexa-, deca-, dodeca-, and tetradecasaccharide were inactive in the thrombin inhibition assay, whereas the activity of the hexadeca-, octadeca-, and eicosasaccharide increased with size in this assay. The IC_{50} values show that the eicosamer is half as potent as standard heparin. Increasing the chain length would probably improve the thrombin inhibitory potency since the higher activity of the longer chains (compare **26**–**28**) reflects the well-known[2] greater ability of longer heparin fragments to electrostatically attract thrombin.

Using the imidate glycosylation procedure,[13] we have synthesized for the first time oligosaccharide molecules displaying the dual (anti-factor Xa and anti-thrombin) activity of heparin mediated by AT III. Regarding the long standing question[6] about the minimum size of heparin fragments able to catalyze thrombin inhibition, the present data restrict the choice to a pentadeca- or hexadecasaccharide.

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[15] All new compounds were analyzed by ^1H NMR spectroscopy, by mass spectrometry, and occasionally by HPLC. Combustion analyses were systematically performed on disaccharidic building blocks only. Selected analytical data: ^1H NMR data were collected at 500 MHz in D_2O (external standard TSP; for polar compounds) or in $CDCl_3$ (internal standard TMS). The NMR data are given for anomeric protons of the nonreducing end (NR) to the reducing end (R) units. Mass spectrometry data were collected with liquid secondary ion mass spectrometry (LSI-MS) or ESI-MS. **1**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 4.64 (7.5; NR), 5.52 (3.7; NR-1), 4.63 (8.1; NR-2), 5.48 (3.5; R-2), 5.10 (6.5; R-1), 5.10 (3.5; R); LSI-MS: m/z: 2280.4 [$M-Na]^-$; $[\alpha]_D = +30$ ($c=1$ in H_2O). **2**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 4.66 (ca. 8; NR), 5.54 (3.7; NR-1), 4.64 (ca. 8; NR-2), 5.54 (3.7; R-2), 4.63 (ca. 8; R-1), 5.14 (3.6; R); LSI-MS: m/z: 2192.8 [$M-Na]^-$; $[\alpha]_D = +43$ ($c=0.7$ in H_2O). **3**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 5.10 (ca. 1; NR), 5.41 (ca. 3; NR-1), 5.06 (2.2; NR-2), 5.41 (ca. 3; R-2), 5.09 (ca. 1; R-1), 5.15 (3.7; R); LSI-MS: m/z: 2192.6 [$M-Na]^-$; $[\alpha]_D = +28$ ($c=1$ in H_2O). **7**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 4.16 (8; NR), 5.43 (3.5; NR-1), 4.03 (8; NR-2), 4.88 (ca. 3; R-2), 5.47 (6.1; R-1), 5.05 (ca. 3; R); $[\alpha]_D = +76$ ($c=0.3$ in CH_2Cl_2). **10**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 4.17 (ca. 8; NR), 5.39 (3.8; NR-1), 4.20 (ca. 8; NR-2), 5.33 (3.6; R-2), 4.14 (ca. 8; R-1), 4.56 (3.5; R); $[\alpha]_D = +86$ ($c=0.6$ in CH_2Cl_2). **15**: ^1H NMR: δ ($J_{1,2}$ [Hz]) = 4.90 (4.3; NR), 5.10 (3.9; NR-1), 5.23 (6.5; NR-2), 5.12 (3.9; R-2), 4.89 (6.8; R-1), 4.56 (ca. 3; R); $[\alpha]_D = +23$ ($c=0.5$, CH_2Cl_2). The ^1H NMR spectra of **16**–**22** were very similar in terms of chemical shifts, and, as expected, only the relative intensities of the signals varied between compounds. Resonances for the distinguishable anomeric protons: δ ($J_{1,2}$ [Hz]) = 4.92 (4–4.3;

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NR), 5.10 (3.3–3.5; NR-1), 5.26 (6–7; R-1), 4.56 (3.5; R). Optical rotations of **16**–**22** were all in the range +20–22 ($c = 0.5–1$ in H_2O). Positive-mode LSI-MS (thioglycerol + NaCl/thioglycerol + KF): **16**: *m/z*: 2771/2787; **17**: *m/z*: 3402/3418; **18** (after cleavage of the levulinoyl group): *m/z*: 3934/3950; **19**: *m/z*: 4664/4680; **20**: *m/z*: not determined/5310; **21**: *m/z*: not determined/5940. The ^{1}H NMR spectra of **23**–**28** were very similar in terms of chemical shifts, and, as expected, only the relative intensities of the signals varied between compounds. Resonances for the distinguishable anomeric protons: δ ($J_{1,2}$ [Hz]) = 5.08–5.11 (1–2; NR), 5.38–5.41 (3–4; NR-1), 5.04–5.09 (1–2; CNR), 5.40–5.42 (3–4; CR), 5.05–5.09 (1–2; R-1), 5.10–5.15 (3.5; R). Optical rotations were all in the range +27–34 ($c = 0.4–0.6$ in H_2O); ESI-MS (monoisotopic mass/average mass/experimental mass ± standard deviation): **23**: *m/z*: 3603.5/3606.3/3605.13 ± 0.9; **24**: *m/z*: 4297.5/4300.7/4296.8 ± 0.9; **25**: *m/z*: 4991.4/4995.2/4993.0 ± 2.2; **26**: *m/z*: 5685.3/5689.6/5687.6 ± 2.3; **27**: *m/z*: 6379.2/6384.1/6381.4 ± 3.2; **28**: *m/z*: 7073.1/7078.5/7077.3 ± 3.2.

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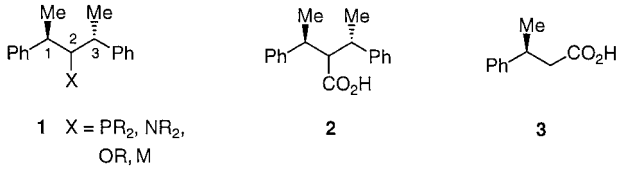
New Chiral Ligands with Nonstereogenic Chirotopic Centers for Asymmetric Synthesis**

Claus-Dieter Graf, Christophe Malan, and Paul Knochel*

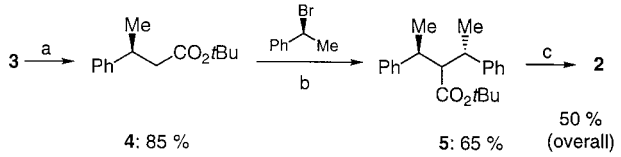
The design of new chiral ligands for asymmetric synthesis is an active field of research.[1] To obtain an efficient transfer of the stereochemistry the chiral information of the ligand should be as close as possible to the reaction center. This concept led to the development of *P*-chiral phosphanes[2] and to the ingenious design of "chiral pockets"[3] that give impressive enantioselectivities. Alternatively, ligands with chiral secondary organic groups linked to phosphorus or nitrogen atoms have also been used with excellent results in enantioselective reactions.[4] However, many of these ligands involve a challenging synthesis that requires the linkage of a sterically demanding secondary chiral carbon center to a heteroatom (P or N). Stimulated by the work of Mislow and Siegel on local chirality[5] we report the preparation of several new pseudo-C_2-symmetric ligands of type **1** and their utility in asymmetric synthesis. All these ligands avoid the difficulty of



1 X = PR_2, NR_2, OR, M **2** **3**

controlling the stereochemistry of the C(2) carbon center attached to the heteroatom (P or N).

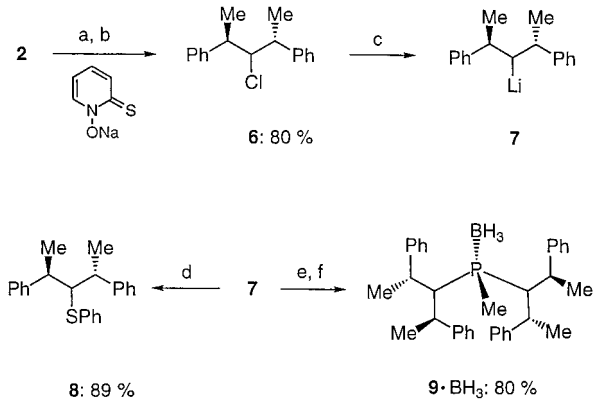
In accordance with the definition of Mislow and Siegel,[5] the center C(2) is not a chiral center, but rather a chirotopic center (a center in a chiral environment). This represents a great synthetic advantage since it avoids the necessity to control the stereochemistry at C(2). We chose the carboxylic acid **2** as the key intermediate for the preparation of ligands of type **1**. The esterification of commercially available (*S*)-3-phenylbutyric acid (**3**) with isobutene provides the *tert*-butyl ester **4**, which was alkylated in a clean S_N2-reaction with (*S*)-1-bromoethylbenzene (88% *ee*)[6] (Scheme 1). Simple recrystallization of (*S*,*S*)-*tert*-butyl ester **5** from pentane/acetone



Scheme 1. a) Isobutene, H_2SO_4 cat., CH_2Cl_2, −15→25 °C, 14 h, 85%; b) LDA, THF, −78 °C, 1.5 h, then HMPA (1.0 equiv), (*S*)-PhCH(Br)CH_3 (1.5 equiv), −20→25 °C, 65%; c) *p*-TosOH cat., toluene, 110 °C, 14 h, 95%. HMPA = hexamethyl phosphoramide; *p*-TsOH = *para*-toluenesulfonic acid.

removed the 10% contamination of the *meso* isomers, and provides the pure ester **5** (65% yield). The free carboxylic acid **2** is then obtained by the acid catalysed cleavage of the *tert*-butyl ester **5**. This simple reaction sequence has been performed on a 10-g scale with an overall yield of about 50%.

The carboxylic acid **2** was readily converted into the corresponding alkyl chloride **6** by a radical decarboxylation.[7] Thus, **2** was converted into its corresponding acid chloride followed by treatment with the sodium salt of 2-mercaptopyridine-*N*-oxide with simultaneous photolysis (Scheme 2).



Scheme 2. a) $SOCl_2$, 90 °C, 3 h; b) NaC_5H_4NOS, DMAP cat., CCl_4, 80 °C, *hv* (300 W), 2 h; c) lithium 4,4″-di-*tert*-butylbiphenylide, THF, −78 °C, 5 min; d) $(PhS)_2$, THF, −78→25 °C; e) $MePCl_2$, THF, −78→25 °C; f) $BH_3 \cdot SMe_2$. DMAP = 4-dimethylaminopyridine.

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