Total Synthesis

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Chemical Synthesis of a Heparan Sulfate Glycopeptide: Syndecan-1**

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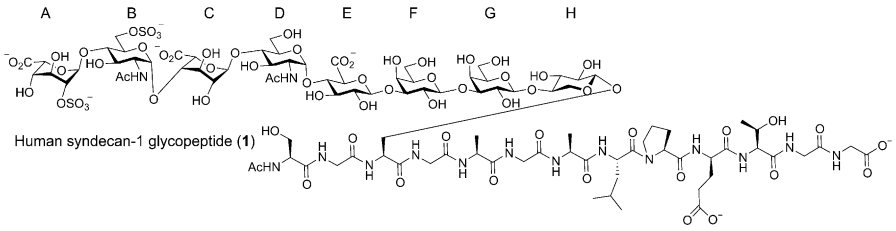
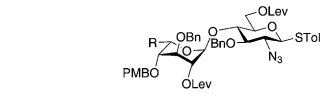
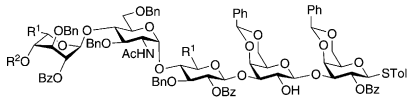


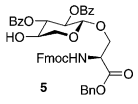
Heparan sulfate proteoglycans (HSPGs), which are composed of three parts: heparan sulfate (HS), a tetrasaccharide linker, and the core protein, are ubiquitous components of the mammalian cell surface and the extracellular matrix.[1] This family of molecules can serve as receptors for many adhesion molecules and growth factors such as fibroblast growth factor, integrin, Wnt proteins, and herpes simplex virus glycoprotein D.[2] HSPGs play important roles in a variety of biological processes including cancer development, angiogenesis, viral infection, and wound repair,[3] and thus renders them interesting targets for the development of novel therapeutic interventions.[4] Although the biological activities of HSPGs have been largely attributed to the HS chains, there is increasing evidence that both the HS chain and the core protein can be important for directing the biological functions.[3a,5] Naturally existing HSPGs are highly heterogeneous mixtures, wherein a single core protein contains diverse HS structures. This diversity renders it extremely challenging to isolate HSPGs bearing a homogeneous HS chain, thus hindering a thorough understanding of the structure–function relationship. Chemical synthesis of HSPGs can reduce the structural heterogeneity and provide sufficient quantities for biological evaluations. Although much work has been done on the synthesis of HS[6,7] and the tetrasaccharide linker,[8] no synthetic methods are available to date for the preparation HSPGs. Herein, we report our studies on the synthesis of HS glycopeptides containing homogenous HS glycans.

We are interested in human syndecan-1, an important HSPG on the cell membrane.[4,9] Our synthetic target is the HS glycopeptide **1** from the extracellular domain of syndecan-1, which contains the binding sites for many receptors.[9d] The octasaccharide in **1** incorporates typical structural features of HSPGs, including the full tetrasaccharide linker, glucosamine (GlcN) linked α to both glucuronic acid (GlcA) and iduronic acid (IdoA), 2O sulfation, 6O sulfation, and N acetylation. Successful synthesis of this molecule will lay the groundwork for accessing other HS glycopeptides.

To prepare the octasaccharide of the glycopeptide **1**, our original strategy adapted a $2+5+1$ glycosylation approach, wherein the linkages between units B (GlcN) and C (IdoA), and units G and H were to be formed by coupling the disaccharide **2** with pentasaccharide **3** and the pentasaccharide donor **4** with xyloside serine derivative **5**, respectively.







Although the α-glycosyl linkage between GlcN and IdoA was formed stereospecifically using monosaccharide building blocks in our previous study,[10] the coupling between **2** and **3** failed to yield the desired heptasaccharide and donor decomposition products were isolated as the major side products. Varying the protective groups on **2** and **3** did not improve the situation. The failure was attributed to the reduced glycosylation power of these building blocks towards unreactive acceptors compared to their monosaccharide counterparts. This reduced reactivity was presumably a result of their larger sizes and the electron-withdrawing properties of the additional glycan units, which can reduce their reactivity towards acceptors.[11] In addition to the difficulty encountered in the $2+5$ coupling, the $5+1$ glycosylation of the pentasaccharide donor **4** with the xyloside serine acceptor **5** was also not productive. These setbacks led us to consider a new $3+2+3$ synthetic route wherein the difficult linkages between B and C, as well as G and H were to be formed earlier in the synthesis.

The $3+2+3$ strategy called for the preparation of the ABC trisaccharide **7**, DE disaccharide **8**, and FGH trisac-

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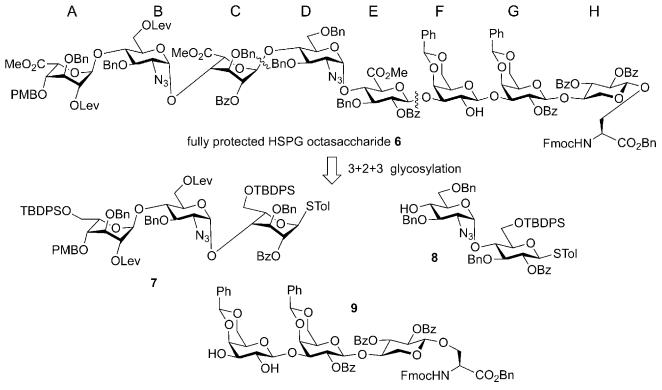
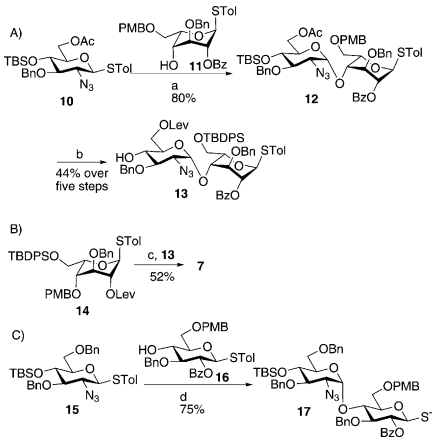


Figure 1. Retrosynthetic analysis of octasaccharide amino ester **6**. Bn = benzyl, Bz = benzoyl, Fmoc = 9-fluorenylmethoxycarbonyl, Lev = levulinoyl, PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, STol = thiotolyl.

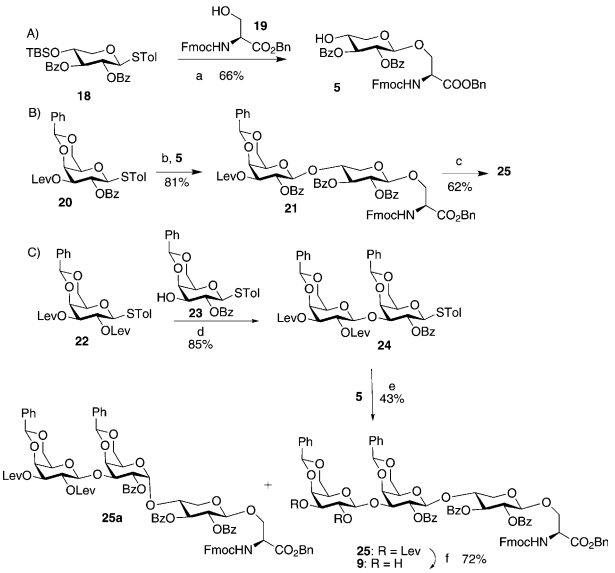
charide **9** (Figure 1). The synthesis of **7** started from the coupling of the donor **10** with acceptor **11** using the preactivation protocol[12] with the promoter system of *p*-TolSCl/AgOTf.[13] This procedure afforded the α-linked BC disaccharide **12** in 80% yield with complete stereoselectivity (Scheme 1A). All the preactivation-based glycosylation reactions were performed with a slight excess (1.1 equiv) of the glycosyl donor compared to the acceptor. Previously, when the PMB group was used to mask the 6O-position of the glycosyl donors, the electron-rich PMB moiety participated in the reaction by forming a 1,6-anhydro sugar, thus shutting down the desired glycosylation.[10] To avoid this side reaction, the PMB group in **12** was replaced by a TBDPS group with subsequent deprotection/protection sequences, thus generating the disaccharide acceptor **13**. Coupling of the idosyl thioglycoside **14** with **13** produced the ABC trisaccharide **7** (Scheme 1B).

The middle DE disaccharide **8** was formed in 75% yield by reaction of the glucosamine donor **15** with glucoside acceptor **16** under the preactivation reaction conditions (Scheme 1C). Removal of the TBS moiety with subsequent exchange of PMB with TBDPS produced **8**.

With the ABC and DE modules in hand, we turned our attention to the preparation of the FGH trisaccharide acceptor **9**. The TBS-protected xyloside donor **18** reacted with **19** with subsequent TBS removal, thus leading to the acceptor **5** (Scheme 2A). The formation of the challenging GH linkage was then tested using the galactoside donor **20**, which successfully glycosylated **5** to give **21** in 81% yield (Scheme 2B). This result suggested that the difficulty in the glycosylation of **5** with the pentasaccharide **4** was indeed a result of the additional glycans on the pentasaccharide donor.



Scheme 1. Reagents and conditions: a) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **11**, TTBP, −78 °C-0 °C; b) 1. $Mg(OMe)_2$, CH_2Cl_2, −20 °C-0 °C; 2. LevOH, EDC-HCl, DMAP, CH_2Cl_2; 3. DDQ, CH_2Cl_2/H_2O (10:1); 4. HF/pyridine; 5. TBDPSCl, imidazole, CH_2Cl_2; c) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **13**, TTBP, −78 °C–0 °C; d) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **16**, TTBP, −78 °C-0 °C; e) 1. DDQ, CH_2Cl_2/H_2O (10:1); 2. HF/Pyridine; 3. TBDPSCl, imidazole, CH_2Cl_2. DMAP = 4-(dimethylamino)pyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, M.S. = molecular sieves, TBS = *tert*-butyldimethylsilyl, Tf = trifuoromethanesulfonyl, TTBP = 2,4,6-tri(*tert*-butyl)pyrimidine.

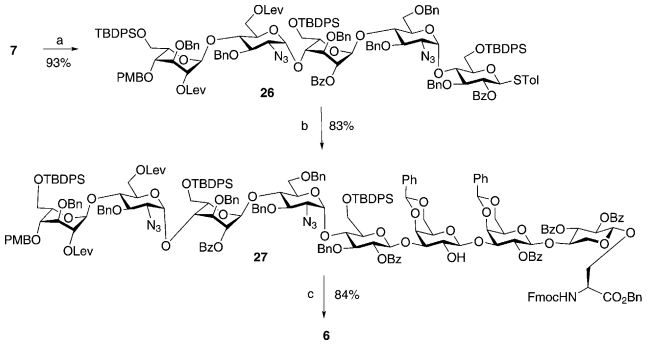


Scheme 2. Reagents and conditions: a) 1. AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **19**, TTBP, −78 °C–0 °C; 2. Tf_2O, THF, H_2O; b) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **5**, TTBP, −78 °C–0 °C; c) 1. AcOH, NH_2NH_2, CH_2Cl_2/MeOH (1:1); 2. **22**, AgOTf, *p*-TolSCl, 4 Å M.S., TTBP, −78 °C-0 °C; d) AgOTf, *p*-TolSCl, MS 4 Å, −78 °C, then **23**, TTBP, −78 °C–0 °C; e) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **5**, TTBP, −78 °C–0 °C; f) AcOH, NH_2NH_2, CH_2Cl_2/MeOH (1:1).

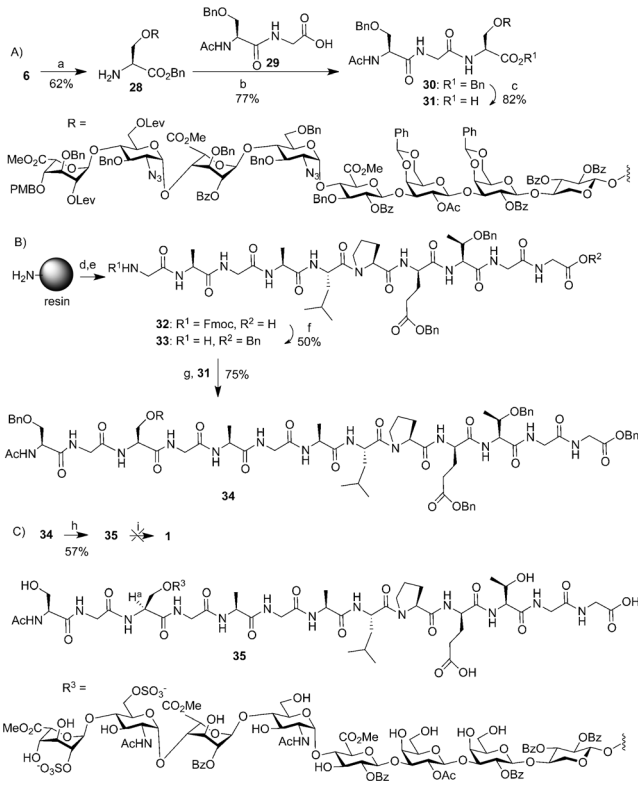
To prepare the trisaccharide **9**, the diLev-protected galactoside donor **22** glycosylated the acceptor **23**, thus forming the digalactoside **24** in 85% yield (Scheme 2C). Compound **24** was then subjected to reaction with **5**. The desired trisaccharide **25** was obtained in 43% yield in addition to the α-anomer **25a** (45%). We tested various glycosylation conditions (donor/acceptor ratio, solvent, temperature, etc.). However, none of these trials improved the stereoselectivity. Considering the high stereoselectivity in the formation of **21** and the disaccharide donor **24** bearing a 2O-Bz moiety (which can function as a participating neighbouring group) at the reducing end, the loss of stereoselectivity in reaction of **24**

with **5** was intriguing and the exact reason is unknown. Several other groups have reported the loss of 1,2-*trans* selectivities using 2O-acyl-protected galactosyl donors.[14] As an alternative, the Lev group in **21** was removed and the resulting acceptor was glycosylated with **22** to generate **25** in 62% yield (Scheme 2B). The two Lev groups in **25** were removed by hydrazine acetate to afford the FGH trisaccharide acceptor **9** (Scheme 2C).

Having prepared the three required modules, we investigated the union of these building blocks. The 3+2 coupling between **7** and **8** proceeded smoothly to produce the pentasaccharide **26** in an excellent 93% yield (Scheme 3). Subsequent 5+3 coupling between **26** and **9** gave the octasaccharide **27** in 83% yield, thus completing the oligosaccharide backbone of the glycopeptide. The octasaccharide **27** was treated with HF in pyridine to cleave the TBDPS protective groups and expose three primary hydroxy groups, which were oxidized[15] and subsequently converted into methyl esters[16] to afford the octasaccharide amino ester **6** for peptide chain elongation.



Scheme 3. Reagents and conditions: a) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **8**, TTBP, −78 °C–0 °C; b) AgOTf, *p*-TolSCl, 4 Å M.S., −78 °C, then **9**, TTBP, −78 °C–0 °C; c) 1. HF/pyridine; 2. TEMPO, BAIB, $CH_2Cl_2/H_2O/t$BuOH (4:1:4); 3. MeI, K_2CO_3, DMF. BAIB = [bis-(acetoxy)iodo]benzene, DMF = *N*,*N*′-dimethylformamide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyl-oxyl.



Scheme 4. Reagents and conditions: a) 1. Ac_2O, pyridine, 50 °C; 2. piperidine, CH_2Cl_2; b) HATU, DIPEA, DMF; c) Pd/C, H_2, NH_4OAc, CH_2Cl_2/MeOH (1:1); d) multiple rounds of automated solid phase peptide synthesis; e) TFA/H_2O/Phenol/TIPS; f) 1. BnBr, DIPEA, DMF; 2. piperidine, DMF; g) HATU, DMF; h) 1. Zn, $CuSO_4$ (sat.), Ac_2O/THF/HOAc; 2. NH_2NH_2-H_2O, HOAc, CH_2Cl_2/MeOH (1:1); 3. SO_3-Et_3N, DMF, 55 °C; 4. H_2, Pd/C, CH_2Cl_2/MeOH (1:1); i) base-catalyzed hydrolysis. DIPEA = diisopropylethylamine, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TFA = trifluoroacetic acid, TIPS = triisopropylsilane, THF = tetrahydrofuran.

To avoid the undesired reaction at the 2-OH group of unit F in **6** during O sulfation, we protected the 2-OH with an acetyl (Ac) group, with subsequent treatment with piperidine to expose the amino group (**28**; Scheme 4A). The free amine **28** was then subject to coupling with the dipeptide **29** to afford the glycopeptide **30**. Selective hydrogenation of **30** in the presence of NH_4OAc[17] generated the free carboxylic acid **31** without affecting the benzyl ethers in the molecule.

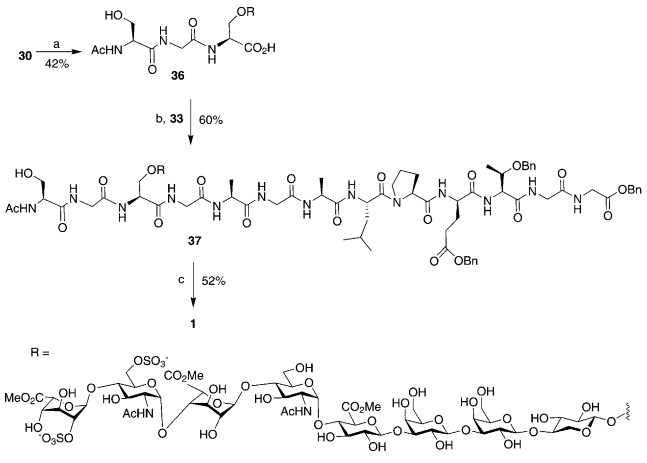
Parallel to oligosaccharide synthesis, solid-phase peptide synthesis was performed to prepare the C-terminal peptide **33** (Scheme 4B). As the final product will contain acid sensitive O sulfates, the traditional peptide deprotection promoted by a strong acid needs to be avoided. Given this consideration, the side chains of glutamic acid and threonine were protected as the benzyl ester and benzyl ether, respectively. The peptide was prepared on chlorotrityl resin and cleaved from the solid phase by acid treatment (TFA/H_2O/Phenol/TIPS). The free carboxylic acid terminal was subsequently protected as the benzyl ester and the N-terminal Fmoc was removed to generate the decapeptide **33** with a free amino terminal. Coupling of the octasaccharide carboxylic acid **31** with **33** without any base additive[18] successfully produced the glycopeptide **34** in 75% yield. It was important to omit the base during this step to avoid the β elimination of the glycan chain from the peptide backbone.

To accomplish the deprotection of the fully protected glycopeptide **34**, the right reaction sequence is critical. Despite the fact that simultaneous hydrogenolysis of the benzyl ethers and the azido groups in HS oligosaccharide synthesis were reported before,[7i,10,19] treatment of **34** under catalytic hydrogenation conditions led to a complex reaction mixture. To overcome this, we resorted to selective reduction of azide by zinc and copper sulfate with simultaneous acetylation of the newly liberated free amines (Scheme 4C).[20] The acetylated glycopeptides were then subjected to selective removal of the Lev groups by hydrazine acetate with subsequent O sulfation of the free hydroxy groups and hydrogenation, thus producing glycopeptide **35**. Although hydrolysis of the acetate and benzoate esters was the only step remaining to the final glycopeptides, it proved to be extremely

challenging. We investigated a variety of reagents including LiOOH, NaOH, and LiOH with pH values ranging from 8 to 11. Unfortunately, with pH values around 8.5, Bz could not be removed while at higher pH values, we observed a significant degree of β-elimination of the glycan, which is a common problem in glycopeptide synthesis.[21]

The failure to deprotect **35** prompted us to redesign our deprotection sequence. Since β-elimination is presumably caused by deprotonation of the α proton of the glycosylated serine (marked H^a in **35**), we envisioned that if the serine carboxylic acid is kept in its free form, its deprotonation should raise the pK_a value of the α proton on the neighboring carbon atom as a result of electrostatic repulsion, thus reducing the potential for β-elimination. Furthermore, Kihlberg and co-workers reported that partially deprotected glycopeptide was more stable against β-elimination compared to the fully protected form.[21] Thus, an alternative route was designed to first remove all the protecting groups on compound **30** except the three methyl esters, and to couple this partially deprotected glycopeptide to peptide **33**. The assembled glycopeptide could then be transformed into **1** by hydrogenation and mild base treatment since methyl esters are more sensitive to base hydrolysis. To test this, we converted **30** into its partially protected form **36** (azide reduction/acetylation, Lev removal, O sulfation, hydrogenation, and transesterification; Scheme 5). For the transesterification step, the pH was carefully maintained at 9.5 to minimize β-elimination while retaining the methyl esters by NaOMe treatment. All Ac and Bz groups were cleaved under these reaction conditions after 40 hours. With compound **36** in hand, we tested its coupling with the peptide **33**. It was shown that sulfates did not affect peptide coupling reactions.[18] Indeed, reaction of **36** with **33** produced the glycopeptide **37** in 60% yield. Subsequent hydrogenation and methyl ester hydrolysis afforded the final glycopeptide **1**.

In conclusion, we have established a strategy for the first synthesis of the highly complex structure of the syndecan-1 HS glycopeptide. The protective groups utilized and the sequences for glycosyl linkage formation and protective group removal are critical for the successful synthesis. We believe the approach established and knowledge gained can be applied to the synthesis of other HS glycopeptides. Work in this regard as well as investigation of the exciting biological functions of the prepared HSPG bearing homogenous HS glycans is currently ongoing.



Scheme 5. Reagents and conditions: a) 1. Zn, CuSO4 (sat.), Ac_2O/THF/HOAc (2:3:1); 2. NH2NH2-H2O, HOAc, CH_2Cl_2/MeOH (1:1); 3. SO_3-Et_3N, DMF, 55 °C; (4) H_2, Pd/C, CH_2Cl_2/MeOH (1:1); 5. NaOMe, MeOH, pH = 9.5; b) HATU, 2,4,6-collidine, DMF; c) 1. H_2, Pd/C, CH_2Cl_2/MeOH (1:1); 2. LiOH, CH_3OH/H_2O (1:1), pH = 9.5.

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Communications

Total Synthesis

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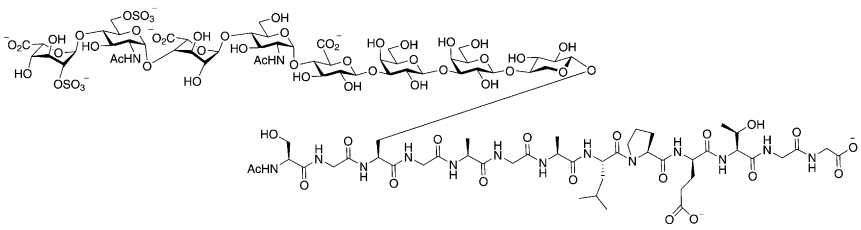
Chemical Synthesis of a Heparan Sulfate Glycopeptide: Syndecan-1



Finishing first: The highly complex structure of the title compound (see picture) was assembled. The protective groups utilized, as well as the sequences for formation of the glycosyl linkages and protecting group removal are critical to the success of the synthesis. This first preparation of a heparan sulfate glycopeptide lays the foundation for accessing other members of this class of molecules.