[Review Paper]

Facile Synthesis of Biofunctional Oligosaccharides of Chondroitin Sulfate

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Chondroitin sulfate (CS) is present in many animal tissues with various sulfation patterns and is important in biological events. Mechanisms of interaction between CS and signal proteins have been widely investigated to allow the chemical synthesis of CS oligosaccharides. Sophisticated synthetic approaches adopting *de novo* synthesis starting from the corresponding monosaccharide have mainly been performed. This strategy usually employs stepwise glycan elongation, protecting group manipulation, and regiospecific sulfate formation to systematically obtain different types of bioactive CS oligosaccharides. On the other hand, the semi-synthetic method via optimized hydrolysis of CS polymer was performed for obtaining repeating disaccharide as an alternative strategy. The disaccharide unit obtained was again manipulated to form the desired CS oligosaccharides equipped with sulfates at specific positions. In addition, chemical reconstruction including regiospecific sulfate formation of natural CS and CS-like polysaccharides has recently been explored. This review overviews the synthetic approaches to obtain biofunctional CS oligosaccharides emphasizing these aspects.

Keywords

Chondroitin sulfate, Oligosaccharide, Polysaccharide, Carbohydrate, Synthesis

1. Introduction

Coal and crude oil, the so-called fossil fuels, have many very beneficial uses as energy and chemical resources, the main components of which are hydrocarbons. For example, many pharmaceuticals are made of oil derivatives. Biologically active molecules contain hetero atoms such as oxygen, sulfur, and phosphorus, which are minor components in coal and crude oil, but are indispensable for biological functions. Glycans (oligomers or polymers of carbohydrates) have recently been identified as “the third chain of life” after nucleic acids and proteins. Carbohydrates have functions as energy carriers and structure-forming molecules, but recent findings have demonstrated that glycans also regulate many activities in organisms as signaling molecules¹⁾. For example, antithrombin-binding heparin pentasaccharide inhibits blood coagulation²⁾. Consequently, interest is increasing for oligo- and polysaccharides for medical uses. Functional oligosaccharides are available from natural sources, but the quality of natural products is not always consistent. In contrast, chemical synthesis of oligosaccharides by stepwise elongation of the corresponding monosaccharides (*de novo* synthesis) provides controlled quality, although multiple steps are needed to obtain the desired com-

pound. Alternatively, specific oligosaccharides are available via the optimized degradation of natural polysaccharides³⁾.

Most connective tissues in animals, such as cartilage, contain an extracellular matrix based on hyaluronan, collagen, and proteoglycans. Chondroitin sulfate (CS) is one type of glycosaminoglycan, which is the glycan part of proteoglycans. CS is only found in animal tissues. Natural CS is mainly formed of a linear polysaccharide consisting of the repeating disaccharide unit -3) β GalNAc(1-4) β GlcA(1- (GalNAc, *N*-acetylgalactosamine; GlcA, glucuronic acid), which are regiospecifically sulfated and exhibit various biological activities at the oligosaccharide level. CS can be classified into several subtypes based on sulfation patterns, such as CS-A or CS-C (**Fig. 1**). Sulfation patterns are species- and tissue-specific⁴⁾, and dynamically change with growth and proliferation⁵⁾. Therefore, naturally occurring CS polysaccharides contain randomly sulfated oligosaccharides as biofunctional domains.

2. Naturally Occurring CS, Specifically Sulfated Polysaccharides

We previously isolated CS from 9 species of fish and 3 of squid, and established the amount and sulfation patterns⁴⁾. Fish tissues predominantly contained CS-A and CS-C. Many fish contain a few hundred milligrams of CS per 100 g of dry defatted tissue. The dor-

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Fig. 1 Structural Diversity of Chondroitin Sulfates with Various Sulfation Patterns

sal fin of the yellowfin sole (*Limanda aspera*) contains more than 1300 mg of CS per 100 g of dry defatted tissue, whereas other flatfish, such as the flathead flounder (*Hippoglossoides dubius*), contain less than 200 mg. Squid (*Thysanoteuthis rhombus*) contains a larger amount of CS (*ca.* 350 mg per 100 g of dry defatted tissue) in the skin than that in the mantle (2 mg per 100 g of dry defatted tissue)⁶⁾. The CS in all tissues of several species of squid is characteristically composed of the CS-E-type $\sim 20\%$, in contrast to other animals⁴⁾. Sharks generally contain large amounts of CS and are commercially used as a CS resource. We previously demonstrated that the blue shark (*Prionace glauca*) and the shortfin mako shark (*Isurus oxyrinchus*) contained more than 1800 mg of CS per 100 g of dry defatted tissue in their fins, whereas the dusky shark (*Carcharhinus obscurus*), smooth hammerhead (*Sphyrna zygaena*), and scalloped hammerhead (*Sphyrna lewini*) did not⁷⁾. These findings indicated that CS is universally synthesized in every animal, but in quantities that markedly differ among species, and is also localized in different tissues. CS is utilized in health supplements as well as pharmaceuticals, but the quality is not always consistent due to the randomly arranged disaccharide units that covalently bind to each other linearly with different types of sulfation patterns. Therefore, equivalent sulfation degree and sulfation pattern are difficult to achieve in CS polymers.

3. Chemical Reconstruction of CS Oligo- and Polysaccharides

Extensive efforts have been made to clarify the exact structure of the functional domains of CS oligosaccha-

rides related to various bioactivities^{8)~11)}. Three approaches have been employed to synthesize CS oligosaccharides: CS polymers as a precursor for repeating disaccharides and the reconstruction of building blocks, stepwise elongation starting from appropriate monosaccharides (*de novo* synthesis), and chemical modifications to natural CS and CS-like polymers. These synthetic efforts are described here in detail.

3. 1. Natural CS Polysaccharides as Building Block Precursors

Natural CS consists of a repeating disaccharide, GlcA-GalNAc, in which sulfates are randomly formed. The first correct disaccharide structure of the CS repeating disaccharide obtained by acid hydrolysis was reported as β GlcA-GalNAc in 1951¹²⁾. Three years later, CS was hydrolyzed with 1 N sulfuric acid to give β GlcA-GalNH₂ in 67 % yield¹³⁾.

In 2006, Jacquinet and Lopin-Bon reported the synthesis of a CS-C tetrasaccharide utilizing β GlcA-GalNAc, a repeating disaccharide obtained via the hydrolysis of a natural CS polysaccharide as a precursor unit³⁾. Optimized hydrolysis conditions can transfer all the heterogeneous sulfates at random positions into free hydroxyl groups. The disaccharide with appropriate protecting groups was converted to the suitably protected disaccharide donor as the trichloroacetimidate (**1**) and the acceptor (**2**) for glycan elongation up to a hexasaccharide as shown in **Scheme 1**. Subsequent sulfate formation at the two primary positions afforded the CS-C tetrasaccharide³⁾. Stepwise elongation of the disaccharide unit **1** achieved the synthesis of biotinylated CS di-, tetra-, hexa-, and octasaccharides. In addition, the use of a GalNAc donor (**3**) for elongation synthesized the corresponding tri-, penta-, and heptasaccharides¹⁴⁾.

Reaction conditions: a) 0.5 M H_2SO_4 , 100 °C, 6 h, then 0.02 M HCl/MeOH , 0 °C, 4 d.; b) $\text{TCACl}/\text{pyridine}$, 0 °C, 52 % from polymer; c) PhCHO , TFA , 1 d; then $\text{Ac}_2\text{O}/\text{pyridine}$, 16 h, 68 %; d) 75 % $\text{TFA}/\text{CH}_2\text{Cl}_2$, 0 °C, 4 h, then $\text{Ac}_2\text{O}/\text{pyridine}$, 16 h, 80 %; e) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}/\text{DMF}$, 30 min, then CCH_3CN , $\text{DBU}/\text{CH}_2\text{Cl}_2$, 30 min, 60 %; f) 2-naphtylmethanol, $\text{BF}_3 \cdot \text{OEt}_2/\text{CH}_2\text{Cl}_2$, -60 to -20 °C, 3 h, 87 %; g) NaOMe/MeOH , then 2-methoxypropane, CSA/DMF , 2 h, 65 %; h) LevOH , N,N' -dicyclohexylcarbodiimide, 4-dimethylaminopyridine/ CH_2Cl_2 , 1 h, 90 %; i) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone/ CH_2Cl_2 - MeOH , 1 d, then CCH_3CN , $\text{DBU}/\text{CH}_2\text{Cl}_2$, 30 min, 66 %; j) $\text{HO}(\text{CH}_2)_2\text{NHZ}$, $\text{TMSOTf}/\text{CH}_2\text{Cl}_2$, 30 min, 54 %; k) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}/\text{pyridine}$, 8 min, 89 %; l) Bu_3SnH , AIBN/PhH , dimethylacetamide, 80 °C, 4 h; m) LiOH , $\text{H}_2\text{O}_2/\text{THF}$, -10 °C to rt, 16 h, then 4 M NaOH/MeOH , 4 h.; n) H_2 , $\text{Pd-C}/\text{H}_2\text{O}$, 20 h.

Abbreviations: TCA, $\text{CCl}_3\text{C}(=\text{O})-$; Ac, $\text{MeC}(=\text{O})-$; Lev, $\text{MeC}(=\text{O})(\text{CH}_2)_2\text{C}(=\text{O})-$; Ph, C_6H_5- ; Z, $\text{PhCH}_2\text{OC}(=\text{O})-$; TMSOTf , $\text{Me}_3\text{SiOSO}_2\text{CF}_3$; DMF, N,N -dimethylformamide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; CSA, camphorsulfonic acid; TFA, CF_3COOH ; AIBN, azoisobutyronitrile.

Scheme 1 Reconstruction of CS Oligosaccharides Based on $\beta\text{GlcA-GalNTCA}$ from Natural CS via Optimized Hydrolysis^{3),14)}

The common disaccharide (4) was obtained by adopting the same strategy and converted into various types of CS oligosaccharides with free reducing terminals: disaccharides of CS-D, -E, -K, -L, and -M; tetrasaccharides of CS-A, -C, -E, -D, -K, and -L; and hexasaccharides of CS-A, -C, and -E (Scheme 2)^{15),16)}. Synthesis of biotinylated CS-OA and -OC tetrasaccharides equipped with heterogeneous sulfates was also recently reported¹⁷⁾.

3. 2. Stepwise Elongation for the Synthesis of CS Oligosaccharides

Jacquinet's group has been using the glucosaminyl donor as the trichloroacetamide (NTCA), which showed good β -selectivity in glycosylation steps and was easily converted to the corresponding acetamide by tributylstannan (Bu_3SnH) and azobisisobutyronitrile (AIBN). The stereochemistry of glucosyl C-4 was inverted into the galactosyl configuration. The first example is depicted in Scheme 3¹⁸⁾. Synthesis of CS-A and -C pentasaccharides was initially reported in 2000¹⁹⁾. Two

years later, CS-D tetra- and hexasaccharides were made using the $\beta\text{GlcA-GalNTCA}$ -type disaccharide as a repeating unit. The stereochemistry of C-4 was already inverted at the disaccharide level. The trichloroacetamide at C-2 exerted a good neighboring group effect, even in glycan elongation²⁰⁾.

Synthesis of $\text{GlcA-GalNAc4,6-diS}$ and the dimer was reported in 2004²¹⁾. Suitably protected GlcA and GalNTCA were coupled to give a β -linked disaccharide, which was converted into the corresponding disaccharide donor and acceptor, and then coupled together to give the β -linked tetrasaccharide. Subsequent sulfate formation and deprotection procedures afforded the desired CS-E tetrasaccharide. CS-E tetrasaccharide had positive effects on the outgrowth of hippocampal neurons, whereas the corresponding tetrasaccharide with no sulfate and CS-E disaccharide did not exert this effect²¹⁾.

Our group synthesized a CS-A tetrasaccharide (20) in 1995²²⁾, and we reported the systematic synthesis of

Reaction conditions: a) 0.5 M H_2SO_4 , 100 °C, 6 h, then 0.02 M HCl /MeOH, 0 °C, 4 d.; b) TCACl /pyridine, 0 °C, 52 % from polymer; c) PhCHO , TFA, 1 d; then Ac_2O /pyridine, 16 h, 68 %; d) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}$ /DMF, 30 min, then CCH_3CN , $\text{DBU}/\text{CH}_2\text{Cl}_2$, 30 min, 60 %; e) 2-naphthylmethanol, $\text{BF}_3 \cdot \text{OEt}_2/\text{CH}_2\text{Cl}_2$, -60 to -20 °C, 3 h, 79 %; f) NaOMe/MeOH , then 2-methoxypropane, CSA/DMF , 2 h, 65 %; g) LevOH , DCC , $\text{DMAP}/\text{CH}_2\text{Cl}_2$, 1 h, 92 %. Abbreviations: NAP, 2-naphthylmethyl; Bz, $\text{PhC}(=\text{O})$ -.

Scheme 2 Synthesis of CS Oligosaccharides with Sulfates at Specific Positions^{15),16)}

Reaction conditions: a) *N*-iodosuccinimide, TMSOTf , molecular sieves 4A/ CH_2Cl_2 , 0 °C, 15 min, 90 %; b) thiourea/pyridine-EtOH, 80 °C, 1.5 h, 92 %; c) 75 % AcOH , 100 °C, 30 min; then $\text{PhC}(=\text{O})\text{CN}$ /pyridine, 20 h, 90 % (2 steps); d) Tf_2O /pyridine, -15 °C, 1 h; then $\text{Bu}_4\text{N}^+\text{NO}_2^-/\text{DMF}$, 15 h, 87 %; e) Bu_3SnH , AIBN/PhH -dimethylacetamide, 80 °C, 92 %; f) $\text{SO}_3 \cdot \text{NMe}_3/\text{DMF}$, 65 °C, 24 h; then ion-exchange resin (Na^+)/EtOAc-MeOH- H_2O , 93 %; g) $\text{NaOH}/\text{aq. MeOH}$, 6 h, 87 %.

Scheme 3 *De novo* Synthesis of CS-A Trisaccharide¹⁸⁾

CS-O, -A, -C, and -E as di-, tri-, and tetrasaccharides (**11-22**) in 1998²³⁾. The effective synthesis of CS-E hexa- and octasaccharides (**23**, **24**) was achieved in 2004 (**Fig. 2**)^{24),25)}.

These syntheses used the GalNAc-GlcA-type disaccharide as a building block, which was different from other groups. Our strategy has three advantages, as shown in **Scheme 4**.

The first advantage is complete β -selectivity in the first glycosylation step, Gal (**25**) + GlcA (**26**). Perfect β -selectivity in the coupling reaction to **27** was enabled although the azide group did not exert a neighboring group effect at the C-2 of the galactosyl donor. In this

reaction, the trichloroacetimidoyl group at the anomeric position needs to be in the α -orientation. In contrast, β -imidate afforded an almost equal mixture of α - and β -glycosides. This finding suggested that the $\text{S}_{\text{N}}2$ reaction occurred in the case of α -imidate, whereas the more reactive β -imidate may use the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}1$ and 2 reactions. Although the protecting groups on the galactose residue slightly affected the coupling yield and stereoselectivity, we ultimately identified the optimum reaction conditions as “low temperature in CH_2Cl_2 with α -imidate at high concentration”²⁵⁾.

The second advantage is perfect stereocontrol in the elongation step (**28** + **29**). The GlcA residue at the

Fig. 2 Systematically Synthesized CS Oligosaccharides^{22)~25)}

reducing end of the glycosyl donor carries the *p*-methylbenzoyl (MBz) group at *O*-2, which exerts a neighboring group effect in the glycosylation procedure. Furthermore, the positive charge of the carbocation generated after removal of the leaving group at the anomeric position may be delocalized in the MBz group.

The third advantage is that the auxiliary of the NAC group at the non-reducing terminal of the acceptor (**29**) enabled higher coupling yields by forming interglycosidic imidate (**30**)²⁵⁾. Compound **30** may separate into two disaccharides at closed positions and the acceptor part may attack the carbocation from the β -face to give a tetrasaccharide (**31**). We achieved gram-scale synthesis of the CS hexasaccharide (**23**) with effective coupling yields. Synthesized CS-E hexasaccharide exerted positive effects in the treatment of arthritis²⁶⁾.

We synthesized biotinylated CS tetrasaccharides with the sulfation patterns OO, AA, CC, DD, and EE. Some of these synthetic probes have affinity for midkine or the antibodies 2H6 and LY111. CS-EE exhibited the highest affinity for midkine among the tetrasaccharides synthesized. 2H6 and LY111 are antibodies for CS-A, but also recognize CS-DD^{27),28)}.

3.3. Chemical Modification of CS Polysaccharide

Extensive efforts enabled the synthesis of sulfate/nonsulfate of CS polysaccharides, as described previously²⁹⁾. In 2011, Bedini and his co-workers developed a procedure to obtain CS polysaccharides derived from *Escherichia coli* O5:K4:H4 with the same structure as the repeating disaccharide region of CS, -3) β GalNAc(1-4) β GlcA(1-. The capsular polysaccharide from *E. coli* is not a real CS, but the glycan structure is the same as the real CS repeating polysaccharide. This CS-like polysaccharide is also named CS in this

review. This polysaccharide has no sulfate, but has a fructose branch at *O*-3 of GlcA that may be removed by mild hydrolysis. The polysaccharide was modified via benzylidenation at *O*-4,6, acetylation at *O*-2,3, oxidative cleavage of benzylidene acetal, and subsequent conversion to sulfate at 4- or 6-position to obtain CS monosulfate (4S, 40 %; 6S, 47 %)³⁰⁾. Higher regioselective conversion to sulfate was achieved on the CS polymer: CS-C (6S) and -E (4,6-diS) were obtained at 0 °C and 50 °C in 71 % and 90 % yield, respectively. Triphenylmethylation at *O*-6 on the CS polymer, and subsequent conversion to sulfate gave CS-A (4S, 60 %). The synthesis of trisulfated CS was also described in 2012³¹⁾. Chemical synthesis of E-type rich (52.2 %) CS was also achieved using natural CS-A consisting of 21.2 % and 78.8 % of CS-C (6S) and -A (4S), respectively, from bovine trachea³²⁾.

4. Conclusion

The characteristic bioactivities of CS are mainly derived from sulfates at specific positions. This review examined facile synthetic approaches to obtain CS oligosaccharides with different sulfation patterns by adopting sophisticated *de novo* synthesis and semi-synthetic methods as well as reconstruction of natural CS. The use of synthetic CS oligosaccharides has clarified the biological mechanisms; slight positional change of the sulfate groups on CS exhibited dramatic differences in the biological activities on the oligosaccharide level. The differences in affinity between biotinylated CS-O, -A, -C, -D, and -E tetrasaccharides and midkine or antibodies clearly illustrate the bioactivities of CS oligosaccharide. We also demonstrated that chemically

Reaction conditions: a) H_2 , Lindlar cat. AcOH/EtOAc ; then Ac_2O , 91 %; b) $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6/\text{aq. MeCN}$; then CCl_3CN , $\text{DBU/CH}_2\text{Cl}_2$, 89 % (2 steps); c) $\text{H}_2\text{NNH}_2 \cdot \text{AcOH/EtOAc-toluene}$, quant. Abbreviation: MBz, $p\text{-MeC}_6\text{H}_4\text{C}(=\text{O})\text{-}$.

Scheme 4 Synthetic Pathway of CS Tetrasaccharide²⁵⁾

synthesized CS-E hexasaccharide exerted positive effects in the treatment of arthritis. Historically, glycosaminoglycans and proteoglycans have been named “mucopolysaccharides” and used as medicines. Biofunctional CS oligosaccharides, one of the components of these glycoconjugates, may become a “Glycomedicine” in the future.

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要 旨

生化学機能を持つコンドロイチン硫酸オリゴ糖の精密化学合成

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コンドロイチン硫酸 (CS) は多くの動物組織に存在し、糖鎖の特定の水酸基がさまざまに硫酸化されている。これらの硫酸基と CS のもつ特異的な生化学的現象が深く関連していることが近年急速に解明されつつある。その詳細な機構を明らかにするために、化学的に再構築されたオリゴ糖を用いることは上策である。本稿では系統的な CS オリゴ糖合成法として、単糖からオリゴ糖に糖鎖を逐次的に組み上げる *de novo synthesis* や、

天然 CS 多糖を酸加水分解して得た繰返し二糖単位を CS オリゴ糖に再構築する *semi-synthetic method* について概観する。一方、天然に存在する CS はそれ自体が資源として有益であるが、これらに化学的な操作を行うことでも生化学的に効果のある CS 多糖やオリゴ糖として再生成することができる。これら CS オリゴ糖合成にかかる最近の進歩についても述べる。