Synthesis of L-Hexopyranosyl Fluorides Enabled by Radical Decarboxylative Fluorination: Assembly of a Pentasaccharide Repeating Unit Corresponding to Extracellular Polysaccharide S-88

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Abstract

L-Hexoses are key components of many biologically relevant natural products and pharmaceuticals. As rare sugars, L-hexoses are not readily obtained from natural sources. Access to L-hexose building blocks from commercially available and inexpensive D-sugars is highly desirable from the viewpoints of organic synthesis and drug discovery. As demonstrated by the convenient preparation of L-glucosyl, L-galactosyl, and L-mannosyl fluorides from readily available β-D-C-glucosyl, β-D-C-mannosyl, and β-D-C-galactosyl derivatives, we describe a novel and efficient approach to the demanding L-glycosyl fluorides. The transformation features the installation of anomeric hydroxymethyl group under mild conditions and head-to-tail inversion of sugar rings through radical decarboxylative fluorination of uronic acids. The power of this protocol is highlighted by the first assembly of a pentasaccharide repeating unit of Pseudomonas ATCC 31554 extracellular polysaccharide (S-88). This synthesis relies on the efficient extension of sugar chain at the sterically hindered hydroxy group and the facile introduction of L-mannosyl unit using L-mannosyl fluoride as glycosylating agent. The methods developed in this work would provide new tools to the arsenal of synthesis of L-sugar building blocks and of assembly of glycans containing L-sugar moieties.

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Synthesis of L-Hexopyranosyl Fluorides Enabled by Radical Decarboxylative Fluorination: Assembly of a Pentasaccharide Repeating Unit Corresponding to Extracellular Polysaccharide S-88

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Keywords

L-Glycosyl fluorides | Extracellular Polysaccharide S-88 | Radical decarboxylation | Oligosaccharide synthesis | Uronic acids

Comprehensive Summary

L-Hexoses are key components of many biologically relevant natural products and pharmaceuticals. As rare sugars, L-hexos

Background and Originality Content

L-Hexoses are essential components of glycans and glycoconjugates of biological relevance.[1] They are also valuable building blocks of certain therapeutic applications. For instance, L-glucose tracers that emit fluorescence show potential in identifying and characterizing cancerous cells among such cell aggregates;[2] Additionally, a recent study has proposed 3,6-anhydro-L-galactose (AHG) as a novel anticariogenic agent due to its higher inhibitory activity against *Streptococcus mutans* than commonly used xylitol.[3]Furthermore, agarobiose and agarooligosaccharides-containing AHG have also demonstrated anticariogenic activity.[4] It is worth noting that L-hexoses are considered rare sugars, which are not able to be obtained from natural sources on a scale. As a result, to meet the demand for L-sugars, numerous strategies have been designed and developed to substantially access to such architectures.[5] They include C-5 configuration inversion of readily available D-sugars,[6]site-selective epimerization of L-sugars,[7]one-carbon homologation of pentoses,[8]head-to-tail inversion,[9] *de novo*synthesis,[10] and C-H functionalization of 6-deoxy-L-hexoses.[12] According to "sugar mapping",[13] L-glucose, L-galactose, and L-mannose are good precursors to the other L-sugars. We thereby envisaged that ready preparation of L-glucose, L-galactose, and L-mannose would be an ideal route to access L-sugars by use of biomass-derived and inexpensive D-sugars (D-glucose, D-mannose, and D-galactose) and L-sugars (L-rhamnose and L-fucose). In this context, Li and co-workers have described a methodology for the conversion of D-glucosyl acetate into orthogonally protected L-glucosyl acetate following a head-to-tail inversion.[9] The transformation features one-carbon extension of sugar chain at the anomeric position through $Co_2(CO)_8$-catalyzed silyloxymethylation and head-to-tail inversion by use of $Pb(OAc)_4$-mediated decarboxylative acetoxylation. The prepared L-glucosyl acetate was converted into L-galactosyl or L-mannosyl acetate by epimerizing the C4- or the C2-OH. Additionally, the same strategy was applied by Li and colleagues (Scheme 1a) to synthesize L-glucose and L-mannose derivatives starting from 1-methyl-(β-D-*C* -glucosyl)ethanone and 1-methyl-2-(β-D-*C* -galactosyl)ethanone constructs.[9] Due to the limited reactivity exhibited by glycosyl acetates, it is inevitable to covert L-glycosyl acetates into more reactive glycosyl donors, such as glycosyl imidates, thioglycosides, and glycosyl fluorides. A significant breakthrough was achieved by the Pedersen group (Scheme 1b) utilizing the methodology developed by Hartwig and co-workers to prepare 1,3-diol through iridium-catalyzed C-H activation directed by a hydroxy group.[11] They successfully accomplished the transformation of L-rhamnose and L-fucose into L-mannose and L-galactose, respectively.[12] Furthermore, the same group extended this strategy to achieve synthesis of all eight L-hexopyranosyl thioglycoside donors from their corresponding 6-deoxy-L-hexopyranosyl thioglycosides.[7]Recently, we have successfully recorded a head-to-tail switch strategy that enables the convenient synthesis of uncommon 6-deoxy-D-/L-heptopyranosyl fluorides. In this method, allyl α-D-*C* -glycosides are employed as the starting materials. This approach is noteworthy as it represents one of the limited options available for generating L-sugar settings, which can be directly utilized as glycosyl donors (Scheme 1c).[14-17]The remarkable characteristics of the transformation encompass two-carbon elongation of a sugar chain at the anomeric position, along with shortening of a one-carbon segment through either radical decarboxylative fluorination[14] of uronic acids or radical dehydroxymethylative fluorination[15]of sugar primary alcohols. We employed these methodologies for the assembly of *Camplybater jejuni* strain CG8486[16] and BH0142[17]capsular hexasaccharides composed of -3)-β-D-6d*ido* Hep*p* -(1-4)-β-D-Glc*p* NAc-(1- and -3)-α-D-6d*ido* Hep*p* -(1-4)-α-D-Gal*p* -(1- disaccharide repeating units. These oligosaccharides have the potential to serve as antigens against *C. jejuni* infections.

Drawing inspiration from the aforementioned advancements and acknowledging the biological relevance of glycans containing L-sugar units, this study presents the synthesis of L-glucosyl, L-galactosyl, and L-mannosyl fluorides utilizing a head-to-tail switch strategy (Scheme 1d). Our hypothesis is that the desired L-glycosyl fluorides can be obtained by means of radical decarboxylative fluorination of hydroxymethyl β-D-*C* -uronic acid derivatives.[14] The introduction of anomeric hydroxymethyl group can be achieved by reduction of the corresponding aldehydes. These aldehydes can be prepared from 1-phenyl-2-(β-D-*C* -glycosyl)ethanones, which can be easily derived from the condensation of diphenyl 1,3-pentandione with cost-effective and readily available D-glucose, D-galactose, and D-mannose.[18]

Scheme 1 Strategies for the synthesis of L-sugars

Results and Discussion

Synthesis of L-glucopyranosyl fluoride and L-galactosyl fluorides

In order to implement the concept, our study commenced with preparing L-glucopyranosyl fluoride from the acetyl-protected 1-phenyl-2-(β-D-*C* -glucosyl)ethanone**1a** [18] (Scheme 2). Initially, we attempted to convert **1a** to olefin **2a** by means of the procedure which was reported by the Prasad group.[19] However, **1a** was subjected to reduction with $NaBH_4$ followed by P_2O_5-mediated dehydration of the alcohol in CH_2Cl_2 at room temperature, resulting in a 36% yield of olefin **2a** . The unsatisfactory yield and the difficulty in separating **2a** from a viscous and dark reaction mixture prompted us to seek a more convenient approach to **2a** . Fortunately, treatment of **1a** with $NaBH_4$followed by triflic anhydride in the presence of 2,6-lutidine at -40°C in CH_2Cl_2[20] yielded the desired vinyl *C* -glycoside **2a** in 75% yield. The dehydration reaction occurred through triflation of the hydroxy group and simultaneous elimination of the reactive triflate. It should be noted that the Liang group recently disclosed a novel approach to*C* -vinyl glycosides through a Heck-type coupling reaction of glycosyl bromide with styrenes under visible light and palladium dual catalysis, providing a new way to the constructs like**2a** .[21] With olefin **2a** in hand, we successfully made benzyl (Bn)-protected β-D-glucopyranosyl methanol**3a** in 52% overall yield through a four-step reaction sequence composed of deacetylation, the benzylation of resultant alcohol, the oxidative cleavage of C-C double bond, and the reduction of liberated aldehyde. Conversion of **3a** into uronic acid **5a** was achieved in 79% yield through a four-step reaction sequence consisting of the benzoyl protection of primary hydroxy group in **3a**(leading to **4a**), the chemoselective acetolysis of the benzyl ether of primary hydroxy group, selective

Scheme 2 Synthesis of L-glucopyranosyl fluoride and L-galactopyranosyl fluoride

Reagents and conditions: (a) $NaBH_4$, MeOH, ice bath; (b) 2,6-lutidine, Tf_2O, CH_2Cl_2, 75% for **2a** over two steps, 82% for **2b** over two steps; (c) 60% NaH, MeOH; (d) BnBr, 60% NaH, DMF; (e) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane/H_2O; (f) $NaBH_4$, MeOH, 52% for **3a** over four steps, 59% for **3b** over four steps; (g) BzCl, DMAP, pyridine; (h) TFA, Ac_2O; (i) AcCl, MeOH (j) TEMPO, BAIB, CH_2Cl_2/H_2O, 79% for**5a** over four steps, 64% for **5b** over four steps; (k) Selectfluor, KF·$2H_2O$, Ag_2CO_3, acetone/H_2O, 62% for **6a** , 65% for **6b** . BnBr = Benzyl bromide; DMF =*N* ,*N* -dimethyl formamide; BzCl = Benzoyl chloride; DMAP = 4-*N* ,*N* -dimethylaminopyridine; TFA = Trifluoroacetic acid; AcCl = Acetyl chloride; TEMPO = 2,2,6,6-Tetramethylpiperidinooxy; BAIB = Iodobenzene diacetate.

deacetylation with methanolic hydrogen chloride, and the oxidation of the obtained alcohol with TEMPO/BAIB. Uronic acid **5a** was subjected to Ag_2CO_3-mediated radical oxidatively decarboxylative fluorination[14] to afford 62% of the expected L-glucosyl fluoride **6a** as an α/β 1:1 mixture. Following the same procedure as above, the olefin**2b** , derived from 1-phenyl-2-(β-D-*C* -mannosyl)ethanone**1b** , was smoothly transformed into L-galactosyl fluoride**6b** with α/β 2.4:1 stereoseletivity in 23% overall yield over nine steps.

Assembly of a pentasaccharide repeating unit corresponding to extracellular polysaccharide S-88

Having achieved success in synthesizing L-glycosyl fluoride from the corresponding D-sugars, our focus now shifts towards the application of this method in the synthesis of intricate oligosaccharides obtained from*Pseudomonas* ATCC 31554 extracellular polysaccharide (S-88). S-88 is a representative gellan which shows potential in food, chemical, and pharmaceutical industries due to its functional characteristics.[22] Furthermore, recent discoveries have revealed the probiotic potential of gellan oligosaccharides derived from the hydrolysis of S-88, as they have the capability to modulate gut flora in a manner that promotes human health.[23] S-88 is composed of a pentasaccharide repeating unit made up of a backbone of -4)-α-L-mannopyranosyl (L-Man*p*)-(1-3)-β-D-glucopyranosyl (Glc*p*)-(1-4)-β-D-glucuronic acid (Glc*p* A)-(1-4)-β-D-Glc*p* -(1- and a branch of α-L-rhamnopyranosyl (Rha*p*) appended to C3-OH of D-Glc*p* at the reducing end.[24] The occurrence of L-Man*p* moiety and of D-Glc*p* A residue linked to the sterically hindered C4-OH of D-Glc*p* makes S-88 an attractive, but synthetically challenging target. The pursuit of comprehending the intricate structure and functionalities of S-88 has driven our motivation to engage in chemical syntheses of

S-88 oligosaccharides. Herein, we report the synthesis of a pentasaccharide fragment (**7**) corresponding to the repeating unit of extracellular polysaccharide S-88. The synthesis features the successful construction of challenging glycosidic linkage by which D-Glc*p* A is appended to D-Glc*p* and the efficient installation of L-mannosyl moiety with L-mannosyl fluoride as the glycosyl donor. L-mannosyl fluoride was prepared from D-galactose *via* a head-to-tail inversion strategy.

Highly efficient incorporation of uronic acid residues is crucial for assembly of oligosaccharides containing such units. Typically, two strategies are employed to accomplish this objective.[25] The first approach involves the postglycosylation oxidation strategy, wherein an oligosaccharide backbone is constructed before converting a sugar into its uronic acid form through oxidation. Despite additional protecting group manipulations required, the advantages of this approach lie in the higher reactivity of non-oxidized building blocks than the corresponding carboxylate counterparts, deceased side reactions associated with epimerization α to carboxylate, and β-elimination leading to the formation of 4-deoxy-hex-4-enopyranuronic acid.[26] The second is preglycosylation oxidation strategy, that is, directly using a uronic acid-based building block as glycosylating donor and acceptor. Its strength is to prevent oxidation event on a complex setting. However, the presence of carboxylate substituent imposes challenges to glycosylation reaction due to the withdrawing-electron effect of carboxylate resulting in decreased reactivity of the building blocks as glycosyl donor and acceptor.[27] Mindful of these considerations, we designed two retrosynthetic plans for the target pentasaccharide**7** . As depicted in Scheme 3, we envisioned that the target molecule **7** could be obtained from the fully protected pentasaccharide **8** by a global deprotection. Glycan **8**in turn was planned to assemble by glycosylation of L-mannopyranosyl fluoride **9** with tetrasaccharide either **10** or**11** . Compound **9** could be traced back to readily available 1-phenyl-2-(β-D-*C* -galactossyl) ethanone**12** [18]. Fluoride **9** is designed to possess a benzoyl at C2-OH to ensure the formation of 1,2-*trans*

Scheme 3 Retrosynthetic analysis of pentasaccharide fragment (**7**) of extracellular polysaccharide S-88

Scheme 4 Synthesis of L-mannosyl fluoride **9**

Reagents and conditions: (a) $NaBH_4$, MeOH, ice bath; (b) 2,6-lutidine, Tf_2O, CH_2Cl_2, 70% over two steps; (c) MeONa, MeOH; (d) $PhCH(OMe)_2$, CSA, 40°C, CH_3CN; (e) BnBr, KOH, 18-Crown-6, THF, 72% over three steps; (f) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane/H_2O; (g) $NaBH_4$, MeOH, 73% over two steps; (h) BzCl, DMAP, pyridine; (i)*p* -TsOH·H_2O, CH_2Cl_2/MeOH, 79% over two steps; (j) TBSCl, DMAP, pyridine; (k) BzCl, DMAP, pyridine; (l) 70% HF·pyridine, CH_3CN, 76% for three steps; (m) TEMPO, BAIB, CH_2Cl_2/H_2O, 93%; (n) Selectfluor, KF·2H_2O, Ag_2CO_3, acetone/H_2O, 88%. CSA = Camphorsulfonic acid; THF = Tetrahydrofuran; TBSCl =*tert* -Butyldimethylsilyl chloride.

glycosidic bonds through neighboring group participation. Given the strength and weakness of post- or preglycosylation oxidation strategy, tetrasaccharides either **10** or **11** embedded by GlcA*p* residue could be constructed by coupling reaction of disaccharide acceptor **13** with either uronic acid-based disaccharide donor **14** or the corresponding non-oxidized donors**15** . These disaccharides **13** , **14** , and**15** could be disconnected to D-glucosyl thioglycoside**16** and L-rhamnosyl trichloroacetimidate (TCAI) **17** . Glucosyl thioglycoside **16** was designed to allow for direct incorporation of rhamnosyl residue at C3-OH while 4,6-*O* -benzylidene would facilitate the incorporation of carboxylate group and the glycosylation of C4-OH by the hydrolysis of acetal functionality and subsequent differentiation between the primary alcohol and the secondary one. The presence of 2-*O* -benzoyl (Bz) substituent in **16** could enable anchimerically assisted glycosylation leading to β-glucosidic linkage formation. The incorporation of a spacer 6-amino-hexanoxyl at the reducing end would provide feasibility for conjugation of **7** with biomolecules such as carrier protein. Orthogonal levulinoyl (Lev) group on the disaccharide fragment either **14** or **15** allows for its chemoselective removal and ensuing glycosylation at that site.

Our synthesis began with the preparation of rare L-mannosyl fluoride**9** following a head-to-tail switch strategy (Scheme 4). Similar to the synthesis of **6a** and **6b** , *C* -galactoside**12** was converted to vinyl *C* -glycoside **18** in 70% yield over two steps. To differentiate the 4-OH and the 6-OH from the 2,3-diol for late-stage equipment of benzoyl group at the C4-OH and the formation of carboxylic acid, **18** was converted into**19** in

72% yield over three steps involving deacetylation, the benzylidene protection of 4,6-diol, and the benzylation of 2,3-diol. The oxidative cleavage of C-C double bond in **19** followed by the reduction of aldehyde group led to the introduction of hydroxymethyl at the anomeric position, providing 73% of **20** over two steps. Benzoyl protection of **20** coupled with hydrolysis of benzylidene produced diol **21** in 79% overall yield. Selective benzoyl protection of C4-OH was smoothly realized leading to **22** in 76% overall yield through TBS protection of the primary hydroxy group, the benzoylation of the remaining secondary hydroxy group, and the cleavage of TBS ether with hydrogen fluoride-pyridine complex. Uronic acid**23** , prepared by oxidation of **22** in 93% yield, was exposed to Ag_2CO_3-mediated decarboxylative fluorination to give rise to the required α-L-mannosyl fluoride **9** in 88% yield as the sole product.

Having successfully prepared the L-mannosyl fluoride **9** , we turned to constructing the tetrasaccharide **10** . To this end, disaccharide acceptor **13** was first made. As shown in Scheme 5a,

Scheme 5 Synthesis of disaccharide acceptor **13** as well as donors **14** and **28**

Reagents and conditions: (a) TMSOTf, -40 °C, CH_2Cl_2, 4 Å MS, 87%; (b) Et_3SiH, TFA, 5 Å MS, CH_2Cl_2, 91%, (c) $HO(CH_2)_6N_3$, NIS, AgOTf, 4 Å MS, -20 °C, CH_2Cl_2, 70%; (d) $BF_3{\cdot}Et_2O$, -40 °C, CH_2Cl_2, 4 Å MS, 77%; (e) TCCA, H_2O, ice bath, acetone; (f) *o* -hexynylbenzoic acid, DCC, DMAP, THF, 70% over two steps. TMSOTf = Trimethylsilyl trifluoromethanesulfonate; MS = Molecular sieve; NIS =*N* -Iodosuccimide; AgOTf = Silver triflate; TCCA = Trichloroisocyanuric acid; DCC = Dicyclohexylcarbodiimide; *n* -Bu =*n* -butyl.

Glucose-derived alcohol **16** [27] was glycosylated with Bz-masked L-rhamnosyl TCAI**17** [28]. The coupling reaction proceeded smoothly and delivered the desired disaccharide **24** in 81% yield in CH_2Cl_2 at -40°C under the catalysis of 0.1 equiv of TMSOTf. Reductive ring- opening of the benzylidene in **24** with TFA and Et_3SiH in the presence of 5 Å molecular sieves resulted in the formation of **25** with C4'-OH free in 91% yield. Reactivity-based chemoselective glycosylation of 6-azido-1-hexanol[29] with **25** produced disaccharide glycoside **13** in 70% yield under the combined promotion of NIS and AgOTf. The reaction left C4'-OH intact, which is ready for sugar chain elongation at this site.

With **13** in hand, the application of preglycosylation oxidation strategy was first explored in construction of tetrasaccharide**10** . We therefore embarked on the preparation of uronic acid-based disaccharide **14** . As outlined in Scheme 5b, $BF_3{\cdot}Et_2O$-catalyzed glycosylation of**26** [30] with**27** [31] supplied 77% of disaccharide**14** in CH_2Cl_2 in the presence of 4 Å MS. At this stage, the coupling reaction of **14** and**13** was explored. As tabulated in Table 1, we were disappointed to find that the reaction under the promotion of NIS with either TfOH or Lewis acids such as AgOTf and TBSOTf supplied the desired tetrasaccharide **10** in the best yield up to 23% (Table 1, entries 1–5). Gold-catalyzed glycosylation of challenging nucleophiles with glycosyl *ortho* -alkynylbenzoate donors has

Table 1 Optimization of glycosylation reactions of acceptor**13** with donor **14** or**28**

Entry	Donor	Promoters (equiv)	Solvent	T (°C)	Yield (%)
1	**14**	TfOH (0.2)/NIS (2.5)	PhMe	-78 to -40	16
2	**14**	TfOH (0.2)/NIS (2.5)	$CHCl_3$	-40	trace
3	**14**	TfOH (0.2)/NIS (2.5)	DCE	-40	trace
4	**14**	AgOTf (0.4)/NIS (2.5)	PhMe	0	10
5	**14**	TBSOTf (0.4)/NIS (2.5)	PhMe	0	23
6	**28**	$(PhO)_3PAuCl$ (0.75)/AgOTf (0.75)	PhCl	0	37
7	**28**	$(PhO)_3PAuCl$ (0.3)/AgOTf (0.3)	PhCl	-20	30
8	**28**	$(PhO)_3PAuCl$ (0.3)/$AgNTf_2$ (0.3)	PhCl	0	21
9	**28**	Ph_3PAuCl (0.3)/AgOTf (0.3)	PhCl	0	13

TfOH = Trifluoromethanoic acid; DCE = 1,2-Dichloroethane; TBSOTf =*tert* - Butyldimethylsilyl trifluo-

rmethansulfonate; $AgNTf_2$ = Sliver bis(trifluoromethane sulfonimide); T = temperature.

proven to be a powerful tool for constructing structurally complex molecules.[32] Encouraged by these advances and in order to improve the preparation efficacy of tetrasaccharide**10** , we converted thioglycoside **14** into glycosyl*ortho* -hexnylbenzoate (OABz) donor **28** in 70% yield through a two-step reaction sequence involving TCCA-mediate hydrolysis of thioglycoside and subsequent DCC-promoted esterification of the resultant hemiacetal with *ortho* -hexynylbenzoic acid (Scheme 5b). The impact of various factors, including gold salts, silver salts, and reaction temperature, was scrutinized on the outcome of glycosylation of**28** with **13** . It was found that the reaction gave

Scheme 6 Synthesis of pentasaccharide **7**

Reagents and conditions: (a) *p* -TsOH·H_2O, 40 °C, CH_2Cl_2/MeOH; (b) TBSCl, DMAP, pyridine, 89% over two steps; (c) **26** , BF_3·Et_2O, -40 °C, CH_2Cl_2, 4 Å MS, 77%; (d) **13** , NIS, TBSOTf, 0 °C, PhMe, AW-300 MS, 65%; (e) 70% HF·pyridine, pyridine, 93%; (f) TEMPO, BAIB, CH_3CN/H_2O; (g) MeI, $NaHCO_3$, DMF, 89% over two steps; (h) NH_2·NH_2·H_2O (5.0 equiv), AcOH (10.0 equiv), CH_2Cl_2, 97%; (i)**9** , Cp_2ZrCl_2, AgOTf, -20 °C, $PhCF_3$, 4 Å MS, 90%; (j) LiOH·H_2O, 30% H_2O_2, THF/H_2O, 92%; (k) 10% Pd/C, H_2, 1 M HCl, THF/*i* -PrOH/H_2O, 74%. Cp_2ZrCl_2 = Bis(pentamethylcyclopentadienyl) zirconium dichloride.

tetrasaccharide **10** in the best yield of 37% under the promotion of 0.75 equiv of $(PhO)_3PAuOTf$, *in situ*generated from equal molar units of $(PhO)_3PAuCl$ and AgOTf. We attributed the unsatisfactory outcome mentioned above to the low reactivity of uronic acid-based donors and weak nucleophilicity of the C4'-OH due to steric hinderance resulting from the presence of the adjacent 3'-*O* -L-rhaminosyl residue.

Basing on the observations of the Huang group that increasing the reactivity of glycosyl donors favors the glycosylation of glycosyl acceptors with weak nucleophilicity,[33] we moved our focus to the construction of tetrasaccharide **11** following a postglycosylation oxidation strategy. For this purpose, glucopyranosyl thioglycoside acceptor **30** was made from**29** [34] through hydrolysis of benzylidene and regioselective TBS protection of the resulting primary hydroxy group. Then thioglycoside **30** was subjected to glycosylation with glucosyl TCAI donor **26** . Under the catalysis of BF_3·Et_2O the reaction worked well and afforded the expected disaccharide **15** in 77% yield.

With disaccharides **15** and **13** in hand, glycosylation between them was executed (Scheme 6). To our delight, the reaction efficiently proceeded and provided the desired tetrasaccharide**11** in 65% yield when slowly adding a solution of **15**to a flask charged with **13** , 2.5 equiv of NIS, and 0.2 equiv of TBSOTf in toluene at 0 °C. The transformation of**11** into the uronic acid-embedded counterpart **31** was uneventfully achieved by the removal of TBS masking group, the oxidation of primary hydroxy group, and methylation of the resulting carboxylic acid. The orthogonal cleavage of Lev group with hydrazine acetate furnished alcohol **32** that is ready for mannosylation *via*the formation of α-glycosidic linkage.

After obtaining tetrasaccharide **32** and L-mannosyl fluoride**9** , we proceeded to synthesize the desired pentasaccharide**7** . (Scheme 6). Tetrasaccharide **32** was mannosylated with glycosyl fluoride **9** under the action of 1.2 equiv of Cp_2ZrCl_2 and 2.4 equiv of AgOTf to afford the fully protected pentasaccharide **8** in a high yield of 90%. It should be noted that the coupling could also promoted with $(C_6F_5)_3B$·$(H_2O)_n$as the initiator.[35] However, the reaction required 0.6 equiv of $(C_6F_5)_3B$·$(H_2O)_n$and pentasaccharide **8** was obtained in 59% yield in $PhCF_3$ in the presence of 4 Å MS.

With **8** successfully prepared, its deprotection was performed. Pentasaccharide **8** was treated with LiOH·H_2O in the presence of H_2O_2 in a mixed solvent of H_2O and THF, resulting in concomitant hydrolysis of one methyl ester and five benzoates to afford hexol **S7** in 92% yield (see the Supporting Information). Then, exposure of the hexol**S7** to 1 atmosphere of dihydrogen in the presence of palladium over charcoal and 1 M HCl resulted in hydrogenolysis of one benzylidene and benzyl ethers as well as hydrogenation of azido substituent, uneventfully affording the desired the target pentasaccharide **7**in 74% yield.

Conclusions

We have developed an efficient protocol for synthesis of rare L-glycosyl fluorides using a head-to-tail inversion strategy. L-glucosyl/galactosyl/mannosyl fluorides were successfully prepared with readily available 1-phenyl-2-(β-D-*C* -glucosyl, mannosyl, and galactosyl)ethanone as the starting materials. The transformation involves installing the anomeric hydroxymethyl group and switching the sugar ring in a head-to-tail manner through radical oxidative decarboxylative fluorination of uronic acids. To demonstrate the practical application of our protocol, we successfully assembled the pentasaccharide repeating unit of extracellular polysaccharide S-88 for the first time. The synthesis is characterized by sugar chain extension at a sterically hindered hydroxy group and the incorporation of a L-mannosyl residue with L-mannosyl fluoride as the glycosylating agent. Considering the challenges associated with accessing biologically important oligosaccharides and glycoconjugates that contain L-sugar residue(s), our work offers an additional tool for the synthesis of these constructs.

Experimental

Experimental procedures and characterization data are available in Supporting Information.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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A novel and efficient approach has been established for the synthesis of demanding L-glycosyl fluorides. This approach is ex