Available online at www.sciencedirect.com
ScienceDirect
Chinese Journal of Natural Medicines 2022, **20**(5): 387-392
doi: 10.1016/S1875-5364(22)60149-3
Chinese Journal of Natural Medicines

•Research article•

Chemical synthesis of a synthetically useful L-galactosaminuronic acid building block

QIN Chun-Jun[1], HOU Hong-Li[1], DING Mei-Ru[1], QI Yi-Kuan[1], TIAN Guang-Zong[1], ZOU Xiao-Peng[1], FU Jun-Jie[1], HU Jing[2], YIN Jian[1*]

[1] *Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, School of Biotechnology, Jiangnan University, Wuxi 214122, China ;*
[2] *Wuxi School of Medicine, Jiangnan University, Wuxi 214122, China*

Available online 20 May, 2022

[ABSTRACT] Most bacterial cell surface glycans are structurally unique, and have been considered as ideal target molecules for the developments of detection and diagnosis techniques, as well as vaccines. Chemical synthesis has been a promising approach to prepare well-defined oligosaccharides, facilitating the structure-activity relationship exploration and biomedical applications of bacterial glycans. L-Galactosaminuronic acid is a rare sugar that has been only found in cell surface glycans of gram-negative bacteria. Here, an orthogonally protected L-galactosaminuronic acid building block was designed and chemically synthesized. A synthetic strategy based on glycal addition and TEMPO/BAIB-mediated C6 oxidation served well for the transformation of commercial L-galactose to the corresponding L-galactosaminuronic acid. Notably, the C6 oxidation of the allyl glycoside was more efficient than that of the selenoglycoside. In addition, a balance between the formation of allyl glycoside and the recovery of selenoglycoside was essential to improve efficiency of the NIS/TfOH-catalyzed allylation. This synthetically useful L-galactosaminuronic acid building block will provide a basis for the syntheses of complex bacterial glycans.

[KEY WORDS] L-galactosaminuronic acid; Chemical synthesis; Orthogonal protection; Glycal addition; C6 oxidation
[CLC Number] R284 **[Document code]** A **[Article ID]** 2095-6975(2022)05-0387-06

Introduction

Cells are generally coated by a carbohydrate layer, such as *N*-glycans, *O*-glycans and glycosaminoglycans in mammalian cells, lipopolysaccharides (LPS) and capsular polysaccharides (CPS) in bacterial cells. Compared with the mammalian cell surface glycans, bacterial cell surface glycans are structurally more diverse as reflected in the monosaccharide composition and modification [1]. Structurally unique bacterial glycans act as a barrier between the cell wall and the environment, structural components of biofilms, and is essential for host-pathogen interactions [2]. Thus, bacterial glycans have been widely used in the development of vaccines against bacterial infectious diseases. Currently, carbohydrate-based vaccines against *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Salmonella typhi* and *Haemophilus influenzae* are protecting people worldwide [3]. To improve the medical application of bacterial cell surface glycans, an important natural product resource, it is necessary to explore their structure-activity relationship. Since degradation of isolated glycans usually produces structurally heterogeneous fragments, chemical synthesis is a more effective approach to prepare structurally well-defined and pure oligosaccharides [4-10], facilitating the structure-activity relationship exploration [11-14].

Various deoxyaminosugars, the most important structural characteristic of bacterial glycans, have been considered as potential active sites and attractive synthesis targets [1]. In nature, L-galactosaminuronic acid has been only found in cell surface glycans of some gram-negative pathogenic bacteria, such as *Pseudomonas aeruginosa* O3 and O10 *O*-antigens [15], *Arenibacter palladensis* KMM 3961^T *O*-antigen [16], *Vibrio vulnificus* YJ016 [17] and CECT 5198 *O*-antigens [18], and

[Received on] 24-Nov.-2021
[Research funding] This work was supported by the National Natural Science Foundation of China (Nos. 22077052, 21877052, 21907039), the China Postdoctoral Science Foundation (2020M681487), the National Key R&D Program of China (2020YFA0908304), the Natural Science Foundation of Jiangsu Province (BK20180030, BK20190575), the National First-class Discipline Program of Light Industry Technology and Engineering (LITE2018-14), the 111 Project (111-2-06), the Open Project of Key Laboratory of Carbohydrate Chemistry and Biotechnology (Jiangnan University), Ministry of Education (KLCCB-KF202005), the Natural Science Foundation of Xuzhou (KC19154).
[*Corresponding author] Tel: +86 0510-85328229, E-mail: jianyin@jiangnan.edu.cn
These authors have no conflict of interest to declare.

Pseudoalteromonas haloplanktis ATCC 14393 *O*-antigen [19] (Fig. 1). Notably, all the reported L-galactosaminuronic acids exist in natural glycans in an *α*-configuration. This rare and specific aminouronic acid is thought to play roles in pathogen colonization and infection, as well as modulating host immune response. Yokota *et al*. had evaluated the immunological activity of isolated *P. aeruginosa* LPSs, and found that *N*-acetyl-L-galactosaminuronic acid was an epitope common to the serotypes A and H (Homma) *O*-polysaccharides recognized by a protective human monoclonal antibody [20]. Nevertheless, a comprehensive understanding of the biological roles of glycans containing L-galactosaminuronic acid still needs access to rationally designed synthetic fragments and derivatives.

The synthetically useful L-galactosaminuronic acid building block is essential for the construction of complex bacterial glycans and their derivatives. Although intense efforts have been devoted for the synthesis of amino-L-sugars [21-27], chemical synthesis of L-galactosaminuronic acid has not yet been reported. Syntheses of other aminosugars and glycuronic acids have taught valuable lessons for the preparation of synthetically useful L-galactosaminuronic acid building block. Nucleophilic substitution and glycal addition are two widely used methods for introducing amino groups into sugar rings. Nucleophilic substitution can be used to install amino or azido group at each position of the sugar ring accompanied by inversion of configuration [27-29]. Glycal addition is specific to installation of an azido group at C2 of the peracetylated glycal with a sugar type-dependent stereoselectivity [26, 27]. Azido group, the most frequently used precursor and protecting group of amino group, is stable under acidic, basic and oxidation conditions and can be efficiently reduced using various methods [30]. Due to the non-participation nature, azido group has been employed to improve the outcomes of glycosylation reactions, such as C2 azido group in glycosyl donors can enhance the construction of 1,2-cis-2-amino *α*-glycosidic bonds, C3 azido group in glycosyl donors can avoid an intramolecular cyclization side reaction [27]. In addition, the C4 hydroxyl group of a 2-azidoglycosyl acceptor was more nucleophilic than that of 2-aminosugars bearing other amino-protecting groups [31]. Glycuronic acids can be prepared from neutral sugars by the 2,2,6,6-tetramethyl-1-piperidinyloxyl, free radical (TEMPO)-mediated oxidation which has regioselective specificity towards primary hydroxyl groups [27, 32].

The most suitable starting material for the synthesis of rare L-galactosaminuronic acid is the commercially available L-galactose, which can be obtained from natural sources (seaweeds [33] or flaxseed [34]), from D-galactose *via* 1-*O*-protected L-galactitol [35, 36], from L-xylose *via* 1-deoxy-1-nitro-L-galactitol [35], from D-mannose *via* oxidative decarboxylation of intermediate heptanoic acid [37], from non-sugar compounds such as quebrachitol [38], furfural [39], 2-butene-1,4-diol [40], or L-ascorbic acid [41]. Here, we report a study on the chemical synthesis of an orthogonally protected L-galactosaminuronic acid building block, which will be helpful for the assembly of complex glycans.

Result and Discussion

Retrosynthetic analysis

The L-galactosaminuronic acid hemiacetal **1** was designed as an orthogonally protected building block, and can be easily converted to the corresponding glycosyl donor, such as imidate [42], thioglycoside, *o*-alkynylbenzoate [5, 43] and 2-(2-propylsulfinyl)benzyl glycoside [44, 45] (Fig. 2). Since all the reported L-galactosaminuronic acids exist in nature in an *α*-configuration, an azido group was chosen as precursor of the C2 amino group to enhance the *α*-selectivity of glycosylation reactions. On the other hand, the azido group can be easily transformed to an acyl-protected amino group to facilitate the *β*-glycosylation. The C3 and C4 hydroxyl groups were protected by 2-naphthylmethyl ether (Nap) and levulinoyl ester (Lev), respectively, allowing the orthogonal deprotection for regioselective glycosylation. The C6 carboxylic acid group

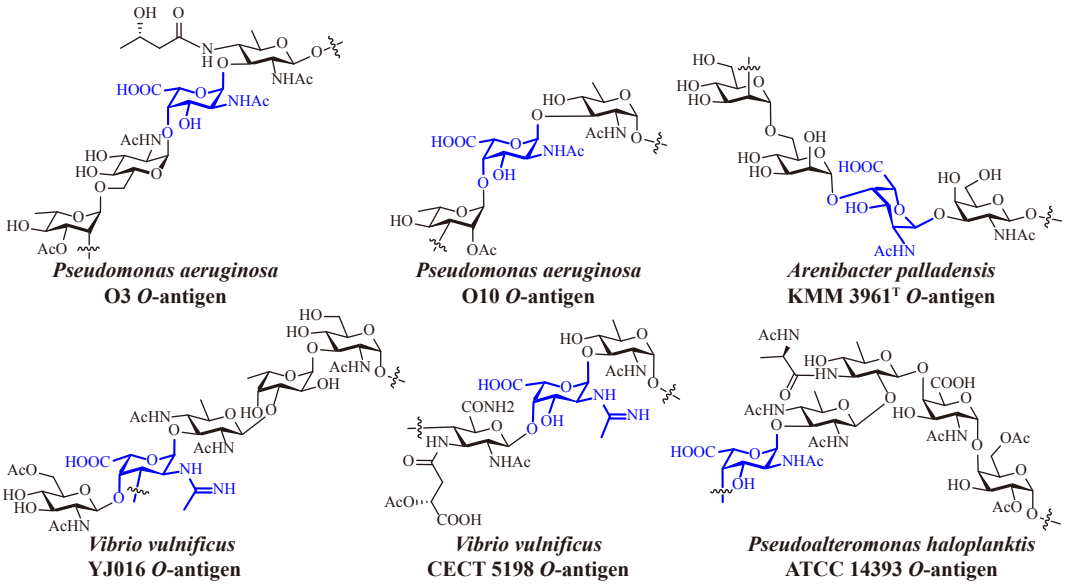


Fig. 1 Representative structures of bacterial glycans containing L-galactosaminuronic acid

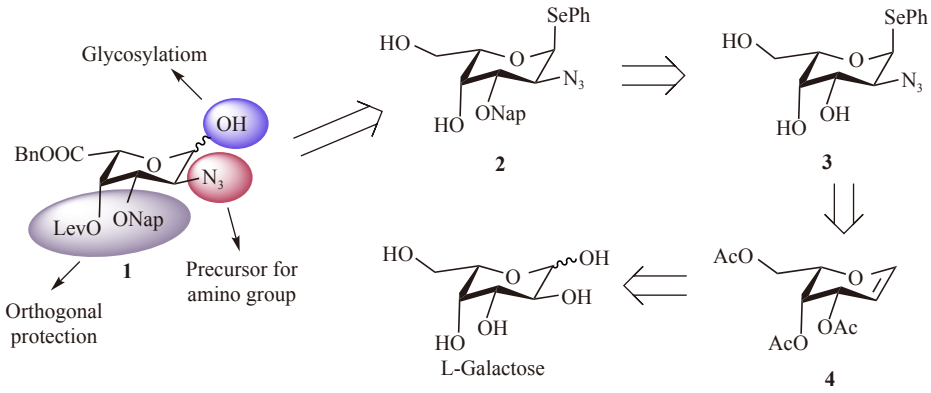


Fig. 2 Retrosynthetic analysis of L-galactosaminuronic acid building block 1

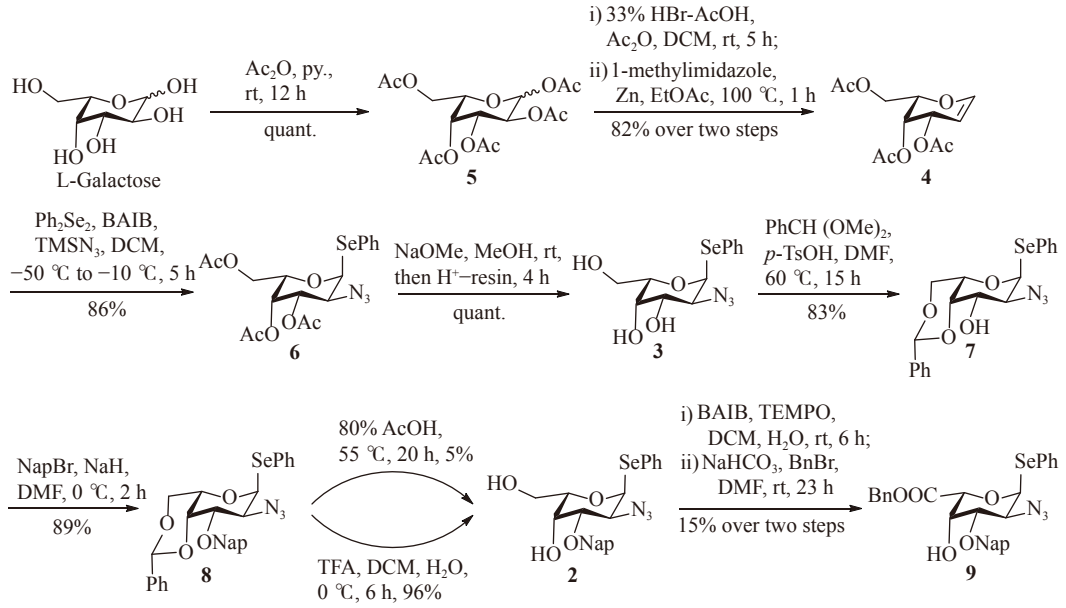
was protected using benzyl (Bn) group, which can be efficiently removed by alkaline hydrolysis or Pd/C hydrogenation. The L-galactosaminuronic acid **1** can be obtained from L-galactosamine **3** through regioselective protection/deprotection and C6 oxidation. Azidoselenation was employed to produce **3** from L-galactal **4**, which in turn can be obtained from commercial L-galactose.

Attempt to prepare L-galactosaminuronate 9

Peracetylation of L-galactose quantitatively produced compound **5** [37], which was converted to L-galactal **4** [46] through a bromination of anomeric position and subsequent zinc-mediated elimination reaction in 82% overall yield (Scheme 1). The diphenyl diselenide (Ph_2Se_2)/trimethylsilyl azide ($TMSN_3$)-mediated azidoselenation of **4** gave C2 azide sugar **6** [46] in 86% yield without any detectable stereoisomer. After deacetylation, the triol **3** was protected by 4,6-*O*-benzylidene to produce compound **7** in 83% overall yield. Alcohol **7** was treated with 2-naphthylmethyl bromide (NapBr) and sodium hydride at room temperature to afford 3-*O*-Nap derivative **8** in 89% yield. Treatment of **8** with 80% acetic acid aqueous solution at 55 °C, a generally employed method, failed to efficiently remove the 4,6-*O*-benzylidene protecting group. The removal of 4,6-*O*-benzylidene was achieved by using trifluoroacetic acid at room temperature in 96% yield, indicating that the acidic stability of 4,6-*O*-benzylidene in L-galactose is higher than that in other sugar types. TEMPO/[bis-(acetoxy)-iodo]benzene (BAIB)-mediated selective oxidation of the C6 hydroxyl group in compound **2**, and subsequent benzyl esterification of the thus-formed carboxylic acid furnished **9** in only 15% overall yield. The low yield of oxidation reaction mainly resulted from a decomposition of the selenoglycoside **2**. Although TEMPO/BAIB-mediated oxidation has proved to be useful for the selective oxidation of C6 hydroxyl group in thio- and selenoglycosides, the only two cases of C6 oxidation of selenoglycosides with this method gave corresponding selenoglycuronic acids merely in moderate yields [47, 48]. It was indicated that the selenoglycoside **2** may not be a suitable precursor for the preparation of L-galactosaminuronic acid. To address this challenge, it was decided to change the anomeric protecting group of the L-galactosamine intermediate.

Synthesis of allyl glycoside 10

The allyl group, a mildly and selectively removable anomeric protecting group, was employed to replace the selen-



Scheme 1 Attempt to prepare L-galactosaminuronate 9

ophenyl group due to its higher oxidative stability. Considering the compound **6** was the most abundant intermediate in our hand, this selenoglycoside was used as a glycosyl donor to react with allyl alcohol (AllOH). To enhance the stereoselectivity of allylation, the *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH)-promoted glycosylation was performed in MeCN, a *β*-selectivity-enhancing solvent [49]. According to the reported glycosylations with phenyl selenoglycosides [50], the compound **6** and AllOH (10 equiv) were treated with 0.25 equiv of TfOH and 5 equiv of NIS at −35 °C. After 3.5 hours of reaction, selenoglycoside **6** was completely consumed and converted to desired allyl glycoside **10** in only 36% yield (Table 1, entry 1). Considering the thioglycosides are generally activated by 1−3 equiv of NIS [51-54], it was speculated that the low yield of glycosylation might be due to the excess of NIS (5 equiv). A glycosylation with an increased ratio of AllOH (20 equiv) and a decreased ratio of NIS (1.2 equiv) furnished product **10** in 31% yield, alongside recovering donor **6** (48%) after 27 hours of reaction (entry 2). Notably, the yield of allyl glycoside **10** based on recovered **6** was 60%, which was significantly higher than that of the previous trial. This result indicated that the addition ratio of NIS was essential for the outcome of this glycosylation. Further study of condition optimization suggested that the most appropriate addition ratio of NIS might be higher than 1.2 equiv to promote the conversion of compound **6**. In addition, the allyl glycoside was obtained with exclusive *β*-selectivity, which may be greatly attributed to the solvent effect of MeCN. While the addition of NIS was increased up to 2.5 equiv, no significant increase in the production of **10** can be detected by TLC after 6 hours of reaction. Although product **10** was obtained in a higher yield (53%), the yield based on recovered **6** was only slightly increased due to the lower recovery rate of **6** (22%) (entry 3). The increase in the addition ratio of NIS (3 equiv) and the prolongation of the reaction time (10 and 12 hours) failed to further improve the yield of **10** (entries 4, 5).

Since the 3 equiv seems to be an appropriate addition ratio of NIS, an optimization of the addition ratio of TfOH may be useful for improving the productivity. After 12 hours of reaction, a glycosylation promoted by 0.3 equiv of TfOH and 3 equiv of NIS afforded product **10** in 58% yield and in 76% yield based on recovered **6** (24%) (entry 6). These results suggested that the conversion of the selenoglycoside **6** under NIS/TfOH-promoted glycosylation may have reached its ultimate limit, and maximizing the recovery of **6** is the key to improving the efficiency of this reaction. It was found that shortening reaction time to 8 hours efficiently improved the recovery rate of **6** (44%) (entry 7). Finally, the target allyl glycoside **10** can be stereoselectively produced in 54% yield and in 96% yield based on recovered selenoglycoside **6**.

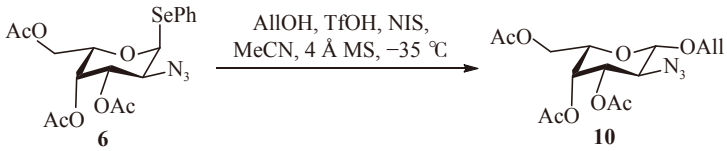
Synthesis of L-galactosaminuronic acid building block 1

The synthesis of L-galactosaminuronic acid building block **1** commenced with quantitative removal of the acetyl groups in **10** under Zemplén condition to obtain **11** (Scheme 2). Treatment of triol **11** with benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid (*p*-TsOH) at 60 °C afforded 4,6-*O*-benzylidene protected compound **12** in 86% yield. Installation of *O*3-Nap and subsequent removal of the 4,6-*O*-benzylidene group furnished **14** in 84% overall yield. TEMPO/BAIB-mediated oxidation of the C6 hydroxyl group in diol **14**, and subsequent benzyl esterification of the corresponding carboxylic acid proceeded smoothly to give L-galactosaminuronate **15** in 65% overall yield. The C4 hydroxyl group in **15** was further protected by levulinoyl (Lev) group [55] to afford **16** in 97% yield. The allyl glycoside **16** was treated with SeO_2 and AcOH in 1,4-dioxane under reflux to produce the target L-galactosaminuronic acid building block **1** in 81% yield.

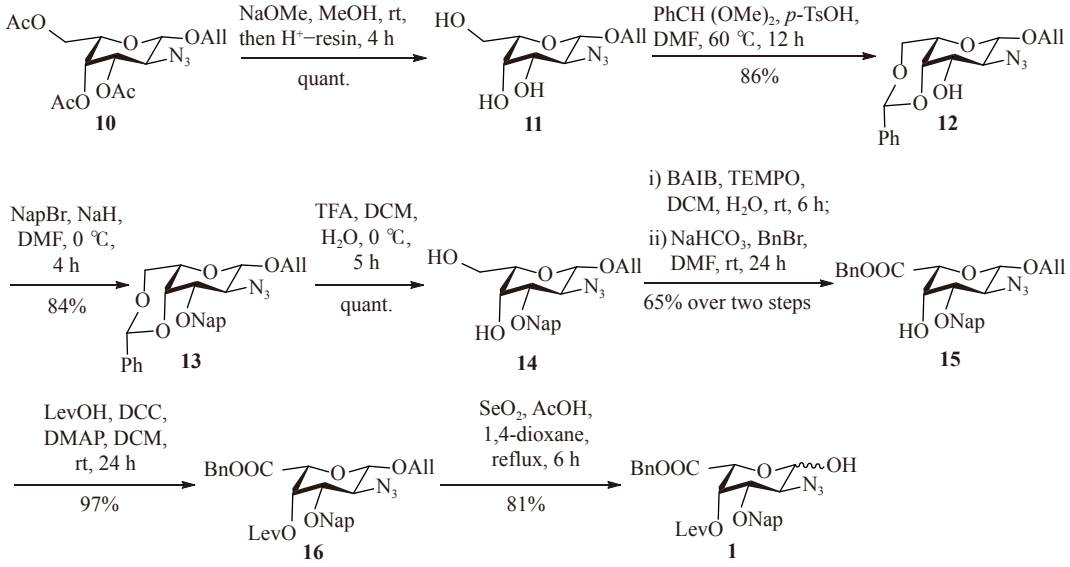
Conclusion

Chemical synthesis of an orthogonally protected L-galactosaminuronic acid building block **1** was achieved. Glycal addition served well for the transformation of commercial L-galactose to the corresponding L-galactosamine. The L-galactosaminuronic acid was successfully obtained from 4,6-diol derivative with TEMPO/BAIB-mediated regioselective oxidation. Notably, the C6 oxidation of the allyl glycoside **14** was more efficient than that of the selenoglycoside **2** bearing the same protecting groups. The NIS/TfOH-catalyzed glycosylation of selenoglycoside **6** with AllOH in MeCN, a *β*-selectivity-enhancing solvent, afforded allyl glyc-

Table 1 Stereoselective allylation of selenoglycoside 6



Entry	AllOH/equiv	TfOH/ equiv	NIS/equiv	*t*/h	Yield/%	Recovery of 6/%	Yield based on recovered 6/%
1	10	0.25	5	3.5	36	0	36
2	20	0.25	1.2	27	31	48	60
3	20	0.25	2.5	6	53	22	68
4	20	0.25	3	10	46	31	67
5	20	0.25	3	12	49	32	72
6	20	0.3	3	12	58	24	76
7	20	0.3	3	8	54	44	96



Scheme 2 Synthesis of L-galactosaminuronic acid building block 1

oside **10** with exclusive *β*-selectivity. In addition, a balance between the formation of allyl glycoside and the recovery of selenoglycoside is a key to improve efficiency of the allylation. The C2 azido group in **1** was designed to enhance the α-selectivity of glycosylation, and can be easily transformed to amino or amide groups. The *O*3-Nap and *O*4-Lev in **1** will allow the orthogonal deprotection for regioselective glycosylation. This orthogonally protected L-galactosaminuronic acid building block will be useful for the syntheses of complex bacterial glycans.

Experimental

All detailed experimental data were provided in supplementary material.

References

[1] Li R, Yu H, Chen X. Recent progress in chemical synthesis of bacterial surface glycans [J]. *Curr Opin Chem Biol*, 2020, **58**: 121-136.

[2] Hsu C, Hung S, Wu C, *et al*. Toward automated oligosaccharide synthesis [J]. *Angew Chem Int Ed Engl*, 2011, **50**(50): 11872-11923.

[3] Anish C, Schumann B, Pereira C, *et al*. Chemical biology approaches to designing defined carbohydrate vaccines [J]. *Chem Biol*, 2014, **21**(1): 38-50.

[4] Wu Y, Xiong D, Chen S, *et al*. Total synthesis of mycobacterial arabinogalactan containing 92 monosaccharide units [J]. *Nat Commun*, 2017, **8**: 14851.

[5] Zhu Q, Shen Z, Chiodo F, *et al*. Chemical synthesis of glycans up to a 128-mer relevant to the *O*-antigen of *Bacteroides vulgatus* [J]. *Nat Commun*, 2020, **11**(1): 4142.

[6] Tian G, Qin C, Liu Z, *et al*. Total synthesis of the *Helicobacter pylori* serotype O2 *O*-antigen α-(1 → 2)- and α-(1 → 3)-linked oligoglucosides [J]. *Chem Commun*, 2020, **56**(3): 344-347.

[7] Li W, Silipo A, Gersby L, *et al*. Synthesis of bradyrhizose oligosaccharides relevant to the *Bradyrhizobium O*-antigen [J]. *Angew Chem Int Ed Engl*, 2017, **56**(8): 2092-2096.

[8] Yu K, Bi N, Xiong C, *et al*. Synthesis of defined and functionalized glycans of lipoteichoic acid: a cell surface polysaccharide from *Clostridium difficile* [J]. *Org Lett*, 2017, **19**(12): 3123-3126.

[9] Zhang Y, Chen Z, Huang Y, *et al*. Modular synthesis of nonadecasaccharide motif from *Psidium guajava* polysaccharides: orthogonal one-pot glycosylation strategy [J]. *Angew Chem Int Ed Engl*, 2020, **59**(19): 7576-7584.

[10] Zhang Y, He H, Chen Z, *et al*. Merging reagent modulation and remote anchimeric assistance for glycosylation: highly stereoselective synthesis of *α*-glycans up to a 30-mer [J]. *Angew Chem Int Ed Engl*, 2021, **60**(22): 12597-12606.

[11] Yin J. Chemical glycobiology drives the discovery of carbohydrate-based drugs [J]. *Chin J Nat Med*, 2020, **18**(10): 721-722.

[12] Zhang X, Yao W, Xu X, *et al*. Synthesis of fucosylated chondroitin sulfate glycoclusters: a robust route to new anticoagulant agents [J]. *Chem-Eur J*, 2018, **24**(7): 1694-1700.

[13] Zhang Q, Gimeno A, Santana D, *et al*. Synthetic, zwitterionic Sp1 oligosaccharides adopt a helical structure crucial for antibody interaction [J]. *ACS Cent Sci*, 2019, **5**(8): 1407-1416.

[14] Seeberger P. Discovery of semi- and fully-synthetic carbohydrate vaccines against bacterial infections using a medicinal chemistry approach [J]. *Chem Rev*, 2021, **121**(7): 3598-3626.

[15] King J, Kocincova D, Westman E, *et al*. Lipopolysaccharide biosynthesis in *Pseudomonas aeruginosa* [J]. *Innate Immun*, 2009, **15**(5): 261-312.

[16] Tomshich S, Isakov V, Komandrova N, *et al*. Structure of the *O*-specific polysaccharide of the marine bacterium *Arenibacter palladensis* KMM 3961T containing 2-acetamido-2-deoxy-L-galacturonic acid [J]. *Biochemistry (Moscow)*, 2012, **77**(7): 87-91.

[17] Senchenkova S, Shashkov A, Knirel Y, *et al*. Structure of a polysaccharide from the lipopolysaccharide of *Vibrio vulnificus* clinical isolate YJ016 containing 2-acetimidoylamino-2-deoxy-L-galacturonic acid [J]. *Carbohydr Res*, 2009, **344**(8): 1009-1013.

[18] Shashkov A, Senchenkova S, Chizhov A, *et al*. Structure of a polysaccharide from the lipopolysaccharides of *Vibrio vulnificus* strains CECT 5198 and S3-I2-36, which is remarkably similar to the *O*-polysaccharide of *Pseudoalteromonas rubra* ATCC 29570 [J]. *Carbohydr Res*, 2009, **344**(15): 2005-2009.

[19] Hanniffy O, Shashkov A, Senchenkova S, *et al*. Structure of an acidic *O*-specific polysaccharide of *Pseudoalteromonas haloplanktis* type strain ATCC 14393 containing 2-acetamido-2-deoxy-D- and -L-galacturonic acids and 3-(*N*-acetyl-D-alanyl)amino-3, 6-dideoxy-D-glucose [J]. *Carbohydr Res*, 1999, **321**(1-2): 132-138.

[20] Yokota S, Ochi H, Uezumi I, *et al*. *N*-Acetyl-L-galactosaminuronic acid as an epitope common to the *O*-polysaccharides of *Pseudomonas aeruginosa* serotype A and H (Homma) recognized by a protective human monoclonal antibody [J]. *Eur J Biochem*, 1990, **192**(1): 109-113.

[21] Danieli E, Proietti D, Brogioni G, *et al*. Synthesis of *Staphylococcus aureus* type 5 capsular polysaccharide repeating unit using novel L-FucNAc and D-FucNAc synthons and immunochemical evaluation [J]. *Bioorg Med Chem*, 2012, **20**(21): 6403-6415.
[22] Sanapala S, Kulkarni S. Expedient route to access rare deoxy amino L-sugar building blocks for the assembly of bacterial glycoconjugates [J]. *J Am Chem Soc*, 2016, **138**(14): 4938-4947.
[23] Liu H, Zhang Y, Wei R, *et al*. Total synthesis of *Pseudomonas aeruginosa* 1244 pilin glycan *via* de novo synthesis of pseudaminic acid [J]. *J Am Chem Soc*, 2017, **139**(38): 13420-13428.
[24] Zeng J, Sun G, Yao W, *et al*. 3-Aminodeoxypyranoses in glycosylation: Diversity-oriented synthesis and assembly in oligosaccharides [J]. *Angew Chem Int Ed Engl*, 2017, **56**(19): 5227-5231.
[25] Zeng J, Wang R, Zhang S, *et al*. Hydrogen-bonding-assisted exogenous nucleophilic reagent effect for *β*-selective glycosylation of rare 3-amino sugars [J]. *J Am Chem Soc*, 2019, **141**(21): 8509-8515.
[26] Qin C, Liu Z, Ding M, *et al*. Chemical synthesis of the *Pseudomonas aeruginosa* O11 *O*-antigen trisaccharide based on neighboring electron-donating effect [J]. *J Carbohyd Chem*, 2020, **39**(8): 374-397.
[27] Qin C, Schumann B, Zou X, *et al*. Total synthesis of a densely functionalized *Plesiomonas shigelloides* serotype 51 aminoglycoside trisaccharide antigen [J]. *J Am Chem Soc*, 2018, **140**(8): 3120-3127.
[28] Song W, Cai J, Zou X, *et al*. Applications of controlled inversion strategies in carbohydrate synthesis [J]. *Chin Chem Lett*, 2018, **29**(1): 27-34.
[29] Ning Y, Qin C, Sun W, *et al*. Anomeric configuration-dependence of the Lattrell-Dax epimerization from D-glucose to synthetically useful D-allose derivatives [J]. *Chin J Nat Med*, 2020, **18**(10): 723-728.
[30] Liu L, Zha J, DiGiandomenico A, *et al*. Synthetic enterobacterial common antigen (ECA) for the development of a universal immunotherapy for drug-resistant *Enterobacteriaceae* [J]. *Angew Chem Int Ed Engl*, 2015, **54**(37): 10953-10957.
[31] Crich D and Dudkin V. Why are the hydroxy groups of partially protected *N*-acetylglucosamine derivatives such poor glycosyl acceptors, and what can be done about it? A comparative study of the reactivity of *N*-acetyl-, *N*-phthalimido-, and 2-azido-2-deoxy-glucosamine derivatives in glycosylation. 2-Picolinyl ethers as reactivity-enhancing replacements for benzyl ethers [J]. *J Am Chem Soc*, 2001, **123**(28): 6819-6825.
[32] Zhao M, Qin C, Li L, *et al*. Conjugation of synthetic trisaccharide of *Staphylococcus aureus* type 8 capsular polysaccharide elicits antibodies recognizing intact bacterium [J]. *Front Chem*, 2020, **8**: 258.
[33] Nunn J, von Holdt M. Red-seaweed polysaccharides. Part II. Porphyra capensis and the seperation of D- and L-galactose by crystallization [J]. *J Chem Soc*, 1957, **0**: 1094-1097.
[34] Anderson E. The preparation of L-galactose from flaxseed mucilage [J]. *J Biol Chem*, 1933, **100**(1): 249-253.
[35] Doboszewski B, Herdewijn P. 1,2;3,4-Di-*O*-isopropylidene-L-galactose synthesis from its D-enantiomer [J]. *Tetrahedron Lett*, 2012, **53**(17): 2253-2256.
[36] Orii R, Izumi M, Kajihara Y, *et al*. Efficient synthesis of L-galactose from D-galactose [J]. *J Carbohyd Chem*, 2015, **34**(9): 560-566.
[37] Xia T, Li Y, Yin Z, *et al*. Synthesis of L-glucose and L-galactose derivatives from D-sugars [J]. *Chin Chem Lett*, 2014, **25**(9): 1220-1224.
[38] Chida N, Suzuki M, Suwama M, *et al*. Synthesis of D- and L-galactose derivatives from quebrachitol [J]. *J Carbohyd Chem*, 1989, **8**(3): 319-332.
[39] Takeuchi M, Taniguchi T, Ogasawara K. Back to the sugars: a new enantio and diastereocontrolled route to hexoses from furfural [J]. *Synthesis*, 1999, **0**(2): 341-354.
[40] Covell D, Vermeulen N, Labenz N, *et al*. Polyol synthesis through hydrocarbon oxidation: De novo synthesis of L-galactose [J]. *Angew Chem Int Ed Engl*, 2006, **45**(48): 8217-8220.
[41] Kim K, Cho B, Shin I. A new efficient method for the synthesis of L-galactose [J]. *Bull Korean Chem Soc*, 2002, **23**(9): 1193-1194.
[42] Yu B, Tao H. Glycosyl trifluoroacetimidates. Part 1: preparation and application as new glycosyl donors [J]. *Tetrahedron Lett*, 2001, **42**(12): 2405-2407.
[43] Yu B. Gold(I)-catalyzed glycosylation with glycosyl *o*-alkynylbenzoates as donors [J]. *Acc Chem Res*, 2018, **51**(2): 507-516.
[44] Shu P, Xiao X, Zhao Y, *et al*. Interrupted pummerer reaction in latent-active glycosylation: glycosyl donors with a recyclable and regenerative leaving group [J]. *Angew Chem Int Ed Engl*, 2015, **54**(48): 14432-14436.
[45] Xiao X, Zhao Y, Shu P, *et al*. Remote activation of disarmed thioglycosides in latent-active glycosylation *via* interrupted pummerer reaction [J]. *J Am Chem Soc*, 2016, **138**(40): 13402-13407.
[46] Litjens R, den Heeten R, Timmer M, *et al*. An expedient synthesis of the repeating unit of the acidic polysaccharide of the bacteriolytic complex of lysoamidase [J]. *Chem-Eur J*, 2005, **11**(3): 1010-1016.
[47] Hagen B, van Dijk J, Zhang Q, *et al*. Synthesis of the *Staphylococcus aureus* strain M capsular polysaccharide repeating unit [J]. *Org Lett*, 2017, **19**(10): 2514-2517.
[48] van den Bos L, Codee J, van der Toorn J, *et al*. Thioglycuronides: Synthesis and application in the assembly of acidic oligosaccharides [J]. *Org Lett*, 2004, **6**(13): 2165-2168.
[49] Khatuntseva E, Sherman A, Tsvetkov Y, *et al*. Phenyl 2-azido-2-deoxy-1-selenogalactosides: a single type of glycosyl donor for the highly stereoselective synthesis of *α*- and *β*-2-azido-2-deoxy-D-galactopyranosides [J]. *Tetrahedron Lett*, 2016, **57**(6): 708-711.
[50] Kikkeri R, Lepenies B, Adibekian A, *et al*. *In vitro* imaging and *in vivo* liver targeting with carbohydrate capped quantum dots [J]. *J Am Chem Soc*, 2009, **131**(6): 2110-2112.
[51] Schlegel M, Hutter J, Eriksson M, *et al*. Defined presentation of carbohydrates on a duplex DNA scaffold [J]. *Chembiochem*, 2011, **12**(18): 2791-2800.
[52] Tian G, Hu J, Qin C, *et al*. Chemical synthesis and immunological evaluation of *Helicobacter pylori* serotype O6 tridecasaccharide *O*-antigen containing a DD-heptoglycan [J]. *Angew Chem Int Ed Engl*, 2020, **59**(32): 13362-13370.
[53] Zou X, Qin C, Pereira C, *et al*. Synergistic glycosylation as key to the chemical synthesis of an outer core octasaccharide of *Helicobacter pylori* [J]. *Chem-Eur J*, 2018, **24**(12): 2868-2872.
[54] Zou X, Qin C, Hu J, *et al*. Total synthesis of D-glycero-D-manno-heptose 1*β*, 7-bisphosphate with 3-*O*-amyl amine linker and its monophosphate derivative [J]. *Chin J Nat Med*, 2020, **18**(8): 628-632.
[55] Cai J, Hu J, Qin C, *et al*. Chemical synthesis elucidates the key antigenic epitope of the autism-related bacterium *Clostridium bolteae* capsular octadecasaccharide [J]. *Angew Chem Int Ed Engl*, 2020, **59**(46): 20529-20537.

Cite this article as: QIN Chun-Jun, HOU Hong-Li, DING Mei-Ru, QI Yi-Kuan, TIAN Guang-Zong, ZOU Xiao-Peng, FU Jun-Jie, HU Jing, YIN Jian. Chemical synthesis of a synthetically useful L-galactosaminuronic acid building block [J]. *Chin J Nat Med*, 2022, **20**(5): 387-392.