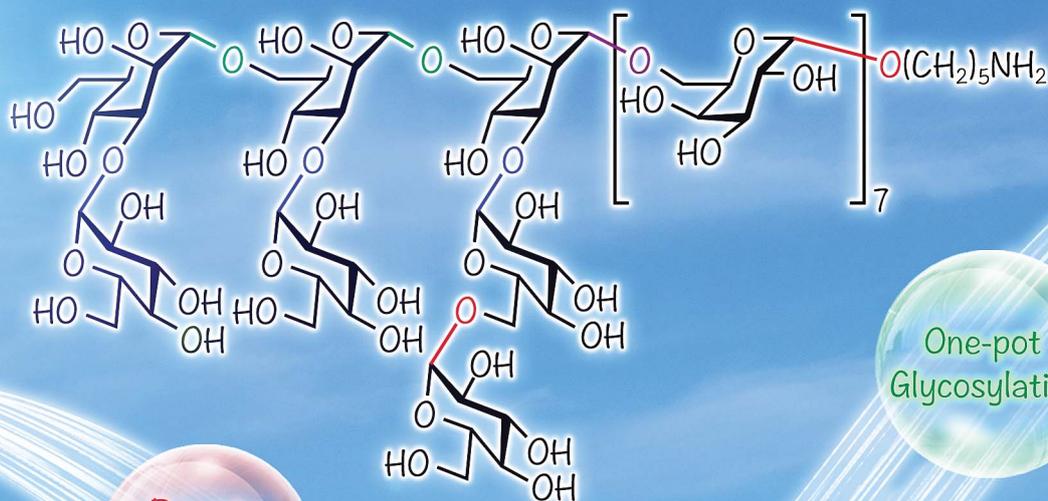


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RMRAA
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One-pot
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Total synthesis of *Lentinus giganteus* glycans with antitumor activities via stereoselective α -glycosylation and orthogonal one-pot glycosylation strategies†

Yunqin Zhang,^a Yanlei Hu,^b Shanshan Liu,^a Haiqing He,^a Roujing Sun,^a Gang Lu^{ID}*^b and Guozhi Xiao^{ID}*^a

The accessibility to long, branched and complex glycans containing many 1,2-*cis* glycosidic linkages with precise structures remains a challenging task in chemical synthesis. Reported here is an efficient, stereoselective and orthogonal one-pot synthesis of a tetradecasaccharide and shorter sequences from *Lentinus giganteus* polysaccharides with antitumor activities. The synthetic strategy consists of: (1) newly developed merging reagent modulation and remote anchimeric assistance (RMRAA) α -(1→6)-galactosylation in a highly stereoselective manner, (2) DMF-modulated stereoselective α -(1→3)-glucosylation, (3) RMRAA stereoselective α -(1→6)-glucosylation, (4) several orthogonal one-pot glycosylations on the basis of *N*-phenyltrifluoroacetimidate (PTFAI) glycosylation, Yu glycosylation and *ortho*-(1-phenylvinyl)benzoate (PVB) glycosylation to streamline oligosaccharide synthesis, and (5) convergent [7 + 7] glycosylation for the final assembly of the target tetradecasaccharide. In particular, this new RMRAA α -galactosylation method has mild reaction conditions, broad substrate scopes and significantly shortened step counts for the heptasaccharide synthesis in comparison with 4,6-*di-tert*-butylsilylene (DTBS) directed α -galactosylation. Furthermore, DFT calculations shed light on the origins of remote anchimeric assistance effects (3,4-OBz > 3,4-OAc > 4-OBz > 3-OBz) of acyl groups.

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Introduction

Carbohydrates are essential and the most abundant biomolecules with crucial roles in various biological processes, including cell growth and proliferation, viral and bacterial infection, and immune responses.^{1,2} In comparison with the synthesis of proteins and DNA *via* the gene-regulated process, glycan biosynthesis is a stepwise and non-template-driven process, which often involves post-translational modifications in the Golgi apparatus and endoplasmic reticulum, and often results in heterogeneous and complex carbohydrate sequences. Isolation of homogeneous and pure glycans from natural sources is a formidable task. Chemical synthesis is a scalable and reliable means to prepare pure and well-defined glycans for developing new therapeutic agents and deciphering their

functions.^{3–16} However, compared with the routine and efficient automated solid-phase synthesis of oligonucleotides and peptides, the synthesis of glycans is much more challenging and lags behind. The major issues in glycan synthesis are regio- and stereochemical problems, and it is often time-consuming and requires tedious carbohydrate synthesis.^{17,18} Indeed, cases of the total synthesis of long, branched and complex glycans with many 1,2-*cis* glycosidic linkages and over 10 units are still limited.^{19–27} Therefore, the development of efficient strategies for the synthesis of long, branched and complicated carbohydrates containing diverse 1,2-*cis* glycosidic linkages is direly needed and remains challenging in chemical synthesis.

In 2016, a novel neutral polysaccharide LGPS-1 (Fig. 1) with a tetradecasaccharide repeating unit was isolated from *Lentinus giganteus*, which is an edible mushroom and widely distributed in South China.²⁸ LGPS-1 glycan has the following unique structural characteristics: (1) a long glycan chain with seven 1,2-*cis*-galactosidic linkages at the reducing end, which are challenging to construct in an efficient and highly stereoselective manner; (2) four challenging 1,2-*cis* glucosidic bonds in the side chain; (3) two 3,6-branched mannose motifs at the nonreducing end. LGPS-1 could induce HepG2 cell apoptosis *via* intrinsic mitochondrial apoptosis and PI3K/Akt signaling pathways, which involved caspase-3 activation, RARP-1 cleavage, the loss

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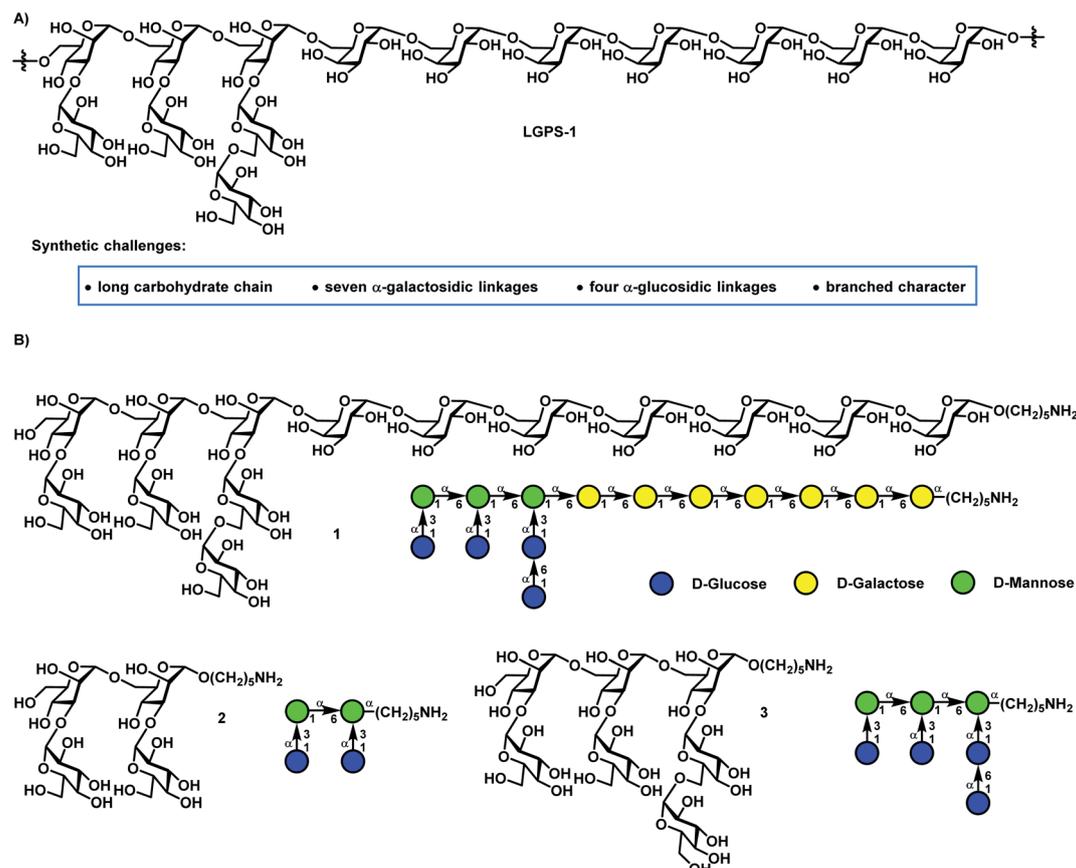


Fig. 1 (A) The structure of polysaccharide LGPS-1 from *Lentinus giganteus*, and (B) the structures of the tetradecasaccharide repeating unit 1 and shorter sequences (2 and 3).

of mitochondrial membrane potential, the release of cytochrome c into the cytoplasm and the inhibition of the phosphorylation of Akt. Intrigued by their interesting biological activities as well as novel and challenging structures, we selected the tetradecasaccharide repeating unit 1 and shorter sequences 2 and 3 of LGPS-1 as synthetic targets for in-depth biological studies on the structure–activity relationships and exploitation of their unknown biological functions.

Different from the traditional synthesis of glycans, one-pot glycan assembly not only omits the workups of glycosylation interval and purification of the intermediates, but also accelerates the synthesis and reduces chemical waste.^{17a,25,29} Herein, through the orthogonal one pot glycosylation strategy with glycosyl *N*-phenyltrifluoroacetimidate³⁰ (PTFAI) as the donor, and glycosyl *ortho*-alkynylbenzoates³¹ (ABz) (Yu glycosylation) and glycosyl *ortho*-(1-phenylvinylbenzoates)³² (PVB) as the bifunctional acceptors, we report the stereoselective synthesis of *Lentinus giganteus* glycans 1–3. The following steps are highlighted in our synthetic strategies: (1) a new stereoselective α -galactosylation method *via* a merging reagent modulation and remote anchimeric assistance (RMRAA) glycosylation strategy, (2) DMF-modulated α -(1 \rightarrow 3)-glucosylation in a highly stereoselective manner, (3) the RMRAA glycosylation strategy for highly stereoselective α -(1 \rightarrow 6)-glucosylation, (4) several

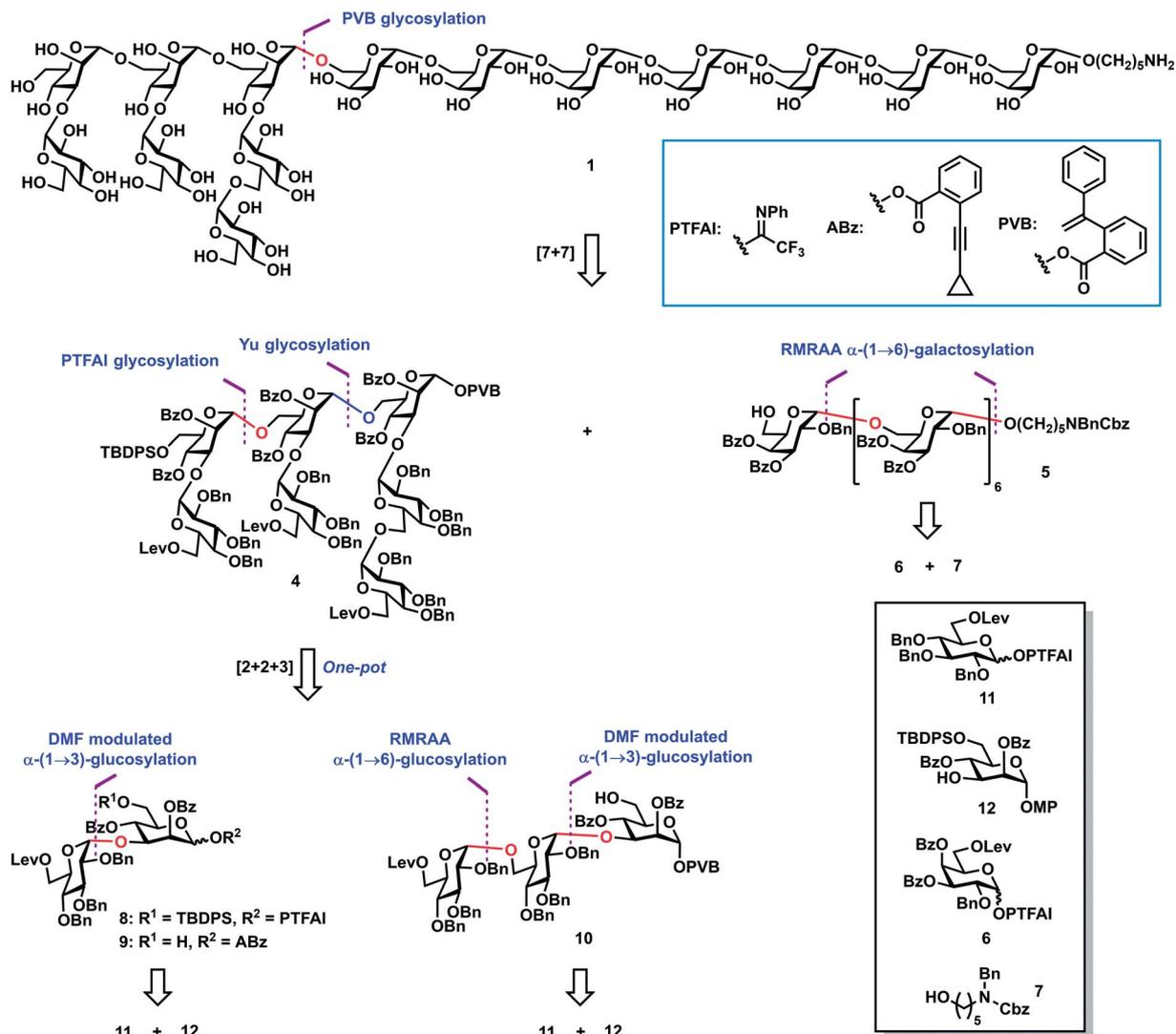
orthogonal one-pot glycosylations to streamline oligosaccharide synthesis, and (5) convergent [7 + 7] glycosylation for the final assembly of the target tetradecasaccharide 1.

Results and discussion

Retrosynthesis

Retrosynthetic analysis (Scheme 1) of tetradecasaccharide 1 showed that the assembly can be achieved *via* the convergent [7 + 7] 1,2-*trans* stereoselective mannosylation of glycosyl PVB 4 and the heptasaccharide acceptor 5. As for the preparation of heptasaccharide acceptor 5, galactosyl PTFAI 6 and the linker HO(CH₂)₅NBnCbz 7 were selected to undergo the iterative and stereoselective α -galactosylation and deprotection of Lev for chain elongation. The design of monosaccharide building block 6 was based on stereoselective α -galactosylation studies, as described below. As for the synthesis of another heptasaccharide donor 4, three-component orthogonal one-pot 1,2-*trans* stereoselective mannosylation of disaccharide PTFAI 8, disaccharide ABz 9, and trisaccharide PVB 10 was designed to assemble 4. As for the synthesis of α -Glc-(1 \rightarrow 3)-Man disaccharides 8–9 and α -Glc-(1 \rightarrow 6)- α -Glc-(1 \rightarrow 3)-Man trisaccharide 10, an α -(1 \rightarrow 3) glycosyl linkage can be built by DMF-modulated stereoselective 1,2-*cis* glucosylation of glycosyl PTFAI donor 11



Scheme 1 Retrosynthetic analysis of the tetradecasaccharide **1**.

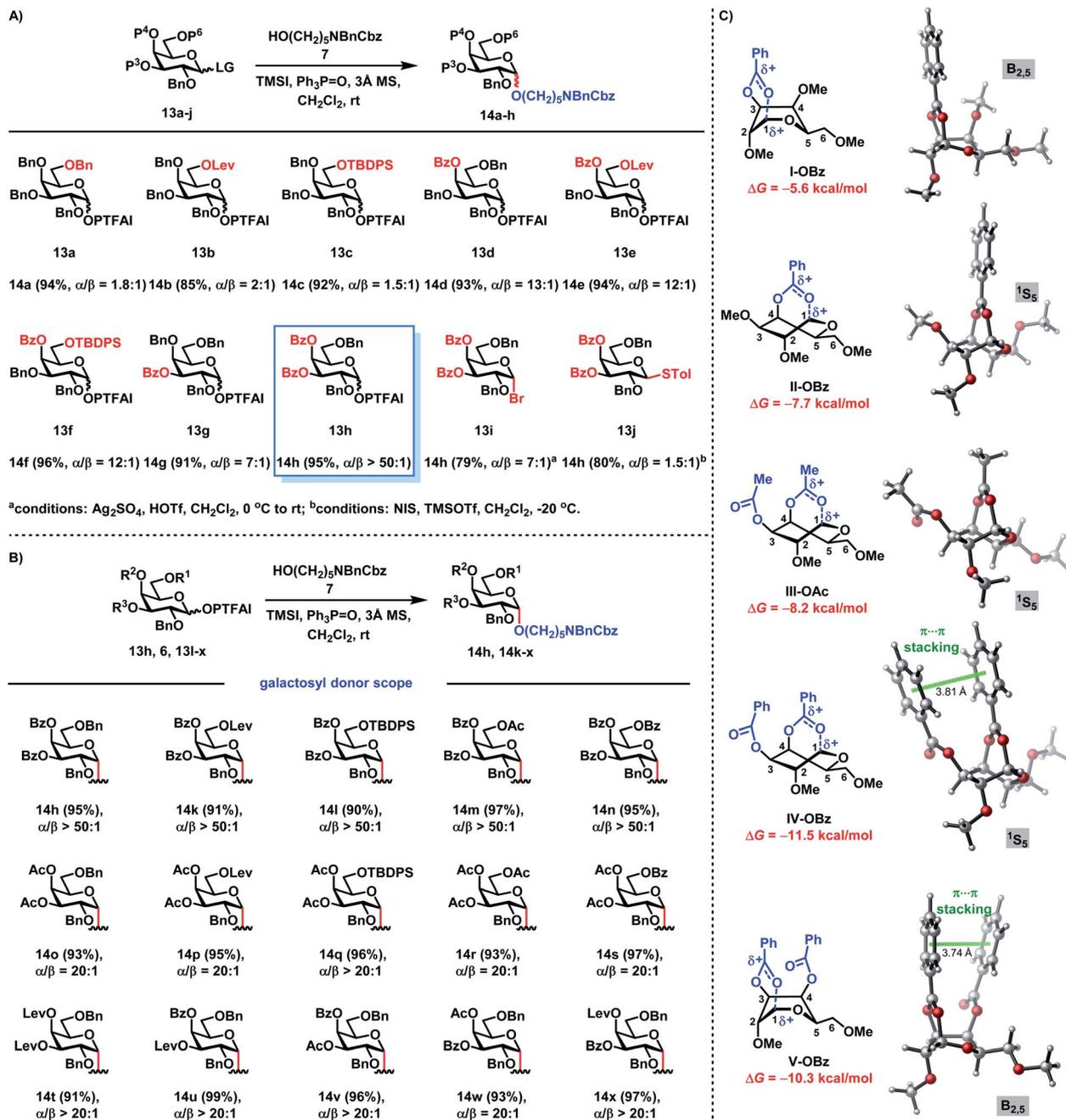
and the mannoside acceptor **12**,³³ while an α -(1→6) glycosyl bond can be stereoselectively constructed *via* the recently developed RMRAA glycosylation of 6-*O*-levulinoyl (Lev) glucosyl PTFAI donor **11**.^{25b}

Reaction optimization of α -galactosylation

Recently, we introduced the RMRAA glycosylation strategy for the highly stereoselective assembly of 1,2-*cis* glucosyl linkages.^{25b} We wondered whether this RMRAA glycosylation strategy could be extended to α -galactosylation. The highly reactive primary alcohol linker **7** as a strong nucleophile acceptor was selected to investigate 1,2-*cis* galactosylation with galactosyl donors **13** (Scheme 2A). When perbenzyl group-protected galactosyl PTFAI **13a** was coupled with **7** using a TMSI and Ph₃PO reagent combination, the monosaccharide **14a** was generated in 94% yield with a low selectivity (α/β = 1.8 : 1). To our surprise, when the C-6-Bn group in **13a** was replaced with the Lev group with the remote anchimeric assistance effect or the TBDPS group with the steric shielding effect

in **13b** or **13c**, low stereoselectivities (α/β = 2 : 1 for Lev; α/β = 1.5 : 1 for TBDPS) were also obtained, which was totally different from that of 1,2-*cis* glucosylation.^{25b} Interestingly, when the C-4-Bn group was exchanged with the Bz group in **13d**, the stereoselectivity was dramatically improved (α/β = 13 : 1).³⁴ The additional replacement of the C-6-Bn group with the Lev group or the TBDPS group in **13e** or **13f** did not have beneficial effects on the stereoselectivities (α/β = 12 : 1 for **13e** and **13f**). When the C-3-Bn group was replaced with the Bz group in **13g**, an improved stereoselectivity (α/β = 7 : 1) was also obtained. To our delight, when both C-3 and C-4 Bn groups were exchanged with Bz groups in **13h**, the monosaccharide **14h** was prepared in an excellent yield (95%) with an excellent stereoselectivity (α/β > 50 : 1). In comparison, without reagent modulation (TMSI and Ph₃PO), when **13h** was coupled with **7** in the activation of TMSOTf, a moderate stereoselectivity (α/β = 5 : 1) of **14h** was obtained. Furthermore, when the corresponding galactosyl bromide **13i** was glycosylated with **7** under Demchenko's protocol (Ag₂SO₄, HOTf, CH₂Cl₂, 0 °C to rt),³⁵ a moderate





Scheme 2 (A) Reaction optimization of α -galactosylation; (B) the scope of galactosyl PTFAI donors; (C) computed geometries of β -oxocarbenium stabilized by remote acyl groups. The relative free energies (ΔG) are with respect to the oxocarbenium without the stabilization of remote acyl groups.

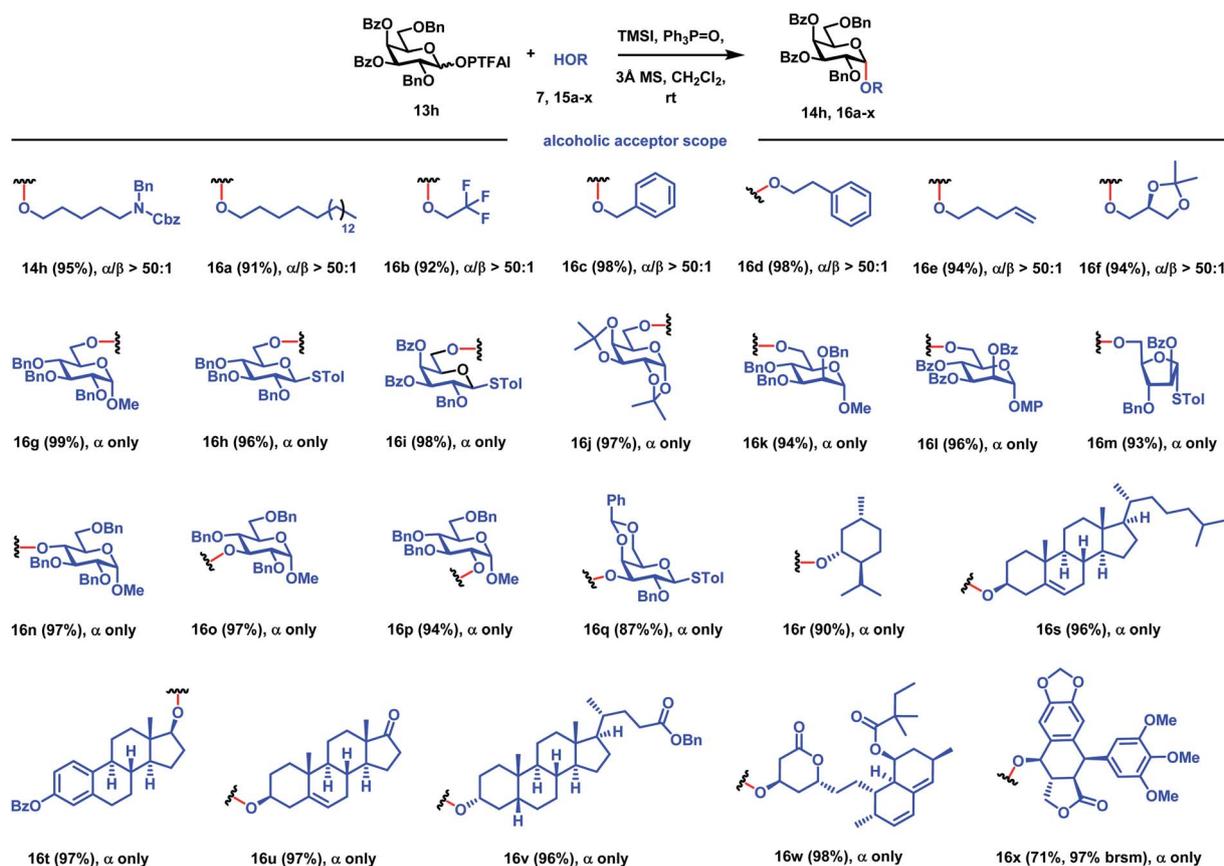
stereoselectivity ($\alpha/\beta = 7:1$ for **13i**) was obtained. A low stereoselectivity ($\alpha/\beta = 1.5:1$ for **13j**) was also obtained when the thioglycoside **13j** was coupled with **7** under Seeberger's protocol (NIS, TMSOTf, CH_2Cl_2 , -20°C).³⁶ These results clearly demonstrate that highly stereoselective 1,2-*cis* galactosylation can be achieved *via* the RMRAA glycosylation strategy. Moreover, the scalability of this RMRAA α -galactosylation protocol was demonstrated by the efficient synthesis of **14h** on a 1.4 g scale in 92% isolated yield.

The scope of galactosyl PTFAI donors

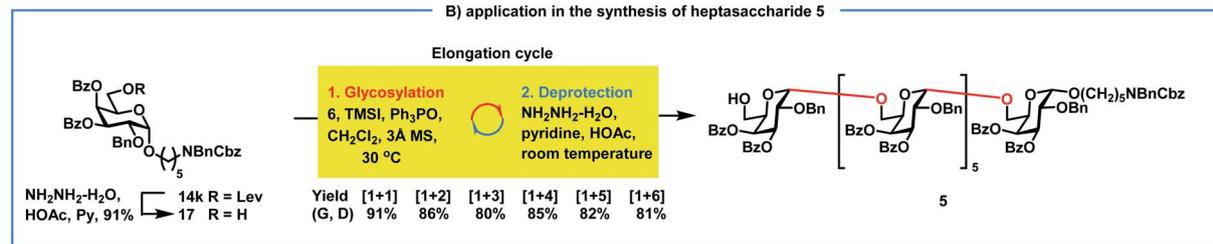
We next investigated the scope of galactosyl PTFAI donors using the linker **7** as a strong nucleophile and TMSI and Ph_3PO as the reagent combination (Scheme 2B). When both C3 and C4 positions were fixed for Bz groups, the C6 position was suitable for various groups including Lev, TBDPS, Ac and Bz in galactosyl donors (**6**, **13l-n**), providing the corresponding α -galactosides **14k-n** in excellent yields (90–97%) with outstanding stereoselectivities ($\alpha/\beta > 50:1$). Besides the Bz group, Ac or Lev groups



A) Scope of stereoselective glycosylation of galactosyl PTFAl donor 13h



B) application in the synthesis of heptasaccharide 5

Scheme 3 (A) The scope of RMRAA 1,2-*cis* galactosylation; (B) application to the synthesis of heptasaccharide 5.

were also suitable acyl groups for both C3 and C4 positions in donors (**13o–s**), and the corresponding α -galactosides **14o–s** were obtained in 91–97% yields with excellent stereoselectivities ($\alpha/\beta \geq 20:1$). Interestingly, when C3 and C4 positions were installed with different acyl groups in donors (**13t–x**), α -galactosides **14t–x** were also prepared in 93–99% yields with great stereocontrol ($\alpha/\beta \geq 20:1$).

DFT calculations

In order to better understand the remote anchimeric assistance with acyl groups, we performed DFT calculations at the M06-2X/6-311+G(d,p)-SMD//M06-2X/6-31G(d)-SMD level of theory to rationalize the origins of highly stereoselective α -galactosylation (Scheme 2C). The results indicate that, compared to the oxocarbenium without remote anchimeric assistance, the acyl groups (OAc or OBz) at C3 and/or C4 positions can

thermodynamically favor the formation of β -oxocarbenium (Scheme 2C). This kind of structure shields the β -face and favors the α -face S_N2 nucleophilic attack to afford 1,2-*cis* glycosylation. Moreover, the participation of remote acyl groups exhibits different capacities for stabilizing β -oxocarbenium. The general trend is that the two acyl groups at C3 and C4 positions (**IV-OBz**, **V-OBz** and **III-OAc**) are superior to one acyl group (**I-OBz** and **II-OBz**). In particular, although having two acyl groups, the 3,4-OBz groups (in **IV-OBz** and **V-OBz**) are more effective than the 3,4-OAc groups (in **III-OAc**) to stabilize the formed β -oxocarbenium. This is mostly due to the attractive $\pi \cdots \pi$ stacking interactions between phenyl groups in **IV-OBz** with the ¹S₅ conformation and **V-OBz** with the B_{2,5} conformation. The computed stability of the β -oxocarbenium reveals that the choice of remote acyl groups is critical for the high-level stereocontrol of galactosylation. The relative stability order of the β -

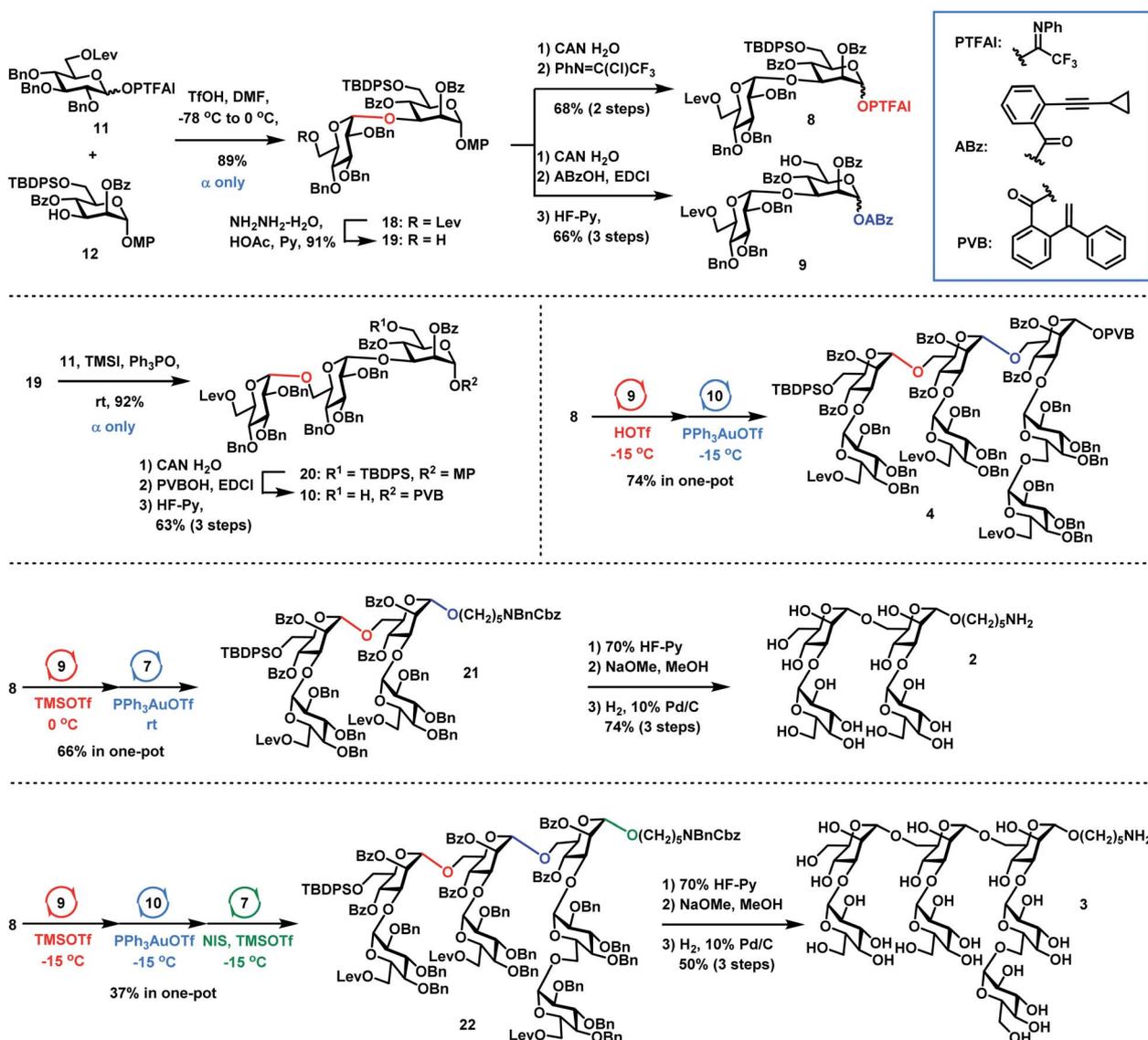


oxocarbenium (3,4-OBz > 3,4-OAc > 4-OBz > 3-OBz) is fully consistent with the experimental observations (Scheme 2A and B). Together with the β -phosphonium iodide modulated by Ph_3PO and TMSI, the thermodynamically favored β -oxocarbenium with a rational choice of remote anchimeric acyl groups can significantly suppress the undesired oxocarbenium species, thus favoring the nucleophilic $\text{S}_{\text{N}}2$ displacement for excellent 1,2-*cis* galactosylation.

The scope of alcoholic acceptors in α -galactosylation

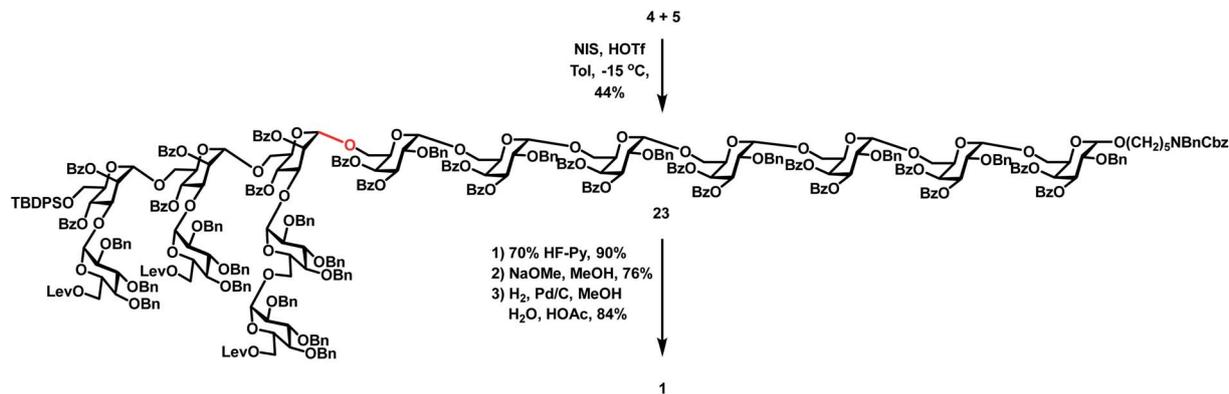
Next, the scope of α -galactosylation with 3,4-di-*O*-Bz galactosyl PTFAI donor **13h** was investigated (Scheme 3A). We were pleased to discover that a wide range of primary alcohols **15a-f** including such strong nucleophiles as 1-octadecanol, benzyl alcohol, 2-phenylethanol and 4-penten-1-ol were coupled smoothly with **13h**, providing α -galactosides **16a-f** in 91–98% yields with excellent stereoselectivities ($\alpha/\beta > 50 : 1$). It is worth

noting that other glycosylation methods often failed to achieve highly stereoselective 1,2-*cis* glycosylation when highly reactive primary alcohols were used as strong nucleophile acceptors.^{37–43} Glycosylation of carbohydrate acceptors **15g-m** including *D*-glucopyranosyl, *D*-galactopyranosyl, *D*-mannopyranosyl and *D*-arabinofuranosyl primary alcohols with **13h** also proceeded smoothly, generating the corresponding disaccharides **16g-m** in excellent yields (93–99%) as single α isomers. Carbohydrate secondary alcohols **15n-q** including the hindered O4-position of glucose were also glycosylated efficiently with **13h**, producing α -(1 \rightarrow 4), (1 \rightarrow 3), and (1 \rightarrow 2)-disaccharides **16n-q** in 87–97% yields with complete stereocontrol. Gal- α -(1 \rightarrow 3)-Gal disaccharide **16q** is a part of the structural motif of the α -Gal epitope, which could produce acute rejections during xenotransplantations.⁴⁴ Besides carbohydrate acceptors, bioactive molecules **15r-v** including menthol **15r**, cholesterol **15s**, estradiol benzoate **15t**, epiandrosterone **15u** and lithocholic



Scheme 4 Orthogonal one-pot synthesis of shorter sequences **2** and **3** and heptasaccharide donor **4**.





Scheme 5 Synthesis of the target tetradecasaccharide 1.

benzoate **15v** were also amenable to this galactosylation method, furnishing the corresponding α -galactosides **16r–v** in excellent yields with complete stereoselectivities. Impressively, even complex bioactive molecules like simvastatin **15w** with antihyperlipidemic and anti-inflammatory activities and podophyllotoxin **15x** with antitumor and antiviral activities are also suitable acceptors, generating galactosylated simvastatin **16w** and galactosylated podophyllotoxin **16x** with only an α isomer in 98% and 71% yields, respectively. It is worth noting that diverse functional groups including acetal (**15f**, **15j**, **15q** and **15x**), alkene (**15e**, **15s** and **15u**), thioacetal (**15h**, **15i**, **15m** and **15q**), ketone (**15u**), 1,3-diene (**15w**), lactone (**15w** and **15x**) and electron-rich phenyl (**15x**) moieties were well tolerated in the reactions, which clearly proved the mild reaction conditions of this new method.

Synthesis of heptasaccharide 5

We next applied this stereoselective α -galactosylation method to the synthesis of the heptasaccharide acceptor **5**. As can be seen from Scheme 3B, the iterative application of this RMRAA α -(1 \rightarrow 6)-galactosylation of **6** and deprotection of the Lev group proceeded successfully, providing the elongated heptasaccharide **5** with excellent yields and complete stereoselectivities, which is ready for convergent [7 + 7] glycosylation. All α -Gal configurations of **5** were confirmed by the chemical shifts of anomeric carbon centers between 97.1 ppm and 97.8 ppm. Although 4,6-di-*tert*-butylsilylene (DTBS) directed galactosylation could also achieve highly selective α -galactosylation,⁴⁵ it usually needs five steps to achieve one sugar unit elongation for the synthesis of the heptasaccharide acceptor **5**, including: (1) glycosylation; (2) deprotection of the 4,6-di-*tert*-butylsilylene protecting group; (3) selective protection of the C6-OH group; (4) protection of the resulting C4-OH group; and (5) deprotection of the C6-OH group for the next sugar elongation cycle. In contrast, the current RMRAA α -galactosylation only needs two steps (glycosylation and deprotection of the 6-*O*-Lev group) for elongation of one sugar unit, which significantly reduces the step counts.⁴⁶

Synthesis of 2–4

The synthesis of *Lentinus giganteus* glycans **2** and **3** and heptasaccharide donor **4** commenced with the α -Glc-(1 \rightarrow 3)-Man

disaccharide **18**, which was obtained in 89% yield by DMF-modulated α -(1 \rightarrow 3)-glucosylation between **11** (1.5 equiv.) and **12** under Codee's conditions (TfOH, DMF, -78 °C to 0 °C) (Scheme 4). The α -Glc configuration was confirmed by the chemical shift of the newly formed anomeric carbon center of **18** (99.2 ppm). Oxidative deprotection of the anomeric 4-methoxyphenyl group in **18** with ceric ammonium nitrate (CAN) afforded the hemiacetal intermediate, which was converted to disaccharide PTFAI **8** via the imidate installation, and disaccharide ABz **9** by esterification with ABzOH and deprotection of the TBDPS group with 70% HF-Py. The further coupling of 6-*O*-Lev equipped donor **11** (1.5 equiv.) with disaccharide **19** derived from **18** under TMSI-Ph₃PO reaction conditions successfully furnished the α -Glc-(1 \rightarrow 6)- α -Glc-(1 \rightarrow 3)-Man trisaccharide **20** as a single α isomer in 92% yield, which was converted to trisaccharide PVB **10** in 63% overall yield via the following functional groups transformation: (1) removal of the anomeric *para*-methoxyphenyl group with CAN in H₂O; (2) condensation of the resulting hemiacetal with PVBOH; (3) deprotection of the TBDPS group with 70% HF-Py. As for the synthesis of **2**, coupling of disaccharide PTFAI donor **8** (1.2 equiv.) with disaccharide ABz **9** (1.0 equiv.) in the catalysis of TMSOTf at 0 °C furnished the tetrasaccharide intermediate, which underwent further Yu glycosylation with HO(CH₂)₅NBnCbz **7**, providing the desired tetrasaccharide **21** in 66% yield in one-pot. Removal of the TBDPS group in **21** with 70% HF-Py, deprotection of all Bz groups and Lev groups with NaOMe in MeOH, and global removal of the Cbz group and all Bn groups (H₂, 10% Pd/C) successfully generated the desired shorter sequence **2** in 74% overall yield. As for the synthesis of **4** and **3**, sequential coupling of PTFAI donor **8** (1.2 equiv.), ABz **9** (1.0 equiv.) and PVB **10** (0.9 equiv.) afforded the desired heptasaccharide **4** in 74% yield in a one-pot manner. Alternatively, orthogonal one-pot glycosylation of PTFAI donor **8** (1.2 equiv.), ABz **9** (1.0 equiv.), PVB **10** (0.9 equiv.) and HO(CH₂)₅NBnCbz **7** (1.5 equiv.) successfully produced the desired heptasaccharide **22** in 37% overall yield. The desired shorter sequence **3** was prepared in 50% overall yield via removal of the TBDPS group with 70% HF-Py, deprotection of all Lev and Bz groups with NaOMe in MeOH, and hydrogenolysis of 13 Bn groups and one Cbz group with 10% Pd/C. It was noted that orthogonal one-pot glycosylation based



on PTFAI glycosylation, Yu glycosylation and PVB glycosylation precluded such issues as aglycon transfer inherent to thioglycoside-based orthogonal one-pot glycosylation.

Synthesis of the target tetradecasaccharide 1

With the desired heptasaccharides **4** and **5** in hand, we embarked on the final assembly of tetradecasaccharide **1**. The identification of conditions for efficient [7 + 7] glycosylation between donor **4** and acceptor **5** was not trivial. Various conditions failed to achieve effective coupling due to the formation of significant amounts of donor hydrolyzed and eliminated products or an acceptor TMS-capped side product. Ultimately, glycosylation of heptasaccharide donor **4** and heptasaccharide acceptor **5** in the presence of NIS and HOTf in toluene at $-15\text{ }^{\circ}\text{C}$ successfully generated the desired tetradecasaccharide **23** in an acceptable 44% yield (Scheme 5). Finally, removal of the TBDPS group with 70% HF-Py, deprotection of three Lev groups and twenty Bz groups with NaOMe in MeOH, and global hydrogenolysis of 20 Bn groups and one Cbz group with 10% Pd/C in **23** successfully produced tetradecasaccharide **1** in 57% overall yield over three steps.

The ^1H NMR spectra of tetradecasaccharide **1** and the shorter sequences **2** and **3** with the highlighted chemical shifts of the anomeric protons are shown in Fig. 2. The structures of **1**–**3** were confirmed by their NMR signal assignment and MAIDI-TOF and ESI mass spectra. In-depth biological studies

could be carried out for the synthetic *Lentinus giganteus* glycans **1**–**3** installed with a pentyl amine linker at the reducing end.

Conclusions

Herein we describe highly stereoselective α -glycosylation and orthogonal one-pot glycosylation strategies for the first chemical synthesis of the tetradecasaccharide repeating unit **1** and shorter sequences **2** and **3** from *Lentinus giganteus* glycans, which have antitumor activities through inducing apoptosis. Several steps are highlighted in our synthetic approach: (1) newly developed highly stereoselective RMRAA α -(1 \rightarrow 6)-galactosylation, (2) stereoselective α -(1 \rightarrow 3)-glucosylation *via* DMF-modulation, (3) highly stereoselective α -(1 \rightarrow 6)-glucosylation *via* the RMRAA glycosylation strategy, (4) several one-pot glycosylations to facilitate glycan synthesis, and (5) convergent [7 + 7] glycosylation for the synthesis of the final target tetradecasaccharide. In particular, the new RMRAA α -galactosylation method enjoys mild reaction conditions, broad substrate scopes and highly shortened step counts in the synthesis of heptasaccharide **5** in comparison with DTBS directed α -galactosylation. Furthermore, DFT calculations uncovered the origins of remote anchimeric assistance effects (3,4-OBz > 3,4-OAc > 4-OBz > 3-OBz) of acyl groups. We believe that the present work will inspire the advances of other synthetic strategies

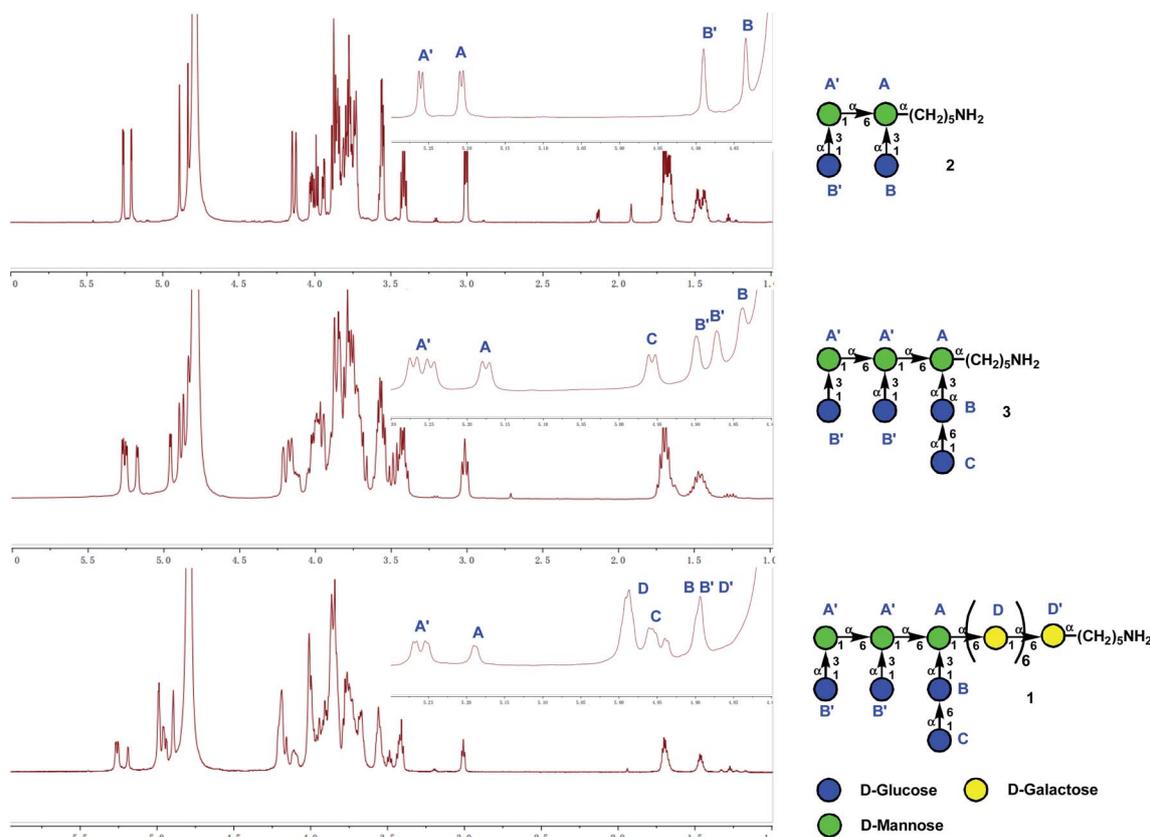


Fig. 2 Evidence for structures of **1** and the shorter sequences **2** and **3** by NMR spectroscopy.



towards streamlining the chemical synthesis of long, branched and complex glycans with many 1,2-*cis*-glycosidic linkages.⁴⁷

Data availability

Experimental data including experimental procedures, characterization data, and NMR spectra for new compounds; mechanistic experiments; detailed computational studies, calculated structures, and energies is accessible in the ESI.†

Author contributions

G. X. conceived the idea, designed the research, supervised the work and wrote the manuscript. Y. Z. made the initial discovery and performed all experiments. S. L., H. H. and R. S. performed some experiments. Y. H. and G. L. performed DFT calculations. Y. H. and G. L. performed DFT calculations and wrote part of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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