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One-Pot Stereospecific Synthesis of 1,4-Oligosaccharides by Glycal-Derived Vinyl Epoxides Assembly

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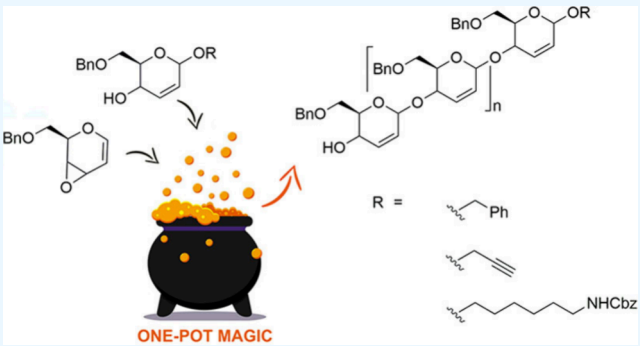
ABSTRACT: Recently, naturally occurring linear 1,4-glycans have attracted remarkable attention for their activity in cancer and neurodegenerative disease treatment. Classical chemical synthetic strategies for linear 1,4-oligosaccharides are considerably time-consuming due to orthogonal protection/deprotection, the introduction of leaving groups, and various forms of activation of the glycosylation reaction. Herein, we present a new one-pot microwave-activated reiterative assembly of glycal-derived vinyl epoxides in an uncatalyzed substrate-dependent stereospecific process for the preparation of both β-1,4-D-Gulo and α-1,4-D-Manno oligosaccharides.



INTRODUCTION

Glycans represent key structures in glycobiology in consideration of their capability to encode information for molecular recognition and to serve as determinants of protein folding, stability, and pharmacokinetics.[1−3] Recently, natural occurring linear 1,4-glycans have been the object of several studies, such as Mannan, a polysaccharide derived from the yeast cell wall that contains mostly linear β-1,4-linked mannose backbone, which has been used as cancer vaccines,[4−6] and GV-971, a natural sodium linear β-1,4-oligomannate as an Alzheimer's disease (AD) therapeutic agent with a unique multitarget action.[7]

Although chemical synthesis of oligosaccharides has proven to be an indispensable part of modern glycobiology, it is greatly hampered by its insufficient efficiency, and so far, assembly of polysaccharides remains one of the most challenging tasks for synthetic chemists. Only a limited number of examples have been reported in the literature in the past few decades.[8−12]

However, chemists have synthesized quite a lot of important oligosaccharides, but the chemical synthesis of oligosaccharides, even for simple linear chains, is often a discrete stepwise process, which still makes extensive use of orthogonal protection protocols, the introduction of leaving groups and activators for total control of the molecular outcome, in an extremely time-consuming fashion.[13−15]

We now report a new process that allows for the first time direct synthetic access to linear 2,3-unsaturated 1,4-oligosaccharides from glycal-derived vinyl epoxides.

RESULTS AND DISCUSSION

Previous work from our laboratories has shown that the vinyl epoxides **1α** or **2β** represent excellent glycosyl donors for the synthesis of simple 1,4-*O*- or *C*-glycosides or more complex glycoconjugates, on the basis of a stereospecific, uncatalyzed glycosylation process, based on the 1,4-conjugated addition of several nucleophiles to the glycal epoxides.[16−25] This discovery led us to pursue the prospect of achieving a reiterative glycosylation process to address the long-standing challenge of direct synthesis of 1,4-oligosaccharides, differently functionalized on the first unit, starting from glycal-derived vinyl epoxides. It was envisioned (Scheme 1) that the use of 2,3-unsaturated glycosydes (**Iα** or **Iβ**), that are also allylic alcohols, obtained from the typical conjugated addition process of an opportune alcohol nucleophile to the vinyl epoxide **1α** or **2β**, could represent the first glycosyl acceptor (initiator). This initiator is able to react with the epoxide (glycosyl donor **1α** or **2β**), to allow the formation of a disaccharide (**IIα** or **IIβ**), which now represents the new glycosyl acceptor able to ensure the chain elongation. In fact, this species reacts *in situ* again with the epoxide donor in a reiterative one-pot assembly process for the construction of well-defined oligosaccharides **IIIα** or **IIIβ** (2−6 units, n = 0−4, Scheme 1), which can be

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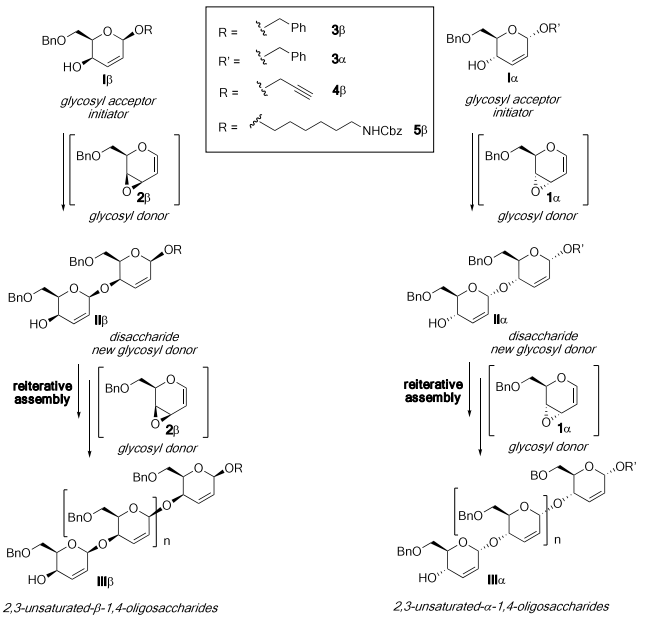
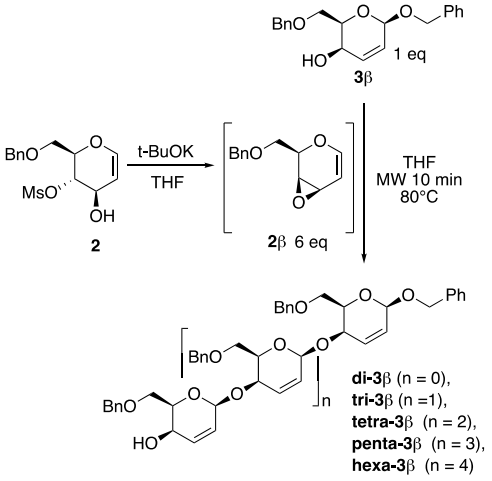
Scheme 1. Reiterative Assembly of Vinyl Epoxides 1*α* and 2*β*



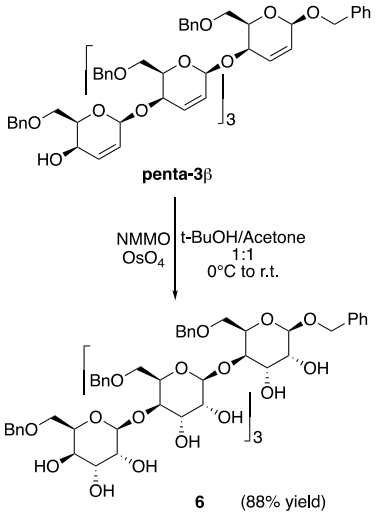
Scheme 2. Microwave-Activated Reiterative Assembly of Vinyl Epoxide 2*β* with Initiator 3*β*



further elaborated upon to obtain either *β*-1,4-D-Gulo or *α*-1,4-D-Manno oligosaccharides, depending on the vinyl epoxide used (**1*α*** or **2*β***).

This hypothesis, unfortunately, using the previously reported protocol,[16,17] which consists in the simple reaction of the glycosyl donor with the glycosyl acceptor at room temperature without any catalyst, was not successful. In fact, all the initiators **I*α*** or **I*β***, prepared following the reported protocol[16] from vinyl epoxide **1*α*** or **2*β***, using benzyl alcohol (**3*α*** or **3*β***), propargyl alcohol (**4*β***), and *N*-Cbz protected hexanolamine (**5*β***) as the nucleophiles, when used (3 equiv) in the reaction with vinyl epoxides **1*α*** or **2*β*** (1 equiv),[17] allows only irrelevant amounts of the corresponding disaccharides **II*α*** or **II*β***. Interestingly, in the search for the reason why the typical protocol did not work with nucleophiles **3*α***, **3*β***, **4*β***, and **5*β*** and cannot be applicable to the reiteration of the process, we demonstrated, by computational studies, that alcohols **I*α*** and **I*β***, which are secondary allylic alcohols embedded in a

Scheme 3. Dihydroxylation of penta-3*β*



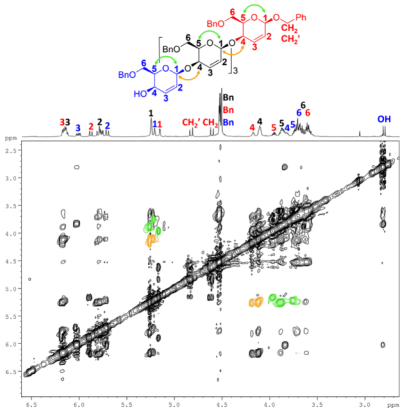
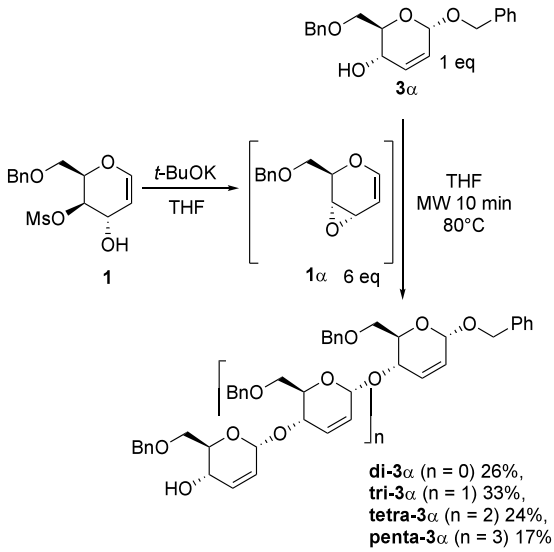


Figure 1. NOESY map for **penta-3*β*** with key NOE effects highlighted.

Scheme 4. Reiterative Assembly of Vinyl Epoxide 1*α* with Initiator 3*α*



dihydropyran-like structure, unexpectedly, were inert at room temperature for the reaction with vinyl epoxide **1*α*** or **2*β***. Indeed, a calculation of the local softness on the hydroxyl

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Scheme 5. Dihydroxylation of tri-3α

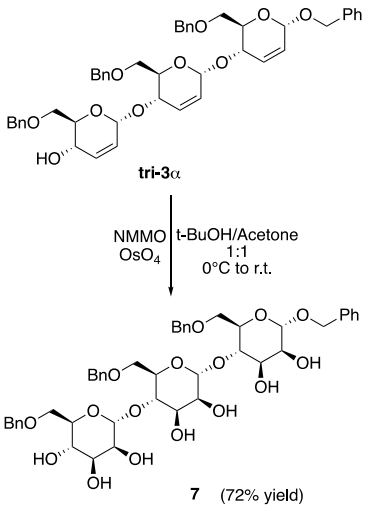
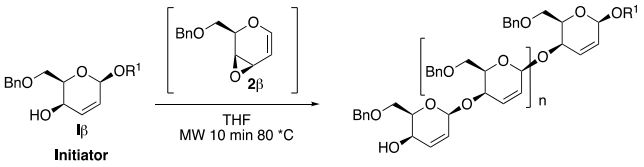
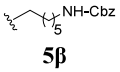


Table 1. Synthesis of 1,4-Oligosaccharides by Assembly of Epoxide 2β with Different Initiators



Entry	R^1	2β/Initiator molar ratio	Molar Distribution (%)[a]	Conversion (%)[b]
1	 **3β**	6	**di-3β**[c] 17%, **tri-3β** 22%, **tetra-3β** 22%, **penta-3β** 18%, **hexa-3β** 11%, hepta 6%, octa 4%,	73%
2	 **4β**	6	**di-4β** 36%, **tri-4β** 41%, **tetra-4β** 18%, penta 5%	50%
3	 **5β**	6	**di-5β** 36%, **tri-5β** 33%, **tetra-5β**18%, penta 9%, hexa 4%	42%

[a]Normalized HPLC areas; see SI for details. [b]Based on the decrease of the HPLC peak area of the initiator; see SI for details. [c]Oligosaccharides in bold are isolated and characterized.

oxygen atom by means of global softness and Fukui function (Table S1)[26−29] showed that **3*β***, **4*β***, and **5*β*** are weak nucleophiles. Moreover, the nucleophilicity of the OH group on the C4 position is influenced by the nature of R in the conjugated C1 position (nucleophilicity **3*β*** ≈ **4*β*** > **5*β***). This discovery led us to pursue the prospect of a necessary activation to realize the reiterative glycosylation process with these relatively unreactive nucleophiles.

However, thermal reflux conditions were still ineffective; in fact, only starting material was recovered at 80 °C for 12 h, or decomposition of the starting material was observed when the reaction was heated at 100 °C for 5 h. Then the possibility of using microwave irradiation, a more efficient (based on an electromagnetic radiation absorption rather than a heat transfer), safer, and greener way to heat up chemical processes, was explored: much to our delight, the use of simple microwave irradiation gave the needed kinetic activation to promote a dramatic efficiency of the glycosylation process, resulting in the regio- and stereoselective formation of 2,3-unsaturated 1,4-oligosaccharides. This experimental result suggests specific nonthermal effects of MW, able to determine an efficient reactivity of these inert nucleophiles that cannot be explained by thermal effects.[30−32]

For example, in the optimized procedure (Scheme 2), treatment of benzyl glycoside **3*β*** (1 equiv) and vinyl epoxide **2*β*** (6 equiv), prepared *in situ* by base catalyzed cyclization of *trans*-hydroxy mesylate **2**, in THF and subsequent microwave irradiation at 80 °C for 10 min, led to an efficient reiterative straightforward glycosylation process. After aqueous workup, the reaction crude exclusively included 2,3-unsaturated-1,4-oligosaccharides and only traces of unreacted initiator **3*β*** (Figures S16 and S17).

The postworkup ^{1}H-NMR spectrum (Figure S16) is remarkably clean, and it is in line with a mixture of 2,3-unsaturated 1,4-*O*-glycosides underlining, for this new reiterative process, a complete 1,4-regiocontrol of the reaction. All of the main oligomers were isolated by chromatography and characterized by NMR. In particular, the NMR study of pentasaccharide (**penta-3*β***) allowed us to determine its stereochemistry (see the SI for details). The absolute configuration of all the new C1 and C4 stereocenters generated in the reaction was determined on the basis of the known configurations of C1, C4, and C5 of the initiator-terminus unit and of C5 of all other units.[25] Figure 1 reports a detail of the NOESY map of **penta-3*β***, which clearly confirms the total *β*-stereoselectivity of the process, thanks to the repetitive NOE correlation (Figure 1, gold) between the H4 and the H1 proton atoms of the adjacent units. As a further proof, the intraunit NOE cross peaks (Figure 1, green) between every H5 and H1 atom independently confirm the *β*-configuration of all the anomeric carbons. Therefore, the reiterative assembly of epoxide **2*β*** gave rise exclusively to 2,3-unsaturated- *β*-1,4-oligosaccharides. This close correspondence demonstrated between the configuration of the pentasaccharide (**penta-3*β***) and that of the starting epoxide (**2*β***) is rationalizable on the basis of the expected coordination between the *O*-nucleophile and the epoxide oxygen atom in the form of a hydrogen bond.[18]

The molar distribution of the oligomers was estimated by HPLC, by normalizing each peak area over the number of phenyl rings in the structure. For the described oligomerization of **2*β*** with **3*β*** (Table 1, entry 1), the distribution was centered between the trimer and the tetramer. The conversion of the process was calculated on the basis of the decrease in the level of initiator **3*β*** assessed by HPLC by means of calibration plots. Moreover, for the oligomerization of **2*β*** with **3*β***, the conversion is remarkably good, around 73%.

To stress the versatility of the process, we realized the assembly of epoxide **2*β*** with initiator **4*β*** (terminal alkyne, key functionality for next elaborations by click chemistry, Table 1, entry 2) and **5*β*** (Cbz-protected amine, useful linker toward

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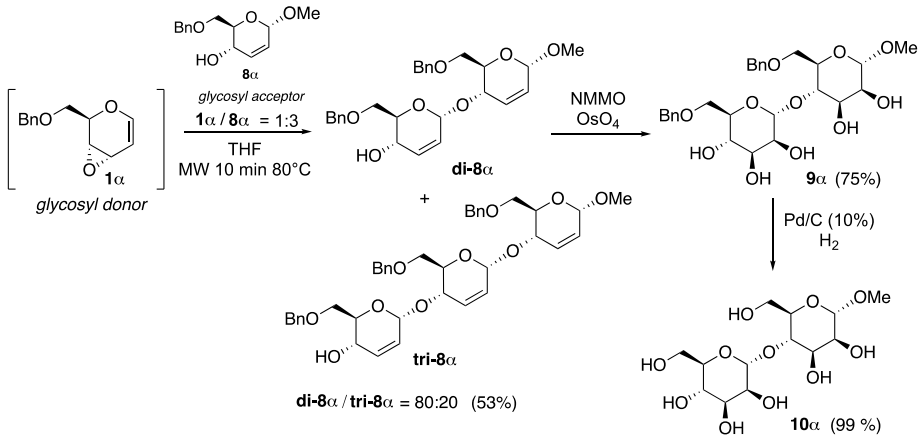
Scheme 6. Synthesis of Disaccharide 10α



the synthesis of glycoconjugates, Table 1, entry 3). The molar distribution of the oligosaccharides obtained and the overall conversion are reported in Table 1.

Both entry 2 and 3 in Table 1 involving initiator **4*β*** and **5*β***, respectively, were characterized by slightly lower conversions with respect to entry 1, and a molar distribution centered between disaccharide and trisaccharide. This is probably due, as previously mentioned, to the lower nucleophilicity of both of these initiators (Table S1), which affects the rate of formation of the disaccharide, which represents the rate-determining step of all of the processes. As for the oligomerization of **2*β*** with **3*β***, all the oligosaccharides isolated from the assembly of **2*β*** with **4*β*** and **5*β*** were characterized by NMR (for **tri-4*β*** and **tri-5*β***, the identity was also confirmed by MALDI, SI) confirming the complete 1,4-regio and *β*-stereoselectivity of the process.

The 2,3-unsaturated oligosaccharides synthesized are key compounds for the construction of deoxy and fully oxygenated sugars.[10,23] This way, **penta-3*β*** derivative has been fully dihydroxylated by means of *N*-methyl morpholine *N*-oxide (NMMO)/OsO_4 protocol, to afford oligosaccharide **6**, by a complete sterically favored *α*-facial stereoselective electrophilic addition (Scheme 3).[10,23,24]

The D-gulo stereochemistry of pentasaccharide **6** was assessed by NMR (and the identity was also confirmed by MALDI, SI), confirming that the dihydroxylation process occurred on the less hindered *α*-face of the alkene present in each unit of **penta-3*β***. This is clearly demonstrated by the upfield change of the anomeric resonances from 5.25 to 5.15 ppm in **penta-3*β*** to 4.65−4.75 ppm in **6**, with a change in their *J* constant from 2.8 to 8.2 Hz, that are typical of *trans* diaxial scalar coupling.[23]

To extend the scope of this method for the stereocontrolled one-pot synthesis of linear 2,3 unsaturated 1,4 oligosaccharides, we also carried out the reiterative assembly of diastereoisomeric epoxide **1*α*** with benzyl glycoside initiator **3*α***, which unlocks easy access to D-Mannose-based 1,4-linear oligosaccharides (Scheme 4).

Following the new protocol for the vinyl epoxide assembly, we successfully obtained a pool of oligomers, with a molar distribution of oligosaccharides centered on the trimer (33%) with a conversion of 52%. The four main isolated oligomers were characterized by NMR (**tetra-3*α*** also by MALDI). In particular, **tetra-3*α*** was investigated in detail (see SI), and as previously stated, taking advantage of known absolute configurations on C1, C4, and C5 of the initiator, the NOE correlations between protons H1 (5.07−5.21 ppm) and H4 (4.03−4.10 and 4.19−4.26 ppm) of the adjacent unit (Figure S68) unequivocally confirmed the oligomers as 2,3-unsaturated-*α*-1,4-oligosaccharides.

The remarkably complete *α*-stereoselectivity obtained by using vinyl epoxide **1*α*** clearly demonstrated that the process is stereospecific: the oligomerization of **1*α*** will form 2,3-unsaturated-*α*-1,4-oligosaccharides, while epoxide **2*β*** will always give rise to 2,3-unsaturated-*β*-1,4-oligosaccharides.

Moreover, the 2,3 unsaturated *α*-1,4 trisaccharide **tri-3*α*** was submitted to a *cis*-dihydroxylation with OsO_4/NMMO (Scheme 5), and in this case, the *β*-stereoselective attack of the electrophile is directed by the allyl substituents at C4 and C1, now located in the *α*-face.[23,33] Therefore, the corresponding dihydroxylated derivative **7**, which represents a 1,4-trisaccharide with a manno configuration, was the only stereoisomer obtained (65% yield).

To highlight the versatility of this procedure, which allows fast reactivity of relatively unreactive nucleophiles, we synthesized disaccharide **10*α***, which represents, for example, an epitope to better understand the carbohydrate recognition process by lectins[34] and a key Mannobioside to elucidate the mechanism of the interaction mode between antibiotic BMY-28864 (*Pm*) and mannose residues as well as the biological action of this antibiotic.[35] Using a 1:3 ratio between the glycosyl donor **1*α*** and the glycosyl acceptor **8*α***,[16] the microwave activated process is centered on the production of disaccharide **di-8*α***, obtained only together with trisaccharide **tri-8*α*** (ratio **di-8*α*/tri-8*α*** 80:20 (Scheme 6). Di- and trisaccharide were separated by chromatography, and **di-8*α*** was subjected to a *cis*-dihydroxylation with the typical OsO_4/NMMO protocol, to afford manno-derivative **9*α***. Debenzylation of **9*α*** under palladium-catalyzed hydrogenation afforded the desired, fully deprotected, disaccharide **10*α***.[36]

CONCLUSIONS

In conclusion, we have successfully realized a new, fast, and versatile one-pot stereospecific reiterative glycal-derived vinyl epoxide assembly for the preparation of linear *β*-1,4-D-Gulo and *α*-1,4-D-Manno oligosaccharides (2−6 units). It is noteworthy that the access to 2,3-unsaturated-1,4 oligosaccharides reinforce the interest for this methodology, especially considering that these structures are rather appealing in Medicinal Chemistry as unnatural sugars,[24,37−39] and also

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emphasizing a rare complete control over the desired degree of lipophilicity/hydrophilicity of the oligosaccharides synthesized. Moreover, the possibility of constructing the first unit bearing different functionalities opens several chances of easy glycoconjugation reactions of these products with various molecular/supramolecular entities such as proteins, synthetic polymers, nanoparticles, and metal complexes. Studies are in progress to synthesize long and branched polysaccharides exploiting this versatile new methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05247.

Full computational and experimental details and characterization data for all products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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