



Promoter-Controlled Synthesis and Conformational Analysis of Cyclic Mannosides up to a 32-mer

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Abstract: Cyclodextrins are widely used as carriers of small molecules for drug delivery owing to their remarkable host properties and excellent biocompatibility. However, cyclic oligosaccharides with different sizes and shapes are limited. Cycloglycosylation of ultra-large bifunctional saccharide precursors is challenging due to the constrained conformational spaces. Herein we report a promoter-controlled cycloglycosylation approach for the synthesis of cyclic α -(1 $\rightarrow$ 6)-linked mannosides up to a 32-mer. Cycloglycosylation of the bifunctional thioglycosides and (Z)-ynenoates was found to be highly dependent on the promoters. In particular, a sufficient amount of a gold(I) complex played a key role in the proper preorganization of the ultra-large cyclic transition state, providing a cyclic 32-mer polymannoside, which represents the largest synthetic cyclic polysaccharide to date. NMR experiments and a computational study revealed that the cyclic 2-mer, 4-mer, 8-mer, 16-mer, and 32-mer mannosides adopted different conformational states and shapes.

Introduction

Cyclic oligosaccharides are a family of macrocycle molecules which are made up of monosaccharide units linked by glycosidic bonds in a ring shape. Owing to their remarkable host properties for the formation of stable inclusion complexes with different guest molecules, cyclic oligosaccharides, especially the well-known cyclodextrins (CDs), have found wide application in pharmaceutical formulations, materials science, analytical chemistry, and the food industry.^[1–5] In particular, CDs and their analogues have been extensively used to enhance the stability, solubility and bioavailability of active pharmaceutical ingredients (APIs) by taking advantage of the supramolecular assembly of host-guest complexes.^[6] The development of CDs and their analogues as carriers of small-molecule drugs for drug delivery has attracted wide attention owing to their medium-sized hydrophobic cavity and excellent biocompatibility.^[7,8] However, the types of naturally occurring cyclic oligosaccharides obtained by enzymatic conversion are rare, thus impeding the understanding of structure–function relationships of cyclic oligosaccharides.

The recognition ability of cyclic oligosaccharides on guest molecules mainly relies on the size and the shape of their internal hydrophobic cavities.^[1,9] In comparison with native CDs, novel artificial cyclic oligo- and polysaccharides with different chemical microenvironments may possess diverse host properties for complexation with varied sizes of hydrophobic molecules. To date, conformational and functional studies of large-sized cyclic polysaccharides remain scarce due to the lack of pure cyclic polysaccharides in useful quantities. Therefore, access to sufficient amounts of well-defined cyclic polysaccharides is the key to exploring their potential as chiral receptors of various substrates for specific interactions.

Chemical synthesis of cyclic oligosaccharides must involve a cycloglycosylation step, which poses different challenges as compared with intermolecular glycosylation in traditional oligosaccharide synthesis.^[10,11] There are two main strategies for the construction of cyclic oligosaccharides. One strategy involves cyclooligomerization of a bifunctional saccharide monomer, which acts as both glycosyl donor and acceptor for the synthesis of a series of cyclic oligomers. By means of polycondensation of a disaccharide monomer installed with the cyanoethylidene and trityl groups at the appropriate positions, a range of cyclic oligosaccharides were obtained in one pot, in which the cyclic tetradecasaccharide composed of alternating D- and L-

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rhamnose moieties was the largest synthetic cyclic polysaccharide so far.^[12] Although this approach is efficient for the preparation of cyclic oligosaccharides from simple and readily available monomers, such as mono-, di-, and trisaccharides,^[10,13] the degree of polymerization is not controllable, resulting in the formation of multiple cyclic oligomers with different ring sizes that are notoriously difficult to separate.

In the second strategy, cycloglycosylation of a preformed linear bifunctional oligosaccharide precursor prepared by multistep elongation sequences predominantly leads to a cyclic oligosaccharide with a defined number of monomer units. To our knowledge, since the first total synthesis of cyclodextrins by Ogawa and co-workers,^[14] various types of cyclic oligosaccharides, which are limited to no more than deca-saccharides,^[15–17] as well as the smallest cyclodextrins CD3 and CD4,^[18] have been accessed synthetically based on this strategy. Due to the limited conformational space, in the case of ultra-large bifunctional precursors containing over ten monosaccharide units, the desired cyclic transition states for efficient ring closure are considered to be very difficult

to achieve. Thus, synthesis of ultra-large cyclic polysaccharides remains a daunting challenge.

Herein, we report promoter-controlled cycloglycosylation for the synthesis of a series of α -(1 $\rightarrow$ 6)-linked cyclic mannosides **1–5** of various sizes (Figure 1). Through cycloglycosylation of a linear bifunctional 32-mer polymannoside precursor under high-dilution conditions, a cyclic 32-mer polymannoside **5**, which represents the largest cyclic polysaccharide synthesized to date, was achieved. NMR experiments and a computational study of the cyclic 2-mer, 4-mer, 8-mer, 16-mer, and 32-mer mannosides were performed to provide information on the conformational states and shapes of different sizes of cyclic mannosides.

Results and Discussion

To synthesize the cyclic mannosides, the bifunctional saccharide precursor for intramolecular coupling is required to serve as both glycosyl donor and alcohol acceptor in one molecule. We envision that such a mannose-containing bifunctional system should be adequately stable when it is

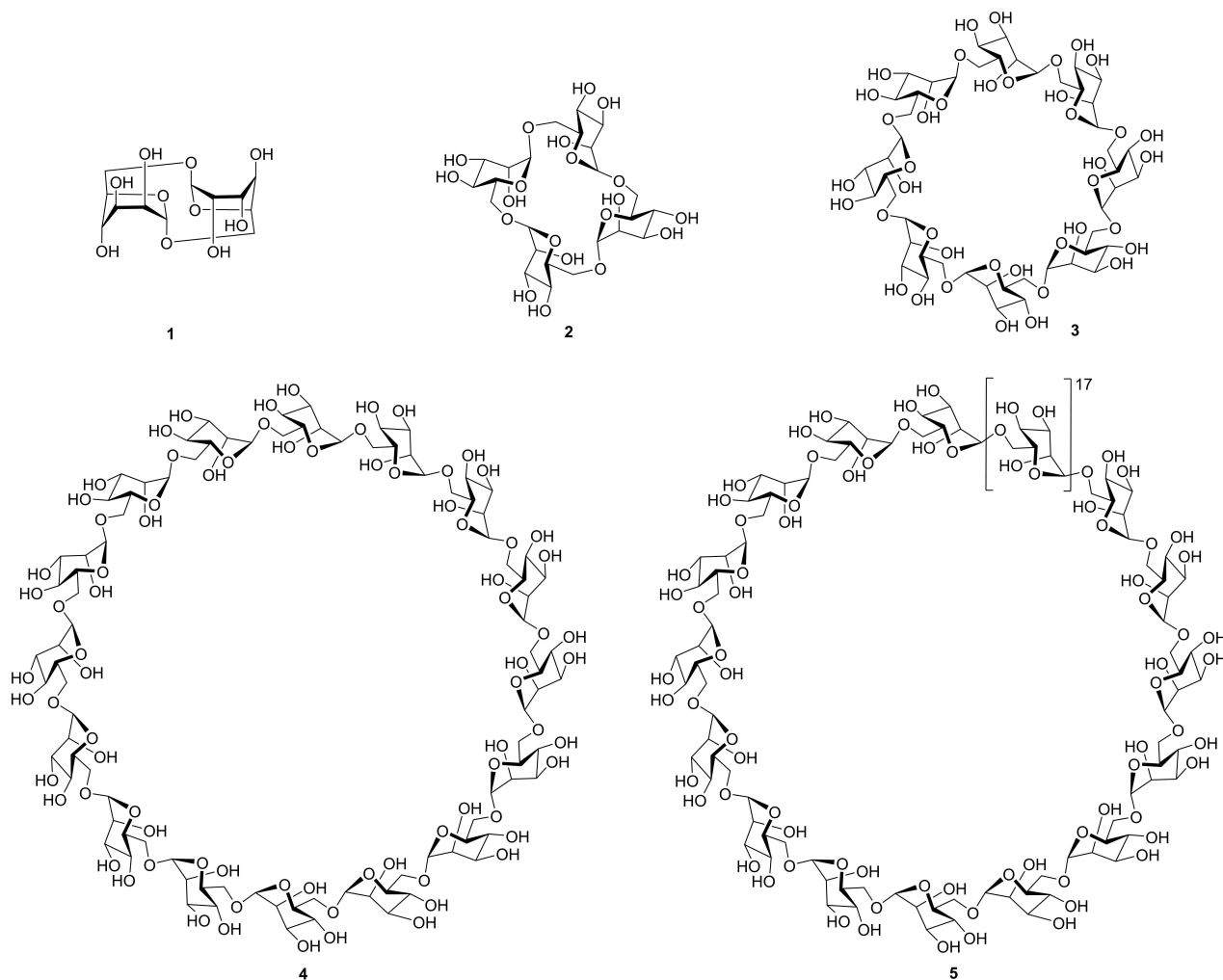


Figure 1. The structures of cyclic mannosides **1–5**.

prepared by releasing a free hydroxy group, relatively easy to synthesize, and reactive enough for an effective stereocontrolled cycloglycosylation. The 2-methyl-5-*tert*-butylphenyl thiomannoside was selected as the building block for sugar chain elongation because it is odorless and might avoid glycoside transfer.^[19] To reduce the occurrence of intermolecular glycosylation of the bifunctional precursors, high-dilution conditions, in which the concentration of the bifunctional precursors is set at 0.001 M, are employed to promote the intramolecular cyclization.^[20]

Initially, the stable and odorless α -(1 $\rightarrow$ 6)-linked disaccharide thioglycoside **6**^[21] containing a free hydroxy group at the C6 position was chosen as the bifunctional precursor for the synthesis of cyclic mannosides (Table 1). Under the activation of NIS (1.2 equiv.) and TMSOTf (0.1–0.2 equiv.) in dichloromethane at room temperature, almost no reaction occurred (entries 1 and 2). Unexpectedly, increasing the amount of NIS to 5 equivalents resulted in the formation of cyclic dimannoside **8** in 84 % yield (entry 3). These results implied that an excess amount of promoters dramatically accelerates the cycloglycosylation of the bifunctional disaccharide precursor. On the other hand, the stable glycosyl (*Z*)-ynenoate donor^[21–23] **7** (see the Supporting Information for details) was subjected to a catalytic cycloglycosylation under the promotion of Ph₃PAuOTf (0.1 equiv.) and TfOH (0.1 equiv.) in dichloromethane at room temperature. In contrast to that of the bifunctional disaccharide thioglycoside precursor **6**, cycloglycosylation of the bifunctional disaccharide (*Z*)-ynenoate precursor **7** afforded cyclic dimannoside **8** in 67 % yield, accompanied by the formation of a small amount of cyclic tetramer **9** in 23 % yield (entry 4).

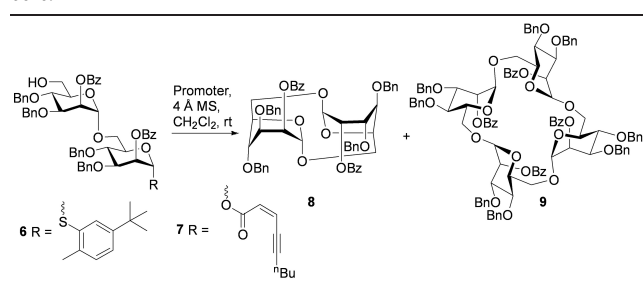
Because of the spatial restrictions, the conformations of the mannopyranosyl moieties of small-sized cyclic disaccharide **8** may not exist predominantly in the most stable ⁴C₁ or ¹C₄ forms. The NMR spectra of cyclic dimannoside **8** were consistent with the pattern of a monosaccharide moiety due to the symmetry of cyclic dimannoside **8** (see the Supporting

Information for details). By analysis of the ¹H, ¹³C, and 2D NMR spectra, the structure of compound **8** was unambiguously confirmed. The ¹J_{C1,H1} coupling constant (¹J_{C1,H1} = 177.8 Hz) and the ³J_{H-3,H-4} coupling constant (³J_{H-3,H-4} = 0 Hz) suggest that the mannopyranosyl rings of cyclic dimannoside **8** may adopt a B_{1,4} conformation.

Following this, cycloglycosylation of the bifunctional tetrasaccharide precursors, including thioglycoside **10** and glycosyl (*Z*)-ynenoate **11** (see the Supporting Information for details), was explored (Table 2). With thioglycoside **10** as the bifunctional precursor, almost no cyclic product was produced in the presence of NIS (5 equiv.) and TMSOTf (0.2 equiv.; entry 1). By increasing the amount of NIS to 6 equivalents for complete conversion of thioglycoside **10**, the cycloglycosylation took place to give the cyclic tetramer **9** in a low yield of 34 % along with the formation of a complex mixture of unknown by-products (entry 2). By replacing the promoters with more reactive IBr (2 equiv.) and AgOTf (3 equiv.),^[24] the cycloglycosylation of thioglycoside **10** was effective, providing cyclic tetrasaccharide **9** in satisfactory yield (78 %, entry 3). To our delight, cycloglycosylation of glycosyl (*Z*)-ynenoate **11** under the catalysis of Ph₃PAuOTf (0.1 equiv.) and TfOH (0.1 equiv.) proceeded smoothly to provide the small cyclic tetramer **9** in excellent yield (92 %, entry 4).

Next, we turned our attention to the synthesis of medium-sized cyclic octamer **14** through cycloglycosylation of the bifunctional octasaccharide precursors, that is, thioglycoside **12** and glycosyl (*Z*)-ynenoate **13** (see the Supporting Information for details; Table 3). Cycloglycosylation of the bifunctional thioglycoside precursor **12** with the assistance of NIS (6 equiv.) and TMSOTf (0.2 equiv.) led to only trace amounts of the desired cyclic octamer **14** (entry 1). Notably, with NIS (8 equiv.) and TMSOTf (0.3 equiv.) as promoters, cyclic octamer **14** was isolated in moderate yield (69 %) owing to the incomplete conversion of the bifunc-

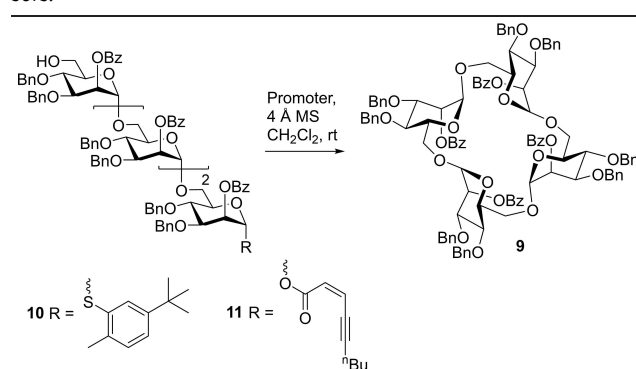
Table 1: Cycloglycosylation of the bifunctional dimannoside precursors.



Entry	Precursor	Promoter (equiv.)	Product (yield, %) ^[a]
1	6	NIS (1.2), TMSOTf (0.1)	8 (trace)
2	6	NIS (1.2), TMSOTf (0.2)	8 (trace)
3	6	NIS (5), TMSOTf (0.2)	8 (84)
4	7	Ph ₃ PAuOTf (0.1), TfOH (0.1)	8 (67) + 9 (23)

[a] Yield of the isolated product. Bz = benzoyl, Bn = benzyl, MS = molecular sieves, NIS = *N*-iodosuccinimide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, rt = room temperature.

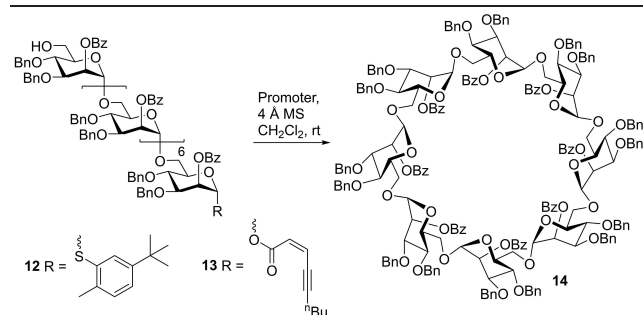
Table 2: Cycloglycosylation of the bifunctional tetramannoside precursors.



Entry	Precursor	Promoter (equiv.)	Yield [%] ^[a]
1	10	NIS (5), TMSOTf (0.2)	trace
2	10	NIS (6), TMSOTf (0.2)	34
3	10	IBr (2), AgOTf (3)	78
4	11	Ph ₃ PAuOTf (0.1), TfOH (0.1)	92

[a] Yield of the isolated product.

Table 3: Cycloglycosylation of the bifunctional octamannoside precursors.



Entry	Precursor	Promoter (equiv.)	Yield [%] ^[a]
1	12	NIS (6), TMSOTf (0.2)	trace
2	12	NIS (8), TMSOTf (0.3)	69
3	12	IBr (2), AgOTf (3)	90
4	13	Ph ₃ PAuOTf (0.2), TfOH (0.1)	92

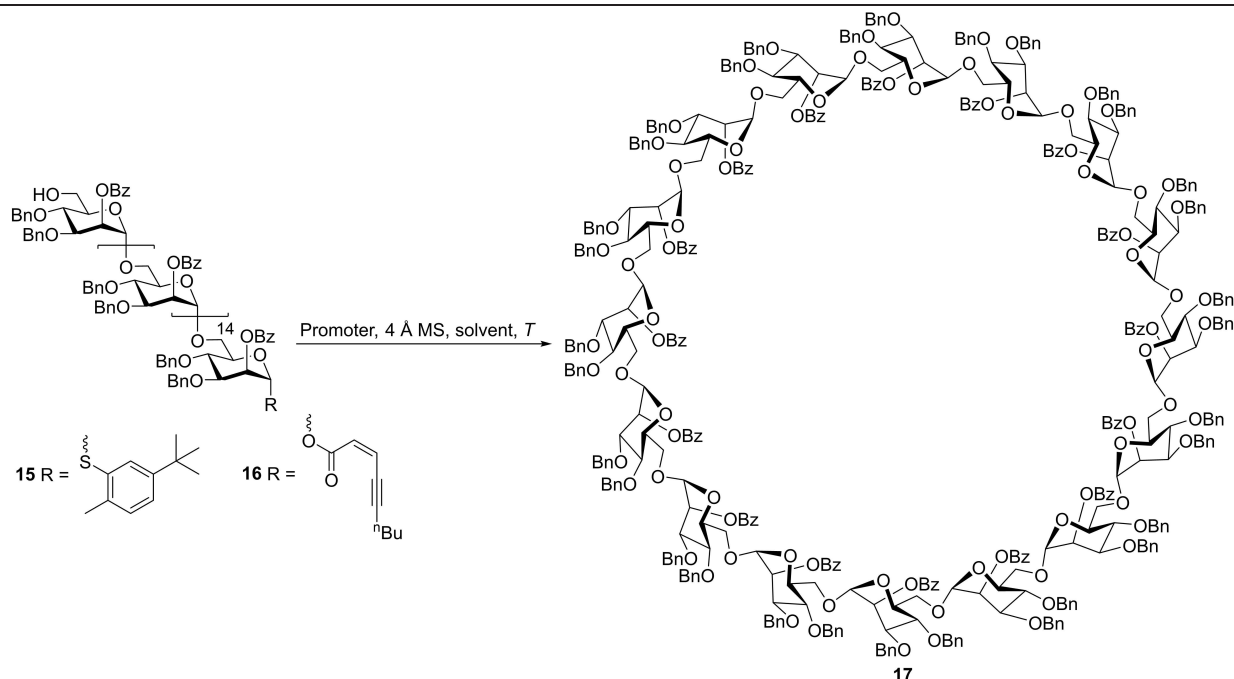
[a] Yield of the isolated product.

tional precursor (entry 2). Cycloglycosylation of **12** with IBr (2 equiv.) and AgOTf (3 equiv.) as promoters proceeded efficiently to afford cyclic octamer **14** in 90 % yield (entry 3). These results suggested that with the elongation of the linear

oligosaccharide chain, the more effective promoters for cycloglycosylation of bifunctional thioglycoside precursor were the combination IBr/AgOTf instead of the promoter system NIS/TMSOTf. Similar to cycloglycosylation of the bifunctional tetrasaccharide (*Z*)-ynenoate **11**, treatment of the bifunctional octasaccharide (*Z*)-ynenoate **13** with Ph₃PAuOTf (0.2 equiv.) and TfOH (0.1 equiv.) resulted in a clean and efficient macrocyclization reaction, affording the desired cyclic octamer **14** in 92 % yield (entry 4). The efficient cycloglycosylation of the bifunctional octasaccharide precursors for the synthesis of medium-sized cyclic oligosaccharides was in good agreement with the previous observations in the synthesis of α -, β -, and γ -CDs.^[10]

The construction of the large-sized cyclic hexadecasaccharide **17** is a demanding task because the constrained conformation spaces of the bifunctional hexadecasaccharide precursors have a low probability to undergo prearrangement into the desired cyclic transition state for efficient cycloglycosylation. Under the optimal thioglycoside activation conditions (2 equiv. of IBr and 3 equiv. of AgOTf) for the synthesis of cyclic tetra- and octasaccharides, cycloglycosylation of the bifunctional hexadecasaccharide thioglycoside **15**^[21] between 0 °C and room temperature afforded cyclic 16-mer **17** in 71 % yield albeit with minor amounts of hydrolyzed products (Table 4, entry 1). Nevertheless, when the hexadecasaccharide (*Z*)-ynenoate **16** (see the Supporting

Table 4: Cycloglycosylation of the bifunctional hexadecamannoside precursors.



Entry	Precursor	Promoter (equiv.)	Solvent	T [°C]	Yield [%] ^[a]
1	15	IBr (2), AgOTf (3)	CH ₂ Cl ₂	0 to rt	71
2	16	Ph ₃ PAuOTf (0.2), TfOH (0.1)	CH ₂ Cl ₂	rt	trace
3	16	Ph ₃ PAuOTf (0.6), TfOH (0.1)	CH ₂ Cl ₂	rt	23
4	16	Ph ₃ PAuOTf (0.6), TfOH (0.1)	toluene	0 to rt	52

[a] Yield of the isolated product.

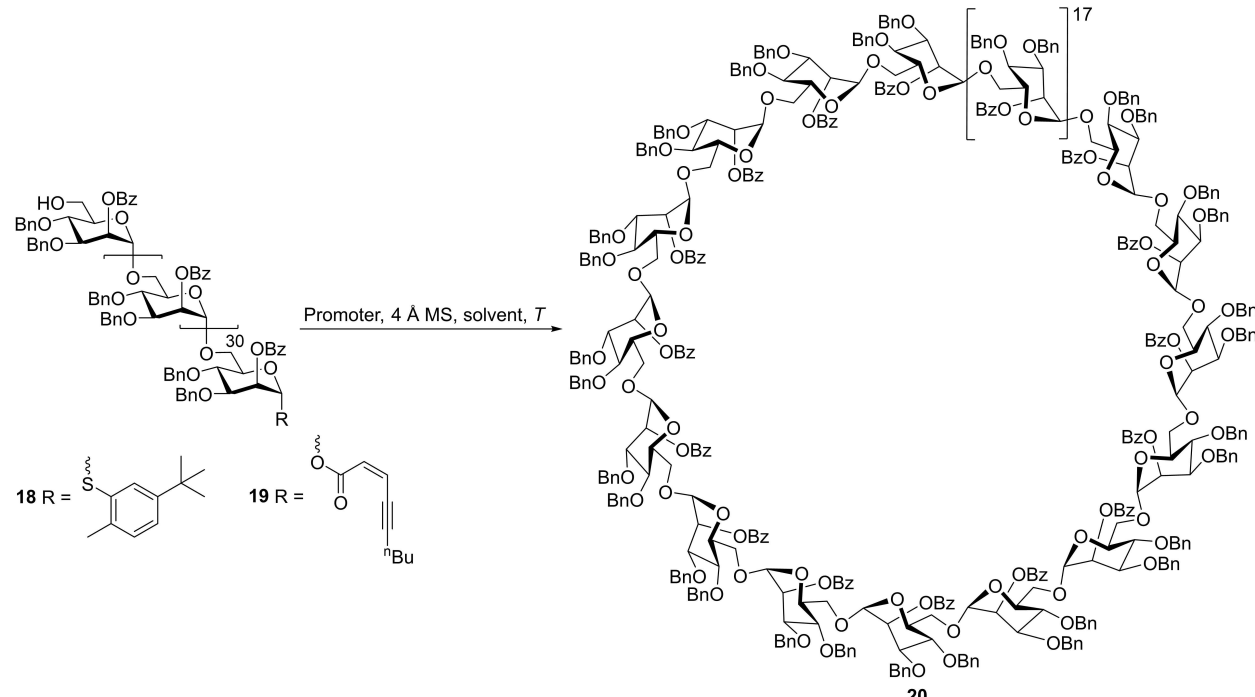
Information for details) was used as the bifunctional precursor, almost no reaction occurred under the catalysis of Ph_3PAuOTf (0.2 equiv.) and TfOH (0.1 equiv.) in CH_2Cl_2 at room temperature (entry 2). By increasing the amount of Ph_3PAuOTf to 0.6 equivalents, the cycloglycosylation under similar conditions produced cyclic 16-mer **17** in very low yield (23 %) owing to significant hydrolysis of bifunctional precursor **16** (entry 3). By replacing the solvent dichloromethane with toluene and simultaneously controlling the temperature at 0°C with warming to room temperature, cycloglycosylation under similar conditions enabled the formation of cyclic 16-mer **17** in moderate 52 % yield, although small amounts of hydrolyzed products and highly polar unknown compounds were also observed (entry 4). These results indicated that substoichiometric amounts of gold(I) promoter in toluene are favorable for the intramolecular coupling of the bifunctional (*Z*)-ynenoate **16** to provide the large-sized cyclic hexadecasaccharide **17**.

In view of the even more constrained conformation space of the ultra-long linear bifunctional 32-mer polymannoside precursors, synthesis of the ultra-large cyclic 32-mer polymannoside **20** is extremely challenging. Indeed, almost

no desired product was formed when cycloglycosylation of the bifunctional 32-mer thioglycoside **18** (see the Supporting Information for details) was carried out under the optimized conditions (2 equiv. of IBr and 3 equiv. of AgOTf) in dichloromethane at room temperature (Table 5, entry 1). By increasing the amounts of IBr and AgOTf to 8 and 12 equivalents, respectively, a very small amount of cyclic 32-mer polymannoside **20** (18 %) was generated along with a complex reaction system (entry 2). Similar results were observed when the temperature was further decreased to -20°C or the solvent was replaced with toluene.

Based on our previous experience in the synthesis of the ultra-long linear 32-mer polymannoside,^[21] we first chose 2 equivalents of Ph_3PAuOTf and 0.3 equivalents of TfOH to promote the cycloglycosylation of the bifunctional 32-mer (*Z*)-ynenoate **19** (see the Supporting Information for details) in CH_2Cl_2 at room temperature. However, only a low yield of cyclic 32-mer polymannoside **20** (34 %) was formed, accompanied by the hydrolyzed products and unknown by-products (entry 3). By employing toluene as the solvent, a similar cycloglycosylation gave cyclic 32-mer polymannoside **20** in a slightly higher yield (40 %, entry 4). Almost no

Table 5: Cycloglycosylation of the bifunctional 32-mer polymannoside precursors.



Entry	Precursor	Promoter (equiv.)	Solvent	$T [^\circ\text{C}]$	Yield [%] ^[a]
1	18	IBr (2), AgOTf (3)	CH_2Cl_2	rt	trace
2	18	IBr (8), AgOTf (12)	CH_2Cl_2	rt	18
3	19	Ph_3PAuOTf (2), TfOH (0.3)	CH_2Cl_2	rt	34
4	19	Ph_3PAuOTf (2), TfOH (0.3)	toluene	rt	40
5	19	Ph_3PAuOTf (2), TfOH (0.3)	toluene	-40	trace
6	19	Ph_3PAuOTf (2), TfOH (0.3)	toluene	0	50
7	19	Ph_3PAuOTf (0.9), TfOH (0.1)	toluene	-40 to 0	46
8	19	SPhosAuNTf_2 (0.9), TfOH (0.1)	toluene	-40 to 0	56

[a] Yield of the isolated product. SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl.

reaction took place when the cycloglycosylation temperature was set at -40°C , whereas adjusting the temperature to 0°C favored the cycloglycosylation, affording cyclic 32-mer **20** in 50 % yield (entries 5 and 6). Furthermore, we found that catalytic amounts of the gold(I) complex and TfOH were not reactive enough to promote the cycloglycosylation of the bifunctional 32-mer (*Z*)-ynenoate **19**, and the cycloglycosylation proceeded well in toluene at -40 to 0°C when an almost stoichiometric amount of Ph_3PAuOTf (0.9 equiv.) and a catalytic amount of TfOH (0.1 equiv.) were employed as promoters, providing cyclic 32-mer **20** in comparable yield (46 %, entry 7). When the gold(I) complex was changed to the more reactive SPhosAuNTf₂ (0.9 equiv.), the cycloglycosylation proceeded smoothly to provide the ultra-large cyclic 32-mer polymannoside **20** in satisfactory yield (56 %, entry 8). Thus, a stoichiometric amount of gold(I) promoter in toluene was crucial for inducing effective cycloglycosylation in the synthesis of ultra-large cyclic 32-mer **20**.

As indicated by the cycloglycosylation results for bifunctional precursors of different lengths, both the promoter system/leaving group and the stoichiometry are important for the cycloglycosylation, probably owing to the reactivity match and mismatch of the donor and acceptor.^[25] Under the high-dilution conditions, the poor nucleophilicity of the ultra-long linear polymannoside acceptor required the addition of a stoichiometric amount of promoter for effective cycloglycosylation, in which quenching of the promoter might be a competing reaction. Dichloromethane was suitable for the cycloglycosylation to form small- and medium-sized cyclic oligosaccharides in good to excellent yields. However, employing toluene as the solvent could promote the challenging cycloglycosylation to provide the large-sized cyclic polymannosides in higher yields than for dichloromethane, which might arise from the stabilizing effect of the π electrons of the phenyl ring on the transient glycosyl oxocarbenium ions.

Global deprotection of cyclic mannosides **8**, **9**, **14**, **17**, and **20** was met with difficulties due to the decreased solubility of the partially deprotected intermediates in the solvent system and the purification and characterization of highly polar and ultra-large cyclic polymannosides.^[26] After screening the solvent system, the deprotection sequence involving saponification with sodium methoxide in methanol and dichloromethane followed by hydrogenolysis over Pd/C in a mixture of THF and water proceeded well to remove all the benzoyl and benzyl groups in cyclic mannosides **8**, **9**, **14**, **17**, and **20** (Scheme 1). After purification by a combination of ion-exchange column chromatography, Sephadex LH-20 column and reverse phase C18 column chromatography, the target cyclic mannosides **1–5** were obtained in 63–77 % yield over two steps. The structures of cyclic mannosides **1–5** were fully confirmed by ^1H and ^{13}C NMR spectroscopy as well as high-resolution mass spectra (HRMS).

Relaxation and diffusion NMR experiments provided information on the dynamic properties of compounds **1–5** in solution. The experimental conditions were chosen considering 1 mg of each sample dissolved in deuterated water at 310 K. Considering identical execution conditions of the NMR measurements, relaxation and diffusion parameters

were influenced by the molecular size and shape adopted by the sample. The inversion recovery pulse sequence was used to measure T1 spin-lattice relaxation times, while T2 spin-spin relaxation measurements were obtained by using Carr–Purcell–Meiboom–Gill pseudo-2D experiment. No remarkable T2 differences were observed among the samples, with the exception of **1**, which showed a dramatically low T2 value (Table S1). This result supported the broadness of NMR signals of the cyclic 2-mer, and likely a tendency to form aggregates that reduced the tumbling rate. The tendency to form viscous solutions at a low concentration further supported the low solubility of **1** and low hydrophilic properties. T1 values increased with the molecular weight, although **5** showed a slightly lower T1 value than **4**. Pulsed-field gradient (PFG) NMR measurements were performed to determine the self-diffusion coefficients (*D*) of cyclic mannosides.^[27] The parameters that defined the decay functions, diffusion time (Δ) and diffusion gradient length (δ), were optimized through 1D DOSY NMR, and then 2D DOSY NMR experiments were acquired with a linear gradient incremented. Values of diffusion coefficient calculated increased in accordance with the corresponding molecular weight, except for **5**, which showed a *D* value higher than expected (Figure 2). Overall, the trend of relaxation and diffusion NMR properties followed our expectation and confirmed the low overall hydrophilicity of **1**; conversely, the higher conformational freedom of the biggest cyclic mannosides **4** and **5** supported a higher hydrophilicity and the population of numerous conformational states and shapes.

Then, a preliminary computational study was performed to evaluate the conformational behavior of **1–5** in solution. The exocyclic group of the α -1,6 Man residues can potentially experience three different staggered rotamers around the C5–C6 bond (*gg*, *gt* and *tg*), thus imparting remarkable conformational variability to the synthesized cyclic mannosides. With the aim of verifying the preferred rotamer distribution, we evaluated $^3J_{(\text{H5},\text{H6})}$ values and demonstrated a propensity for $\omega = 60^{\circ}$ (*gt*), especially for the smaller cyclic

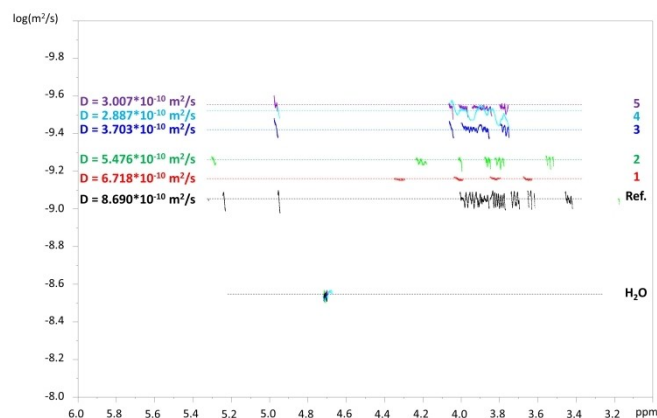
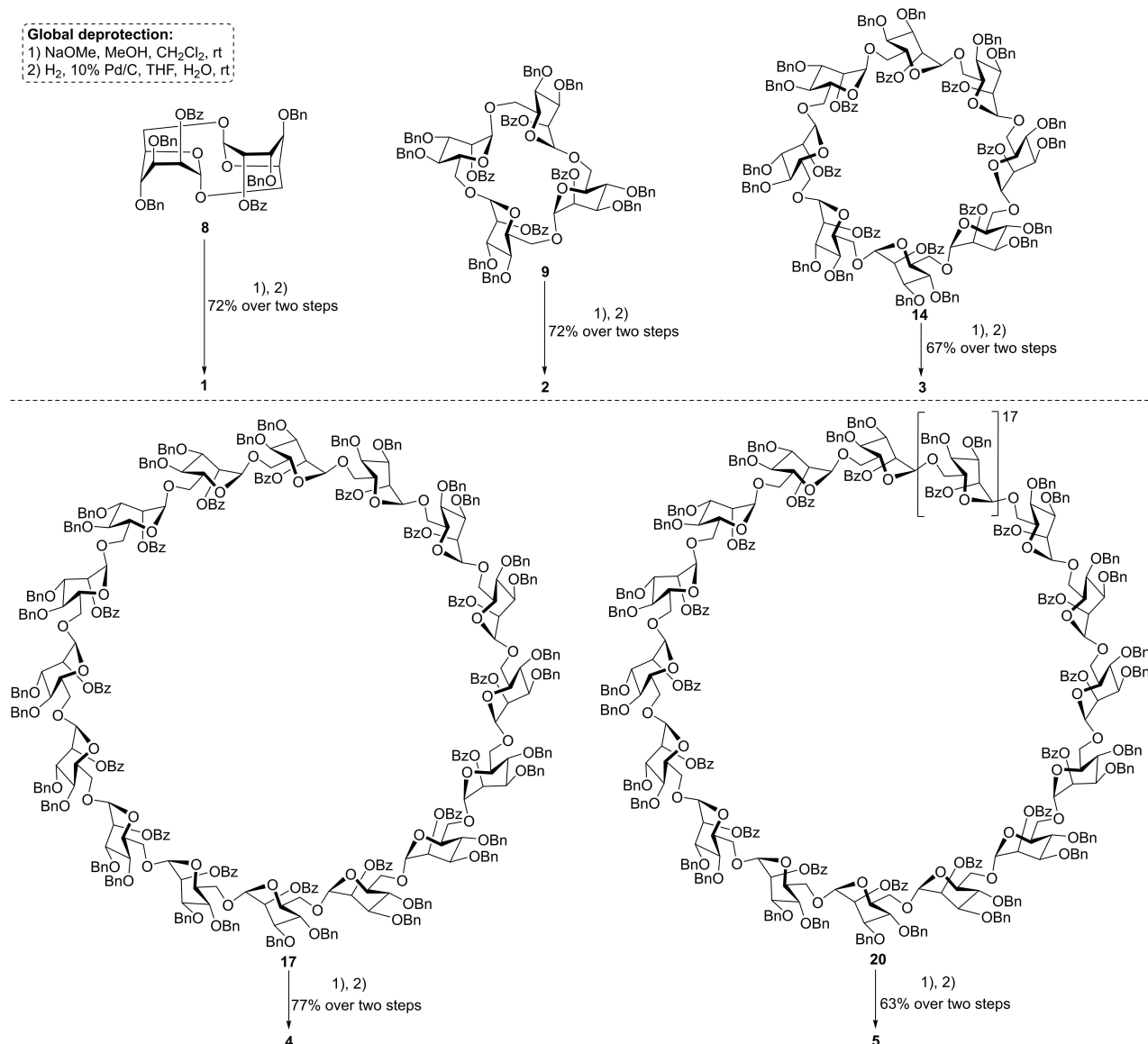


Figure 2. 2D DOSY spectra acquired on samples **1–5** in D_2O at 310 K. The intensities of different proton signals were integrated, normalized and fitted according to a following decay function: $I = I_0 \exp(-D^*(G^*\gamma^*\delta)^2*(\Delta\delta/3-\tau/2))$. DOSY = diffusion ordered spectroscopy.



Scheme 1. Synthesis of cyclic mannosides 1–5.

mannans. The longest, particularly samples **4** and **5**, possessed higher number and variability in terms of rotamer distribution in solution, and consequently showed higher flexibility and conformational freedom (Figures S1–S6). Based on the different conformational shapes and cavity formation of these cyclic mannosides, they can be used to form inclusion complexes with various sizes of small molecules and drugs. Further modification of these cyclic mannosides with different types of functional groups may expand their application as drug carriers and therapeutic agents.

Conclusion

In conclusion, we have developed a promoter-controlled cycloglycosylation approach for the synthesis of cyclic

mannosides up to a 32-mer with bifunctional thioglycosides and (*Z*)-ynenoates as bifunctional precursors. Under high-dilution conditions, the promoters were found to have a remarkable effect on the cycloglycosylation of bifunctional saccharide precursors. In particular, activation of the ultra-long saccharide (*Z*)-ynenoates by a stoichiometric amount of a gold(I) complex induced proper preorganization of the ultra-large cyclic transition state, leading to effective formation of the largest cyclic 32-mer mannoside **5** synthesized to date. NMR experiments and a computational study indicated that the cyclic mannosides **1–5** adopted different conformational states and shapes. Further application of these synthetic cyclic mannosides in drug delivery and carbohydrate-based materials is underway.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carbohydrates • Conformational Analysis • Cyclic Oligosaccharides • Cycloglycosylation • Glycosylation

- [1] a) J. Szejtli, *Chem. Rev.* **1998**, 98, 1743–1754; b) J. Szejtli, *Pure Appl. Chem.* **2004**, 76, 1825–1845; c) G. Crini, *Chem. Rev.* **2014**, 114, 10940–10975.
- [2] S. V. Kurkov, T. Loftsson, *Int. J. Pharm.* **2013**, 453, 167–180.
- [3] J. F. Feng, M. Tan, S. Zhang, B. J. Li, *Macromol. Rapid Commun.* **2021**, 42, 2100497.
- [4] L. Szente, J. Szeman, *Anal. Chem.* **2013**, 85, 8024–8030.
- [5] a) Y. Liu, Y. Chen, X. Gao, J. Fu, L. Hu, *Crit. Rev. Food Sci. Nutr.* **2022**, 62, 2627–2640; b) Y. Liu, D. E. Sameen, S. Ahmed, Y. Wang, R. Lu, J. Dai, S. Li, W. Qin, *Food Chem.* **2022**, 370, 131026.
- [6] A. Matencio, F. Garcia-Carmona, J. M. Lopez-Nicolas, *Food Funct.* **2016**, 7, 2367–2373.
- [7] A. C. Santos, D. Costa, L. Ferreira, C. Guerra, M. Pereira-Silva, I. Pereira, D. Peixoto, N. R. Ferreira, F. Veiga, *Drug Delivery Transl. Res.* **2021**, 11, 49–71.
- [8] D. A. Real, K. Bolanos, J. Priotti, N. Yutronic, M. J. Kogan, R. Sierpe, O. Donoso-Gonzalez, *Pharmaceutica* **2021**, 13, 2131–2167.
- [9] a) K. Koizumi, Y. Okada, S. Horiyama, T. Utamura, T. Higashiura, M. Ikeda, *J. Inclusion Phenom.* **1984**, 2, 891–899; b) T. Uchiyama, M. Kawamura, T. Urugami, H. Okuno, *Carbohydr. Res.* **1993**, 241, 245–248.
- [10] a) G. Gattuso, S. A. Nepogodiev, J. F. Stoddart, *Chem. Rev.* **1998**, 98, 1919–1958; b) K. Maiti, G. K. Samanta, G. C. Daskhan, N. Jayaraman, *Carbohydr. Chem.* **2017**, 42, 165–209.
- [11] a) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, 48, 1900–1934; *Angew. Chem.* **2009**, 121, 1932–1967; b) Y. Yang, X. Zhang, B. Yu, *Nat. Prod. Rep.* **2015**, 32, 1331–1355; c) M. M. Nielsen, C. M. Pedersen, *Chem. Rev.* **2018**, 118, 8285–8358; d) X. Li, Y. Yang, *Chin. J. Chem.* **2022**, 40, 1714–1728.
- [12] a) P. R. Ashton, S. J. Cantrill, G. Gattuso, S. Menzer, S. A. Nepogodiev, A. N. Shipway, J. F. Stoddart, D. J. Williams, *Chem. Eur. J.* **1997**, 3, 1299–1314; b) P. R. Ashton, C. L. Brown, S. Menzer, S. A. Nepogodiev, J. F. Stoddart, D. J. Williams, *Chem. Eur. J.* **1996**, 2, 580–591; c) P. M. Collins, M. Ali, *Abstracts of Eighth European Carbohydrate Symposium (EUROCARB VIII)*, Seville, Spain, **1995**, pA-93.
- [13] a) S. Paul, S. Raghothama, N. Jayaraman, *Carbohydr. Res.* **2009**, 344, 177–186; b) G. C. Daskhan, N. Jayaraman, *Chem. Commun.* **2014**, 50, 8554–8557; c) S. Houdier, P. J. A. Vottero, *Angew. Chem. Int. Ed.* **1994**, 33, 354–356; *Angew. Chem.* **1994**, 106, 365–367; d) H. Endo, M. Ochi, M. A. Rahman, T. Hamada, T. Kawano, T. Nokami, *Chem. Commun.* **2022**, 58, 7948–7951.
- [14] a) T. Ogawa, Y. Takahashi, *Carbohydr. Res.* **1985**, 138, C5–C9; b) Y. Takahashi, T. Ogawa, *Carbohydr. Res.* **1987**, 164, 277–296; c) Y. Takahashi, T. Ogawa, *Carbohydr. Res.* **1987**, 169, 127–149.
- [15] a) M. Mori, Y. Ito, J. Uzawa, T. Ogawa, *Tetrahedron Lett.* **1990**, 31, 3191–3194; b) M. Nishizawa, H. Imagawa, Y. Kan, H. Yamada, *Tetrahedron Lett.* **1991**, 32, 5551–5554; c) H. Kuyama, T. Nukada, Y. Ito, Y. Nakahara, T. Ogawa, *Carbohydr. Res.* **1995**, 268, C1–C6; d) T. Ogawa, *Chem. Soc. Rev.* **1994**, 23, 397–407.
- [16] a) M. Wakao, K. Fukase, S. Kusumoto, *J. Org. Chem.* **2002**, 67, 8182–8190; b) K. S. Kim, B. Y. Lee, S. H. Yoon, H. J. Jeon, J. Y. Baek, K. S. Jeong, *Org. Lett.* **2008**, 10, 2373–2376.
- [17] a) M. L. Gening, D. V. Titov, A. A. Grachev, A. G. Gerbst, O. N. Yudina, A. S. Shashkov, A. O. Chizhov, Y. E. Tsvetkov, N. E. Nifantiev, *Eur. J. Org. Chem.* **2010**, 2465–2475; b) D. V. Titov, M. L. Gening, A. G. Gerbst, A. O. Chizhov, Y. E. Tsvetkov, N. E. Nifantiev, *Carbohydr. Res.* **2013**, 381, 161–178.
- [18] D. Ikuta, Y. Hirata, S. Wakamori, H. Shimada, Y. Tomabechi, Y. Kawasaki, K. Ikeuchi, T. Hagimori, S. Matsumoto, H. Yamada, *Science* **2019**, 364, 674–677.
- [19] M. Collot, J. Savreux, J.-M. Mallet, *Tetrahedron* **2008**, 64, 1523–1535.
- [20] a) L. Rossa, F. Vögtle, *Top. Curr. Chem.* **1983**, 113, 1–86; b) H. Someya, T. Seki, G. Ishigami, T. Itoh, Y. Saga, Y. Yamada, S. Aoki, *Carbohydr. Res.* **2020**, 487, 107888.
- [21] X. Li, C. Li, R. Liu, J. Wang, Z. Wang, Y. Chen, Y. Yang, *Org. Lett.* **2019**, 21, 9693–9698.
- [22] a) X. Li, Z. Ma, R. Liu, M. Hurevich, Y. Yang, *Chin. J. Chem.* **2021**, 39, 3309–3314; b) L. Zhang, Y. Zhang Q Hua, T. Xu, J. Liu, Y. Zhu, Y. Yang, *Org. Lett.* **2022**, 24, 8381–8386; c) R. Liu, Y. Chen, J. Zheng, L. Zhang, T. Xu, P. Xu, Y. Yang, *Org. Lett.* **2022**, 24, 9479–9484.
- [23] B. Yu, *Acc. Chem. Res.* **2018**, 51, 507–516.
- [24] a) A. Meijer, U. Ellervik, *J. Org. Chem.* **2004**, 69, 6249–6256; b) A. Meijer, U. Ellervik, *J. Org. Chem.* **2002**, 67, 7407–7412.
- [25] a) S. van der Vorm, T. Hansen, J. M. A. van Hengst, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codee, *Chem. Soc. Rev.* **2019**, 48, 4688–4706; b) P. Xu, W. Xu, Y. Dai, Y. Yang, B. Yu, *Org. Chem. Front.* **2014**, 1, 405–414.
- [26] a) S. Wang, Y. Yang, Q. Zhu, G.-Q. Lin, B. Yu, *Curr. Opin. Chem. Biol.* **2022**, 69, 102154; b) G. Fittolani, T. Tyrikos-Ergas, D. Vargová, M. A. Chaube, M. Delbianco, *Beilstein J. Org. Chem.* **2021**, 17, 1981–2025.
- [27] Q. Zhu, Z. Shen, F. Chiodo, S. Nicolardi, A. Molinaro, A. Silipo, B. Yu, *Nat. Commun.* **2020**, 11, 4142.

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