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Practical and Scalable Synthesis of α-(1→4)-Linked Polysaccharides Composed of 6-*O*-Methyl-D-glucose

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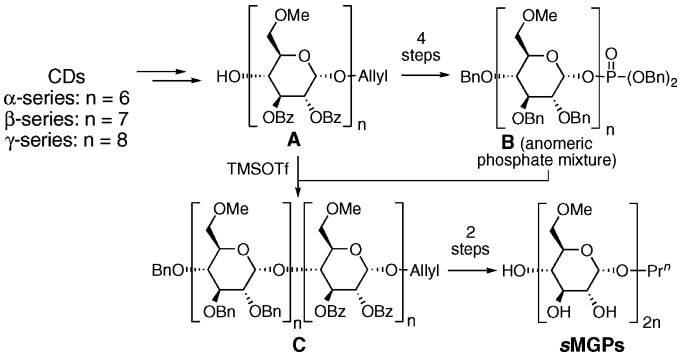
ABSTRACT



A second-generation synthesis of synthetic 6-*O*-methyl-D-glucose-containing polysaccharides (*s*MGPs) is reported. Glycosidation acceptor A and donor B are prepared from α-, *β*-, and *γ*-cyclodextrins in high yields. The glycosidation of A and B, followed by deprotection, furnishes *s*MGP 12-, 14-, and 16-mers. This synthesis has appealing features such as scalability, operational simplicity, and high overall yield.

In conjunction with our continuing efforts to study the product-regulation mechanism for the fatty acid biosynthesis in *Mycobacterium smegmatis*, we recently reported a synthesis of *synthetic* 6-*O*-methyl-D-glucose-containing polysaccharides (*s*MGPs, **7** in Scheme 1), which were designed based on the structure of 6-*O*-methyl-D-glucose-containing polysaccharides (MGPs), the saponification product of *natural* 6-*O*-methyl-D-glucose-containing lipopolysaccharides (MGLPs) (Figure 1).[1,2]

In the first-generation synthesis, we developed an efficient method for transforming cyclodextrin (CD) derivatives into linear oligosaccharides, which were used as building blocks for *s*MGPs (Scheme 1).[2] With the use of these *s*MGPs and *synthetic* 3-*O*-methyl-D-mannose-containing polysaccharides (*s*MMPs), we were able to demonstrate that *synthetic* polysaccharides mimic the chemical and biological roles of *natural* polysaccharides.[3] With this exciting result in hand, we realized that it had become critically important to secure the supply of a relatively large quantity of *s*MGPs for further studies. The first-generation synthesis is highly convergent and has served well for us to secure a series of *s*MGPs. However, we noticed that the key glycosidation in this synthesis was not ideal for a large-scale synthesis. Namely, this glycosidation was performed in the presence of the Mukaiyama acid ($SnCl_3ClO_4$, prepared in situ from $AgClO_4$ and $SnCl_4$).[4] Unlike in the *s*MMP series, the amount of the Mukaiyama acid required in the *s*MGP series increased with an increase in the substrate size. For large oligomers, more

(1) For isolation and characterization of MGLPs, see (a) Lee, Y. C.; Ballou, C. E. *J. Biol. Chem.* **1964**, *239*, PC3602. (b) Forsberg, L. S.; Dell, A.; Walton, D. J.; Ballou, C. E. *J. Biol. Chem.* **1982**, *257*, 3555. For the revised structure of MG(L)P, see (c) Tuffal, G.; Albigot, R.; Rivière, M.; Puzo, G. *Glycobiology* **1998**, *8*, 675.

(2) Meppen, M.; Wang, Y.; Cheon, H.-S.; Kishi, Y. *J. Org. Chem.* **2007**, *72*, 1941.

(3) (a) Cheon, H.-S.; Wang, Y.; Ma, J.; Kishi, Y. *ChemBioChem* **2007**, *8*, 353. (b) Papaioannou, N.; Cheon, H.-S.; Lian, Y.; Kishi, Y. *ChemBioChem*, in press.

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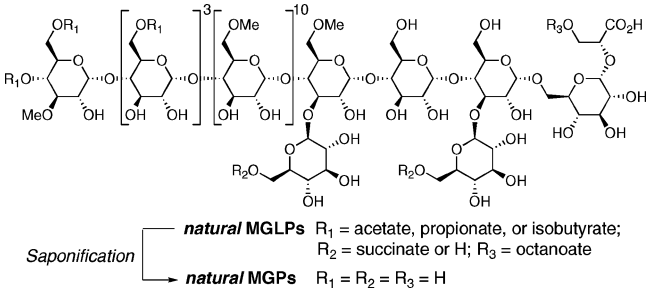
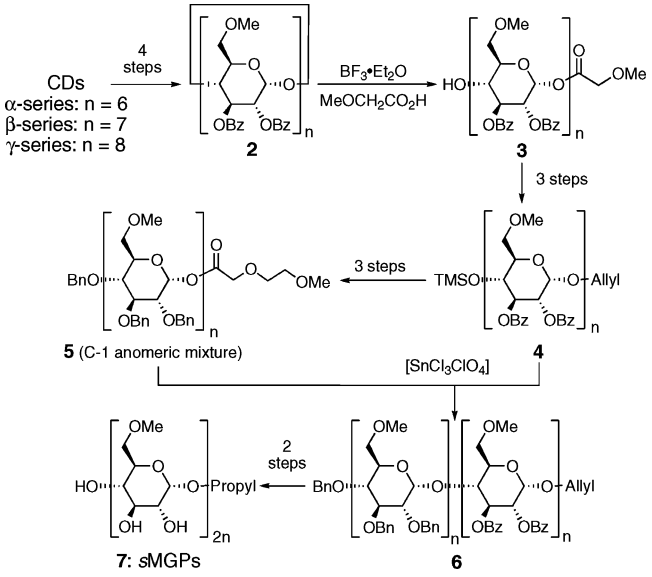


Figure 1. Structures of *natural* MGLPs and MGPs.

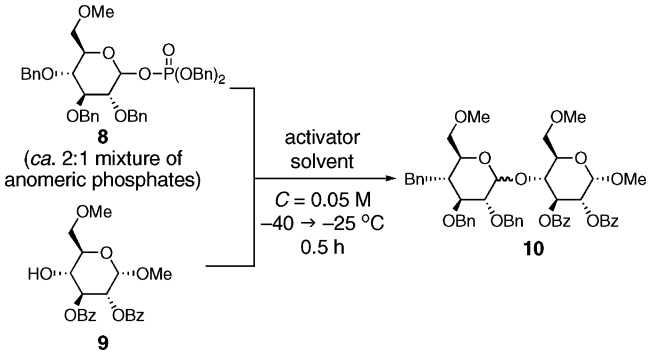
than 1 equiv of the acid was required; for an example, 3 equiv of the acid were used to effectively achieve the coupling of 14-mer **5** ($n = 14$) with 6-mer **4** ($n = 6$) to form 20-mer **6**. The handling of a large amount of the Mukaiyama acid presented a technical challenge, thereby urging us to revisit the glycosidation. In this letter, we wish to report a scalable, operationally simple, and high-yielding synthesis of *s*MGPs.

Scheme 1. First-Generation Synthesis of *s*MGPs



Using the monomeric substrates (Table 1), we screened a variety of the glycosidation methods reported in the literature.[5] Through this screening, the glycosidation via an anomeric phosphate, originally reported by Hashimoto, Honda, and Ikegami, emerged as the most promising candidate;[6,7] in particular, we were encouraged by the

Table 1. Effects of the Solvent and Activator



entry	activator	solvent	yield[a]	selectivity (α:β)
1	TMSOTf	CH_2Cl_2	90%	5:1
2	TMSOTf	THF	10%	10:1
3	TMSOTf	CH_3CN	80%	1.4:1
4	$BF_3{\cdot}Et_2O$	CH_2Cl_2	24%	3.3:1
5	HBF_4	CH_2Cl_2	50%	2.5:1
6	TMSOTf	Et_2O	88%	20:1
7	TMSOTf	$CH_2Cl_2-Et_2O$[b]	91%	20:1

[a] Combined yield of α- and β-linked isomers. [b] A 1:1 mixture of $CH_2Cl_2-Et_2O$.

operational simplicity. Unlike in the *s*MMP series,[8] we could not take advantage of the C2 acyl group for controlling the stereochemical course of glycosidation. However, choosing either diethyl ether or a 1:1 mixture of diethyl ether and methylene chloride as a solvent, we can achieve a high stereoselectivity.[9] Overall, the phosphate-based glycosidation shows several appealing features, including operational simplicity, high stereoselectivity, and high yield.

These appealing features encouraged us to extend the phosphate-based glycosidation to the synthesis of *s*MGPs. Our first task was the preparation of oligosaccharide anomeric phosphates. Among several methods known for the preparation of anomeric phosphates, we adopted the protocol reported by Wong,[10] with two modifications: (1) $NaHCO_3$ was added to accelerate the phosphitylation with a lower loading of $Et_2NP(OBn)_2$ and (2) 1-*H* 1,2,4-triazole was used

(4) (a) Mukaiyama, T.; Takashima, T.; Katsurada, M.; Aizawa, H. *Chem. Lett.* **1991**, 533. (b) Mukaiyama, T.; Katsurada, M.; Takashima, T. *Chem. Lett.* **1991**, 985. (c) Mukaiyama, T.; Matsubara, K.; Sasaki, T.; Mukaiyama, T. *Chem. Lett.* **1993**, 1373.

(5) For comprehensive monographs, general reviews, and examples relevant to this work, see references 9, 10, and 11 cited in Hsu, M. C.; Lee, J.; Kishi, Y. *J. Org. Chem.* **2007**, *72*, 1931.

(6) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685.

(7) Seeberger has extensively used anomeric phosphates for both solution- and solid-phase syntheses. For examples of solution-phase synthesis, see (a) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211. (b) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545. (c) Codee, J. D. C.; Seeberger, P. H. *ACS Symp. Ser.* **2007**, *960*, 150−164 and references cited therein. For recent examples of solid-phase synthesis, see (d) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523. (e) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770 and references cited therein.

(8) Cheon, H.-S.; Lian, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 3323.

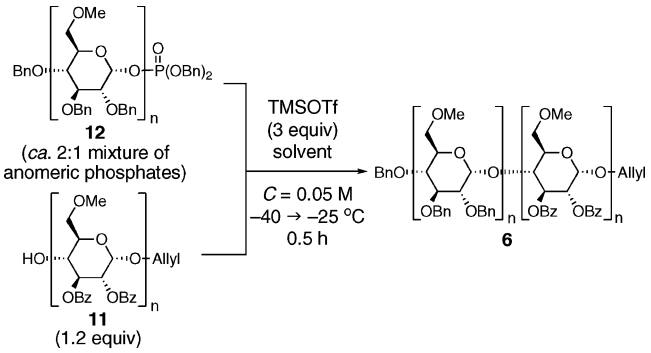
(9) The stereoselectivity of the coupled product was determined from the ^1H NMR spectrum of the crude product, and the stereochemistry was assigned by nuclear Overhauser effect studies. It was further confirmed after deprotection to *s*MGPs; the glycosidic protons of β-linked anomers are known to give resonances shifted to upfields compared to those of the corresponding α-linked anomers.

(10) (a) Pederson, R. L.; Esker, J.; Wong, C.-H. *Tetrahedron* **1991**, *47*, 2643. (b) Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260.

to substitute potentially explosive 1-*H* tetrazole. In this manner, the anomeric phosphates (ca. 2:1 anomeric mixtures) were readily obtained from the corresponding hexoses in a two-step, one-pot sequence, that is, the formation of phosphites, followed by H_2O_2 oxidation. The anomeric phosphates thus prepared were stable for at least several weeks in a refrigerator (4 °C).

Unfortunately, because of the poor solubility of substrates in the oligosaccharide series (entry 1, Table 2), we could not employ the conditions optimized for the synthesis of disaccharide (entries 6 and 7, Table 1). This technical difficulty was overcome by using methylene chloride as the solvent, and then the scalability and reliability were demonstrated (Table 2). However, the use of methylene chloride as the solvent caused the stereoselectivity of glycosidation to decline from >20:1 to 5:1. Fortunately, the reduction in stereoselectivity did not present a technical problem for the isolation of the desired α-anomer in a pure form; as the α-anomers were found to be much less polar than the *β*-anomers, flash column chromatography (silica gel) was sufficient to isolate the pure desired products. By this manner, the pure α-anomer was isolated in approximately 60% yields for all the cases.

Table 2. Glycosidation in the Oligomer Series

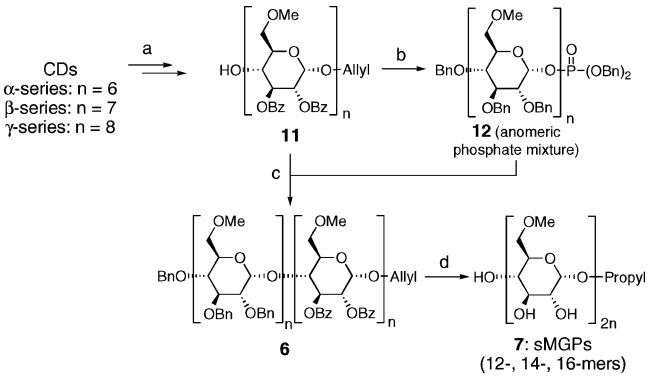


entry	*n*	scale (donor)	solvent	yield[a]	selectivity (α:*β*)
1	7	10 mg	CH_2Cl_2−Et_2O[b]	<20%	
2	6	29 mg	CH_2Cl_2	70%	5:1
3	7	90 mg	CH_2Cl_2	72%	5:1
4	7	1.17 g	CH_2Cl_2	71%	5:1
5	8	110 mg	CH_2Cl_2	71%	5:1
6	8	1.32 g	CH_2Cl_2	70%	5:1

[a] Combined yield of α- and *β*-linked isomers. [b] A 1:1 mixture of CH_2Cl_2−Et_2O.

In conclusion, we have developed a second-generation synthesis of *s*MGPs (Scheme 2). The key step in this synthesis is the phosphate-based glycosidation, **11** + **12** → **6**. This glycosidation is operationally simple and suited for gram-scale synthesis; indeed, we were able to carry out a synthesis, starting with 6.8 g of *β*-CD and obtaining more than 400 mg of *s*MGP 14-mer.

Scheme 2. Synthesis of *s*MGPs from CDs[a]



[a] Reagents and conditions: (a) See reference 2. (b) (1) (i) NaOMe, CH_2Cl_2−MeOH; (ii) BnBr, NaH, DMF, 73%; (2) $(Ph_3P)_3RhCl$, EtOH−toluene, reflux, followed by H_3O^+ workup, 76%; (3) $Et_2NP(OBn)_2$, 1*H*-1,2,4-triazole, $NaHCO_3$, CH_2Cl_2, followed by H_2O_2 workup, 85%; (c) TMSOTf, CH_2Cl_2, −40 → −25 °C, 60% (α-anomer). (d) (i) H_2, $Pd(OH)_2$ on C, CH_2Cl_2−MeOH; (ii) NaOMe, CH_2Cl_2−MeOH, 73%. Note: Indicated yields are for the *β*-CD series, and comparable yields were observed for both the α- and *γ*-CD series.

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Supporting Information Available: Experimental details and ^1H NMR spectra (12 pages). This material is available free of charge via the Internet at http://pubs.acs.org

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