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Synthesis of PI-88 analogue using novel *O*-glycosidation of *exo*-methylenesugars

Rie Namme, Takashi Mitsugi, Hideyo Takahashi and Shiro Ikegami*

School of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan

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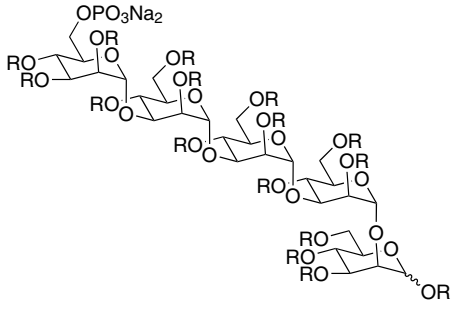
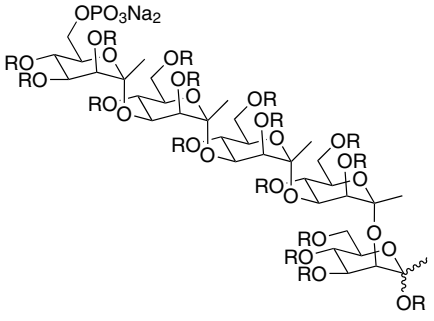
Abstract—Acid-promoted α-stereoselective *O*-glycosidation of 1-*exo*-methylenesugars was successfully applied to the synthesis of a PI-88 analogue. By using methanesulfonic acid as a promoter, 1′-*C*-methyl-α-disaccharides with *p*-methoxybenzyl protection were obtained in high yield. The sequence of selective deprotection and glycosidation provided 1-*C*-methyl-pentasaccharide efficiently.

In this decade, the development of new drug candidates involving tumor metastasis and angiogenesis inhibitory properties has been an attractive approach to cancer therapy. Heparanase is one of the key enzymes implicated in this issue. It has been known that sulfated polysaccharides such as heparin, dextran sulfate and xylan sulfate are effective inhibitors of heparanase and thus suppress tumor metastasis.[1] In 1999, Parish et al. developed phosphomannopentaose sulfate (PI-88) (**1**) from the yeast *P. holstii*, which consists of five mannose units linked with α-glycosidic bonds (Fig. 1). It shows potent heparanase inhibitory activity and antiangiogenesis properties, and is undergoing a Phase II clinical program in metastatic melanoma.[2]

We have previously demonstrated an efficient *O*-glycosidation of 1-*exo*-methylenesugars promoted by trifluoromethanesulfonic acid (TfOH).[3] Using glucose-derived glycosyl acceptors, α-ketodisaccharides were obtained in excellent yield. It was the first example of acid-promoted *O*-glycosidation of *exo*-glycals.[4–6] It should be noted that the glycosidic linkages are formed in a completely α-stereoselective manner. Taking advantage of this α-selective glycosidation, we explored the synthesis of a ketoside type of oligosaccharides. For our attempt to synthesize new biologically active compounds, the synthesis of 1-*C*-methyl-substituted mannosyl pentasaccharide **2** which mimics PI-88, was undertaken utilizing our α-stereoselective *O*-glycosidation of *exo*-glycals.



1: Phosphomannopentaose sulfate (PI-88)
(R = SO_3Na or H)



2: Methyl-substituted analogue of PI-88
(R = SO_3Na or H)

Figure 1.

Keywords: 1-*exo*-Methylenesugar; *O*-Glycosidation; PI-88; Heparanase inhibitor.
* Corresponding author. Tel.: +81 426 85 3728; fax: +81 426 85 1870; e-mail: shi-ike@pharm.teikyo-u.ac.jp

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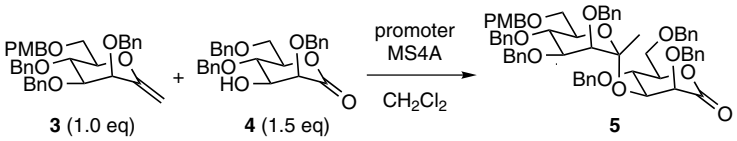
Table 1. The glycosidation of **3** and **4** using various acids as a promoter



Entry	Promoter	(Mol %)	Temp (°C)	Time	**5**	**6**	**7**	**8** Yield (%)
1	TfOH	10	−78	30 min	49	14	4	—
2	TMSOTf	10	0	20 min	—	67	40	—
3	TMSOTf	10	−78	1 h	45	—	—	—
4	MsOH	20	0	20 min	38	—	—	17
5	MsOH	20	−78	90 min	77	—	—	—
6	TFA	50	0	7 h	15	—	—	46
7	CSA	20	−78 → −5	8 h	34	—	—	29

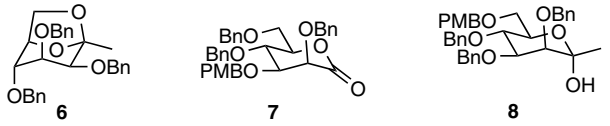
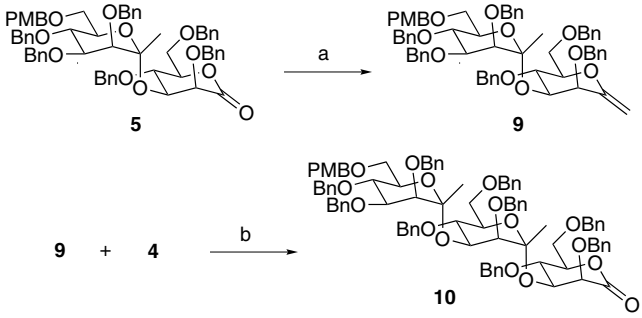


Figure 2.



Scheme 1. Reagents and conditions: (a) Cp_2TiMe_2, toluene, 80 °C, 67%; (b) MsOH, MS4A, CH_2Cl_2, −78 °C, 36%.

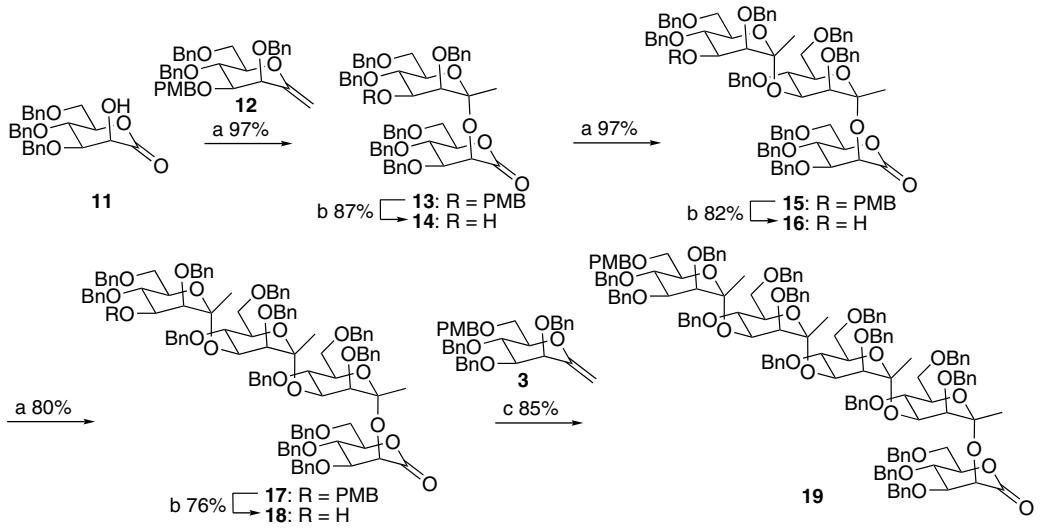
For the construction of 1-*C*-methyl-substituted oligosaccharides, the *p*-methoxybenzyl (PMB) group was used to differentiate hydroxyl groups in 1-*exo*-methylenesugars. After glycosidation with a hydroxylactone acceptor, the obtained disaccharides can be converted into the corresponding glycosyl donors by the methylenation and also into the acceptors by the selective removal of PMB. Although TfOH gave the best result in the case of *O*-glycosidation of *O*-benzyl protected methylenesugars,[3a] we found that *O*-glycosidation of 6-*O*-(*p*-methoxybenzyl)-1-*exo*-methylenesugar **3** with the hydroxylactone **4** under strongly acidic conditions was not promising (Table 1).[7] When strong acids such as TfOH and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were used as a promoter, the 1′-*C*-methyl-α-disaccharide **5**[8] was obtained in low yield. Probably, cleavage of the PMB ether took place and cyclized product **6** was formed (Fig. 2, entries 1 and 2). Interestingly, the intermolecular migration of the PMB group occurred at the same time to afford 3-*O*-(*p*-methoxybenzyl)-mannonolactone **7**. Trifluoroacetic acid (TFA) did not promote *O*-glycosidation sufficiently and the hydrated product **8** was formed instead (entry 6). After a survey of various acids, it was found that methanesulfonic acid (MsOH) was the best promoter, which did not cause the removal of PMB and promoted the desired *O*-glycosidation efficiently with α-stereoselectivity (entry 5).

Then our attention was focused on sugar chain-elongation. At first, methylenation of a disaccharide lactone and the subsequent glycosidation were examined. The methylenation of the disaccharide **5** with Cp_2TiMe_2 afforded disaccharide donor **9**,[9,3b] then the second glycosidation was tried. To our disappointment, disaccharidic *exo*-glycals were not suitable for the MsOH-promoted glycosidation with alcohols. The *O*-glycosidation of the *exo*-glycal **9** resulted in drastic decrease of reactivity, and the corresponding trisaccharide **10** was obtained in 36% yield (Scheme 1). Therefore, we gave up this strategy.

Next, we tried glycosidation of monosaccharidic *exo*-glycals with oligosaccharidic acceptors. The 3′-*O*-(*p*-methoxybenzyl)-disaccharide **13**[8] was similarly prepared by the glycosidation of **12** with **11**, then selectively deprotected with DDQ to provide the disaccharidic glycosyl acceptor **14**. In contrast to the glycosidation of the disaccharidic *exo*-glycal **9**, the glycosidation of **12** with the disaccharide **14** proceeded smoothly in the same manner and the trisaccharide **15** was obtained as a single isomer. Furthermore, the chain-elongation sequence, involving removal of PMB and subsequent glycosidation, furnished the pentasaccharide **19** in 25% overall yield from **11** in seven steps (Scheme 2).

In conclusion, we have designed a 1-*C*-methyl-substituted analogue of PI-88, and a synthetic study was explored based on the novel *O*-glycosidation of *exo*-glycals. It was found that MsOH was the best promoter in this glycosidation for the substrate containing the PMB ether, and thus mannosyl pentasaccharide **19** was synthesized. To study the biological activities, further conversion to the PI-88 analogue is under investigation.

Typical experimental procedure: To a mixture of 1-*exo*-methylenesugar **12** (104 mg, 0.18 mmol), hydroxylactone **11** (68 mg, 0.15 mmol) and molecular sieves 4A (90 mg)



Scheme 2. Synthesis of pentasaccharide. Reagents and conditions: (a) **12** (1.5 equiv), MsOH, MS4A, CH_2Cl_2, −78 °C; (b) DDQ, CH_2Cl_2, H_2O, 0 °C; (c) **3** (1.5 equiv), MsOH, MS4A, CH_2Cl_2, −78 °C.

in CH_2Cl_2 (1.8 mL), were added MsOH (2.0 μL, 0.03 mmol) at −78 °C. The reaction mixture was stirred for 90 min at −78 °C, then quenched with triethylamine. After removal of the solvent, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane 1:3) to give disaccharide **13** (149 mg, 97%).

Acknowledgements

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7. Cleavage of a PMB ether under acidic conditions has been reported: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
8. Characterization data: Compound **5**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.36–7.09 (m, 32H, Ar*H*), 6.73–6.71 (m, 2H, Ar*H*), 5 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.84 (d, 1H, *J* = 11.5 Hz, ArCH_2–), 4.73 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.73 (d, 1H, *J* = 11.5 Hz, ArCH_2–), 4.62 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.60 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.52–4.30 (m, 11H), 4.23 (d, 1H, ArCH_2–), 4.03 (m, 1H, 5′-H), 4.94 (m, 1H, 4-H), 3.88 (dd, 1H, *J* = 9.62, 9.62 Hz, 4′-H), 3.73 (s, 3H, ArOCH_3), 3.62 (dd, 1H, *J* = 10.7, 4.9 Hz, 6-H), 3.54 (dd, 1H, *J* = 10.7, 4.9 Hz, 6-H), 3.36 (m, 3H), 1.29 (s, 3H, –CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.2, 158.9, 1309, 138.8, 138.7, 137.6, 137.0, 136.9, 130.8, 129.3, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.3, 127.2, 113.5, 102.4, 80.7, 79.8, 79.5, 74.9, 74.7, 74.4, 74.2, 74.0, 73.4, 73.2, 73.0, 72.7, 72.6, 72.0, 70.1, 69.5, 68.7, 55.2, 22.4. Compound **13**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.35–7.16 (m, 30H, Ar*H*), 7.13–7.10 (m, 2H, Ar*H*), 6.84–6.81 (m, 2H, Ar*H*), 4.95 (d, 1H, *J* = 11.6 Hz, ArCH_2–), 4.85–4.82 (m, 2H, ArCH_2–), 4.78 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.70 (d, 1H, *J* = 11.3 Hz, ArCH_2–), 4.62 (d, 1H, *J* = 12.6 Hz, ArCH_2–), 4.61 (d, 1H, *J* = 11.6 Hz, ArCH_2–), 4.55–4.51 (m, 4H, ArCH_2–), 4.47 (d, 1H, *J* = 12.1 Hz, ArCH_2–), 4.43–4.41 (m, 1H, 3′-H), 4.40 (d, 1H, *J* = 12.1 Hz, ArCH_2–), 4.33 (d, 1H, *J* = 11.6 Hz, ArCH_2–), 4.29 (d, 1H, *J* = 11.6 Hz, ArCH_2–), 4.13 (ddd, 1H, *J* = 4.1, 4.1, 7.4 Hz, 5-H), 4.04 (ddd, 1H, *J* = 3.9, 3.9, 9.6 Hz, 5′-H), 3.88 (dd, 1H, *J* = 9.6, 9.4 Hz, 4′-H), 3.82 (dd, 1H, *J* = 1.1, 2.5 Hz, 3-H), 3.80 (dd, 1H, *J* = 1.1, 7.4 Hz, 4-H), 3.71 (s, 3H, ArOCH_3), 3.63 (m, 1H, 2-H), 3.64–3.63 (m, 2H, 6′-H), 3.57–3.56 (m, 2H, 6-H), 1.15 (s, 3H, –CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.0 (1-C), 159.1, 138.7, 138.5, 137.7, 137.5, 136.9, 131.0, 129.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 113.7, 102.7 (1′-C), 80.5 (3′-C), 79.2 (2′-C), 78.1 (5-C), 77.5 (3-C), 75.8 (4-C), 74.7 (Ar*C*H$_2$–), 74.5 (4′-C), 73.9 (Ar*C*H$_2$–), 73.4 (Ar*C*H$_2$–), 73.1 (5′-C), 73.0 (Ar*C*H$_2$–), 72.9 (Ar*C*H$_2$–), 72.1 (Ar*C*H$_2$–), 71.9

(ArCH_2–), 69.4 (6′-C), 68.7 (6-C), 67.8 (2-C), 55.1 (ArOCH_3), 21.9 (–CH_3).

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