CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis and biological evaluation of O-methylated glycolipids related to PGLs via direct stereoselective glycosidation and sequential Suzuki-Miyaura coupling using boracyclane

Authors: Ko Sato, Zakaria Omahdi, Kensuke Shibata, Koh-hei Sonoda, Sho Yamasaki, and Hiroshi Tanaka

To be cited as: *Chem. Eur. J.* 10.1002/chem.201703684

Link to VoR: http://dx.doi.org/10.1002/chem.201703684

Supported by
ACES

WILEY-VCH

10.1002/chem.201703684

WILEY-VCH

Synthesis and biological evaluation of *O*-methylated glycolipids related to PGLs via direct stereoselective glycosidation and sequential Suzuki-Miyaura coupling using boracyclane

Ko Sato,[a] Zakaria Omahdi, [b,d,e] Kensuke Shibata, [b,c,e] Koh-hei Sonoda, [c] Sho Yamasaki,[b,d,e] and Hiroshi Tanaka*[a]

Abstract: Synthesis of *O*-methylated glycolipids related to the sugars in PGLs via direct stereoselective glycosidation is reported. Treatment of 2-*O*-methyl-rhamnosyl imidates with I_2 and *n*-Bu_4NOTf resulted in their activation under low temperature and provided the α-rhamnosides with excellent α-selectivity. *n*-Bu_4NOTf enhanced the electorophilicity of iodine. This methodology improved the efficiency of the synthesis of both PGL-1 and PGL-tb1 sugars. The process involved the formation of 2-*O*-naphthylmethyl-α-rhamnoside and 2-*O*-methyl-α-fucoside. Sequential Suzuki-Miyaura coupling using synthetic glycosides, boracyclane, and aryl bromides provided glycolipids related to PGL sugars, and was accomplished with a one-pot process. Finally, we elucidated the immunosuppresive activities of all these synthetic compounds and found that a phenyl 3-*O*-α-rhamnosyl-2-*O*-methyl-α-rhamnoside possessing a 6-(2-naphthyl)hexyl group exhibited the strongest inhibitory effect.

Introduction

Phenolic glycolipids (PGLs) are a family of glycolipids found on the cell surface of mycobacteria and are composed of the combination of a partially *O*-methylated sugar and a diacylated lipid[1] — 3,6-di-*O*-methyl β-glucoside (PGL-1 **1**)[2] and 2,3,4-tri-*O*-methyl-α-fucoside (PGL-tb1 **2**)[3] are isolated from *M. leprae* and *M. tuberculosis*, respectively (Figure 1). Glycolipids are a unique motif for mycobacteria and are targets for the epitopes of anti-mycobacteria vaccines. In 2004, Barry and co-workers found that the PGLs contained in *M. tuberculosis* inhibited an innate immune response mediated by Toll-like receptor 2 (TLR2) [4] The Prandi and Astarie-Dequeker group recently revealed that PGL-1 inhibited TNF-α secretion in complement receptor 3-mediated (CR3) phagocytosis.[5] The inhibitory effect reduces inflammatory responses in infected human macrophages, which helps their survival in a host human body.[6,7] Biological evaluation of chemically synthesized glycosides related to PGLs has revealed that *O*-methylated sugars are the structural determinant that attenuates the inhibitory effect. On the other hand, the lipids are recognition elements that are essential for receptor binding.[9c] However, the mechanisms and precise structure-activity relationships remain unclear. Therefore, an effective method for the synthesis of partially *O*-methylated glycosides varied at the lipid portion in order to understand the structure/activity relationships and develop effective immunomodulating compounds.

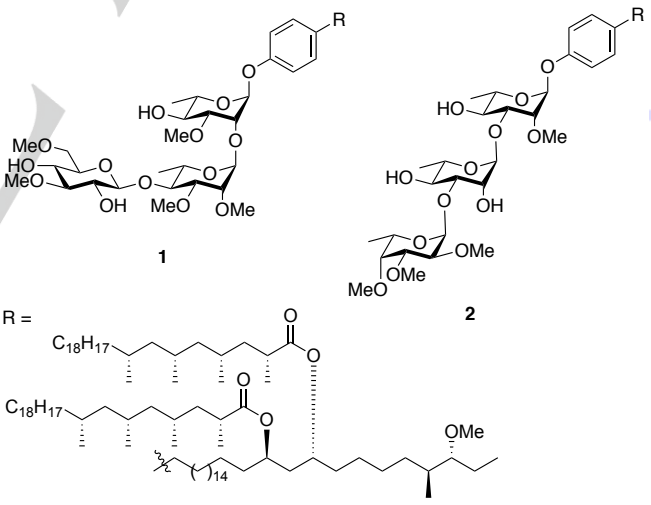
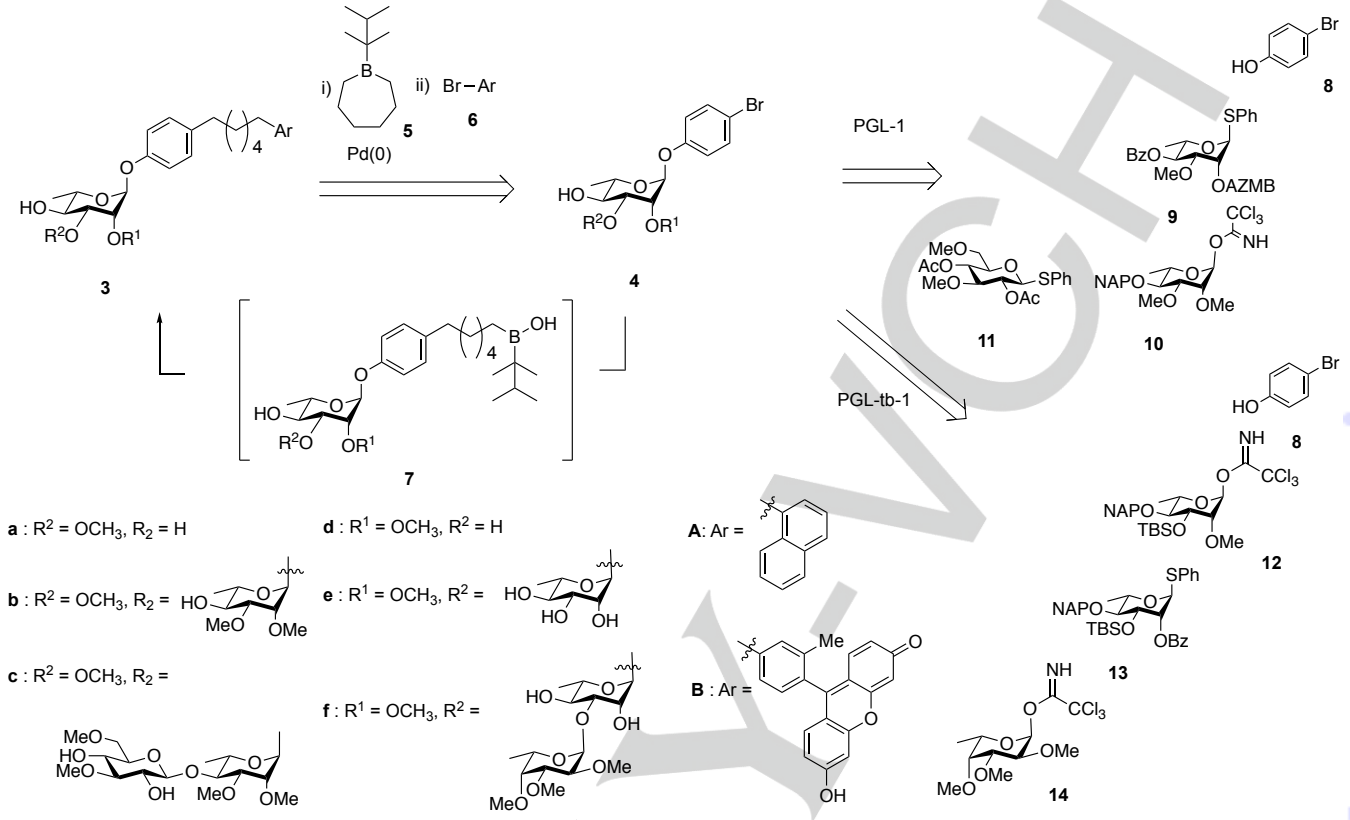


Figure 1. Structures of PGL-1 (**1**) and PGL-tb1 (**2**)

Preparation of these PGL-1 and PGL-tb1-related compounds has been reported by several research groups.[5,8-10] A total synthesis of PGL-tb1 reported by Minnaard involved Sonogashira coupling of a 4-iodophenyl glycoside and a terminal alkyne for the synthesis of the 4-alkylphenyl glycoside.[8] Formation of 2-*O*-methyl-α-rhamnosides and fucosides is a key step in preparation of the sugar part. *O*-methylation of the C2

[a] K. Sato and Prof Dr H. Tanaka
Department of Chemical Science and Engineering
Tokyo Institute of Technology
2-12-1-H101 Ookayama, Meguro Tokyo Japan152-8552
E-mail: thiroshi@apc.titech.ac.jp
[b] O. Zakaria, Dr. K. Shibata and Prof Dr. Yamasaki
Division of Molecular Immunology, Medicinal Institute of Bioregulation
Kyushu University
3-1-1 Maidashi, Higashiku, Fukuoka, Japan 812-8582
[c] Prof Dr. K. Sonoda
Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka, Japan 812-8582
[d] Current address: Department of Molecular Immunology, Research Institute for Microbial Diseases, and Laboratory for Molecular Immunology, Osaka University
3-1 Yamadaoka, Suita 565-0871, Japan.Osaka University, Suita, 565-0871, Japan
[d] Current address: WPI Immunology Frontier Research Center (iFReC) Osaka University
3-1 Yamadaoka, Suita 565-0871, Japan.Osaka University, Suita, 565-0871, Japan

10.1002/chem.201703684



Scheme 1. Strategy for the synthesis of the phenyl glycosides **3** based on the structure of PGL-1 (**1**) and PGL-tb1 (**2**).

hydroxy group renders neighboring group participation unavailable. Anomeric effect, however, can promote α-selective glycosylation without neighboring group participation, but the stereoselectivity of the glycosidation derived from an anomeric effect would be moderate and would frequently depend on the structures of glycosyl donors and acceptors.[11] We speculated that a post-glycosidation modification approach involving α-selective glycosidation promoted by a 2-*O*-acyl protecting group followed by *O*-methylation after selective removal of the acyl protecting group could be a highly reliable method for the synthesis of 2-*O*-methyl-α-rhamnosides. Obviously, the required modification step after construction of the sugar chain would increase the number of synthetic steps, and these would not be adaptable to the synthesis of 2-*O*-methyl-α-fucosides possessing an equatorial-orientated C2 oxygen functional group. On the other hand, we had previously reported an efficient synthesis of 2-deoxy-α-glycosides via the glycosidation of 2-deoxyglycosyl imidates with IBr and *n*-Bu_4NBr under basic conditions.[12] We further speculated that this method could involve a S_N2-like substitution of *in situ*-generated and unstable β-glycosyl halides with glycosyl acceptors that could provide the 2-deoxy-α-glycosides, which would make it adaptable to the direct synthesis of 2-*O*-methyl-α-glycosides. Herein, we report the preparation of PGL-1 and PGL-tb1 containing 4-bromophenyl glycosides by direct α-selective glycosidation of 2-*O*-methyl-glycosyl imidates and modification of the glycosides by sequential Suzuki-Miyaura palladium-catalyzed cross-coupling using a boracyclane.[13] In addition, we also review the immunosuppressive activity of glycolipids.

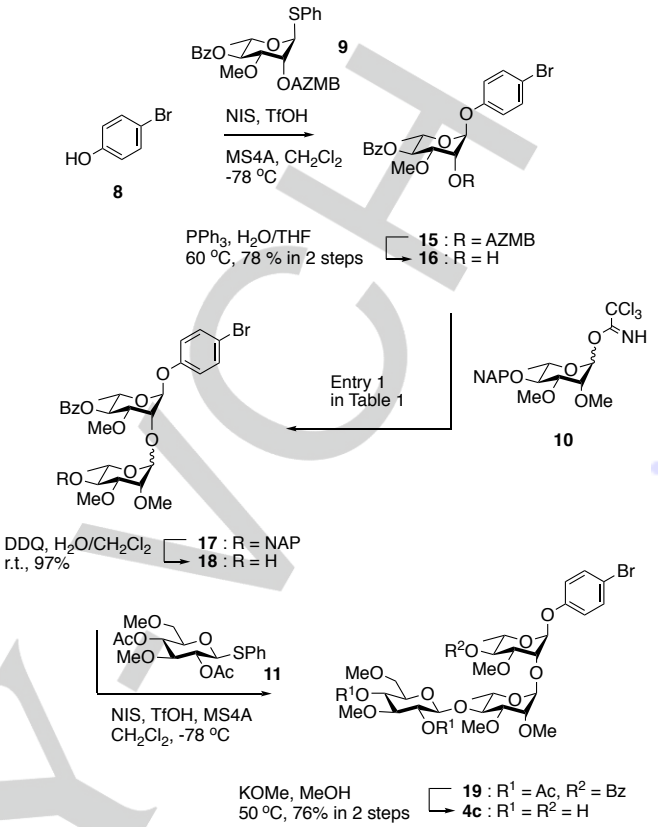
Results and Discussion

Scheme 1 shows our strategy for the synthesis of the phenyl glycosides **3a-fA** and **3a-cB**, which are related to PGL-1 and PGL-tb1 trisaccharides. The phenyl glycosides **3a-fA** and **3a-cB** possessing an alkyl chain and terminally functionalized with either a naphthyl group or a fluorescent dye were designed as targets in this project. The naphthyl group mimics the lipid portion of PGLs. The fluorescent-labelled glycosides **3a-cB** were used as chemical probes for the identification and detection of target proteins. The 4-alkylphenyl glycosides **3a-fA** and **3a-cB** were prepared from the corresponding 4-bromophenyl glycosides **4a-f** via sequential Suzuki-Miyaura palladium-catalyzed cross-coupling using boracyclane **5** and the aryl bromides **6A** and **6B**.[13] Suzuki-Miyaura coupling of glycosides **4a-f** with boracyclane **5** provided the acyclic borinic acid **7**. The acyclic borinic acid **7** shows low reactivity toward transmetallation to palladium species compared with the cyclic trialkylborane **5** and undergoes Suzuki-Miyaura cross coupling

at a higher reaction temperature to provide an asymmetrically functionalized alkyl chain.[14] Functional group compatibility of Suzuki-Miyaura cross coupling allows the direct use of protecting group-free carbohydrates **4a-f** as building blocks. This would allow 4-bromopheny glycoside **4c** containing PGL-1 glycosides to be prepared from 4-bromophenol (**8**), 2-*O*-methyl-thiorhamnoside **9**, 2-*O*-acyl-rhamnosyl imidate **10,** and 3,6-di-*O*-methyl-thioglucoside **11**. The 2-*O*-methyl-α-rhamnosyl bond could be prepared using our previously reported conditions for the synthesis of 2-deoxyl-α-glycosides. The 4-bromophenyl glycoside **4f** containing the PGL-tb1 glycosides could be prepared from 4-bromophenol (**8**), 2-*O*-methyl-rhamnosyl imidate **12**, rhamnoside **13**, and 2,3,4-tri-*O*-methyl-fucosyl imidate **14**.

Synthesis of the trisaccharide **4c** from *p*-bromophenol (**8**) was examined (Scheme 2). Treatment of thioglycoside **9** and *p*-bromophenol with NIS and a catalytic amount of TfOH at -78 °C, followed by removal of the 2-(azidomethyl)benzoate (AZMB)[15] with PPh_3, provided α-rhamnoside **16** in 78% yield with a complete α-selectivity. We next examined α-selective glycosidation of the 2,3-di-*O*-methylglycosyl imidate **10** (Table 1). Exposure of the glycosyl imidate **10** under the previously reported conditions for α-selective glycosidation of 2,6-dideoxy sugar using IBr and *n*-Bu_4NBr resulted in a poor coupling yield of **17** after 40 h (entry 1). Substitution with an electron-withdrawing oxygen at the C2 position could reduce the reactivity of glycosyl imidate **10** at a greater rate than that of 2,6-dideoxylglycosyl imidates. On the other hand, treatment of glycosyl imidate **10** and acceptor **16** with I_2 and *n*-Bu_4NOTf at -50 °C in toluene provided disaccharide **17** in 92% yield with α/β = 96:4 (entry 2). The use of CH_2Cl_2, EtCN and Et_2O as solvents reduced the α-selectivity of **17** (entries 3-5). The use of neither I_2 alone nor I_2 combined with *n*-Bu_4NI at the same temperature could not activate glycosyl imidate **10** (entries 6 and 7). These results suggested that the triflate anion might play an important role in the activation of I_2. Use of TMSOTf or BF_3•OEt_2 as an activator for the glycosyl donor **10** resulted in a reduction in the α-selectivity of **17**. These results clearly indicated that these activation conditions would be effective for the α-selective glycosidation of 2-*O*-methyl-rhamnoside. Oxidative removal of the NAP ester with DDQ provided alcohol **18** in 97% yield. Glycosylation of alcohol **18** with thioglycoside **11** and NIS and a catalytic amount of TfOH, followed by solvolysis of the esters, provided trisaccharide **4c** in 76% yield in 2 steps. The $^1J_{CH}$-coupling constants (161, 169 and 171 Hz) of the anomeric positions of **4c** indicated that the trisaccharide **4c** involved two α-glycosides and a β-glycoside.

Synthesis of the trisaccharide **4f** from *p*-bromophenol (**8**) was examined (Scheme 3). Treatment of glycosyl imidate **12** and *p*-bromophenol (**8**) with I_2 and *n*-Bu_4NOTf at -50 °C in toluene provided disaccharide **20**, followed by cleavage of the *tert*-butyldimethylsilyl (TBS) ether with tetrabutylammonium fluoride (TBAF) to provide α–rhamnoside **21** in 91% yield with complete α-selectivity. Glycosylation of the α-rhamnoside **21** at the C3 hydroxyl group with thiorhamnoside **13** possessing an ester-protecting group at the C2 hydroxyl group with NIS and



Scheme 2. Synthesis of the trisaccharide **4c** from 4-bromophenol (**8**)

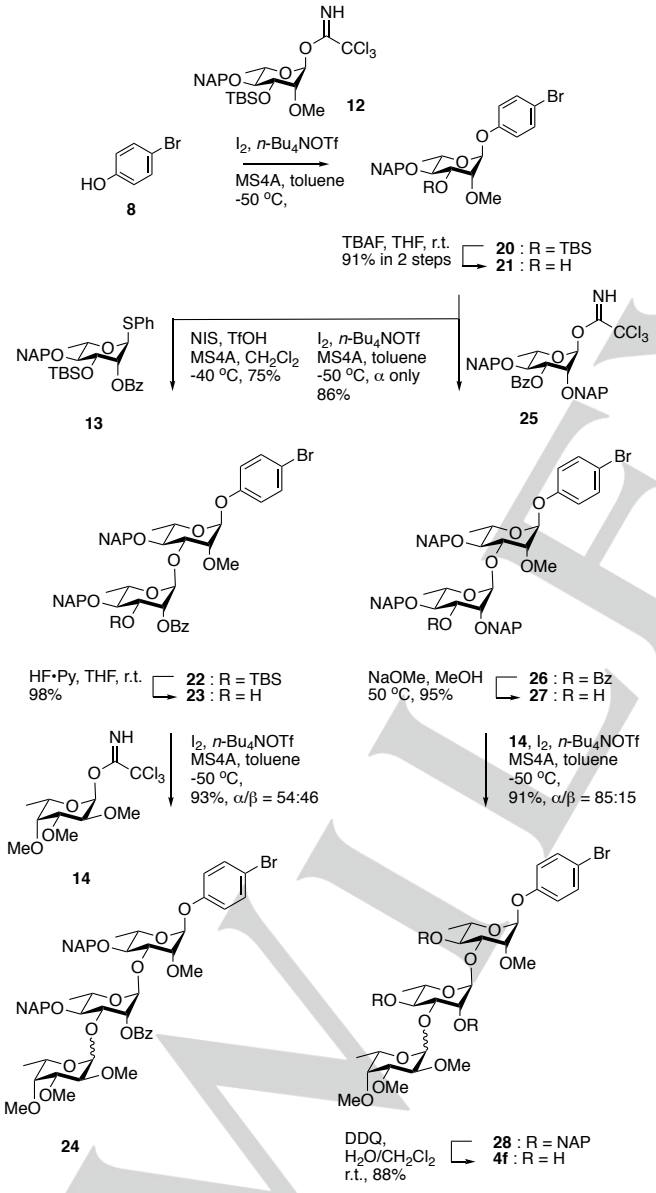
Table 1. α-Selective glycosidation of the 2,3-*O*-dimethylrhamnosyl imidate **10**

Entry[l]	Activator	Solvent	Temp [°C]	Yield[c] (%)	α/β[d]
1[a]	IBr, n-Bu_4NBr, then DIEA	CH_2Cl_2	r.t.	43	α only
2	I_2, *n*-Bu_4NOTf	toluene	-50	92	96:4
3	I_2, *n*-Bu_4NOTf	CH_2Cl_2	-50	93	78:22
4	I_2, *n*-Bu_4NOTf	EtCN	-50	50	58:42
5	I_2, *n*-Bu_4NOTf	Et2O	-50	73	50:50
6	I_2	toluene	-50	-	
7	I_2, *n*-Bu_4NI	toluene	-50	-	
8[b]	TMSOTf	toluene	-78	88	85:15
9[b]	BF_3•OEt_2	toluene	-78	87	85:15

[a] Reaction time is 40 h. [b] AW300 was used instead of MS4A. [c] isolated yields. [d] The ratio was determined based on ^1H NMR spectra

TfOH provided α-rhamnoside **22** in 75% yield. Removal of the TBS ether of α-glycoside **22** with HF•pyridine provided the alcohol **23** in 98% yield. Treatment of disaccharide **23** and 2,3,4-tri-*O*-methyl-fucosyl imidate **14** with I_2 and *n*-Bu_4NOTf at -50 °C in toluene provided an anomeric mixture of trisaccharide **24** in 93% yield with an α/β ratio of 54:46. We envisaged that the insufficient α-selectivity might be caused by the low reactivity of the *O*3 hydroxyl group due to the electronwithdrawing acyl-protecting group at the *O*2 hydroxyl group. We next planned a stereoselective preparation and glycosylation of a 2-*O*-alkyl

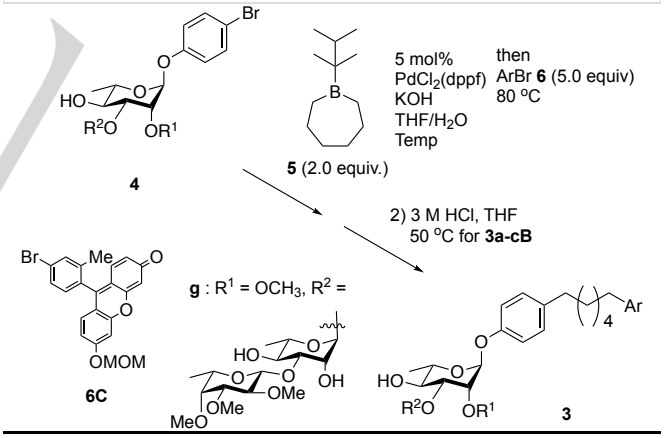
protected disaccharide. Treatment of α-rhamnoside **23** and the 2-*O*-(2-naphthyl)methyl-rhamnosyl imidate **25** with I_2 and *n*-Bu_4NOTf at -50 °C provided the α-rhamnoside **26** in 86% yield with a complete α-selectivity. Subsequent solvolysis of benzoate with MeOH under basic conditions provided disaccharide **27** in 95% yield. Treatment of disaccharide **27** and 2,3,4-tri-*O*-methyl fucosyl imidate **14** under the same reaction conditions as that for **24** provided trisaccharide **28** in 91% yield with an improved α-selectivity (α/β = 85:15). The oxidative removal of the NAP ether of an anomeric mixture of **28** with DDQ provided an anomeric mixture of trisaccharide **4f** in 88% yield. Further purification of the mixture of **4f** by HPLC provided pure α-glycoside **4f**. The $^1J_{CH}$-coupling constants (166, 168 and 171 Hz) of the anomeric positions of **4f** indicated that all of the glycosyl bonds of **4f** are α.



Scheme 3. Synthesis of the trisaccharide **4f** from the phenol **8**

We next examined one-pot sequential Suzuki-Miyaura coupling using the 4-bromophenyl glycosides **4a-g**, the cyclic boron compound **5**, and 1-bromonapthalene (**6A**) (Table 2). Glycoside **4g** was an anomeric isomer of 2,3,4-tri-*O*-methy-α-fucoside. Treatment of trisaccharide **4c** and 2.0 equiv. of cyclic boron compound **5** at 60 °C for 5.0 h, followed by reaction with 5.0 equiv. of 1-naphthylbromide (**6A**) at 80 °C for 19 h provided phenyl glycoside **4cA** possessing a 6-(2-naphthyl)hexyl group in 75% yield (entry 3). Use of other phenyl glycosides, **4a, 4b** and **4d-g**, as the first substrate resulted in the corresponding 4-(6-(2-naphthyl)hexyl)phenyl glycosides **3aA, 3bA** and **3d-gA** in good yields (70 to 90%) (entries 1,2,4-6). The reaction temperature required for the first cross-coupling reaction varied depending on the substrate. We next examined the fluorescent labelling of glycosides **3** using brominated TokyoGreen®[16] unit **6B**. After the reaction of phenyl glycoside **4c** and the cyclic boron compound **5** under the above-described conditions, the brominated TokyoGreen®unit **6B** was added to the reaction mixture. The reaction mixture was stirred at 80 °C. However, the desired fluorescent-labelled product was not observed. High solubility of the brominated TokyoGreen® unit **6B** in H_2O under basic conditions might reduce the concentration of the reagent **6B** in the organic solvent. In addition, a strong electron-donating phenoxide would coordinate the palladium species and might reduce its reactivity towards oxidative addition. To overcome these problems, we used the methoxymethyl ether **6C** as the third building block. After the reaction of phenyl glycoside **4a-c** and the cyclic boron compound **5** under the above-described conditions, the methoxymethyl ether **6C** was added to the

Table 2. Sequential Suzuki-Miuayra coupling using the boracyclane **5**



Entry	4	6	Product	Yield [%]
1	**4a**	**6A**	**3aA**	69
2	**4b**	**6A**	**3bA**	73
3	**4c**	**6A**	**3cA**	75
4	**4d**	**6A**	**3dA**	83
5	**4e**	**6A**	**3eA**	92
6	**4f**	**6A**	**3fA**	78
7	**4g**	**6A**	**3gA**	80
8	**4a**	**6C**	**3aB**	50
9	**4b**	**6C**	**3bB**	75
10	**4c**	**6C**	**3cB**	86

reaction mixture. After heating at 80 °C for 17 h, the desired coupling product was generated. The crude material was exposed to acidic conditions for hydrolysis of the methoxymethyl ether to provide TokyoGreen® labelled PGL-1 trisaccharide **3a-cB** in 50, 75 and 86% yields in 2 steps based on **4a-c**, respectively.

Finally, we tested the immunomodulating functions of synthetic glycosides **3a-gA** and **4a-g** on bone-marrow-derived macrophage (BMM) stimulated with trehalose-6,6'-dimycolate (TDM).[17] TDM is the most abundant glycolipid in the mycobacterial cell wall and promotes an innate immunity response mediated with Mincle, C-type lectin receptors on macrophage.[18] In the first screening, BMMs stimulated with TDM (25 mg) were incubated with 100 ng of the compounds **3a-gA** and **4a-g** for 24 h. The phenyl bromides **4a-g** did not inhibit the secretion of TNF-α (shown in the supporting information). On the other hand, some naphthyl derivatives showed inhibitory activity in a dose-dependent manner (Figure 2). Moreover, a proliferation assay confirmed that these results were not due to the toxicity of the compounds. Among a series of PGL-1 related glycosides, the trisaccharide **3cA** exhibited the strongest activity. There results are comparable to those of a previous report using activated THP-1 cells with TLR2 ligands.[9c] On the other hand, we found 3-*O*-a-rhamnosyl-2-*O*-methyl-α-rhamnoside **3eA** to be the strongest ligand among a series of PGL-tb1-realted glycosides. Although the glycolipids containing the disaccharide unit were found in mycobacteria, there exists only one report on the biological evaluation of related compounds.[19] In 2014, Lowary and co-workers reported that the cytokine inhibition activity of synthetic disaccharide **30** on activated THP-1 cells with TLR2 ligands was weaker than that of PGL-1 trisaccharide **29** (Figure 3).[9c] However, no reports have compared the inhibitory activity of the PGL-tb1 series of glycosides.

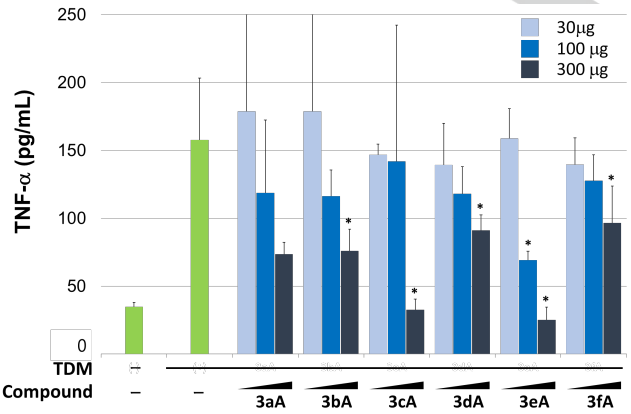


Figure 2. Cytokine inhibition assay of the glycosides **3a-fA** in dose dependent manner. (* : $p < 0.05$)

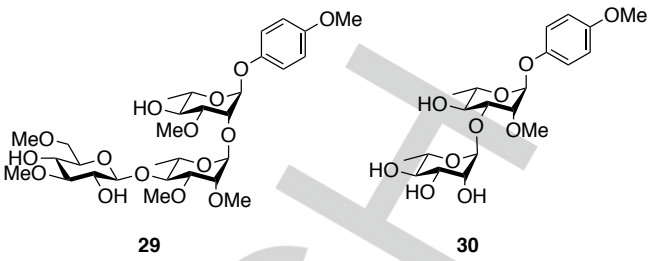


Figure 3. Structure of the phenyl glycosides **30** and **31** reported by Lowary's group.

Conclusions

Herein, we report the synthesis of *O*-methylated glycolipids related to PGL sugars by direct stereoselective glycosidation. We prepared 4-bromophenyl glycoside **4a-c** containing PGL-1 glycosides from 4-bromophenol (**8**), 2-*O*-acyl-thiorhamnoside **9**, 2-*O*-methyl-rhamnosyl imidate **10**, and 3,6-di-*O*-methyl-thioglucoside **11**. Treatment of 2-*O*-methyl-rhamnosyl imidate with I_2 and *n*-Bu_4NOTf efficiently provided α-rhamnoside with excellent α-selectivity, and enhanced the electorophilicity of iodine. On the other hand, 4-bromophenyl glycoside **4d-f** containing PGL-tb1 glycosides were prepared from 4-bromophenol (**8**), 2-*O*-methyl-rhamnosyl imidate **12**, 2-*O*-(2-naphthylmethyl)-rhamnosyl imidate **13b**, and 2,3,4-tri-*O*-methyl-fucosyl imidate **14**. Use of the (2-naphthyl)methyl ether as an *O*-2-protecting group of rhamnoside **13b** improved the total yield of desired α-linked trisaccharide **4f**. Sequential Suzuki-Miyaura coupling using the synthetic glycosides **4a-g**, boracyclane **5** and arylbromide **6A** and **6B** smoothly proceeded to provide the glycolipids **3a-gA** in a one-pot process. Finally, we elucidated the immunosuppresive activity of the synthetic compounds and found that phenyl 3-*O*-α-rhamnosyl-2-*O*-methyl-α-rhamnoside possessing a 6-(2-naphthyl)hexyl group exhibited the strongest inhibitory effect from among a series of PGL-tb1-realted glycosides. Attachment of tri-*O*-methyl-α-fucoside at the C3 hydroxyl group of the terminal rhamnoside reduced the inhibitory activity. Elucidation of the role of non-*O*-methyl-rhamnoside and a mode of action for phenyl glycoside that involves identification of the target protein is now in progress.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (Grant-in-aid No. 26102720).

Keywords: Innate immunity • Palladium coupling• Glycosylation• Natural product synthesis• Immunosuppresive activities

[1] a) M. B. Goren, P. J. Brennan in *Tuberculosis* (Eds.: G. P. Youmans), W. B. Saunders, Philadelphia, **1979**, pp. 69-193; b) D. D. Barnes, M. L. E. Lundaha, Ed C. Lavelle, E. M. Scanlan, *ACS Chem. Biol.* **2017**, *12*, 1969-1979.

[2] a) S. W. Hunter, P. J. Brennan, *J. Bacteriol.* **1981**, 728-735; b) S. W. Hunter, T. Fujiwara, P. J. Brennan, *J. Biol. Chem.* **1982**, *257*, 15072-15078.

[3] M. Daffe, C. Lacave, M.-A. Laneelle, G. Laneelle, *Eur. J. Biochem.* **1987**, *167*, 155-160.

[4] M. B. Reed, P. Domenech, C. Manca, H. Su, A. K. Barczak, B. N. Kreiswirth, G. Kaplan, C. E. Barry III, *Nature* **2004**, *431*, 84-87.

[5] A. Arbues, W. Malaga, P. Constant, C. Guilhot, J. Prandi, C. Astarie-Dequeker, *ACS Chem. Biol.* **2016**, *11*, 2865-2875.

[6] Immunomodulatory effect of PGL-1, see: a) M. A. Neill, S. J. Klebanoff, *J. Exp. Med.* **1988**, *167*, 30-42; b) C. L. Silva, L. H. Faccioli, N. T. Foss, *Int. J. Lepr. Other Mycovact. Dis.* **1993**, *61*, 107-108; c) V. Ng, G. Zanazzi, R. Timpl, J. F. Talts, J. L. Salzer, P. J. Brennan, A. Rambukkana, *Cell*, **2000**, *103*, 511-524; d) G. Tabouret, C. Astarie-Dequeker, C. Demangel, W. Malaga, P. Constant, A. Ray, N. Honore, N. F. Bello, E. Perez, M. Daffe, C. Guilhot, *PLoS Pathog.* **2010**, *6*, e1001159.

[7] Immunomodulatory effect of PGL-tb1, see: a) K. Pethe, D. L. Swenson, S. Alonso, J. Anderson, C. Wang, D. G. Russell, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 13642-13647; b) H. Gan, J. Lee, F. Ren, M. Chen, H. Kornfeld, H. G. Remold, *Nat. Immun.* **2008**, *9*, 1189-1197.

[8] Total synthesis of PGL-tb1: S. Barroso, R. Castelli, M. P. Baggelaar, D. Geerdink, B. T. Ter Horst, E. Casas-Arce, H. S. Overleeft, G. A. Van der Marel, J. D. C. Codee, A. J. Minnaard, *Angew. Chem. Int. Ed.* **2012**, *51*, 11774-11777.

[9] Synthesis of PGL-1 analogues, see: a) T. Fujiwara, G. O. Aspicall, S. W. Hunter, P. J. Brennan, *Carbohydr. Res.* **1987**, *163*, 41-52; b) A. Borbas, A. Liptak, *Carbohydr. Res.* **1993**, *241*, 99-116; c) H. R. H. Elsaidi, D. R. Barreda, C. W. Cairo, T. L. Lowary, *ChemBioChem* **2013**, *14*, 2153-2159.

[10] Synthesis of PGL-tb1 analogues, see: a) G. H. Veeneman, S. H. Van Leeuwen, H. Zuurmond, J. H. J. Van Boom, *Carbohydr. Chem.* **1990**, *9*, 783-796; b) M. K. Gurjar, G. Viswanadham, *J. Carbohydr. Chem.* **1991**, *10*, 481-485; c) T. Fujiwara, *Agric. Biol. Chem.* **1991**, *55*, 2123; d) J. Bourke, C. F.Brereton, S. V. Gordon, E. C. Lavelle, E. M. Scanlan, *Org. Biomol. Chem.* **2014**, *12*, 1114-1123; e) H. R. H. Elsaidi and T. L. Lowary, *ChemBioChem* **2014**, *15*, 1176-1182; f) H. R. H. Elsaidi, T. L. Lowary, *Chem. Sci.* **2015**, *6*, 3161-3172.

[11] a) R. R. Schmidt, J. Michel, *Tetrahedron Lett.* **1984**, *25*, 821; b) I. Cumpstey, *Org. Biomol. Chem.* **2012**, *10*, 2503-2508.

[12] H. Tanaka, A. Yoshizawa, S. Chijiwa, J. Ueda, M. Takagi, K. Shinya, T. Takahashi, *Chem. Asian. J.* **2009**, *4*, 1114-1125.

[13] R. Suzuki, S. Fuse, H. Tanaka, *Eur. J. Org. Chem.* **2016**, *21*, 3471-3481.

[14] K. Matos, J. A. Soderquist, *J. Org. Chem.* **1988**, *63*, 461-470.

[15] T. Wada, A. Ohkubo, A. Mochizuki, M. Sekine, *Tetrahedron Lett.* **2001**, *42*, 1069-1072.

[16] Y. Urano, M. Kamiya, K. Kanda, T. Ueno, K. Hirose, T. Nagano, *J. Am. Chem. Soc.* **2005**, *127*, 4888-4894.

[17] H. Noll, H. Bloch, J. Asselineau, E. Lederer, *Biochim. Biophys. Acta* **1956**, *20*, 299-309.

[18] a) E. Ishikawa, T. Ishikawa, Y. S. Morita, K. Toyonaga, H. Yamada, O. Takeuchi, T. Kinoshita, S. Akira, Y. Yoshikai, S. Yamasaki, *J. Exp. Med* **2009**, *206*, 2879-2888; b) Y. Miyake, K. Toyonaga, D. Mori, S. Kakuta, Y. Hoshino, A. Oyamada, H. Yamada, K. Ono, M. Suyama, Y. Iwakura, Y. Yoshikai, S. Yamasaki, *Immunity* **2013**, *38*, 1050-1062.

[19] A. Vercellone, G. Puzo, *J. Biol. Chem.* **1989**, *264*, 7447-7454.

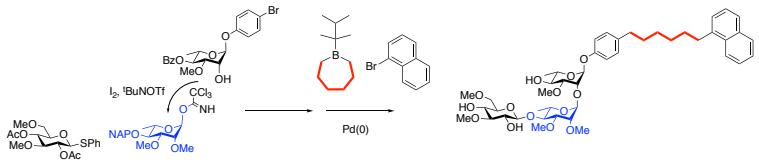
10.1002/chem.201703684

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

FULL PAPER



Synthesis of *O*-methylated glycolipids related to the sugars in PGLs via direct stereoselective glycosidation and sequential Suzuki-Miyaura coupling using synthetic glycosides, boracyclane, and aryl bromides is reported. Among them, The phenyl 3-*O*-α-rhamnosyl-2-*O*-methyl-α-rhamnoside possessing a 6-(2-naphthyl)hexyl group exhibited the strongest immunosuppresive activity .

*Ko Sato, Omahdi Zakaria, Kensuke Shibata, Koh-hei Sonoda, Sho Yamasaki and Hiroshi Tanaka**

Page No. – Page No.

Synthesis and biological evaluation of O-methylated glycolipids related to PGLs via direct stereoselective glycosidation and sequential Suzuki-Miyaura coupling using boracyclane