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Odorless benzenethiols in synthesis of thioglycosides and its application for glycosylation reactions

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Abstract—*p*-Octyloxybenzenethiol (**2**) was synthesized as a new odorless benzenethiol. Moreover, preparation of thioglycosides using **2** and their application for glycosylation reactions were attempted. As a result, it was found that the thioglycosides were as excellent glycosyl donors as 4-dodecylphenyl 1-thio-glycosides, which were previously reported by our group, and more useful than the previous donors in terms of fine chemistry in glycosylation reaction activated with silver triflate and *N*-iodosuccinimide (NIS). In addition, this method was applicable to the sialylation with NIS and triflic acid. All procedures from the preparation of thioglycosides to the glycosylation reaction could be attained completely under conditions where no malodor was generated.

Phenyl 1-thio-glycosides have been used as excellent glycosyl donors in glycosylation reaction not only by conventional methods but also on solid or polymer supports;[1] however, malodorous smells are unavoidable on synthesizing the thioglycosides and during the glycosylation reactions due to liberated benzenethiol. We have developed odorless organosulfur reagents, for example, dodecylmercaptane and dodecyl methyl sulfide, and exhibited their utility in organic reactions, such as Corey–Kim oxidation and demethylation of methyl ethers.[2] Our strategy for designing odorless organosulfur reagents was simple, for example, the higher molecular weight organosulfur reagents are less malodorous. Moreover, we recently published the preparation of 4-dodecylphenyl 2,3,4,6-*O*-tetraacetyl-1-thio-D-glucoside and its application to glycosylation reaction, where *p*-dodecylbenzenethiol (**1**) prepared by reduction of the corresponding benzenesulfonyl chloride with lithium aluminum hydride was used as an excellent substitute of benzenethiol.[3] In spite of the fact that the reaction proceeded in good yield, the reaction condition activated with $BF_3{\cdot}Et_2O$ and *N*-iodosuccinimide (NIS) seemed to be too drastic to apply to the synthesis of more complex biologically active oligosaccharides. In addition, commercially available *p*-dodecylbenezenesulfonyl chloride includes undecylbenzenesulfonyl and tridecylbenzenesulfonyl chlorides as contaminants because the sulfonyl chloride could be prepared from the corresponding sulfonic acid, which is mainly purchased as industrial material for cleansers or detergents. Since the contaminants in the sulfonyl chloride were difficult to be removed by distillation, synthetic intermediates in each step contained inseparable analogs having more or less methylenes in the linear dodecyl chains.

Therefore, we herein would like to report the design and synthesis of a new odorless benzenethiol (**2**) and further application of the odorless benzenethiol to the synthesis of more complex oligosaccharides than that prepared in the previous report,[3] while Kobayashi reported utility of thiosalycylate in the synthesis of galacto- and fuco-oligosaccharides.[4] In the present study, we chose β-D-*N*-acetylglucosaminyl(1-2)-β-D-mannopyranosyl(1-6)-α-D-glucopyranoside (**3a**) as a target molecule because it was reported that a neoglyco-conjugate bearing **3a** as a glycosyl moiety was a good substrate of *N*-acetylglucosaminyltransferase V (GnTase V),[5] of which the activity is related to the metastatic potency of tumor cells, and *O*-methylated and deoxygenated derivatives (**3b**,**3c**) are potent inhibitors against GnTase V (Fig. 1).[6]

First, in order to synthesize **2**, phenol (**4**) was alkylated with octyl bromide in the presence of potassium carbonate to afford octyl phenyl ether (**5**), which was next

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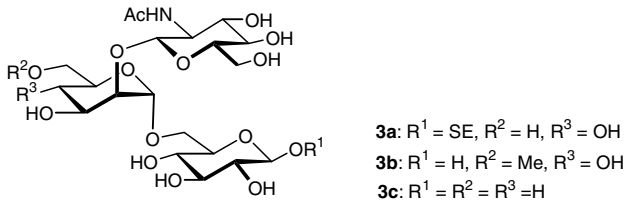


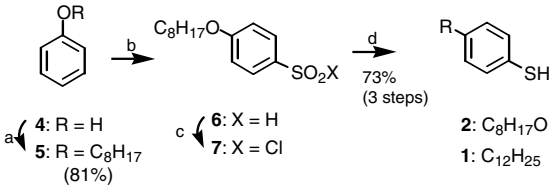
Figure 1. Target trisaccharide (**3a**) and its related compounds.

treated with concentrated sulfuric acid at room temperature. The obtained *p*-octyloxybenzenesulfonic acid (**6**) was derived to the corresponding sulfonyl chloride (**7**) with thionyl chloride, and successive reduction of **7** with lithium aluminum hydride gave **2**, which was completely odorless, in 59% overall yield (Scheme 1).[7]

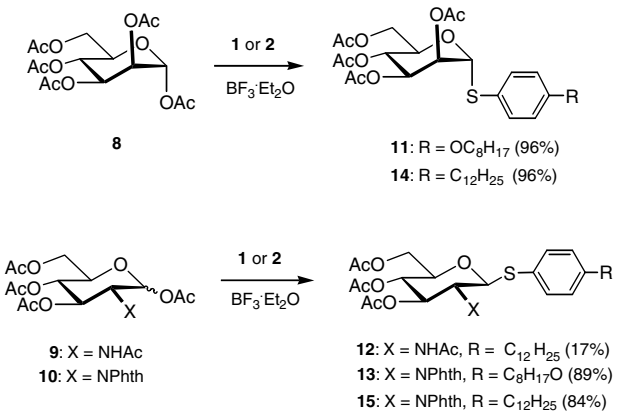
Thus, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl acetate (**8**) and 2-acetamido-3,4,6-tri-*O*-acetyl-D-glucopyranosyl acetate (**9**) were treated with **2** in the presence of boron trifluoride etherate to prepare the glycosyl donors. While the former (**8**) was transformed to 1-phenylthiomannoside (**11**) in excellent yield (96%), the latter reaction employing **9** as a substrate did not proceed well but afforded **12** albeit in quite low yield. And then, 2-phthalimido-3,4,6-tri-*O*-acetyl-D-glucopyranosyl acetate (**10**) was subjected to the same reaction shown above and the desired 1-thio-glycoside (**13**)[8] was obtained in good yield (89%). The corresponding *p*-dodecylphenyl 1-thio-glycosides (**14**,**15**) were also synthesized in order to compare the reactivities in glycosylation reactions (Scheme 2).[9]

Next, transformation of the thiomannosides (**11**, **14**) to aryl 3-*O*-benzyl-4,6-benzyliden-1-thio-mannosides (**16**, **17**) was attempted. The acetyl groups of **11** and **14** were cleaved by saponification with 0.5 % potassium hydroxide in methanol, and the hydroxyl groups of the generated aryl 1-thio-D-mannosides (**18**, **19**) were treated with dichlorotoluene to afford benzylidene protected mannosides (**20**, **21**). In order to cleave the protecting group of the hydroxyl group at the C-2 position reductively, **20** and **21** were treated with lithium aluminum hydride in the presence of aluminum chloride.

Although it was reported that the hydroxyl group at the C-2 position was selectively regenerated from mannose derivatives having an (*R*)-configured benzylidene group while the hydroxyl group at the C-3 position was obtained from the derivative with (*S*)-configuration under the same condition,[10] mixtures of (*R*)- and (*S*)-isomers of **20** and **21** were, respectively, subjected to the reaction



Scheme 1. Synthesis of *p*-octyloxybenzenethiol (**2**). Reagents: (a) $C_8H_{17}Br$, K_2CO_3; (b) H_2SO_4; (c) $SOCl_2$; (d) $LiAlH_4$.

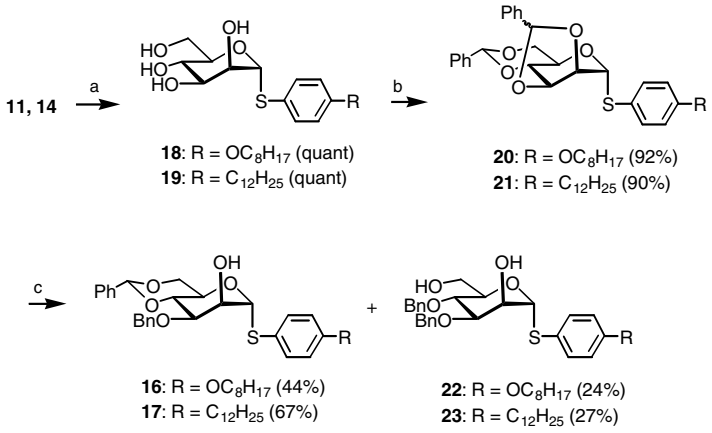


Scheme 2. Synthesis of thioglycosides using odorless benzenethiols (**1** and **2**).

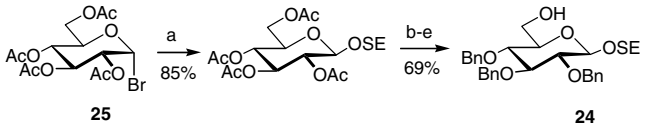
due to difficulty of separation. The reaction of **21** afforded the desired product (**17**) in higher yield (67%) than the conversion from **20** to **16**[11] (44%). It was in good contrast with the report by Lipták[10] that the products, in which only the hydroxyl group on the C-3 position was deprotected, were not observed but aryl 3,4-di-*O*-benzyl-1-thio-D-mannosides (**22**, **23**) were obtained as minor products in both cases (Scheme 3).

On the other hand, 2-trimethylsilylethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**24**) was synthesized as a glycosyl acceptor by a synthetic route, where 1-bromo-2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**25**) was treated with 2-trimethylsilylethanol in the presence of silver oxide in dichloromethane, followed by a series of four reactions comprising saponification of the acetyl group with methanolic sodium hydroxide, protection of primary alcohol at the C-6 position with trityl chloride in pyridine, *O*-benzylation of the remaining hydroxyl groups, and acid treatment for deprotection of the trityl group at C-6 (Scheme 4).

Mannosylation of allyl 2,3,4-tri-*O*-benzyl-α-D-glucoside with **17** in the presence of $BF_3{\cdot}Et_2O$ and NIS, which was attempted as a pretest, did not afford the desired product but gave 1,1-linked dimannoside (**26**); therefore, the hydroxyl groups of **16** and **17** were acetylated with acetic anhydride and pyridine to yield **27** and **28**, respectively. Thus, mannosylation of **24** with **27** and/or **28** by the activation with silver triflate and NIS,[12] a milder activator than a combination of reagents employed previously,[3] was tried and gave disaccharides **29**[13] in good yield (83% from **27**, and 90% from **28**). After cleavage of the acetyl group of **29** with sodium methoxide, the obtained α-D-mannosyl(1-6)-β-D-glucopyranoside derivative (**30**) was *N*-acetylglucosaminylated with **13** and/or **15** in the presence of silver triflate and NIS to give trisaccharide **31** in excellent yield (93% from **13**, and 92% from **15**).[14] The phthaloyl group of **31** was removed by hydrazine hydrate to yield **32**, of which the amino group was acetylated to derive to acetamide (**33**),[15] followed by deprotection with saponification with sodium methoxide and successive hydrogenation with palladium–carbon in acidic medium composed of methanol and



Scheme 3. Synthesis of aryl 1-thio-D-mannoside derivatives. Reagents: (a) KOH, MeOH; (b) $PhCHCl_2$, pyr.; (c) $LiAlH_4$, $AlCl_3$.

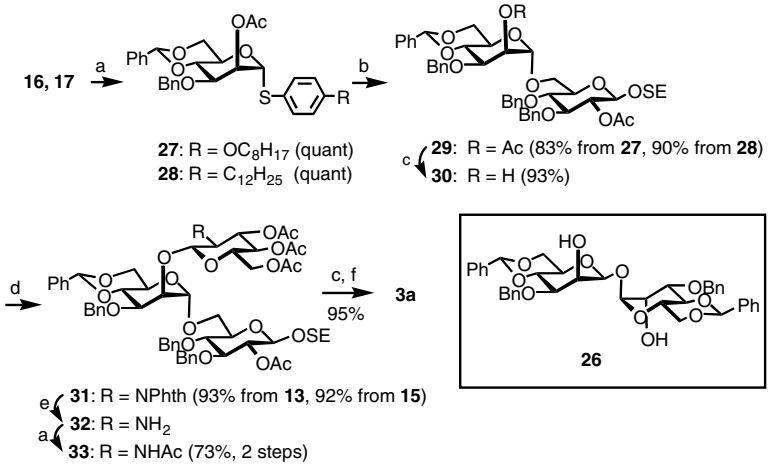


Scheme 4. Synthesis of acceptor substrate (**24**). Reagents: (a) Ag_2O, $Me_3SiCH_2CH_2OH$; (b) KOH, MeOH; (c) TrCl; (d) BnBr, NaH; (e) HCl.

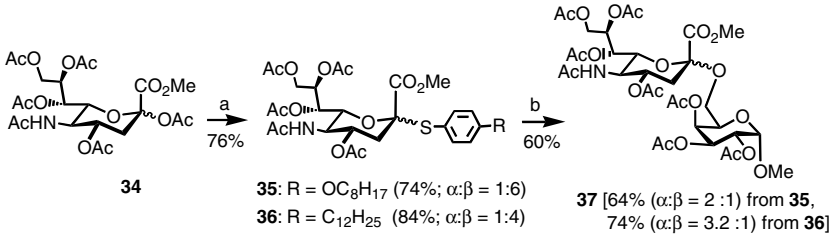
formic acid. A series of the reactions gave the desired trisaccharide (**3a**) (Scheme 5).

For further application of the odorless benzenethiols to glycosylation reaction, we attempted synthesis of sialyl oligosaccharides. Methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetylneuraminate (**34**) was first treated with *p*-octyloxybenzenethiol (**2**) and *p*-dodecylbenzenethiol (**1**) to give 4-octyloxyphenyl 2-thio-sialoside (**35**) and 4-dodecylphenyl 2-thio-sialoside (**36**), respectively, in satisfactory yield. Sialylation of methyl-2,3,4-tri-*O*-acetyl-α-D-galactoside with **35** or **36** in the presence of triflic acid and NIS in acetonitrile[16] afforded sialoside (**37**) in good yield (64% and 74%) (Scheme 6).

In conclusion, we have succeeded in establishing a new practical method of glycosylation where odorless benzenethiols (**1**,**2**) were used as reagents for the synthesis of thioglycosides and no malodor was produced during preparation of the thioglycosides and synthesis of saccha-



Scheme 5. Synthesis of trisaccharide (**3a**). Reagents and conditions: (a) Ac_2O, pyr.; (b) compound **27** or **28**, NIS (2.5 equiv), AgOTf, −50 °C; (c) NaOMe; (d) compound **13** or **15**, NIS (2.5 equiv), AgOTf, −50 °C; (e) NH_2NH_2; (f) Pd–C/H_2, HCO_2H.



Scheme 6. Synthesis of Sialoside (**37**). Reagents and conditions: (a) **1** or **2**, $BF_3{\cdot}Et_2O$; (b) methyl 2,3,4-tri-*O*-acetyl-1-*O*-α- D-galactoside, TfOH (cat.), NIS (2 equiv), CH_3CN, −40 °C.

rides. It is noteworthy that there were almost no differences in terms of chemical yield and anomeric selectivities between the reactions using thioglycosides prepared with **2** and those prepared with **1**. Thus, newly synthesized odorless thiol **2** was convenient to use for the purpose of fine chemistry while the previously prepared thiol was useful for industrial and large-scale synthesis. Our method would be widely acceptable as a general method in many syntheses of biologically active oligosaccharides subjected in both solid and homogeneous phases.

Acknowledgments

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References and notes

1. For example (a) Nicolaou, K. C. *J. Am. Chem. Soc.* **1997**, *119*, 449; (b) Hanashima, S.; Manabe, S.; Inamori, K.; Taniguchi, N.; Ito, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 5674.
2. (a) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207; (b) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569; (c) Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177; (d) Ohsugi, S.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron* **2003**, *59*, 8393; (e) Node, M. *Foods & Food Ingredients J. Jpn.* **2004**, *209*, 88; (f) Nishide, K.; Patra, P. K.; Matoba, M.; Shanmugasundaram, K.; Node, M. *Green Chem.* **2004**, *6*, 142; (g) Nishide, K.; Ohsugi, S.; Miyamoto, T.; Kumar, K.; Node, M. *Monatsh. Chem.* **2004**, *135*, 189; (h) Nishide, K.; Node, M. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 895; (i) Patra, P. K.; Nishide, K.; Fuji, K.; Node, M. *Synthesis* **2004**, 1003.
3. Hasegawa, J.; Hamada, M.; Miyamoto, T.; Nishide, K.; Kajimoto, T.; Uenishi, J.; Node, M. *Carbohydr. Res.* **2005**, *340*, 2360.
4. Dohi, H.; Nishida, Y.; Tanaka, H.; Kobayashi, K. *Synlett* **2001**, 1446; Nishida, Y.; Tsurumi, T.; Sasaki, K.; Watanabe, K.; Dohi, H.; Kobayashi, K. *Org. Lett.* **2003**, *5*, 3775.
5. Kahn, S. H. *Carbohydr. Res.* **1989**, *193*, 125.
6. Khan, S. H.; Crawley, S. C.; Kanie, O.; Hindsgaul, O. *J. Biol. Chem.* **1993**, *268*, 2468.
7. Preparation of **2**: sulfuric acid (5.0 ml) was added to octyl phenyl ether (5.0 g), and the mixture was stirred for 30 min at room temperature. The mixture was poured into a saturated aqueous solution of sodium chloride, and appearing precipitates were collected by suction. After drying the precipitates by freeze-dry, a part of the obtained sodium sulfonate (2.0 g) was treated with refluxed thionyl chloride (7.5 ml) for 8–10 h to convert to sulfonyl chloride, which was reduced with $LiAlH_4$ (600 mg) in refluxed tetrahydrofuran (45 ml) for 10 h. The reaction residue obtained by usual work-up was purified by silica gel column chromatography (hexane/ethyl acetate = 100:1) afforded **2**.
8. ^{1}H NMR (300 MHz, $CDCl_3$); δ: 0.89 (br t, J = 7.0 Hz, 3H), 1.2–1.6 (m, 12H), 1.78 (quint, J = 7.0 Hz, 2H), 1.83, 2.01, and 2.10 (each s, 3H), 3.84 (ddd, J = 2.4, 4.6, and 10.1 Hz, 1H, H-5), 3.93 (t, J = 6.6 Hz, 2H, $PhOCH_2$), 4.19 (dd, A part of AB type, J = 2.4 and 12.3 Hz, 1H, H-6), 4.27 (dd, B part of AB type, J = 4.6 and 12.3 Hz, 1H, H-6), 4.28 (t, J = 10.1 Hz, H-4, 1H), 5.09 (t, J = 9.6 Hz, 1H, H-3), 5.57 (d, J = 10.5 Hz, 1H, H-1), 5.75 (dd, J = 10.5 and 9.6 Hz, H-2), 6.78 and 7.33 (each d, AB type, J = 8.8 Hz, 1H), 7.75 and 7.88 (each dd, AB type, J = 3.0 and 5.3 Hz, 1H).
9. General method for the synthesis of thioglycosides: boron trifluoride diethyl etherate (0.6 ml) was added to a solution of odorless benzenethiol (**1** or **2**, 4.5 mmol) and peracetylated monosaccharide (4.0 mmol) in dichloromethane (20 ml) at 0 °C, and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and condensed in vacuo. The residue was purified by silica gel chromatography to afford the desired thioglycoside.
10. Lipták, A.; Imre, J.; Harangi, J.; Nanasi, P.; Nezmelyi, A. *Tetrahedron* **1982**, *38*, 3721; and also see Watanabe, S.; Sueyoshi, T.; Ichikawa, M.; Uehara, C.; Iwamura, M. *Org. Lett.* **2001**, *3*, 255.
11. ^{1}H NMR (300 MHz, $CDCl_3$) of **13**; δ: 0.89 (br t, J = 7.0 Hz, 3H), 1.2–1.6 (m, 12H), 2.14 (s, 3H), 3.85 (t, J = 9.9 Hz, 1H), 3.93 (t, J = 6.6 Hz, 2H, $PhOCH_2$), 4.01 (dd, J = 3.5 and 9.9 Hz, 1H), 4.12 (t, J = 9.9 Hz, 1H), 4.23 (dd, J = 4.8 and 10.3 Hz, 1H), 4.38 (dt, J = 4.8 and 9.9 Hz, 1H), 4.68 and 4.73 (each d, AB type, J = 12.2 Hz, 1H), 5.28 (d, J = 1.5 Hz, 1H, H-1), 5.60 (dd, J = 1.5 and 3.5 Hz, 1H, H-2), 5.64 (s, 1H, PhCH<), 6.81 (d, J = 8.8 Hz, 2H), 7.2–7.4 (m, 10H), 7.52 (d, J = 8.8 Hz, 2H).
12. Konradsson, P.; Udodong, U.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.
13. ^{1}H NMR of **29** (300 MHz, $CDCl_3$); δ: 0.1 (s, 9H), 1.0 (m, 2H), 2.16 (s, 3H), 3.4–4.1 (m, 13H), 4.20 (br d, J = 6.0 Hz, 1H), 4.37 (d, J = 7.9 Hz, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.63 (d, J = 11.9 Hz, A part of AB, 1H), 4.70 (d, J = 11.9 Hz, B part of AB, 1H), 4.74 (dd, J = 4.0 and 11.0 Hz, 1H), 4.81 (d, J = 10.0 Hz, 1H), 4.86 (d, J = 1.5 Hz, 1H, man-1), 4.96 (dd, J = 4.3 and 11.0 Hz, 2H), 5.46 (dd, J = 1.5 and 4.0 Hz, 1H, man-2), 5.61 (s, 1H, PhCH<), 7.1–7.4 (m, 23H), 7.46 (m, 2H).
14. General method for glycosylation: silver triflate (32 mg) and NIS (70 mg) were successively added to a suspension of thioglycoside (0.125 mmol), acceptor glycoside (0.125 mmol), and molecular sieves 4A (200 mg) in dichloromethane (5 ml), and the mixture was stirred at room temperature. After the reaction, the reaction mixture was filtrated through Celite®, and the filtrate was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous solution of sodium thiosulfate, dried over $MgSO_4$, and condensed in vacuo. The residue was purified by silica gel chromatography.
15. ^{1}H NMR of **33** (300 MHz, $CDCl_3$); δ: −0.01 (s, 9H), 1.05 (m, 2H), 1.83 (s, 3H, NHAc), 2.01, 2.02, and 2.03 (each s, 3H, OAc), 3.76 and 3.44 (each t, J = 9.0 Hz, 2H), 3.55–3.95 (m, 12H), 4.05–4.25 (m, 5H), 4.27 (dd, J = 5.0 and 12.1 Hz, 1H), 4.40 (d, J = 10.4 Hz, 1H), 4.42 (d, J = 13.4 Hz, 1H), 4.73 (s, 2H), 4.75–4.80 (m, 2H), 4.84 (d, J = 1.7 Hz, 1H), 4.90–5.05 (m, 2H), 5.04 (d, J = 19.8 Hz, 1H), 5.52 (dd, J = 1.7 and 3.0 Hz, 1H, man-2), 5.53 (d, J = 19.8 Hz, 1H), 5.59 (s, 1H, PhCH<), 7.1–7.4 (m, 23H), 7.43 (m, 2H).
16. Hasegawa, A.; Nagahama, T.; Ohki, H.; Hotta, K.; Ishida, H.; Kiso, M. *J. Carbohydr. Res.* **1991**, *10*, 493; Veeneman, G. H.; van Leeumen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.