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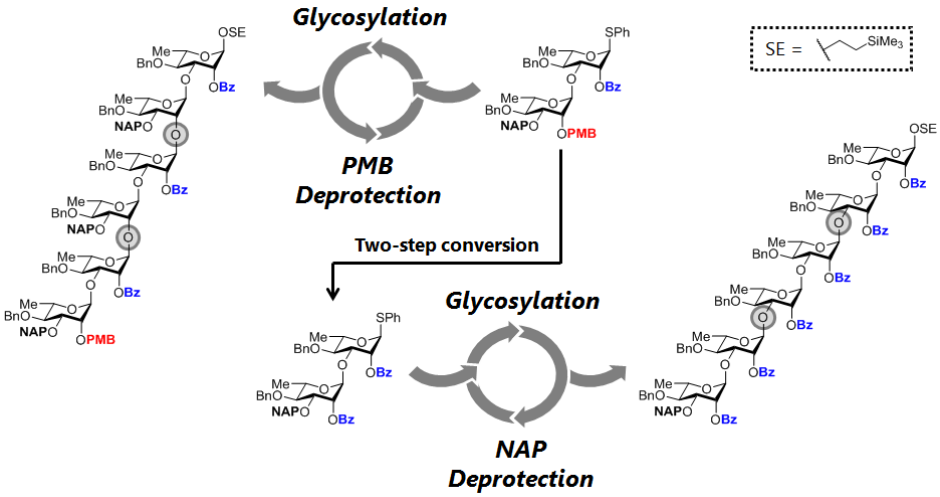
Graphical abstract



Title

A concise synthesis of rhamnan oligosaccharides with alternating α-(1→2)/(1→3)-linkages and repeating α-(1→3)-linkages by iterative α-glycosylation using disaccharide building blocks

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Abstract

A concise synthetic route to rhamnan oligosaccharides with alternating α-(1→2)/(1→3)-linkages and repeating α-(1→3)-linkages is reported. This synthesis was achieved by iterative α-glycosylation using disaccharide building blocks and through orthogonal coupling between thioglycosides of L-rhamnose. To investigate the detailed structure-activity relationship of rhamnan sulfate from *Monostroma nitidum* against herpes simplex virus type 2, the synthesized oligosaccharides, bearing different orthogonal protecting groups (i.e., benzoyl, benzyl, 2-naphthylmethyl, and/or *p*-methoxybenzyl) are expected to be suitable for conversion into a range of rhamnan structures with diverse sulfation patterns.

Keywords:

Rhamnan oligosaccharide, Iterative α-glycosylation, Orthogonal coupling, Rhamnan sulfate, *Monostroma nitidum*, Herpes simplex virus type 2

1. Introduction

Sulfated polysaccharides from marine algae have been widely studied in recent years due to their

unique chemical structures and interesting biological activities [1,2]. For example, fucoidan, which has been isolated from brown seaweed, is a sulfated α-L-fucose-rich polysaccharide that exhibits antitumor, anticoagulant, and anti-inflammatory activities [3,4]. Recently, Takahashi and Toshima et al. demonstrated the structure-activity relationships of natural fucoidan and the corresponding synthetic sulfated oligofucosides for the induction of apoptosis in MCF-7 human breast cancer cells [5,6, 7]. In addition, sulfated rhaman polysaccharides (e.g., rhamnan sulfate, RS) from green seaweed, which mainly composed of α-L-rhamnopyranosyl (Rha) residues, possess potent antiviral effects against enveloped viruses [8,9]. Lee et al. elucidated the fine structure of RS extracted from *Monostroma nitidum*, and found that it contained alternating (1→2)/(1→3)-linked and repeating (1→3)-linked α-L-Rha moieties as its backbone (types I and II, respectively, **Figure 1**) [10]. They also evaluated its antiviral activity against herpes simplex virus type 2 (HSV-2), and demonstrated its potential for use as a novel anti-HSV-2 agent. However, it remains unclear which residues in this structure are required to impart such anti-HSV-2 activity. Thus, with the future aim of investigating the detailed structure-activity relationship of RS, we planned an efficient and convergent synthesis of rhamnan oligosaccharides with diverse sulfation patterns. For this purpose, we herein describe a concise synthetic route to type I and II rhamnan oligosaccharides via iterative α-glycosylation using disaccharide building blocks.

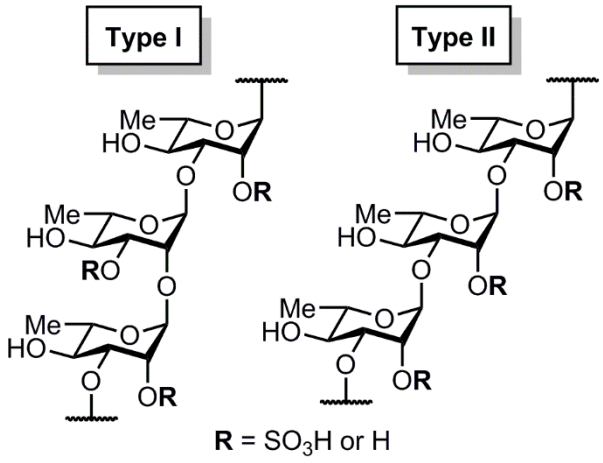
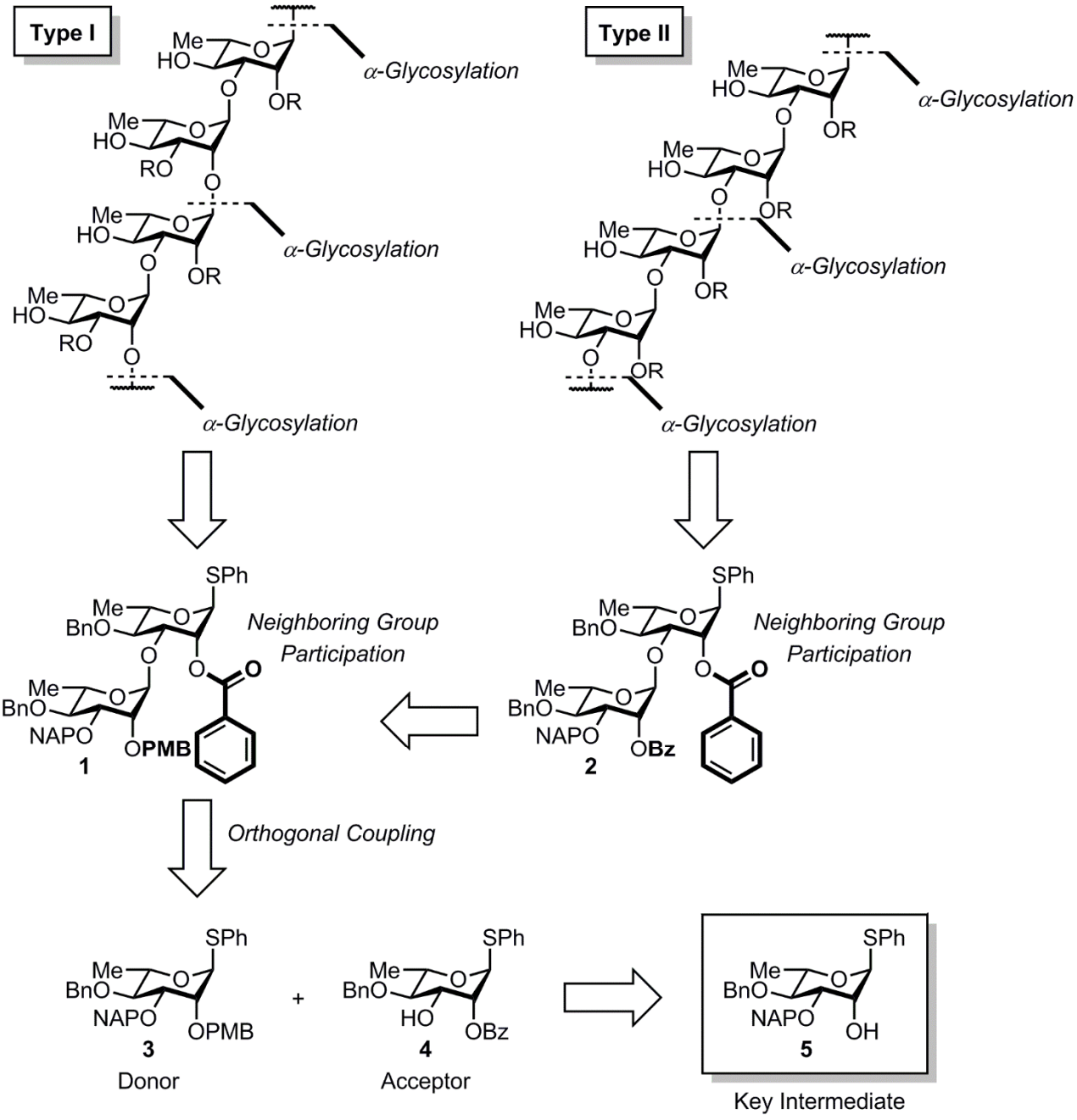


Figure 1. Chemical structure of rhamnan sulfate obtained from *Monostroma nitidum*.

2. Results and Discussion

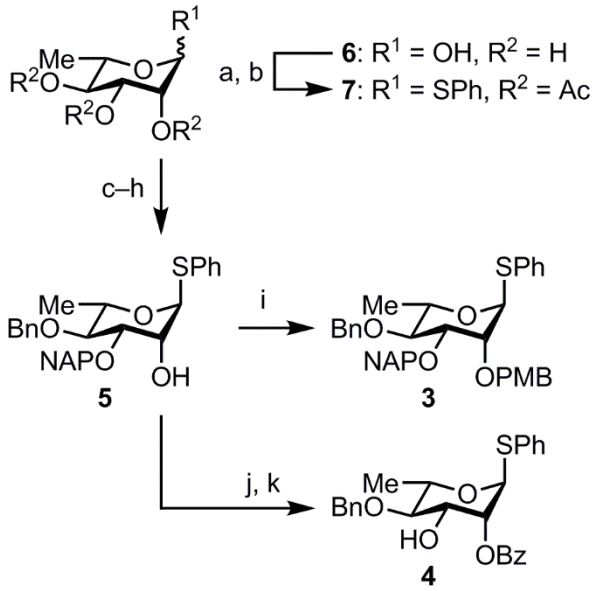
Retrosynthetically, rhamnan oligosaccharides are efficiently assembled via iterative α-selective glycosylation using building blocks **1** and **2**, each possessing a 2-*O*-benzoyl (Bz) group that permits neighboring group participation [11] (**Scheme 1**). Disaccharide **1**, which can be constructed by orthogonal coupling [12] between thioglycosides **3** and **4**, is readily converted into **2** via two synthetic steps, and the required thioglycosides are prepared from key intermediate **5** via a number of protecting group manipulations.



Scheme 1. Retrosynthetic analysis of rhamnan oligosaccharides with alternating α-(1→2)/(1→3)-linkages and repeating α-(1→3)-linkages.

As shown in **Scheme 2**, our synthetic efforts began with the preparation of key intermediate **5**.

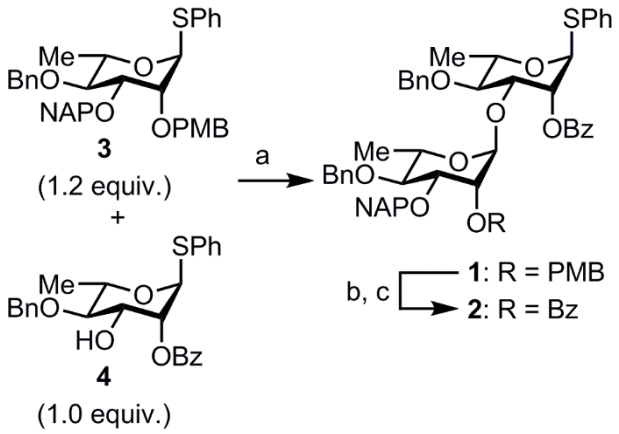
Accordingly, the acetylation of commercially available L-Rha **6** followed by coupling with thiophenol in the presence of a boron trifluoride etherate catalyst gave per-*O*-acetylated thioglycoside **7** [13] with good α-selectivity (α:β = 4:1) in 87% yield on the multigram scale (i.e., > 50 g). To facilitate analysis of the prepared compounds, α-isomer of **7** was employed for the following synthetic sequence. Thus, a benzyl (Bn) group was introduced at the 4-position through deacetylation of **7α** and regioselective formation of the 2,3-*O*-acetonide. Following removal of this acetonide group, the C3 hydroxyl moiety was alkylated using 2-napthylmethyl bromide (NAPBr) via tin-acetal activation [14] to afford the key intermediate **5** in 53% yield from **7α**. With compound **5** in hand, alkylation at the 2-position with *p*-methoxybenzyl chloride (PMBCl) provided monosaccharide donor **3** (92%), while treatment of **5** with benzoyl chloride (BzCl) in pyridine and subsequent deprotection of the NAP group using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [15] yielded monosaccharide acceptor **4** (78%).



Scheme 2. Preparation of monosaccharides **3**, **4**, and **5**. Reagents and conditions: (a) Ac_2O, pyridine, 23 °C, 17 h; (b) PhSH, $BF_3{\cdot}Et_2O/CH_2Cl_2$, 23 °C, 5 h, 87% (α:β = 4:1) over two steps; (c) NaOMe, MeOH, 23 °C, 1 h; (d) DMP, *p*-TsOH·H_2O/MeCN, 23 °C, 1 h; (e) NaH/DMF, then BnBr, 4 °C to 23 °C, 1 h; (f) 90% aq. AcOH, 80 °C, 24 h; (g) Bu_2SnO/toluene, 120 °C, 1 h; (h) NAPBr, TBAI/toluene, 120 °C, 16 h, 53% over six steps from **7*α***; (i) NaH/DMF, then PMBCl, 4° C to 23 °C, 1 h, 92%; (j) BzCl, pyridine, 4°C to 23 °C, 1 h; (k) DDQ, $MeOH/CH_2Cl_2$, 23 °C, 12 h, 78% over two steps. DMP = 2,2-Dimethoxypropane, TBAI = Tetrabutylammonium iodide

The synthesis of disaccharides **1** and **2** was then carried out as illustrated in **Scheme 3**. More specifically, orthogonal coupling [12] of the armed thioglycoside **3** and the disarmed thioglycoside **4** was achieved in the presence of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) [16] to yield the desired coupling product **1** in 50% yield. The observed vicinal $J_{C1,H1}$ coupling

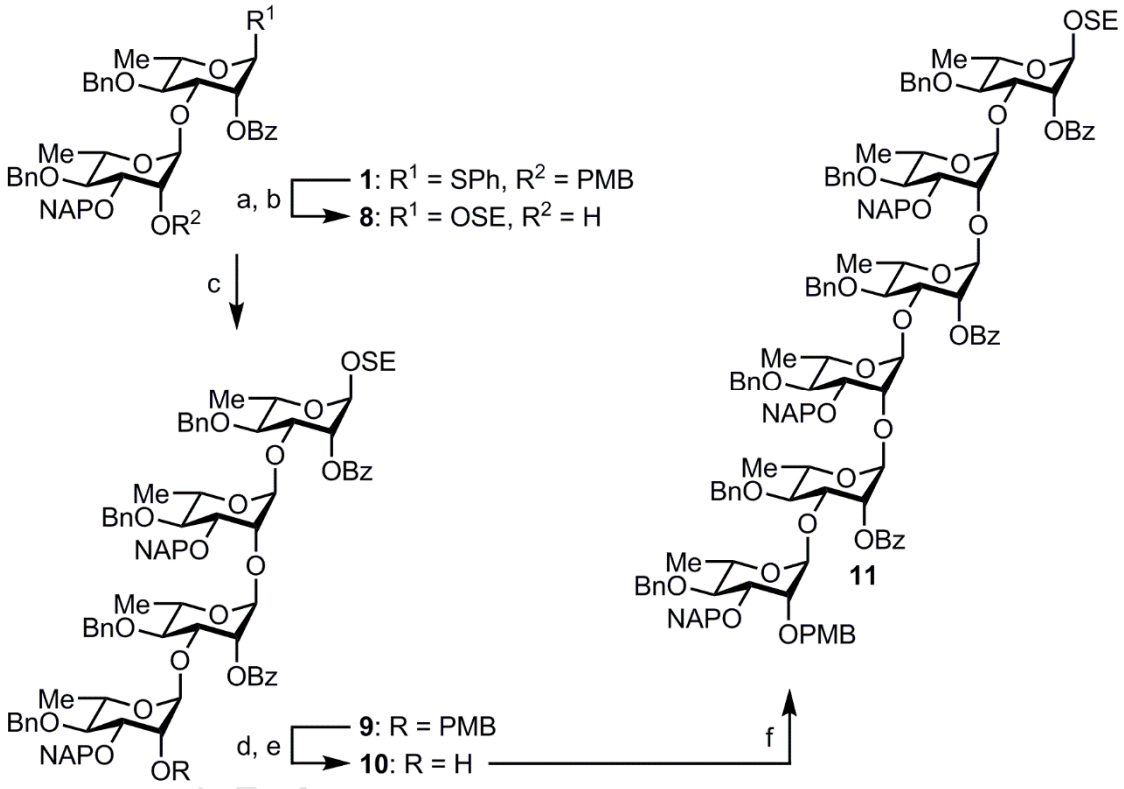
constant and C1 chemical shift (i.e., 167 Hz and 100 ppm) of the non-reducing end L-Rha unit in **1** indicated that the α configuration was adopted at the anomeric center [17,18]. The conversion of **1** into **2** was achieved by removal of the PMB group [19] and subsequent benzoylation.



Scheme 3. Synthesis of disaccharide building blocks **1** and **2**. Reagents and conditions: (a) NIS, TfOH/CH_2Cl_2, −78 °C to −60 °C, 2 h, 50% (α only); (b) 90% aq. AcOH, 80 °C, 6 h, 68%; (c) BzCl, pyridine, 4 °C to 23 °C, 30 min, 94%.

With disaccharides **1** and **2** in hand, the type I and II rhamnan oligosaccharides were prepared via iterative α-glycosylation by neighboring group participation of the 2-*O*-Bz group. More specifically, to prepare the oligosaccharide with alternating α-(1→2)/(1→3)-linkages (**Scheme 4**), the PMB group was cleanly removed under mildly acidic conditions after capping the reducing end of **1** with 2-(trimethylsilyl)ethanol (SEOH) to ultimately furnish disaccharide acceptor **8** in 73% yield over

two steps. The glycosylation of **8** with **1** using the NIS/TfOH system proceeded in an α-selective manner to afford the desired coupling product **9** in 76% yield. Subsequent PMB deprotection of **9** gave **10**, which was coupled with **1** to produce hexasaccharide **11** with complete α-selectivity but in a rather poor yield (36%).

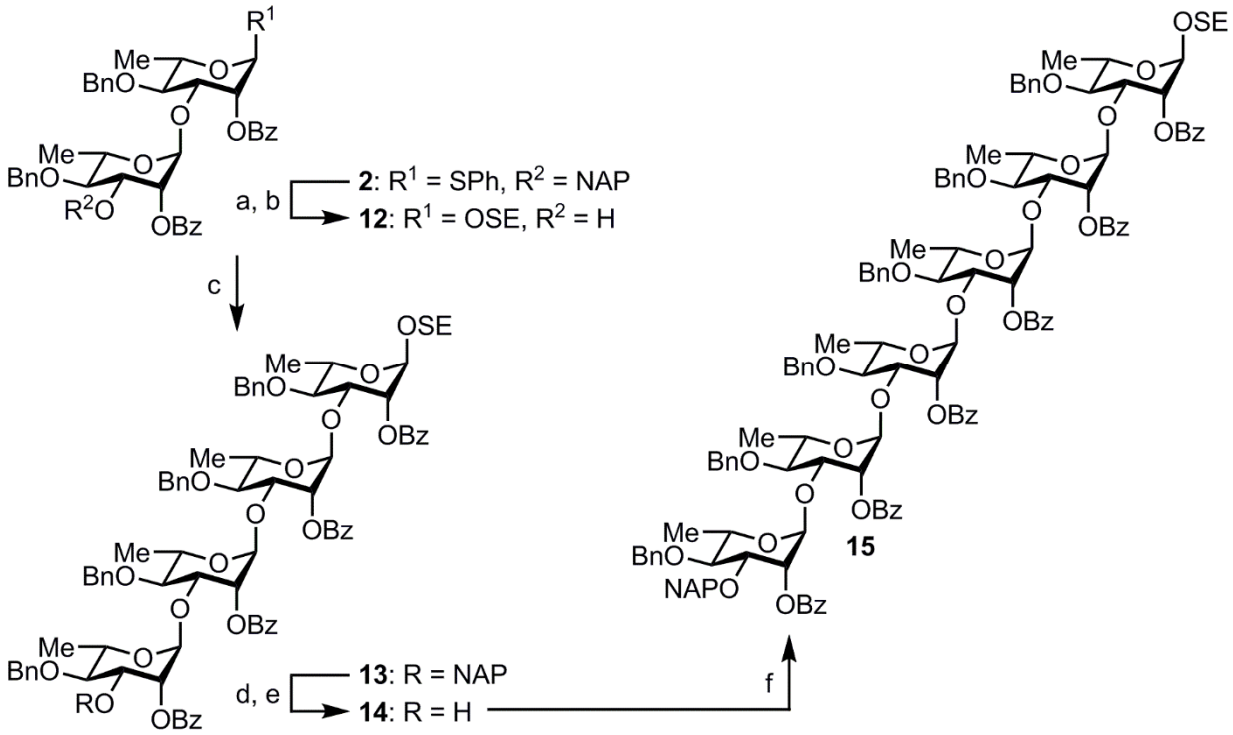


Double column

Scheme 4. Synthesis of oligosaccharides with alternating α-(1→2)/(1→3)-linkages using iterative glycosylation from disaccharide building block **1**. Reagents and conditions: (a) SEOH (1.5 equiv.), NIS, TfOH/CH_2Cl_2, 4° C, 10 min, 70% (α only); (b) 90% aq. AcOH, 80 °C, 48 h, 73%; (c) **1** (1.2 equiv.), NIS, TfOH/CH_2Cl_2, 4 °C, 30 min, 76% (α only); (d) 90% aq. AcOH, 80 °C, 48 h, 73%; (e) **1**

(2.0 equiv.), NIS, TfOH/CH_2Cl_2, 4 °C, 30 min, 36% (α only).

We also elongated the oligosaccharide chain through repeating α-(1→3)-linkages (**Scheme 5**). Initially, a two-step reaction sequence was followed consisting of end capping of compound **2** with SEOH and removal of the NAP group to obtain acceptor **12**. Finally, a synthetic cycle involving α-glycosylation with **2** and NAP deprotection using DDQ was employed to systematically construct tetrasaccharide **13** and hexasaccharide **15** (via acceptor **14**) through high yielding coupling reactions in 83% and 92%, respectively.



Scheme 5. Synthesis of oligosaccharides with repeating α-(1→3)-linkages using iterative

glycosylation from disaccharide building block **2**. Reagents and conditions: (a) SEOH (1.5 equiv.), NIS, TfOH/CH_2Cl_2, 4 °C, 10 min, 67% (α only); (b) DDQ, MeOH/CH_2Cl_2, 23 °C, 12 h, 72%; (c) **2** (1.2 equiv.), NIS, TfOH/CH_2Cl_2, 4 °C, 30 min, 83% (α only); (d) DDQ, MeOH/CH_2Cl_2, 23 °C, 12 h, 70%; (e) **2** (2.0 equiv.), NIS, TfOH/CH_2Cl_2, 4 °C, 30 min, 92% (α only).

In summary, we successfully developed a concise synthetic route to rhamnan hexasaccharides with alternating α-(1→2)/(1→3)-linkages and repeating α-(1→3)-linkages by iterative α-glycosylation using disaccharide building blocks. It is particularly noteworthy that one of these disaccharides was successfully constructed via orthogonal coupling between armed and disarmed thioglycosides originating from L-rhamnose. The prepared oligosaccharides, bearing a range of different orthogonal protecting groups (i.e., benzoyl, benzyl, 2-naphthylmethyl, and/or *p*-methoxybenzyl), are suitable for conversion into several rhamnan structures with diverse sulfation patterns. Studies into the detail structure-activity relationship of rhamnan sulfate against herpes simplex virus type 2 are currently underway in our laboratory.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded using JEOL ECA-500 and Bruker Ascend™-400

spectrometers, respectively. High resolution mass spectrometry (HRMS) was carried out on a Bruker Daltonics micrOTOF electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. The specific optical rotations of the products were determined using a Horiba SEPA-300 high sensitive polarimeter. All reagents were purchased from Tokyo Chemical Industry (Tokyo, Japan), Wako Pure Chemical Industries (Osaka, Japan), or Sigma-Aldrich (St. Louis, MO). All reaction solvents were pre-dried using 4Å molecular sieves prior to use. Thin layer chromatography was performed using glass-backed Merck silica gel 60 TLC plates coated with the F_{254} fluorescent indicator. The developed TLC plates were observed using UV light (254 nm) and by staining with a *p*-anisaldehyde solution. Purification was carried out using flash column chromatography (Kanto Chemical, Silica Gel 60N, 40–50 μm) and gel filtration (Pharmacia, Sephadex LH-20). The NMR spectra of all new compounds are available in the Supplementary Materials.

3.2. Phenyl 4-O-benzyl-3-O-(2-naphthylmethyl)-1-thio-α-L-rhamnopyranoside (**5**)

To a suspension of phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside **3** (46.0 g, 120 mmol) in methanol (120 mL) was added sodium methoxide (28% wt. solution in methanol: 2.32 g, 12.0 mmol) before stirring for 1 h at 23 °C under nitrogen atmosphere. The reaction mixture was acidified with Muromac® (H^+ form) and filtered off. The resulting solution was concentrated *in vacuo* and exposed to high vacuum. For acetonide formation, the deacetylated crude product (120 mmol) was dissolved

in a mixed solution of acetonitrile/2,2-dimethoxypropane (120 mL/29.5 mL, 240 mmol) before treatment with p-toluenesulfonic acid monohydrate (2.28 g, 12.0 mmol). After stirring for 1 h at 23 °C under nitrogen atmosphere, the reaction mixture was quenched by triethylamine (33.5 mL, 240 mmol). The resulting solution was concentrated *in vacuo* and exposed to high vacuum. For benzyl ether protection, the 2,3-*O*-acetonide crude product (120 mmol) was dissolved in *N*,*N'*-dimethylformamide (120 mL) before cooling to 4 °C using ice bath under nitrogen atmosphere. After addition of sodium hydride (60% wt. in oil: 7.18 g, 180 mmol) portionwise over 1 h, benzyl bromide (17.1 mL, 144 mmol) was added and the reaction was stirred for additional 1 h at 23 °C. The mixture was treated with triethylamine (16.7 mL, 120 mmol) for quenching unreacted benzyl bromide and poured into satd. aq. NH_4Cl (120 mL) to precipitate a pale brown solid. After filtration, the solid was washed with water (600 mL) and 50% aq. methanol (600 mL). For acetonide deprotection, the 2,3-*O*-acetonide-4-*O*-benzyl crude product (120 mmol) was dissolved in 80% aq. acetic acid (240 mL) before heating to 60 °C using oil bath. After stirring for 24 h, the reaction mixture was allowed to cool to 23 °C and concentrated *in vacuo*. The resulting syrup was dissolved in hot ethyl acetate (200 mL) and cooled to 4 °C using ice bath to precipitate a white solid. After filtration, the solid was washed with a mixed solution of ethyl acetate/hexane (200 mL/400 mL) to give the corresponding 4-*O*-benzyl product **S1** (34.8 g, 84%) as a white solid. For regioselective 2-napthylmethyl ether protection, **S1** (3.46 g, 9.99 mmol) was dissolved in toluene (100 mL) before

addition of dibutyltin oxide (2.48 g, 9.96 mmol). After stirring for 1 h at 120 °C using oil bath under nitrogen atmosphere, the reaction mixture was cooled to 23 °C and evaporated until dry. The resulting syrup was dissolved in toluene (100 mL) before addition of 2-napthylmethyl bromide (3.32 g, 15.0 mmol) and tetrabutylammonium iodide (369 mg, 1.00 mmol). After stirring for 16 h at 80 °C using oil bath under nitrogen atmosphere, the reaction mixture was cooled to 23 °C and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:6 → 1:3) to give the title compound **5** (3.06 g, 63%) as a white foam.

$[\alpha]_D$ −169.4° (c 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.21 (m, 17H, Ph), 5.52 (s, 1H, H-1), 4.93–4.65 (m, 4H, -*CH*Ph×4), 4.27 (brs, 1H, H-2), 4.20 (m, 1H, H-5), 3.92 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.55 (t, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 2.76 (brs, 1H, OH), 1.31 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.0, 134.1, 133.2, 133.1, 131.4, 129.0, 128.4, 128.4, 127.9, 127.9, 127.7, 127.7, 127.3, 126.8, 126.2, 126.1, 125.8, 87.0, 80.1, 80.1, 75.4, 72.2, 70.1, 68.9, 17.8; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 509.1751, $C_{30}H_{30}O_4S$ calcd for $[M+Na]^+$ 509.1757.

3.3. Phenyl

4-O-benzyl-2-O-(4-methoxybenzyl)-3-O-(2-naphthylmethyl)-1-thio-α-L-rhamnopyranoside (**3**)

To a solution of phenyl 4-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-L-rhamnopyranoside **5** (2.44 g, 5.01 mmol) in *N*,*N*'-dimethylformamide (10.0 mL) was added sodium hydride (60% wt. in oil: 302

mg, 7.55 mmol) portionwise over 20 min at 4 °C using ice bath under nitrogen atmosphere before addition of *p*-methoxybenzyl chloride (0.82 mL, 6.05 mmol). After stirring for 1 h at 23 °C, the reaction mixture was quenched with triethylamine (1.4 mL, 10.0 mmol) and satd. aq. NH_4Cl (50 mL). The resulting solution was extracted with ethyl acetate (50 mL×3) and washed with brine (50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by recrystallization with ethyl acetate/hexane to give the title compound **3** (2.79 g, 92%) as a white solid.

$[\alpha]_D$ −32.2° (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–6.77 (m, 21H, Ph), 5.46 (s, 1H, H-1), 5.00–4.55 (m, 6H, -*CH*Ph×6), 4.15 (m, 1H, H-5), 4.00 (brs, 1H, H-2), 3.90 (m, 1H, H-3), 3.70 (m, 4H, H-4 and OMe), 1.36 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.5, 135.7, 134.6, 133.2, 132.9, 131.3, 129.8, 129.6, 128.9, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 126.4, 126.0, 125.8, 125.8, 113.7, 85.8, 80.5, 79.9, 76.0, 75.3, 72.0, 71.7, 69.3, 55.1, 17.9; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 629.2327, $C_{38}H_{38}O_5S$ calcd for $[M+Na]^+$ 629.2332.

3.4. Phenyl 2-O-benzoyl-4-O-benzyl-1-thio-α-L-rhamnopyranoside (**4**)

To a solution of phenyl 4-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-L-rhamnopyranoside **5** (1.90 g, 3.90 mmol) in pyridine (7.8 mL) was added benzoyl chloride (0.54 mL, 4.65 mmol) at 4 °C using ice bath before stirring for 1 h at 23 °C under nitrogen atmosphere. After quenching with methanol (0.40

mL, 0.99 mmol), the mixture was evaporated with toluene (10 mL×3) and purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:6) to give the corresponding 2-*O*-benzylated compound **S2** (2.20 g, 96%) as a yellow syrup.

S2 (1.01 g, 1.69 mmol) was dissolved in a mixed solution of dichloromethane/methanol (6.8 mL/1.7 mL) before addition of 2,3-dichloro-5,6-dicyanobenzoquinone (461 mg, 2.03 mmol). After stirring for 12 h at 23 °C, the reaction mixture was diluted with ethyl acetate (100 mL). The resulting solution was washed with satd. aq. $NaHCO_3$ (100 mL×2) and brine (100 mL). The aqueous layers were extracted with ethyl acetate (100 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:6) to give the title compound **4** (604 mg, 78%) as a white foam.

$[\alpha]_D$ −118.2° (c 3.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.04–7.22 (m, 10H, Ph), 5.61 (m, 1H, H-2), 5.55 (s, 1H, H-1), 4.87 (d, 1H, *J* = 11.2 Hz, -*CH*Ph), 4.77 (d, 1H, *J* = 11.2 Hz, -*CH*Ph), 4.30 (m, 1H, H-5), 4.21 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 3.56 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4), 2.42 (brs, 1H, OH), 1.41 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 138.0, 133.8, 133.2, 131.6, 129.7, 129.5, 128.9, 128.4, 128.3, 128.0, 127.8, 127.5, 85.8, 81.5, 75.0, 74.8, 70.9, 68.7, 17.9; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 473.1399, $C_{26}H_{26}O_5S$ calcd for $[M+Na]^+$ 473.1393.

3.5. Phenyl

4-O-benzyl-2-O-(4-methoxybenzyl)-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benz

oyl-4-O-benzyl-1-thio-α-L-rhamnopyranoside (**1**)

A mixture of donor **3** (757 mg, 1.25 mmol) and acceptor **4** (467 mg, 1.04 mmol) in dichloromethane (2.1 mL) was premixed with molecular sieves 4Å (460 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to −78 °C using dry ice/acetone. After addition of *N*-iodosuccinimide (287 mg, 1.28 mmol) and trifluoromethanesulfonic acid (27 μL, 0.31 mmol), the reaction mixture was stirred warming up to −60 °C over 2 h and quenched with trimethylamine (0.43 mL, 3.09 mmol) at −60 °C before addition of a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (20 mL/20 mL) at 4 °C using ice bath. After additional 10 min stirring, the resulting mixture was filtered through a pad of Celite® with chloroform (40 mL). The organic layer was separated from the aqueous layer and washed with brine (40 mL). The aqueous layers were extracted with chloroform (40 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate: hexane = 1:10 → 1:8) to give the title compound **1** (482 mg, 50%) as a white foam.

$[\alpha]_D$ −73.7° (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–6.74 (m, 31H, Ph), 5.64 (brs, 1H, H-2^a), 5.56 (s, 1H, H-1^a), 5.06 (s, 1H, H-1^b), 4.88–4.45 (m, 8H, -*CH*Ph×8), 4.25 (m, 1H, H-5^a), 4.16 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3^a), 3.81–3.69 (m, 6H, H-2^b, H-3^b, H-5^b and OMe), 3.60–3.53

(m, 2H, H-4^{a} and H-4^{b}), 1.29 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^{a}), 1.19 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^{b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.1, 138.8, 138.0, 136.0, 133.8, 133.2, 133.2, 132.8, 131.8, 130.2, 129.9, 129.7, 129.3, 129.0, 128.4, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.6, 127.4, 127.4, 127.3, 126.1, 126.0, 125.7, 125.7, 113.7, 100.1 ($J_{C1,H1}$ = 167 Hz), 85.7, 80.3, 80.2, 79.4, 78.0, 75.3, 74.9, 74.5, 74.4, 72.2, 72.2, 69.1, 55.1, 17.9, 17.8; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 969.3630, $C_{58}H_{58}O_{10}S$ calcd for $[M+Na]^+$ 969.3643.

3.6. Phenyl

2-O-benzoyl-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-1-thio-α-L-rhamnopyranoside (**2**)

Disaccharide **1** (200 mg, 211 μmol) was dissolved in 90% aq. acetic acid (4.2 mL) and the reaction was allowed to warm to 80 °C using oil bath before stirring at the same temperature for 6 h. The resulting mixture was evaporated with toluene (5 mL×2) and purified with flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:4) to give the corresponding de-PMB product **S3** (118 mg, 68%) as a white foam.

A solution of **S3** (195 mg, 236 μmol) in pyridine (1.2 mL) was cooled to 4 °C using ice bath before addition of benzoyl chloride (82 μL, 706 μmol). After stirring for 30 min at 23 °C under nitrogen atmosphere, the reaction mixture was quenched with methanol (96 μL, 2.37 mmol) and evaporated

with toluene (2 mL×2). The resulting syrup was dissolved in a mixed solution of ethyl acetate/water (20 mL/20 mL). The organic layer was separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted with ethyl acetate (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:6) to give the title compound **2** (207 mg, 94%) as a white foam.

$[\alpha]_D$ −11.8° (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–7.16 (m, 32H, Ph), 5.69 (m, 1H, H-2^b), 5.67 (m, 1H, H-2^a), 5.57 (s, 1H, H-1^a), 5.24 (s, 1H, H-1^b), 4.86–4.53 (m, 6H, -*CH*Ph×6), 4.26 (m, 2H, H-3^a and H-5^a), 3.99 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 9.4 Hz, H-3^b), 3.87 (m, 1H, H-5^b), 3.66 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4^a), 3.53 (t, 1H, $J_{4,5}$ = 9.4 Hz, H-4^b), 1.34 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.23 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.6, 138.5, 137.7, 135.5, 133.8, 133.3, 133.2, 132.8, 129.9, 129.8, 129.7, 129.0, 128.5, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.4, 125.8, 125.7, 99.6, 85.7, 80.4, 79.7, 78.0, 77.7, 75.5, 74.7, 74.3, 71.5, 69.7, 69.2, 68.9, 18.0, 17.9; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 953.3334, $C_{57}H_{54}O_{10}S$ calcd for $[M+Na]^+$ 953.3330.

3.7. 2-Trimethylsilylethyl

4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rha

mnopyranoside (**8**)

A mixture of disaccharide **1** (1.27 g, 1.34 mmol), 2-trimethylsilylethanol (0.29 mL, 2.02 mmol), and *N*-iodosuccinimide (369 mg, 1.64 mmol) in dichloromethane (6.7 mL) was premixed with molecular sieves 4Å (670 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath. After addition of trifluoromethanesulfonic acid (36 μL, 199 mmol), the reaction mixture was stirred for 10 min at the same temperature and quenched with a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (20 mL/20 mL). After additional 10 min stirring, the resulting solution was filtered through a pad of Celite® with chloroform (40 mL). The organic layer was separated from the aqueous layer and washed with brine (40 mL). The aqueous layers were extracted with chloroform (40 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:6 → 1:4) to give the desired glycoside **S4** (897 mg, 70%) as a white foam.

S4 (218 mg, 228 μmol) was dissolved in 90% aq. acetic acid (4.6 mL) and the reaction was allowed to warm to 80 °C using oil bath before stirring at the same temperature for 48 h. The resulting mixture was evaporated with toluene (5 mL×2) and purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:6 → 1:3) to give the title compound **8** (140 mg, 73%) as a white foam.

$[\alpha]_D$ −14.1° (c 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.15 (m, 22H, Ph), 5.31 (brs, 1H, H-2^a), 5.05 (s, 1H, H-1^b), 4.83 (s, 1H, H-1^a), 4.78–4.48 (m, 6H, -*CH*Ph×6), 4.19 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9.4 Hz, H-3^a), 3.88 (brs, 1H, H-2^b), 3.80–3.70 (m, 4H, H-3^b, H-5^a, H-5^b and -*CH*CH_2Si), 3.48 (m, 2H, H-4^a and -*CH*CH_2Si), 3.38 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4^b), 2.33 (brs, 1H, OH), 1.27 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.13 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^b), 0.98–0.83 (m, 2H, -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 138.6, 138.0, 135.4, 133.2, 133.1, 133.0, 130.1, 129.8, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.4, 126.5, 126.1, 126.0, 125.7, 101.2, 96.7, 80.6, 79.8, 79.6, 77.8, 77.2, 75.3, 74.6, 73.2, 72.2, 69.2, 68.2, 67.6, 65.3, 18.0, 17.9, 17.7, -1.3; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 857.3682, $C_{49}H_{58}O_{10}Si$ calcd for $[M+Na]^+$ 857.3691.

3.8. 2-Trimethylsilylethyl

4-O-benzyl-2-O-(4-methoxybenzyl)-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→2)-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**9**)

A solution of donor **1** (184 mg, 194 μmol), acceptor **8** (133 mg, 159 μmol), and *N*-iodosuccinimide (53.1 mg, 236 μmol) in dichloromethane (1.6 mL) was premixed with activated molecular sieves 4Å (350 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath. After

addition of trifluoromethanesulfonic acid (4.2 μL, 47 μmol), the reaction mixture was stirred at the same temperature for 30 min and quenched with a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (10 mL/10 mL). After additional 10 min stirring, the resulting mixture was filtered through a pad of Celite® with chloroform (20 mL). The organic layer was separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted with chloroform (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by gel filtration (sephadex LH-20, chloroform/methanol = 1/1) and flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:6) to give the title compound **9** (202 mg, 76%) as a white foam.

$[\alpha]_D$ −25.3° (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–6.68 (m, 48H, Ph), 5.55 (brs, 1H, H-2^c), 5.30 (brs, 1H, H-2^a), 5.09 (s, 2H, H-1^b and H-1^c), 5.00 (s, 1H, H-1^d), 4.86–4.33 (m, 15H, H-1^a and -*CH*Ph×14), 4.24 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3^c), 4.13 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.3 Hz, H-3^a), 3.86–3.39 (m, 17H, H-2^b, H-2^d, H-3^b, H-3^d, H-4^a, H-4^b, H-4^c, H-4^d, H-5^a, H-5^b H-5^c, H-5^d, OMe and -*CH*CH_2Si×2), 1.21 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.13 (m, 9H, H-6^b, H-6^c and H-6^d), 0.99–0.84 (m, 2H, -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.4, 159.1, 138.9, 138.8, 138.2, 138.0, 136.2, 135.9, 133.2, 133.2, 133.2, 133.0, 132.8, 132.8, 130.3, 130.2, 130.1, 129.8, 129.8, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 126.2, 126.1, 125.9, 125.8, 125.7, 125.5, 113.6, 101.0, 99.8, 96.6, 80.4, 80.3,

80.1, 79.8, 79.7, 79.0, 78.5, 76.0, 75.4, 75.1, 74.8, 74.6, 74.5, 73.1, 72.8, 72.3, 72.2, 72.1, 69.0, 68.3, 67.6, 65.3, 55.1, 18.0, 17.9, 17.8, 17.7, -1.3; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 1693.7251, $C_{101}H_{110}O_{20}Si$ calcd for $[M+Na]^+$ 1693.7252.

3.9. 2-Trimethylsilylethyl 4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→2)-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**10**)

Tetrasaccharide **9** (202 mg, 121 μmol) was dissolved in 90% aq. acetic acid (2.4 mL) and the reaction was allowed to warm to 80 °C before stirring at the same temperature for 48 h. The resulting mixture was evaporated with toluene (5 mL×2) and purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:4 → 1:3) to give the title compound **10** (137 mg, 73%) as a white foam.

$[\alpha]_D$ −18.3° (c 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.12 (m, 44H, Ph), 5.54 (dd, 1H, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 3.2 Hz, H-2^c), 5.29 (dd, 1H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.2 Hz, H-2^a), 5.09 (brs, 1H, H-1^b), 5.06 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1^c), 5.00 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1^d), 4.84 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1^a), 4.82–4.26 (m, 12H, -<u>*CH*</u>Ph×12), 4.24 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3^c), 4.13 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3^a), 3.90–3.63 (m, 9H, H-2^b, H-2^d, H-3^b, H-3^d, H-5^a, H-5^b H-5^c, H-5^d and

-<u>*CH*</u>CH_2Si), 3.51–3.37 (m, 5H, H-4[a], H-4[b], H-4[c], H-4[d] and -<u>*CH*</u>CH_2Si), 2.33 (brs, 1H, OH), 1.21 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6[a]), 1.17 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6[d]), 1.10 (m, 6H, H-6[b] and H-6[c]), 0.99–0.84 (m, 2H, -CH_2<u>*CH*</u>Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.4, 138.8, 138.6, 138.0, 138.0, 135.9, 135.4, 133.2, 133.2, 133.1, 133.1, 133.0, 132.8, 130.2, 130.1, 129.8, 129.8, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.2, 126.5, 126.3, 126.1, 126.0, 125.9, 125.7, 125.7, 125.5, 101.0, 100.9, 98.9, 96.6, 80.5, 80.2, 79.9, 79.8, 79.7, 79.0, 78.4, 77.2, 77.1, 76.4, 75.1, 75.1, 74.7, 74.6, 73.2, 72.7, 72.3, 72.1, 69.1, 69.0, 68.4, 68.3, 67.6, 65.3, 18.0, 18.0, 17.9, 17.7, 17.7, -1.3; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 1573.6679, $C_{93}H_{102}O_{19}Si$ calcd for $[M+Na]^+$ 1573.6677.

3.10. 2-Trimethylsilylethyl 4-O-benzyl-2-O-(4-methoxybenzyl)-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→2)-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→2)-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**11**)

A mixture of donor **1** (170 mg, 179 μmol), acceptor **10** (137 mg, 88.3 μmol), and *N*-iodosuccinimide (60.4 mg, 268 μmol) and in dichloromethane (2.7 mL) was premixed with activated molecular sieves 4Å (270 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath.

After addition of trifluoromethanesulfonic acid (4.7 μL, 53.1 μmol), the reaction mixture was stirred at the same temperature for 30 min and quenched with a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (10 mL/10 mL). After additional 10 min stirring, the resulting mixture was filtered through a pad of Celite® with chloroform (20 mL). The organic layer was separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted with chloroform (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by gel filtration (sephadex LH-20, chloroform/methanol = 1/1) and flash column chromatography (silica gel, ethyl acetate:hexane = 1:4 → 1:3) to give the title compound **11** (76.7 mg, 36%) as a colorless syrup.

$[\alpha]_D$ −6.2° (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–6.67 (m, 70H, Ph), 5.57 (brs, 1H, H-2^e), 5.53 (brs, 1H, H-2^c), 5.29 (brs, 1H, H-2^a), 5.08 (m, 3H, H-1^b, H-1^c H-1^d and H-1^e), 4.99 (s, 1H, H-1^f), 5.00 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1^d), 4.84 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1^a), 4.86–4.32 (m, 21H, H-1^a and -*CH*Ph×20), 4.25 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.4 Hz, H-3^e), 4.20 (dd, 1H, $J_{2,3}$ = 2.6 Hz, $J_{3,4}$ = 9.4 Hz, H-3^c), 4.13 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.6 Hz, H-3^a), 3.87–3.39 (m, 23H, H-2^b, H-2^d, H-2^f, H-3^b, H-3^d, H-3^f, H-4^a, H-4^b, H-4^c, H-4^d, H-4^e, H-4^f, H-5^a, H-5^b, H-5^c, H-5^d, H-5^e, H-5^f, OMe and -*CH*CH_2Si×2), 3.51–3.37 (m, 5H, H-4^a, H-4^b H-4^c, H-4^d and -*CH*CH_2Si), 2.33 (brs, 1H, OH), 1.21 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.13 (m, 15H, H-6^b, H-6^c, H-6^d, H-6^e and H-6^f), 0.99–0.84 (m, 2H, -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.4, 159.0, 138.9, 138.8,

138.1, 137.9, 136.2, 135.9, 135.9, 133.2, 133.1, 133.1, 133.0, 132.8, 130.3, 130.2, 130.1, 130.1, 129.8, 129.7, 129.2, 128.4, 128.3, 128.3, 128.3, 128.1, 128.1, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 127.3, 127.2, 126.2, 126.2, 126.0, 125.9, 125.9, 125.8, 125.7, 125.5, 113.6, 101.0, 100.6, 99.7, 98.9, 98.7, 96.6, 80.3, 80.2, 80.1, 80.1, 79.9, 79.8, 79.7, 79.1, 79.0, 78.5, 77.2, 76.9, 76.3, 75.9, 75.4, 75.1, 75.0, 74.7, 74.6, 74.6, 74.5, 73.1, 72.8, 72.7, 72.3, 72.2, 72.1, 72.0, 69.0, 68.9, 68.9, 68.3, 68.3, 67.5, 65.3, 55.1, 18.0, 18.0, 18.0, 17.8, 17.8, 17.8, 17.7, -1.3; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 2410.0227, $C_{145}H_{154}O_{29}Si$ calcd for $[M+Na]^+$ 2410.0237.

3.11. 2-Trimethylsilylethyl

2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosi de (**12**)

A mixture of disaccharide **2** (107 mg, 115 μmol), 2-trimethylsilylethanol (25 μL, 174 μmol), and *N*-iodosuccinimide (32.0 mg, 138 μmol) in dichloromethane (0.58 mL) was premixed with molecular sieves 4Å (120 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath. After addition of trifluoromethanesulfonic acid (3.1 μL, 35.0 μmol), the reaction mixture was stirred for 10 min at the same temperature and quenched with a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (10 mL/10 mL). After additional 10 min stirring, the resulting solution was filtered through a pad of Celite® with chloroform (20 mL). The organic layer was

separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted with chloroform (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:12 → 1:8) to give the desired glycoside **S5** (72.3 mg, 67%) as a colorless syrup.

S5 (647 mg, 689 μmol) was dissolved in a mixed solution of dichloromethane/methanol (2.8 mL/0.7 mL) before addition of 2,3-dichloro-5,6-dicyanobenzoquinone (154 mg, 678 μmol) After stirring for 12 h at 23 °C, the reaction mixture was evaporated until dry and dissolved in ethyl acetate (40 mL). The resulting solution was washed with satd. aq. $NaHCO_3$ (40 mL×2), and brine (40 mL). The aqueous layers were extracted with ethyl acetate (40 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting syrup was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:8 → 1:4) to give the title compound **12** (396 mg, 72%) as a white foam.

$[\alpha]_D$ +30.5° (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.18 (m, 20H, Ph), 5.38 (brs, 1H, H-2^b), 5.32 (brs, 1H, H-2^a), 5.17 (s, 1H, H-1^b), 4.91–4.60 (m, 5H, H-1^a and -<u>*CH*</u>Ph×4), 4.26 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3^a), 4.07 (m, 1H, H-3^b), 3.89–3.73 (m, 3H, H-5^a, H-5^b and -<u>*CH*</u>CH_2Si), 3.60 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4^a), 3.48 (m, 1H, -<u>*CH*</u>CH_2Si), 3.40 (t, 1H, $J_{4,5}$ = 9.5 Hz, H-4^b), 2.08 (brs, 1H, OH), 1.31 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.25 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^b), 0.98–0.83 (m, 2H, -CH_2<u>*CH*</u>Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.9, 138.2, 137.9,

133.2, 133.2, 129.9, 129.8, 129.8, 129.7, 128.5, 128.4, 128.3, 128.3, 128.2, 127.8, 127.7, 127.7, 99.4, 96.7, 81.2, 80.8, 77.2, 75.5, 73.9, 73.2, 73.1, 69.8, 68.2, 67.7, 65.2, 18.1, 17.9, 17.8, -1.3; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 821.3325, $C_{45}H_{54}O_{11}Si$ calcd for $[M+Na]^+$ 821.3328.

3.12. 2-Trimethylsilylethyl 2-O-benzoyl-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**13**)

A mixture of donor **2** (141 mg, 151 μmol), acceptor **12** (103 mg, 129 μmol), and *N*-iodosuccinimide (43.1 mg, 192 μmol) in dichloromethane (1.3 mL) was premixed with activated molecular sieves 4Å (560 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath. After addition of trifluoromethanesulfonic acid (3.4 μL, 38 μmol), the reaction mixture was stirred at the same temperature for 30 min and quenched with a mixed solution of satd. aq. $NaHCO_3$ /satd. aq. $Na_2S_2O_3$ (10 mL/10 mL). After additional 10 min stirring, the resulting mixture was filtered through a pad of Celite® with chloroform (20 mL). The organic layer was separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted with chloroform (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:6 → 1:4) to give the

title compound **13** (174 mg, 83%) as a white foam.

$[\alpha]_D$ +55.5° (c 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.12 (m, 47H, Ph), 5.56 (brs, 1H, H-2^d), 5.49 (brs, 1H, H-2^c), 5.47 (brs, 1H, H-2^b), 5.33 (brs, 1H, H-2^a), 5.22 (s, 1H, H-1^c), 5.06 (s, 1H, H-1^b), 5.00–4.43 (m, 12H, H-1^a, H-1^d and -*CH*Ph×10), 4.28 (dd, 1H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3^a), 4.21 (dd, 1H, $J_{2,3}$ = 1.8 Hz, $J_{3,4}$ = 9.2 Hz, H-3^c), 4.15 (dd, 1H, $J_{2,3}$ = 1.8 Hz, $J_{3,4}$ = 9.2 Hz, H-3^b), 3.90 (dd, 1H, $J_{2,3}$ = 1.8 Hz, $J_{3,4}$ = 9.6 Hz, H-3^d), 3.86–3.72 (m, 5H, H-5^a, H-5^b, H-5^c, H-5^d and -*CH*CH_2Si), 3.63–3.39 (m, 5H, H-4^a, H-4^b, H-4^c, H-4^d and -*CH*CH_2Si), 1.30 (d, 3H, $J_{5,6}$ = 5.8 Hz, H-6^a), 1.13 (d, 3H, $J_{5,6}$ = 5.8 Hz, H-6^d), 1.02–0.83 (m, 8H, H-6^b, H-6^c and -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.7, 165.4, 138.5, 138.5, 138.0, 137.9, 135.5, 133.2, 133.1, 133.1, 132.8, 130.0, 129.9, 129.9, 129.8, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.5, 127.5, 127.3, 126.4, 125.8, 125.8, 125.6, 99.3, 99.0, 98.9, 96.5, 80.4, 80.0, 79.9, 79.7, 78.1, 77.8, 77.2, 77.1, 76.9, 75.6, 74.7, 74.5, 73.1, 72.9, 72.6, 71.4, 69.5, 68.6, 68.6, 68.5, 67.6, 65.3, 18.1, 17.8, 17.8, -1.4; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 1641.6583, $C_{96}H_{102}O_{21}Si$ calcd for $[M+Na]^+$ 1641.6575.

3.13. 2-Trimethylsilylethyl 2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamn

opyranoside (**14**)

Tetrasaccharide **13** (174 mg, 107 mmol) was dissolved in a mixed solution of dichloromethane/methanol (0.86 mL/0.21 mL) before addition of 2,3-dichloro-5,6-dicyanobenzoquinone (25.2 mg, 111 mmol). After stirring for 12 h at 23 °C, the reaction mixture was evaporated until dry and dissolved in ethyl acetate (20 mL). The resulting solution was washed with satd. aq. $NaHCO_3$ (20 mL×2), and brine (20 mL). The aqueous layers were extracted with ethyl acetate (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting syrup was purified by flash column chromatography (silica gel, ethyl acetate:hexane = 1:4 → 1:2) to give the title compound **14** (110 mg, 70%) as a colorless syrup.

$[\alpha]_D$ +39.8° (c 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.17 (m, 40H, Ph), 5.49 (brs, 1H, H-2^d), 5.41 (brs, 1H, H-2^c), 5.33 (brs, 1H, H-2^b), 5.28 (brs, 1H, H-2^a), 5.22 (s, 1H, H-1^c), 5.04 (s, 1H, H-1^b), 5.01–4.54 (m, 10H, H-1^a, H-1^d and -*CH*Ph×8), 4.28 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 9.3 Hz, H-3^a), 4.21 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3^c), 4.14 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3^b), 4.01 (m, 1H, H-3^d), 3.86–3.72 (m, 5H, H-5^a, H-5^b, H-5^c, H-5^d and -*CH*CH_2Si), 3.63–3.45 (m, 4H, H-4^a, H-4^b, H-4^c and -*CH*CH_2Si), 3.32 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4^d), 1.30 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6^a), 1.13 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6^d), 1.04–0.83 (m, 8H, H-6^b, H-6^c and -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.8, 165.7, 165.4, 138.2, 137.9, 133.2, 133.1, 129.9,

129.8, 129.7, 129.7, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.7, 127.5, 99.2, 99.0, 98.9, 96.5, 81.1, 80.4, 80.2, 79.8, 78.0, 77.4, 76.5, 75.6, 74.7, 74.6, 73.8, 73.1, 72.9, 72.7, 69.7, 68.6, 68.6, 68.1, 67.6, 65.2, 18.1, 17.8, -1.4; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 1501.5950, $C_{85}H_{94}O_{21}Si$ calcd for $[M+Na]^+$ 1501.5949.

3.14. 2-Trimethylsilylethyl 2-O-benzoyl-4-O-benzyl-3-O-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranosyl-(1→3)-2-O-benzoyl-4-O-benzyl-α-L-rhamnopyranoside (**15**)

A mixture of donor **2** (79.8 mg, 85.7 μmol), acceptor **14** (62.8 mg, 42.4 μmol), and *N*-iodosuccinimide (29.1 mg, 129 μmol) in dichloromethane (0.85 mL) was premixed with activated molecular sieves 4Å (250 mg) for 30 min at 23 °C under nitrogen atmosphere before cooling to 4 °C using ice bath. After addition of trifluoromethanesulfonic acid (2.3 μL, 26 μmol), the reaction mixture was stirred at the same temperature for 30 min and quenched with a mixed solution of satd. aq. $NaHCO_3$/satd. aq. $Na_2S_2O_3$ (10 mL/10 mL). After additional 10 min stirring, the resulting mixture was filtered through a pad of Celite® with chloroform (20 mL). The organic layer was separated from the aqueous layer and washed with brine (20 mL). The aqueous layers were extracted

with chloroform (20 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by gel filtration (sephadex LH-20, chloroform/methanol = 1/1) and flash column chromatography (silica gel, ethyl acetate:hexane = 1:4 → 1:3) to give the title compound **15** (89.7 mg, 92%) as a colorless syrup.

$[\alpha]_D$ +61.3° (c 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.11 (m, 67H, Ph), 5.54 (brs, 1H, H-2^f), 5.46 (brs, 1H, H-2^e), 5.39 (m, 3H, H-2^b, H-2^c and H-2^d), 5.32 (brs, 1H, H-2^a), 5.21 (s, 1H, H-1^e), 5.03–4.42 (m, 19H, H-1^a, H-1^b, H-1^c, H-1^d, H-1^f and -*CH*Ph×14), 4.27 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.3 Hz, H-3^a), 4.19 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3^e), 4.13 (m, 3H, H-3^b, H-3^c and H-3^d), 3.89 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3^f), 3.84–3.70 (m, 7H, H-5^a, H-5^b, H-5^c, H-5^d, H-5^e, H-5^f and -*CH*CH_2Si), 3.62–3.38 (m, 7H, H-4^a, H-4^b, H-4^c, H-4^d, H-4^e, H-4^f and -*CH*CH_2Si), 1.30 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6^a), 1.11 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6^f), 1.00–0.83 (m, 13H, H-6^b, H-6^c, H-6^d, H-6^e and -CH_2*CH*Si×2), 0.00 (s, 3H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.7, 165.5, 165.4, 165.4, 138.5, 138.0, 137.9, 135.5, 133.2, 133.1, 133.1, 132.8, 130.0, 129.9, 129.8, 129.8, 129.7, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 126.3, 125.8, 125.8, 125.6, 99.3, 98.9, 98.9, 98.8, 96.5, 80.4, 80.0, 79.9, 79.8, 79.8, 79.7, 78.1, 77.8, 77.5, 77.2, 77.2, 76.9, 76.9, 75.6, 74.7, 74.7, 74.5, 73.1, 72.9, 72.7, 72.7, 72.6, 71.4, 69.5, 68.6, 68.6, 68.6, 68.5, 68.5, 68.5, 67.6, 65.3, 18.1, 17.8, 17.8, 17.8, -1.4; HRMS (ESI-TOF) m/z: found $[M+Na]^+$ 2321.9208, $C_{136}H_{142}O_{31}Si$ calcd for $[M+Na]^+$

2321.9197.

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19. Although the reaction conversion was approximately 80%, the PMB deprotection was terminated in 4 h. Prolonged reaction time led to hydrolysis of the terminal thioglycosidic linkage and removal of NAP group. We speculate that these side reactions were caused by the PMB carbocation generated *in situ*. Jung, M. E.; Koch, P. *Tetrahedron Lett.* **2011**, *52*, 6051–6054.

Highlights

- Rhamnan hexasaccharides with novel alternating and repeating linkages were prepared
- The hexasaccharides were synthesized by iterative glycosylation with disaccharides
- Synthesis of disaccharides was achieved by orthogonal coupling with thioglycosides