Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 10083–10091

Efficient stereoselective synthesis of oligosaccharides of *Streptococcus pneumoniae* serotypes 6A and 6B containing multiple 1,2-*cis* glycosidic linkages

Archana R. Parameswar, Papapida Pornsuriyasak, Nicole A. Lubanowski and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, MO 63121, USA

Received 31 May 2007; revised 5 July 2007; accepted 10 July 2007
Available online 19 July 2007

Abstract—The synthesis of the repeating units of pneumococcal polysaccharide serotypes 6A and 6B and derivatives thereof is described. Application of *S*-benzoxazolyl and *S*-thiazolinyl glycosides allowed rapid oligosaccharide assembly and provided complete stereoselectivity in challenging 1,2-*cis* glucosylations and galactosylations. The oligosaccharide assembly was accomplished in an efficient manner by selective activation of thioimidoyl leaving groups over thioglycosides.

1. Introduction

Involvement of complex glycostructures in a variety of damaging and healing processes has already been acknowledged by development of carbohydrate-based vaccines[1–3] and therapeutics.[4,5] The bacteria *Streptococcus pneumoniae* (SPn) have become one of the most frequent causes of pneumonia, bacteremia, and meningitis in the elderly, immunocompromised, and, especially, in young children. As a matter of fact, SPn has one of the largest public health and economic impacts amongst all bacterial infectious diseases. The incidence of pneumococcal infection varies geographically, but elevated rates have been observed in both developed and developing countries. In accordance with the joint United Nations Children's Fund (UNICEF)/World Health Organization (WHO) survey, over 2 million children die annually worldwide due to pneumonia, accounting for almost 20% of deaths under age five.[6] More than half of these deaths are attributed to SPn. This situation is further complicated by the rapid increase in anti-microbial drug resistance during the last decade. Since the SPn bacterial cell is surrounded by a polysaccharide capsule, preventive vaccination based on polysaccharide or saccharide–protein conjugates is a suitable tool against the bacterial invasion.[7]

Amongst over 90 elucidated SPn serotypes,[8] 6A and 6B are equally important causes of bacterial infections.[9] In addition, this serogroup has been ranked within the top three causes of invasive pneumococcal disease worldwide.[10] This fact stimulated extensive structural studies leading to establishing the structures of capsular polysaccharides of both 6A and 6B (Fig. 1).[11–13] Serotype-specific antibodies are formed in response to vaccination with the pneumococcal polysaccharide or saccharide–protein conjugate, so it was believed that due to similarity in the carbohydrate core structures of SPn6A and SPn6B, the elicited antibodies would be cross-reactive against both types.[12,14–16] As a result, only hydrolytically more stable and, hence, easier accessible natural isolate of SPn6B was selected and included in all currently licensed multi-component vaccines. A common approach to vaccine development is based on the isolated natural polysaccharides either neat or conjugated to a protein carrier. A number of linear chemical syntheses of SPn6B, their mimetics, and conjugates have also emerged.[17–22]

Recent cross-reactivity studies challenged the hypothesis of the cross-reactivity by determining that SPn6B-based vaccines produce 6B-specific antibodies that cross-react with SPn6A at a much lower rate.[9,22–24] In this context, similar observations had also been made for the capsular polysaccharide types 19F and 19A.[25] Hence, the importance of including the SPn6A carbohydrate conjugates in the future generations of multi-serotype anti-SPn vaccines has been acknowledged.[26] However, the achievement of this is challenging for a number of reasons, major of which is low hydrolytic stability of SPn6A isolates that results in their low availability in sufficiently pure form.[27] A possible solution for this would be the chemical synthesis of the related sugar derivatives and their application as oligosaccharide–protein conjugate vaccine components. Although natural[28]

Keywords: Carbohydrates; *Streptococcus pneumoniae*; Synthetic vaccines; Glycosylation; Oligosaccharides; Thioimidates.
* Corresponding author. E-mail: demchenkoa@umsl.edu

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.036

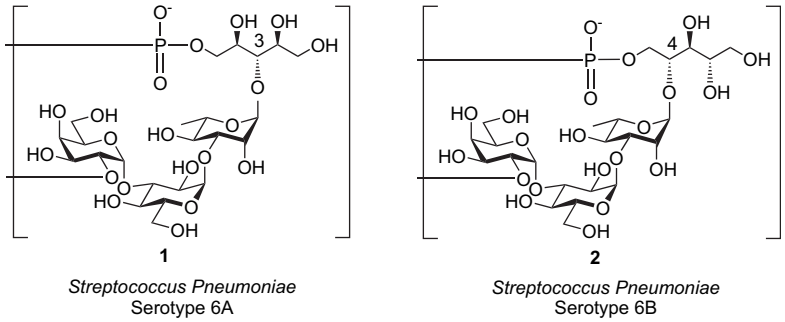


Figure 1. Compound numbers **1** and **2** correspond to the phosphateless pseudo-tetrasaccharide units only.

and synthetic saccharides[17–19] of the SPn6A series have been investigated, no systematic studies have yet emerged. Herein, we report the application of new thioimidoyl methodology developed in our laboratory to efficient stereoselective synthesis of pseudo-disaccharides, pseudo-trisaccharides, and pseudo-tetrasaccharides (**1**–**6**, Figs. 1 and 2) structurally related to SPn6A and SPn6B.

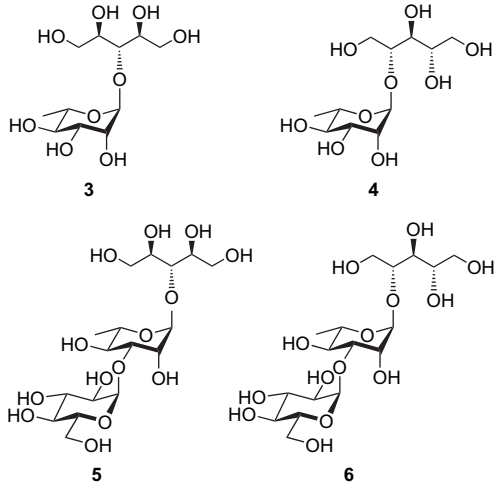


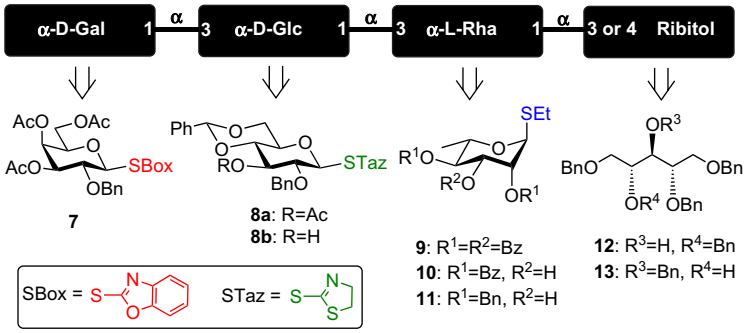
Figure 2.

2. Retrosynthetic analysis

SPn6A and SPn6B repeating units consist of structurally similar complex pseudo-tetrasaccharides **1** and **2**, respectively (Fig. 1), which in the natural polysaccharide are connected via a phosphate (5→2‴) linkage. Both **1** and **2** bear a terminal D-galactosyl residue, which is α-glycosidically linked (1,2-cis) to the C-3 of a D-glucose unit; the latter is linked via 1,2-*cis*-glycosidic bond to the C-3 of L-rhamnose, which is connected via α-glycosidic linkage (1,2-trans) to the C-3 of D-ribitol (SPn6A) or C-4 of D-ribitol (SPn6B). Efficient chemical synthesis of the repeating units of SPn6A, SPn6B and structurally related glycoconjugates thereof will help to quickly obtain substantial quantities of pure samples for immunological studies and subsequent fully synthetic vaccine development.

From the chemical point of view, a number of synthetic challenges could be anticipated. It should be noted that even nowadays chemical synthesis of complex carbohydrates of this caliber, especially those containing 'difficult' 1,2-*cis* glycosidic linkages, is still regarded as laborious and inefficient.[29] Our goal was to investigate whether the application of glycosyl thioimidates, excellent building blocks for 1,2-cis glycosylation,[30,31] would allow high 1,2-cis stereoselectivity and yields when applied to the synthesis of pneumococcal oligosaccharides. Therefore, the use of the anomeric thioimidoyl moieties, *S*-benzoxazolyl (SBox) or *S*-thiazolinyl (STaz), was projected for the introduction of 1,2-*cis* glycosidic linkages of oligosaccharides **1**, **2**, **5**, and **6**. A non-participating group at C-2, *O*-benzyl, is required to facilitate the introduction of 1,2-*cis*-linked galactose and glucose units. Since the thioimidoyl moiety can be selectively activated over conventional thioglycosides,[32] *S*-ethyl moiety was chosen for the introduction of the rhamnose unit.

Having analyzed the target oligosaccharide structures and possible challenges associated with their synthesis, we narrowed down possible candidates for the key building blocks to the following compounds: D-galactose (**7**), D-glucose (**8a**,**b**), L-rhamnose (**9**–**11**) and D/L- or D-ribitol (**12** or **13**, respectively, Scheme 1).[33] A variety of rhamnose derivatives



Scheme 1. Retrosynthetic analysis of oligosaccharides of SPn6A and SPn6B.

were to be investigated in an attempt to optimize the stereoselectivity and yield of rhamnosylation.

3. Synthesis of building blocks

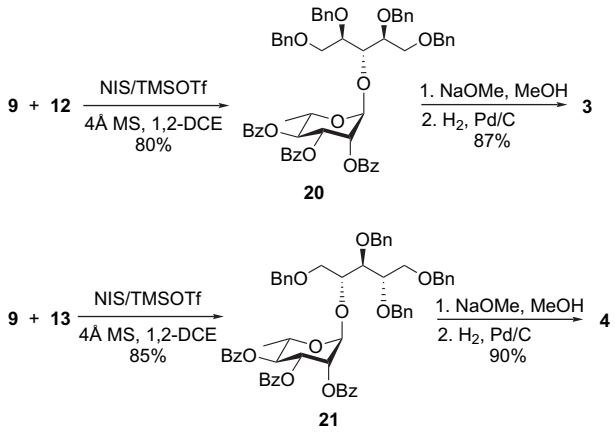
Synthesis of the 3-OH ribitol building block **12** was carried out from known precursor **14** as shown in Scheme 2.[34] Thus, allylation of **14** was accomplished in 99% yield and the resulting compound **15** was subjected to acetal cleavage followed by benzylation to afford fully protected intermediate **17** in over 90% yield for two steps. Deallylation of **17** using $PdCl_2$ in MeOH lead to glycosyl acceptor **12** in 95% yield. It is noteworthy that the synthesis of compound **12** has been previously accomplished using less expeditious pathways.[18] Unfortunately, the direct use of 3-OH ribitol **14** as glycosyl acceptor was found to be impractical. Partial loss of acetal protecting groups that has occurred during glycosylation resulted in the formation of an inseparable mixture.

Synthesis of 4-OH ribitol building block **13**, a component of SPn6B, was achieved by the reduction of known compound **18**[35] to obtain **19**[36] in 90% yield (Scheme 2). The intermediate **19** was then regioselectively benzylated under phase transfer conditions to afford 4-OH glycosyl acceptors **13** as a major regioisomer in 52% yield. Other building blocks, D-galactose (**7**),[30] D-glucose (**8a**,**b**),[32] and L-rhamnose (**9**–**11**),[37–39] have been obtained as described previously.

4. Oligosaccharide synthesis

For the synthesis of pseudo disaccharides **3** and **4**, fully protected rhamnose building block **9** was used as a glycosyl donor. Coupling of **9** with ribitol acceptors **12** and **13** in the presence of NIS/TMSOTf afforded glycosides **20** and **21** with complete α-selectivity in 80 and 85% yield, respectively (Scheme 3). Complete 1,2-trans stereoselectivity achieved herein is credited to the use of a neighboring participating substituent in **9**. The compounds obtained were then subjected to a two-step sequential deprotection: deacylation (NaOMe in MeOH) and hydrogenation using palladium on charcoal to obtain pseudo-disaccharides **3** and **4** in 87 and 90% yield, respectively, over two steps.

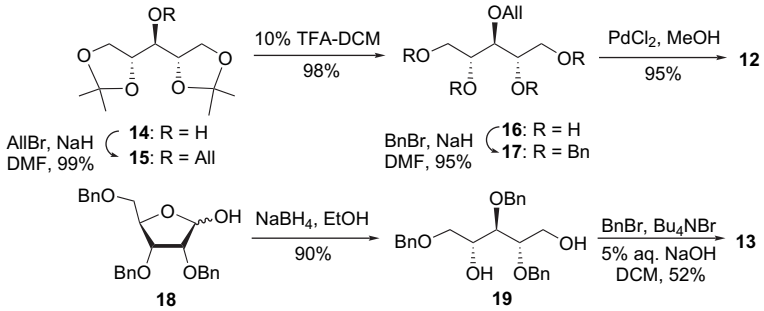
For the synthesis of pseudo-trisaccharides **5** and **6**, disaccharide intermediate **22** was obtained in 72% yield by selective activation of the STaz moiety of glycosyl donor **8a** over the



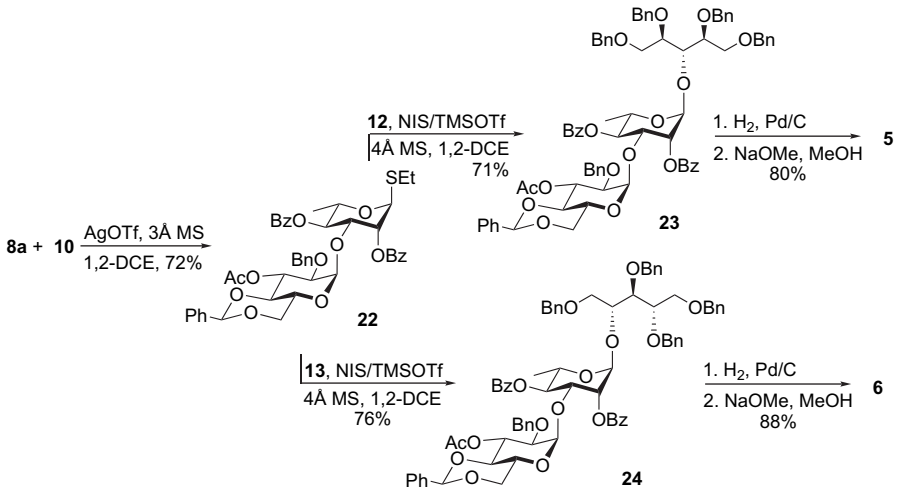
Scheme 3. Synthesis of pseudo-disaccharides of SPn6A (**3**) and SPn6B (**4**).

S-ethyl moiety of glycosyl acceptor **10** in the presence of silver(I) triflate (Scheme 4). This reaction proceeded with complete 1,2-cis stereoselectivity as no traces of the diastereomer were detected by analyzing crude reaction mixture. Subsequently, the *S*-ethyl moiety of **22** was activated with NIS and TMSOTf for glycosylation of glycosyl acceptors **12** and **13**. As a result, saccharides **23** and **24** were isolated in 71 and 76% yield, respectively. These rhamnosylations also proceeded with complete α-stereoselectivity. The protected pseudo-trisaccharides **23** and **24** were subjected to standard deprotection conditions, deacylation followed by hydrogenation, to afford compounds **5** and **6** in 80 and 88% yield, respectively.

Finally, we were aimed for the synthesis of pseudo-tetrasaccharides **1** and **2**, the ultimate targets of this work. For this purpose, we first investigated sequential activation of the SBox moiety of **7** over the STaz moiety of glucosyl acceptor **8b**. Unfortunately, this reaction resulted in the formation of an unseparable mixture of anomers (α–β=7/1). This misfortune stimulated us to adopt a new strategy, according to which glucosyl donor bearing the STaz leaving group (**8a**) was first selectively activated over the *S*-ethyl moiety of the rhamnose acceptor (**11**) in the presence of AgOTf. Although this reaction was performed in 1,2-dichloroethane, a solvent that does not normally favor α-glycosylation, the disaccharide **25** was obtained as a single α-anomer (1,2-cis) in 81% yield (Scheme 5). Subsequently, 3′-acetyl group in **25** was removed by Zemplen method and the resulting disaccharide acceptor **26** was coupled with glycosyl donor **7**. Selective



Scheme 2. Synthesis of ribitol acceptors **12** and **13**.

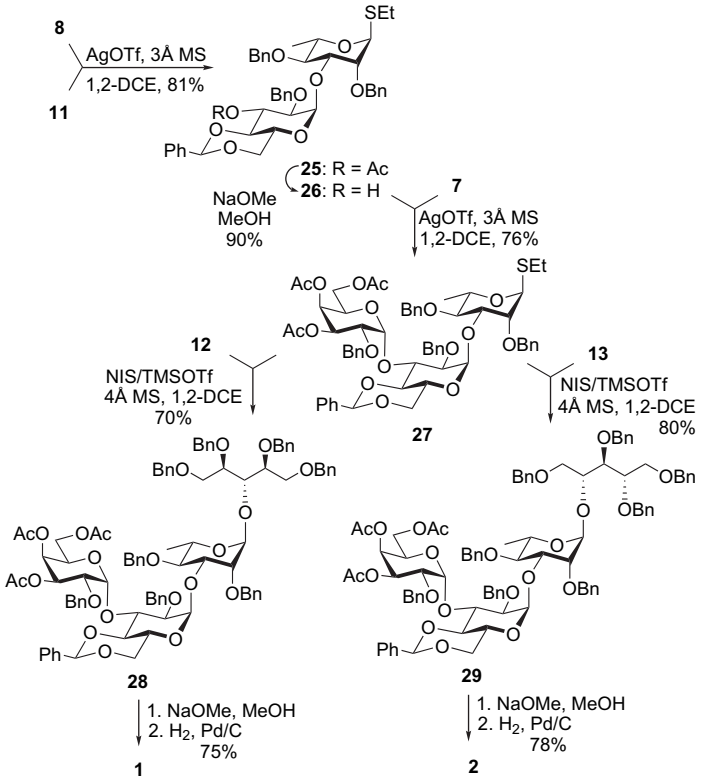


Scheme 4. Synthesis of pseudo-trisaccharides of SPn6A (**5**) and SPn6B (**6**).

activation of the SBox moiety over the *S*-ethyl moiety was accomplished in the presence of AgOTf, and, in this case, trisaccharide **27** was obtained with complete α-selectivity in 76% yield. No trace of the β-anomer could be detected by analysis of the crude reaction mixture. To complete the assembly, the trisaccharide **27** was coupled with ribitol acceptors **12** and **13** in the presence of NIS and TMSOTf. As a result, pseudo-tetrasaccharide derivatives **28** and **29** were obtained in 70 and 80% yield, respectively. Finally, the deprotection of **28** and **29** was carried out using conventional deacylation–hydrogenation sequence to afford pseudo-tetrasaccharides **1** and **2** in 75 and 78% yield, respectively.

5. Conclusions and future directions

We developed an efficient convergent approach to the synthesis of pneumococcal oligosaccharides of SPn6A and SPn6B. Rapid oligosaccharide assembly was accomplished by selective activation of the STaz and SBox leaving group of glycosyl donors over the *S*-ethyl anomeric moiety of glycosyl acceptors. Application of the STaz and SBox methodologies has also allowed completely stereoselective introduction of two challenging 1,2-*cis* glycosidic moieties. It is to be expected that the protocol reported herein will be suitable for the synthesis of recently discovered structurally



Scheme 5. Synthesis of pseudo-tetrasaccharides of SPn6A (**1**) and SPn6B (**2**).

similar serotypes SPn6C and SPn6D.[40] Further studies related to the synthesis of spacer-containing oligosaccharides for subsequent conjugation and immunological studies are underway in our laboratory.

6. Experimental part

6.1. 3-*O*-Allyl-1,2:4,5-di-*O*-isopropylidene-D/L-ribitol (15)

Allyl bromide (0.75 mL, 8.62 mmol) was added to a stirring solution of 1,2:4,5-di-*O*-isopropylidene-D/L-ribitol (**14**, 1.0 g, 4.3 mmol) in dry DMF (10 mL) at 0 °C. Sodium hydride (60% suspension in mineral oil, 12.9 mmol) was added slowly until evolution of hydrogen gas has seized. The reaction mixture was stirred for 20 min at rt until complete disappearance of starting material as indicated by TLC. The reaction mixture was poured in crushed ice (~100 mL), stirred for 15 min, and extracted with ethyl acetate/ether (1/1, v/v, 3×100 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford compound **15** as a syrup (1.16 g, 99% yield). Analytical data: R_f=0.50 (ethyl acetate–hexanes, 1/5, v/v); $[\alpha]_D^{26}$ −0.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 1.27, 1.35 (2 s, 12H, 4×CH_3), 3.57 (dd, 1H, $J_{3,4}$=4.8 Hz, H-3), 3.59–3.99 (m, 4H, H-1, 5), 4.01–4.05 (m, 2H, H-2, 4), 4.17 (m, 2H, OCH_2), 5.06–5.21 (m, 2H, CH_2=), 5.80–5.91 (m, 1H, =CH–) ppm; ^{13}C NMR: δ 25.7 (×2), 25.8 (×2), 66.2 (×2), 74.2, 76.6 (×2), 78.8, 110.0 (×2), 117.3, 135.3 ppm, HR-EIMS $[M-CH_3]^+$ calcd for $C_{13}H_{21}O_5$ 257.1384, found 257.1389.

6.2. 3-*O*-Allyl-D/L-ribitol (16)

To a stirred solution of **15** (1.16 g, 4.6 mmol) in CH_2Cl_2 (10 mL), 90% aq trifluoroacetic acid (1 mL) was added dropwise and the reaction was kept for 30 min at rt until complete disappearance of the starting material (monitored by TLC). The reaction mixture was neutralized with triethylamine (~1 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (methanol–dichloromethane gradient elution) to afford compound **16** as a syrup (0.81 g, 98% yield). Analytical data: R_f=0.46 (methanol–dichloromethane, 1/5, v/v); $[\alpha]_D^{28}$ −1.5 (*c* 1.0, methanol); ^{1}H NMR (CD_3OD): δ 3.47 (dd, 1H, $J_{2,3}$=5.7 Hz, H-3), 3.57–3.63 (m, 2H, H-5), 3.70–3.75 (m, 2H, H-1), 3.79–3.84 (m, 2H, H-2, 4), 4.13–4.16 (m, 2H, OCH_2), 5.09–5.27 (m, 2H, CH_2=), 5.84–5.98 (m, 1H, =CH–) ppm; ^{13}C NMR (CD_3OD): δ 65.1 (×2), 72.6 (×2), 73.9, 82.1, 117.9, 136.7 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_8H_{16}O_5Na$ 215.0895, found 215.0895.

6.3. 3-*O*-Allyl-1,2,4,5-tetra-*O*-benzyl-D/L-ribitol (17)

Benzyl bromide (2.5 mL, 21.1 mmol) was added to a stirring solution of **16** (0.81 g, 4.21 mmol) in dry DMF (15 mL) at 0 °C. Sodium hydride (60% suspension in mineral oil, 1.26 g, 31.6 mmol) was added slowly until evolution of hydrogen gas has seized. The reaction mixture was stirred for 30 min at rt until complete disappearance of starting material as indicated by TLC. The reaction mixture was poured in crushed ice (~50 mL), stirred for 15 min, and extracted with ethyl acetate/ether (1/1, v/v, 3×80 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford compound **17** as a syrup (2.27 g, 98% yield). Analytical data for **17** were essentially the same as reported previously.[18]

6.4. 1,2,4,5-Tetra-*O*-benzyl-D/L-ribitol (12)

To a stirring solution of **17** (1.5 g, 2.7 mmol) in MeOH (15 mL), $PdCl_2$ (0.6 g) was added and the reaction mixture was stirred at rt for 12 h. The solid was then filtered-off through Celite, washed with methanol (3×10 mL), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford compound **12** as a syrup (1.29 g, 93% yield). Analytical data: R_f=0.42 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{23}$ +4.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 3.54–3.60 (m, 2H, H-2,4), 3.63–3.68 (m, 4H, H-1, 5), 3.98 (dd, 1H, $J_{3,4}$=10.9 Hz, H-3), 4.38–4.62 (m, 8H, 4×CH_2Ph), 7.16–7.25 (m, 20H, aromatic) ppm; ^{13}C NMR δ 70.7 (×2), 72.1, 72.5 (×2), 73.9 (×2), 78.6 (×2), 128.1 (×3), 128.1 (×3), 128.2 (×4), 128.4 (×4), 128.8 (×4), 128.9 (×4), 136.6, 138.9 ppm; HR-FABMS $[M+H]^+$ calcd for $C_{33}H_{37}O_5$ 513.2641, found 513.2642. It should be noted that partial analytical data for **12** were reported previously.[18]

6.5. 2,3,5-Tri-*O*-benzyl-D-ribitol (19)

To a stirring suspension of $NaBH_4$ (350 mg, 9.2 mmol) in absolute ethanol (17 mL) at 0 °C, was added a solution of 2,3,5-tri-*O*-benzyl-D-ribose (**18**, 2.28 g, 5.4 mmol) in absolute ethanol (19 mL) and the reaction mixture was stirred for 15 min at rt. Upon completion, 96% aq acetic acid was added until pH 5 (~1.0 mL). The resulting mixture was diluted with DCM (100 mL), washed with 1 M HCl (30 mL), and water (2×30 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford compound **19** as a syrup (2.07 g, 90% yield). Analytical data: R_f=0.53 (ethyl acetate–hexanes, 2/3, v/v); $[\alpha]_D^{22}$ +19.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 3.55–3.58 (m, 2H, H-5), 3.69–3.76 (m, 2H, H-2, 3), 3.78–3.82 (m, 2H, H-1), 3.92–4.02 (m, 1H, H-4), 4.38–4.71 (m, 6H, 3×CH_2Ph), 7.13–7.21 (m, 15H, aromatic) ppm; ^{13}C NMR: δ 61.6, 71.2, 71.6, 72.6, 74.0, 74.6, 79.9, 80.0, 128.4 (×3), 128.5 (×2), 128.6 (×2), 128.7 (×2), 129.0 (×2), 129.1 (×4), 138.5, 138.6 (×2) ppm; HR-FABMS $[M+H]^+$ calcd for $C_{26}H_{31}O_5$ 423.2172, found 423.2176. It should be noted that the synthesis and partial analytical data of compound **19** was previously described.[36,41]

6.6. 1,2,3,5-Tetra-*O*-benzyl-D-ribitol (13)

To a solution of compound **19** (724 mg, 1.71 mmol) in CH_2Cl_2 (15 mL), BnBr (0.3 mL, 1.22 mmol) was added followed by Bu_4NBr (110 mg, 0.34 mmol) and 5% aq NaOH (4.5 mL). The reaction mixture was stirred for 16 h under reflux (50 °C), then cooled to rt, diluted with CH_2Cl_2 (50 mL), and washed with saturated aq $NaHCO_3$

(15 mL) and water (3×15 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexanes gradient elution) to afford **13** as white crystals (458 mg, 52% yield). Also the regioisomer (2,3,4,5-tetra-*O*-benzyl-D-ribitol) was isolated in 32% yield. Analytical data for **13**: R_f=0.46 (ethyl acetate–toluene, 3/7, v/v); $[\alpha]_D^{22}$ +18.1 (*c* 1.0, $CHCl_3$); mp 40 °C; ^{1}H NMR: δ 3.59–3.61 (m, 2H, H-5), 3.68–3.73 (m, 1H, H-3), 3.76–3.84 (m, 2H, H-1), 3.92–3.96 (m, 1H, H-2), 3.98–4.04 (m, 1H, H-4), 4.50–4.75 (m, 8H, 4×*CH*$_2$Ph), 7.18–7.33 (m, 20H, aromatic) ppm; ^{13}C NMR: δ 70.3, 71.6, 71.8, 73.1, 74.0 (×2), 74.3, 79.5, 79.7, 128.1, 128.2 (×2), 128.3 (×3), 128.4 (×2), 128.5 (×2), 128.6 (×2), 128.9 (×4), 129.0 (×4), 138.7, 138.8, 138.9, 139.0 ppm; HR-FABMS $[M+H]^+$ calcd for $C_{33}H_{37}O_5$ 513.2641, found 513.2642.

6.7. Typical glycosylation procedures: preparation of di- and oligosaccharides

Method A: AgOTf-promoted activation of the STaz and SBox glycosyl donors. A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in $ClCH_2CH_2Cl$ (2 mL) was stirred under argon for 1.5 h. Freshly conditioned AgOTf (0.22 mmol) was added and the reaction mixture was stirred for 15 min at rt, then diluted with CH_2Cl_2, the solid was filtered-off, and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $NaHCO_3$ (15 mL) and water (3×10 mL), the organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) or Sephadex LH-20 (methanol–dichloromethane, 1/1, v/v elution) to afford a di- or a trisaccharide derivative.

Method B: NIS/TMSOTf-promoted activation of S-ethyl glycosyl donors. A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in $ClCH_2CH_2Cl$ (2 mL) was stirred for 1 h under argon. NIS (0.25 mmol) and TMSOTf (0.025 mmol) were added at 0 °C and the reaction mixture was stirred for 10 min. Upon completion, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with 20% aq $Na_2S_2O_3$ (15 mL) and water (3×10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) or Sephadex LH-20 (methanol–dichloromethane, 1/1, v/v elution) to afford a di- or an oligosaccharide derivative.

6.7.1. 3-*O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-1,2,4,5-tetra-*O*-benzyl-D/L-ribitol (20). This compound was obtained by Method B from ethyl 2,3,4-tri-*O*-benzoyl-1-thio-L-rhamnopyranoside **9** and **12** in 80% yield. Analytical data for **20**: R_f=0.49 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +56.3 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.14 (d, 3H, H-6′), 3.70–3.77 (m, 2H, H-1), 3.79–3.82 (m, 2H, H-5), 3.89–3.91 (m, 1H, H-2), 3.99–4.01 (m, 1H, H-4), 4.31–4.34 (m, 2H, H-3, 5′), 4.45–4.75 (m, 8H, 4×*CH*$_2$Ph), 5.30 (s, 1H, H-1′), 5.54–5.67 (m, 2H, H-2′, 4′), 5.73–5.87 (m, 1H, H-3′), 7.21–8.09 (m, 35H, aromatic) ppm; ^{13}C NMR: δ 17.9, 67.9, 69.2, 70.3 (×2), 71.5, 72.4, 72.7 (×3), 73.9 (×3), 78.5, 98.4, 128.1 (×3), 128.2 (×2), 128.4 (×2), 128.5 (×6), 128.9 (×6), 129.0 (×3), 129.1 (×2), 129.2 (×2), 130.1 (×3), 130.4 (×4), 130.6 (×2), 133.9 (×3), 139.9 (×4), 166.1, 166.2, 166.4 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{60}H_{58}O_{12}Na$ 993.3826, found 993.3840.

6.7.2. 4-*O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-1,2,3,5-tetra-*O*-benzyl-D-ribitol (21). This compound was obtained by Method B from **9** and **13** in 85% yield. Analytical data for **21**: R_f=0.51 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +39.6 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.15 (d, 3H, H-6′), 3.71–3.90 (m, 6H, H-1, 2, 3, 5), 4.26–4.36 (m, 1H, H-5′), 4.42–4.81 (m, 9H, H-4, 4×*CH*$_2$Ph), 5.48 (s, 1H, H-1′), 5.64 (dd, 1H, $J_{2',3'}$=9.9 Hz, H-3′), 5.78–5.87 (m, 2H, H-2′, 4′), 7.19–8.12 (m, 35H, aromatic) ppm; ^{13}C NMR: δ 18.0, 67.7, 70.6, 70.7, 71.4, 71.6, 72.5, 73.3, 73.9 (×2), 76.4, 78.7, 79.5, 97.4, 128.1 (×2), 128.2 (×2), 128.3 (×3), 128.4 (×3), 128.5 (×3), 128.6 (×3), 128.7 (×2), 128.9 (×6), 129.1 (×2), 129.9 (×2), 130.0, 130.2 (×4), 130.5 (×2), 133.6, 133.8, 133.9, 138.7 (×2), 138.9 (×2), 165.8, 165.9, 166.3 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{60}H_{58}O_{12}Na$ 993.3826, found 993.3840.

6.7.3. *O*-(α-L-Rhamnopyranosyl)-(1→3)-D/L-ribitol (3). To a solution of **20** (100 mg, 0.103 mmol) in dry methanol (1.0 mL) was added 1 M NaOMe till pH=10 (~0.1 mL). The reaction mixture was stirred for 15 h at rt, then neutralized with Dowex (H^+), filtered, and concentrated in vacuo. The crude residue was dissolved in ethyl acetate/ethanol (1/1, v/v, 2.0 mL) and 10% Pd–C (20 mg) was added. The reaction mixture was stirred under an atmosphere of H_2 for 15 h. The catalyst was then filtered-off, washed with methanol, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on Sephadex G-15 (water elution) to afford compound **3** as a syrup (26.8 mg, 87% yield). Analytical data: R_f=0.52 (methanol–dichloromethane, 1/1, v/v); $[\alpha]_D^{26}$ −45.4 (*c* 0.8, H_2O); ^{1}H NMR (D_2O): δ 1.20 (d, 3H, H-6′), 3.37 (dd, 1H, $J_{3',4'}$=9.7 Hz, H-4′), 3.52–3.58 (m, 2H, H-1b, 5b), 3.66–3.74 (m, 5H, H-1a, 5a, 3, 3′, 5′), 3.82–3.88 (m, 2H, H-2, 4), 3.90 (dd, 1H, $J_{2',3'}$=1.7 Hz, H-2′), 4.88 (d, 1H, $J_{1',2'}$=1.7 Hz, H-1′) ppm; ^{13}C NMR (D_2O): δ 16.9 (C-6′), 62.7 (C-1), 63.0 (C-5), 69.7 (C-5′), 70.5 (C-3′), 70.7 (C-2′), 71.1 (C-4), 72.0 (C-2), 72.2 (C-4′), 80.2 (C-3), 100.9 (C-1′) ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{11}H_{22}O_9Na$ 321.1161, found 321.1171.

6.7.4. *O*-(α-L-Rhamnopyranosyl)-(1→4)-D-ribitol (4). Compound **4** was obtained from **21** in 90% yield as described for the synthesis of compound **3**. Analytical data: R_f=0.43 (methanol–dichloromethane, 1/1, v/v); $[\alpha]_D^{25}$ −34.3 (*c* 1, H_2O); ^{1}H NMR (D_2O): δ 1.23 (d, 3H, H-6′), 3.51 (dd, 1H, $J_{3',4'}$=9.6 Hz, H-4′), 3.69 (dd, 1H, $J_{1a,1b}$=4.9 Hz, H-1b), 3.77–3.86 (m, 4H, H-2, 3, 3′, 5′), 3.90 (dd, 1H, H-1a), 3.93 (d, 1H, $J_{5a,5b}$=3.1 Hz, H-5b), 3.95–3.99 (m, 2H, H-4, 5a), 4.07 (dd, 1H, $J_{2',3'}$=1.7 Hz, H-2′), 5.07 (d, 1H, $J_{1',2'}$=1.5 Hz, H-1′) ppm; ^{13}C NMR (D_2O): δ 16.9 (C-6′), 59.7 (C-5), 62.9 (C-1), 69.5 (C-2), 70.6 (C-3′), 70.7 (C-2′), 71.9 (C-3), 72.3 (C-4′, 5′), 78.9 (C-4), 100.5 (C-1′) ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{11}H_{22}O_9Na$ 321.1161, found 321.1171.

6.7.5. Ethyl *O*-(3-*O*-acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (22). The title compound was obtained by Method A from 2-thiazolinyl 3-*O*-acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**8a**) and ethyl 2,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**10**) in 72% yield. Analytical data: R_f=0.48 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +81.9 (*c* 1, $CHCl_3$); mp 74–76 °C; ^{1}H NMR: δ 1.28 (t, 3H, CH_2CH_3), 1.32 (d, 3H, H-6), 1.78 (s, 3H, $COCH_3$), 2.59–2.72 (m, 2H, CH_2CH_3), 3.24 (dd, 1H, $J_{4',5'}$=9.6 Hz, H-4′), 3.28–3.37 (m, 2H, H-2′, 6b′), 3.65 (dd, 1H, $J_{4',5'}$=4.8 Hz, H-5′), 3.84 (dd, 1H, $J_{5',6a'}$=4.8 Hz, H-6′), 4.22–4.37 (m, 4H, H-3, 5, CH_2Ph), 4.93 (d, 1H, $J_{1',2'}$=3.6 Hz, H-1′), 5.15–5.19 (m, 2H, H-3′, *CH*Ph), 5.43 (d, 1H, $J_{1,2}$=1.4 Hz, H-1), 5.52–5.60 (m, 2H, H-2, 4), 7.00–8.05 (m, 20H, aromatic) ppm; ^{13}C NMR: δ 14.7, 15.6, 18.2, 21.4, 26.4, 30.3, 63.5, 68.1, 69.1, 70.9, 71.6, 73.0, 73.4, 73.9, 79.8, 82.9, 96.1, 101.7, 126.8 (×2), 128.2, 128.3 (×2), 128.4 (×2), 128.8 (×2), 129.3 (×4), 130.0 (×2), 130.3 (×2), 133.7, 133.9, 137.7, 138.3, 130.6 (×2), 166.1, 166.9, 169.8 ppm; HR-FABMS $[M+H]^+$ calcd for $C_{44}H_{47}O_{12}S$ 799.2788, found 799.2796.

6.7.6. *O*-(3-*O*-Acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-*O*-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzyl-D/L-ribitol (23). The title compound was obtained by Method B from **22** and **12** in 71% yield. Analytical data: R_f=0.33 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +48.7 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.15 (d, 3H, H-6′), 1.88 (s, 3H, $COCH_3$), 3.32 (dd, 1H, $J_{1a,1b}$= 9.6 Hz, H-1a), 3.39–3.45 (m, 2H, H-2′, 5a), 3.68–3.79 (m, 4H, H-1b, 2, 4, 5b), 3.85–3.90 (m, 2H, H-3′, H-4′), 3.96–4.02 (m, 1H, H-3), 4.20–4.34 (m, 4H, H-5′, 5″, 6a″, 6b″), 4.46–4.68 (m, 8H, 4×CH_2Ph), 5.05 (d, 1H, $J_{1',2'}$=3.5 Hz, H-1′), 5.17–5.26 (m, 3H, H-1″, 3″, C*H*Ph), 5.55–5.58 (m, 2H, H-2″, 4″), 7.00–8.07 (m, 40H, aromatic) ppm; ^{13}C NMR: δ 18.3, 21.5, 63.4, 68.1, 69.2, 69.5, 69.6, 70.8, 71.0, 72.7, 72.8 (×2), 72.9, 73.1, 73.8, 73.9, 77.3, 77.7, 78.2, 78.6, 79.9, 95.6, 98.4, 101.8, 127.0, 128.1, 128.2 (×4), 128.3 (×3), 128.5 (×5), 128.8 (×3), 128.9 (×4), 129.0 (×6), 129.1 (×3), 129.4, 130.2 (×2), 130.4 (×2), 130.7 (×2), 133.7, 133.9, 166.2, 166.9, 169.8 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{75}H_{76}O_{17}Na$ 1271.4981, found 1271.4978.

6.7.7. *O*-(3-*O*-Acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-*O*-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→4)-1,2,3,5-tetra-*O*-benzyl-D-ribitol (24). The title compound was obtained by Method B from **22** and **13** in 76% yield. Analytical data: R_f=0.41 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +45.7 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.07 (d, 3H, H-6′), 1.72 (s, 3H, $COCH_3$), 3.20 (dd, 1H, $J_{3'',4''}$= 9.6 Hz, H-4″), 3.26–3.34 (m, 2H, H-3, 2″), 3.55–3.67 (m, 4H, H-5, 5″, 6b″), 3.70–3.79 (m, 4H, H-1, 2, 6a″), 4.12–4.17 (m, 1H, H-5′), 4.25–4.29 (m, 1H, H-4), 4.30–4.36 (m, 1H, $J_{1',2'}$=1.3 Hz, H-1′), 5.47 (dd, 1H, $J_{3',4'}$=10.9 Hz, H-4′), 5.62 (d, 1H, $J_{2',3'}$=2.3 Hz, H-2′), 6.80–8.02 (m, 40H, aromatic) ppm; ^{13}C NMR: δ 18.4, 21.5, 63.3, 68.1, 69.2, 70.7 (×2), 70.9, 72.2, 72.6, 73.1, 73.3, 74.0, 74.1 (×2), 74.2, 76.4, 77.2, 79.1, 79.7, 79.9, 94.9, 97.4, 101.7, 126.9 (×3), 128.1, 128.2 (×2), 128.3 (×5), 128.4 (×3), 128.5 (×2), 128.6 (×4), 128.8 (×2), 129.0 (×8), 129.1 (×2), 129.3, 130.1, 130.2, 130.3 (×2), 130.7 (×2), 133.7, 133.9, 137.7, 138.4, 138.8 (×2), 139.0 (×3), 166.3, 166.8, 169.8 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{75}H_{76}O_{17}Na$ 1271.4981, found 1271.4978.

6.7.8. *O*-(α-D-Glucopyranosyl)-(1→3)-*O*-(α-L-rhamnopyranosyl)-(1→3)-D/L-ribitol (5). The title compound was obtained from **23** in 80% yield as described for the synthesis of compound **3**. Analytical data: R_f=0.52 (methanol–dichloromethane–water, 9/9/2, v/v); $[\alpha]_D^{26}$ +37.1 (*c* 0.7, H_2O); ^{1}H NMR (D_2O): δ 1.36 (d, 3H, H-6′), 3.53 (dd, 1H, $J_{4'',5''}$=9.2 Hz, H-4″), 3.60–3.65 (m, 2H, H-4′, 2″), 3.68–3.74 (m, 2H, H-1b, 5b), 3.82–3.93 (m, 8H, H-1a, 3, 5a, 3′, 5′, 3″, 6a″, 6b″), 3.98–4.05 (m, 3H, H-2, 4, 5″), 4.25 (dd, 1H, $J_{2',3'}$=2.7 Hz, H-2′), 5.07 (d, 1H, $J_{1',2'}$=1.8 Hz, H-1′), 5.15 (d, 1H, $J_{1'',2''}$=3.8 Hz, H-1″) ppm; ^{13}C NMR (D_2O): δ 17.0 (C-6′), 60.6 (C-5′), 62.7 (C-1), 63.0 (C-5), 67.4 (C-2′), 69.7 (C-4″), 69.8 (C-6″), 70.5 (C-4′), 71.1 (C-2″), 71.8 (C-5″), 72.1 (C-2, 4), 73.3 (C-3″), 75.8 (C-3′), 80.2 (C-3), 95.9 (C-1″), 100.5 (C-1′) ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{17}H_{32}O_{14}Na$ 483.1690, found 483.1684.

6.7.9. *O*-(α-D-Glucopyranosyl)-(1→3)-*O*-(α-L-rhamnopyranosyl)-(1→4)-D-ribitol (6). The title compound was obtained from **24** in 88% yield as described for the synthesis of compound **3**. Analytical data: R_f=0.55 (methanol–dichloromethane–water, 9/9/2, v/v); $[\alpha]_D^{25}$ +13.2 (*c* 1.0, H_2O); ^{1}H NMR (D_2O): δ 1.35 (d, 3H, H-6′), 3.51 (dd, 1H, $J_{4'',5''}$=9.5 Hz, H-4″), 3.60–3.64 (m, 2H, H-4, 2″), 3.68 (dd, 1H, $J_{1a,1b}$=6.7 Hz, H-1b), 3.78–3.94 (m, 9H, H-1a, 2, 3, 5b, 3′, 5′, 3″, 6a″, 6b″), 3.96–4.05 (m, 3H, H-4, 5a, 5″), 4.28 (dd, 1H, $J_{2',3'}$=2.4 Hz, H-2′), 5.12 (d, 1H, $J_{1',2'}$=1.6 Hz, H-1′), 5.14 (d, 1H, $J_{1'',2''}$=3.8 Hz, H-1″) ppm; ^{13}C NMR (D_2O): δ 17.1 (C-6′), 59.8 (C-5), 60.6 (C-6′), 62.9 (C-1), 67.4 (C-2′), 69.7 (C-3″, 5′), 70.6 (C-4″), 71.8 (C-2″), 71.9 (C-4′), 72.0 (C-3), 72.3 (C-5″), 73.3 (C-2), 75.9 (C-3′), 79.0 (C-4), 95.9 (C-1″), 100.2 (C-1′) ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{17}H_{32}O_{14}Na$ 483.1690, found 483.1684.

6.7.10. Ethyl *O*-(3-*O*-acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (25). The title compound was obtained by Method A from **8a** and ethyl 2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**11**) in 80% yield. Analytical data for **25** were essentially the same as reported previously.[32]

6.7.11. Ethyl *O*-(2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (26). A solution of NaOMe in MeOH (1.0 M, 0.2 mL, 1.0 mmol) was added to a stirred suspension of **25** (160 mg, 0.35 mmol) in methanol (2.0 mL) and the reaction mixture was stirred for 15 h at rt. The reaction mixture was then neutralized with Dowex (H^+), filtered, and concentrated in vacuo to yield crude **26** as a white foam 99%. Analytical data: R_f=0.38 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{27}$ 7.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 1.20 (t, 3H, CH_2CH_3), 1.29 (d, 3H, H-6), 2.54 (q, 2H, CH_2CH_3), 3.44–3.52 (m, 2H, H-2′, 5′), 3.62–3.70 (m, 3H, H-3, 4′, 6a′), 3.98–4.05 (m, 4H, H-2, 4, 5, 6b′), 4.06–4.21 (m, 2H, H-3′, OH), 4.55–4.96 (m, 6H, 3×CH_2Ph), 5.12 (d, 1H, $J_{1',2'}$=3.5 Hz, H-1′), 5.26 (d, 1H, $J_{1,2}$=1.8 Hz, H-1), 5.47 (s, 1H, C*H*Ph), 7.20–7.37 (m, 20H, aromatic) ppm; ^{13}C NMR: δ 15.2, 18.0, 25.6, 30.0,

62.9, 68.8, 69.1, 70.8, 72.7, 73.0, 79.3, 80.4, 81.6, 82.0, 95.2, 102.2, 126.7 (×2), 127.9 (×2), 128.0 (×2), 128.2, 128.3 (×2), 128.4 (×4), 128.5 (×2), 128.6 (×2), 128.7 (×2), 129.3, 137.4, 137.9, 138.2, 138.3 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{42}H_{48}O_9SNa$ 751.2917, found 751.2929.

6.7.12. Ethyl *O*-(2-*O*-benzyl-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-(1→3)-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (27). The title compound was obtained by Method A from benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-galactopyranoside (**7**) and **26** in 76% yield. Analytical data: R_f=0.49 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{26}$ +48.8 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.25 (t, 3H, CH_2CH_3), 1.32 (d, 3H, H-6), 1.84, 1.97, 2.00 (3 s, 9H, 3×$COCH_3$), 2.56–2.66 (q, 2H, CH_2CH_3), 3.55 (dd, 1H, $J_{5'',6a''}$=6.3 Hz, $J_{6a'',6b''}$=11.1 Hz, H-6b″), 3.63–3.74 (m, 5H, H-2, 4, 2′, 4′, 2″), 3.76–3.87 (m, 1H, H-6a″), 4.04–4.10 (m, 4H, H-3, 5, 5′, 6b′), 4.18 (dd, 1H, $J_{5',6a'}$=5.4 Hz, $J_{6a',6b'}$=10.3 Hz, H-6a′), 4.25 (d, 1H, CH_2Ph), 4.39 (dd, 1H, $J_{3',4'}$=9.4 Hz, H-3′), 4.47–4.52 (m, 2H, H-5″, 1/2 CH_2Ph), 4.61–4.74 (m, 4H, 2×CH_2Ph), 4.96 (d, 1H, 1/2 CH_2Ph), 5.21 (d, 1H, $J_{4'',5''}$=2.3 Hz, H-4″), 5.25 (d, 1H, $J_{1',2'}$=3.4 Hz, H-1′), 5.30–5.38 (m, 3H, H-1, 3″, CHPh), 5.57 (d, 1H, $J_{1'',2''}$=3.6 Hz, H-1″), 6.95–7.43 (m, 25H, aromatic) ppm; ^{13}C NMR: δ 15.3, 18.2, 20.8, 20.9 (×2), 21.0 (×2), 25.7, 31.2, 61.7, 62.7, 66.2 (×2), 68.8 (×2), 69.2, 71.2, 72.5 (×2), 72.9 (×2), 75.7, 75.9, 80.3, 81.6, 82.9, 94.2, 96.6, 102.3, 126.7 (×2), 126.8 (×3), 127.3, 127.7 (×3), 127.9, 128.0 (×4), 128.3 (×3), 128.7 (×5), 128.8 (×3), 129.5, 137.4, 137.8, 138.0, 138.2, 170.2, 170.3, 170.6 ppm; HR-FABMS $[M+H]^+$ calcd for $C_{61}H_{70}O_{17}SNa$ 1129.4231, found 1129.4238.

6.7.13. *O*-(3,4,6-Tri-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-*O*-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzyl-D/L-ribitol (28). The title compound was obtained by Method B from **12** and **27** in 70% yield. Analytical data: R_f=0.47 (ethyl acetate–hexanes, 2/3, v/v); $[\alpha]_D^{25}$ +55.4 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.27 (d, 3H, H-6′), 1.82, 1.96, 1.98 (3 s, 3H, 3×$COCH_3$), 3.52–3.57 (m, 2H, H-4′, 5b), 3.60–3.65 (m, 5H, H-1a, 4, 4″, 6a″, 6a‴), 3.69–3.76 (m, 6H, H-2, 2′, 2‴, 4‴, 6b″, 6b‴), 3.79–3.86 (m, 3H, H-5a, 3′, 5′), 3.95 (dd, 1H, H-2″), 3.99 (m, 1H, H-5″), 4.05–4.13 (m, 4H, H-1b, 3, 3″, 5‴), 4.26 (d, 1H, 1/2 CH_2Ph), 4.32–4.68 (m, 14H, 7×CH_2Ph), 4.99 (d, 1H, 1/2 CH_2Ph), 5.16 (d, 1H, $J_{1''',2'''}$=2.1 Hz, H-1‴), 5.18 (d, 1H, $J_{1'',2''}$=3.4 Hz, H-1″), 5.33 (dd, 1H, $J_{3''',4'''}$=3.3 Hz, H-3‴), 5.38 (s, 1H, CHPh), 5.56 (d, 1H, $J_{1',2'}$=3.4 Hz, H-1′), 6.95–7.40 (m, 45H, aromatic) ppm; ^{13}C NMR: δ 18.5, 20.9, 21.2 (×2), 30.1, 62.0, 62.6, 66.4, 69.1, 69.3 (×2), 70.3, 70.5, 71.3, 72.6, 72.8, 73.0 (×2), 73.1 (×2), 73.7, 73.8, 74.6, 76.0, 78.3 (×3), 78.9, 79.9, 83.2, 93.1, 96.7, 98.8, 102.5, 126.9 (×2), 127.5 (×2), 127.8 (×2), 127.9 (×6), 128.0 (×2), 128.1 (×2), 128.3 (×2), 128.4 (×2), 128.5 (×3), 128.6 (×2), 128.7 (×5), 128.7 (×3), 128.8 (×2), 128.9 (×2), 129.7, 137.6 (×2), 138.2 (×2), 138.4 (×2), 138.5 (×2), 138.6 (×2), 138.7 (×2), 138.8 (×2), 138.9 (×2), 170.3, 170.5, 170.8 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{92}H_{100}O_{22}Na$ 1579.6604, found 1579.6609.

6.7.14. *O*-(3,4,6-Tri-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-*O*-(2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→3)-*O*-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→4)-1,2,3,5-tetra-*O*-benzyl-D-ribitol (29). The title compound was obtained by Method B from **13** and **27** in 76% yield. Analytical data: R_f=0.49 (ethyl acetate–hexanes, 3/7, v/v); $[\alpha]_D^{27}$ +54.9 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.25 (d, 3H, H-6′), 1.84, 1.97, 1.99 (3 s, 3H, 3×$COCH_3$), 3.55–3.60 (m, 2H, H-5), 3.63–3.77 (m, 10H, H-1, 2, 3, 2′, 4′, 2‴, 4‴, 6a″, 6b‴), 3.79–3.90 (m, 4H, H-4, 3′, 5′, 6b″), 3.96–3.99 (m, 2H, H-2″, 5″), 4.08–4.11 (m, 1H, H-3″), 4.20 (dd, 1H, $J_{5''',6a'''}$=2.7 Hz, $J_{6a''',6b'''}$=9.2 Hz, H-6a‴), 4.23 (dd, 2H, CH_2Ph), 4.29–4.32 (m, 1H, H-5‴), 4.38–4.70 (m, 12H, 6×CH_2Ph), 5.08 (dd, 2H, CH_2Ph), 5.26 (d, 1H, $J_{1''',2'''}$=3.5 Hz, H-1‴), 5.31 (d, 1H, $J_{1'',2''}$=3.4 Hz, H-1″), 5.33 (s, 2H, H-3‴, CHPh), 5.56 (d, 1H, $J_{1',2'}$=3.5 Hz, H-1′), 7.14–7.43 (m, 45H, aromatic) ppm; ^{13}C NMR: δ 14.6, 18.6 (×2), 21.1 (×2), 21.3 (×3), 23.2, 30.2 (×2), 32.4, 62.2, 62.6, 66.6, 69.2, 69.5, 70.4, 71.4, 72.6, 72.8, 72.9, 73.2, 73.8, 73.9, 74.2, 74.9, 76.1, 78.8, 79.8, 83.3, 96.8, 97.4, 102.5, 127.1 (×2), 127.6 (×3), 127.9 (×4), 128.0, 128.1 (×2), 128.2 (×2), 128.3 (×3), 128.4 (×2), 128.5, 128.6 (×2), 128.7 (×3), 128.77 (×2), 128.80 (×6), 128.83 (×3), 128.9 (×2), 129.0 (×2), 129.1 (×2), 129.7, 137.7, 138.3, 138.6 (×3), 138.7, 138.8, 138.9, 142.4, 142.7, 142.9, 170.4, 170.6, 170.9 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{92}H_{100}O_{22}Na$ 1579.6604, found 1579.6609.

6.7.15. *O*-(α-D-Galactopyranosyl)-(1→3)-*O*-(α-D-glucopyranosyl)-(1→3)-*O*-(α-L-rhamnopyranosyl)-(1→3)-D/L-ribitol (1). The title compound was obtained from **28** in 75% yield as described for the synthesis of compound **3**. Analytical data: R_f=0.33 (methanol–dichloromethane–water, 9/9/2, v/v); $[\alpha]_D^{26}$ +78.2 (*c* 0.8, H_2O); ^1H NMR (D_2O): δ 1.25 (d, 3H, H-6′), 3.53 (dd, 1H, $J_{4',5'}$=9.7 Hz, H-4′), 3.58–3.65 (m, 4H, H-2″, 4″, 5a, 6a″), 3.70 (dd, 2H, $J_{6a''',6b'''}$=11.2 Hz, H-6a‴, 6b‴), 3.72–3.82 (m, 8H, H-1a, 1b, 2, 3, 5b, 3′, 5′, 2‴), 3.84–3.90 (m, 3H, H-4, 3″, 3‴), 3.92–3.96 (m, 3H, H-4‴, 5″, 6b″), 4.15 (dd, 1H, $J_{2',3'}$=2.3 Hz, H-2′), 4.19 (dd, 1H, $J_{4''',5'''}$=6.3 Hz, H-5‴), 4.97 (d, 1H, $J_{1',2'}$=1.7 Hz, H-1′), 5.05 (d, 1H, $J_{1'',2''}$=6.0 Hz, H-1″), 5.33 (d, 1H, $J_{1''',2'''}$=3.9 Hz, H-1‴) ppm; ^{13}C NMR (D_2O): δ 16.9, 60.3, 61.1, 62.5, 62.9, 67.1, 68.8, 69.3, 69.6, 69.7, 70.0, 70.3, 70.4, 70.9, 71.0, 71.7, 71.9, 75.5, 79.8, 80.1, 95.6, 99.5, 100.3 ppm; HR-FABMS $[M+Na]^+$ calcd for $C_{23}H_{42}O_{19}Na$ 645.2218, found 645.2210.

6.7.16. *O*-(α-D-Galactopyranosyl)-(1→3)-*O*-(α-D-glucopyranosyl)-(1→3)-*O*-(α-L-rhamnopyranosyl)-(1→4)-D-ribitol (2). The title compound was obtained from **29** in 78% yield as described for the synthesis of compound **3**. Selected analytical data: R_f=0.33 (methanol–dichloromethane–water, 9/9/2, v/v); $[\alpha]_D^{27}$ +70.7 (*c* 1.0, H_2O); ^1H NMR (D_2O): δ 1.26 (d, 3H, H-6′), 3.53 (dd, 1H, $J_{4',5'}$=9.7 Hz, H-4′), 3.58–3.64 (m, 4H, H-1b, 5b, 2″, 6a″), 3.66–3.75 (m, 8H, H-1a, 2, 5′, 4″, 6b″, 2‴, 6a‴, 6b‴), 3.78–3.81 (m, 2H, H-3, 3‴), 3.83–3.89 (m, 4H, H-4, 5a, 3′, 3″), 3.94–3.96 (m, 2H, H-2′, 5‴), 5.02 (br s, 1H, H-1′), 5.06 (d, 1H, $J_{1'',2''}$=3.7 Hz, H-1″), 5.34 (d, 1H, $J_{1''',2'''}$=3.8 Hz, H-1‴) ppm; ^{13}C NMR data for **2** were essentially the same as reported previously;[42] HR-FABMS $[M+Na]^+$ calcd for $C_{23}H_{42}O_{19}Na$ 645.2218, found 645.2210.

Acknowledgements

The authors thank ACS PRF (42397-G1) and NSF (CAREER CHE-0547566) for financial support of this research; NSF for grants to purchase the NMR spectrometer (CHE-9974801) and the mass spectrometer (CHE-9708640) used in this work; Dr. R. S. Luo for assistance with 500 MHz 2D NMR experiments; and Dr. R. E. K. Winter and Mr. J. Kramer for HRMS determinations.

Supplementary data

General experimental techniques and spectra for all new compounds. This material is available free of charge via the Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.036.

References and notes

1. Kuberan, B.; Linhardt, R. J. *Curr. Org. Chem.* **2000**, *4*, 653–677.
2. Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863.
3. Pozsgay, V. *Adv. Carbohydr. Chem. Biochem.* **2001**, *56*, 153–199.
4. *Carbohydrate-Based Drug Discovery*; Wong, C. H., Ed.; Wiley-VCH: Weinheim, 2003.
5. *Carbohydrate Drug Design*; Klyosov, A. A., Witczak, Z. J., Platt, D., Eds.; ACS: Washington, DC, 2006; Vol. 932.
6. http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/ISBN_92_806_4048_8.htm, 2006.
7. Wuorimaa, T.; Kayhty, H. *Scand. J. Immunol.* **2002**, *56*, 111–129.
8. Kamerling, J. P. *Streptococcus Pneumoniae, Molecular Biology and Mechanisms of Disease*; Tomasz, A., Ed.; Mary Ann Liebert: Larchmont, New York, NY, 2000; Vol. 3, pp 81–114.
9. Vakevainen, M.; Eklund, C.; Eskola, J.; Kayhty, H. *J. Infect. Dis.* **2001**, *184*, 789–793.
10. Robinson, D. A.; Briles, D. E.; Crain, M. J.; Hollingshead, S. K. *J. Bacteriol.* **2002**, *184*, 6367–6375.
11. Rebers, P. A.; Heidelberger, M. *J. Am. Chem. Soc.* **1961**, *83*, 3056–3059.
12. Robbins, J. B.; Lee, C. J.; Rastogi, S. C.; Schiffman, G.; Henrichsen, J. *Infect. Immun.* **1979**, *26*, 1116–1122.
13. Robbins, J. B.; Austrian, R.; Lee, C. J.; Rastogi, S. C.; Schiffman, G.; Henrichsen, J.; Makela, P. H.; Broome, C. V.; Facklam, R. R., et al. *J. Infect. Dis.* **1983**, *148*, 1136–1159.
14. Alonsodevelasco, E.; Verheul, A. F. M.; Verhoef, J.; Snippe, H. *Microbiol. Rev.* **1995**, *59*, 591–603.
15. Moreau, M.; Schulz, D. *J. Carbohydr. Chem.* **2000**, *19*, 419–434.
16. Ledwith, M. *Curr. Opin. Pediatr.* **2001**, *13*, 70–74.
17. Slaghek, T. M.; van Vliet, M. J.; Maas, A. A. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1989**, *195*, 75–86.
18. Slaghek, T. M.; van Oijen, A. H.; Maas, A. A. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1990**, *207*, 237–248.
19. Slaghek, T. M.; Maas, A. A. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1991**, *211*, 25–39.
20. Thijssen, M. J. L.; van Rijswijk, M. N.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1998**, *306*, 93–109.
21. Thijssen, M. J. L.; Bijkerk, M. H. G.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1998**, *306*, 111–125.
22. Jansen, W. T. M.; Hogenboom, S.; Thijssen, M. J. L.; Kamerling, J. P.; Vliegenthart, J. F. G.; Verhoef, J.; Snippe, H.; Verheul, A. F. M. *Infect. Immun.* **2001**, *69*, 787–793.
23. Saeland, E.; Jakobsen, H.; Ingolfsdottir, G.; Sigurdardottir, S. T.; Jonsdottir, I. *J. Infect. Dis.* **2001**, *183*, 253–260.
24. Quataert, S.; Martin, D.; Anderson, P.; Giebink, G. S.; Henrichsen, J.; Leinonen, M.; Granoff, D. M.; Russell, H.; Siber, G.; Faden, H.; Barnes, D.; Madore, D. V. *Immunol. Invest.* **2001**, *30*, 191–207.
25. Penn, R. L.; Lewin, E. B.; Douglas, R. G., Jr.; Schiffman, G.; Lee, C. J.; Robbins, J. B. *Infect. Immun.* **1982**, *36*, 1261–1262.
26. Echaniz-Aviles, I. G.; Solorzano-Santos, F. *Salud Publica Mexico* **2001**, *43*, 352–367.
27. Zon, G.; Szu, S. C.; Egan, W.; Robbins, J. D.; Robbins, J. B. *Infect. Immun.* **1982**, *37*, 89–103.
28. Schneerson, R.; Robbins, J. B.; Parke, J. C., Jr.; Bell, C.; Schlesselman, J. J.; Sutton, A.; Wang, Z.; Schiffman, G.; Karpas, A.; Shiloach, J. *Infect. Immun.* **1986**, *52*, 519–528.
29. Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79.
30. Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455–458.
31. Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072.
32. Pornsuriyasak, P.; Demchenko, A. V. *Chem.—Eur. J.* **2006**, *12*, 6630–6646.
33. Note: compounds **1**, **3**, **5**, **12**, **15**–**17**, **20**, **25**, and **28** represent (or possess) symmetric D/L-*meso*-ribitol moiety.
34. Xie, Z. F.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 973–980.
35. Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605–4609.
36. Austin, P. W.; Hardy, F. E.; Buchanan, J. G.; Baddiley, J. *J. Chem. Soc.* **1964**, 2128–2137.
37. Pozsgay, V. *Carbohydr. Res.* **1979**, *69*, 284–286.
38. Auzanneau, F. I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13–24.
39. Pozsgay, V. *Carbohydr. Res.* **1992**, *235*, 295–302.
40. Park, I.; Pritchard, D. G.; Cartee, R.; Brandao, A.; Brandileone, M. C. C.; Nahm, M. H. *J. Clin. Microbiol.* **2007**. doi:10.1128/JCM.02199-06
41. Boullanger, P.; Descotes, G. *Carbohydr. Res.* **1982**, *110*, 153–158.
42. Van Dam, J. E. G.; Breg, J.; Komon, R.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1989**, *187*, 267–286.