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A Highly α-Stereoselective Synthesis of Oligosaccharide Fragments of the Vi Antigen from *Salmonella typhi* and Their Antigenic Activities

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Abstract: In this paper, a convenient approach to the synthesis of the repeating α-(1→4)-linked *N*-acetyl galactosaminuronic acid units from the capsular polysaccharide of *Salmonella typhi* is reported. The exclusively α-stereoselective glycosylation reactions were achieved by using oxazolidinone-protected glycosides as building blocks based on a pre-activation protocol. Di-, tri-, and tetrasaccharides were prepared by this short and efficient approach in high yields. The enzyme-linked immunosorbent assay experiments show that our synthetic tri- and tetrasaccharide had much higher antigenic activities than previously reported ones in the inhibition of antibody binding by the native polysaccharide. The results demonstrate that the antigenic activities of saccharides can be strengthened greatly by increasing the number of acetyl groups present.

Keywords: antigens · glycosylation · oxazolidinones · *salmonella typhi* · stereoselectivity · Vi antigens

Introduction

Typhoid fever is caused by *Salmonella typhi* and remains an important health threat in many parts of the world, with an estimated 16 million cases and 600 000 deaths occurring annually.[1] Although the incidence is negligible in many developed countries, those who travel to epidemic areas, live in the rural parts of the country, and military personnel are frequently subject to the illness. The emergence of multi-drug resistant *Salmonella typhi* strains has increased the impact of this disease.[2]

The Vi antigen is a capsular polysaccharide found mainly in *Salmonella typhi* and *Salmonella paratyphi C*, two serotypes of *Salmonella* that are responsible for severe infections in humans.[3] It is a linear homopolymer of α-(1→4)-linked *N*-acetyl galactosaminuronic acid, variably *O*-acetylated at the C3 position (Figure 1).[4] This antigen increases the resistance to post-phagocytic oxidative burst.[5] The antigen disrupts the binding of the C3 complement factor to the surface of *Salmonella typhi* and helps bacteria to reduce the killing by the serum, the killing via the alternative pathway of the complement, and opsonization as can be measured by phagocytosis by the human polymorphonuclear leukocytes (PMNs). It was also found that strains of *Salmonella typhi* containing the Vi antigen are less susceptible to killing by H_2O_2 than strains without this antigen.[6] As an immunogenic capsular polysaccharide, the purified Vi polysaccharide (Vi PS) of *Salmonella typhi* has become an effective vaccine to combat typhoid disease.[7]

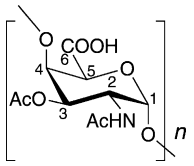

Figure 1. The repeating unit of the *Salmonella typhi* Vi antigen.

The industrial production of the typhoid Vi capsular polysaccharide vaccine comprises extrication and purification from cultures of the *Salmonella typhi* strain.[7c] The process is controlled by strict checks at various stages and the product is a mixture of polysaccharides with inhomogeneous sizes and structures. This can cause a quality control problem. Sinaÿ and co-workers have chemically synthesized the corresponding di-, tri-, tetra-, and hexa-saccharides and shown that the tetra- and hexa-saccharides were able to inhibit antibody binding by native polysaccharides.[8] However, the whole synthetic route was long and complicated. Herein, we report a convenient and highly α-selective approach to the synthesis of the repeating α-(1→4)-linked *N*-acetyl galactosaminuronic acid units. The antigenic activities of these synthetic oligosaccharide fragments are also investigated.

Results and Discussion

Synthesis: Since oxazolidinone-protected glucosamine as an α-selective glycosyl donor was first described by the Kerns group,[9] subsequent investigations have been focused on its *N*-acetyl analogues, confirming that the ring-fused oxazolidi-

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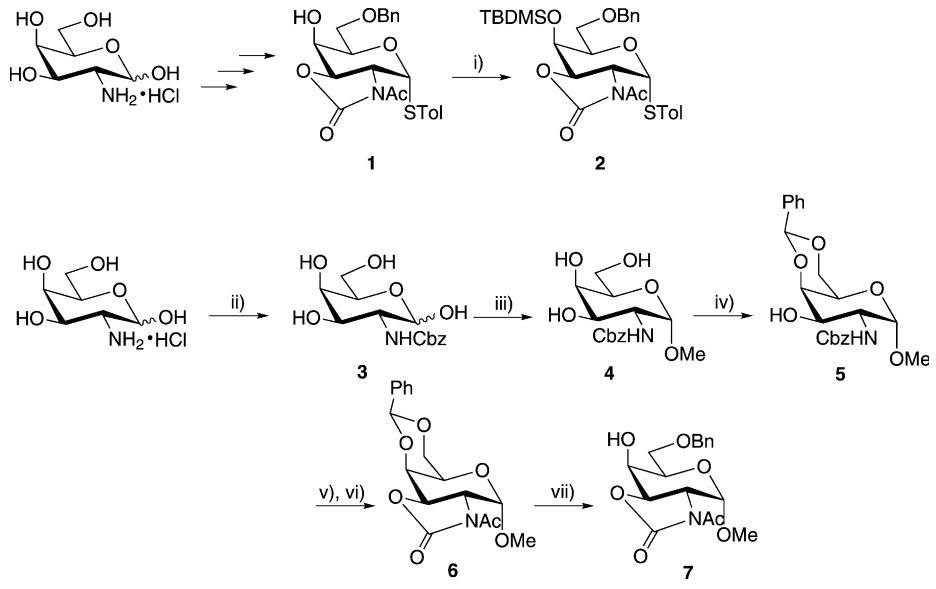
none moiety is an effective nonparticipating group for the stereoselective synthesis of α-linked 2-amino-2-deoxy-D-hexopyranosides.[10] This protecting group has also been introduced onto glycosyl acceptors to enhance the reactivity of the 4-hydroxy group during glycosylations[11] because the tied-back nature of the oxazolidinone can reduce the hindrance around the nucleophilic oxygen.[12] Moreover, the *N*-acetyloxazolidinone functionality also decreases the tendency for amide glycosylation[13] and removes the possibility of problematic hydrogen-bonding networks.[14] Recently, our group has also achieved advances in the stereochemistry of glycosylations by virtue of oxazolidinone protecting-group strategies,[15] and the application of this protecting group to the chemical synthesis of oligosaccharide fragments has been realized.[16] *N*-Acetyloxazolidinone is not only able to serve as a stereoselective directing group and an orthogonal protecting group, but can also be easily removed by chemoselective deprotection.[11,17] Consequently, we decided to introduce it into the galactosamine moiety to construct the oligosaccharides of the Vi antigen.

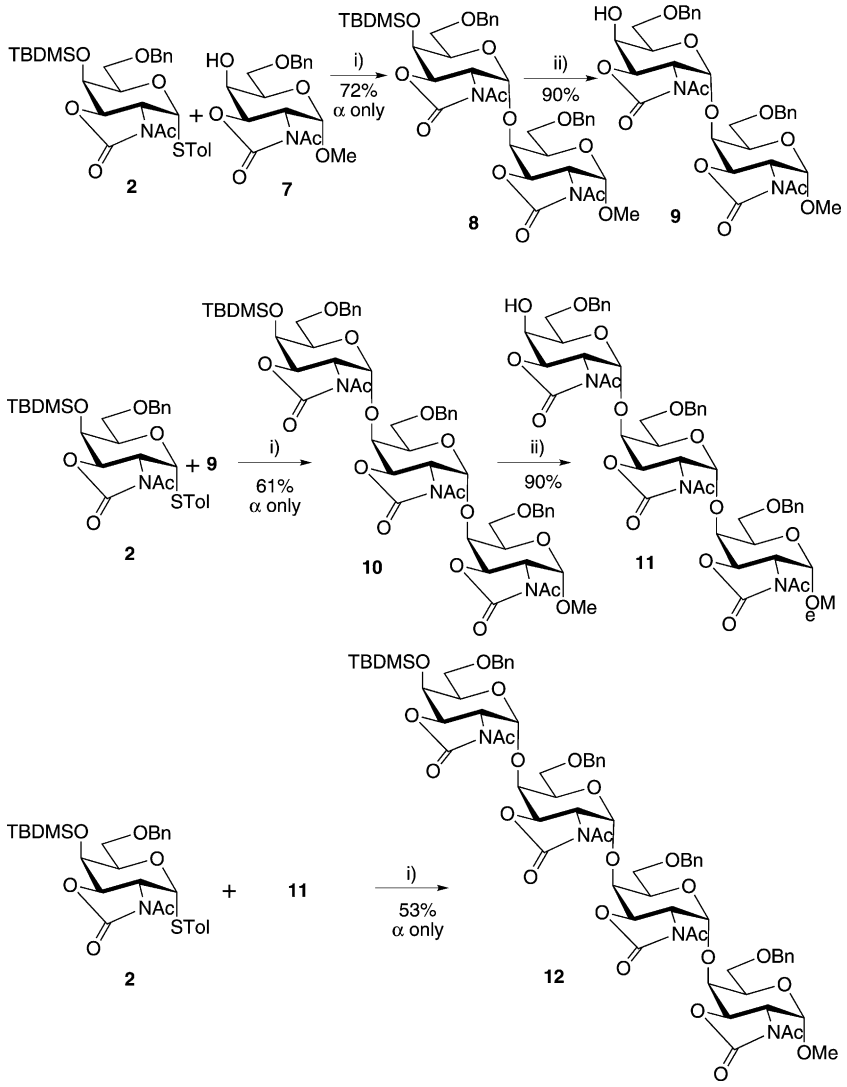
Both the oxazolidinone-containing glycosyl donor and the acceptor can be readily prepared from commercially available D-galactosamine hydrochloride in high yield on a large scale (Scheme 1). Compound **1** was prepared according to a previously published approach,[16] and then underwent silylation with *tert*-butyldimethylsilyl chloride to afford the thioglycoside **2** as the donor in quantitative yield. In the synthesis of the acceptor the amino functionality of D-galactosamine was protected with the benzyloxycarbonyl group to give compound **3**. This was followed by glycosylation with methanol to produce methyl glycoside **4**. The two hydroxyl groups in **4** were protected with benzylidene to afford compound **5** smoothly. 2,3-Oxazolidinone-protected compound **6** was formed after treatment of **5** with sodium hydride followed by acetylation. The reductive cleavage of the benzylidene acetal in **6** by using $Et_3SiH/TfOH$[18] provided acceptor **7** with a free hydroxyl group at the 4 position.

As an alternative mode of glycosylation, the "pre-activation" protocol[19] has triggered considerable interest, meaning that a glycosyl donor is completely activated and consumed (by TLC detection) prior to the addition of a glycosyl acceptor. This protocol has been successfully applied to oligosaccharide assembly. Under the pre-activation conditions, the coupling reaction of donor **2** with acceptor **7** was performed first. After trying different promoter systems, the best result was obtained by using a combination of diphenyl sulfoxide (Ph_2SO) and triflic anhydride (Tf_2O),[20] along with the hindered base TTBP.[21] By using this procedure, disaccharide **8** was produced exclusively as the α-anomer in 72% isolated yield (Scheme 2). After desilylation of **8**, the new acceptor **9** was produced smoothly. Repeating the glycosylation step with the same donor **2** and the synthetic method based on the pre-activation protocol, trisaccharide **10** was obtained as the α-only product in 61% yield. The silyl group in **10** was then removed to give trisaccharide acceptor **11**. In the same way, the coupling reaction of donor **2** with acceptor **11** successfully provided tetrasaccharide **12** as the α-only product in 53% isolated yield. It is noteworthy that a small amount of the acceptors remained unreacted during the glycosylation reactions and these materials were recycled. The coupling yield of each α product was quantitative based on the recovery of the glycosyl acceptor. As the reactivity of the 4-OH group decreased, that is, as the acceptor became larger, the amount of unreacted acceptor increased, leading to the lower yields of the α-only products.

As we have developed an effective method to increase the length of the repeating α-(1→4)-linked *N*-acetylgalactosamine units, our attention was then focused on the deprotection of these oligosaccharides to form the final products as repeating α-(1→4)-1inked *N*-acetyl galactosaminuronic acids. As shown in Scheme 3, disaccharide **8** was first hydrolyzed by using water to remove the oxazolidinone group. It was found that the cleavage of the silyl ether in **8** also occurred during the hydrolysis process. Subsequent acetylation afforded compound **13**, which was subjected to a



Scheme 1. The synthesis of the monosaccharide building blocks. Reagents and conditions: i) *tert*-butyldimethylsilyl chloride (TBDMSCl), imidazole, DMF, 70°C, 48 h, quantitative; ii) benzyloxycarbonyl chloride (CbzCl), $NaHCO_3$, H_2O, 0°C, 17 h, 85%; iii) HCl, MeOH, reflux, overnight, 80%; iv) $PhCH(OMe)_2$, camphorsulfonic acid (CSA), CH_3CN, RT, 10 min, quantitative; v) NaH, DMF, 0°C to RT, 30 min; vi) Ac_2O, pyridine, 4-dimethylaminopyridine (DMAP), 1 h, 75% for two steps; vii) Et_3SiH, trifluoromethanesulfonic acid (TfOH), CH_2Cl_2, −72°C, 1 h, 73%.



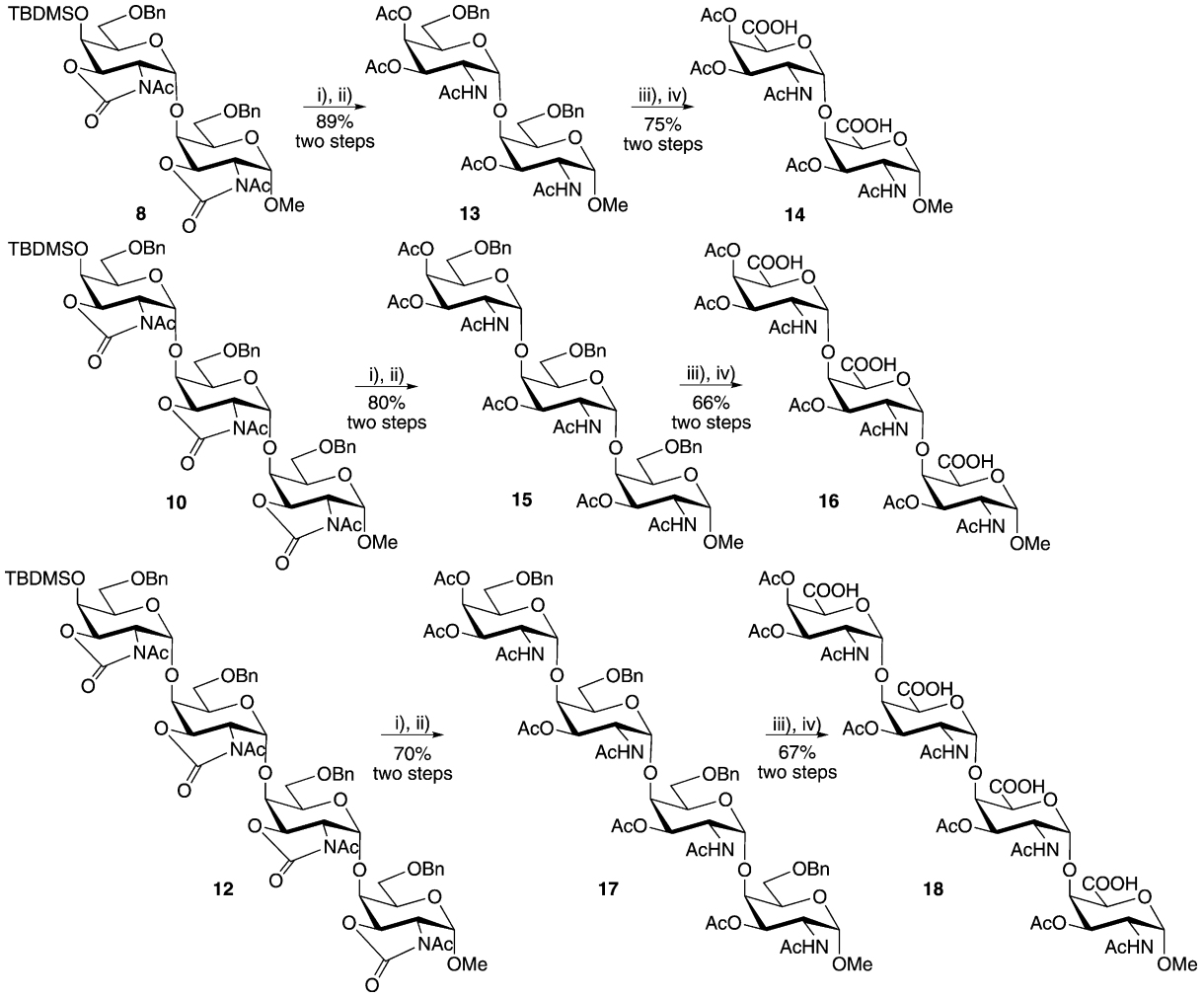
Scheme 2. The Synthesis of the di-, tri-, and tetrasaccharides. Reagents and conditions: i) Ph_2SO, Tf_2O, 2,4,6-tri-*tert*-butylpyrimidine (TTBP), CH_2Cl_2, −72 °C to RT, ≈3 h; ii) tetra-*n*-butylammonium fluoride (TBAF)/THF, RT, 10 min.

tandem hydrogenolysis and oxidation operation to afford uronic acid **14** in good isolated yield. Following this convenient and efficient deprotection and oxidation procedure, trisaccharide **10** and tetrasaccharide **12** were converted into the corresponding uronic acids **16** and **18** in high yields (Scheme 3).

Antigenic assay: To explore the antigenic activity of these synthetic saccharide moieties of the Vi antigen (compounds **14**, **16**, and **18**), a test of the inhibition of antibody binding by the native polysaccharide was performed by use of the enzyme-linked immunosorbent assay (ELISA). First, 96-well plates were coated with the Vi PS. Then, serial concentrations of Vi PS, **14**, **16**, and **18** were separately mixed with anti-Vi serum before addition to the coated plates. An anti-rabbit IgG antibody labeled with horseradish peroxidase was employed as a secondary antibody for colorimetric detection (OD, optical density).

Vi PS itself as an inhibitor provided a standard curve implying that it provides inhibition from 0.05 to 10 $\mu g\,mL^{-1}$ (Figure 2), with an IC_{50} value around 1 $\mu g\,mL^{-1}$. The inhibition by tetrasaccharide **18** gradually increased from 0.1 $\mu g\,mL^{-1}$ and grew sharply from 10 to 500 $\mu g\,mL^{-1}$ (Figure 2). Its IC_{50} value was around 100 $\mu g\,mL^{-1}$, nearly 100 times that of Vi PS. The best inhibition it provided was around 77 %. The inhibition curve produced for trisaccharide **16** fluctuated at low concentrations and increased gradually from 50 $\mu g\,mL^{-1}$ (Figure 2). The highest inhibition was around 41 % at 500 $\mu g\,mL^{-1}$, which is below the IC_{50} value for this compound. The inhibition by disaccharide **14** was low and changed little when the concentration was increased, indicating that disaccharide **14** had no distinct competitive inhibition activity, although its activity may be increased at concentrations higher than 500 $\mu g\,mL^{-1}$ (Figure 2, Table 1).

In the work of Sinaÿ and coworkers,[8] a similar Vi PS standard curve was provided. However, the disaccharide and trisaccharide they synthesized showed no immunogenic activity in the range 0 to 500 $\mu g\,mL^{-1}$. Inhibition by their tetrasaccharide was detected from 100 $\mu g\,mL^{-1}$ but had not reached 30 % at 500 $\mu g\,mL^{-1}$. The inhibition by their hexasaccharide reached nearly 90 % at 500 $\mu g\,mL^{-1}$, with the IC_{50} value being nearly 100–200 times that of Vi PS. In our case, the only change was in the terminal protecting group of the "donor" end of the polysaccharide, which was an acetyl group instead of a methyl, but the competitive inhibitory ability of our tetrasaccharide **18** was much higher than that of their tetrasaccharide and was similar to that of their hexasaccharide. Moreover, the antigenic activity of our synthetic trisaccharide **16** was significant and much higher than that of their tetrasaccharide. Studies into the immunochemical properties of the Vi antigen have shown the presence of at least two antigenic determinants. One of them is the *O*-acetyl moiety at C3, which plays a dominant role. The other antigenic determinant involves both carboxyl and *N*-acetyl groups.[22] It may be infer-



Scheme 3. The deprotection and oxidation of the di-, tri-, and tetrasaccharides. Reagents and conditions: i) NaOH (aqueous)/1,4-dioxane (1:1), 40 °C, ≈2–5 h; ii) Ac_2O, DMAP, pyridine, 0 °C to RT, ≈2–10 h; iii) H_2, Pd/C, THF/AcOH/H_2O (4:2:1), ≈2–5 h; iv) $NaIO_4$, $RuCl_3{\cdot}xH_2O$, $CCl_4/CH_3CN/H_2O$ (2:2:3), overnight.

red from our results that the antigenic activity of short oligosaccharides of the Vi antigen could be strengthened greatly by increasing the number of acetyl groups. This could even remedy the detrimental effects of shorter sugar chains.

Conclusion

We have developed a short and efficient approach to constructing fragments of the repeating α-(1→4)-1inked *N*-acetyl galactosaminuronic acid of the *Salmonella typhi* Vi antigen in high yields. The use of the *N*-acetyloxazolidinone-protected glycosides based on a pre-activation protocol was effective in providing exclusively α-stereoselective glycosylation and greatly reduced the number of steps in the functional group transformation. Examination of the competitive inhibition by use of the ELISA showed that the synthetic tri- and tetrasaccharides (**16** and **18**) had greatly improved antigenic activities in comparison with previous literature reports. Our data seems to be complementary to the finding that the O-acetyl moiety plays a dominant role in antigenic determinants. It was found that the antigenic activity of short oligosaccharides could be strengthened significantly by increasing the number of acetyl groups. Further extension of this protocol and evaluation of the bioactivity are now underway.

Experimental Section

General: All chemicals purchased were reagent grade and were used without further purification unless otherwise stated. Dichloromethane (CH_2Cl_2), pyridine, and acetonitrile (CH_3CN) were distilled over calcium hydride (CaH_2). Methanol was distilled from magnesium. DMF was stirred with CaH_2 and distilled under reduced pressure. All glycosylation reactions were carried out under anhydrous conditions with freshly distilled solvents, unless otherwise stated. Reactions were monitored by analytical thin-layer chromatography on silica gel 60 F_{254} precoated on aluminum plates (E. Merck). Spots were detected under UV (254 nm) light and/or by staining with acidic ceric ammonium molybdate. Solvents were evaporated under reduced pressure by use of a below 40 °C bath. Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column

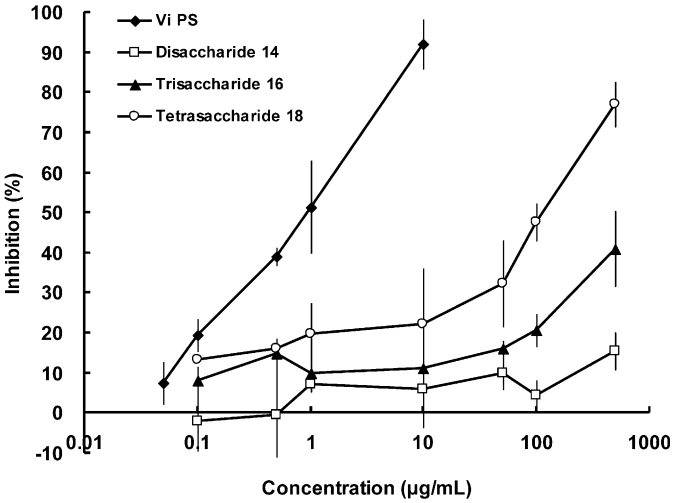


Figure 2. The results of the ELISA for the competitive inhibition of Vi PS and the synthetic oligosaccharides. The 96-well plates were coated with Vi PS (0.5 μg mL^{-1}). Anti-Vi serum (1:250 dilution) was first mixed with an equivalent volume of saccharides **14**, **16**, and **18** (0.05–500 μg mL^{-1}) before being applied to coated plates. The data are reported as the mean ± SD of measurements performed in triplicate.

Table 1. The competitive percentage inhibition for the ELISA.

Concentration [μg mL^{-1}]	Vi PS	Disaccharide **14**	Trisaccharide **16**	Tetrasaccharide **18**
0.05	7.53 ± 5.46	–	–	–
0.1	19.39 ± 4.20	−2.02 ± 7.76	8.05 ± 3.68	13.27 ± 0.62
0.5	39.06 ± 2.44	−0.47 ± 15.45	14.87 ± 0.70	16.06 ± 2.75
1	51.39 ± 11.76	7.28 ± 2.30	9.81 ± 3.41	19.85 ± 7.71
10	92.06 ± 6.38	5.87 ± 9.75	11.01 ± 3.95	22.06 ± 14.16
50	–	9.85 ± 4.36	16.01 ± 2.16	32.27 ± 10.92
100	–	4.55 ± 3.94	20.67 ± 4.31	47.61 ± 4.93
500	–	15.46 ± 4.78	40.95 ± 9.59	77.00 ± 5.84

chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Varian INOVA-500 or an Advance DRX Bruker-400 spectrometer at 25 °C. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in deuterated chloroform. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ ($\delta = 77.00$ ppm). Mass spectra were recorded by using a PE SCLEX QSTAR spectrometer. Elemental analysis data were recorded on a Vario EL-III elemental analyzer.

***para*-Tolyl 2-acetamido-4-*O*-*tert*-butyldimethylsilyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-α-D-galactopyranoside (2)**: A mixture of compound **1**[16] (1.5 g, 3.39 mmol), *tert*-butyldimethylsilyl chloride (4.09 g, 27.1 mmol), and imidazole (0.69 g, 10.2 mmol) in dry DMF (8.2 mL) was heated at 70 °C for 48 h. After the TLC showed the complete disappearance of **1**, the reaction mixture was extracted with EtOAc (90 mL), and the organic layer was washed with saturated aqueous NH_4Cl (30 mL × 2) and water (30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 15:1) to give **2** as a colorless viscous oil (1.89 g, quantitative). $R_f = 0.8$ (hexane/EtOAc, 3:1); $[\alpha]_D^{24} = +177.0$ ($c = 2.9$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.37$–7.29 (m, 7H; Ar), 7.05 (d, 2H, $J = 8.0$ Hz; Ar), 6.10 (d, 1H, $J_{1,2} = 4.4$ Hz; H1), 4.62 (dd, 1H, $J_{2,1} = 4.4$, $J_{2,3} = 12.4$ Hz; H2), 4.55 (d, 1H, $J = 11.6$ Hz; PhCH_2), 4.50 (d, 1H, $J = 11.6$ Hz; PhCH_2), 4.42–4.38 (m, 3H; H3, H4, H5), 3.70 (dd, 1H, $J = 6.8$, 9.6 Hz; H6a), 3.58 (dd, 1H, $J = 6.0$, 9.2 Hz; H6b), 2.54 (s, 3H; CH_3), 2.30 (s, 3H; CH_3), 0.90 (s, 9H; *t*Bu), 0.11 (s, 3H; CH_3), 0.10 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 171.51, 152.95, 138.25, 137.77, 133.17, 129.84, 128.70, 128.37, 127.73, 127.65, 87.44, 76.90, 73.39, 71.49, 68.48, 66.54, 55.12, 25.78, 23.94, 21.10, 18.18, −4.38, −5.13 ppm; MS (ESI): *m*/*z*: 558 $[M+H]^+$, 575 $[M+NH_4]^+$, 580 $[M+Na]^+$, 596 $[M+K]^+$; elemental analysis calcd (%) for $C_{29}H_{39}NO_6SSi$: C 62.45, H 7.05, N 2.51; found: C 62.34, H 7.15, N 2.38.

Methyl 2-benzyloxycarbonylamino-4,6-*O*-benzylidene-2-deoxy-α-D-galactopyranoside (5): Benzaldehyde dimethyl acetal (1.03 g, 1.02 mL, 6.78 mmol) was added dropwise to a stirred solution of compound **4**[23] (1.48 g, 4.52 mmol) and camphorsulfonic acid (105 mg, 0.45 mmol) in dry CH_3CN (15 mL) at room temperature. The pH value was about 2–3. The solution was then stirred for 10 min, at which time TLC showed the complete disappearance of **4**. The reaction mixture was quenched with Et_3N to give a pH around 7 and then concentrated in vacuo. The crude product was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:2) to give **5** as a white amorphous solid (1.87 g, quantitative). $R_f = 0.4$ (hexane/EtOAc, 1:2); $[\alpha]_D^{24} = +98.3$ ($c = 2.4$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.51$ (d, 2H, $J =$ 4.8 Hz; Ar), 7.38–7.31 (m, 8H; Ar), 5.58 (s, 1H; PhC*H*), 5.13 (d, 1H, $J =$ 12.0 Hz; PhCH_2), 5.08 (d, 1H, $J = 12.0$ Hz; PhCH_2), 5.06 (d, 1H, $J =$ 8.8 Hz; NH), 4.86 (d, 1H, $J_{1,2} = 3.2$ Hz; H1), 4.29 (dd, 1H, $J = 0.8$, 12.4 Hz; H6a), 4.23 (d, 1H, $J_{4,3} = 3.2$ Hz; H4), 4.21–4.16 (m, 1H; H2), 4.08 (dd, 1H, $J = 1.2$, 12.4 Hz; H6b), 3.82 (td, 1H, $J_{3,2} = J_{3,OH} = 11.2$, $J_{3,4} =$ 3.2 Hz; H3), 3.68 (s, 1H; H5), 3.39 (s, 3H; CH_3), 2.51 ppm (d, 1H, $J =$ 11.2 Hz; 3OH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 156.88$, 137.47, 136.26, 129.16, 128.53, 128.22, 126.30, 101.26, 99.70, 75.48, 69.32, 69.12, 67.06, 62.82, 55.52, 52.18 ppm; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}NO_7Na$: 438.1523 $[M+Na]^+$; found: 438.1532.

Methyl 2-acetamido-4,6-*O*-benzylidene-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (6): Compound **5** (4.0 g, 9.63 mmol) was dissolved in dry DMF (100 mL) and cooled to 0 °C under a nitrogen atmosphere. NaH (0.28 g, 11.6 mmol) was added carefully to the solution. Once the bubbles had vanished, the reaction was gradually warmed to room temperature and stirred for a further 30 min. After the TLC showed the complete disappearance of **5**, the mixture was dropped slowly into a large amount of iced water and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. After addition of DMAP (58.8 mg, 0.48 mmol), the mixture was dissolved in pyridine (20 mL). The solution was cooled to 0 °C and acetic anhydride (9.8 g, 9.05 mL, 96.1 mmol) was added dropwise. The resulting mixture was gradually warmed to room temperature and stirred for a further 1 h. The mixture was concentrated, and the residue purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give **6** as a white amorphous solid (2.52 g, 75 % for two steps). $R_f = 0.4$ (hexane/EtOAc, 1:1); $[\alpha]_D^{24} = +91.4$ ($c = 2.8$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.52$–7.49 (m, 2H; Ar), 7.39–7.36 (m, 3H; Ar), 5.70 (d, 1H, $J_{1,2} = 2.8$ Hz; H1), 5.62 (s, 1H; PhC*H*), 4.72 (dd, 1H, $J_{3,4} = 2.4$, $J_{3,2} =$ 12.4 Hz; H3), 4.60 (s, 1H; H4), 4,51 (dd, 1H, $J_{2,1} = 2.8$, $J_{2,3} = 12.4$ Hz; H2), 4.35 (dd, 1H, $J = 0.8$, 12.8 Hz; H6a), 4.23 (dd, 1H, $J = 1.6$, 12.8 Hz; H6b), 4.12 (s, 1H; H5), 3.66 (s, 3H; CH_3), 2.49 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.41$, 152.97, 136.97, 129.28, 128.26, 126.18, 100.36, 98.31, 72.99, 71.77, 69.89, 63.16, 56.15, 55.17, 23.85 ppm; MS (ESI): *m*/*z*: 350 $[M+H]^+$, 367 $[M+NH_4]^+$, 372 $[M+Na]^+$, 388 $[M+K]^+$; elemental analysis calcd (%) for $C_{17}H_{19}NO_7$: C 58.45, H 5.48, N 4.01; found: C 58.19, H 5.48, N 3.94.

Methyl 2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (7): Et_3SiH (205 mg, 281 μL, 1.76 mmol) and TfOH (177 mg, 104 μL, 1.18 mmol) were added to a stirred mixture of **6** (206 mg, 0.59 mmol) and activated 4 Å molecular sieves (830 mg, powder) in CH_2Cl_2 (8.3 mL) at −72 °C under a nitrogen atmosphere. After being stirred for 1 h at −72 °C, Et_3N (1 mL) and MeOH (1 mL) were added successively. The mixture was then filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2.5:1) to give **7** as a colorless viscous oil (151 mg, 73 %). $R_f = 0.5$ (hexane/EtOAc, 1:1); $[\alpha]_D^{24} = +98.0$ ($c = 2.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.39$–7.30 (m, 5H; Ar), 5.60 (d, 1H, $J_{1,2} = 2.4$ Hz; H1), 4.64–4.56 (m, 3H; PhCH_2 × 2, H3), 4.47 (s, 1H; H4), 4.20 (dd, 1H, $J_{2,1} = 2.4$, $J_{2,3} = 12.4$ Hz; H2), 3.85 (t, 1H, $J = 4.4$ Hz; H5), 3.80–3.77 (m, 2H; H6a, H6b), 3.42 (s, 3H; CH_3), 3.28 (d, 1H, $J = 2.0$ Hz; 4-OH),

2.49 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.56, 153.19, 137.21, 128.47, 127.94, 127.70, 97.69, 74.92, 73.75, 69.67, 69.50, 66.49, 55.91, 54.83, 23.79 ppm; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{22}NO_7$: 352.1391 $[M+H]^+$; found: 352.1395.

Methyl (2-acetamido-4-*O*-*tert*-butyldimethylsilyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (8): Tf_2O (14.3 mg, 8.4 μL, 0.051 mmol) was added to a stirred mixture of **2** (24.8 mg, 0.044 mmol), Ph_2SO (9.6 mg, 0.048 mmol), TTBP (22.0 mg, 0.88 mmol), and activated 4 Å molecular sieves (500 mg, powder) in CH_2Cl_2 (5 mL) at −72 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and, after the complete disappearance of **2** as detected by TLC, a solution of acceptor **7** (10.4 mg, 0.030 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise to the mixture. The mixture was slowly warmed to room temperature, stirred for a further 2 h and quenched with Et_3N (0.1 mL). The precipitate was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to give **8** as a colorless foam (16.7 mg, 72%). R_f = 0.5 (hexane/EtOAc, 2:1); $[\alpha]_D^{24}$ = +92.7 (*c* = 3.7 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.27 (m, 10H; Ar), 5.80 (d, 1H, $J_{1',2'}$ = 2.4 Hz; H1′), 5.55 (d, 1H, $J_{1,2}$ = 2.8 Hz; H1), 4.69 (d, 1H, *J* = 11.6 Hz; PhCH_2), 4.65 (dd, 1H, $J_{3',2'}$ = 12.4, $J_{3',4'}$ = 1.6 Hz; H3′), 4.58 (dd, 1H, $J_{3,2}$ = 12.4, $J_{3,4}$ = 1.6 Hz; H3), 4.53–4.51 (m, 3H; PhCH_2×3), 4.47 (s, 1H; H4′), 4.40 (s, 1H; H4), 4.36 (dd, 1H, $J_{2',1'}$ = 2.4, $J_{2,3}$ = 12.0 Hz; H2), 4.19 (dd, 1H, $J_{2,1}$ = 2.8, $J_{2,3}$ = 12.4 Hz; H2), 4.10 (t, 1H, *J* = 6.4 Hz; H5′), 3.91 (t, 1H, *J* = 6.4 Hz; H5), 3.64–3.59 (m, 1H; H6a′), 3.53–3.43 (m, 3H; H6b′, H6a, H6b), 3.41 (s, 3H; CH_3), 2.48 (s, 3H; CH_3), 2.46 (s, 3H; CH_3), 0.89 (s, 9H; *t*Bu), 0.08 ppm (s, 6H; CH_3×2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.01, 171.41, 152.97, 152.66, 137.82, 137.80, 128.41, 128.34, 127.78, 127.75, 127.71, 127.62, 97.36, 96.78, 74.71, 73.78, 73.22, 73.06, 71.23 (2C), 70.09, 67.53, 67.35, 66.27, 56.04, 55.80, 55.01, 25.80, 23.83, 18.17, −4.51, −5.13 ppm; HRMS (ESI): *m*/*z* calcd for $C_{39}H_{52}N_2O_{13}SiNa$: 807.3131 $[M+Na]^+$; found: 807.3131.

Methyl (2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (9): Compound **8** (149 mg, 0.19 mmol) was dissolved in TBAF/THF (1 M; 2 mL). The solution was then stirred for 10 min, at which time TLC showed the complete disappearance of **8**. The reaction mixture was extracted with EtOAc (50 mL) and the organic layer was washed with satutated aqueous NH_4Cl (15 mL×2) and water (10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give **9** as a colorless foam (114 mg, 90%). R_f = 0.4 (hexane/EtOAc, 1:1); $[\alpha]_D^{24}$ = +125.7 (*c* = 1.4 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.29 (m, 10H; Ar), 5.89 (d, 1H, $J_{1',2'}$ = 1.2 Hz; H1′), 5.54 (d, 1H, $J_{1,2}$ = 2.8 Hz; H1), 4.73 (d, 1H, *J* = 11.6 Hz; PhCH_2), 4.66–4.50 (m, 8H; PhCH_2×3, H3′, H3, H4′, H4, H2′), 4.19 (dd, 1H, $J_{2,1}$ = 2.8, $J_{2,3}$ = 12.4 Hz; H2), 4.05 (t, 1H, *J* = 4.0 Hz; H5′), 3.91 (t, 1H, *J* = 6.8 Hz; H5), 3.81 (d, 2H, *J* = 4.0 Hz; H6a′, H6b′), 3.58 (s, 1H; 4′-OH), 3.56–3.51 (m, 1H; H6a), 3.47 (dd, 1H, *J* = 6.4, 9.2 Hz; H6b), 3.40 (s, 3H; CH_3), 2.49 (s, 3H; CH_3), 2.48 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.09, 171.35, 153.03, 152.77, 137.82, 137.10, 128.62, 128.45, 128.10, 127.88, 127.85, 127.81, 97.33, 96.96, 74.32, 73.98, 73.79, 73.11, 70.75, 69.93, 67.16, 67.08, 56.09, 55.93, 54.63, 23.83 ppm; HRMS (ESI): *m*/*z* calcd for $C_{33}H_{38}N_2O_{13}Na$: 693.2266 $[M+Na]^+$; found: 693.2264.

Methyl (2-acetamido-4-*O*-*tert*-butyldimethylsilyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (10): Tf_2O (20.7 mg, 12.2 μL, 0.073 mmol) was added to a stirred mixture of **2** (36.2 mg, 0.065 mmol), Ph_2SO (14 mg, 0.069 mmol), TTBP (32.0 mg, 0.13 mmol), and activated 4 Å molecular sieves (500 mg, powder) in CH_2Cl_2 (5 mL) at −72 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and, after the complete disappearance of **2** as detected by TLC, a solution of acceptor **9** (29 mg, 0.043 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise to the mixture. The mixture was slowly warmed to room temperature, stirred for a further 2 h, and quenched with Et_3N (0.1 mL). The precipitate was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give **10** as a colorless foam (29 mg, 61%). R_f = 0.5 (hexane/EtOAc, 2:1); $[\alpha]_D^{24}$ = +106.7 (*c* = 1.2 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.26 (m, 15H; Ar), 5.82 (d, 2H, *J* = 2.8 Hz; H1″, H1′), 5.54 (d, 1H, $J_{1,2}$ = 2.8 Hz; H1), 4.70 (d, 1H, *J* = 11.6 Hz; PhCH_2), 4.67–4.62 (m, 3H; PhCH_2, H3″, H3′), 4.57–4.50 (m, 6H; PhCH_2×4, H3, H4″), 4.47 (s, 1H; H4′), 4.38 (s, 1H; H4), 4.35 (dd, 1H, $J_{2'',1''}$ = 2.8, $J_{2'',3''}$ = 12.4 Hz; H2″), 4.25 (dd, 1H, $J_{2',1'}$ = 2.8, $J_{2',3'}$ = 12.4 Hz; H2′), 4.18 (dd, 1H, $J_{2,1}$ = 2.8, $J_{2,3}$ = 12.4 Hz; H2), 4.15 (t, 1H, *J* = 6.8 Hz; H5″), 4.06 (t, 1H, *J* = 6.4 Hz; H5′), 3.91 (t, 1H, *J* = 6.8 Hz; H5), 3.61–3.57 (m, 1H; H6a″), 3.53–3.44 (m, 5H; H6b″, H6a′, H6b′, H6a, H6b), 3.41 (s, 3H; CH_3), 2.47 (s, 3H; CH_3), 2.45 (s, 3H; CH_3), 2.42 (s, 3H; CH_3), 0.88 (s, 9H; *t*Bu), 0.07 ppm (d, 6H, *J* = 2.8 Hz; CH_3×2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.93, 171.43, 152.98, 152.54, 137.98, 137.85, 137.80, 128.43, 128.37, 127.76, 127.66, 127.57, 97.42, 96.71, 96.53, 74.69, 73.68, 73.34, 73.22, 73.06, 72.88, 71.34, 71.18, 70.83, 70.39, 69.92, 67.65, 67.20, 66.65, 66.36, 56.07, 55.80, 55.69, 55.01, 25.80, 23.80, 18.18, −4.50, −5.13 ppm; HRMS (ESI): *m*/*z* calcd for $C_{55}H_{70}N_3O_{19}Si$: 1104.4367 $[M+H]^+$; found: 1104.4343.

Methyl (2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (11): Compound **10** (34.5 mg, 0.03 mmol) was dissolved in TBAF/THF (1 M; 2 mL). The solution was then stirred for 10 min, at which time TLC showed the complete disappearance of **10**. The reaction mixture was extracted with EtOAc (50 mL) and the organic layer was washed with saturated aqueous NH_4Cl (15 mL×2) and water (10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give **11** as a colorless foam (27.8 mg, 90%). R_f = 0.4 (hexane/EtOAc, 1:1); $[\alpha]_D^{24}$ = +96.2 (*c* = 1.6 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.27 (m, 15H; Ar), 5.92 (s, 1H; H1″), 5.81 (d, 1H, $J_{1',2'}$ = 2.0 Hz; H1′), 5.53 (d, 1H, $J_{1,2}$ = 2.0 Hz; H1), 4.72–4.46 (m, 13H; PhCH_2×6, H2″, H3″, H3′, H3, H4″, H4′, H4), 4.25 (dd, 1H, $J_{2',1'}$ = 2.0, $J_{2',3'}$ = 12.4 Hz; H2′), 4.18–4.12 (m, 2H; H2, H5″), 4.01 (s, 1H; H5′), 3.90 (t, 1H, *J* = 6.8 Hz; H5), 3.78 (d, 2H, *J* = 4.0 Hz; H6a″, H6b″), 3.52–3.43 (m, 5H; 4″-OH, H6a′,H6b′, H6a, H6b), 3.40 (s, 3H; CH_3), 2.48 (s, 3H; CH_3), 2.46 ppm (s, 6H; CH_3×2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.00, 171.89, 171.49, 153.06, 152.63, 152.56, 137.95, 137.79, 137.14, 128.61, 128.45, 128.41, 128.06, 127.81, 127.80, 127.69, 127.62, 97.41, 96.83, 96.50, 74.30, 73.90, 73.67, 73.28, 73.08, 72.92, 71.25, 70.25, 69.97, 69.90, 69.81, 67.18, 67.06, 66.38, 56.11, 55.82, 55.76, 54.62, 23.84, 23.80 ppm; HRMS (ESI): *m*/*z* calcd for $C_{49}H_{59}N_4O_{19}$: 1007.3768 $[M+NH_4]^+$; found: 1007.3789.

Methyl (2-acetamido-4-*O*-*tert*-butyldimethylsilyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-galactopyranoside (12): Tf_2O (56.1 mg, 33 μL, 0.20 mmol) was added to a stirred mixture of **2** (106 mg, 0.19 mmol), Ph_2SO (38.4 mg, 0.19 mmol), TTBP (94.4 mg, 0.38 mmol), and activated 4 Å molecular sieves (1.5 g, powder) in CH_2Cl_2 (15 mL) at −72 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and, after the complete disappearance of **2** as detected by TLC, a solution of acceptor **11** (94.2 mg, 0.095 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise to the mixture. The mixture was slowly warmed to room temperature, stirred for a further 2 h, and quenched with Et_3N (0.1 mL). The precipitate was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **12** as a colorless foam (72 mg, 53%). R_f = 0.4 (hexane/EtOAc, 2:1); $[\alpha]_D^{21}$ = +110.9 (*c* = 2.6 in $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.38–7.26 (m, 20H; Ar), 5.84 (d, 1H, $J_{1''',2'''}$ = 3.0 Hz; H1‴), 5.82 (d, 1H, $J_{1'',2''}$ = 3.0 Hz; H1″), 5.80 (d, 1H, $J_{1',2'}$ = 3.0 Hz; H1′), 5.54 (d, 1H, $J_{1,2}$ = 2.5 Hz; H1), 4.72–4.46 (m, 15H; PhCH_2×8, H3‴, H3″, H3′, H3, H4‴, H4″, H4′), 4.38 (s, 1H; H4), 4.33 (dd, 1H, $J_{2''',1'''}$ = 3.0, $J_{2''',3'''}$ = 12.5 Hz; H2‴), 4.25–4.22 (m, 2H; H2″, H2′), 4.19–4.10 (m, 3H; H2, H5‴, H5″) 4.05 (t, 1H, *J* = 6.5 Hz; H5′), 3.90 (t, 1H, *J* = 6.5 Hz; H5), 3.58 (dd, 1H, *J* = 2.5, 9.0 Hz; H6a‴), 3.52–3.42 (m, 7H; H6b‴, H6a″, H6b″, H6a′, H6b′, H6a, H6b), 3.40 (s, 3H; CH_3),

2.47 (s, 3H; CH_3), 2.44 (s, 3H; CH_3), 2.41 (s, 6H; $CH_3\times2$), 0.87 (s, 9H; *t*Bu), 0.07 (s, 3H; CH_3), 0.06 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.95, 171.93, 171.82, 171.41, 152.96, 152.55, 152.41, 137.97, 137.88, 137.82, 128.44, 128.41, 128.39, 128.37, 127.79, 127.76, 127.67, 127.61, 97.43, 96.77, 96.56, 96.49, 74.69, 73.69, 73.31, 73.23, 73.09, 72.89, 72.87, 71.38, 71.21, 70.97, 70.82, 70.51, 70.20, 69.92, 67.69, 67.18, 66.76, 66.53, 66.40, 56.09, 55.83, 55.68, 55.03, 25.81, 23.79, 23.73, 23.68, 18.19, −4.49, −5.13 ppm; HRMS (ESI): *m*/*z* calcd for $C_{71}H_{90}N_5O_{25}Si$: 1440.5689 $[M+NH_4]^+$; found: 1440.5702.

Methyl (2-acetamido-3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (13): Compound **8** (10.5 mg, 0.013 mmol) was dissolved in a mixed solvent consisting of aqueous NaOH (1 M) and 1,4-dioxane (1.6 mL, 1:1) and then heated at 40 °C for 2 h. After the TLC showed the complete disappearance of **8**, the reaction mixture was quenched with hydrochloric acid to give a pH around 7 and then concentrated in vacuo. After the addition of DMAP (0.08 mg, 0.65 μmol), the mixture was dissolved in pyridine (1 mL). The solution was cooled to 0 °C and acetic anhydride (0.5 mL) was added dropwise. The resulting mixture was gradually warmed to room temperature and stirred for a further 2 h. The crude product was purified by column chromatography on silica gel (MeOH/EtOAc, 1:50) to give **13** as a colorless viscous oil (8.9 mg, 89 % for two steps). R_f = 0.8 (MeOH/EtOAc, 1:10); $[\alpha]_D^{24}$ = +110.7 (c = 1.4 in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.22 (m, 10H; Ar), 5.99 (d, 1H, J = 9.6 Hz; NH), 5.70 (d, 1H, J = 9.2 Hz; NH), 5.54 (d, 1H, J = 1.6 Hz; H4′), 5.22–5.19 (m, 2H; H3′, H3), 5.04 (d, 1H, $J_{1',2'}$ = 3.6 Hz; H1′), 4.78 (d, 1H, $J_{1,2}$ = 3.6 Hz; H1), 4.63–4.35 (m, 7H; PhC$H_2\times4$, H2′, H2, H5′), 4.20 (d, 1H, J = 2.0 Hz; H4), 3.97 (t, 1H, J = 7.2 Hz; H5), 3.49 (d, 2H, J = 7.2 Hz; H6a, H6b), 3.41 (d, 2H, J = 6.4 Hz; H6a′, H6b′), 3.38 (s, 3H; CH_3), 2.05 (s, 3H; CH_3), 2.01 (s, 3H; CH_3), 2.00 (s, 3H; CH_3), 1.95 (s, 3H; CH_3), 1.94 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.67, 170.55, 170.13, 170.08, 169.83, 137.35, 137.22, 128.47, 128.34, 128.01, 127.90, 127.78, 127.72, 98.37, 97.50, 73.61, 73.29, 71.75, 69.35, 68.70, 68.37, 67.86, 67.61, 67.42, 66.81, 55.42, 48.91, 47.91, 23.29, 23.26, 20.76, 20.71, 20.60 ppm; HRMS (ESI): *m*/*z* calcd for $C_{37}H_{48}N_2O_{14}Na$: 767.2998 $[M+Na]^+$; found: 767.2994.

Methyl (2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosideuronate (14): Compound **13** (15 mg, 0.020 mmol) was dissolved in a mixed solvent consisting of THF, AcOH, and water (2.8 mL, 4:2:1) and then Pd/C (10 %; 15 mg) was added. The mixture was stirred under a hydrogen atmosphere. After stirring for 2 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was dissolved in a mixed solvent consisting of CCl_4, CH_3CN, and water (1.75 mL, 2:2:3), and then sodium periodate (42.8 mg, 0.2 mmol) and hydrated ruthenium trichloride (0.18 mg, 0.88 μmol) were added to the mixture. The mixture was stirred overnight and then concentrated in vacuo. The residue was subjected to C18 reverse-phase column chromatography (MeOH/H_2O, 1:10) to give **14** as a colorless foam (9.0 mg, 75 % for two steps). R_f = 0.2 (MeOH/EtOAc, 1:1); $[\alpha]_D^{24}$ = +116.7 (c = 0.3 in MeOH); ^{1}H NMR (D_2O, 500 MHz): δ = 5.81 (dd, 1H, $J_{4',3'}$ = 3.0, $J_{4',5'}$ = 1.5 Hz; H4′), 5.39 (dd, 1H, $J_{3',2'}$ = 11.5, $J_{3',4'}$ = 3.0 Hz; H3′), 5.33 (dd, 1H, $J_{3,2}$ = 11.5, $J_{3,4}$ = 2.5 Hz; H3), 5.22 (d, 1H, $J_{1',2'}$ = 3.5 Hz; H1′), 5.14 (d, 1H, J = 1.5 Hz; H5′), 4.98 (d, 1H, $J_{1,2}$ = 4.0 Hz; H1), 4.75 (s, 1H; H5), 4.68 (d, 1H, J = 2.0 Hz; H4), 4.52 (dd, 1H, $J_{2,1}$ = 3.5, $J_{2,3}$ = 11.5 Hz; H2), 4.44 (dd, 1H, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 11.5 Hz; H2′), 3.45 (s, 3H; CH_3), 2.17 (s, 3H; CH_3), 2.02 (d, 6H, J = 2.5 Hz; $CH_3\times2$), 1.99 ppm (d, 6H, J = 0.5 Hz; $CH_3\times2$); ^{13}C NMR (D_2O, 100 MHz): δ = 174.57, 174.42, 173.04 (2C), 172.71, 171.68, 171.14, 99.04, 98.28, 76.42, 69.59, 69.41, 69.38, 69.03, 67.65, 55.74, 47.81, 47.10, 21.97, 21.67, 19.93, 19.85, 19.78 ppm; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{33}N_2O_{16}$: 593.1825 $[M+H]^+$; found: 593.1824.

Methyl (2-acetamido-3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (15): Compound **10** (35 mg, 0.032 mmol) was dissolved in a mixed solvent consisting of aqueous NaOH (1 M) and 1,4-dioxane (4.0 mL, 1:1) and then heated at 40 °C for 2 h. After the TLC showed the complete disappearance of **10**, the reaction mixture was quenched with hydrochloric acid to give a pH around 7 and concentrated in vacuo. After addition of DMAP (0.19 mg, 1.6 μmol), the mixture was dissolved in pyridine (2 mL). The solution was cooled to 0 °C and acetic anhydride (1.0 mL) was then added dropwise. The resulting mixture was gradually warmed to room temperature and stirred for a further 2 h. The crude product was purified by column chromatography on silica gel (MeOH/EtOAc, 1:50) to give **15** as a colorless viscous oil (27.2 mg, 80 % for two steps). R_f = 0.7 (MeOH/EtOAc, 1:10); $[\alpha]_D^{24}$ = +145.9 (c = 0.4 in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.23 (m, 15H; Ar), 6.05 (d, 1H, J = 9.2 Hz; NH), 6.02 (d, 1H, J = 9.6 Hz; NH), 5.61 (d, 1H, J = 9.6 Hz; NH), 5.56 (d, 1H, J = 2.8 Hz; H4″), 5.34 (dd, 1H, $J_{3'',4''}$ = 2.8, $J_{3'',2''}$ = 11.6 Hz; H2″), 5.23 (dd, 1H, $J_{3',4'}$ = 2.8, $J_{3',2'}$ = 11.6 Hz; H2′), 5.16 (dd, 1H, $J_{3,4}$ = 2.4, $J_{3,2}$ = 11.2 Hz; H2), 5.05 (s, 2H; H1″, H1′), 4.74 (d, 1H, $J_{1,2}$ = 3.2 Hz; H1), 4.65–4.35 (m, 12H; PhC$H_2\times6$, H2″, H2′, H2, H4′, H5″, H5′), 4.13 (d, 1H, J = 2.4 Hz; H4), 3.95 (t, 1H, J = 7.2 Hz; H5), 3.49–3.41 (m, 6H; H6a″, H6b″, H6a′, H6b′, H6a, H6b), 3.39 (s, 3H; CH_3), 2.05 (s, 3H; CH_3), 2.04 (s, 3H; CH_3), 2.00 (s, 3H; CH_3), 1.95 (s, 3H; CH_3), 1.92 (s, 3H; CH_3), 1.91 (s, 3H; CH_3), 1.86 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.47, 171.27, 170.65, 170.18, 170.13, 170.07, 169.70, 137.37, 136.89, 128.47, 128.42, 128.38, 128.09, 128.08, 127.96, 127.91, 127.78, 98.60, 97.43, 97.38, 73.61, 73.35, 73.27, 71.84, 71.48, 69.80, 69.04, 68.83, 68.37, 67.74, 67.60, 67.29, 66.75, 66.33, 55.41, 49.09, 48.54, 47.97, 23.32, 23.27, 23.22, 20.81, 20.74, 20.59, 20.45 ppm; HRMS (ESI): *m*/*z* calcd for $C_{54}H_{69}N_3O_{20}Na$: 1102.4367 $[M+Na]^+$; found: 1102.4379.

Methyl (2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-(2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosideuronate (16): Compound **15** (26 mg, 0.024 mmol) was dissolved in a mixed solvent consisting of THF, AcOH, and water (3.5 mL, 4:2:1) and then Pd/C (10 %; 26 mg) was added. The mixture was stirred under a hydrogen atmosphere. After stirring for 2 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was dissolved in a mixed solvent consisting of CCl_4, CH_3CN, and water (3.5 mL, 2:2:3), and then sodium periodate (77.2 mg, 0.36 mmol) and hydrated ruthenium trichloride (0.33 mg, 1.6 μmol) were added to the mixture. The mixture was stirred overnight and then concentrated in vacuo. The residue was subjected to C18 reverse-phase column chromatography (MeOH/H_2O, 1:12) to give **16** as a colorless foam (13.3 mg, 66 % for two steps). R_f = 0.1 (MeOH/EtOAc, 1:1); $[\alpha]_D^{24}$ = +298.0 (c = 0.4 in MeOH); ^{1}H NMR (D_2O, 500 MHz): δ = 5.79 (s, 1H; H4″), 5.42 (dd, 1H, $J_{3'',2''}$ = 12.0, $J_{3'',4''}$ = 2.5 Hz; H3″), 5.37–5.32 (m, 2H; H3′, H3), 5.22 (d, 1H, $J_{1'',2''}$ = 3.5 Hz; H1″), 5.20 (d, 1H, $J_{1',2'}$ = 3.5 Hz; H1′), 5.09 (s, 1H; H5″), 5.07 (s, 1H; H4′), 4.96 (d, 1H, $J_{1,2}$ = 3.5 Hz; H1), 4.75 (s, 2H; H5′, H5), 4.70 (d, 1H, J = 2.0 Hz; H4), 4.53 (dd, 1H, $J_{2,1}$ = 3.5, $J_{2,3}$ = 11.5 Hz; H2), 4.50 (dd, 1H, $J_{2',1'}$ = 3.5, $J_{2',3'}$ = 11.5 Hz; H2′), 4.44 (dd, 1H, $J_{2'',1''}$ = 3.5, $J_{2'',3''}$ = 11.5 Hz; H2″), 3.44 (s, 3H; CH_3), 2.16 (s, 3H; CH_3), 2.02 (s, 3H; CH_3), 2.00 (s, 9H; $CH_3\times3$), 1.97 (s, 3H; CH_3), 1.96 ppm (s, 3H; CH_3); ^{13}C NMR (D_2O, 100 MHz): δ = 174.58, 174.40, 173.00, 172.70, 172.47, 171.45, 171.29, 171.13, 99.11, 98.71, 98.27, 76.48, 75.95, 70.42, 69.61, 69.42, 69.34, 68.91, 68.60, 67.56, 55.76, 47.83, 47.43, 47.07, 21.99, 21.91, 21.66, 19.92, 19.83, 19.75 ppm; HRMS (ESI): *m*/*z* calcd for $C_{33}H_{45}N_3O_{23}Na$: 874.2336 $[M+Na]^+$; found: 874.2296.

Methyl (2-acetamido-3,4-di-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-(2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-(1→4)-2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-galactopyranoside (17): Compound **12** (46 mg, 0.032 mmol) was dissolved in a mixed solvent consisting of aqueous NaOH (1 M) and 1,4-dioxane (4.0 mL, 1:1) and then heated at 40 °C for 10 h. After the TLC showed the complete disappearance of **12**, the reaction mixture was quenched with hydrochloric acid to give a pH around 7 and concentrated in vacuo. After addition of DMAP (0.19 mg, 1.6 μmol), the mixture was dissolved in pyridine (2 mL). The solution was cooled to 0 °C and acetic anhydride (1.0 mL) was added dropwise. The resulting mixture was gradually warmed to room temperature and stirred for a further 10 h. The crude product was purified by column chromatography on silica gel (MeOH/EtOAc, 1:20) to give **17** viscous oil (32.0 mg, 70 % for two steps). R_f = 0.6 (MeOH/EtOAc, 1:10); $[\alpha]_D^{23}$ = +175.4 (c = 0.5 in MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.23 (m, 20H; Ar), 6.14 (d, 1H, J = 9.5 Hz; NH), 6.11 (d, 1H, J = 9.5 Hz; NH), 6.00 (d, 1H, J = 10.0 Hz; NH), 5.60

(d, 1H, J=9.5 Hz; NH), 5.55 (d, 1H, J=1.5 Hz; H4‴), 5.36 (dd, 1H, $J_{3''',4'''}$=2.5, $J_{3''',2'''}$=11.5 Hz; H3‴), 5.28 (dd, 1H, $J_{3'',4''}$=2.5, $J_{3'',2''}$=11.5 Hz; H3″), 5.24 (dd, 1H, $J_{3',4'}$=3.0, $J_{3',2'}$=11.5 Hz; H3′), 5.15 (dd, 1H, $J_{3,4}$=2.5, $J_{3,2}$=11.5 Hz; H3), 5.05 (d, 1H, $J_{1''',2'''}$=4.0 Hz; H1‴), 5.03 (d, 1H, $J_{1'',2''}$=3.5 Hz; H1″), 4.99 (d, 1H, $J_{1',2'}$=4.0 Hz; H1′), 4.73 (d, 1H, $J_{1,2}$=3.5 Hz; H1), 4.67–4.29 (m, 16H; PhCH_2×8, H4″, H2‴, H2″, H2′, H2, H5‴, H5″, H5′), 4.25 (d, 1H, J=2.5 Hz; H4′), 4.13 (d, 1H, J=2.5 Hz; H4), 3.95 (t, 1H, J=7.0 Hz; H5), 3.51–3.35 (m, 8H; H6a‴, H6b‴, H6a″, H6b″, H6a′, H6b′, H6a, H6b), 3.34 (s, 3H; CH_3), 2.05 (s, 3H; CH_3), 2.04 (s, 3H; CH_3), 2.00 (s, 3H; CH_3), 1.96 (s, 3H; CH_3), 1.92 (s, 3H; CH_3), 1.91 (s, 3H; CH_3), 1.88 (s, 3H; CH_3), 1.86 (s, 3H; CH_3), 1.85 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=171.47, 171.26, 171.05, 170.66, 170.37, 170.28, 170.21, 170.16, 169.86, 137.37, 137.28, 137.01, 136.86, 128.49, 128.42, 128.38, 128.12, 128.06, 127.96, 127.85, 127.79, 98.56, 97.47, 97.35, 97.11, 73.60, 73.36, 73.32, 71.71, 71.29, 71.23, 69.72, 69.37, 69.12, 69.02, 68.92, 68.86, 68.34, 67.69, 67.59, 67.32, 66.86, 66.31, 55.40, 49.03, 48.69, 48.58, 47.87, 23.24, 23.18, 23.13, 20.80, 20.72, 20.61, 20.42 ppm; HRMS (ESI): m/z calcd for $C_{71}H_{90}N_4O_{26}Na$: 1437.5736 $[M+Na]^+$; found: 1437.5745.

Methyl (2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-(2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-(2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosyluronate)-(1→4)-2-acetamido-3-*O*-acetyl-2-deoxy-α-D-galactopyranosideuronate (18): Compound **17** (19.1 mg, 0.013 mmol) was dissolved in a mixed solvent consisting of THF, AcOH, and water (3.5 mL, 4:2:1) and then Pd/C (10%; 19.1 mg) was added. The mixture was stirred under a hydrogen atmosphere. After stirring for 5 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was dissolved in a mixed solvent consisting of CCl_4, CH_3CN, and water (3.5 mL, 2:2:3), and then sodium periodate (57.6 mg, 0.27 mmol) and hydrated ruthenium trichloride (0.25 mg, 1.2 μmol) were added to the mixture. The mixture was stirred overnight and then concentrated in vacuo. The residue was subjected to C18 reverse-phase column chromatography (MeOH/H_2O, 1:12) to give **18** as a colorless foam (10.0 mg, 67% for two steps). R_f=0.1 (MeOH/EtOAc, 1:1.5); $[\alpha]_D^{23}$=+192.3 (c=0.3 in MeOH); ^{1}H NMR (D_2O, 400 MHz): δ=5.78 (dd, 1H, $J_{4',5'}$=1.6, $J_{4',3'}$=1.6 Hz; H4‴), 5.43 (dd, 1H, $J_{3,2}$=11.6, $J_{3,4}$=2.8 Hz; H3), 5.40–5.32 (m, 3H; H3′, H3″, H3‴), 5.21 (d, 1H, $J_{1',2'}$=4.0 Hz; H1′), 5.20 (d, 1H, $J_{1'',2''}$=3.6 Hz; H1″), 5.18 (d, 1H, $J_{1''',2'''}$=3.6 Hz; H1‴), 5.04 (s, 2H; H5‴, H5″), 4.99 (s, 1H; H5′), 4.96 (d, 1H, $J_{1,2}$=3.6 Hz; H1), 4.73–4.72 (m, 2H; H4″, H4′), 4.69 (d, 1H, J=2.4 Hz; H4), 4.55–4.48 (m, 3H; H2, H2′, H2″), 4.43 (dd, 1H, $J_{2''',3'''}$=11.6, $J_{2''',1'''}$=3.6 Hz; H2‴), 3.43 (s, 3H; CH_3), 2.15 (s, 3H; CH_3), 2.01–1.97 ppm (m, 24H; CH_3×8); ^{13}C NMR (D_2O, 125 MHz): δ=175.37, 175.19, 173.82, 173.53, 173.35, 172.60, 172.36, 172.22, 172.09, 99.92, 99.52 (2C), 99.05, 77.28, 76.78, 71.42, 70.50, 70.21, 69.85, 69.52, 69.46, 68.53, 56.51, 48.63, 48.27, 48.20, 47.87, 22.80, 22.74, 22.70, 22.44, 20.71, 20.64, 20.57 ppm; HRMS (ESI): m/z calcd for $C_{43}H_{58}N_4O_{30}Na$: 1133.3028 $[M+Na]^+$; found: 1133.3038.

Antibody-binding analyses: The investigation into the ability of the synthetic oligosaccharides to inhibit binding of the antibody to its native polysaccharide was performed by use of the enzyme-linked immunosorbent assay (ELISA). Briefly, high-binding flat-bottom 96-well EIA/RIA plates (corning-costar, NY14831) were coated with 100 μL of Vi PS (Vi polysaccharide vaccine, lot: 20100101, CDC, Beijing, China) per well at a concentration of 0.5 μg mL^{-1} in CBC coating buffer (Na_2CO_3 (15 mM) and $NaHCO_3$ (35 mM); pH 9.6). After incubation at 4°C overnight, the plates were washed three times with PBS (200 μL per well). After addition of blocking solution (PBS, 3% BSA; 200 μL per well), the plates were incubated for 1 h at 37°C. Vi PS, compounds **14**, **16**, and **18** were diluted with the diluent buffer (PBS, 1% BSA) to a series of concentrations (0–10 μg mL^{-1} for Vi PS; 0–500 μg mL^{-1} for the synthetic saccharides). The anti-Vi serum (serum of rabbit immunized by the Vi PS vaccine, Institute of Biological Products, Lanzhou, China) was diluted 250 fold in the diluent buffer. The plates were then washed three times with PBS after incubation. The serial concentrations of Vi PS, **14**, **16**, and **18** were mixed with anti-Vi serum separately (50 μL+50 μL per well) before being added to the coated plates, which were then incubated for 1 h at 37°C. The plates were washed three times with PBS and a secondary antibody labeled with horseradish peroxidase (100 μL per well; goat-anti-rabbit LgG-HRP, Santa cruz) diluted 5000 fold in diluent buffer was added. The plates were incubated for 1 h at 37°C. After three washes with PBS, the reaction was developed with *O*-phenylenediamine (OPD; 100 μL per well) in the dark for 15 min and stopped with H_2SO_4 (2 M; 100 μL per well). Optical density (OD) values were measured at 490 nm with an ELISA plate reader (TECAN, sunrise). The control consisted of Vi PS coated wells incubated without the inhibitors (serum (50 μL)+diluent buffer (50 μL)) and had the maximum optical density (ODm). The percentage inhibition was calculated by using the equation: X%=100%×(ODm−ODx)/(ODm−ODo). ODo is the optical density of blank wells. Every concentration was tested in triplicate. The data were reported as the mean ±SD of the measurements performed in triplicate.

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