Synthesis of the Trisaccharide and Tetrasaccharide Moieties of the Potent Immunoadjuvant QS-21

Xiangming Zhu,*[a,b] Biao Yu,[a] Yongzheng Hui,[a] and Richard R. Schmidt[b]

Keywords: Carbohydrates / Glycosylation / Glycosides / Immunostimulants / Saponin / Trichloroacetimidates

The title trisaccharide and tetrasaccharide moieties have been synthesized as part of our research programme to construct the complex triterpenoid saponin QS-21, a potent immunoadjuvant, which has been used in a series of clinical immunization trials. In view of the unwillingness of glucuronic acid as glycosyl acceptor, the branched glucuronic acid-containing trisaccharide **20** was synthesized from D-glucose, which was in turn glycosylated at positions 2 and 3, followed by oxidation at position 6, in a linear sequence of 15 steps and in good overall yield. The apiose-containing tetrasaccharide **36** was constructed by a linear glycosylation strategy from the non-reducing terminal sugar, D-apiose, which was prepared from D-xylose by a known procedure, also in a linear sequence of 15 steps.

Introduction

QS-21,[1,2] an acylated bidesmosidic triterpenoid saponin isolated from *Quillaja saponaria* Molina (Rosaceae), is a potent immunoadjuvant that has been shown to enhance both humoral and cell-mediated immune responses in a host of vaccine formation assays.[3] A number of clinical trials with QS-21 as an adjuvant have been performed, initially for cancer vaccines (melanoma, breast and prostate) and subsequently for infectious diseases (HIV-1, influenza, herpes, malaria and hepatitis B).[4] It appears optimally effective as an adjuvant for vaccines against pathogens that require a potent cytotoxic T-lymphocyte response as an important component of protective immunity. More than 1600 volunteers have been immunized with vaccines containing QS-21, the most common side effect being pain/tenderness at the injection site, which is dose-related and usually of short duration.[4,5]

Structurally, QS-21 consists of a triterpene (quillaic acid) with two attached sugar chains (one branched trisaccharide and one unbranched tetrasaccharide) and a dimeric fatty acyl group joined to the reducing terminal sugar of the tetrasaccharide,[2] as shown in Figure 1. Attracted by its amazing structure and promising bioactivities, we carried out synthetic studies relating to the acylated triterpenoid saponin after having accomplished the determination of the absolute stereochemistry within the acyl moiety of quillaja saponins.[6,7] Here we present the synthesis of the trisaccharide[8] and tetrasaccharide moieties of the natural product.

[a] State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China
[b] Fachbereich Chemie, Universität Konstanz, Fach M 725, 78457 Konstanz, Germany
Fax: (internat.) +49-7531-883135
E-mail: Richard.Schmidt@uni-konstanz.de

Results and Discussion

The trisaccharide moiety of QS-21 is composed of a β-D-glucuronic acid residue connected at position 2 with a β-D-galactose residue and at position 3 with a β-D-xylose residue. The presence of a β-D-glucuronic acid residue linked to another sugar in position 2 is common in a large variety of natural products, especially saponins.[9] It is well documented that glycosylation of glucuronic acid derivatives usually gives low product yields due to the electron-withdrawing 5-carboxyl group,[10] which decreases the nucleophilicity of the hydroxy groups on glucuronide acceptors remarkably. In view of this, an indirect but more conventional strategy was applied to the synthesis of the trisaccharide fragment in question, the desired glucuronide being prepared by introduction of the carboxyl group after coupling with a glucopyranoside moiety.[11]

To carry out the synthetic scheme, glucoside **1** (All = Allyl) was prepared in 57% yield from D-glucose by a known procedure[12] and then selectively acylated with pivaloyl chloride to give the desired 2-pivaloylated glucoside **2**[13] in 58% yield (Scheme 1). Silylation of **2** with *tert*-butyldimethylsilyl chloride (TBS-Cl) followed by deacylation with DIBAL-H smoothly provided an almost quantitative yield of the sugar alcohol **4**,[14] a potential glycosyl acceptor in the subsequent glycosidation reaction. Unexpectedly, however, the glycosylation of **4** with galactosyl trichloroacetimidate **5**[15] in the presence of catalytic amounts of $BF_3{\cdot}OEt_2$ gave the ortho ester **6** in 83% yield. A variety of attempts to avoid this unwanted side reaction, including the

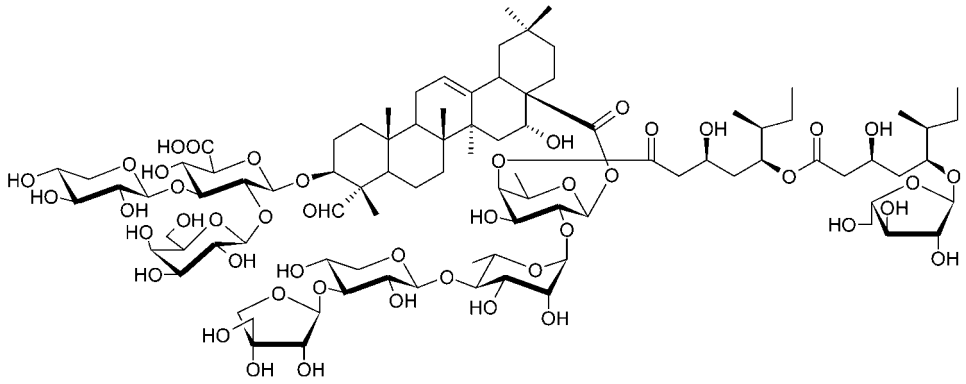
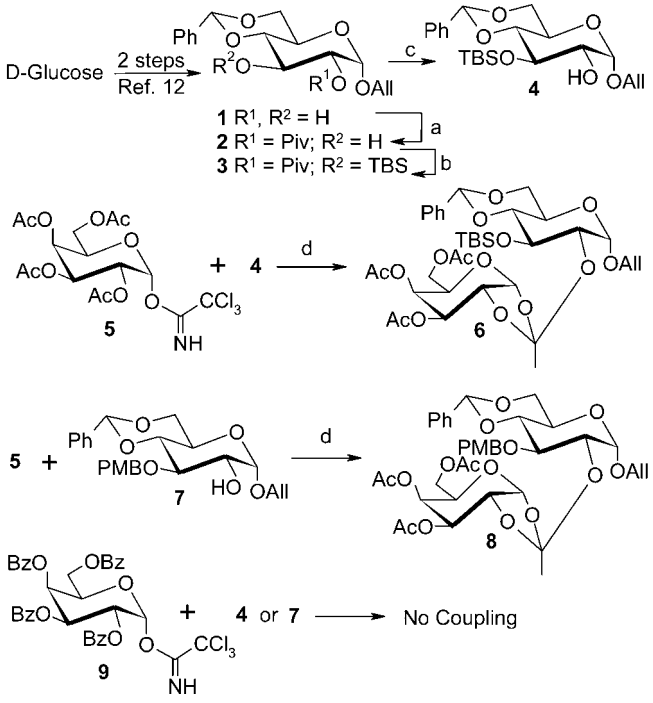
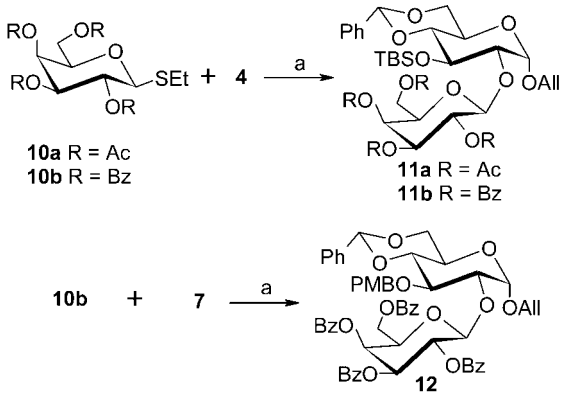


Figure 1. Molecular Structure of QS-21



Scheme 1. Formation of ortho esters **6** and **8**; reagents and conditions: (a) PivCl, Py, 0 °C, 58%; (b) TBSCl, imidazole, DMAP, DMF, 99%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 98%; (d) $BF_3{\cdot}Et_2O$ (cat.), 4 Å molecular sieves, CH_2Cl_2, −50 °C, **6** (83%); **8** (92%)

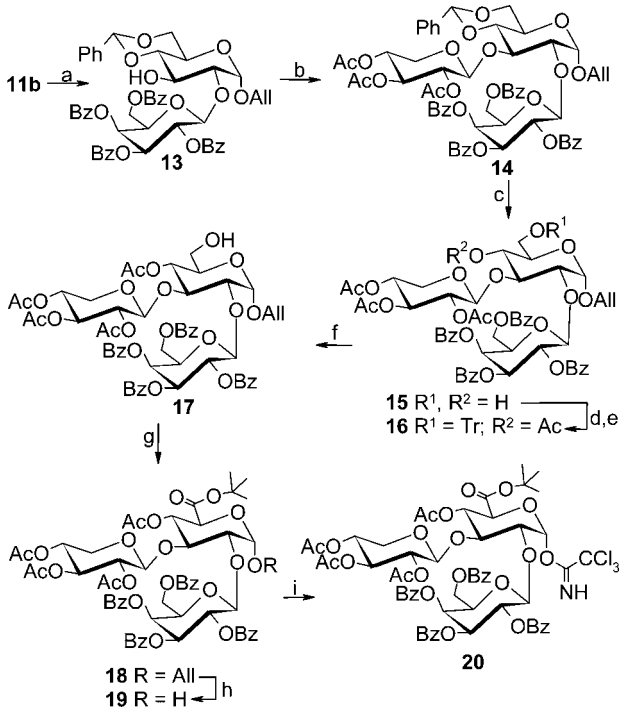


Scheme 2. Synthesis of Gal(1 → 2)Glc disaccharides; reagents and conditions: (a) NIS, AgOTf, 4 Å molecular sieves, CH_2Cl_2, −20 °C, **11a** (70%); **11b** (97%); **12** (quant.)

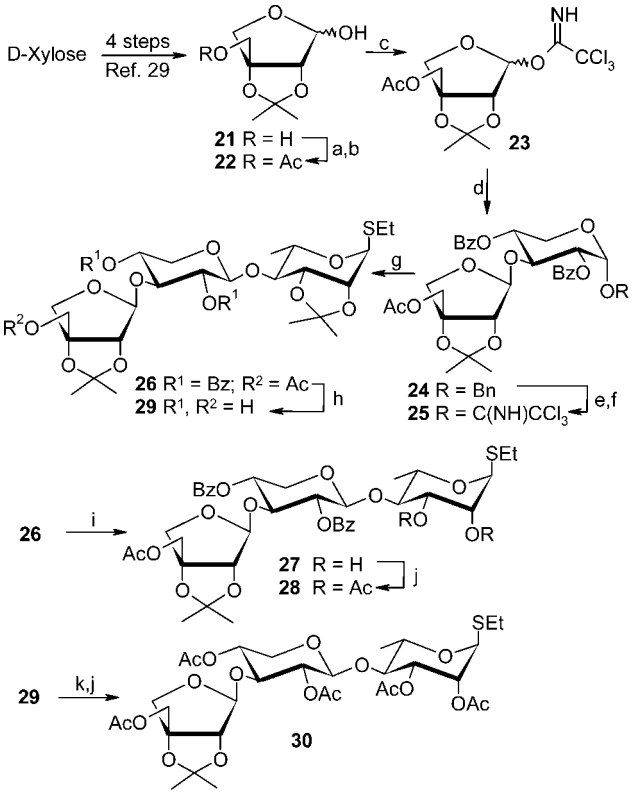
inverse procedure,[16] were unsuccessful, and surprisingly, ortho ester **6** was readily formed under a variety of conditions.[17] Even TfOH-promoted (TfOH = triflic acid) coupling between **4** and **5** also gave the ortho ester **6** in almost quantitative yield. A change of neighbouring group in the acceptor from TBS to PMB also did not bring about the expected product, and similarly, ortho ester **8** was produced in 92% yield by glycosylation of **7**[18] with **5**. To reduce the risk of ortho ester formation, per-benzoylated galactosyl imidate **9**[14] was prepared and treated with **4** or **7**, as shown in Scheme 1. No coupling took place under the normal Schmidt glycosidation conditions, however.[19,20]

The above failure was attributed to steric hindrance of the acceptors. From our experience in carbohydrate synthesis, we anticipated that the use of thioglycosides[21] instead of imidates as glycosyl donors should favour the production of the desired products, so the thioglycosides **10a**[22] and **10b**[23] were prepared and coupled with the above glucosyl acceptors **4** and **7**, as shown in Scheme 2. As anticipated, glycosylation of **4** with thioglycoside **10a** with promotion by NIS/AgOTf[24] smoothly generated the desired disaccharide **11a** in high yield (70%). Similarly, coupling of sugar alcohols **4** and **7** with thioglycoside **10b** also gave the corresponding desired disaccharides **11b** and **12**, both in almost quantitative yields.

The ready formation of disaccharides **11** and **12** was in sharp contrast with the above Schmidt glycosylation reactions. The precise mechanistic details underlying the different behaviour observed for trichloroacetimidate and thioglycoside donors are not yet clear. With the disaccharide **11b** to hand, the synthetic scheme was then continued as shown in Scheme 3. Desilylation of **11b** with HF−Py[25] furnished the sugar alcohol **13** in 83% yield, and this was further glycosylated with peracetyl thioxyloside[26] in the presence of NIS/AgOTf to afford the desired 2,3-branched trisaccharide **14**, smoothly and in almost quantitative yield. Treatment of **14** with 80% HOAc gave the diol **15**, which was selectively tritylated and subsequently acetylated to produce sugar **16**. This was then subjected to detritylation, as shown in Scheme 3, to give sugar **17**, with one free hydroxy group at position 6 of the glucose residue. The conversion of glucoside **17** into the corresponding glucuronide **18** was effected



Scheme 3. Synthesis of trisaccharide imidate **20**; reagents and conditions: (a) HF/Py, 83%; (b) 1.2 equiv. donor, NIS, AgOTf, 4 Å molecular sieves, CH_2Cl_2, −20 °C, quant.; (c) 80% HOAc, 70 °C, 77%; (d) TrCl, Py, 80 °C; (e) Ac_2O, Py, room temp., 92% (2 steps); (f) 80% HOAc, 50 °C, 61%; (g) PDC, *t*BuOH, Ac_2O, CH_2Cl_2, 90%; (h) $[Pd(PPh_3)_4]$, HOAc, 80 °C, 98%; (i) CCl_3CN, DBU, CH_2Cl_2, 86%



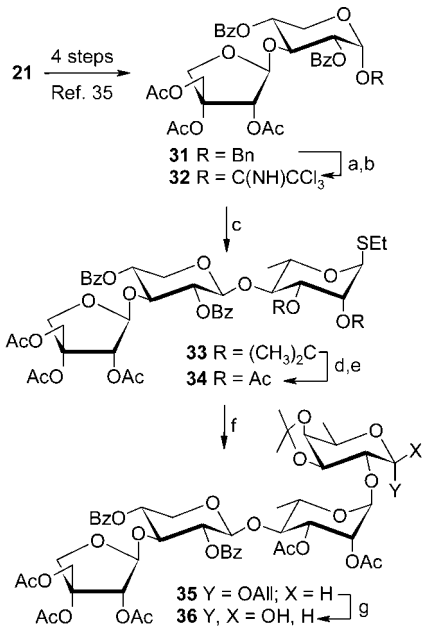
Scheme 4. Synthesis of trisaccharide intermediate **26**; reagents and conditions: (a) Ac_2O, Py, 82%; (b) NH_3/THF/MeOH, 0 °C, 49%; (c) CCl_3CN, DBU, CH_2Cl_2, 98%; (d) 1.1 equiv. acceptor, 0.3 equiv. TMSOTf, 4 Å molecular sieves, CH_2Cl_2, −4 °C, 72%; (e) H_2, 10% Pd/C, 1 atm, room temp.; (f) CCl_3CN, DBU, CH_2Cl_2, 89% (2 steps); (g) 1.1 equiv. acceptor, 0.2 equiv. TMSOTf, 4 Å molecular sieves, CH_2Cl_2, −50 °C, 95%; (h) NaOMe, MeOH, 68%; (i) various conditions, see: Ref.[34]; (j) Ac_2O, Py, quant.; (k) Dowex 50 W (H^+); for other conditions, see ref.[34]

by PDC oxidation[27] in the presence of *t*BuOH, and **18** was produced in excellent yield (90%). Subsequently, treatment of **18** with catalytic amounts of $[Pd(PPh_3)_4]$[28] in the presence of HOAc produced the desired hemiacetal **19** in almost quantitative yield, and this was smoothly further converted into the trichloroacetimidate **20** in 86% yield. The trisaccharide portion of QS-21 was thus furnished and ready for its total synthesis.

In view of the linear structure of the tetrasaccharide moiety of QS-21, we planned to construct it by a linear glycosylation strategy, by extending the sugar chain one by one from the non-reducing terminal sugar. In practice, the branched sugar 2,3-*O*-isopropylidene-D-apiofuranose **21** was firstly prepared from D-xylose in 21% overall yield by a literature procedure[29] and was subjected to acetylation,[30,31] followed by selective deacetylation to afford a 40% overall yield of the desired hemiacetal **22**, which was subsequently converted into apiosyl donor **23** by addition of CCl_3CN. Under Schmidt glycosidation conditions,[20] trichloroacetimidate **23** was coupled with pre-prepared xylosyl acceptor[32] to give the desired disaccharide **24** in 72% yield, and this was then converted into the corresponding imidate **25** in two steps by hydrogenation with H_2 followed by imidation with CCl_3CN. Coupling of sugar **25** with the pre-prepared rhamnosyl acceptor,[33] as shown in Scheme 4, was performed in the presence of TMSOTf, affording the desired di-*O*-isopropylidenated trisaccharide **26** in excellent yield (95%).

To our surprise, however, the subsequent removal of the two isopropylidene groups from **26** failed under various conditions.[34] Under most conditions only compound **27** was produced, which could be converted to trisaccharide **28** by acetylation. The *O*-deisopropylidenation was also conducted on compound **24**, but this also failed. Harsher conditions were also applied to the deacylated compound **29** to cleave the isopropylidene groups, but only sugar **30** was provided after acetylation, as a result of the extraordinary stability of the isopropylidene group at the apiose residue.

The synthetic route therefore had to be modified as shown in Scheme 5, and the cleavage of isopropylidene from apiose was carried out at an earlier stage in this scheme. Disaccharide **31** was prepared by use of the fully acetylated apiosyl donor as described previously,[35] and converted into trichloroacetimidate **32** by hydrogenation with H_2, followed by treatment with CCl_3CN. Compound **32** was then coupled with the same rhamnosyl acceptor as used above under Schmidt conditions to give the desired trisaccharide **33**, which was treated with 80% HOAc and subsequently acetylated to afford thioglycoside **34**. Glycosylation of the fourth sugar residue, allyl 3,4-*O*-isopropylidene-α-D-fucopyranoside as acceptor,[36] with sugar **34** as glycosyl donor was performed in the presence of NIS/AgOTf, giving the



Scheme 5. Synthesis of tetrasaccharide **36**; reagents and conditions: (a) H_2, 10% Pd/C, 50 atm, 40 °C; (b) CCl_3CN, DBU, CH_2Cl_2, 33% (2 steps); (c) 1.3 equiv. acceptor, 0.2 equiv. TMSOTf, 4 Å molecular sieves, CH_2Cl_2, 88%; (d) 80% HOAc, 50 °C; (e) Ac_2O, Py, 76% (2 steps); (f) 1.2 equiv. acceptor, NIS, AgOTf, 4 Å molecular sieves, CH_2Cl_2, 91%; (g) $I(CF_2)_8F$, $Na_2S_2O_4$, $NaHCO_3$, CH_3CN/H_2O, then Zn/NH_4Cl, EtOH, reflux, 57%

tetrasaccharide **35** in 91% yield; chemoselective removal of the 3a,4a-*O*-isopropylidene group should now enable the attachment of the acyl side chain which is part of QS-21. Compound **35** was further subjected to deallylation conditions[37] to afford the sugar **36** in reasonable yield (57%), ready for the transformation into a glycosyl donor.

In summary, the synthesis of the trisaccharide and tetrasaccharide moieties of the potent immunoadjuvant QS-21 is reported. The trisaccharide portion, the glucuronic acid-containing sugar **20**, was constructed starting from D-glucose in a linear sequence in good overall yield. The tetrasaccharide portion, the apiose-containing sugar **36**, was synthesized starting from D-xylose in a linear sequence of 15 steps. Further work towards the completion of the synthesis of QS-21 is in progress.[38]

Experimental Section

General Remarks: Solvents were distilled from the appropriate drying agents before use. Unless otherwise stated, all reactions were performed in oven-dried glassware under an argon atmosphere in dry solvents and monitored by TLC on silica gel HF_{254} (0.5 mm, Qingdao, China). Spots were viewed by UV light or by treatment with 10% H_2SO_4 in methanol followed by heating. Flash chromatography was performed with the indicated solvent system on silica gel H (400 mesh, Qingdao, China). Optical rotations were measured with a Perkin−Elmer 241 MC polarimeter. NMR spectra were recorded with Bruker AM 300 or Inova 600 spectrometers in $CDCl_3$ as solvent and with tetramethylsilane as an internal reference. Mass spectra were recorded with HP5989A or VG Quattro mass spectrometers. Elemental analyses were performed with a Perkin−Elmer Model 2400 instrument. Yields refer to chromatographically pure compounds and are calculated on the basis of reagents consumed.

Ortho Ester 6: Freshly activated powdered molecular sieves (4 Å, ≈ 1 g) were added to a solution of donor **5** (1.64 g, 3.32 mmol) and acceptor **4** (1.23 g, 2.91 mmol) in CH_2Cl_2 (15 mL) under Ar and the mixture was stirred at room temperature for 30 min, after which it was cooled to −50 °C and boron trifluoride etherate (10 mg/mL in CH_2Cl_2, 2.4 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. Et_3N was added to quench the reaction, and the mixture was filtered through a pad of Celite and concentrated to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 7:1 → 5:1) to afford the title compound **6** (1.8 g, 83%) as a white foam: $[\alpha]_D^{21}$ = +56.6 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.06 (s, 3 H), 0.82 (s, 9 H), 1.70 (s, 3 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 3.43 (t, *J* = 9.5 Hz, 1 H), 3.58 (dd, *J* = 8.8, 3.6 Hz, 1 H), 3.69 (t, *J* = 10.2 Hz, 1 H), 3.82 (m, 1 H), 3.98−4.34 (m, 8 H), 5.02 (m, 2 H), 5.19−5.36 (m, 2 H), 5.42 (t, *J* = 2.6 Hz, 1 H), 5.48 (s, 1 H), 5.77 (d, *J* = 4.7 Hz, 1 H), 5.94 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.1, 169.8, 137.3, 133.1, 128.9, 128.1, 126.2, 121.8, 118.1, 101.9, 98.0, 97.2, 82.6, 75.0, 73.7, 71.3, 70.0, 69.0, 68.8, 68.6, 65.9, 62.2, 61.2, 25.8, 23.9, 25.6, 20.8, 20.7, 20.6, 18.3, −4.2, −4.6 ppm. ESI MS: *m*/*z* = 776 [M + Na^+], 792 [M + K^+]. $C_{36}H_{52}O_{15}Si$ (752.9): calcd. C 57.43, H 6.96; found C 57.43, H 7.00.

Ortho Ester 8: The coupling of donor **5** (124 mg, 0.25 mmol) and acceptor **7** (98 mg, 0.23 mmol) was performed in the same way as described for **6** to give ortho ester **8** (160 mg, 92%) as a white foam: $[\alpha]_D^{21}$ = +46.9 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 3 H), 2.06 (s, 6 H), 2.09 (s, 3 H), 3.78 (s, 3 H), 3.97−3.58 (m, 1 H), 4.31−4.01 (m, 8 H), 4.72 (AB peak, *J* = 12.6 Hz, 2 H), 4.98 (d, *J* = 3.6 Hz, 1 H), 5.03 (dd, *J* = 9.6, 3.4 Hz, 1 H), 5.22−5.38 (m, 2 H), 5.41 (t, *J* = 2.7 Hz, 1 H), 5.55 (s, 1 H), 5.77 (d, *J* = 4.9 Hz, 1 H), 5.95 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 170.0, 169.8, 159.1, 137.3, 133.5, 130.7, 129.7, 128.9, 128.2, 126.0, 121.3, 118.3, 113.6, 101.2, 97.8, 97.5, 82.2, 75.1, 73.9, 73.4, 71.1, 69.0, 68.6, 65.8, 62.4, 61.3, 55.2, 23.9, 20.7, 20.5 ppm. EI MS: *m*/*z* = 427, 331, 121. $C_{38}H_{46}O_{16}\cdot 0.5H_2O$ (767.8): calcd. C 59.45, H 6.17; found C 59.57, H 6.13.

Allyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranoside (11a): A mixture of thioglycoside **10a** (75 mg, 0.19 mmol), sugar alcohol **4** (67 mg, 0.16 mmol) and powdered molecular sieves (4 Å, 60 mg) in CH_2Cl_2 (3 mL) was stirred at room temperature under Ar for 30 min and then cooled to −20 °C. NIS (54 mg, 0.24 mmol) was added to this mixture, followed by the addition of a solution of AgOTf (20 mg, 0.078 mmol) in toluene (0.2 mL). The reaction mixture was allowed to warm slowly and stirred for 15 min after initiation, and then quenched with Et_3N. The suspension was diluted with EtOAc and filtered through a pad of Celite, and the filtrate was washed successively with 10% $Na_2S_2O_3$ and water. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give **11a** (83 mg, 70%) as a white foam: $[\alpha]_D^{20}$ = +28.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.04 (s, 3 H), 0.04 (s, 3 H), 0.71 (s, 9 H), 1.97 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.17 (s, 3 H), 3.38 (t, *J* = 9.3 Hz, 1 H), 3.68 (t, *J* = 10.1 Hz, 1 H), 3.70 (dd, *J* = 9.1, 3.6 Hz, 1 H), 3.89 (m, 2 H), 4.04−4.20 (m, 5 H), 4.24 (dd, *J* = 10.2, 4.9 Hz, 1 H), 4.84 (d, *J* = 7.9 Hz, 1 H), 4.93 (d, *J* = 3.6 Hz, 1 H), 4.97 (dd, *J* = 10.4, 3.4 Hz, 1 H), 5.22 (m, 1 H), 5.24 (t, *J* = 10.5 Hz, 1 H),

5.35−5.42 (m, 2 H), 5.45 (s, 1 H), 5.95 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.2, 170.1, 169.2, 137.2, 134.1, 129.1, 128.1, 126.5, 117.1, 102.4, 101.0, 98.8, 82.8, 78.7, 71.3, 71.2, 70.8, 69.4, 69.2, 68.9, 67.1, 62.2, 61.1, 26.0, 21.1, 20.6, 20.5, 18.2, −4.2, −4.3 ppm. ESI MS: *m*/*z* = 776 [M + Na^+], 1529 [2M + Na^+]. $C_{36}H_{52}O_{15}Si$ (752.9): calcd. C 57.43, H 6.96; found C 57.02, H 6.99.

Allyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranoside (11b): A mixture of donor **10b** (0.81 g, 1.26 mmol), acceptor **4** (0.44 g, 1.04 mmol) and powdered molecular sieves (4 Å, 0.4 g) in CH_2Cl_2 (15 mL) was stirred at room temperature under Ar for 30 min and then cooled to −15 °C. NIS (0.35 g, 1.56 mmol) was added to this mixture, followed by addition of a solution of AgOTf (134 mg, 0.52 mmol) in toluene (1.0 mL). The reaction mixture was allowed to warm to room temperature and stirred for 30 min, and then quenched with Et_3N. The suspension was diluted with EtOAc and filtered through a pad of Celite, and the filtrate was washed successively with 10% $Na_2S_2O_3$ and water. The organic layer was dried with $MgSO_4$, and concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 6:1 → 5:1) to give **11b** (1.01 g, 97%) as a white foam: $[\alpha]_D^{21}$ = +83.2 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (t, *J* = 9.6 Hz, 1 H), 3.64 (t, *J* = 10.2 Hz, 1 H), 3.78 (dd, *J* = 9.1, 3.7 Hz, 1 H), 3.88 (m, 1 H), 4.07−4.33 (m, 5 H), 4.44 (dd, *J* = 11.3, 6.0 Hz, 1 H), 4.64 (dd, *J* = 11.3, 7.0 Hz, 1 H), 5.13 (d, *J* = 3.7 Hz, 1 H), 5.18 (d, *J* = 7.9 Hz, 1 H), 5.22−5.27 (m, 1 H), 5.41 (s, 1 H), 5.42−5.50 (m, 1 H), 5.57 (dd, *J* = 10.4, 3.4 Hz, 1 H), 5.90 (dd, *J* = 10.4, 7.8 Hz, 1 H), 5.96 (d, *J* = 2.5 Hz, 1 H), 6.04 (m, 1 H), 7.15−8.10 (m, 25 H) ppm. ^{13}C NMR (75 MHz,$CDCl_3$): δ = 166.0, 165.6, 165.5, 165.4, 137.2, 134.1, 133.8, 133.6, 133.3, 133.2, 133.1, 130.3, 130.0, 129.9, 129.7, 129.6, 129.5, 129.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.8, 126.5, 117.2, 102.3, 101.4, 99.0, 82.8, 79.3, 72.1, 71.6, 71.0, 70.4, 69.2, 68.9, 68.3, 62.2, 62.0, 25.9, 18.1, −4.2, −4.4 ppm. ESI MS: *m*/*z* = 1023 [M + Na^+], 1047 [M + 1 + $2Na^+$]. $C_{56}H_{60}O_{15}Si{\cdot}2H_2O$ (1037.2): calcd. C 64.85, H 6.22; found C 64.85, H 5.72.

Allyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-*para*-methoxylbenzyl-α-D-glucopyranoside (12): The coupling of donor **10b** (51 mg, 79.6 μmol) and acceptor **7** (30 mg, 70 μmol) was performed in the same way as described for **11b** to give ortho ester **12** (77 mg, 100%) as a white foam: $[\alpha]_D^{21}$ = +79.0 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.37, 4.50 (AB peak, *J* = 12.6 Hz, 2 H), 4.61 (dd, 1 H), 5.16 (d, *J* = 3.6 Hz, 1 H), 5.20 (d, *J* = 8.2 Hz, 1 H), 5.21−5.25 (m, 1 H), 5.40−5.47 (m, 1 H), 5.50 (s, 1 H), 5.60 (dd, *J* = 10.4, 3.3 Hz, 1 H), 5.98 (m, 3 H), 6.68, 6.93 (AB peak, *J* = 8.5 Hz, 2 H), 7.20−7.67 (m, 17 H), 7.78−8.12 (4d, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 165.6, 165.5, 165.1, 159.0, 137.4, 133.9, 133.6, 133.3, 133.1, 130.6, 130.0, 129.8, 129.7, 129.4, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 126.1, 117.34, 117.25, 114.0, 113.5, 102.4, 101.4, 98.7, 82.2, 80.4, 74.5, 72.0, 71.4, 70.0, 69.1, 68.9, 68.2, 62.4, 62.1, 55.2 ppm. ESI MS: *m*/*z* = 1029 [M + Na^+], 1052 [M + $2Na^+$]. $C_{58}H_{54}O_{16}{\cdot}0.5H_2O$ (1016.1): calcd. C 68.56, H 5.46; found C 68.23, H 5.38.

Allyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→2)-4,6-*O*-benzylidene-α-D-glucopyranoside (13): Disaccharide **11b** (1.02 g, 1.02 mmol) was dissolved in dry Py (4 mL) and cooled to 0 °C under Ar. HF in Py (70%, 2 mL) was added dropwise. The mixture was stirred at room temperature overnight, and then neutralized with aqueous $NaHCO_3$, diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give a residue that was purified by flash column chromatography (petroleum ether/EtOAc, 3:1) to afford the title compound **13** (751 mg, 83%) as a white foam: $[\alpha]_D^{28}$ = +99.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (t, *J* = 9.8 Hz, 1 H), 3.71 (m, 2 H), 3.88 (m, 1 H), 3.99−4.37 (m, 5 H), 4.48 (dd, *J* = 11.4, 5.9 Hz, 1 H), 4.56 (dd, *J* = 11.5, 7.1 Hz, 1 H), 5.05 (d, *J* = 3.6 Hz, 1 H), 5.17−5.22 (d, *J* = 7.9 Hz, 2 H), 5.32−5.39 (m, 1 H), 5.50 (s, 1 H), 5.60 (dd, *J* = 10.5, 3.4 Hz, 1 H), 5.85 (dd, *J* = 10.6, 7.9 Hz, 1 H), 5.94 (m, 1 H), 5.98 (d, *J* = 3.0 Hz, 1 H), 7.20−8.10 (m, 25 H) ppm. EI MS: *m*/*z* = 579, 334, 105, 57. $C_{50}H_{46}O_{15}{\cdot}H_2O$ (904.9): calcd. C 66.37, H 5.35; found C 65.94, H 5.13.

Allyl 4,6-*O*-Benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranoside (14): Ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside[26] (22 mg, 68.7 μmol) and acceptor **13** (52 mg, 58.6 μmol) were dissolved in CH_2Cl_2 (1.5 mL) containing activated powdered molecular sieves (4 Å, 30 mg) under Ar. The mixture was stirred at room temperature for 30 min and then cooled to −20 °C. NIS (19 mg, 84 μmol) was added, followed by a solution of AgOTf (7 mg) in dry toluene (0.2 mL). The cooling bath was removed and the suspension was allowed to warm to room temperature with stirring for around 30 min, after which the reaction was quenched with Et_3N and the mixture was filtered through Celite. The filtrate was diluted with EtOAc, washed successively with 10% $Na_2S_2O_3$ and cold water, and then dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:1 → 2:1) to give the trisaccharide **14** (67 mg, quant.) as a white foam: $[\alpha]_D^{22}$ = +43.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 6 H), 2.11 (s, 3 H), 2.82 (dd, *J* = 12.1, 6.9 Hz, 1 H), 3.46 (t, *J* = 9.5 Hz, 1 H), 3.67 (t, *J* = 10.3 Hz, 1 H), 3.87 (m, 1 H), 3.91 (dd, *J* = 9.5, 3.8 Hz, 1 H), 3.97 (dd, *J* = 12.4, 4.9 Hz, 1 H), 4.12 (m, 1 H), 4.19−4.34 (m, 4 H), 4.42 (dd, *J* = 11.2, 6.3 Hz, 1 H), 4.63 (dd, *J* = 11.0, 6.5 Hz, 1 H), 4.75 (m, 1 H), 4.85 (m, 3 H), 5.03 (d, *J* = 3.8 Hz, 1 H), 5.10 (d, *J* = 7.9 Hz, 1 H), 5.21−5.26 (m, 1 H), 5.41−5.47 (m, 1 H), 5.46 (s, 1 H), 5.63 (dd, *J* = 10.5, 3.5 Hz, 1 H), 5.85 (dd, *J* = 10.5, 7.9 Hz, 1 H), 5.98 (d, *J* = 2.8 Hz, 1 H), 5.90−6.02 (m, 1 H), 7.20−8.11 (m, 25 H) ppm. ESI MS: *m*/*z* = 1168 [M + 1 + Na^+], 1191 [M + 1 + $2Na^+$]. $C_{61}H_{60}O_{22}{\cdot}H_2O$ (1163.1): calcd. C 62.99, H 5.37; found C 62.90, H 5.23.

Allyl 2-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranoside (15): A solution of trisaccharide **14** (145 mg, 0.13 mmol) in HOAc (80%, 4 mL) was stirred at 70 °C overnight, and then concentrated in vacuo to give a residue, which was azeotroped three times with toluene and purified by flash column chromatography (petroleum ether/EtOAc, 2:1) to afford the title compound **15** (103 mg, 77%) as a white foam: $[\alpha]_D^{18}$ = +62.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 2.01 (s, 3 H), 2.26 (s, 3 H), 2.60 (t, *J* = 10.2 Hz, 1 H), 3.40 (t, *J* = 8.9 Hz, 1 H), 3.67−3.74 (m, 3 H), 3.79−3.96 (m, 3 H), 4.14 (m, 1 H), 4.20−4.31 (m, 3 H), 4.41 (dd, *J* = 11.4, 6.3 Hz, 1 H), 4.63 (dd, *J* = 11.4, 7.0 Hz, 1 H), 4.77 (t, *J* = 8.9 Hz, 1 H), 4.82 (m, 1 H), 4.88 (d, *J* = 8.0 Hz, 1 H), 4.92 (d, *J* = 7.8 Hz, 1 H), 5.02 (d, *J* = 3.6 Hz, 1 H), 5.26−5.31 (m, 1 H), 5.50−5.57 (m, 1 H), 5.56 (dd, *J* = 10.5, 3.4 Hz, 1 H), 5.90 (dd, *J* = 10.6, 7.9 Hz, 1 H), 5.96 (d, *J* = 2.8 Hz, 1 H), 5.96−6.07 (m, 1 H), 7.20−8.11 (m, 20 H) ppm. ESI MS: *m*/*z* = 1079 [M + Na^+], 1102 [M + $2Na^+$]. $C_{54}H_{56}O_{22}{\cdot}H_2O$ (1075.0): calcd. C 60.02, H 5.19; found C 60.33, H 5.44.

Allyl 4-*O*-Acetyl-6-*O*-triphenylmethyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-

D-glucopyranoside (16): TrCl (79 mg, 0.28 mmol) was added under Ar to a stirred solution of the sugar diol **15** (188 mg, 0.18 mmol) in dry Py (1.6 mL). The mixture was stirred at 80 °C for 2 h, and then concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give a white foam, the tritylated intermediate (213 mg, 92%): $[\alpha]_D^{21}$ = +59.3 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.04 (s, 3 H), 2.26 (s, 3 H), 2.60 (t, *J* = 9.6 Hz, 1 H), 3.14 (br. s, 1 H), 3.25−3.49 (m, 3 H), 3.80−3.98 (m, 4 H), 4.22−4.37 (m, 4 H), 4.50 (dd, *J* = 11.0, 6.4 Hz, 1 H), 4.64 (dd, *J* = 11.0, 6.4 Hz, 1 H), 4.77−4.85 (m, 2 H), 4.91 (d, *J* = 8.0 Hz, 1 H), 5.00 (d, *J* = 8.0 Hz, 1 H), 5.15 (d, *J* = 3.8 Hz, 1 H), 5.31−5.35 (m, 1 H), 5.60 (m, 2 H), 5.96 (dd, *J* = 10.7, 7.9 Hz, 1 H), 6.01 (d, *J* = 3.3 Hz, 1 H), 6.10 (m, 1 H), 7.20−8.12 (m, 35 H) ppm. ESI MS: *m*/*z* = 1322 [M + 1 + Na^+], 1344 [M + 2Na^+]. $C_{73}H_{70}O_{22}\cdot H_2O$ (1317.4): calcd. C 66.56, H 5.51; found C 66.89, H 5.43.

Ac_2O (0.05 mL) was added to a solution of the above tritylated trisaccharide (88 mg, 67.7 μmol) in Py (2 mL), and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give the title compound **16** (93 mg, quant.) as a white foam: $[\alpha]_D^{24}$ = +61.1 (*c* = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H), 1.99 (s, 3 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 3.10 (m, 2 H), 3.72 (m, 1 H), 3.85 (dd, *J* = 11.0, 3.6 Hz, 1 H), 3.94 (m, 1 H), 4.08−4.16 (m, 2 H), 4.21−4.38 (m, 3 H), 4.44−4.50 (m, 2 H), 4.58−4.79 (m, 5 H), 5.01 (d, *J* = 7.9 Hz, 1 H), 5.14 (d, *J* = 3.8 Hz, 1 H), 5.28−5.38 (m, 1 H), 5.52−5.62 (m, 2 H), 5.92 (dd, *J* = 10.7, 7.9 Hz, 1 H), 5.98 (d, *J* = 3.5 Hz, 1 H), 6.01−6.16 (m, 1 H), 7.20−8.11 (m, 35 H) ppm. ESI MS: *m*/*z* = 1364 [M + 1 + Na^+], 1387 [M + 1 + 2Na^+]. $C_{75}H_{72}O_{23}\cdot H_2O$ (1359.4): calcd. C 66.27, H 5.49; found C 66.42, H 5.41.

Allyl 4-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranoside (17): Compound **16** (358 mg, 0.27 mmol) was treated with HOAc (80%, 5 mL) at 50 °C for 4 h, and the solvent was then removed under reduced pressure to give the crude product, which was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to afford the title compound **17** (179 mg, 61%) as a white foam: $[\alpha]_D^{28}$ = +69.2 (*c* = 1.1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 2.00 (s, 6 H), 2.03 (s, 3 H), 2.14 (s, 3 H), 2.55 (m, 1 H), 3.52 (dd, *J* = 12.4, 4.0 Hz, 1 H), 3.64 (d, *J* = 12.4 Hz, 1 H), 3.74−3.80 (m, 2 H), 3.83 (dd, *J* = 9.4, 3.0 Hz, 1 H), 4.10−4.17 (m, 1 H), 4.21−4.29 (m, 3 H), 4.43 (dd, *J* = 11.2, 6.0 Hz, 1 H), 4.52 (d, *J* = 5.6 Hz, 1 H), 4.61 (dd, *J* = 11.3, 8.9 Hz, 1 H), 4.72 (m, 3 H), 4.81 (t, *J* = 9.6 Hz, 1 H), 5.01 (d, *J* = 7.8 Hz, 1 H), 5.10 (d, *J* = 2.9 Hz, 1 H), 5.28, 5.51 (m, 2 H), 5.61 (dd, *J* = 10.5, 3.1 Hz, 1 H), 5.91 (dd, *J* = 10.5, 7.9 Hz, 1 H), 5.98 (d, *J* = 2.7 Hz, 1 H), 6.02 (m, 1 H), 7.20−8.09 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.0, 169.7, 169.2, 166.0, 165.4, 165.2, 133.7, 133.44, 133.35, 129.9, 129.8, 129.7, 129.2, 129.0, 128.9, 128.7, 128.5, 128.3, 117.3, 101.3, 99.1, 97.8, 78.7, 74.6, 72.2, 71.9, 71.8, 71.3, 70.1, 69.3, 69.1, 68.8, 68.2, 61.9, 61.4, 61.3, 21.2, 20.9, 20.7 ppm. ESI MS: *m*/*z* = 1122 [M + 1 + Na^+], 1145 [M + 1 + 2Na^+]. $C_{56}H_{58}O_{23}\cdot H_2O$ (1117.1): calcd. C 60.21, H 5.41; found C 60.32, H 5.23.

***tert*-Butyl [Allyl 4-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranoside]uronate (18):** PDC (35 mg, 91 μmol), Ac_2O (43 μL) and *t*BuOH (85 μL) were added to a stirred solution of sugar alcohol **17** (50 mg, 45.5 μmol) in CH_2Cl_2 (0.6 mL). The mixture was stirred at room temperature for 6 h, and then poured into a pad of silica gel containing EtOAc. The precipitated solid was filtered and washed with EtOAc, and the filtrate was concentrated in vacuo. Silica gel chromatography (petroleum ether/EtOAc, 2:1) yielded the title compound **18** (48 mg, 90%) as a white foam: $[\alpha]_D^{26}$ = +59.3 (*c* = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.00 (s, 9 H), 2.14 (s, 3 H), 2.52 (m, 1 H), 3.77 (m, 1 H), 3.91 (dd, *J* = 10.9, 3.4 Hz, 1 H), 4.14−4.33 (m, 5 H), 4.46 (m, 2 H), 4.55 (dd, *J* = 11.2, 6.7 Hz, 1 H), 4.67−4.76 (m, 3 H), 4.98−5.08 (m, 2 H), 5.17 (d, *J* = 3.6 Hz, 1 H), 5.28−5.32 (m, 1 H), 5.50−5.56 (m, 1 H), 5.59 (dd, *J* = 10.7, 3.3 Hz, 1 H), 5.90 (dd, *J* = 10.7, 7.8 Hz, 1 H), 5.98 (d, *J* = 3.2 Hz, 1 H), 5.97−6.09 (m, 1 H), 7.20−8.10 (m, 20 H) ppm. ESI MS: *m*/*z* = 1191 [M + Na^+], 1214 [M + 2Na^+]. $C_{60}H_{64}O_{24}$ (1169.1): calcd. C 61.64, H 5.52; found C 61.28, H 5.57.

***tert*-Butyl [4-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranose]uronate (19):** $[Pd(PPh_3)_4]$ (13 mg, 11.2 μmol) and HOAc (0.6 mL) were added to allyl glycoside **18** (40 mg, 34 μmol) under Ar. The mixture was protected from light and stirred at 80 °C for 1 h, and then filtered through a short silica gel column. The solvent was removed under vacuum to give the crude product, which was purified by flash column chromatography (petroleum ether/EtOAc, 2:1) to afford the hemiacetal **19** (38 mg, 98%) as a white foam: $[\alpha]_D^{26}$ = +61.9 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.61 (m, 1 H), 3.76−3.93 (m, 2 H), 4.07−4.19 (m, 2 H), 4.29 (m, 1 H), 4.39−4.62 (m, 3 H), 4.73 (m, 3 H), 5.02 (m, 2 H), 5.48 (d, *J* = 8.9 Hz, 1 H), 5.65 (dd, *J* = 10.6, 3.4 Hz, 1 H), 5.85 (dd, *J* = 10.6, 7.8 Hz, 1 H), 5.98 (d, *J* = 3.2 Hz, 1 H), 7.16−8.10 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 169.7, 169.1, 167.0, 166.2, 165.5, 165.3, 133.7, 133.6, 133.4, 129.9, 129.8, 129.7, 129.2, 128.9, 128.7, 128.6, 128.3, 101.7, 99.2, 92.1, 82.5, 79.1, 74.6, 72.2, 71.7, 71.0, 70.1, 69.6, 69.1, 68.7, 68.2, 62.0, 61.3, 29.7, 27.8, 20.9, 20.7 ppm. ESI MS: *m*/*z* = 1151 [M + Na^+], 1174 [M + 2Na^+]. $C_{57}H_{60}O_{24}$ (1129.1): calcd. C 60.64, H 5.36; found C 60.75, H 5.70.

***tert*-Butyl [4-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-α-D-glucopyranosyl Trichloroacetimidate]uronate (20):** CCl_3CN (20 μL, 0.2 mmol) and catalytic DBU were added to a solution of **19** (33 mg, 29.2 μmol) in CH_2Cl_2 (2 mL). After stirring at room temperature for 30 min, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 2:1 +1% Et_3N) to furnish the title compound **20** (32 mg, 86%) as a white foam. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.00 (s, 3 H), 2.01 (s, 6 H), 2.14 (s, 3 H), 2.59 (m, 1 H), 3.80 (dd, *J* = 10.9, 3.4 Hz, 1 H), 4.10 (dd, *J* = 11.2, 6.6 Hz, 1 H), 4.19 (t, *J* = 9.2 Hz, 1 H), 4.25−4.31 (m, 2 H), 4.40−4.48 (m, 2 H), 4.57−4.76 (m, 4 H), 5.02 (d, *J* = 7.8 Hz, 1 H), 5.13 (t, 1 H), 5.56 (dd, *J* = 10.7, 3.3 Hz, 1 H), 5.80 (dd, *J* = 10.7, 7.8 Hz, 1 H), 5.96 (d, *J* = 3.2 Hz, 1 H), 6.74 (d, *J* = 3.6 Hz, 1 H), 7.18−8.05 (m, 20 H), 8.74 (s, 1 H) ppm. ESIMS: *m*/*z* = 1296 [M + Na^+], 1319 [M +2Na^+].

3′-*O*-Acetyl-2,3-*O*-isopropylidene-α/β-D-apiofuranose (22): Compound **21**[29] (2.47 g, 13 mmol) was dissolved in dry Py (40 mL), and Ac_2O (2.85 mL) was added to this mixture at 0 °C. The resulting mixture was stirred at room temperature overnight, and was then diluted with EtOAc, washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated. The residue was dissolved in NH_3-THF/MeOH (100 mL) and stirred at 0 °C until all the starting material was consumed (TLC). The solvent was then evaporated and the residue was puri-

fied by flash column chromatography (petroleum ether/EtOAc, 3:1) to give a colourless syrup, the title compound **22** (1.2 g, 40%) as an α/β mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.48 (s, 3 H), 2.10 (s, 3 H), 4.00 (AB peak, *J* = 12.3 Hz, 2 H, H-4), 4.24 and 4.41 (AB peak, *J* = 11.7 Hz, 2 H, H-3), 4.38 (s, 1 H, H-2α), 5.05 (d, *J* = 2.8 Hz, 1 H, H-1β), 5.42 (s, 1 H, H-1α) ppm. EI MS: *m*/*z* = 217, 173, 157, 43.

3′-*O*-Acetyl-2,3-*O*-isopropylidene-α/β-D-apiofuranosyl Trichloroacetimidate (23): A solution of hemiacetal **22** (253 mg, 1.1 mmol), CCl_3CN (0.6 mL, 6 mmol) and catalytic DBU in CH_2Cl_2 (7 mL) was stirred at room temperature for 20 min, after which the solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography (petroleum ether/EtOAc, 7:1 + 1% Et_3N) to give the title compound **23** (402 mg, 98%) as a colourless syrup. Imidate **23** was found to decompose in the NMR tube and was therefore immediately used in the next step without further identification.

Benzyl 3-*O*-(3′-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-apiofuranosyl)-2,4-di-*O*-benzoyl-α-D-xylopyranoside (24): A suspension of imidate **23** (244 mg, 0.65 mmol), benzyl 2,4-di-*O*-benzoyl-α-D-xylopyranoside (333 mg, 0.74 mmol) and activated powdered molecular sieves (4 Å, 700 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature for 15 min. It was then cooled to −15 °C, and a solution of TMSOTf (5 mL, 0.05 M) in CH_2Cl_2 was slowly added to the reaction mixture. After stirring for another 30 min, the reaction mixture was quenched with Et_3N and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 6:1 → 4:1) to afford the disaccharide **24** (386 mg, 90%) as a white foam. A small amount of α-isomer produced in this step could be removed completely after next reaction. **24:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (AB peak, *J* = 12.3 Hz, 2 H), 3.79−3.90 (m, 2 H), 3.91 and 4.06 (AB peak, *J* = 11.8 Hz, 2 H), 4.22 (s, 1 H), 4.58 (t, *J* = 9.6 Hz, 1 H), 4.50 and 4.75 (AB peak, *J* = 12.6 Hz, 2 H), 5.17−5.25 (m, 2 H), 5.36 (s, 1 H), 7.10−8.10 (m, 15 H) ppm. EI MS: *m*/*z* = 648, 556, 368, 341, 215, 105. $C_{36}H_{38}O_{12}\cdot H_2O$ (680.7): calcd. C 63.52, H 5.92; found C 63.21, H 5.62.

3-*O*-(3′-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-apiofuranosyl)-2,4-di-*O*-benzoyl-α-D-xylopyranosyl Trichloroacetimidate (25): A suspension of **24** (428 mg, 0.65 mmol) and Pd/C (10%, 114 mg) in EtOAc/95% EtOH (1:1, 20 mL) was stirred at room temperature under H_2 atmosphere (1 atm) for 6 h and then filtered. The filtrates were concentrated in vacuo. Flash column chromatography of the residue (petroleum ether/EtOAc, 2.5:1) gave the desired hemiacetal (372 mg, quant.) as a colourless syrup, which was directly used in the next reaction. Catalytic DBU (one drop) was added to a solution of the above hemiacetal (141 mg, 0.25 mmol) and CCl_3CN (0.14 mL, 1.4 mmol) in CH_2Cl_2 (3 mL), and the resulting mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:1 + 1% Et_3N) to furnish the title compound **25** (158 mg, 89%) as a white foam: $[\alpha]_D^{20}$ = −21.7 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.22 (s, 3 H), 1.34 (s, 3 H), 1.91 (s, 3 H), 3.67 (AB peak, *J* = 10.2 Hz, 2 H), 3.85−4.14 (m, 4 H), 4.24 (s, 1 H), 4.59 (t, *J* = 9.5 Hz, 1 H), 5.33 (m, 2 H), 5.34 (s, 1 H), 6.61 (d, *J* = 3.8 Hz, 1 H), 7.40−8.08 (m, 10 H), 8.59 (s, 1 H) ppm. EI MS: *m*/*z* = 702, 556, 215, 105. $C_{31}H_{32}O_{12}NCl_3\cdot 0.5H_2O$ (726.0): calcd. C 51.29, H 4.58, N 1.93; found C 51.07, H 4.28, N 2.31.

Ethyl 3′-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-α-L-rhamnoside (26): A suspension of imidate **25** (127 mg, 0.18 mmol), ethyl 2,3-*O*-isopropylidene-1-thio-α-L-rhamnoside (47 mg, 0.19 mmol) and activated powdered molecular sieves (4 Å, 100 mg) in CH_2Cl_2 (3 mL) was stirred at room temperature for 15 min and then cooled to −50 °C, and a solution of TMSOTf (0.72 mL, 0.05 M) in CH_2Cl_2 was slowly added to the reaction mixture. After stirring for 30 min, the reaction mixture was quenched with Et_3N, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 6:1) to yield the title compound **26** (135 mg, 95%) as a white foam: $[\alpha]_D^{19}$ = −102.5 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (m, 12 H), 1.33 (s, 3 H), 1.52 (s, 3 H), 1.99 (s, 3 H), 2.62−2.50 (m, 2 H), 3.56 (dd, *J* = 12.0, 7.0 Hz, 1 H), 3.60 (dd, *J* = 10.0, 7.5 Hz, 1 H), 3.72 and 3.77 (AB peak, *J* = 10.2 Hz, 2 H), 3.94 (m, 1 H), 4.00 (t, *J* = 5.8 Hz, 1 H), 4.05 (d, *J* = 6.0 Hz, 1 H), 4.22−4.26 (m, 2 H), 4.03 and 4.18 (AB peak, *J* = 11.7 Hz, 2 H), 4.28 (s, 1 H), 5.11 (td, *J* = 7.1, 4.5 Hz, 1 H), 5.21 (m, 2 H), 5.25 (s, 1 H), 5.47 (s, 1 H), 7.41−8.06 (m, 10 H) ppm. EI MS: *m*/*z* = 788, 555, 323, 105. $C_{40}H_{50}O_{15}S$ (802.9): calcd. C 59.88, H 6.28; found C 60.15, H 6.22.

Ethyl 3′-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-α-L-rhamnoside (28): A typical set of conditions for the removal of isopropylidene from **26** is described as follows: a solution of **26** (140 mg, 0.17 mmol) in 90% HOAc (3 mL) was stirred at 90 °C overnight and then concentrated in vacuo, and the traces of HOAc and water were removed by coevaporation several times with toluene. The crude product **27** was dissolved in Py (2.5 mL) and Ac_2O (0.6 mL) and stirred overnight at room temperature, and was then diluted with EtOAc, washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 4:1 → 3:1) to afford the title compound **28** (108 mg, 73%) as a white solid: $[\alpha]_D^{28}$ = −147.4 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.4 Hz, 3 H), 1.26 (s, 3 H), 1.33 (s, 3 H), 1.36 (d, *J* = 6.3 Hz, 3 H), 1.86 (s, 3 H), 1.99 (s, 3 H), 2.10 (s, 3 H), 2.59 (m, 2 H), 3.62 (dd, *J* = 12.1, 6.6 Hz, 1 H), 3.75 (AB peak, *J* = 10.2 Hz, 2 H), 3.79 (t, *J* = 5.9 Hz, 1 H), 4.20 (m, 3 H), 4.02 and 4.19 (AB peak, *J* = 11.8 Hz, 2 H), 4.26 (s, 1 H), 4.94 (d, *J* = 5.5 Hz, 1 H), 5.07 (dd, *J* = 9.9, 3.3 Hz, 1 H), 5.11 (s, 1 H), 5.14 (m, 2 H), 5.24 (s, 1 H), 5.27 (dd, *J* = 3.3, 1.5 Hz, 1 H), 7.40−8.04 (m, 10 H) ppm. EI MS: *m*/*z* = 556, 341, 275, 215, 105. $C_{41}H_{50}O_{17}S$ (846.9): calcd. C 58.15, H 5.95; found C 57.72, H 5.89.

Ethyl 2,3-*O*-Isopropylidene-β-D-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-α-L-rhamnoside (29): A solution of NaOMe (0.23 mL, 0.1 M) in MeOH was added to a solution of protected sugar **26** (188 mg, 0.23 mmol) in dry MeOH (3 mL). The reaction mixture was stirred at room temperature overnight. Amberlite IRC-85 resin was added until a pH of approximately 5 was obtained. The mixture was then filtered and concentrated to give the crude product **29** (87 mg, 68%) as a white solid, which was directly used in the next step without purification.

Ethyl 3′-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-acetyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-α-L-rhamnoside (30): A solution of **29** (53 mg, 96 μmol) in MeOH/H_2O (3:2, 5 mL) was treated at 70 °C overnight with Dowex 50 W (H^+) resin (500 mg). The resin was removed and washed with MeOH, and the solution was evaporated under vacuum to give a residue, which was then dissolved in Ac_2O (0.5 mL) and Py (2 mL) and stirred overnight at room temperature. After having been quenched with MeOH, the mixture was diluted with EtOAc, washed success-

ively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:1) to furnish the title compound **30** (54 mg, 78%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36, 1.44 (2s, 6 H, Me_2C), 1.86 (s, 3 H, Ac), 1.92 (s, 3 H, Ac), 1.97 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.60 (m, 2 H, SCH_2CH_3), 3.26 (dd, $J_{5,5'}$ = 11.8, $J_{5,4}$ = 9.2 Hz, 1 H, xyl-5), 3.65 (t, $J_{3,2}$ = $J_{3,4}$ = 9.6 Hz, 1 H, xyl-3), 3.73 (t, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, 1 H, rha-4), 3.79 and 3.92 (AB peak, J_{gem} = 10.0 Hz, 2 H, api-4), 4.07 (m, 2 H, xyl-5′, rha-5), 4.26 (s, 1 H, api-2), 4.13 and 4.30 (AB peak, J_{gem} = 11.8 Hz, 2 H, api-3), 4.55 (d, $J_{1,2}$ = 7.6 Hz, 1 H, xyl-1), 4.86 (m, 2 H, xyl-2, xyl-4), 5.05 (s, 1 H, api-1), 5.13 (s, 1 H, rha-1), 5.16 (dd, $J_{3,2}$ = 3.4, $J_{3,4}$ = 9.7 Hz, 1 H, rha-3), 5.24 (dd, $J_{2,3}$ = 3.4, $J_{2,1}$ = 1.5 Hz, 1 H, rha-2) ppm.

2,4-Di-*O*-benzoyl-3-*O*-(2,3,3′-tri-*O*-acetyl-β-D-apiofuranosyl)-α-D-xylopyranosyl trichloroacetimidate (32): A suspension of disaccharide **31**[35] (1.64 g, 2.32 mmol) and Pd/C (10%, 1.2 g) in EtOAc/95% EtOH (1:2, 30 mL) was stirred at 40 °C under H_2 atmosphere (50 atm) for 1 days and then filtered. The filtrates were concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 5:1 → 3:1) to afford the desired hemiacetal (532 mg, 37%) as a colourless syrup, together with recovered starting material **31** (983 mg, 60%). Catalytic DBU (one drop) was added to a solution of the above hemiacetal (450 mg, 0.73 mmol) and CCl_3CN (0.4 mL, 4 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred at room temperature for 30 min and then concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:1 + 1% Et_3N) to afford the imidate **32** (495 mg, 89%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 1.88 (s, 3 H), 1.89 (s, 3 H), 3.92 (m, 3 H), 4.13 (dd, *J* = 11.1, 5.9 Hz, 1 H), 4.28 and 4.47 (AB peak, *J* = 12.6 Hz, 2 H), 4.51 (t, *J* = 9.6 Hz, 1 H), 5.17 (s, 1 H), 5.24 (s, 1 H), 5.33−5.43 (m, 2 H), 6.59 (d, *J* = 3.6 Hz, 1 H), 7.51−8.05 (m, 10 H), 8.61 (s, 1 H) ppm. EI MS: *m*/*z* = 599, 340, 259, 105.

Ethyl 2,3,3′-Tri-*O*-acetyl-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-α-L-rhamnoside (33): A suspension of imidate **32** (169 mg, 0.22 mmol), ethyl 2,3-*O*-isopropylidene-1-thio-α-L-rhamnoside (59 mg, 0.24 mmol) and activated powdered molecular sieves (4 Å, 200 mg) in CH_2Cl_2 (6 mL) was stirred at room temperature for 15 min and then cooled to −50 °C, and a solution of TMSOTf (0.88 mL, 0.05 M) in CH_2Cl_2 was slowly added. After stirring for 30 min, the reaction mixture was quenched with Et_3N, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 3:1) to yield the title compound **33** (165 mg, 88%) as a white foam: $[\alpha]_D^{21}$ = −137.2 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26−1.32 (m, 9 H), 1.54 (s, 3 H), 1.77 (s, 3 H), 1.91 (s, 3 H), 1.99 (s, 3 H), 2.50 (m, 1 H), 2.62 (m, 1 H), 3.59 (m, 2 H), 3.93−4.06 (m, 5 H), 4.20 (t, *J* = 7.2 Hz, 1 H), 4.27 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.35 and 4.61 (AB peak, *J* = 12.0 Hz, 2 H), 5.21 (m, 4 H), 5.25 (s, 1 H), 5.47 (s, 1 H), 7.41−8.06 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 168.8, 167.8, 164.8, 164.3, 132.6, 132.4, 129.3, 129.1, 127.7, 127.6, 108.6, 105.5, 98.4, 83.0, 78.7, 77.3, 75.7, 75.4, 71.7, 71.2, 69.1, 64.0, 61.9, 61.0, 27.3, 25.7, 23.7, 20.3, 19.9, 19.4, 16.9, 13.9 ppm. EI MS: *m*/*z* = 786, 728, 599, 322, 259. $C_{41}H_{50}O_{17}S$ (846.9): calcd. C 58.15, H 5.95; found C 58.32, H 5.93.

Ethyl 2,3,3′-Tri-*O*-acetyl-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-acetyl-1-thio-α-L-rhamnoside (34): A solution of **33** (361 mg, 0.43 mmol) in HOAc (80%, 10 mL) was stirred at 50 °C overnight and then concentrated in vacuo, and the traces of HOAc and water were removed by coevaporation several times with toluene. The residue was dissolved in Py (10 mL) and Ac_2O (0.4 mL) and stirred overnight at room temperature, and was then diluted with EtOAc, washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 4:1 → 3:1) to afford the title compound **34** (108 mg, 73%) as a white foam: $[\alpha]_D^{21}$ = −130.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 1.38 (d, *J* = 6.6 Hz, 3 H), 1.82 (s, 3 H), 1.91 (s, 3 H), 1.93 (s, 3 H), 2.01 (s, 3 H), 2.11 (s, 3 H), 2.61 (m, 2 H), 3.67 (dd, *J* = 12.3, 6.0 Hz, 1 H), 3.78 (t, *J* = 9.6 Hz, 1 H), 3.99 and 4.06 (AB peak, *J* = 10.8 Hz, 2 H), 4.18 (m, 2 H), 4.33 (dd, *J* = 12.3, 3.6 Hz, 1 H), 4.36 and 4.68 (AB peak, *J* = 12.3 Hz, 2 H), 4.97 (d, *J* = 4.8 Hz, 1 H), 5.10 (dd, *J* = 7.2, 3.6 Hz, 1 H), 5.12 (d, *J* = 1.2 Hz, 1 H), 5.17−5.26 (m, 2 H), 5.19 (s, 1 H), 5.26 (s, 1 H), 5.29 (dd, *J* = 3.3, 1.5 Hz, 1 H), 7.33−8.07 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 169.9, 169.6, 169.2, 168.6, 165.5, 164.7, 133.4, 129.8, 129.7, 129.5, 129.2, 128.4, 128.3, 106.0, 100.0, 83.6, 81.7, 76.4, 75.2, 72.5, 72.3, 71.7, 71.1, 69.5, 67.5, 62.4, 61.1, 25.3, 21.0, 20.9, 20.8, 20.6, 20.1, 17.9, 14.7 ppm. ESI MS: *m*/*z* = 913 [M + Na^+], 936 (M +2Na^+). $C_{42}H_{50}O_{19}S\cdot 0.5H_2O$ (899.9): calcd. C 55.96, H 5.71; found C 56.05, H 5.60.

Allyl 2,3,3′-Tri-*O*-acetyl-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-acetyl-α-L-rhamnosyl-(1→2)-3,4-*O*-isopropylidene-α-D-fucopyranoside (35): A mixture of trisaccharide **34** (22 mg, 24.7 μmol), allyl 3,4-*O*-isopropylidene-α-D-fucopyranoside (7 mg, 28.7 μmol) and 4E powdered molecular sieves (20 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature under Ar for 30 min and then cooled to −20 °C. NIS (8 mg, 36 μmol) was added to this mixture, followed by addition of a solution of AgOTf (3 mg, 11.7 μmol) in toluene (0.5 mL). After stirring for 1 h, the reaction mixture was quenched with Et_3N. The suspension was diluted with EtOAc and filtered through a pad of Celite, and the filtrate was washed successively with 10% $Na_2S_2O_3$ and water. The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 2.5:1→1:1) to give **35** (24 mg, 91%) as a white foam: $[\alpha]_D^{21}$ = −53.0 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31−1.34 (m, 9 H), 1.49 (s, 3 H), 1.74 (s, 3 H), 1.88 (s, 3 H), 1.90 (s, 3 H), 1.97 (s, 3 H), 2.09 (s, 3 H), 3.61 (dd, *J* = 12.3, 6.0 Hz, 1 H), 3.72 (m, 2 H), 3.84 (dd, *J* = 6.5, 3.9 Hz, 1 H), 3.93−4.01 (m, 4 H), 4.11−4.19 (m, 3 H), 4.28−4.34 (m, 3 H), 4.58 (d, *J* = 12.3 Hz, 1 H), 4.82 (d, *J* = 3.9 Hz, 1 H), 4.91 (d, *J* = 5.0 Hz, 1 H), 5.02 (s, 1 H), 5.12−5.23 (m, 6 H), 5.31 (m, 2 H), 5.87 (m, 1 H), 7.37−8.07 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.3, 169.8, 169.5, 169.0, 168.4, 165.4, 164.6, 133.6, 133.4, 133.3, 129.8, 129.7, 129.3, 128.4, 128.3, 117.8, 108.8, 106.2, 100.3, 97.8, 96.9, 83.5, 76.2, 75.8, 75.5, 72.4, 71.9, 71.8, 69.9, 68.6, 67.1, 63.1, 62.5, 61.8, 28.3, 26.4, 20.9, 20.8, 20.5, 20.0, 17.9, 16.2 ppm. ESI MS: *m*/*z* = 1095 [M + Na^+], 1118 [M + 2Na^+]. $C_{52}H_{64}O_{24}$ (1073.1): calcd. C 58.21, H 6.01; found C 58.06, H 5.82.

2,3,3′-Tri-*O*-Acetyl-β-D-apiofuranosyl-(1→3)-2,4-di-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-acetyl-α-L-rhamnosyl-(1→2)-3,4-*O*-isopropylidene-α/β-D-fucopyranose (36): $I(CF_2)_8F$ (50 mg, 0.11 mmol) was added to a stirred solution of **35** (39 mg, 36 μmol) in CH_3CN/H_2O (2:1, 1.5 mL) followed by addition of a mixture of $Na_2S_2O_4$ (42 mg, 0.24 mmol) and $NaHCO_3$ (28 mg, 0.33 mmol). After stirring at room temperature for 10 min, the reaction mixture was diluted with EtOAc, washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The residue was dissolved in dry EtOH (4 mL), Zn dust (26 mg, 0.4 mmol) and NH_4Cl (13 mg,

0.24 mmol) were added, and the resulting mixture was heated at reflux for 50 min and then filtered. The filtrates were concentrated to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to furnish the desired hemiacetal **36** (21 mg, 57%) as an α/β mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30−1.60 (m, 12 H), 2.08 (m, 15 H), 3.62−4.82 (m, 14 H), 5.02−5.40 (m, 8 H), 7.20−8.03 (m, 10 H) ppm. ESI MS: *m*/*z* = 1055 [M + Na^+], 1078 [M + $2Na^+$]. $C_{49}H_{60}O_{24}$·1.5H_2O (1060.0): calcd. C 55.52, H 5.99; found C 55.41, H 5.86.

Acknowledgments

We are grateful for financial support from the National Natural Science Foundation of China (Grant 29925203) and the German Fonds der Chemischen Industrie.

[1] C. R. Kensil, U. Patel, M. Lennick, D. Marciani, *J. Immunol.* **1991**, *146*, 431−437.
[2] N. E. Jacobsen, W. J. Fairbrother, C. R. Kensil, A. Lim, D. A. Wheeler, M. F. Powell, *Carbohydr. Res.* **1996**, *280*, 1−14.
[3] C. R. Kensil, S. Soltysik, D. A. Wheeler, J. Y. Wu, in *Saponins Used in Traditional and Modern Medicine* (Eds.: G. R. Waller, K. Yamasaki), Plenum Press, **1995**; 165−172 and references cited therein.
[4] C. R. Kensil, R. Kammer, *Exp. Opin. Invest. Drugs* **1998**, *7*, 1475−1482.
[5] P. O. Livingston, S. Adluri, F. Helling, T. J. Yao, C. R. Kensil, M. J. Newman, D. Marciani, *Vaccine* **1994**, *12*, 1275−1280.
[6] X. Zhu, B. Yu, Y. Hui, R. Higuchi, T. Kusano, T. Miyamoto, *Tetrahedron Lett.* **2000**, *41*, 717−719.
[7] X. Zhu, W. Zeng, B. Yu, Y. Hui, *Acta Chimica Sinica* **2001**, *59*, 1653−1659.
[8] The synthesis of the trisaccharide moiety has been reported, see: Y. J. Kim, D. G. Gin, *Org. Lett.* **2001**, *3*, 1801−1804.
[9] N. H. Tan, J. Zhou, S. X. Zhao, *Phytochemistry* **1999**, *52*, 153−192.
[10] For a review on glucuronide synthesis, see: A. V. Stachulski, A. N. Jenkins, *Nat. Prod. Rep.* **1998**, 173−186.
[11] For some examples of synthesis of glucuronide-containing oligosaccharides by oxidation at a later stage, see: [11a] B. Mukhopadhyay, N. Roy, *Carbohydr. Res.* **2003**, *338*, 589−596. [11b] B. K. S. Yeung, D. C. Hill, M. Janicka, P. A. Petillo, *Org. Lett.* **2000**, *2*, 1279−1281. [11c] T. M. Slaghek, T. K Hypponen, T. Ogawa, J. P. Kamerling, J. F. G. Vliegenhart, *Tetrahedron Lett.* **1993**, *34*, 7939−7942. [11d] T. M. Slaghek, Y. Nakahara, T. Ogawa, *Tetrahedron Lett.* **1992**, *33*, 4971−4974. [11e] Y. Ichikawa, K. Ichikawa, H. Kuzuhara, *Carbohydr. Res.* **1985**, *141*, 273−282. [11f] M. Bouktaib, A. Atmani, C. Rolando, *Tetrahedron Lett.* **2002**, *43*, 6263−6266.
[12] I. Pelyvas, T. Lindhorst, J. Thiem, *Liebigs Ann. Chem.* **1990**, 761−769.
[13] Z. Yang, W. Lin, B. Yu, *Carbohydr. Res.* **2000**, *329*, 879−884.
[14] S. Rio, J. M. Beau, J. C. Jacquinet, *Carbohydr. Res.* **1991**, *219*, 71−90.
[15] R. R. Schmidt, M. Stumpp, *Liebigs Ann. Chem.* **1983**, *7*, 1249−1256.
[16] A. Toepfer, W. Kinzy, R. R. Schmidt, *Liebigs Ann. Chem.* **1994**, 449−464.
[17] Ortho ester formation during glycosidation reactions is not unusual, for two recent examples with **5** as glycosyl donor, see: [17a] H. Amer, A. Hofinger, P. Kosma, *Carbohydr. Res.* **2003**, *338*, 35−45. [17b] W. J. Sanders, D. D. Manning, K. M. Koeller, L. L. Kiessling, *Tetrahedron* **1997**, *53*, 16391−16422.
[18] T. Yoshida, T. Chiba, T. Yokochi, K. Onozaki, T. Sugiyama, I. Nakashima, *Carbohydr. Res.* **2001**, *335*, 167−180.
[19] R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213−236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212−235.
[20] R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.
[21] P. Fügedi, P. J. Garegg, H. Lönn, T. Norberg, *Glycoconjugate J.* **1987**, *4*, 97−108.
[22] S. Kramer, B. Nolting, A. J. Ott, C. Vogel, *J. Carbohydr. Chem.* **2000**, *19*, 891−922.
[23] A. Dondoni, A. Marra, M. C. Scherrmann, A. Casnati, F. Sansone, R. Ungaro, *Chem. Eur. J.* **1997**, *3*, 1774−1782.
[24] P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313−4316.
[25] K. C. Nicolaou, S. E. Webber, *Synthesis* **1986**, 453−461.
[26] G. Vic, J. J. Hastings, O. W. Howarth, D. H. G. Crout, *Tetrahedron: Asymmetry* **1996**, *7*, 709−720.
[27] M. Nilsson, C. M. Svahn, J. Westman, *Carbohydr. Res.* **1993**, *246*, 161−172.
[28] K. Nakayama, K. Uoto, K. Higuchi, T. Soga, T. Kusama, *Chem. Pharm. Bull.* **1992**, *40*, 1718−1720.
[29] M. Koos, H. S. Mosher, *Carbohydr. Res.* **1986**, *146*, 335−341.
[30] P. Hettinger, H. Schildknecht, *Liebigs Ann. Chem.* **1984**, *6*, 1230−1239.
[31] R. J. Nachman, M. Hönel, T. Williams, R. C. Halaska, H. S. Mosher, *J. Org. Chem.* **1986**, *51*, 4802−4806.
[32] R. F. Helm, J. Ralph, *J. Org. Chem.* **1991**, *56*, 7015−7021.
[33] T. L. Lowary, E. Eichler, D. R. Bundle, *J. Org. Chem.* **1995**, *60*, 7316−7327.
[34] The conditions used for removal of the isopropylidene groups include: [34a] 90% HOAc, 90 °C, overnight. [34b] Dowex 50 W (H^+), 70 °C, CH_3CN/MeOH/H_2O. [34c] DDQ, CH_3CN/H_2O, reflux. [34d] 1% I_2-MeOH, reflux. [34e] $PdCl_2(CH_3CN)_2$, acetone/H_2O. [34f] TFA, THF/H_2O. [34g] BCl_3, CH_2Cl_2.
[35] X. Zhu, B. Yu, Y. Hui, *Chin. J. Chem.* **2000**, *18*, 72−77.
[36] M. Liu, B. Yu, X. Wu, Y. Hui, K. P. Fung, *Carbohydr. Res.* **2000**, *329*, 745−754.
[37] B. Yu, J. Zhang, S. Lu, Y. Hui, *Synlett* **1998**, 29−30.
[38] J. Schimmel, *Dissertation*, Universität Konstanz, **2002**.

Received September 16, 2003

