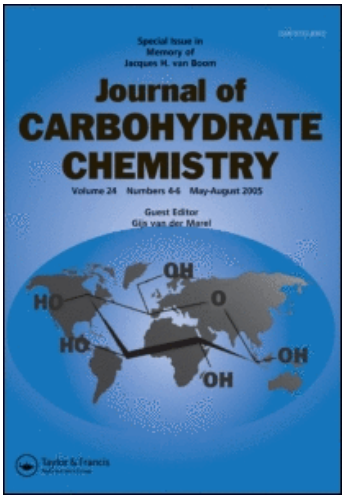

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THE REGIO- AND STEREOSELECTIVE SYNTHESIS OF RHAMNOSE-CONTAINING OLIGOSACCHARIDES *VIA* SUGAR-SUGAR ORTHOESTER FORMATION AND REARRANGEMENT

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ABSTRACT

Convenient regio- and stereoselective syntheses of rhamnose-containing oligosaccharides *via* sugar-sugar orthoester formation and rearrangement are described. 1→3 Linked rhamno di- and trisaccharides were synthesized effectively using unprotected rhamnose residue as the glycosyl acceptor by this methodology.

INTRODUCTION

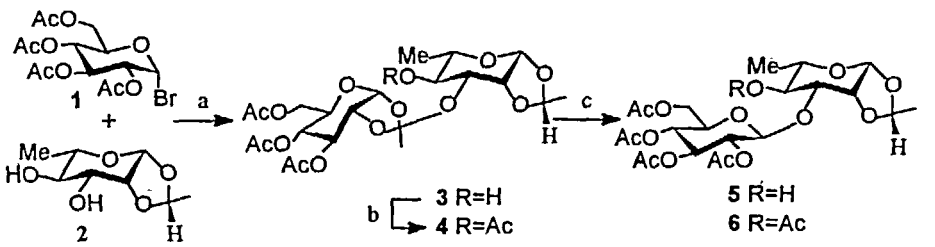
Rhamnose-containing oligosaccharides are widely distributed in natural products, such as triterpenoid glycosides,[1] K-antigens,[2] and a series of phenolic glycolipids from mycobacteria.[3] It is well recognized that the rhamnose containing serogroups of mycobacteria are closely related to opportunistic pulmonary infection[4] and AIDS disseminate infections.[3b] In pursuit of the synthesis of oleanene glycosides from *Spergularia ramosa*, which are used as a remedy for respiratory ailments, tuberculosis, and rickets,[1b] we planned to explore a facile way to prepare these biologically important rhamnose-related oligosaccharides.[5]

Previous work, in rhamnopyranosyl oligosaccharide synthesis, was usually carried out using organotin complexes or phase transfer-catalyzed conditions for differentiation of the 3-, 2-, and 4-OH groups of rhamnose. Thus, the strategies required multi-step reactions and complex protecting groups.[6] Carbohydrate 1,2-orthoesters have long been used for the synthesis of 1,2-*trans* glycosides as well as for temporary 1,2-protecting groups in the synthesis of sugar derivatives and oligosaccharides.[7] However, the remarkable regioselectivity in the formation of sugar-sugar orthoesters has only recently been explored by our group in the regioselective synthesis of glucopyranosyl oligosaccharides.[8] We present here the facile synthesis of the target oligosaccharides *via* sugar-sugar orthoester formation and rearrangement using *O*-acetylglycosyl bromides as the glycosyl donors and unprotected and partially protected rhamnose residues as the glycosyl acceptors.

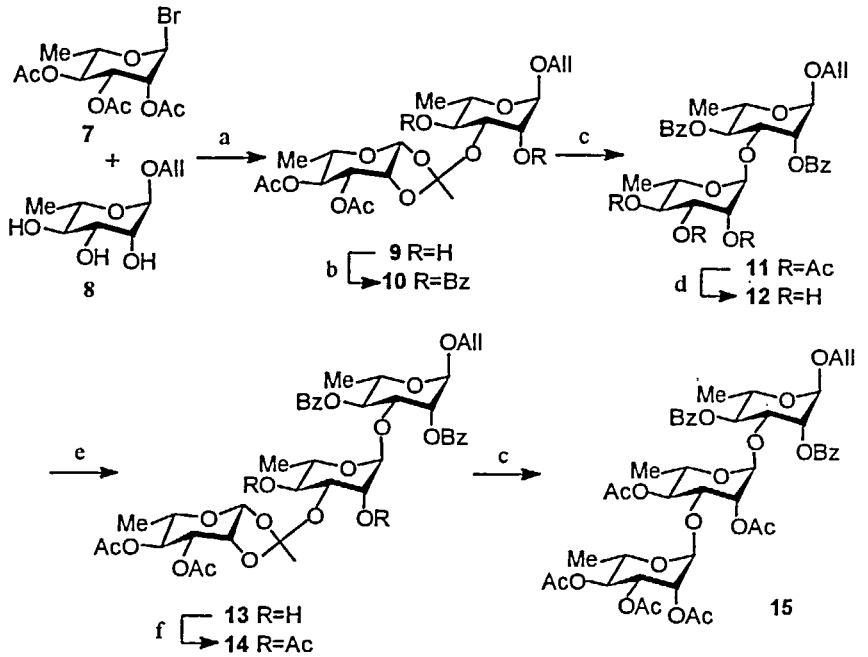
RESULTS AND DISCUSSIONS

As shown in Scheme 1, 1,2-*O*-(*R*-ethylidene)-α-L-rhamnopyranoside (**2**)[9] was employed as the acceptor to couple acetobromoglucose for the study of the regioselectivity in the presence of AgOTf and 2,4-lutidine.

As we expected, 1,3-linked sugar-sugar orthoester 3',4',6'-tri-*O*-acetyl-α-D-glucopyranose 1',2'-(1,2-*O*-(*R*-ethylidene)-β-L-rhamnopyranosid)-3-yl orthoacetate (**3**, *exo*, 72%) was afforded as a major product, together with 4-OH substituted regioisomer (~ 8%). It is worth mentioning that direct glycosylation of **1** with **2** gave a complex mixture containing two disaccharides and one trisaccharide, similar to the results obtained by Kochetkov's group.[7i] The presence of sugar-sugar orthoester in **3** was proven by the coupled ^{13}C NMR spectrum ($J_{C\text{-}1,H\text{-}1}$ = 183 Hz in **3**, typical value for β-glycoside is 155-165 Hz, for α-glycoside is 165-175 Hz),[10] and the regioselectivity was confirmed by its



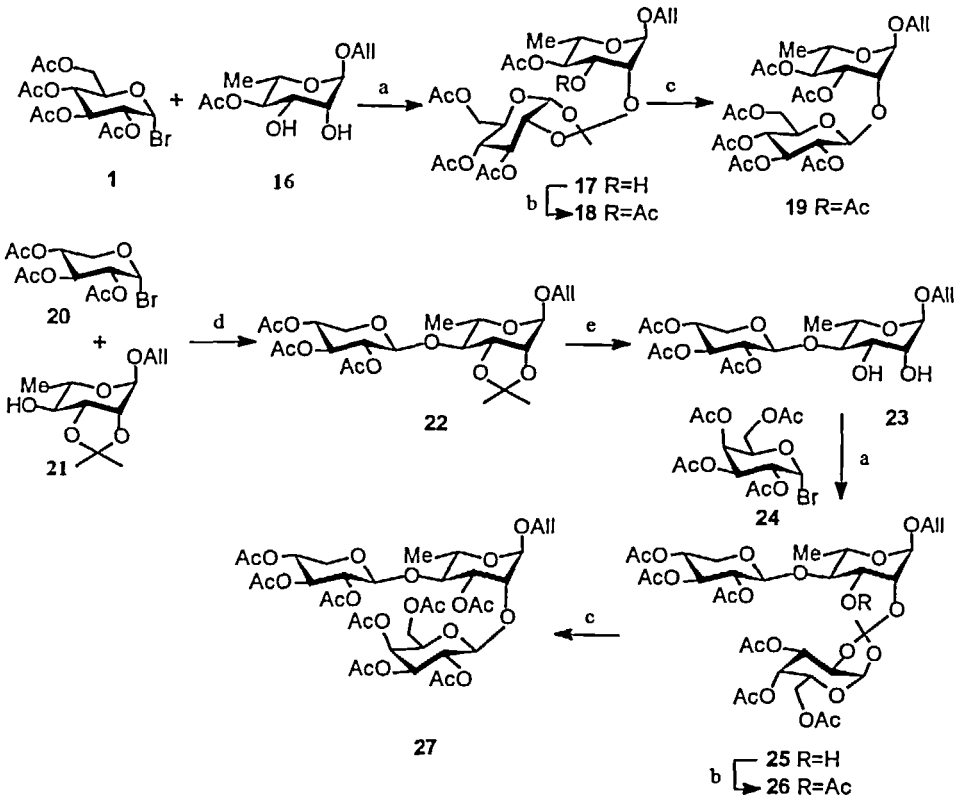
Scheme 1: (a) AgOTf (1.1 equiv of **1**), 2,4-lutidine (1.4 equiv of **1**), 4 Å M.S., anhyd CH_2Cl_2, 0 °C→ rt; (b) Ac_2O, Pyr; (c) TMSOTf (0.1 equiv), anhyd CH_2Cl_2, -5 – -10 °C.



Scheme 2: (a) AgOTf (1.1 equiv of 7), 2,4-lutidine (1.4 equiv of 7), 4 Å M.S., anhyd CH_2Cl_2, 0 °C→ rt; (b) BzCl, Pyr; (c) TMSOTf (0.1 equiv), anhyd CH_2Cl_2, -5 - -10 °C; (d) AcCl in MeOH; (e) 7, reaction (a); (f) Ac_2O, Pyr.

acetylated derivative **4** (H-4 moved to downfield at 4.97 ppm, $J_{3,4} = J_{4,5} = 9.6$ Hz). TMSOTf-catalyzed rearrangement of **4** gave predominantly disaccharide **6** with unique β-linkage ($J_{1',2'} = 8.0$ Hz) in a yield of 81%. Alternatively, direct rearrangement of **3** generated disaccharide **5** as a major component (64%), together with 18% of separable 4-OH glycosylated regioisomer indicating that side reaction occurred in the presence of a free OH during the rearrangement. Thus, the preparation of disaccharide β-D-Glu-(1→3)-α-L-Rha (**5**) merely involves the regioselective formation and rearrangement of sugar-sugar orthoester **3**.

Encouraged by this preliminary study, we next applied this method to the synthesis of 1→3 linked trisaccharide (**15**) which is the partial structure of *Escherichia coli* K26 antigen.[2b] Allyl α-L-rhamnopyranoside (**8**), with free hydroxyl groups on the 2-, 3- and 4-positions, was selected as the acceptor. Coupling of bromide **7** with **8** in the presence of AgOTf and 2,4-lutidine furnished sugar-sugar orthoester **9** (*exo*, 78% based on **8**), together with 4-OH substituted regioisomer (*exo*, ~ 9% based on **8**). No detectable 2-OH substituted regioisomer, or multi-substituted oligosaccharides were obtained.



Scheme 3 (a) AgOTf (1.1 equiv of **1**), 2,4-lutidine (1.4 equiv of **1**), 4 Å M.S., anhyd CH_2Cl_2, 0 °C→ rt; (b) Ac_2O, Pyr; (c) TMSOTf (0.1 equiv.), anhyd CH_2Cl_2, -5 – -10 °C; (d) AgOTf (1.1 equiv), CH_2Cl_2; (e) 95% TFA (aq.).

The regioselectivity at 3-OH of **8** was elucidated from benzoylated orthoester **10** (the chemical shifts of H-2 and H-4 moved downfield to 5.50 and 5.36 ppm, respectively, while H-3 appeared upfield at 4.43 ppm). Rearrangement of **10** afforded **11** which was subsequently treated with 3% of HCl prepared with acetyl chloride in MeOH[11] to give disaccharide **12** in a good yield (76% from **10**). Reiteration of orthoester formation-acetylation-rearrangement using **7** and **12** as the donor and acceptor, respectively, provided linear trisaccharide **15** (66% based on **12**). Unambiguous assignment of the structure of this homo-trisaccharide was accomplished by ^1H-^1H COSY spectroscopy. The upfield chemical shifts at 4.10 and 3.86 ppm for H-3 and H-3' and the characteristic peaks at 5.00, 4.93, and 4.61 ppm for H-1, -1' and -1" clearly indicated the α-(1→3) linkage between rhamnopyranosides.[6,12]

It seems that 3-OH of rhamnose has priority in the orthoester formation based on Schemes 1 and 2. To investigate this observation further, we prepared acceptor **16** using a procedure similar to that published by Dutton.[13] Surprisingly, coupling of **16** with **1** gave 2-linked orthoester **17** (*exo*), contaminated by 3-linked regioisomer in a ratio of 6:1 (87% of total yield). Acetylation of **17** followed by rearrangement gave **19** whose ^{1}H NMR analysis confirmed the 2-OH selectivity (H-3 and H-4 of rhamnose appeared at 5.19, 4.92 ppm, respectively, while H-2 showed at 4.03 ppm). To investigate the acceptor properties in this orthoester formation, disaccharide acceptor **23** with an ether linkage at 4-OH of rhamnose (instead of the ester linkage at 4-OH in **16**) was prepared *via* direct glycosylation of **21** with **20**, followed by hydrolysis by TFA (95% aqueous solution). Coupling of **23** with acetobromogalactose **24** under the same reaction conditions as described for the preparation of **17**, again generated 2-OH glycosylated trisaccharide orthoester **25** (*exo*), which was further transformed into **27** (78% from **23**) *via* TMSOTf-catalyzed rearrangement. The full assignment of this hetero-trisaccharide **27** was supported by ^{1}H-^{1}H COSY spectroscopy, and the regioselectivity of 2-OH and 3-OH (in disaccharide acceptor **23**) is about 8:1. The amazing change in regioselectivity from 3-glycosylation (the triol **8** as the acceptor) to 2-glycosylation (the diol **16** or **23** as the acceptor) revealed that the orthoester formation is very sensitive to the steric factor, and it can recognize minute differences in the steric environment between two hydroxyl groups.

CONCLUSION

In this paper, we have shown highly efficient regio- and stereoselective syntheses of rhamnose-containing oligosaccharides *via* sugar-sugar orthoester formation. The advantages of this methodology are: a) very high 3-regioselectivity when unprotected rhamnose residue was used as the acceptor, and good 2-regioselectivity when rhamnose residue with 2,3-free OH was the acceptor; b) reliable stereochemical outcome in construction of 1,2-*trans* linked oligosaccharides; and c) a reduced number of protecting-deprotecting steps, thus significantly simplifying the complexity of oligosaccharide synthesis.[14] The application of these findings towards the preparation of triterpenoid glycosides[1b] from *Spergularia ramosa* is currently underway.

EXPERIMENTAL

General method. Optical rotations were determined at 23 °C with a Perkin-Elmer Model 241-MC automatic polarimeter. Melting points were determined with a "Mel-Temp" apparatus. Thin-layer chromatography (TLC) was performed on plates precoated with silica gel $60F_{254}$, detection being effected by observation under short wavelength UV light (254 nm), then spraying them with 30% (v/v) H_2SO_4 in MeOH and heating. Column chromatography was performed by elution of silica gel (100-200 mesh) columns. ^1H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ with a Bruker ARX 400 MHz spectrometer. FAB mass spectra were obtained with ThermoQuest TSQ 700.

3',4',6'-Tri-*O*-acetyl-α-D-glucopyranose 1',2'-[1,2-*O*-(*R*-Ethylidene)-β-L-rhamnopyranos]-3-yl Orthoacetate (3). A mixture of **2** (110 mg, 0.58 mmol), 2,4-lutidine (10 μL, 0.87 mmol) and 4 Å M.S. in anhydrous CH_2Cl_2 (15 mL) was precooled with an ice-water bath in a dark room, then bromide **1** (260 mg, 0.63 mmol) and AgOTf (180 mg, 0.69 mmol) were added in 2 equal portions (130 mg of **1** and 90 mg of AgOTf were used as one portion) at 2 h intervals. The mixture was then stirred at room temperature, the reaction being monitored by TLC. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography (1:1.5 EtOAc-petroleum ether) to give **3** (171 mg, 72%): $[\alpha]_D$ –63 ° (*c* 1.2, $CHCl_3$); ^1H NMR δ 1.33 (d, 3H, J = 6.1 Hz, H-6), 1.49 (d, 3H, J = 4.9 Hz, C*H*$_3$CH), 1.83 (s, 3H, C*H*$_3$), 2.09, 2.10, 2.12 (3s, 9H, 3 C*H*$_3$CO), 3.36 (dq, $J_{5,6}$ = 6.1 Hz, H-5), 3.54 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.1 Hz, H-4), 3.77 (dd, 1H, $J_{2,3}$ = 4.2, $J_{3,4}$ = 9.1 Hz, H-3), 3.95 (ddd, 1H, $J_{4',5'}$ = 9.5, $J_{5',6'a}$ = 3.2, $J_{5',6'b}$ = 4.8 Hz, H-5'), 4.10-4.22 (m, 3H, H-2, H-6'a, H-6'b), 4.51 (dd, 1H, $J_{1',2'}$ = 5.3, $J_{2',3'}$ = 3.2 Hz, H-2'), 4.92 (dd, 1H, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 9.5 Hz, H-4'), 5.18 (d, 1H, $J_{1,2}$ = 2.2 Hz, H-1), 5.21 (t, 1H, H-3'), 5.28 (q, 1H, J = 4.9 Hz, CH_3C*H*), 5.75 (d, 1H, $J_{1',2'}$ = 5.3 Hz, H-1'). FAB MS ($C_{22}H_{32}O_{14}$): *m/z* 543 $(M+Na)^+$.

3',4',6'-Tri-*O*-acetyl-α-D-glucopyranose 1',2'-[4-*O*-Acetyl-1,2-*O*-(*R*-ethylidene)-β-L-rhamnopyranos]-3-yl Orthoacetate (4). To a solution of **3** (340 mg) in pyridine (2.5 mL) was added acetic anhydride (1.5 mL). The solution was keep at room temperature for 5 h, then coevaporated with toluene under reduced pressure to give **4** with nearly quantitative yield: $[\alpha]_D$ –69 ° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.21 (d, 3H, $J_{5,6}$ = 6.2, H-6),

1.51 (d, 3H, J = 4.9 Hz, C*H*$_3$CH), 1.75 (s, 3H, C*H*$_3$), 3.46 (dq, 1H, $J_{4,5}$ = 9.5 Hz, H-5), 3.88 (ddd, 1H, H-5'), 3.95 (dd, 1H, $J_{2,3}$ = 4.2, $J_{3,4}$ = 9.6 Hz, H-3), 4.19 (ddd, 2H, $J_{5',6'a}$ = 4.6, $J_{5',6'b}$ = 1.1 Hz, H-6'a, H-6'b), 4.22 (dd, 1H, H-2), 4.44 (dd, 1H, $J_{1',2'}$ = 5.2, $J_{2',3'}$ = 3.1 Hz, H-2'), 4.89 (dd, 1H, $J_{3',4'}$ = 3.1, $J_{4',5'}$ = 9.5 Hz, H-4'), 4.97 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.18 (d, 1H, $J_{1,2}$ = 2.3 Hz, H-1), 5.19 (t, 1H, H-3'), 5.29 (q, 1H, CH$_3$C*H*), 5.67 (d, 1H, $J_{1',2'}$ = 5.2 Hz, H-1').

Anal. Calcd for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09. Found: C, 51.17; H, 6.12.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)-1,2-*O*-(*R*-ethylidene)-β-L-rhamnopyranose (5). A suspension of **3** (210 mg, 0.4 mmol) containing 4 Å M.S. in anhydrous CH_2Cl_2 (20 mL) was cooled to -5 to -10 °C, then TMSOTf (5 μL) was added under N_2 flow. The mixture was stirred at this temperature for about 90 min, then neutralized with Et_3N. After filtration and concentration under diminished pressure, the residue was subjected to column chromatography to give **5** as crystals (135 mg, 64%): mp 154-156 °C; $[\alpha]_D$ –56 ° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 1.33 (d, 3H, J = 6.1 Hz, H-6), 1.48 (d, 3H, J = 4.9 Hz, C*H*$_3$CH), 1.83 (s, 3H, C*H*$_3$C), 2.09, 2.10, 2.12, (3s, 9H, 3 C*H*$_3$CO), 3.36 (dq, 1H, $J_{4,5}$ = 9.2 Hz, H-5), 3.54 (t, 1H, $J_{3,4}$ = 9.2 Hz, H-4), 3.77 (dd, 1H, $J_{2,3}$ = 4.2 Hz, H-3), 3.93-3.96 (m, 1H, H-5'), 4.15 -4.21 (m, 3H, H-2, 2 H-6'), 4.51 (dd, 1H, $J_{1',2'}$ = 5.3, $J_{2',3'}$ = 3.2 Hz, H-2'), 4.92 (dd, 1H, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 9.5 Hz, H-4'), 5.18 (d, 1H, $J_{1,2}$ = 2.2 Hz, H-1), 5.21 (t, 1H, H-3'), 5.30 (q, 1H, CH$_3$C*H*), 5.75 (d, 1H, H-1').

Anal. Calcd for $C_{22}H_{32}O_{14}$: C, 50.77; H, 6.20. Found: C, 50.80; H, 6.18.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-1,2-*O*-(*R*-ethylidene)-β-L-rhamnopyranose (6). The same procedure was used to prepare **6** from **4** as described in the preparation of **5** from **3**: $[\alpha]_D$ –12 ° (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.22 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6), 1.53 (d, 3H, J = 4.9 Hz, C*H*$_3$CH), 2.01, 2.03, 2.04, 2.09 (4s, 12H, 4C*H*$_3$CO), 3.48 (dq, 1H, $J_{4,5}$ = 9.5 Hz, H-5), 3.70 (dt, 1H, $J_{4',5'}$ = 9.8, $J_{5',6'}$ = 3.3 Hz, H-5'), 3.90 (dd, 1H, $J_{2,3}$ = 4.0, $J_{3,4}$ = 9.5 Hz, H-3), 4.18-4.25 (m, 3H, H-2, 2 H-6'), 4.77 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 4.99 (t, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.02 (dd, 1H, $J_{2',3'}$ = 9.4 Hz, H-2'), 5.11 (dd, 1H, $J_{3',4'}$ = 9.4 Hz, H-4'), 5.16 (t, 1H, H-3'), 5.21 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 5.34 (q, 1H, CH$_3$C*H*).

Anal. Calcd for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09. Found: C, 51.15; H, 6.11.

3',4'-Di-*O*-acetyl-β-L-rhamnopyranose 1',2'-(Allyl 2,4-Di-*O*-benzoyl-β-L-rhamnopyranosid)-3-yl Orthoacetate (10). Coupling of **7** (720 mg, 2.04 mmol) and **8**

(380 mg, 1.86 mmol) as described in the preparation of **3** gave 3',4'-di-*O*-acetyl-β-L-rhamnopyranose 1',2'-(allyl β-L-rhamnopyranosid)-3-yl orthoacetate (**9**) as a syrup (628 mg, 78%): ^{13}C NMR ($CDCl_3$) δ 14.12, 17.35, 17.70, 20.62, 20.71, 25.14, 67.70, 68.31, 69.07, 70.07, 70.10, 70.53, 70.67, 74.37, 96.95, 98.34, 116.92, 124.35, 133.87, 169.83, 170.27 ppm. Compound **9** (500 mg, 1.17 mmol) was dissolved in pyridine (3 mL) and to the solution was added benzoyl chloride (0.5 mL, 4.3 mmol). The mixture was stirred at room temperature for 2 h then treated with MeOH to decompose the excess benzoyl chloride. The solution was concentrated under diminished pressure, and the residue was purified on silica gel column chromatography to give **10** (758 mg, 78% based on **8**) as a syrup: $[\alpha]_D$ +54 ° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.18 (d, 3H, $J_{5',6'}$ = 6.4 Hz, H-6') 1.30 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6), 1.59 (s, 3H, C*H*$_3$), 2.03, 2.09 (2s, 6H, 2C*H*$_3$CO), 3.50 (dq, 1H, $J_{4',5'}$ = 9.6 Hz, H-5'), 4.05 (dq, 1H, $J_{4,5}$ = 9.9, H-5), 4.09-4.26 (m, 2H, CH_2=CH-C*H*$_2$-), 4.43 (dd, 1H, $J_{2,3}$ = 3.3, $J_{3,4}$ = 9.9 Hz, H-3), 4.52 (dd, 1H, $J_{1',2'}$ = 2.4, $J_{2',3'}$ = 4.2 Hz, H-2'), 4.90 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 4.95 (t, 1H, $J_{3',4'}$ = 9.6 Hz, H-4'), 5.10 (dd, 1H, H-3'), 5.25-5.33 (m, 2H, C*H*$_2$=CH-CH$_2$-), 5.36 (t, 1H, H-4), 5.46 (d, 1H, H-1'), 5.50 (dd, 1H, H-2), 5.92-6.02 (m, 1H, CH_2=C*H*-CH$_2$-), 7.57-8.11 (m, 10 H, Ph). FAB MS ($C_{35}H_{40}O_{14}$): *m/z* 683 $(M-H)^+$.

Allyl (2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (11). To a solution of **10** (480 mg, 0.7 mmol) in anhydrous CH_2Cl_2 (15 mL) was added TMSOTf (13 μL, 0.07 mmol) as described in the preparation of **5**. Purification on column chromatography gave **11** as a syrup (403 mg, 84%): $[\alpha]_D$ +64 ° (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 1.05 (d, 3H, $J_{5',6'}$ = 6.2 Hz, H-6') 1.20 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6), 1.82, 1.89, 1.90 (3s, 9H, 3C*H*$_3$CO), 3.86 (dq, 1H, $J_{4',5'}$ = 9.9 Hz, H-5'), 3.90 (dq, 1H, $J_{4,5}$ = 9.8 Hz, H-5), 4.05-4.23 (m, 2H, CH_2=CH-C*H*$_2$-), 4.42 (dd, 1H, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.8 Hz, H-3), 4.87 (t, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 9.8 Hz, H-4'), 4.89 (dd, 1H, $J_{2',3'}$ = 3.4 Hz, H-2'), 4.91 (d, 1H, $J_{1',2'}$ = 1.8 Hz, H-1'), 5.01 (dd 1H, $J_{1,2}$ = 1.7 Hz, H-1), 5.07 (dd, 1H, H-3'), 5.25-5.38 (m, 2H, C*H*$_2$=CH-CH$_2$-), 5.45 (dd, 1H, H-2), 5.50 (t, 1H, H-4), 5.92-5.97 (m, 1H, CH_2=C*H*-CH$_2$-), 7.43-8.16 (m, 10H, Ph).

Anal. Calcd for $C_{35}H_{40}O_{14}$: C, 61.40; H, 5.89. Found: C, 61.31; H, 5.88.

Allyl (2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-(2,4-di-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (15). To a solution of **11** (810 mg, 1.18 mmol) in anhydrous MeOH (50 mL) was added acetyl chloride (1.5

mL) at 0 °C. The solution was sealed in a flask and stirred for 10 h at room temperature, then another portion of acetyl chloride (1 mL) was added. The reaction was further monitored by TLC until the starting material disappeared. The solution was neutralized with Et_3N, then concentrated to near dryness. The residue was passed through a short silica gel column obtaining **12** (424 mg, 90%) which was directly used for the following reaction. Coupling of **7** (280 mg, 0.79 mmol) with **12** (403 mg, 0.72 mmol) as described in the preparation of **3** gave **13**, which was acetylated in pyridine with acetic anhydride to furnish **14** as a syrup: ^{1}H NMR δ 1.12, 1.20, 1.26 (3d, 9H, H-6,6',6"), 1.68 (s, 3H, C*H*$_3$), 2.05 (s, 3H, C*H*$_3$CO), 2.08 (s, 6H, 2 C*H*$_3$CO), 2.16 (s, 3H, C*H*$_3$CO), 3.28, 3.46, 3.56 (3dq, 3H, H-5,5',5"), 3.91 (dd, 1H), 4.03-4.10 (m, 2H), 4.22-4.27 (m, 1H, CH_2=CH-C*H*$_2$-), 4.38 (dd, 1H), 4.56 (dd, 1H, $J_{1",2"}$ = 2.3, $J_{2",3"}$ = 4.1 Hz, H-2"), 4.97-5.08 (m, 3H), 5.25-5.29 (m, 2H), 5.32-5.34 (m, 1H, C*H*$_2$=CH-CH$_2$-), 5.37-5.40 (m, 1H, C*H*$_2$=CH-CH$_2$-), 5.41 (dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 3.3 Hz, H-2), 5.48 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 5.60-5.80 (m, 2H, H-1" and CH_2=C*H*-CH$_2$-), 7.47-8.12 (m, 10H, Ph). Intermediate **14** was treated with TMSOTf (0.1 equiv) in anhydrous methylene chloride, as in the preparation of **5** from **3**, to give trisaccharide **15** (397 mg, 66% based on **12**) as a syrup: $[\alpha]_D$ +34 ° (*c* 1.3, $CHCl_3$); ^{1}H-^{1}H COSY NMR ($CHCl_3$) δ 0.72 (d, 3H, $J_{5",6"}$ = 6.3 Hz, H-6"), 1.00 (d, 3H, $J_{5',6'}$ = 6.3 Hz, H-6'), 1.31 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.93, 1.98, 2.00, 2.01, 2.11 (5s, 15H, 5C*H*$_3$CO), 3.57 (dq, 1H, $J_{4",5"}$ = 9.7 Hz, H-5"), 3.84 (dq, 1H, $J_{4',5'}$ = 10.1 Hz, H-5'), 3.86 (dd, 1H, $J_{2',3'}$ = 3.3, $J_{3',4'}$ = 9.8 Hz, H-3'), 4.04-4.09 (m, 2H, $J_{4,5}$ = 9.9 Hz, H-5 and one proton of CH_2=CH-C*H*$_2$-), 4.21-4.24 (m, 1H, one proton of CH_2=CH-C*H*$_2$-), 4.10 (dd, 1H, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.9 Hz, H-3), 4.61 (d, 1H, $J_{1",2"}$ = 1.5 Hz, H-1"), 4.83 (dd, 1H, $J_{1',2'}$ = 1.9, $J_{2',3'}$ = 3.3 Hz, H-1'), 4.89 (dd, 1H, $J_{3",4"}$ = 9.8 Hz, H-4"), 4.91-4.94 (m, 3H, H-1', H-2", H-4'), 5.00 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1), 5.02 (dd, 1H, $J_{2",3"}$ = 3.3 Hz, H-3), 5.25-5.39 (m, 2H, C*H*$_2$=CH-CH$_2$-), 5.47 (dd, 1H, H-2), 5.48 (t, 1H, H-4), 5.91-5.96 (m, 1H, CH_2=C*H*-CH$_2$-), 7.44-8.15 (m, 10 H, Ph)..

Anal. Calcd for $C_{45}H_{54}O_{20}$: C, 59.08; H, 5.95. Found: C, 58.96; H, 6.00.

3',4',6'-Tri-*O*-acetyl-α-D-glucopyranose 1',2'-(Allyl 3,4-Di-*O*-acetyl-α-L-rhamnopyranosid)-2-yl Orthoacetate (18). Coupling of **1** (759 mg, 1.85 mmol) with **16** (413 mg, 1.68 mmol) as described in the preparation of **4** from **1** and **2**, gave **18** as a syrup (715 mg, 74%): $[\alpha]_D$ –93 ° (*c* 2, $CHCl_3$); ^{1}H NMR δ 1.17 (d, 1H, $J_{5,6}$ = 6.3 Hz, H-6), 1.67

(s, 3H, CH_3-), 1.99, 2.00, 2.07, 2.08, 2.09 (5s, 15H, 5CH_3CO), 3.79 (dq, 1H, $J_{4,5}$ = 9.6 Hz, H-5), 3.88 (dt, 1H, $J_{4',5'}$ = 9.4, $J_{5',6'}$ = 4.2 Hz, H-5'), 3.95-3.99 (m, 2H, CH_2=CH-CH_2-), 4.01 (dd, 1H, $J_{1,2}$ = 1.7, $J_{2,3}$ = 3.4 Hz, H-2), 4.15, 4.16 (2s, 2H, 2H-6'), 4.39 (dd, 1H, $J_{1',2'}$ = 5.2, $J_{2',3'}$ = 3.1 Hz, H-2'), 4.71 (d, 1H, H-1), 4.85 (dd, 1H, $J_{3',4'}$ = 1.8 Hz, H-4'), 5.02 (t, 1H, $J_{3,4}$ = 9.6 Hz, H-4), 5.13 (dd, 1H, H-3), 5.16 (dd, 1H, H-3'), 5.18-5.30 (m, 2H, CH_2=CH-CH_2-), 5.65 (d, 1H, H-1'), 5.81-5.91 (m, 1H, CH_2=CH-CH_2-). FAB MS ($C_{27}H_{38}O_{16}$): *m/z* 617 $(M-H)^+$..

Allyl (2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→2)-3,4-di-*O*-acetyl-α-L-rhamnopyranoside (19). Compound **19** (303 mg, 84%) was prepared from **18** (361 mg, 0.58 mmol) using the same procedure as in the preparation of **6** from **4**: $[\alpha]_D$ –76 ° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.19 (d, 3H, J = 6.2 Hz, H-6), 2.02, 2.03, 2.03, 2.07, 2.08, 2.15 (6s, 18H, 6CH_3CO), 3.65 (ddd, 1H, $J_{4',5'}$ = 10.0, $J_{5',6'a}$ = 4.8, $J_{5',6'b}$ = 2.4 Hz, H-5'), 3.82 (dq, 1H, $J_{4,5}$ = 9.8 Hz, H-5), 3.95-4.02 (m, 2H, CH_2=CH-CH_2-), 4.03 (dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 3.2 Hz, H-2), 4.10-4.23 (m, 4H, $J_{6'a,6'b}$ = 10.5 Hz, 2 H-6', CH_2=CH-CH_2-), 4.50 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 4.87 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.92 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, H-4), 5.05 (t, 1H, $J_{3',4'}$ = 10.0 Hz, H-4'), 5.07 (dd, 1H, $J_{2',3'}$ = 10.0 Hz, H-2'), 5.19 (dd, 1H, H-3), 5.22 (t, 1H, H-3'), 5.18, 5.20, 5.27, 5.31 (4dd, 2H, CH_2=CH-CH_2-), 5.83-5.93 (m, 1H, CH_2=CH-CH_2-).

Anal. Calcd for $C_{27}H_{38}O_{16}$: C, 52.43; H, 6.19. Found: C, 52.33; H, 6.21.

Allyl (2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (22). To a solution of **21** (600 mg, 2.46 mmol) containing 4 Å M.S. in anhydrous methylene dichloride (20 mL) was added **20** (831 mg, 2.46 mmol) and AgOTf (640 mg, 2.49 mmol) in a dark room. The mixture was stirred at room temperature for 2 h and then neutralized with Et_3N. After filtration and concentration, the residue was subjected to column chromatography to give **22** (993 mg, 89%) as a syrup: $[\alpha]_D$ +5.8 ° (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 1.25 (d, 3H, J = 6.4 Hz, H-6), 1.35, 1.54 (2s, 6H, C(CH_3)$_2$), 2.02, 2.03, 2.08 (3s, 9H, 3CH_3CO), 3.36 (dd, 1H, H-5'a), 3.41-3.55 (m, 2H, CH_2=CH-CH_2-), 3.90-4.20 (m, 6H, H-1', H-5'b, H-2, H-3, H-4, H-5), 4.80-5.02 (m, 3H, H-1, H-2', H-4'), 5.20 (t, 1H, J = 9.7 Hz, H-3'), 5.22-5.38 (m, 2H, CH_2=CH-CH_2-), 5.80-6.00 (m, 1H, CH_2=CH-CH_2-).

Anal. Calcd for $C_{23}H_{34}O_{12}$: C, 54.97; H, 6.82. Found: C, 55.03; H, 6.79.

Allyl (2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-(1→4)-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)]-3-*O*-acetyl-α-L-rhamnopyranoside (27). Compound **22** (297 mg, 0.65 mmol) was dissolved in trifluoroacetic acid (10 mL, 95% aqueous solution). The solution was stirred at room temperature for 2 h and then concentrated to dryness. The residue was purified on silica gel column chromatography to give **23** (252 mg, 93%) as a syrup. Coupling of **23** (240 mg, 0.58 mmol) and **24** (264 mg, 0.64 mmol) as described in the preparation of **3** obtained trisaccharide orthoester **25**. Acetylation of **25** with acetic anhydride in pyridine gave **26**, which was subjected to TMSOTf catalyzed rearrangement to furnish **27** as a syrup (337 mg, 78% from **23**): $[\alpha]_D$ –29 ° (*c* 1, $CHCl_3$); ^1H-^1H COSY NMR δ 1.29 (d, 1H, $J_{5,6}$ = 6.2 Hz, H-6 of Rha), 2.01, 2.01, 2.04, 2.06, 2.07, 2.13, 2.16, 2.17 (8s, 24H, C*H*$_3$CO), 3.24 (dd, 1H, $J_{4,5}$ = 9.7, $J_{5a,5b}$ = 11.8 Hz, H-5a of Xyl), 3.59 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.7 Hz, H-4 of Rha), 3.69-3.72 (m, 1H, H-5 of Rha), 3.85 (dd, 1H, $J_{5,6a}$ = 6.5, $J_{5,6b}$ = 7.4 Hz, H-5 of Gal), 3.92-3.98 (m, 2H, one proton of CH_2=CH-C*H*$_2$-, H-2 of Rha), 4.05-4,20 (m, 4H, H-5b of Xyl, H-6a, H-6b of Gal, one proton of CH_2=CH-C*H*$_2$-), 4.40 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1 of Gal), 4.54 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1 of Xyl), 4.87 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1 of Rha), 4.89 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2 of Xyl), 4.95-4.98 (m, 1H, H-4 of Xyl), 5.00 (dd, 1H, $J_{2,3}$ = 10.5, $J_{3,4}$ = 3.4 Hz, H-3 of Gal), 5.12 (t, 1H, $J_{3,4}$ = 9.4 Hz, H-3 of Xyl), 5.15 (dd, 1H, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.7 Hz, H-3 Rha), 5.18-5.35 (m, 3H, $J_{1,2}$ = 7.8, $J_{2,3}$ = 10.5 Hz, C*H*$_2$=CH-CH$_2$-, H-2 of Gal), 5.37 (dd, 1H, $J_{4,5}$ = 0.75, $J_{3,4}$ = 3.4 Hz, H-4 Gal), 5.82-5.91 (m. 1H, CH_2=C*H*-CH$_2$-).

Anal. Calcd for $C_{36}H_{50}O_{22}$: C, 51.80; H, 6.04. Found: C, 51.87; H, 6.01.

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