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Synthesis of a carboxyl linker containing P[k] trisaccharide

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Abstract—An efficient synthesis of a P[k] trisaccharide with a functionalized side arm at the reducing end for conjugation to other molecules is presented. Construction of the P[k] trisaccharide with a high α-selectivity was achieved in high yield by coupling a reactive galactosyl phosphite donor with a lactosyl acceptor.
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1. Introduction

Bacterial AB_5 toxins,[1] such as shiga like toxins (SLTs) and cholera toxins, consisting of a single catalytically active A subunit and a pentamer of B subunits govern a wide range of toxic effects in human populations. SLTs have been shown to enter target cells by a crucial recognition event involving tight binding of B subunits with the cell surface glycolipid globotriosylceramide [Gb_3, α-D-Gal-(1→4)-β-D-Gal-(1→4)-β-D-Glc-1→Ceramide].[1b,2] The binding of SLTs to multiple terminal trisaccharide of Gb_3, P[k]-trisaccharide [α-D-Gal-(1→4)-β-D-Gal-(1→4)-β-D-Glc], results in specific recognition and tight interaction.[1–3] Such multiple simultaneous molecular contacts are called as multivalent interaction.[4] The design and synthesis of multivalent ligands to block interactions between toxin B pentamer and its cell-surface receptors has a potential in drug design.[3]

Numerous diverse scaffolds have been generated as powerful multivalent carbohydrate carriers, including low-molecular weight displays,[3c,5] copolymers,[6] dendrimers[7] and nanoparticles.[8] The anchoring of the saccharide units to scaffolds depends critically on the introduction of an appropriately functionalized linker moiety onto the saccharide unit. Therefore, synthetic routes must be developed to attach a linker moiety to the reducing end of the saccharide ligand. The development of the multivalent P[k]-trisaccharide ligand is of particular interest[3] and the present work describes an efficient synthesis of P[k]-trisaccharide with a linker that has carboxyl functionality.

2. Result and discussion

The target P[k]-trisaccharide **1** (Fig. 1) comprises of a lactosyl unit joined to a galactosyl unit via an α(1→4) glycosidic bond and a linker that contains a carboxylic acid, which can be conjugated with scaffolds. Figure 1 depicts the retrosynthetic analysis of the P[k] trisaccharide **1**. The choice of this synthetic route, over two linear consecutive glycosylations, to assemble the trisaccharide with the linker moiety was dictated by many considerations. First, the literature[9] suggests that the coupling of the linker moiety to the assembled trisaccharide is not very efficient and the resulting product is not amenable to further chemical modification. Thus, the required linker moiety must be introduced at an early stage of the

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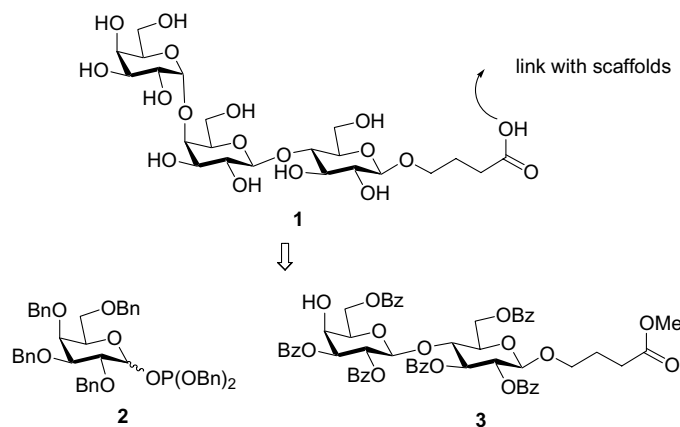
Figure 1. Retrosynthesis of compound **1**.

assembly of the trisaccharide. Secondly, lactose is a readily available starting compound to which pentenyl alcohol can be efficiently attached in only a few steps.[10] The pentenyl moiety can be easily functionalized to a carboxylic acid to furnish the lactosyl intermediate **3**.[11] Finally, although lactoside **3** with electron-withdrawing benzoyl groups markedly reduces the nucleophilicity of the 4′-OH group, such acceptors undergo glycosylation with high stereoselectivity.[12] A related reactive donor is required to obtain a good yield in the glycosylation reaction with the less reactive acceptor. Galactosyl phosphite **2** was selected as donor, because glycosyl phosphites can be easily prepared,[9,13] are moderately stable but highly reactive in glycosylation conditions and are activated by various reagents[14b] over a wide range of temperatures[15,16] (−78 °C to room temperature). Furthermore, benzyl-protected glycosyl phosphites are known to be highly α-selective during glycosylation reactions.[14,16] Also, galactosyl phosphite donors had not been previously used in the synthesis of trisaccharide **1** and the use of this donor should be explored. Based on these considerations, trisaccharide **1** was constructed by using galactosyl phosphite **2** as a donor and lactoside **3** as an acceptor.

The galactosyl donor **2** was prepared from pentaacetate galactoside **4** in a three-step process as shown in Scheme 1. Compound **4** was treated with thiocresol in the presence of BF₃·Et₂O[17] and then the acetate groups were removed with NaOMe/MeOH; benzylation of the resulting residues yielded the desired thiogalactoside **5**

(47% yield for three steps). Treatment of **5** with NBS in acetone/water mixture[18] gave galactoside with a free anomeric hydroxyl group, which was then reacted with DDP (dibenzyl *N*,*N*-diethyl phosphoramidite) in the presence of 1H-tetrazole[13,14] to produce the required benzyl protected galactosyl donor **2** with α/β = 9/1 (69% yield for two steps). Notably, donor **2** can be stored at 4 °C for at least 1 month without decomposing.

The synthesis of lactosyl **3** began with lactose derivative **6**, which was obtained according to a method in the literature, as shown in Scheme 2.[10] The deacetylation of compound **6** was followed by the selective protection of the 4′ and 6′-OH hydroxyl groups of the resulting product as benzylidene acetal.[10] The remaining free hydroxyl groups were then benzoylated to afford **8**; then acid hydrolysis of benzylidene acetal yielded **7**. Notably, the four-step process was performed without purifying each intermediate, resulting in a 44% overall yield. Selective benzoylation of the primary hydroxyl group of compound **7** was achieved using benzoyl chloride at −78 °C, to produce lactoside **8** (73%) with a free hydroxyl at the 4′-position.[19] Ruthenium trichloride[11] catalyzed the oxidation of the olefin moiety in **8**, generating the acceptor **9** (60%). Moreover, a competition between the free 4′-OH group of galactoside and the carboxylic acid of the linker in the acceptor **9** during the glycosylation with the donor **2** was anticipated. Thus, the carboxylic acid group of **9** was selectively protected as the methyl ester using TMSCl in methanol conditions,[20] to afford **3** with an 80% yield.
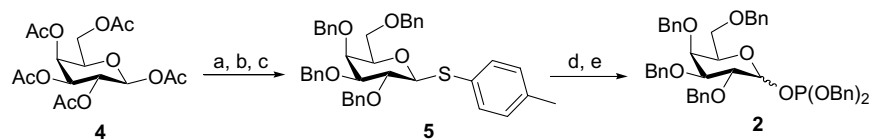
Scheme 1. Synthesis of galactosyl donor **2**. Reagents and conditions: (a) thiocresol, BF₃·OEt₂, CH₂Cl₂, 14 h, rt, 77%; (b) NaOMe, MeOH, 5 h, rt, 88%; (c) NaH, TBAI, BnBr, DMF, 16 h, rt, 69%; (d) NBS, acetone/water (1:9), 3 h, rt, 80%; (e) 1H-tetrazole, DDP, MeCN, 4 Å-MS, 3 h, rt, α:β = 9:1, 86%.
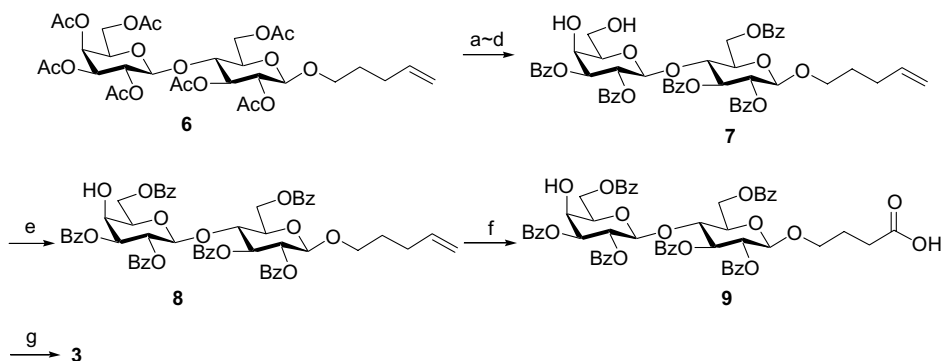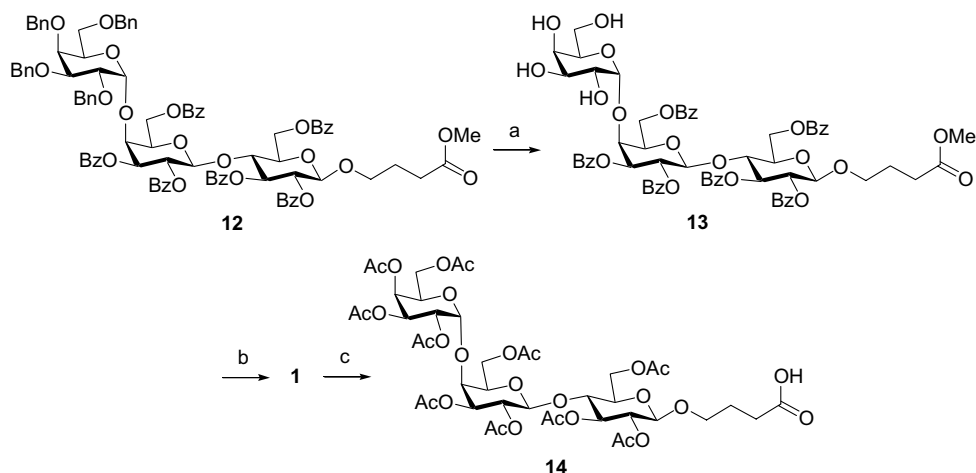
Scheme 2. Synthesis of lactoside acceptor **3**. Reagents and conditions: (a) NaOMe, MeOH; (b) benzaldehyde dimethyl acetal, CSA, MeCN/DMF (5.2), rt; (c) BzCl, pyridine, 14 h, rt; (d) TFA/H$_2$O, CH$_2$Cl$_2$, rt, 4 h, 4 steps 44%; (e) BzCl, pyridine, CH$_2$Cl$_2$, −78 °C–rt, 10 h, 73%; (f) RuCl$_3$/NaIO$_4$, CH$_2$Cl$_2$/MeCN/H$_2$O (2:2:3), 2 h, rt, 60%; (g) TMSCl, MeOH, 14 h, rt, 80%.

With three acceptors, **3**, **8**, and **9**, and donor **2** in hand, glycosylation between the acceptors and the donor could be explored. Table 1 summarizes the results. Glycosylation between acceptor **8** and donor **2** at −15 °C in dichloromethane with 0.1 equiv of TMSOTf (trimethylsilyltriflate) as an activator gave the corresponding trisaccharide **10** in low yield (data not shown). Increasing the amount of activator to 0.5 or 1.0 equiv and increasing the temperature from −15 °C to 0 °C slightly increased yields (entries 1 and 2). Disappointingly, acceptor **9** failed to react with **2** under similar

reaction conditions as were employed in the synthesis of **10** (entries 3 and 4). Finally, acceptor **3** was reacted with donor **2** at various temperatures, as shown in entries 5–8. The yield of the corresponding trisaccharide **12** depended on the reaction temperature, with the maximum obtained yield being 75% at 0 °C. The mixture of compounds **3** and **12** was very difficult to separate by column chromatography or HPLC. Consequently, the yield was determined based on NMR analysis. Notably, only the desired α-anomer products were obtained in the glycosylations of **2** with **3** and **8**. The chemical shift and

Table 1. Glycosylation of donor **2** with acceptors **3**, **8**, and **9**

			2 + Acceptor	TMSOTf, CH$_2$Cl$_2$ ———————→ 4Å-MS	Product	
	Acceptor	Temperature (°C)	Equivalents of TMSOTf	Yield (%)	Product	
1	**8**	−15	0.5	35		
2	**8**	−15 ∼ 0	1	45		
3	**9**	−15	1	—		
4	**9**	−23	1	—		
5	**3**	−23	1	48		
6	**3**	−15	1	50		
7	**3**	0	1	75		
8	**3**	Rt	1	72		

Scheme 3. Reagents and conditions: (a) H$_2$(g)/Pd(OH)$_2$, AcOH, 70%; (b) NaOH, CH$_2$Cl$_2$/MeOH/H$_2$O (2:3:1), 79%; (c) pyridine, Ac$_2$O, 60%.

coupling constant of H-1 at the newly formed anomeric center were 4.70 ppm and 3.2 Hz for **10** and 4.62 ppm and 2.0 Hz for **12**, respectively.

An attempt to oxidize the olefin of **10** resulted in decomposition. As depicted in Scheme 3, trisaccharide **12** was subjected to partial deprotection of the benzyl groups, by hydrogenation with a catalytic amount of Pd(OH)$_2$, to yield separable compound **13** in 70% yield. Compound **13** was further deprotected using sodium hydroxide in a mixed solvent of dichloromethane, methanol, and water to yield the desired target molecule **1** (79%). The trisaccharide **1** was characterized as a fully acetylated derivative **14**.

3. Conclusion

In conclusion, a P^k trisaccharide was constructed using galactosyl phosphite donor **2** and lactoside **3** with high α-selectivity in the formation of the glycosidic bond in a high yield. A study of the conjugation of **14** with various of scaffolds and related multivalent effects will be published in due course.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-400 or 500 MHz. Assignment of ^{1}H NMR spectra was achieved using 2D methods (COSY). Chemical shifts were expressed in ppm using residual CHCl$_3$ as reference. High-resolution mass spectra were obtained by means of a Micromass (Autospec) mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254). Silica gel 60 (E. Merck Co.) was employed for all flash chromatography. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless indicated otherwise. All solvents were dried and distilled by standard techniques.

4.2. Synthesis

4.2.1. *p*-Methylphenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (5).

To a solution of compound **4** (5 g, 12.81 mmol) in CH$_2$Cl$_2$ (25 mL) was added thiocresol (1.9 g, 15.37 mmol) under N$_2$ at room temperature followed by addition of boron trifluoride diethyl etherate (3.25 mL, 25.62 mmol). The resulting mixture was stirred at room temperature for 12 h. Solvent was evaporated in vacuo, and the residue was dissolved in CH$_2$Cl$_2$ and washed with saturated NaHCO$_{3(aq)}$, water and brine. The organic extracts were dried over MgSO$_4$, concentrated and recrystallized from EtOAc/hexane to give the desired compound (4.15 g, 71%). R_f = 0.26 (1:2, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.98 (s, Ac, 3H), 2.05 (s, Ac, 3H), 2.11 (s, Ac, 3H), 2.12 (s, Ac, 3H), 2.36 (s, Me, 3H), 3.92 (td, *J* = 1.2 Hz, *J* = 6.8 Hz, H-5, 1H), 4.12 (dd, *J* = 6.8 Hz, *J* = 11.6 Hz, H-6a, 1H), 4.19 (dd, *J* = 6.8 Hz, *J* = 11.6 Hz, H-6b, 1H), 4.66 (d, *J* = 10.0 Hz, H-1, 1H), 5.05 (dd, *J* = 3.6 Hz, *J* = 10.0 Hz, H-3, 1H), 5.22 (t, *J* = 10.0 Hz, *J* = 10.0 Hz, H-2, 1H), 5.41 (dd, *J* = 1.2 Hz, *J* = 3.6 Hz, H-4, 1H), 7.40 (d, *J* = 8.0 Hz, Ph, 2H), 7.42 (d, *J* = 8.0 Hz, Ph, 2H).

To a solution of the above compound (4.15 g, 9.13 mmol) in CH$_3$OH (83 mL) was added NaOMe (0.42 g) under N$_2$ at rt. The reaction mixture was stirred for 7 h at room temperature. The solvent was evaporated and the residue was purified by column chromatography to give the desired compound (2.30 g, 88%). R_f = 0.48 (1:4, MeOH/CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.38 (s, Me, 3H), 3.55 (dd, *J* = 3.0 Hz, *J* = 9.2 Hz, H-3, 1H), 3.58–3.67 (m, H-2, H-5, 2H), 3.77 (dd, *J* = 5.6 Hz, *J* = 11.6 Hz, H-6a, 1H), 3.83 (dd,

$J = 6.4$ Hz, $J = 11.6$ Hz, H-6b, 1H), 3.96 (d, $J = 3.0$ Hz, H-4, 1H), 4.57 (d, $J = 9.6$ Hz, H-1, 1H), 7.19 (d, $J = 8.0$ Hz, Ph, 2H), 7.52 (d, $J = 8.0$ Hz, Ph, 2H).

DMF (20 mL) was added to a flask containing the above compound (0.57 g, 1.99 mmol) and TBAI (46 mg, 0.12 mmol), then cooled to 0 °C. NaH (0.38 g, 15.93 mmol) was added to the stirred solution over 30 min. BnBr (1.89 mL, 15.93 mmol) was added dropwise and stirred at rt for 12 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc and washed with water and brine. The organic layer extracts were dried over $MgSO_4$ and purified by silica gel chromatography (1:4, EtOAc/hexane) to give compound **5** (0.89 g, 69%). $R_f = 0.67$ (1:4, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.24 (s, Me, 3H), 3.52–3.61 (m, H-3, H-5, H-6, 4H), 3.85 (t, $J = 9.6$ Hz, $J = 9.6$ Hz, H-2, 1H), 3.92 (d, $J = 2.8$ Hz, H-4, 1H), 4.37 (d, $J = 11.6$ Hz, Bn, 1H), 4.42 (d, $J = 11.6$ Hz, Bn, 1H), 4.54 (d, $J = 10.0$ Hz, Bn, 1H), 4.55 (d, $J = 11.6$ Hz, Bn, 1H), 4.67 (s, Bn-6, 2H), 4.68 (d, $J = 10.0$ Hz, Bn, 1H), 4.75 (d, $J = 10.0$ Hz, Bn, 1H), 4.91 (d, $J = 11.6$ Hz, H-1, 1H), 6.94 (d, $J = 8.0$ Hz, SPh, 2H), 7.21–7.35 (m, Bn, 20H), 7.41 (d, $J = 8.0$ Hz, 2H).

4.2.2. 2,3,4,6-Tetra-*O*-benzyl α/β-D-galactopyranosyl phosphite (2).

NBS (370 mg, 2.09 mmol) was added to the flask, which contained compound **5** (900 mg, 1.39 mmol) in acetone/water (1:9) (25 mL) stirred under N_2 at rt for 3 h. However, if the solution becomes colorless, excess amount of NBS should be added in small portions till the orange color persists. The solvent was evaporated in vacuo, the residue was dissolved in EtOAc, organic layer was washed with water, saturated $NaHCO_{3(aq)}$, and brine. The organic layer extracts were dried over $MgSO_4$ and the residue was purified by column chromatography (1:2, EtOAc/hexane) to give the desired compound (0.60 g, 80%). $R_f = 0.30$ (1:2, EtOAc/hexane). To a solution of the above compound (1.5 g, 2.77 mmol) in acetonitrile (15 mL) containing 4 Å molecular sieve, was added 1H-tetrazole (291 mg, 4.16 mmol) and DDP (1.48 mL, 4.162 mmol) under N_2. The reaction mixture was stirred at rt for 3 h. The solvent was removed and the residue was purified by column chromatography (1:2, EtOAc/hexane) to provide compound **2** (1.80 g, 86%). $R_f = 0.62$ (1:2, EtOAc/hexane). ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.35 (dd, $J = 2.6$ Hz, $J = 6.2$ Hz, H-4, 1H), 3.53–3.62 (m, H-6, 2H), 3.91 (dd, $J = 2.6$ Hz, $J = 9.8$ Hz, H-3, 1H), 4.05 (dd, $J = 3.6$ Hz, $J = 9.8$ Hz, H-2, 1H), 4.15–4.18 (m, H-5, 1H), 4.42 (d, $J = 12.0$ Hz, Bn, 2H), 4.49 (d, $J = 12.0$ Hz, Bn, 2H), 4.59 (d, $J = 11.2$ Hz, Bn, 2H), 4.84 (d, $J = 11.2$ Hz, Bn, 2H), 5.02–5.13 (m, P(OBn)$_2$, 4H), 5.29 (d, $J = 3.6$ Hz, H-1, 1H), 7.29–7.38 (m, Bn, 30H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 40.92, 69.76, 69.81, 71.03, 71.52, 74.06, 74.52, 74.60, 75.43, 75.43, 78.53, 88.69, 115.98, 116.07, 116.16, 116.22, 116.28, 116.38, 116.54, 116.67, 116.90.

4.2.3. Pent-4-enyl 2,2′,3,3′,6-penta-*O*-benzoyl-β-D-lactoside (7).

The compound **6**[10] (6.65 g, 9.44 mmol) was dissolved in MeOH (133 mL) then NaOMe (66.5 g) was added. The reaction mixture was stirred at rt for 7 h. The solvent was evaporated to obtain a desired compound (3.67 g), which was used in the next step without further purification, $R_f = 0.08$ (1:4, MeOH/CH$_2$Cl$_2$). Solution of above compound (3.667 g, 9.59 mmol) in CH$_3$CN/DMF (5:2) (56 mL) was added benzaldehyde dimethyl acetal (3.76 mL, 24.94 mmol) and camphor-sulfonic acid (111.4 mg, 0.48 mmol) under N_2. After stirring for 16 h at rt, the mixture was diluted with CH$_2$Cl$_2$. The residue was washed with saturated $NaHCO_{3(aq)}$, and the organic layer was dried over $MgSO_4$ and then concentrated to give desired compound (4.38 g), which was used in the next step without further purification. $R_f = 0.60$ (1:4, MeOH/CH$_2$Cl$_2$).

To a solution of the above compound (4.38 g, 8.79 mmol) in dry pyridine (43 mL), was added benzoyl chloride dropwised (4.40 mL, 87.91 mmol) under N_2. The reaction mixture was stirred at rt for 15 h and then CH$_3$OH was added. Solvent was evaporated in vacuo and the residue was dissolved in EtOAc. Organic layer was washed with water and a solution of 10% HCl. The organic extracts were dried over $MgSO_4$ and evaporated in vacuo to obtain compound (8.32 g), which was used in next step without further purification. $R_f = 0.32$ (1:2, EtOAc/hexane).

A solution of the above compound (8.32 g, 8.28 mmol) in CH$_2$Cl$_2$ (80 mL) was added TFA (9.22 mL, 124.18 mmol) and 2 drops of H_2O. The reaction mixture was stirred at rt for 5 h. The mixture was then diluted with CH$_2$Cl$_2$ before being washed successively with water and a saturated $NaHCO_{3(aq)}$. The organic extracts were dried over $MgSO_4$ and purified by silica gel chromatography (1:1, EtOAc/hexane) to obtain compound **7** (7.12 g, 44% for 4 steps). $[\alpha]_D^{32}$ 54.889 (*c* 1.12, CHCl$_3$), $R_f = 0.34$ (1:1, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.41–1.54 (m, H-b, 2H), 1.77–1.90 (m, H-c, 2H), 3.19 (dd, $J = 6.8$ Hz, $J = 13.2$ Hz, H-6′, 1H), 3.26–3.31 (m, H-5′, H-6′, 2H), 3.37 (td, $J = 6.4$ Hz, $J = 10.0$ Hz, H-a, 1H), 3.72 (td, $J = 6.4$ Hz, $J = 10.0$ Hz, H-a, 1H), 3.77 (ddd, $J = 2.0$ Hz, $J = 4.8$ Hz, $J = 9.6$ Hz, H-5, 1H), 4.11 (t, $J = 9.6$ Hz, H-4, 1H), 4.11–4.12 (m, H-4, 1H), 4.34 (dd, $J = 4.8$ Hz, $J = 12.0$ Hz, H-6a, 1H), 4.52 (dd, $J = 2.0$ Hz, $J = 12.0$ Hz, H-6b, 1H), 4.61 (d, $J = 8.0$ Hz, H-1, 1H), 4.67–4.73 (m, H-e, 2H), 4.71 (d, $J = 8.0$ Hz, H-1′, 1H), 5.02 (dd, $J = 3.6$ Hz, $J = 10.2$ Hz, H-3′, 1H), 5.32 (dd, $J = 8.0$ Hz, $J = 9.6$ Hz, H-2, 1H), 5.47–5.57 (m, H-d, 1H), 5.66 (dd, $J = 9.6$ Hz, $J = 9.6$ Hz, H-3, 1H), 5.67 (dd, $J = 8.0$ Hz, $J = 10.2$ Hz, H-2′, 1H), 7.13–7.53 (m, Bz, 18H), 7.81–7.96 (m, Bz, 12H); [13]C

NMR (100 MHz, CDCl$_3$): δ 28.74, 29.94, 62.47, 62.93, 68.27, 69.45, 70.05, 72.17, 73.15, 73.90, 74.52, 76.83, 101.01, 101.57, 115.01, 128.59, 128.64, 128.86, 129.10, 129.28, 129.63, 129.83, 129.89, 129.96, 130.03, 133.39, 133.52, 133.67, 137.92, 165.35, 165.49, 165.78, 166.00, 166.11. HRMS (FAB) Anal. Calcd for C$_{52}$H$_{50}$O$_{16}$ [M+Na]$^+$: 953.2997; found: 953.2986.

4.2.4. Pent-4-enyl 2,2′,3,3′,6,6′-hexa-O-benzoyl-β-D-lactoside (8). To a solution of compound **7** (2 g, 2.15 mmol) and pyridine (40 mL) in CH$_2$Cl$_2$ (60 mL) at −78 °C was added benzoyl chloride (0.27 mL, 4.30 mmol). Excess of benzoyl chloride (0.27 mL, 4.30 mmol) was added after 2.5 h. The mixture was quenched with MeOH after 6 h and the mixture was concentrated. The residue was purified by column chromatography (1:1, EtOAc/hexane) to give compound **8** (1.61 g, 73%). $[\alpha]_D^{32}$ 65.815 (c 0.15, CHCl$_3$), R_f = 0.50 (1:1, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.52–1.64 (m, H-b, 2H), 1.90–1.97 (m, H-c, 2H), 3.44 (td, J = 6.4 Hz, J = 9.6 Hz, H-a, 1H), 3.62–3.67 (m, H-5′, H-6′, 2H), 3.82 (td, J = 6.4 Hz, J = 9.6 Hz, H-a, 1H), 3.86–3.81 (m, H-5, 1H), 4.12–4.06 (m, H-4′, H-6′, 2H), 4.22 (dd, J = 9.6 Hz, J = 9.6 Hz, H-4, 1H), 4.46 (dd, J = 4.4 Hz, J = 12.0 Hz, H-6a, 1H), 4.59 (dd, J = 1.6 Hz, J = 12.0 Hz, H-6b, 1H), 4.67 (d, J = 7.6 Hz, H-1, 1H), 4.79 (d, J = 8.0 Hz, H-1′, 1H), 4.81–4.76 (m, H-e, 2H), 5.15 (dd, J = 3.6 Hz, J = 10.2 Hz, H-3′, 1H), 5.43 (dd, J = 7.6 Hz, J = 9.6 Hz, H-2, 1H), 5.55–5.66 (tdd, J = 6.8 Hz, J = 10.8 Hz, J = 17.6 Hz, H-d, 1H), 5.73 (dd, J = 7.6 Hz, J = 10.2 Hz, H-2′, 1H), 5.77 (dd, J = 9.2 Hz, J = 9.6 Hz, H-3, 1H), 7.15–7.64 (m, Bz, 15H), 7.91–8.13 (m, Bz, 15H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.59, 29.83, 61.73, 62.62, 66.89, 69.45, 69.75, 71.97, 72.65, 73.07, 73.24, 74.09, 76.34, 101.12, 101.16, 114.93, 128.45, 128.55, 128.71, 128.92, 129.00, 129.53, 129.70, 129.76, 129.84, 129.96, 130.26, 133.25, 133.34, 133.55, 137.81, 165.08, 165.34, 165.76, 165.80, 165.96, 166.12. HRMS (FAB) calcd for C$_{59}$H$_{54}$O$_{17}$ [M+Na]$^+$: 1057.3259; found: 1057.3232.

4.2.5. 3-Carboxypropyl 2,2′,3,3′,6,6′-hexa-O-benzoyl-β-D-lactoside (9). NaIO$_4$ (0.61 g, 2.82 mmol) and RuCl$_3$ (58.5 mg, 0.28 mmol) were added to a vigorously stirred solution of compound **8** (1.46 g, 1.41 mmol) in CH$_2$Cl$_2$/CH$_3$CN/H$_2$O. After 2 h, an additional amount of NaIO$_4$ (0.61 g, 2.82 mmol) was added and the stirring was continued for another 2–3 h. The mixture was then diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and then concentrated. The resulting residues were purified by silica gel chromatography (1:1, EtOAc/hexane) to give compound **9** (0.90 g, 60%), R_f = 0.21 (1:1, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.74–1.82 (m, H-b, 2H), 2.24–2.27 (m, H-c, 2H), 3.48–3.53 (m, H-a, 1H), 3.64–3.70 (m, H-6a′, H-5′, 2H), 3.80–3.86 (m, H-5, H-a, 2H), 4.07–4.12 (m, H-6b′, 1H), 4.14 (d, J = 3.2 Hz, H-4′, 1H), 4.21 (t, J = 9.6 Hz, J = 9.6 Hz, H-4, 1H), 4.47 (dd, J = 4.2 Hz, J = 12.2 Hz, H-6a, 1H), 4.59 (d, J = 11.6 Hz, H-6b, 1H), 4.68 (d, J = 8.2 Hz, H-1, 1H), 4.80 (d, J = 8.0 Hz, H-1′, 1H), 5.12 (dd, J = 3.2 Hz, J = 10.4 Hz, H-3′, 1H), 5.42 (t, J = 8.2 Hz, J = 8.2 Hz, H-2, 1H), 5.73–5.80 (m, H-2′, H-3, 2H), 7.21–7.62 (m, Bz, 15H), 7.91–8.02 (m, Bz, 15H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 24.69, 30.07, 62.05, 62.68, 67.02, 68.82, 69.93, 72.08, 72.88, 73.26, 73.30, 74.29, 76.43, 76.92, 77.23, 77.55, 101.12, 101.28, 128.57, 128.64, 128.64, 128.79, 129.77, 129.84, 129.91, 130.04, 133.442, 133.60, 165.25, 165.49, 165.94, 166.11, 166.21, 177.81. HRMS (FAB) calcd for C$_{58}$H$_{53}$O$_{19}$ [M+H]$^+$: 1053.3181; found: 1053.3190.

4.2.6. 3-Methoxycarbonylpropyl 2′,3′,6′-tri-O-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (3). A solution of the compound **9** (100 mg, 0.10 mmol) in dried MeOH (2 mL) was added trimethylsilyl chloride dropwise (23 µL, 0.209 mmol) and the mixture was stirred for 20 h at rt. The solvent was evaporated in vacuo and the residue was purified by column chromatography (1:2, EtOAc/hexane) to give compound **3** (92 mg, 91%). $[\alpha]_D^{32}$ 59.569 (c 1.25, CHCl$_3$), R_f = 0.15 (1:2, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.77–1.82 (m, H-b, 2H), 2.23 (t, J = 7.6 Hz, H-c, 2H), 3.48–3.53 (m, H-a, 1H), 3.49 (s, Me, 3H), 3.65–3.73 (m, H-5′, H-6′, 2H), 3.81–3.88 (m, H-a, H-5, 2H), 4.13 (dd, J = 5.2 Hz, J = 10.8 Hz, H-5′, 1H), 4.17 (d, J = 3.2 Hz, H-4′, 1H), 4.22 (t, J = 9.2 Hz, J = 9.6 Hz, H-4, 1H), 4.48 (dd, J = 4.8 Hz, J = 12.0 Hz, H-6a, 1H), 4.59 (dd, J = 2.0 Hz, J = 12.0 Hz, H-6b, 1H), 4.69 (d, J = 8.0 Hz, H-1, 1H), 4.81 (d, J = 8.0 Hz, H-1′, 1H), 5.17 (dd, J = 3.2 Hz, J = 10.4 Hz, H-3′, 1H), 5.42 (dd, J = 8.0 Hz, J = 9.6 Hz, H-2, 1H), 5.76 (dd, J = 8.0 Hz, J = 10.4 Hz, H-2′, 1H), 5.77 (dd, J = 9.2 Hz, J = 9.6 Hz, H-3, 1H), 7.23–7.63 (m, Bz, 16H), 7.91–8.03 (m, Bz, 14H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 24.9, 30.16, 51.48, 62.20, 66.72, 67.00, 68.92, 69.94, 72.09, 72.91, 73.24, 73.29, 74.35, 76.41, 101.12, 101.27, 128.51, 128.60, 128.79, 129.04, 129.57, 129.75, 129.82, 129.88, 129.93, 130.02, 133.32, 133.38, 133.56, 165.21, 165.41, 165.85, 165.94, 166.03, 166.18, 173.71. HRMS (FAB) calcd for C$_{59}$H$_{54}$O$_{19}$ [M+Na]$^+$: 1089.3259; found: 1089.3157.

4.2.7. Pent-4-enyl 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (10). A solution of donor **8** (223.6 mg, 0.29 mmol), acceptor **2** (200 mg, 0.19 mmol), and 4 Å molecular sieve in CH$_2$Cl$_2$ (15 mL) was stirred 30 min at 0 °C. A TMSOTf was added to this mixture dropwise (35 µL, 0.19 mmol). The reaction mixture was stirred for 3 h at 0 °C, then filtered through a Celite bed and concentrated. The residues were purified

by column chromatography (1:2, EtOAc/hexane) to give compound **10** (192 mg, 75%). R_f = 0.24 (1:2, EtOAc/hexane); ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.84–0.93 (m, H-b, 2H), 1.87–1.94 (m, H-c, 2H), 2.97 (dd, J = 5.0 Hz, J = 8.2 Hz, H-6′a, 1H), 3.31–3.36 (m, H-5′, 1H), 3.41 (td, J = 6.8 Hz, J = 9.6 Hz, H-a, 1H), 3.65–3.69 (m, H-5″, 1H), 3.79 (td, J = 6.2 Hz, J = 9.6 Hz, H-a, 1H), 3.84–3.89 (m, H-5, 1H), 3.90 (dd, J = 3.2 Hz, J = 10.4 Hz, H-3″, 1H), 3.95 (dd, J = 10.4 Hz, J = 2.4 Hz, H-3″, 1H), 4.07 (br, H-4″, 1H), 4.14–4.19 (m, H-6″a, 1H), 4.18 (d, J = 12.0 Hz, Bn), 4.24 (d, J = 9.6 Hz, H-4, 1H), 4.24–4.27 (m, H-6′b, 1H), 4.30 (d, J = 2.4 Hz, H-4′, 1H), 4.44 (d, J = 11.2 Hz, Bn, 1H), 4.48 (dd, J = 4.4 Hz, J = 12.0 Hz, H-6b, 1H), 4.55 (dd, J = 6.4 Hz, J = 10.8 Hz, H-6″b, 1H), 4.57 (s, Bn, 2H), 4.65 (d, J = 7.6 Hz, H-1, 1H), 4.64–4.79 (m, H-6′b, H-e, Bn, 4H), 4.70 (d, J = 3.2 Hz, H-1″, 1H), 4.81 (d, J = 10.8 Hz, Bn, 2H), 4.87 (d, J = 8.0 Hz, H-1′, 1H), 5.03 (dd, J = 2.4, J = 10.8 Hz, H-3′, 1H), 5.36 (dd, J = 7.6 Hz, J = 9.6 Hz, H-2, 1H), 5.59 (tdd, J = 6.4 Hz, J = 10.2 Hz, J = 17.0 Hz, H-d, 1H), 5.74 (dd, J = 8.0 Hz, J = 10.8 Hz, H-2′, 1H), 5.79 (t, J = 9.6 Hz, J = 9.6 Hz, H-3, 1H), 7.05–7.41 (m, Bn, Bz, 35H), 7.46–7.61 (m, Bz, 5H), 7.79–8.04 (m, Bz, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.70, 29.94, 62.35, 62.74, 67.55, 69.47, 69.95, 70.08, 72.55, 72.86, 73.17, 73.23, 73.26, 73.49, 73.61, 74.65, 74.95, 75.12, 75.70, 76.06, 76.63, 77.43, 77.43, 79.32, 101.12, 101.35, 101.48, 115.01, 127.47, 127.51, 127.59, 127.65, 127.72, 127.74, 127.80, 127.83, 127.87, 128.13, 128.21, 128.24, 128.28, 128.40, 128.46, 128.49, 128.51, 128.61, 128.67, 128.69, 128.78, 128.99, 129.16, 129.18, 129.25, 129.54, 129.70, 129.79, 129.84, 129.93, 129.98, 130.00, 130.03, 130.07, 133.23, 133.27, 133.31, 133.37, 133.40, 137.95, 138.43, 138.72, 139.12, 139.17, 165.24, 165.46, 165.50, 165.83, 166.04, 166.69.

4.2.8. 3-Methoxycarbonylpropyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (12).

The procedure for the synthesis of compound **12** is similar as described in the synthesis of **10**. [α]$_D^{32}$ 55.241 (*c* 1.14, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.24–3.29 (m, H-5′, 1H), 3.35–3.48 (m, H-a, 1H), 3.41 (s, CH$_3$, 3H), 3.58–3.61 (m, H-5″, 1H), 3.71–3.88 (m, H-a, H-5, H-2″, H-3″, 4H), 3.99 (br, H-4″, 1H), 4.07–4.22 (m, H-6″, H-4, H-6′, H-4′, 4H), 4.11 (d, J = 12.4 Hz, Bn, 1H), 4.37 (d, J = 11.2 Hz, Bn, 1H), 4.39–4.48 (m, H-6, H-6″, 2H), 4.48 (s, Bn, 2H), 4.56 (d, J = 7.2 Hz, H-1, 1H), 4.55–4.67 (m, H-6, Bn, 3H), 4.62 (d, J = 3.2 Hz, H-1″, 1H), 4.73 (d, J = 10.8 Hz, Bn, 1H), 4.79 (d, J = 7.6 Hz, H-1′, 1H), 4.96 (dd, J = 10.8 Hz, J = 2.0 Hz, H-3′, 1H), 5.26 (dd, J = 7.2 Hz, J = 9.6 Hz, H-2, 1H), 5.66 (dd, J = 7.6 Hz, J = 10.8 Hz, H-2′, 1H), 5.71 (t, J = 9.6 Hz, H-3, 1H), 7.00–7.53 (m, Bn, Bz, 30H), 7.72–7.95 (m, Bz, 15H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 24.90, 30.18, 51.55, 62.35, 62.67, 67.56, 68.89, 69.96, 70.08, 72.50, 72.86, 73.18, 73.18, 73.31, 73.50, 73.62, 74.64, 74.95, 75.12, 75.69, 76.05, 75.58, 79.32, 101.10, 101.38, 101.48, 127.48, 127.51, 127.60, 127.66, 127.83, 128.21, 128.25, 128.40, 128.47, 128.50, 128.52, 128.63, 128.79, 129.15, 129.25, 129.63, 129.80, 129.84, 129.99, 130.03, 130.08, 133.29, 133.34, 133.42, 138.42, 138.71, 139.12, 139.17, 165.25, 165.48, 165.83, 166.04, 166.70, 173.79. MS (*m/z*) [M+Na]$^+$: 1612.6.

4.2.9. 3-Methoxycarbonylpropyl α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (13).

The compound **12** (350 mg, 0.22 mmol) was dissolved in a small amount of EtOAc and MeOH (2 mL), and then Pd(OH)$_2$ (350 mg) was added. The reaction mixture was purged by argon and then hydrogen, and stirred at rt for 12 h. The reaction mixture was filtered through Celite bed and concentrated. The resulting residue was purified by column chromatography (1:1, EtOAc/hexane) to give compound **13** (190 mg, 70%). [α]$_D^{32}$ 55.843 (*c* 0.44, CHCl$_3$), R_f = 0.39 (1:1, EtOAc/hexane + 10% MeOH); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.78–1.83 (m, H-b, 2H), 2.26 (t, J = 7.2 Hz, H-c, 2H), 3.47–3.53 (m, H-6″a, H-6″b, 2H), 3.50 (s, Me, 3H), 3.60 (ddd, J = 3.6 Hz, J = 10.0 Hz, J = 13.6 Hz, H-a, 1H), 3.69 (dd, J = 3.0 Hz, J = 10.0 Hz, H-3″, 1H), 3.76 (dd, J = 3.6 Hz, J = 10.0 Hz, H-2″, 1H), 3.83–3.96 (m, H-a, H-5, 2H), 3.86 (td, J = 5.6 Hz, J = 6.0 Hz, J = 10.0 Hz, H-5′, 1H), 4.00 (dd, J = 0.8 Hz, J = 3.2 Hz, H-4″, 1H), 4.02–4.08 (m, H-5, 1H), 4.05 (dd, J = 6.0 Hz, J = 10.6 Hz, H-6′a, 1H), 4.34–4.39 (m, H-4, H-4′, 2H), 4.47 (dd, J = 5.6 Hz, J = 10.6 Hz, H-6′b, 1H), 4.56 (dd, J = 5.6 Hz, J = 12.0 Hz, H-6a, 1H), 4.71 (dd, J = 2.0 Hz, J = 12.0 Hz, H-6b, 1H), 4.87–4.89 (m, H-1″, 1H), 4.91 (d, J = 8.0 Hz, H-1, 1H), 5.12 (d, J = 8.0 Hz, H-1′, 1H), 5.39 (dd, J = 8.0 Hz, J = 9.6 Hz, H-2, 1H), 5.43 (dd, J = 2.8 Hz, J = 10.4 Hz, H-3′, 1H), 5.73 (dd, J = 8.0 Hz, J = 10.4 Hz, H-2′, 1H), 5.82 (t, J = 9.6 Hz, J = 9.6 Hz, H-3, 1H), 7.25–7.31 (m, Bz, 19H), 7.94–8.12 (m, Bz, 11H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 26.07, 30.82, 31.07, 52.01, 62.36, 63.88, 64.24, 69.99, 70.69, 71.08, 71.14, 71.89, 72.34, 73.82, 74.44, 74.69, 75.04, 75.27, 76.03, 78.30, 101.96, 102.39, 102.75, 129.66, 129.71, 129.75, 129.94, 130.35, 130.73, 130.78, 130.82, 130.98, 131.03, 131.06, 131.11, 131.37, 134.52, 134.67, 134.74, 166.98, 167.03, 167.36, 167.41, 167.50, 167.55, 175.47. HRMS (FAB) calcd for C$_{65}$H$_{64}$O$_{24}$ [M+Na]$^+$: 1251.3685; found: 1251.3689.

4.2.10. 3-Carboxypropyl α-D-galactopyranosyl-(1→4)-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (1).

To a mixture of compound **13** (150 mg, 0.12 mmol) in CH$_2$Cl$_2$ (6 mL), water (3 mL) and CH$_3$OH (9 mL) was added 1 N NaOH (0.3 mL) and the reaction was stirred

at rt for 12 h. The reaction mixture was neutralized by acidic resin, filtered, and then concentrated. The resulting residue was purified by column chromatography (1:1 MeOH/CH$_2$Cl$_2$) to give compound **1** (57 mg, 79%). R_f = 0.12 (1:1, MeOH/CH$_2$Cl$_2$ twice); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.78–1.88 (m, H-b, 2H), 2.17–2.22 (m, H-c, 2H), 3.23–3.27 (m, 1H), 3.50–3.94 (m, 17H), 3.98 (t, J = 3.6 Hz, 1H), 4.29 (t, J = 6.4 Hz, 1H), 4.2 (d, J = 8.0 Hz, 1H), 4.45 (d, J = 7.6 Hz, 1H), 4.79 (br, H-1″, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 25.86, 33.88, 60.22, 60.38, 60.84, 68.86, 69.36, 69.72, 69.84, 71.05, 71.27, 73.19, 73.36, 74.78, 74.78, 75.34, 78.27, 79.09, 101.13, 102.54, 103.96, 168.36.

4.2.11. 3-Carboxypropyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (14).

To a solution of compound **1** (20 mg, 0.034 mmol) in pyridine (0.2 mL) was added Ac$_2$O (3.2 μL, 0.34 mmol) and the reaction mixture was stirred at rt for overnight. The solvent was evaporated in vacuo, and the resulting residues were dissolved in EtOAc washed by 10% HCl, water, saturated CuSO$_{4(aq)}$, water, saturated NaCO$_{3(aq)}$, and brine. The organic layer was dried over MgSO$_4$ and concentrated. The residues were purified by silica gel chromatography (1:1, EtOAc/hexane) to give compound **14** (21 mg, 60%). $[\alpha]_D^{32}$ 29.269 (*c* 0.33, CHCl$_3$), R_f = 0.29 (1:1, EtOAc/hexane + 10% MeOH); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.88–1.94 (m, H-b, 2H), 2.03 (s, Ac, 3H), 2.10 (s, Ac, 6H), 2.12 (s, Ac, 3H), 2.12 (s, Ac, 3H), 2.13 (s, Ac, 3H), 2.16 (s, Ac, 6H), 2.18 (s, Ac, 6H), 2.20 (s, Ac, 3H), 2.39–2.43 (m, H-c, 2H), 3.63–3.68 (m, H-a, 1H), 3.80–3.84 (m, H-5, 1H), 3.89–3.93 (m, H-4′, H-a, 1H), 4.05–4.08 (t, J = 6.4 Hz, H-4, 1H), 4.14–4.28 (m, H-5, H-6a′, H-6″, 4H), 4.53 (dd, J = 7.4 Hz, J = 11.0 Hz, H-6b′, 1H), 4.55–4.60 (m, H-3, H-5″, H-6a, 3H), 4.68 (d, J = 8.0 Hz, H-1′, 1H), 4.75 (d, J = 7.6 Hz, H-1, 1H), 4.87–4.92 (m, H-2′, 1H), 5.03 (dd, J = 2.6 Hz, J = 10.6 Hz, H-6b, 1H), 5.12 (d, J = 3.2 Hz, H-1″, 1H), 5.17 (dd, J = 7.6 Hz, J = 10.6 Hz, H-2, 1H), 5.23–5.29 (m, H-3′, H-2″, 2H), 5.46 (dd, J = 2.8 Hz, J = 10.8 Hz, H-3″, 1H), 5.61 (d, J = 2.8 Hz, H-4″, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 20.67, 20.82, 20.93, 21.14, 21.34, 26.34, 61.98, 63.80, 63.93, 68.65, 69.08, 69.71, 70.04, 70.14, 71.09, 73.31, 73.69, 74.14, 74.23, 74.59, 77.72, 78.94, 99.30, 100.88, 101.92, 102.22, 171.36, 171.57, 172.05, 172.14, 172.30, 172.52, 172.61. HRMS (FAB) Calcd for C$_{42}$H$_{58}$O$_{28}$ [M+Na]$^+$: 1033.3012; found: 1033.3016.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2004.10.024.

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