Rational Design and Synthesis of a 1,1-Linked Disaccharide That Is 5 Times as Active as Sialyl Lewis X in Binding to E-Selectin

Kazumi Hiruma,[†] Tetsuya Kajimoto,[†] Gabriel Weitz-Schmidt,[‡] Ian Ollmann,[§] and Chi-Huey Wong*[,†,§]

Contribution from the Frontier Research Program, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako-shi, Saitama, 351-01 Japan, and the Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037

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Abstract: We describe here a rational design and synthesis of (3-*O*-carboxymethyl)-β-D-galactopyranosyl α-D-mannopyranoside which is 5 times as active as sialyl Lewis X in binding to E-selectin and also effective against P- and L-selectin. A new method for the 1,1-glycosidic bond formation *via* coupling of protected trimethylsilyl β-D-galactoside and α-mannosyl fluoride in the presence of $BF_3{\cdot}Et_2O$ is described.

Sialyl Lewis X (SLe^x, **1**) is a terminal tetrasaccharide found at the nonreducing end of glycoconjugates expressed especially on the surface of tumor cells and neutrophils. The interaction between SLe^x on neutrophils and E- or P-selectin on the surface of endothelial cells occurs at the early stage of inflammatory response.[1] This finding has led to the development of large-scale synthesis[2] of SLe^x as a potential therapeutic agent for the treatment of such acute symptoms as repurfusion injury.[3]

Recently, however, many mimetics of SLe^x have been reported[4] as potential alternative anti-inflammatory agents because of the high cost associated with the synthesis of SLe^x and its weak activity, low stability, and poor oral activity. As part of our interest in the development of oligosaccharide mimetics,[4b−d] we have designed a novel disaccharide to mimic the active conformation[2,5] of SLe^x (see **2** in Figure 1). In this designed structure, an α-mannosyl group was linked to the anomeric β-OH group of galactose, resulting in the formation of a 1,1-linked disaccharide with all OH groups expected to be in the same orientation and relative through-space distance as that of the fucosyl and the galactosyl groups in the active conformation of SLe^x. A carboxymethyl group was then incorporated into the 3-OH group of the galactose residue. The reason to use this flexible carboxymethyl group is based on the observation that only the carboxyl group of sialic acid is essential for binding[5a] and that the orientation of this negative charge in the bound complex[5c] appears to be different from that in the free form (Figure 2).[2]

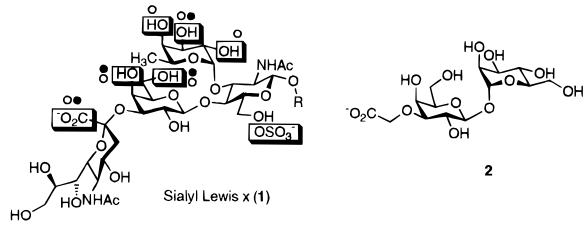

Figure 1. Structure of SLe^x showing the essential functional groups for binding to E-selectin (○), P-selectin (●), and L-selectin (□) and the designed mimetic **2**.

A dihedral energy contour plot (Figure 3) indicates that the bound conformation differs from the stable solution conformation by approximately 1.5 kcal/mol (Figure 4). This difference suggests that it is plausible to design SLe^x mimetics with constrained conformation to mimic the bound form of SLe^x or with small energy barrier flexible conformation to improve the binding affinity. Compound **2** was designed on the basis of these considerations.

Two methods were used to prepare the protected β-D-galactopyranosyl α-D-mannopyranoside as a precursor to **2** (Table 1): one is β-D-galactosylation of 2,3,4,6-tetra-*O*-protected

[†] The Institute of Physical and Chemical Research (RIKEN).
[‡] Sandoz Pharma Preclinical Research.
[§] The Scripps Research Institute.
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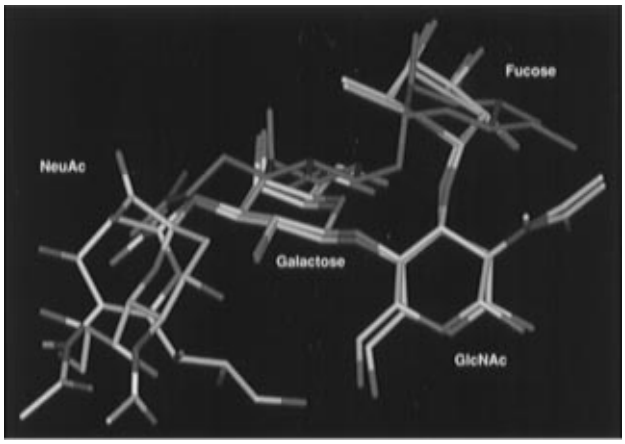
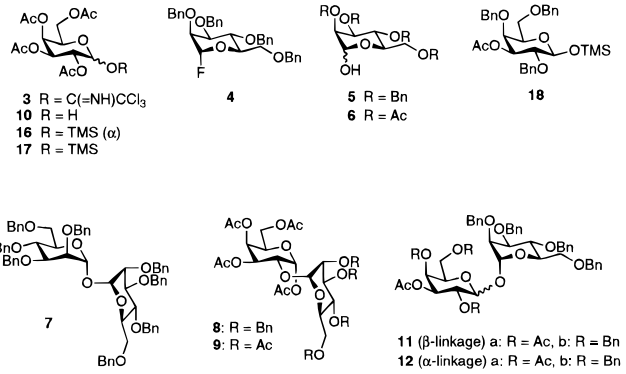


Figure 2. Three overlaid structures showing the bound conformation[5c] (yellow) and the free conformation[2] (white) of SLe^x determined by NMR, and a stable conformation (green) of **2**. A systematic grid search about the glycosidic bonds was performed using the Amber parameter set in Insight/Discover to determine likely stable conformers for **2**. Five low-energy conformations were detected, and the one consistent with NOE measurements in solution was used here ($\Phi_{Man} = 59.2°$; $\Phi_{Gal} = 174.3°$).

D-mannose (entries 1−3) and the other is α-D-mannosylation of 2,3,4,6-tetra-*O*-protected *β*-D-galactose (entry 4). Neighboring group participation is expected in the former reaction, and anomeric effect is expected to assist in forming the α-glycosidic bond in the latter reaction. 2,3,4,6-Tetra-*O*-acetyl-D-galactosyl trichloroacetimidate (**3**)[6] and 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl fluoride (**4**)[6,7] were used initially as galactosyl and mannosyl donors, respectively, in this investigation.



As shown in Table 1, glycosylation between the galactosyl donor **3** and mannosyl acceptors **5** and **6** in the presence of TMSOTf or BF_3·Et_2O afforded the unexpected α-D-mannosyl α-mannoside **7** and/or fully protected α-D-mannopyranosyl-(1→2)-D-galactopyranoses **8** and **9**. Mannosylation of 2,3,4,6-tetra-*O*-acetylgalactose (**10**) using **4** as mannosyl donor, activated with $SnCl_2-AgClO_4$,[7] gave a mixture of 2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzyl α-D-mannopyranoside (**11a**) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**12a**).

The disaccharide **11a** with the desired configuration was deacetylated and the exposed 3,4-hydroxy groups were protected as acetonide followed by benzylation to afford **13**. After cleavage of the acetonide, the product **14** was reacted with di-*n*-butyltin oxide and alkylated with methyl α-bromoacetate to afford lactone **15**. Hydrogenation on Pearlman's catalyst followed by saponification with sodium hydroxide yielded **2** (Scheme 1).

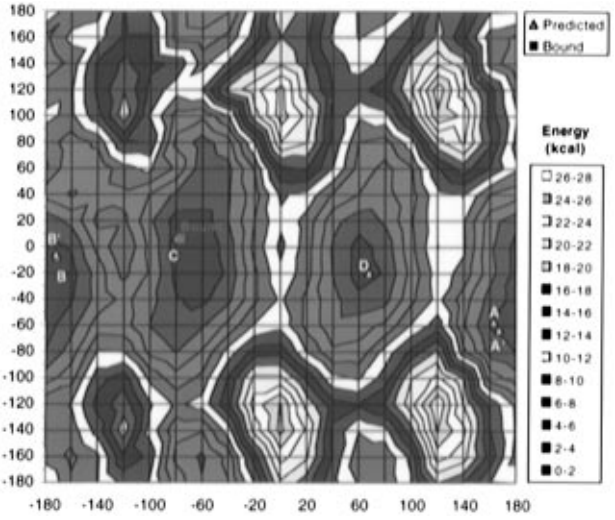


Figure 3. A dihedral energy contour plot showing the conformational energies about the angles Φ and Ψ of the NeuAc−Gal glycosidic linkage in SLe^x as determined by the Amber force field. The letters A, B, C, and D denote conformations which were previously predicted by the HSEA force field[2] to be possible candidates for the solution phase structure of SLe^x. Conformations A′ and B′ are local minima of A and B, respectively, as determined by the MMS force field, and both are consistent with the NMR analysis[2] (A′ is about 1.4 kcal/mol more stable than B′). The conformation of SLe^x when bound to E-selectin is indicated in red.[5c] Stated energies are relative, with the global minimum at $\{\Phi = -60°, \Psi = 0°\}$ as $E = 0$.

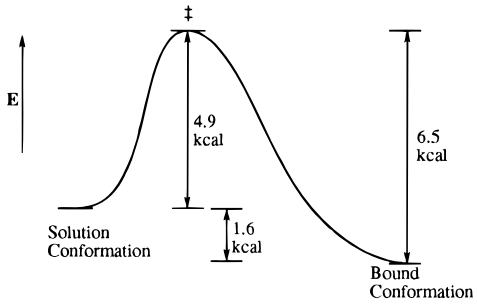


Figure 4. An energy diagram showing the conformation reorganization pathway between the solution phase structure of SLe^x (A′) and the structure of SLe^x when bound to E-selectin determined by constrained computer minimization *in vacuo*. It indicates a probable 5 kcal barrier to the interconversion between the two forms.

To further investigate the stereoselectivity and yield in the glycosylation reaction, we exploited the use of trimethylsilyl glycosides as acceptors (entries 5−9) in reaction with α-mannosyl fluoride **4**. It is interesting that only α-galactoside **12a** was obtained with the use of α-galactoside **16**, and an α/*β* mixture of galactoside was obtained with the use of an α/*β* mixture of acceptor **17**. Reaction of the trimethylsilyl *β*-galactoside **18** with **4** under various conditions, however, did not give the desired *β*-isomer as the sole product, though a relatively high *β*-selectivity was obtained at low temperature. Perhaps some anomerization occurs during the activation. In any case, compound **11b** obtained in this reaction can be more easily converted to **2** (Scheme 2).

In a cell-free assay,[8] compound **2** was found to be 5-fold better than SLe^x as an inhibitor of E-selectin ($IC_{50} = 0.1$ mM) (Figure 5). The increase in activity for **2** compared to SLe^x is perhaps due to the increase in the conformational stability as there is only one glycosidic bond in **2**, and the NOESY experiment shows NOE's between Man-H_1 and Gal-H_2, and

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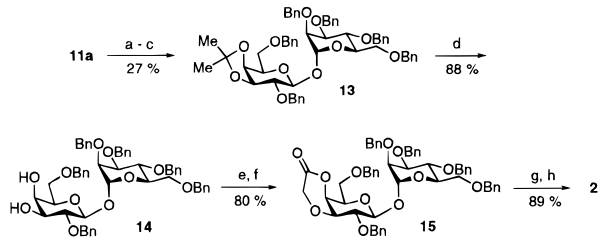
Table 1. Formation of the 1,1-Glycosidic Linkage between D-Mannose and D-Galactose[a]

entry	acceptor	donor (amt, equiv)	promoter (amt, equiv)	solvent	temp (°C)	time (min)	product (yield, %)
1	**5**	**3** (1.4)	TMSOTf (0.1)	CH_2Cl_2	−78 → 0	60 + 120	**7** (28) **8** (23)
2	**5**	**3** (2.0)	$BF_3{\cdot}Et_2O$ (3.0)	CH_2Cl_2	−20	75	**8** (40)
3	**6**	**3** (1.4)	TMSOTf (0.1)	CH_2Cl_2	−20	50	**9** (55)
4	**10**	**4** (1.2)	$SnCl_2-AgClO_4$ (1.2)	$Et_2O-CH_2Cl_2$ (3:1)	−20	150	**12a** (30) **11a** (27)
5	**16**	**4** (1.3)	TMSOTf (0.3)	CH_2Cl_2	−20	45	**12a** (63)
6	**17** (α:β = 1:1.3)	**4** (1.3)	TMSOTf (0.3)	CH_2Cl_2	−20	30	**12a** (36) **11b** (32)
7	**18**	**4** (1.3)	TMSOTf (0.3)	CH_2Cl_2	−20 → −10	60	**12b** (46) **11b** (32)
8	**18**	**4** (1.3)	$BF_3{\cdot}Et_2O$ (0.3)	CH_2Cl_2	−20	30	**12b** (15) **11b** (30)
9	**18**	**4** (1.3)	$BF_3{\cdot}Et_2O$ (0.6)	CH_2Cl_2	−50 → −10	1230	**12b** (16) **11b** (68)

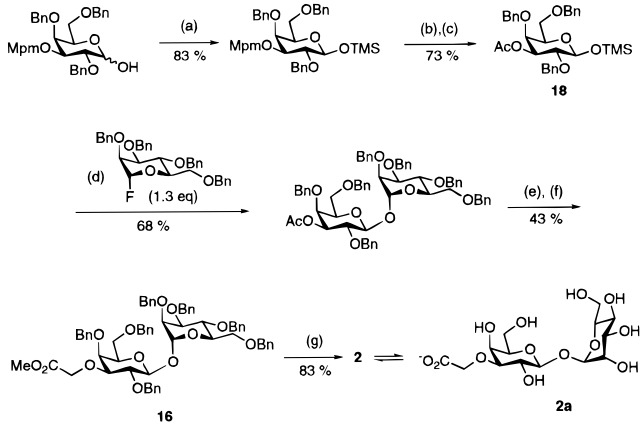
[a] For the synthesis of **5**, see: Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *46*, 2659. For **6** and **10**, see: Klotz, W.; Schmidt, R. R. *J. Carbohydr. Chem.* **1994**, *13*, 1093. For **7**, see: Yoshimura, J.; Hara, K.; Sato, T.; Hashimoto, H. *Chem. Lett.* **1983**, 319. For **16** and **17**, see: Nashed, E. M.; Glaudemans, C. P. J. *J. Org. Chem.* **1989**, *54*, 6116.

Scheme 1[a]



[a] Key: (a) NaOMe in MeOH−$CHCl_3$; (b) 2,2-dimethoxypropane, CSA, then MeOH; (c) NaH/BnBr/DMF; (d) 70% aqueous AcOH; (e) *n*-Bu_2SnO/toluene; (f) $BrCH_2CO_2Me$, *n*-Bu_4NI/toluene; (g) $Pd(OH)_2$/C−H_2; (h) 0.25 N aqueous NaOH.

Scheme 2[a]



[a] Key: (a) $TMSNEt_2$/toluene; (b) DDQ, CH_2Cl_2/H_2O (20:1); (c) Ac_2O/pyridine; (d) $BF_3{\cdot}Et_2O$ (0.6 equiv), −50 to ∼−10 °C, 21 h; (e) NaOMe, MeOH−$CHCl_3$, 95%; (f) Ag_2O, Kl, $BrCH_2CO_2Me$, DMF; (g) (1) $Pd(OH)_2$/C, MeOH, H_2; (2) 0.25 M NaOH.

between Man-H_2 and Gal-H_2. Another NOE was observed between Man-H_1 and Gal-H_1, indicating the existence in equilibrium of a different glycosidic conformation (**2a**) which is perhaps influenced by the exoanomeric effect of Man-1-O. Work is in progress to prepare a rigid structure to mimic **2** and a multivalent SLe^x mimetic in order to further improve the inhibition potency.

Note Added in Proof. Compound **2** is also effective against P- and L-selectin, showing 77% and 71% inhibition, respectively, with 3 mH **2**, compared to 0% and 50% inhibition with 3 mH SLe^x.

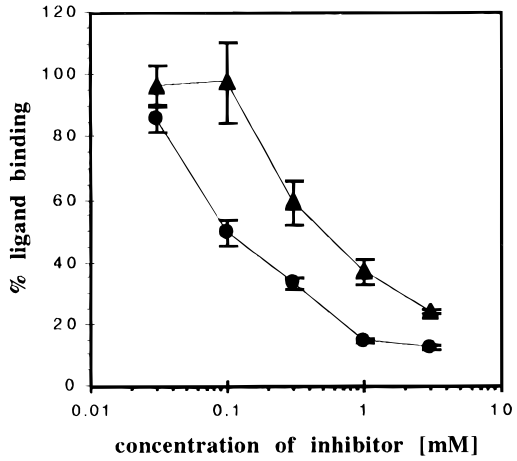


Figure 5. Inhibition of SLe^a−polymer binding to E-selectin: (●) compound **2**; (▲) SLe^x tetrasaccharide. Each point is the mean ± SD of three experiments.

Experimental Section

General Methods. Melting points were measured with a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Dried solvents were used for all reactions. Solutions were evaporated under diminished pressure at a bath temperature not exceeding 50 °C. Optical rotations were measured in a 1.0 dm tube with a Horiba SEPA-200 polarimeter, using chloroform as solvent, unless stated otherwise. ^1H NMR (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were recorded with a JEOL EX-270 spectrometer for solutions in $CDCl_3$, unless stated otherwise, using Me_4Si as the internal standard. Some key compounds were measured with JEOL 400 and 600 MHz spectrometers as indicated. Column chromatography was performed on silica gel (Merck Kieselgel 60). Inhibition analysis was carried out according to the procedure described previously.[8] Computer modeling was performed using the Insight/Discover program (Biosym, San Diego, CA) installed in a Silicon Graphics 4D/35 computer. The conformational energy associated with the dihedral angles about the NeuAc−Gal glycosidic linkage was evaluated by Insight/Discover using the Amber forcefield *in vacuo*. An energetic minimum was determined at 20° increments about angles Φ and Ψ to generate a grid of 324 minimized conformations. To obtain the conformational energy at each point, a few ring atoms within the galactose, *N*-acetylglucosamine, and fucose residues were fixed and an energetic force was applied to constrain the two dihedral angles of the neuraminic acid−galactose glycosidic linkage to a set value. The molecule was minimized under these conditions for 10 000 steps using a VA09A minimization algorithm to resolve steric clashes. The pattern of energies so obtained revealed a series of three local minima at $\Psi \cong 0$, $\Phi \cong \{60, 180, 300)$. These were consistent with the four structures previously predicted[2] by the GESA

(HSEA) force field. (Conformations A and B determined by the HSEA force field belong to the same well.) The bound conformation,[5c] which is almost identical to conformation GESA-C,[2] was within error limits of the global minimum.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (11a). To a solution of 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose (**10**) (610 mg, 1.75 mmol) and 2,3,4,6-tetra-O-benzyl-D-mannopyranosyl fluoride (**4**) (1.14 g, 2.1 mmol, 1.2 equiv) in dry ether (15 mL) and dichloromethane (5 mL) were added under N_2 at −20 °C silver perchlorate ($AgCLO_4$) (435 mg, 2.1 mmol) and stannous chloride ($SnCL_2$) (398 mg, 2.1 mmol), and the mixture was stirred for 150 min at the same temperature. The reaction mixture was diluted with dichloromethane and filtered through Celite. The filtrate was washed with aqueous sodium hydrogen carbonate and saturated NaCl, and dried over anhydrous sodium sulfate, and then the solvent was evaporated. The residue was subjected to column chromatography on silica gel to give *β*-D-galactopyranoside **11a**, α-D-galactopyranoside **12a**, and the unreacted acceptor **10**. The yields are shown in Table 1. ^{1}H-NMR ($CDCl_3$): *δ* 7.48−7.09 (m, 20H, 4Ph), 5.33 (d, $J_{3',4'}$ = 3.3 Hz, H-4′), 5.09 (dd, $J_{1',2'}$ = 7.6 Hz, $J_{2',3'}$ = 10.6 Hz, H-2′), 4.98 (d, $J_{1,2}$ = 2.3 Hz, H-1), 4.96 (dd, H-3′), 4.86, 4.48 (ABq, J = 10.9 Hz, $PhCH_2$), 4.77, 4.64 (ABq, J = 12.5 Hz, $PhCH_2$), 4.69, 4.62 (ABq, J = 12.1 Hz, $PhCH_2$), 4.66 4.50 (ABq, J = 11.9 Hz, $PhCH_2$), 4.57 (d, H-1′), 4.09 (dd, $J_{5',6a'}$ = 7.3 Hz, J_{gem} = 11.2 Hz, H-6a′), 4.05 (brd, 2H, H-4, 5), 3.99 (dd, $J_{5',6b'}$ = 6.1 Hz, H-6b′), 3.91 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.85 (brt, H-5′), 3.78 (brdd, J_{gem} = 10.6 Hz, H-6a), 3.65 (d, H-6b), 3.61 (dd, H-2), 2.14, 1.97, 1.84 (each s, 12H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): *δ* 170.21, 170.04, 169.06 (C═O), 138.42, 138.35, 138.22 (Ph), 128.41−127.49 (Ph), 100.56 (J_{C-H} = 159 Hz, C-1′), 100.43 (J_{C-H} = 159 Hz, C-1′), 100.43 (J_{C-H} = 173 Hz, C-1), 80.00 (C-3), 75.10, 73.39, 72.69 ($PhCH_2$), 74.57 (C-4), 73.89 (C-2), 72.60 (C-5), 70.93 (C-5′), 70.77 (C-3′), 69.00 (C-2′), 68.73 (C-6), 66.79 (C-4′), 61.03 (C-6′), 20.63, 20.58, 20.54, 20.49 ($COCH_3$). Anal. Calcd. for $C_{48}H_{54}O_{15}$: C, 66.20; H, 6.25. Found: C, 65.89; H, 6.26. $[\alpha]^{24}_D$ = +38.8° (*c* = 1.0, $CHCl_3$).

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (12a). ^{1}H-NMR ($CDCl_3$): *δ* 7.48−7.08 (m, 20H, 4Ph), 5.40 (brs, H-4′, 5.32 (d, $J_{1',2'}$ = 2.6 Hz, H-1′), 5.22 (dd, $J_{2',3'}$ = 10.9 Hz, H-2′), 5.18 (dd, $J_{3',4'}$ = 2.3 Hz, H-3′), 5.06 (d, $J_{1,2}$ = 2.0 Hz, H-1), 4.88, 4.52 (ABq, J = 10.9 Hz, $PhCH_2$), 4.76, 4.66 (ABq, J = 12.5 Hz, $PhCH_2$), 4.74, 4.62 (ABq, J = 11.7 Hz, $PhCH_2$), 4.60, 4.50 (ABq, J = 12.2 Hz, $PhCH_2$), 4.03 (dd, $J_{5',6a'}$ = 6.9 Hz, J_{gem} = 10.9 Hz, H-6a′), 3.97−3.87 (m, H-6b′), 3.93 (t, $J_{3,4}$ = 9.6 Hz, H-4), 3.87 (dd, $J_{2,3}$ = 3.0 Hz, H-3), 3.85 (t, H-5′), 3.76−3.60 (m, 3H, H-5, 6a, 6b), 3.53 (dd, H-2), 2.14, 2.04, 1.99, 1.98 (each s, 12H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): *δ* 170.21, 170.10 (C═O), 138.33, 138.20, 137.84 (Ph), 128.43−127.49 (Ph), 94.20 (J_{C-H} = 173 Hz, C-1), 92.26 (J_{C-H} = 179 Hz, C-1′), 89.10 (C-3), 75.10, 73.44, 72.89, 72.76 ($PhCH_2$), 74.93 (C-2), 74.63 (C-4), 73.11 (C-5), 69.02 (C-6), 67.66 (C-4′), 67.39 (C-3′), 66.94 (C-2′), 66.60 (C-5′), 61.46 (C-6′), 20.61 ($COCH_3$). Anal. Calcd for $C_{48}H_{54}O_{15}$: C, 66.20; H, 6.25. Found: C, 65.97; H, 6.25. $[\alpha]^{26}_D$ = +106.3° (*c* = 1.0, $CHCl_3$).

3-*O*-Acetyl-2,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (11b). ^{1}H-NMR ($CDCl_3$): *δ* 7.42−7.07 (m, 35H, 7Ph), 5.14 (d, $J_{1,2}$ = 1.3 Hz, H-1), 4.89 (ABq, 1H, J = 10.2 Hz, $PhCH_2$), 4.85 (dd, $J_{2',3'}$ = 10.9 Hz, $J_{3',4'}$ = 3.6 Hz, H-3′), 4.68−4.43 (m, 10H, $PhCH_2$), 4.53 (d, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.39 (ABq, 1H, J = 12.2 Hz, $PhCH_2$), 4.35, 4.30 (ABq, J = 12.5 Hz, $PhCH_2$), 4.11 (brd, H-5), 4.03 (t, H-4), 3.97−3.89 (m, 2H, H-2,3), 3.76−3.51 (m, 6H, H-6a,6b,2′,4′,5′,6a′), 3.47 (dd, $J_{5',6b'}$ = 6.1 Hz, J_{gem} = 9.1 Hz, H-6b′), 1.84 (s, 3H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): *δ* 170.21 (C═O), 138.74, 138.53, 137.26, 138.11, 137.74, (Ph), 128.34−127.31 (Ph), 102.97 (J_{C-H} = 161 Hz, C-1′), 99.68 (J_{C-H} = 179 Hz, C-1), 79.57 (C-3), 75.01 (C-2′ or C-5′), 74.90, 74.77, 73.23, 73.11, 72.49 ($PhCH_2$), 74.72 (C-4), 74.29 (C-4′), 74.28 (C-3), 72.36 (C-5), 68.92 (C-6), 67.75 (C-6′), 20.76 ($COCH_3$).

General Method of Glycosylation for the Synthesis of Unsymmetrical 1,1-Linked Disaccharides Using Trimethylsilyl Galactoside in the Presence of a Lewis Acid. Silylated galactoside **16**, **17**, or **18** (0.11 mmol) and mannosyl donor **4** (0.14 mmol, 1.3 equiv) were dissolved in dichloromethane (1 mL). After the addition of TMSOTf or BF_3·OEt (0.04 mmol, 0.3 equiv) in dichloromethane (0.1 mL) at a suitable temperature, this solution was kept for 30−60 min as shown in Table 1 to complete the reaction. Triethylamine (0.5 mL) was added to this solution. The mixture was poured into cold aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was subjected to column chromatography on silica gel to give *β*-D-galactopyranoside **11a** or **11b** and/or α-D-galactopyranoside **12a** or **12b**. Reaction conditions and yields are shown in Table 1.

Trimethylsilyl 2,4,6-Tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-*β*-D-galactopyranoside. ^{1}H-NMR ($CDCl_3$): *δ* 7.39−7.20 (m, 17H, 3Ph, MPh), 6.89−6.80 (m, 2H, MPh), 4.93, 4.60 (ABq, J = 11.7 Hz, $PhCH_2$), 4.89, 4.76 (ABq, J = 11.2 Hz, $PhCH_2$), 4.67, 4.62 (ABq, $PhCH_2$), 4.60 (d, $J_{1,2}$ = 7.3 Hz, H-1), 4.44, 4.38 (ABq, J = 11.6 Hz, $PhCH_2$), 3.84 (d, $J_{3,4}$ = 3.0 Hz, H-4), 3.80 (s, 3H, OMc), 3.74 (dd, $J_{2,3}$ = 9.9 Hz, H-2), 3.60−3.51 (m, 3H, H-5,6a,6b), 3.47 (dd, H-3), 0.17 (s, 9H, $SiCH_3$ × 3′).

Trimethylsilyl 3-*O*-Acetyl-2,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside (18). To a stirred solution of 2,4,6-tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-D-galactopyranose (1.24 g, 2.12 mmol) in dry toluene (4 mL) was added *N*-(trimethylsilyl)diethylamine (0.5 mL), and the solvent was evaporated at 40 °C. This manipulation was repeated three times until starting material disappeared on TLC, and then the mixture was dried *in vacuo*. To the residue dissolved in dichloromethane (40 mL) were added water (2 mL) and DDQ (621 mg, 2.60 mmol). The resulting mixture was stirred vigorously at room temperature for 1 h, poured into cold aqueous sodium hydrogen carbonate, and extracted with dichloromethane. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was acetylated using Ac_2O (2 mL) and pyridine (3 mL) and purified on a column of silica gel with hexane−ethyl acetate (8:1) to give silyl *β*-galactoside (917 mg, 75%) and *β*-acetate (113 mg, 10%). ^{1}H-NMR ($CDCl_3$): *δ* 7.42−7.18 (m, 15H, 3Ph), 4.87 (d, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.85, 4.64 (ABq, J = 11.8 Hz, $PhCH_2$), 4.66 (d, $J_{1,2}$ = 7.3 Hz, H-1), 4.59, 4.50 (ABq, J = 11.4 Hz, $PhCH_2$), 4.50, 4.42 (ABq, J = 11.2 Hz, $PhCH_2$), 3.93 (d, H-4), 3.71 (dd, H-2), 3.66 (t, H-5), 3.61−3.54 (m, 2H, H-6a,6b), 1.88 (s, 3H, $COCH_3$), 0.19 (s, 9H, $SiCH_3$ × 3).

3,4-*O*-Isopropylidene-*β*-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside. To a solution of **11a** (239 mg, 0.34 mmol) in dry methanol (3 mL) and chloroform (0.5 mL) was added powdered sodium methoxide (2 spoons by microspatel), and the mixture was stirred at room temperature for 1.5 h. The mixture was neutralized with 1 M HCl and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was dissolved in 2,2-dimethoxypropane (1 mL) and treated with a catalytic amount of DL-camphorsulfonic acid. The resulting mixture was stirred at room temperature for 1 h, and then the solvent wasevaporated. The residue was dissolved in methanol (3 mL), stirred for 5 min, and neutralized with triethylamine, the solvent was evaporated, and the residue purified on a column of silica gel with hexane−ethyl acetate (1:1) to give isopropylidene galactoside (109 mg, 43%) and unreacted *β*-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (119 mg, 50%). ^{1}H-NMR ($CDCl_3$): *δ* 7.42−7.02 (m, 20H, 4Ph), 5.17 (d, $J_{1,2}$ = 1.7 Hz, H-1), 4.83, 4.40 (ABq, J = 10.9 Hz, $PhCH_2$), 4.75, 4.68 (ABq, J = 12.2 Hz, $PhCH_2$), 4.66, 4.61 (ABq, J = 11.9 Hz, $PhCH_2$), 4.64, 4.48 (ABq, J = 12.9 Hz, $PhCH_2$), 4.36 (d, $J_{1',2'}$ = 8.6 Hz, H-1′), 4.15 (t, H-5′), 4.07 (s, H-4′), 4.05 (m, H-3′), 3.92 (d, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.97−3.82 (m, 2H, H-5, OH-6′), 3.75 (t, H-2), 3.73−3.60 (m, 2H, H-6a,6a′), 3.69 (t, H-4), 3.56 (ddd, H-2′), 3.47 (dd, $J_{5',6b'}$ = 8.3 Hz, J_{gem} = 9.9 Hz, H-6b′), 3.40 (dd, $J_{5,6b}$ = 2.3 Hz, J_{gem} = 10.6 Hz, H-6b), 2.72 (d, $J_{2',OH}$ = 3.3 Hz, OH-2′), 1.52, 1.33 (each s, 3H × 2, CCH_3). ^{13}C-NMR ($CDCl_3$): *δ* 138.29, 137.99, 137.39 (Ph), 128.37−127.64 (Ph), 110.42 (CMe_3), 102.09 (C-1′), 98.29 (C-1), 79.62 (C-3), 79.05 (C-3′), 75.31 (C-4), 75.08, 73.16, 72.74, 72.38 ($PhCH_2$), 74.93 (C-5), 74.56 (C-2), 73.77 (C-4′), 73.10 (C-2′), 72.38 (C-5′), 69.65 (C-6), 62.43 (C-6′), 28.20, 26.29 (CMe_2). FAB MS for $C_{43}H_{51}O_{11}$: calcd 743.3431, found 743.3431. $[\alpha]^{24}_D$ = +54.9° (*c* = 1.5, $CHCl_3$).

2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-*β*-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (13). To a suspension of NaH (60% oil dispersion, 67 mg, 1.68 mmol) rinsed with hexane two times

in DMF (0.5 mL) was added dropwise 3,4-*O*-isopropylidene-*β*-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (415 mg, 0.56 mmol) in DMF (2.5 mL), and the mixture was stirred at room temperature overnight (17 h). The reaction mixture was added to benzyl bromide (0.2 mL, 1.68 mmol), stirred at room temperature for 1 h and at 70 °C for 1 h, and then poured into cold water and extracted with ether. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified on a column of silica gel with hexane−ethyl acetate (5:1) to give **13** (326 mg, 63%). ^{1}H-NMR ($CDCl_3$): δ 7.41−7.10 (m, 30H, 6Ph), 5.17 (d, $J_{1,2}$ = 1.3 Hz, H-1), 4.88, 4.50 (ABq, J = 10.9 Hz, $PhCH_2$), 4.68, 4.59 (ABq, J = 11.8 Hz, $PhCH_2$), 4.66 (s, 2H, $PhCH_2$), 4.58, 4.32 (ABq, J = 12.4 Hz, $PhCH_2$), 4.48 (s, 2H, $PhCH_2$), 4.43 (d, $J_{1',2'}$ = 8.3 Hz, H-1′), 4.17−4.06 (m, 4H, H-4,5,3′,4′), 3.96−3.87 (m, 1H, H-3), 3.91 (br t, H-5′), 3.75 (dd, $J_{2,3}$ = 3.0 Hz, H-2), 3.73−3.57 (m, 4H, H-6,6′), 3.77−3.37 (m, 1H, H-2′), 1.38, 1.32 (each s, 3H × 2, CCH_3). ^{13}C-NMR ($CDCl_3$): δ 138.81, 138.56, 138.51, 138.15, 138.10 (Ph), 128.27−127.38 (Ph), 109.87 (CMe_2), 101.47 (C-1′), 99.41 (C-1), 79.77 (C-3), 79.64 (C-2′), 79.25 (C-3′), 74.84, 73.33, 73.12, 72.33, 72.27 ($PhCH_2$), 74.59 (C-4), 74.45 (C-2), 73.59 (C-4′), 72.44 (C-5), 72.50 (C-5′), 69.15, 68.63 (C-6,6′), 27.87, 26.31 (CMe_2). Anal. Calcd for $C_{67}H_{62}O_{11}$: C, 74,165; H, 6.77. Found: C, 73.80; H, 6.87. $[\alpha]^{26}_D$ = +43.8° (*c* = 1.1, $CHCl_3$).

2,6-Di-*O*-benzyl-*β*-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (14). A solution of **13** (240 mg, 0.26 mmol) in acetic acid (5 mL) and water (1.3 mL) was stirred at 60 °C for 3 h, and then the solvent was evaporated. The residue was purified on a column of silica gel with hexane−ethyl acetate (1:2) to give **14** (201 mg, 88%). ^{1}H-NMR ($CDCl_3$): δ 7.44−7.11 (m, 30H, 6Ph), 5.14 (d, $J_{1,2}$ = 1.7 Hz, H-1), 4.90, 4.51 (ABq, J = 10.9 Hz, $PhCH_2$), 4.67, 4.55 (ABq, J = 12.9 Hz, $PhCH_2$), 4.66, 4.56 (ABq, J = 11.5 Hz, $PhCH_2$), 4.58, 4.38 (ABq, J = 12.2 Hz, $PhCH_2$), 4.48 (d, $J_{1',2'}$ = 7.9 Hz, H-1′) 4.46 (s, 2H, $PhCH_2$), 4.27−4.09 (m, 1H, H-5), 4.06 (t, $J_{3,4} = J_{4,5}$ = 8.9 Hz, H-4), 3.99 (t, $J_{3',4'} = J_{4',OH}$ = 3.0 Hz, H-4′), 3.94 (dd, $J_{2,3}$ = 3.0 Hz, H-3), 3.71 (dd, $J_{5,6a}$ = 3.5 Hz, J_{gem} = 10.8 Hz, H-6a), 3.72−3.51 (m, 5H, H-6a,3′,5′,6′), 3.66 (m, H-2), 3.44 (dd, $J_{2',3'}$ = 9.2 Hz, H-2′), 2.69 (d, 4′-OH), 3.40 (d, $J_{3',OH}$ = 5.3 Hz, 3′-OH). ^{13}C-NMR ($CDCl_3$): δ 138.74, 138.47, 138.19, 138.11, 137.63 (Ph), 128.55−127.37 (Ph), 102.89 (C-1′), 99.7 (C-1), 79.50 (C-3), 79.37 (C-2′), 74.90, 74.68, 73.50, 73.17, 72.51, 72.42 ($PhCH_2$), 74.90 (C-2), 74.79 (C-4), 73.33, 72.51 (C-5,5′), 73.08 (C-3′), 69.13, 68.93 (C-6,6′), 68.93 (C-4′). FAB MS for $C_{54}H_{59}O_{11}$: calcd 883.4057, found 883.4058. $[\alpha]^{24}_D$ = +40.2° (*c* = 1.25, $CHCl_3$).

3,4-*O*-(2-Carbonylethylene)-2,6-di-*O*-benzyl-*β*-D-galactopyranosyl 2,3,4,6,-Tetra-*O*-benzyl-α-D-mannopyranoside (15). Diol **14** (76 mg, 0.09 mmol) was refluxed in dry toluene (3 mL) with dibutyltin oxide (23 mg, 0.09 mmol) in a Dean-Stark apparatus for 1 h. The solvent was evaporated, and the residue was dried *in vacuo*, dissolved in dry toluene (3 mL), and then refluxed with *n*-Bu_4NI (32 mg, 0.09 mmol) and a large excess amount of methyl 2-bromo acetate (0.3 mL) for 1 h. The concentrated residue was purified by chromatography (hexane:ethyl acetate = 2:1) to give **15** (64 mg, 80%). ^{1}H-NMR ($CDCl_3$): δ 7.41−7.11 (m, 30H, 6Ph), 5.14 (d, $J_{1,2}$ = 1.7 Hz, H-1), 4.90, 4.51 (ABq, J = 10.9 Hz, $PhCH_2$), 4.72, 4.64 (ABq, J = 11.5 Hz, $PhCH_2$), 4.70, 4.60 (ABq, J = 11.9 Hz, $PhCH_2$), 4.70 (d, $J_{3',4'}$ = 4.0 Hz, H-4′), 4.57, 4.47 (ABq, J = 11.7 Hz, $PhCH_2$), 4.57, 4.38 (ABq, J = 12.0 Hz, $PhCH_2$), 4.52 (d, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.46, 4.37 (ABq, J = 12.2 Hz, $PhCH_2$), 4.16, 3.63 (ABq, J = 18.1 Hz, OCH_2), 4.07−4.02 (m, 2H, H-4,5), 3.97−3.89 (m, 1H, H-3), 3.86 (dd, $J_{2',3'}$ = 9.9 Hz, H-3′), 3.78−3.55 (m, 6H, H-2,6,5′,6′), 3.48 (dd, H-2′). ^{13}C-NMR ($CDCl_3$): δ 166.59 (C═O), 138.58, 138.45, 138.38, 138.00, 137.61, 137.32 (Ph), 128.50−127.39 (Ph), 102.75 (C-1′), 100.02 (C-1), 79.55 (C-3), 74.92, 74.68, 73.48, 73.16, 72.58 ($PhCH_2$), 74.72 (C-2,4), 73.73 (C-4′), 72.87 (C-2′), 72.57 (C-5), 71.97 (C-3′), 71.81 (C-5′), 68.86, 66.45 (C-6,6′), 60.20 (OCH_2). $[\alpha]^{24}_D$ = +35.2° (c = 1.2, $CHCl_3$).

***O*-2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (8).** ^{1}H-NMR ($CDCl_3$): δ 7.49−7.04 (m, 20H, 4Ph), 6.44 (d, $J_{1,2}$ = 3.3 Hz, H-1), 5.44 (d, $J_{3,4}$ = 3.1 Hz, H-4), 5.18 (dd, $J_{2,3}$ = 10.7 Hz, H-3), 5.08 (d, $J_{1',2'}$ = 1.7 Hz, H-1′), 4.93−4.40 (m, 8H, $PhCH_2$), 4.33 (dd, H-2), 4.07 (d, 2H, $J_{5,6}$ = 6.9 Hz, H-6), 3.91−3.59 (m, 6H, H-5,3′,4,5′,6′), 3.55 (dd, $J_{2',3'}$ = 3.0 Hz, H-2′), 2.10, 2.04, 1.96, 1.94 (each s, 12H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): δ 170.43, 170.19, 170.15, 170.06 (C═O), 138.58, 138.20, 138.15, 138.04 (Ph), 128.43−127.39 (Ph), 95.08, 89.51 (C-1,1′), 79.30 (C-3′), 74.84, 73.33, 72.29, 71.90 ($PhCH_2$), 74.38, 73.89, 72.22, 68.95, 68.16, 67.61, 67.51 (C-2,3,4,5,2′,4′,5′), 69.42, 61.44 (C-6,6′), 20.94, 20.65, 20.33 ($COCH_3$).

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-(1→2)-1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (9).** ^{1}H-NMR ($CDCl_3$): δ 5.92 (d, $J_{1,2}$ = 5.0 Hz, H-1), 5.40 (brt, $J_{4,5}$ = 2.3 Hz, H-4), 5.33 (dd, $J_{2',3'}$ = 3.3 Hz, $J_{3',4'}$ = 9.9 Hz, H-3′), 5.26 (t, H-4′), 5.26 (d, $J_{1',2'}$ = 2.0 Hz, H-1′), 5.13 (br t, H-2′), 5.02 (dd, $J_{2,3}$ = 6.8 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.32 (dd, H-2), 4.29−4.02 (m, 6H, H-5,6,5′,6′), 2.17, 2.12, 2.11, 2.10, 2.07, 2.05, 2.00 (each s, 24H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): δ 170.49, 170.44, 170.01, 169.94, 169.86, 169.76, 169.70 (C═O), 98.11 (C-1), 91.56 (C-1′), 73.14 (C-2), 71.12 (C-3), 69.76 (C-2′), 69.13, 69.00 (C-5, 5′), 68.79 (C-3′), 65.97 (C-4′), 65.57 (C-4), 62.52, 61.39 (C-6, 6′), 20.81, 20.70, 20.61, 20.49 ($COCH_3$).

3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl) 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (12b). ^{1}H-NMR ($CDCl_3$): δ 7.42−7.09 (m, 35H, 7Ph), 5.29 (d, $J_{1',2'}$ = 3.6 Hz, H-1′), 5.14 (d, $J_{1,2}$ = 1.7 Hz, H-1), 5.09 (dd, $J_{2',3'}$ = 10.7 Hz, $J_{3',4'}$ = 3.2 Hz, H-3′), 4.86,4.48 (ABq, 1H, J = 10.9 Hz, $PhCH_2$), 4.68, 4.61 (ABq, J = 11.2 Hz, $PhCH_2$), 4.48, 4.40 (ABq, J = 12.0 Hz, $PhCH_2$), 4.56, 4.45 (ABq, J = 11.6 Hz, $PhCH_2$), 4.69−4.45 (m, 6H, $PhCH_2$), 4.07−3.93 (m, 5H, H-3,4,5,2′,4′), 3.79 (br t, H-5′), 3.64−3.58 (m, 2H, H-6), 3.56 (br s, H-2), 3.50 (dd, $J_{5',6a'}$ = 7.3 Hz, J_{gem} = 9.1 Hz, H-6b′), 3.39 (dd, $J_{5',6b'}$ = 6.9 Hz, H-6b′), 1.96 (s, 3H, $COCH_3$). ^{13}C-NMR ($CDCl_3$): δ 170.49 (C═O), 138.69, 138.44, 138.35, 138.13, 138.06, 138.02, 137.83 (Ph), 128.41−127.37 (Ph), 93.84, 92.99 (C-1,1′), 79.55 (C-3), 75.33, 75.17, 74.86, 73.48, 73.33, 72.76, 72.49, 72.40 ($PhCH_2$), 74.81, 72.81, 72.54, 72.36, 69.29, 69.17, 68.39 (C-6,6′), 20.97 ($COCH_3$).

Allyl 3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside. Allyl α-D-galactopyranoside[9] (4.64 g, 21 mmol) was refluxed overnight in dry methanol (100 mL) with dibutyltin oxide (5.75 g, 23 mmol) in a Dean-Stark apparatus. After methanol was removed, the residue was dried *in vacuo*, dissolved in dry toluene (200 mL), and stirred with *n*-Bu_4NI (8.5 g, 23 mmol) and *p*-methoxybenzyl chloride (6.0 mL, 11.1 mmol) at 80 °C for 3 h. The solvent was evaporated, and the residue was purified by chromatography (hexane:ethyl acetate = 3:1) to give allyl 3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside (5.0 g, 70%). $[\alpha]^{25}_D$ = +127.4° (*c* 1.0, $CHCl_3$). Mp: 62−63.5 °C (from EtOAc). ^{1}H-NMR ($CDCl_3$): δ 7.30 (d, 2H, J = 8.58 Hz, Ph), 7.97 (d, 2H, Ph), 5.93 (dddd, J = 17.3 Hz, 5.8 Hz), 5.30 (dq, 1H, J = 1.65 Hz, ═CH_2-*trans*), 5.22 (dq, 1H, ═CH_2-*cis*), 5.02 (d, $J_{1,2}$ = 4.0 Hz, H-1), 4.70, 4.64 (ABq, J = 11.4 Hz, $PhCH_2$), 4.22 (ddt, 1H, J_{gem} = 12.9 Hz, OCH_2), 4.20−3.76 (m, 4H, H-5, 6a,6b, OCH_2), 4.07 (br d, H-4), 3.98 (dd, $J_{2,3}$ = 9.6 Hz, H-2), 3.81 (s, 3H, OMe), 3.65 (dd, $J_{3,4}$ = 3.5 Hz, H-3), 2.6−1.8 (br, 3H, 3OH). ^{13}C-NMR ($CDCl_3$): δ 159.51 (*C*Me), 134.00 (HC═), 129.79, 129.52 (Ph), 118.06 (═CH_2), 114.03 (*C*HCOMe), 97.77 (C-1), 77.93, 69.53, 68.70, 68.43, 68.36, 63.06 (OCH_2), 71.95 ($PhCH_2$), 55.29 (OMe). Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.74; H, 6.93.

Allyl 2,4,6-Tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside. To a suspension of NaH (55% oil dispersion, 980 mg, 22.45 mmol) rinsed with hexane two times in DMF (3 mL) was added dropwise allyl 3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside (1.7 g, 4.99 mmol) in DMF (8 mL), and the mixture was stirred at room temperature for 4 h. The reaction mixture was added to benzyl chloride (2.6 mL, 22.45 mmol), stirred at room temperature overnight, poured into cold water, and extracted with ether. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified on a column of silica gel with hexane−ethyl acetate (10:1) to give allyl 2,4,6-tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside (2.21 g, 73%). ^{1}H-NMR ($CDCl_3$): δ 7.42−7.18 (m, 17H, Ph), 6.87 (d, 2H, J = 8.9 Hz, Ph), 5.93 (dddd, J = 17.3 Hz, J = 10.2 Hz, J = 5.8 Hz, CH═), 5.29 (dq, 1H, J = 1.65 Hz, ═CH_2-*trans*), 5.18 (dq, 1H, ═CH_2-*cis*) 4.94, 4.66 (ABq, J = 11.5 Hz, $PhCH_2$), 4.87 (d, $J_{1,2}$ = 3.3 Hz, H-1), 4.81, 4.66 (ABq, J = 12.2 Hz, $PhCH_2$), 4.77, 4.56 (ABq, J = 11.6 Hz, $PhCH_2$), 4.47, 4.39 (ABq, J = 11.9 Hz, $PhCH_2$), 4.15 (ddt, 1H, J_{gem} =

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12.9 Hz, OCH_2), 4.08−3.91 (m, 4H, H-2, 3, 4, 5, OCH_2), 3.81 (s, 3H, OMe), 3.51 (d, $J_{5,6}$ = 6.6 Hz, H-6). ^{13}C-NMR ($CDCl_3$): δ 159.07 (*C*Me), 138.72, 138.65, 138.02, 131.02, 129.09 (3Ph), 134.00 (HC═), 128.34−127.48 (Ph), 117.86 (═CH_2), 113.73 (*C*HCOMe), 96.32 (C-1), 78.87, 77.21, 76.43, 75.22, 74.68, 73.41, 73.32, 72.92, 69.38, 69.04, 68.21, 55.24 (OMe).

2,4,6-Tri-*O*-benzyl-3-O-[(*p*-methoxyphenyl)methyl]-D-galactopyranose. To a solution of allyl 2,4,6-tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-α-D-galactopyranoside (1.99 g, 3.25 mmol) in dimethyl sulfoxide (25 mL) was added *t*-BuOK (912 mg, 8.13 mmol), and the mixture was stirred at 130 °C for 10 min. The mixture was poured into cold water and extracted with ether. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in acetone (16 mL), added to 1 M HCl (2 mL) and water (2 mL), and then refluxed for 30 min. After acetone was removed, the concentrated mixture was dissolved in chloroform and washed with water, and then the solvent was evaporated. The residue was purified on a column of silica gel with hexane−ethyl acetate (5:2) to give 2,4,6-tri-*O*-benzyl-3-*O*-[(*p*-methoxyphenyl)methyl]-D-galactopyranose (1.66 g, 89%). ^{1}H-NMR ($CDCl_3$): δ 7.42−7.16 (m, 17H, Ph), 6.92−6.79 (m, 2H, Ph), 5.27 (dd, $J_{1,2}$ = 3.3 Hz, $J_{1,OH}$ = 2.3 Hz, H-1α), 4.94, 4.92, 4.90,, 4.83, 4.80, 4.71, 4.69, 4.66 (each ABq, J = 11−12 Hz, $PhCH_2$), 4.63 (d, $J_{1,2}$ = 7.6 Hz, H-1β), 4.58, 4.57 (each ABq, J = 11.6 Hz, $PhCH_2$), 4.47, 4.39 (ABq, J = 11.9 Hz, $PhCH_2$), 4.14 (br t, $J_{5,6}$ = 6.6 Hz, H-5), 4.01 (dd, $J_{2,3}$ = 9.7 Hz, H-2α), 3.91 (dd, $J_{3,4}$ = 2.3 Hz, H-3α), 3.94−3.78 (m, 2−3H), 3.81, 3.80 (each s, 3H × 2, OMe), 3.73 (dd, $J_{2,3}$ = 9.6 Hz, H-2β), 3.63−3.45 (m, 4−5H, H-6), 3.47 (d, J_{gem} = 9.4 Hz, H-6), 3.24−3.13 (br, OHβ), 2.98−2.92 (br, OHα); mp 81−82 °C (from ether−ethyl acetate). Anal. Calcd For $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found: C, 73.29, H, 6.65.

3-*O*-(Carboxymethyl)-β-D-galactopyranosyl α-D-Mannopyranoside (2). Lactone **15** (36 mg, 0.04 mmol) was dissolved in methanol (1.5 mL), and then a catalytic amount of 20% $Pd(OII)_2$ on carbon was added. To the reaction mixture was supplied hydrogen through a balloon. After the reaction was complete in 4 h, the mixture was filtered and concentrated *in vacuo* and then dissolved in 0.25 N aqueous NaOH (0.5 mL). After 10 min, the reaction mixture was neutralized and purified by Sephadex LH-20 chromatography (H_2O) and lyophilized to give **2** (14 mg, 89%). ^{1}H-NMR (25 °C, HDO 4.80 ppm, 600 MHz): δ 5.178 (d, $J_{1,2}$ = 1.70 Hz, H-1), 4.638 (d, $J_{1',2'}$ = 8.12 Hz, H-1′), 1.115 (d, $J_{3',4'}$ = 3.13 Hz, H-4′), 4.103 (s, OCH_2), 3.61 (dd, $J_{2,3}$ = 3.10 Hz, H-2), 3.974 (ddd, $J_{4,5}$ = 10.04 Hz, $J_{5,6a}$ = 2.42 Hz, $J_{5,6b}$ = 6.54 Hz, H-5), 3.904 (dd, $J_{3,4}$ = 9.83 Hz, H-3), 3.900 (d, J_{gem} = 12.18 Hz, H-6a), 3.807 (dd, $J_{5',6'a}$ = 8.11 Hz, J_{gem} = 11.53 Hz, H-6′a), 3.764 (dd, H-6b), 3.753 (dd, $J_{5',6'b}$ = 5.13 Hz, H-6′b), 3.724 (t, H-5′), 3.708 (dd, $J_{2',3'}$ = 9.83 Hz, H-2′), 3.688 (t, H-4), 3.535 (dd, H-3′). ^{13}C-NMR (dioxane, 67.4 ppm, 100 MHz): δ 170.32 (C═O), 103.48 (C-1′), 102.30 (C-1), 82.69 (C-3′), 76.04 (C-5′), 74.31 (C-5), 71.05 (C-3), 70.56, 70.53 (C-2, 2′), 69.19 (OCH2), 67.52 (C-4), 66.02 (C-4′), 61.92, 61.76 (C-6, 6′). $[\alpha]^{24}_D$ = +43.6° (c = 0.22, MeOH:H_2O = 1:1). When galacosyl imidate **3** instead of **4** was used as a glycosyl donor in the same reaction, a migration was observed.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-galactopyranose (8). ^{1}H-NMR: δ 7.49−7.04 (m, 20H, 4Ph), 6.44 (d, $J_{1,2}$ = 3.3 Hz, H-1), 5.44 (d, $J_{3,4}$ = 3.1 Hz, H-4), 5.18 (dd, $J_{2,3}$ = 10.7 Hz, H-3), 5.08 (d, $J_{1',2'}$ = 1.7 Hz, H-1′), 4.93−4.40 (m, 8H, $PhCH_2$), 4.33 (dd, H-2), 4.07 (d, 2H, $J_{5,6}$ = 6.9 Hz, H-6), 3.91, 3.59 (m, 6H, H-5,3′,4′,5′,6′), 3.55 (dd, $J_{2',3'}$ = 3.0 Hz, H-2′), 2.10, 2.04, 1.96, 1.94 (each s, 12H, $COCH_3$). ^{13}C-NMR: δ 170.43, 170.19, 170.15, 170.06 (C═O), 138.58, 138.20, 138.15, 138.04 (Ph), 128.43−127.39 (Ph), 95.08, 89.51 (C-1,1′), 79.30 (C-3′), 74.84, 73.33, 72.29, 71.90 ($PhCH_2$), 74.38, 73.89, 72.22, 68.95, 68.16, 67.61, 67.51 (C-2,3,4,5,2′,4′,5′), 69.42, 61.44 (C-6,6′), 20.94, 20.65, 20.33 ($COCH_3$).

2,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside. To a solution of **11b** (100 mg, 0.10 mmol) in dry methanol (3 mL) and chloroform (0.5 mL) was added powdered sodium methoxide (2 spoons by microspatel), and the mixture was stirred at room temperature for 1 h. The mixture was neutralized with 1 M HCl and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate, the solvent was evaporated, and the residue was purified on a column of silica gel with hexane−ethyl acetate (3:1) to give the title compound (91 mg, 95%). ^{1}H-NMR: δ 7.43−7.08 (m, 35H, 7Ph), 5.14 (br s, H-1), 4.89 (ABq, 1H, J = 10.9 Hz, $PhCH_2$), 4.71 (ABq, 1H, J = 11.6 Hz, $PhCH_2$), 4.75−4.30 (m, 12H, $PhCH_2$), 4.46 (d, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.12 (br d, H-5), 4.04 (t, $J_{3,4}$ = 9.0 Hz, H-4), 3.93 (dd, $J_{2,3}$ = 2.8 Hz, H-3), 3.84 (d, $J_{3',4'}$ = 3.3 Hz, H-4′), 3.73 (dd, $J_{5,6b}$ = 3.8 Hz, J_{gem} = 11.0 Hz, H-6), 3.67−3.47 (m, 6H, H-2,6,3′,5′6′), 3.46 (dd, $J_{2',3'}$ = 9.6 Hz, H-2′), 2.11 (d, $J_{3',OH}$ = 5.6 Hz, OH-3′). ^{13}C-NMR: δ 138.72, 138.51, 138.33, 138.26, 138.13, 137.74 (Ph), 128.46−127.31 (Ph), 102.98 (C-1′), 99.64 (C-1), 79.89, 79.53, 75.49, 74.90, 74.81, 73.91, 73.48 (C-2,3,4,5,2′,3′,4′,5′), 75.06, 74.90, 74.68, 73.26, 73.10, 72.47, 72.35, ($PhCH_2$), 68.89, 68.11 (C-6,6′).

3-*O*-(carboxymethyl)-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl 2,3,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (16). To a stirred mixture of the above compound (29 mg, 0.03 mmol), silver oxide (121 mg, 0.53 mmol), and potassium iodide (42 mg, 0.26 mmol) in DMF (1 mL) was added $BrCH_2COOMe$ (87 mg, 0.57 mmol), and the mixture was stirred at room temperature for 3.7 days. The reaction mixture was diluted with ether and water and then passed through Celite. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified on a column of silica gel with hexane−ethyl acetate (3:1) to give **16** (13 mg, 43%). ^{1}H-NMR ($CDCl_3$): δ 7.41−7.12 (m, 35H, Ph), 5.13 (d, $J_{1,2}$ = 1.3 Hz, H-1), 4.93, 4.66 (ABq, J = 11.7 Hz, $PhCH_2$), 4.87, 4.48 (ABq, J = 10.9 Hz, $PhCH_2$), 4.69−4.48 (m, 6H, $PhCH_2$), 4.57, 4.34 (ABq, J = 12.2 Hz, $PhCH_2$), 4.44 (d, $J_{1',2'}$ = 7.9 Hz, H-1′), 4.29, 4.22 (ABq, J = 16.5 Hz, OCH_2), 4.28 (s, 2H, $PhCH_2$), 4.11 (brd, H-5), 4.05 (t, J = 9.2 Hz, H-4), 4.05 (d, $J_{3',4'}$ = 3.6 Hz, H-4′), 3.93 (dd, $J_{2,3}$ = 3.1 Hz, H-3), 3.66−3.80 (m, 5H, H-6a,2′, OMe), 3.63 (dd, H-2), 3.62−3.42 (m, 4H, H-6b,5′,6′), 3.39 (dd, $J_{2',3'}$ = 9.6 Hz, $J_{3,4}$ = 3.0 Hz, H-3′). ^{13}C-NMR: δ 171.12 (C═O), 138.85, 138.67, 138.56, 138.44, 138.24, 137.92 (Ph), 128.45-127.30 (Ph), 102.98 (C-1′), 99.66 (C-1), 83.49 (C-3′), 79.89 (C-2′), 79.61 (C-3), 75.13 (C-2), 74.77 (C-4), 74.22 (C-4′), 73.62 (C-5′), 72.54 (C-5), 74.93, 74.83, 74.57, 73.24, 73.10, 72.33 ($PhCH_2$), 69.13 (OCH_2), 68.77, 68.56 (C-6,6′).

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