Synthesis of Sialyl Lewis X Mimetics and Related Structures Using the Glycosyl Phosphite Methodology and Evaluation of E-Selectin Inhibition

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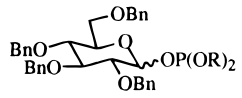
Abstract: This paper describes our recent study of glycosyl phosphites for glycosylation reactions, with particular emphasis on the investigation of protecting group and stereochemistry effects on the anomeric reactivity and stereoselectivity, and the application of this methodology to the synthesis of Lewis X (Le^x), Lewis Y (Le^y), glycopeptides, and sialyl Lewis X (SLe^x) mimetics. Both α-*O*-fucosyl-L-threonine and α-*O*-fucosyl-(1*R*,2*R*)-2-aminocyclohexanol were found to be effective templates for the chemical/enzymatic synthesis of SLe^x mimetics, and some fucopeptides prepared were 5−10 times more active than SLe^x as inhibitors of E-selectin.

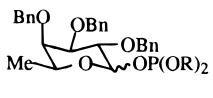
Introduction

Since the introduction of sialyl phosphites as glycosylation reagents,[1,2] the glycosyl phosphite method has been extended to various glycosylation reactions using monosaccharides[3,4] and disaccharides as donor substrates, and both the mechanism and alternative Lewis acids have been investigated.[3,5] In these glycosylation reactions, dibenzyl per-*O*-acetylglycosyl phosphites are generally less reactive than the corresponding per-*O*-benzylglycosyl phosphites, a trend similar to that observed with the use of other glycosylation reagents.[6] The anomeric stereoselectivity of glycosyl phosphites in certain cases is, however, different from that of other glycosylation reagents. For example, β-*O*-glycosides are often selectively obtained using 2,3,4,6-tetra-*O*-benzyl-D-glycosyl phosphite **1a**, **1b**, or **3**,[5a] whereas α-*O*-glycosides are selectively obtained using 2,3,4-tri-*O*-benzyl-6-deoxy-L-galactopyranosyl (L-fucopyranosyl) phosphite **2** (Chart 1). In order to further evaluate the utility of this new glycosylation reaction, we have studied the effects of protecting group and stereochemistry on the glycosylation of glycosyl phosphites using a limited number of examples, including the use of 1,3,5-trimethoxybenzene as a weak nucleophile in *C*-glycosylation reactions[7] and other oxygen species in *O*-glycosylations. A major effort was then directed toward the use of glycosyl phosphites in the synthesis of bioactive *O*-glycosides, especially *O*-fucosides.

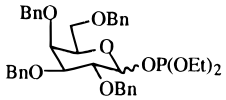
Chart 1. Structure of Glycosyl Phosphites **1**−**3**



1a: R=Bn
1b: R=Et



2



3

Many naturally occurring glycoconjugates contain an α-fucosidic linkage at the nonreducing end and are involved in important intercellular recognition processes. Lewis X (Le^x) trisaccharide **4**, Lewis Y (Le^y) tetrasaccharide **5**,[8] and sialyl Le^x (SLe^x), as shown in Chart 2, for example, are often expressed on the surface of a variety of tumor cells[9] and have emerged as new targets for drug discovery. The monoclonal antibody against Le^y has been shown to be potentially useful for the

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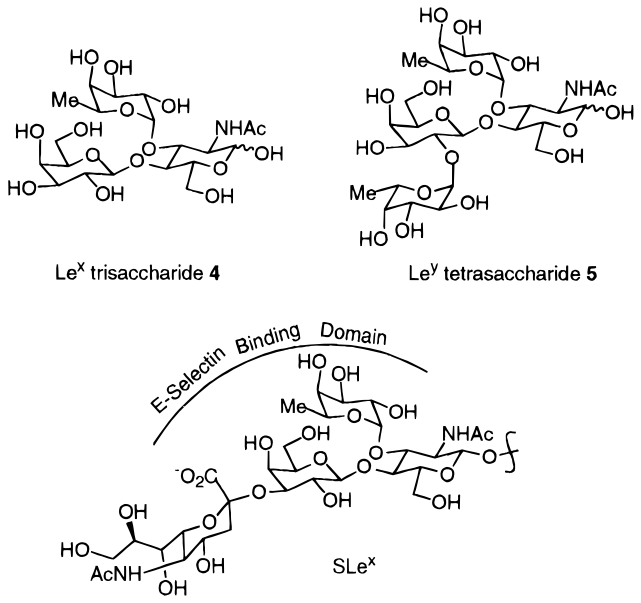
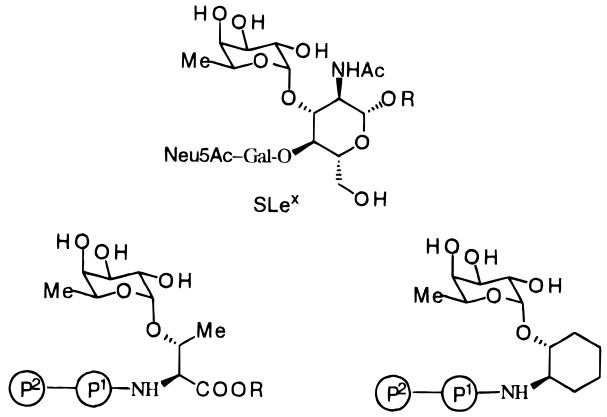
Chart 2. Structure of Le^x, Le^y, and SLe^x



treatment of several human cancers,[10−13] and the sialyl Lewis X (SLe^x) saccharide, a ligand for E-selectin, has been identified as a new anti-inflammatory agent.[14,15a]

Although SLe^x can be prepared on large scales[15a] and currently is being used in clinical trials for the treatment of reperfusion injury and heart attack, it can only be used as an injectable form because it is orally inactive and unstable. As the free and bound conformations[15] of SLe^x, the X-ray structure of the human E-selectin,[16] and the functional groups of SLe^x required for E-selectin interaction[17] are known, current efforts of our group and others have been directed toward the design and synthesis of less complex structures which mimic the active conformation of SLe^x.[18] Our strategy described in this paper is to develop novel fucopeptides as SLe^x mimetics. We chose *O*-α-fucopyranosyl-L-threonine or α-*O*-fucopyranosyl-(1*R*,2*R*)-2-aminocyclohexanol as a template for incorporation of a

Chart 3. Strategy for the Development of SLe^x Mimetics: Use of Thr or (1*R*,2*R*)-2-Aminocyclohexanol as a Template To Fix the Fucosidic and Galactosidic Torsion Angles



hydroxy acid (P^1) to replace the Gal residue and a carboxylate- or sulfate-containing group (P^2) to replace the Neu5Ac residue (Chart 3). Since the two stereogenic centers of Thr or 2-aminocyclohexanol are consistent with the *trans*-diol stereochemistry of the GlcNAc group in SLe^x, the fucose and Gal-mimetic components are expected to have a proper orientation in space to mimic the corresponding Le^x component of SLe^x.

Results and Discussion

***C*-Glycosylations.** In order to further understand the anomeric reactivity and stereoselectivity of glycosyl phosphites, we first prepared both the α- and *β*-anomers of dibenzyl 2,3,4-tri-*O*-acetyl-L-fucosyl phosphites **6** and **7** and both the α- and *β*-anomers of dibenzyl 2,3,4,6-tetra-*O*-acetyl-D-glycosyl phosphites **8**−**10** according to the procedure described previously[1] and examined their *C*-glycosylation reaction[19] with the weak nucleophile 1,3,5-trimethoxybenzene (TMB) in the presence of 0.5 equiv of trimethylsilyl triflate (TMSOTf). Also, the 6-*O*-(*tert*-butyldiphenylsilyl) (TBDPS) and 6-*O*-benzyl derivatives **11** and **12** and 2,3,4-tri-*O*-benzyl-L-fucosyl phosphite **2** were prepared and examined under the same conditions. The results are summarized in Table 1.

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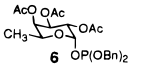
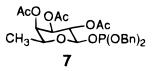
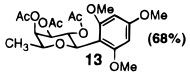
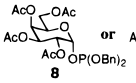
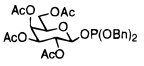
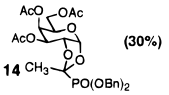
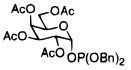
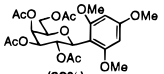
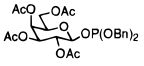
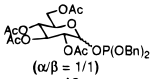
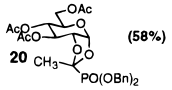
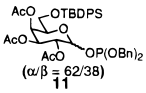
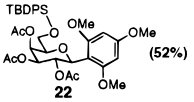
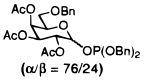
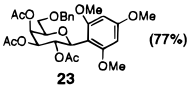
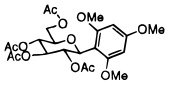
Table 1. Coupling of 1,3,5-Trimethoxybenzene (2 equiv) with Various Glycosyl Phosphites in CH_2Cl_2[a]

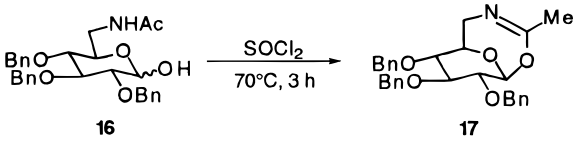
Donor Phosphite	Temperature	Product (Yield)
 **6**	-15°C or -78°C	no reaction
 **7**	-78°C	 (68%) **13**
 or  **8** **9**	-78°C	 (30%) **14**
 **8**	-15°C	**14** (22%) +  (32%) **15**
 **9**	-15°C	**14** (35%) + **15** (48%)
 (α/β = 1/1) **10**	-15°C	 (58%) **20**
 (α/β = 62/38) **11**	-15°C	 (52%) **22**
 (α/β = 76/24) **12**	-15°C	 (77%) **23**

[a] All reactions were carried out in CH_2Cl_2 in the presence of 2 equiv of TMB and 0.5 equiv of TMSOTf for 1 h. For a general procedure, see the Experimental Section.


21

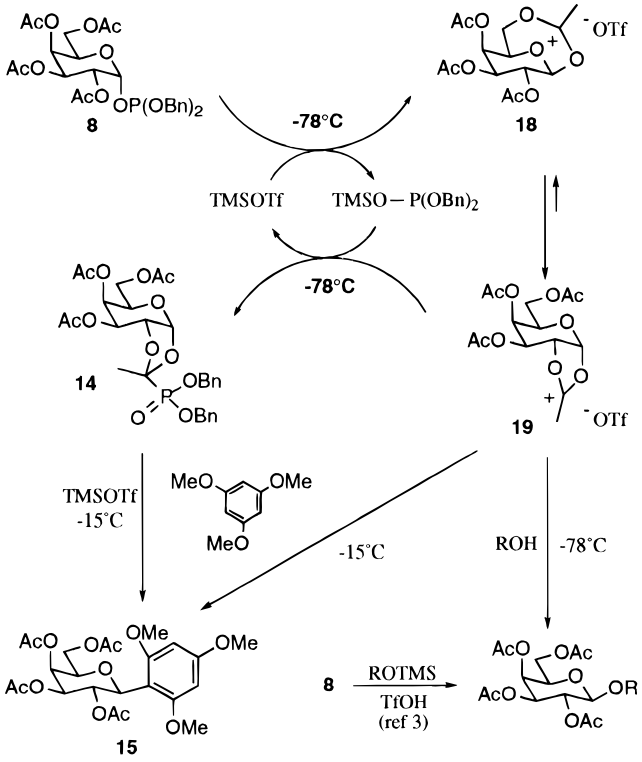
When the reaction was carried out at −78 °C, *β*-fucosyl phosphite **7** gave the expected *C*-fucoside **13**,[3] but no reaction was observed for α-fucosyl phosphite **6** either at this temperature or at −15 °C. However, both α- and *β*-galactosyl phosphites **8** and **9** gave the α-orthoester **14** as the sole product at −78 °C, and a mixture of **14** and *β*-*C*-galactoside **15** was obtained at −15 °C. As expected, *β*-glycosyl phosphites are more reactive than the α-isomers. The 6-ester group of α-galactosyl phosphite perhaps participates in the activation process through the formation of **18** and **19**, as the corresponding 6-deoxy enantiomer **6** is inactive at −78 °C. In an analogous case, the reaction of 6-acetamido-2,3,4-tri-*O*-benzyl-6-deoxy-D-glucopyranose (**16**) with thionyl chloride gave compound **17** (Scheme 1).[20] It was indeed shown in our previous study that both orthoester **14** and the intermediate **19** react at −78 °C with an oxygen nucleophile in the presence of TMSOTf.[3] When the weak nucleophile TMB was used at −78 °C, the only product was **14**, which was isolated and in reaction with TMB and TMSOTf (cat) at −15 °C gave the *β*-*C*-galactoside **15** (Scheme 2). In the *O*-glycosylation reactions, glycosyl phosphites can be activated by TMSOTf, or preferentially by trifluoromethanesulfonic acid (TfOH) generated from the reaction of TMSOTf with the acceptor hydroxyl group.[3] In the *C*-glycosylation reactions at −15 or −78 °C, however, TMSOTf activates glycosyl phosphites instead of TMB as no reaction between TMSOTf and TMB has been observed.

Scheme 1



16 **17**

Scheme 2



8 **14** **15** **18** **19**

While both **8** and **9** gave the corresponding *β*-*C*-galactoside **15** at −15 °C as described above, an α- and *β*-mixture (1:1) of glucosyl phosphite **10**[4e] gave only the α-orthoester **20**,[3] and even a trace amount of *C*-glucoside **21** was not obtained. Perhaps **20** is relatively more stable for activation, and/or the axial group of **8**, **9**, or **14** also participates in the anomeric activation. Indeed, it was observed that the glucose type orthoester **20** was more stable than the galactose type **14** for activation.

To further investigate the effect of the 6-*O*-protecting group of galactosyl phosphite on the *C*-glycosylation reaction, the 6-*O*-(*tert*-butyldiphenylsilyl) derivative **11** (α:*β* = 62:38) and the 6-*O*-benzyl derivative **12** (α:*β* = 76:24) were subjected to the same reaction conditions as those for **8** and **9**. It was found that both reacted faster to give the corresponding *β*-*C*-glycosides **22** and **23** in 52% and 77% yields, respectively, and only trace amounts of the corresponding α-orthoesters were observed. It appears that, in the case of α-phosphites, the ones with a 6-ether type of protecting group are more reactive than those with an ester type of protecting group due to the electronic effect, and the 6-ester derivatives are more reactive than the 6-deoxy derivatives due to the 6-acyl participation in the anomeric activation. This is further supported by the observation that no reaction was observed when **6** was treated with TMB at −78 or −15 °C in the presence of TMSOTf (0.2 equiv). In the case

(19) For other syntheses of *C*-aryl glycosides, see: (a) Mahling, J.-A.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 461. (b) Ramaiah, P. A.; Row, L. R.; Reddy, D. S.; Anjaneyulu, A. S. R.; Ward, R. S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2313. (c) Eade, R. A.; Pham, H.-P. *Aust. J. Chem.* **1979**, *32*, 2483. (d) Mahling, J.-A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 467. (e) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289. (f) Schmidt, R. R.; Hoffmann, M. *Tetrahedron Lett.* **1982**, *23*, 409. (g) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1989**, *30*, 833.

(20) Ueno, T.; Kurihara, N.; Hashimoto, S.; Nakajima, M. *Agric. Biol. Chem.* **1967**, *31*, 1346.

Scheme 3

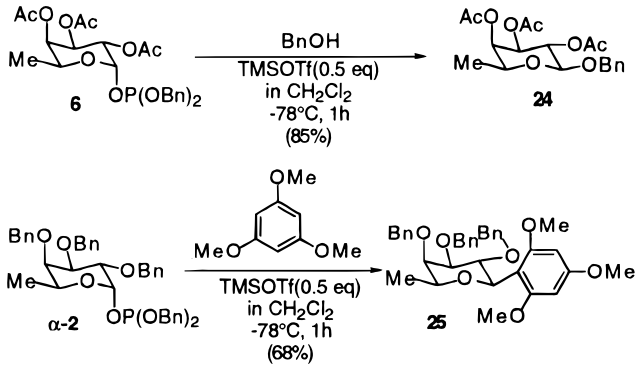
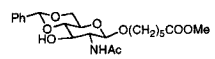
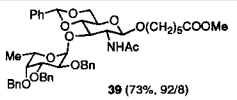
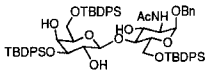
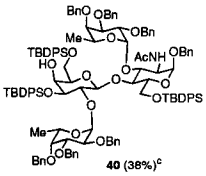
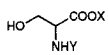
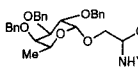
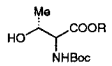
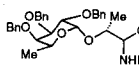
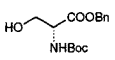
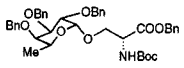
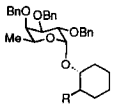


Table 2. Fucosylation of **26**−**38** with Fucopyranosyl Phosphite **2**[a]

Acceptors	Product (Yield, α/β ratio)
 **26**	 **39** (73%, 92/8)
 **27**	 **40** (38%)[c]
 **28**: X = Bn, Y = Boc **29**: X = Bn, Y = Z **30**: X = Bn, Y = Fmoc **31**: X = Bn, Y = H **32**: X = Et, Y = Boc **33**: X = tBu, Y = Boc	 **41**: X = Bn, Y = Boc (70%, 65/35) **42**: X = Bn, Y = Z (72%, 77/23) **43**: X = Bn, Y = Fmoc (69%, 74/26) **44**: X = Bn, Y = H (60%, 73/27) **45**: X = Et, Y = Boc (68%, 50/50) **46**: X = tBu, Y = Boc (66%, 62/38)
 **34**: R = Bn **35**: R = Et	 **47**: R = Bn (84%, 99/1) **48**: R = Et (72%, 71/29)
 **36**	 **49** (77%, 79/21)
 **37**: R = BocNH **38**: R = N_3	 **50**: R = BocNH (58%, 65/35) **51**: R = N_3 (76%, 69/31)

[a] All reactions were carried out in CH_2Cl_2 in the presence of TfOH[b] and 0.8 equiv of **2** for 1 h at −15 °C. For a general procedure, see the Experimental Section. [b] 1.2 equiv for the reaction of **31** and 0.05 equiv for the other reactions were employed. [c] Unable to know the ratio of four diastereomers due to the complex ^{1}H NMR spectrum. It was estimated on the basis of the ^{1}H and ^{13}C NMR that the major product was bis-α-L-fucoside.

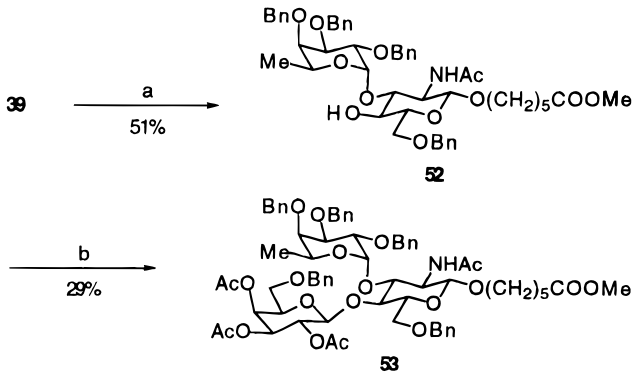
of β-phosphites, interestingly, **7** was more reactive than **9** toward the *C*-nucleophole, presumably due to the electronic effect. Compound **6** is, however, as reactive as **7** toward benzyl alcohol to form the expected β-*O*-glycoside **24** in 85% yield (Scheme 3). Therefore, the differences in the anomeric reactivity and selectivity of glycosyl phosphites are more easily detected with the use of a weaker nucleophile as indicated in the *C*-glycosylation reactions. An explanation of the results from the peracetylated α-phosphite **8** is summarized in Scheme 2.

In order to improve the reactivity of α-fucosyl phosphite in the *C*-glycosylation reactions, the ether derivative 2,3,4-tri-*O*-benzyl-L-α-fucopyranosyl phosphite (**2**) was reacted with TMB under the same conditions, and as expected, the β-*C*-fucoside **25** was obtained in 68% yield (Scheme 3). Some problems

Table 3. Effect of Lewis Acids on the Fucosylation of **26**

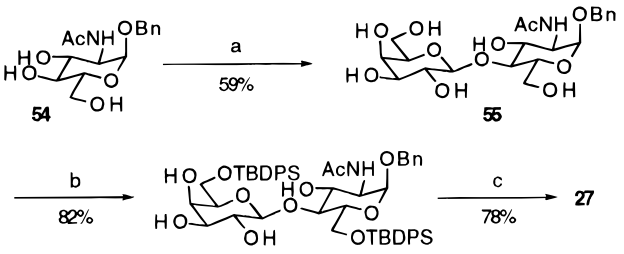
entry	Lewis acid	yield (%)	α:β ratio
1	TfOH (0.05 equiv)	73	92:8
2	TMSOTf (0.05 equiv)	68	92:8
3	TMSOTf (0.5 equiv)	47	92:8
4	$ZnCl_2$ (1.2 equiv)	trace	
5	$ZnCl_2$ (1.2 equiv)/$AgClO_4$ (2.2 equiv)	76	98:2

Scheme 4[a]



[a] Conditions: (a) (i) BH_3−NMe_3, THF, rt, 30 min. (ii) $AlCl_3$, THF, rt, 18 h. (b) **12**, TMSOTf (0.3 equiv), CH_2Cl_2, −20 °C, 1 d.

Scheme 5[a]



[a] Conditions: (a) lactose, β-galactosidase (*B. circulans*), 20 mM phosphate buffer/MeCN (1:1), rt, 48 h. (b) TBDPSCl (2.2 equiv), imidazole, DMF, rt, 8 h. (c) TBDPSCl, (2.0 equiv), imidazole, CH_2Cl_2, rt, 8 h.

have been encountered with the use of glycosyl phosphites. When mannosyl phosphite (with acetyl or benzyl protecting groups) was used in the *C*-glycosylation reaction, traces of unidentified byproducts were formed, but no desired products were observed probably due to the steric hinderance caused by the 2-axial group. The *O*-glycosylations, however, proceeded smoothly.[3] In an attempt to prepare 2-deoxy-2-azidoglycosyl phosphites, the products were not obtained, probably because of the reaction between the azido and phosphite groups.

***O*-Glycosylations and Synthesis of Le^x and Le^y.** With the appropriate choice of protecting groups to maximize the reactivity and yield, compound **2** (α:β = 99:1)[3] was used in the fucosylation of **26**[21] and other hydroxy derivatives (**27**−**38**) in the presence of TfOH, and the results are shown in Table 2. The α-selectivity in the fucosylation of secondary alcohols is relatively high except in reaction with the cyclohexanol derivative.

The fucosylation of **26** with **2** in the presence of 0.05 equiv of TfOH gave **39** (α:β = 92:8) in 73% yield. Using TMSOTf as the promoter, a similar result was observed. However, a lower yield (47%) was obtained when 0.5 equiv of the promoter was used (Table 3). Using a stoichiometric amount of zinc chloride as a promoter in the glycosylation reactions gave a

(21) Lemieux, R.; Bundle, D. R.; Baker, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 4076.

Scheme 6

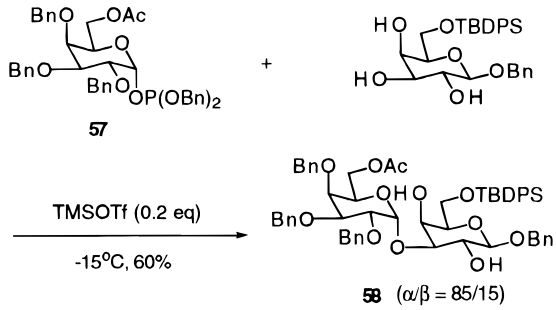
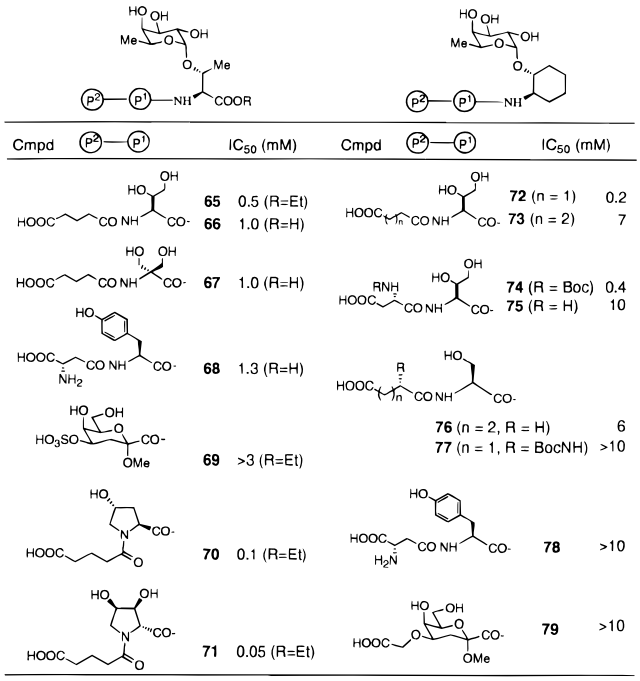
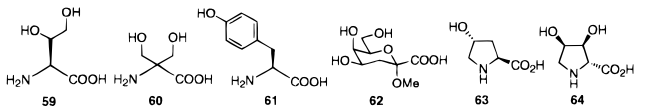


Table 4. Structures and IC_{50} Values of SLe^x Mimetics[a]



[a] IC_{50} values were determined in a cell free assay for inhibition of E-selectin binding to poly-SLe^x and compared to β-methyl SLe^x glycoside (IC_{50} = 0.5 mM).



very low yield (entry 4). A relatively high yield and high α-selectivity were, however, observed in the presence of $AgClO_4$[4f] (entry 5).

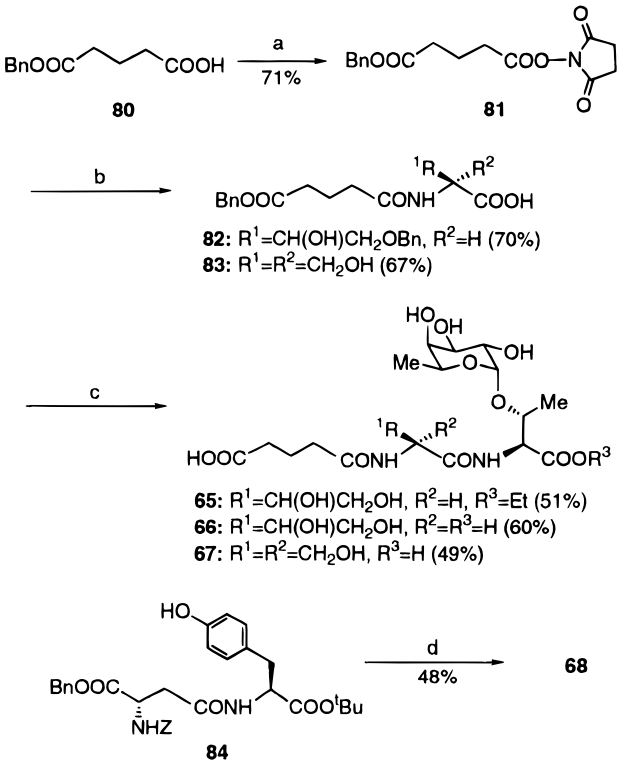
As shown in Scheme 4 compound **39** was then subjected to the selective reduction[22] with borane−trimethylamine complex in the presence of aluminum trichloride to give **52** in 51% yield. The β-galactosylation of **52** was then carried out with **12** (α:β = 33:67) to obtain **53** (β > 99%) which is equivalent to the Le^x trisaccharide **4** (Scheme 4).

For the synthesis of Le^y tetrasaccharide **5**, compound **27** was prepared for fucosylation according to the procedure shown in Scheme 5. The β-galactosidase from *Bacillus circulans* was used in the 4-*O*-β-galactosylation of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**54**) to give the LacNAc derivative **55** in 59% yield.[23] Silylation of **55** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) was carried out in DMF to obtain the 6,6′-di-*O*-TBDPS LacNAc derivative **56**, which was converted to

(22) Garegg, P. J.; Hultberg, H.; Oscarson, S. J. *J. Carbohydr. Chem.* **1983**, *2*, 305.

(23) Takayama, S.; Shimazaki, M.; Wong, C.-H. *Bioorg. Med. Chem. Lett.*, in press.

Scheme 7[a]



[a] Conditions: (a) *N*-hydroxysuccinimide, EDC, DMF, CH_2Cl_2, rt, 2 h. (b) **59**, **60**, DMF, CH_2Cl_2, rt, 15 h. (c) (i) **47**, **48** treated with 30% TFA, Et_3N, HOBt, EDC, CH_2Cl_2, 30 min. (ii) H_2 (1 atm), 20% $Pd(OH)_2$ on C, MeOH, rt, 24 h. (d) (i) 50% TFA, CH_2Cl_2, rt, 3 h. (ii) **47** treated with 30% TFA, HOBt, EDC, CH_2Cl_2, 30 min. (iii) H_2 (1 atm), 20% $Pd(OH)_2$ on C, MeOH, rt, 24 h.

6,3′,6′-tri-*O*-TBDPS LacNAc derivative **27** by further silylation with TBDPSCl in CH_2Cl_2. Double fucosylation of **27** with **2** gave **40**, which is equivalent to the Le^y tetrasaccharide **5**.

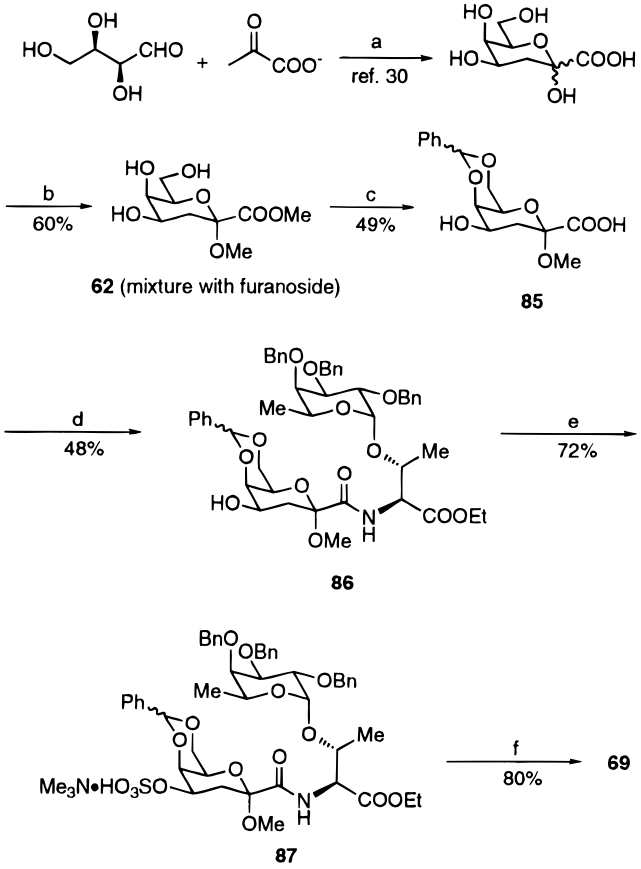
An interesting observation in the *O*-glycosylation using α-galactosyl phosphite with a tri-*O*-acetyl or tri-*O*-benzyl protecting group is that only the β-isomer is obtained as a product. Using the corresponding tri-*O*-benzylglycosyl chloride or bromide,[6a] or trichloroimidate,[6d] however, gave the α-glycoside (in the former case) or a mixture of α- and β-glycosides (in the latter case). To achieve α-galactosylation using the phosphite methodology, the 6-acyl participation strategy was employed with the use of 6-*O*-acetylgalactosyl phosphite **57** as the glycosylation reagent. As shown in Scheme 6, the glycosylation reaction gave an 85:15 α/β mixture of the product.

Sialyl Lewis X Mimetics. We then applied the glycosylation method to the synthesis of fucopeptides as SLe^x mimetics. Though the glycosylation of *N*-acylated β-hydroxy amino acid derivatives is a useful procedure for the synthesis of *O*-linked glycopeptides, this reaction often gives low yields and poor α/β-selectivity.[24] Polt *et al*. attributed the problem to the decreased nucleophilicity of the glycosyl acceptors due to a hydrogen-bonding interaction between the acceptor OH and NH groups.[25] A low α-selectivity was also observed in our fucosylation reaction; however, as shown in Table 2, the α-selectivity in the *O*-α-fucosylation of *N*-acylated β-hydroxy amino acid derivatives **28**−**36**[26] is improved when benzyl ester is used as the

(24) (a) Nicolaou, K. C.; Caufield, T. J.; Kataoka, H.; Stylianides, N. A. *Carbohydr. Res*. **1990**, *202*, 177. (b) Lacombe, J. M.; Pavia, *J. Org. Chem*. **1983**, *48*, 2557. (c) Garg, H. G.; Jeanloz, R. W. *Carbohydr. Res*. **1976**, *49*, 482.

(25) Polt, R.; Szabò, L.; Treiberg, J.; Li, Y.; Hruby, V. J. *J. Am. Chem. Soc*. **1992**, *114*, 10249.

Scheme 8[a]

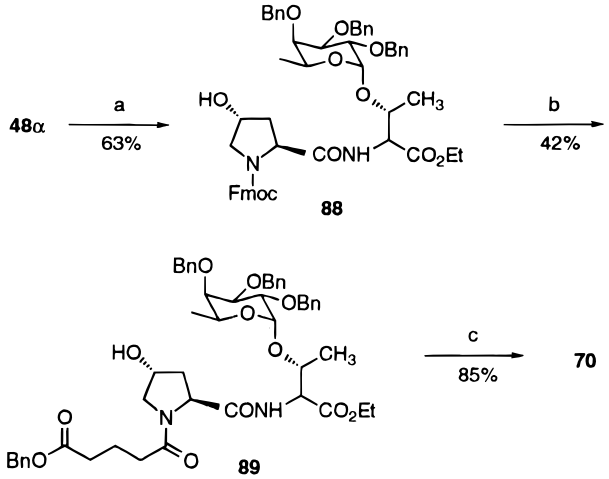


[a] Conditions: (a) sialic acid aldolase. (b) Dowex 50W (H^+), MeOH, reflux, 2 h. (c) (i) $PhCH(OMe)_2$, CSA, DMF, 60 °C, 16 h. (ii) LiOH, MeOH, 25 °C, 2 h. (d) **48** treated with 30% TFA, Et_3N−HOBt, EDC, NMM, DMF, −20 °C to about rt, 12 h. (e) SO_3·NMe_3, Py, rt, 6 h. (f) (i) H_2, $Pd(OH)_2$, MeOH, rt, 12 h. (ii) Dowex 50W-X8 (Na^+), H_2O, 2 h.

carboxyl protecting group. For comparison, the fucosylation of **34** with the trichloroacetoimidate method[6d] gave **47** in 82% yield and 90% α-selectivity. Using the phosphite method, **47** was obtained in 84% yield and 99% α-selectivity. The chemoselective *O*-fucosylation of Ser benzyl ester **31** was accomplished in the presence of 1.2 equiv of TfOH to obtain **44** as a sole product, though the yield was relatively low compared to that of **41**−**43**.

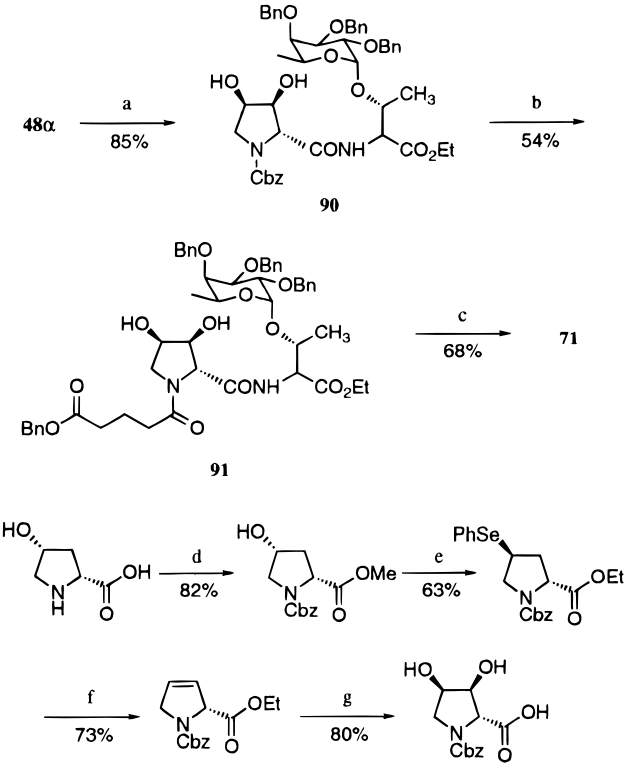
In the synthesis of SLe^x mimetics,[27] compounds **65**−**71** shown in Table 4 were prepared by incorporating hydroxy acids such as **59**−**64**[28−30] and glutarate or aspartate into the *N*-deprotected α-*O*-L-fucosyl derivatives **47** and **48** as described in Schemes 7−10. These fucopeptides were to mimic the configuration and essential functional groups of SLe^x according to the previous studies.[15a,17] Fucopeptides **72**−**79** were synthesized from **51** via reduction with triphenylphosphine[31] according to Schemes 11−13. Deprotection of the BOC group in **50** with trifluoroacetic acid (TFA) also cleaved the glycosidic bond, whereas the glycosidic bonds of **47** and **48** were stable under the same conditions. All the mimetics prepared were stereochemically pure.

Scheme 9[a]



[a] Conditions: (a) (i) 30% TFA, CH_2Cl_2. (ii) Fmoc-4(OH)-L-Pro (1.3 equiv), ECC, HOBt, CH_2Cl_2, rt, 6 h. (b) (i) 40% Et_2NH, THF, 2 h. (ii) **80** (2 equiv) EDC, HOBt, CH_2Cl_2, 6 h. (c) H_2, $Pd(OH)_2$ on C, EtOH/H_2O (2:1), 6 h.

Scheme 10[a]



[a] Conditions: (a) (i) 30% TFA, CH_2Cl_2. (ii) Cbz-(3,4-OH)-D-Pro (1.3 equiv), EDC, HOBt, CH_2Cl_2, rt, 6 h. (b) (i) 10% Pd/C, EtOAc/MeOH (1:1), 2 h. (ii) **80** (2 equiv) EDC, HOBt, CH_2Cl_2, 6 h. (c) H_2, $Pd(OH)_2$, EtOH/H_2O (2:1), 6 h. (d) (i) MeOH, $SOCl_2$, reflux overnight. (ii) Cbz-Cl, DIEA, 2 h. (e) (i) MsCl, Et_3N, CH_2Cl_2. (ii) PhSe−SePh, $NaBH_4$, EtOH, 2 h. (f) H_2O, Pyr, CH_2Cl_2, 2 h. (g) (i) K_2OsO_4, NMO, 0 °C. (ii) 0.1 N LiOH (2 equiv), THF/H_2O (1:1), 4 h.

(26) Compounds **28**, **31**, and **33** were purchased from Bachem Bioscience Inc., and **29**, **30**, **32**, and **34**−**36** were prepared from the corresponding amino acids according to a reported procedure; see: Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makotske, R.; Kulesha, I. D. *J. Org. Chem.* **1977**, *42*, 1287. For the synthesis of **37**, see: Takada, H.; Takagi, S.; Kawakubo, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1196. For the synthesis of **38**, see: Faber, K.; Hönig, H.; Seufer-Wasserthal, P. *Tetrahedron Lett.* **1988**, *29*, 1903.

(27) For the synthesis of **65**, see: Wu, S.-H.; Shimazaki, M.; Lin, C.-C.; Qiao, L.; Moree, W. J.; Weitz-Schmidt, G.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 88.

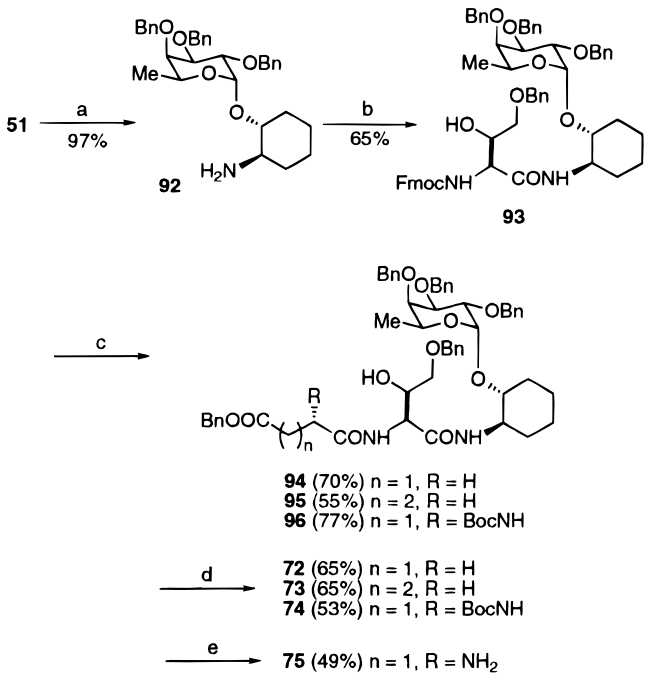
(28) For the synthesis of **59**, see: Vassilev, V. P.; Uchiyama, T.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1995**, *36*, 4081.

(29) For the synthesis of **60**, see: Nakamura, Y.; Shin, C. *Chem. Lett.* **1992**, 49.

(30) For the synthesis of **62**, see: Fitz, W.; Schwark, J.-R.; Wong, C.-H. *J. Org. Chem.* **1995**, *60*, 3663.

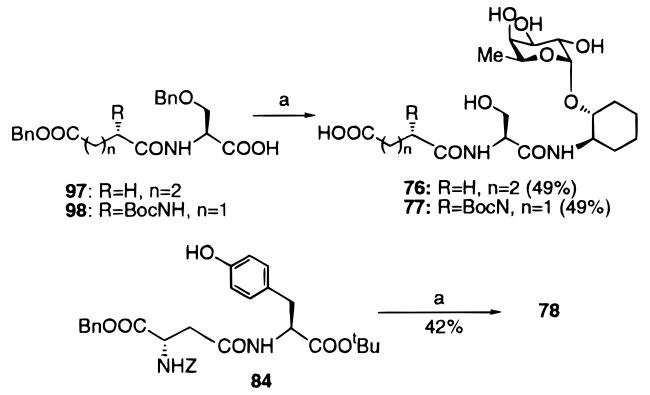
(31) (a) Dong, Z.; Butcher Jr., J. A. *Tetrahedron Lett.* **1991**, *32*, 5291. (b) Greilich, U.; Zimmermann, P.; Jung, K. H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1993**, 859.

Scheme 11[a]



[a] Conditions: (a) Ph_3P, benzene, reflux, 15 h. (b) (i) *N*-Fmoc derivative of **59**, HOBt, EDC, CH_2Cl_2, 0 °C to about rt, 6 h. (c) (i) Et_2NH, CH_2Cl_2, rt, 7 h. (ii) Succinic acid or glutaric acid monobenzyl ester or *N*-Boc-aspartic acid β-benzyl ester, HOBt, EDC, CH_2Cl_2, 0 °C to about rt, 9 h. (d) H_2 (1 atm), 20% $Pd(OH)_2$ on C, MeOH, rt, 6 h. (e) H_2 (1 atm), 20% $Pd(OH)_2$ on carbon, MeOH, rt, 18 h.

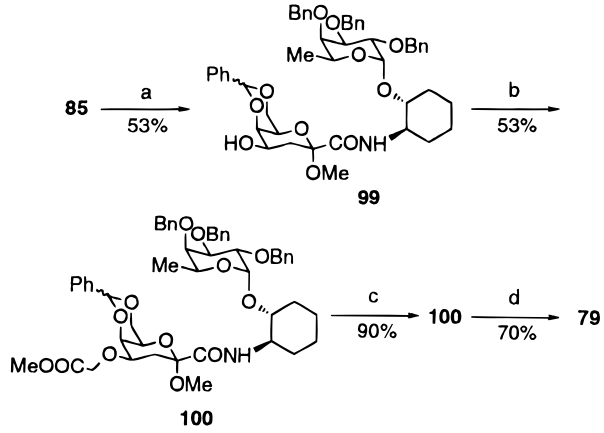
Scheme 12[a]



[a] Conditions: (a) (i) 50% TFA, CH_2Cl_2, rt, 3 h. (ii) **92**, HOBt, EDC, CH_2Cl_2, rt, 20 h. (iii) H_2 (1 atm), 20% $Pd(OH)_2$ on C, MeOH, rt, 6 h.

The activities of these fucopeptides were determined and their IC_{50} values in inhibiting the SLe^x glycoconjugate binding to E-selectin[32] are shown in Table 4. According to the results, all the functional groups required for E-selectin binding in SLe^x exist in **65**, and as expected it exhibited the same activity as SLe^x (IC_{50} = 0.5 mM). Compounds **66** and **67** are slightly less active than SLe^x, probably due to the presence of a free carboxyl group in the Thr moiety. Compound **68** is, however, surprisingly active as the OH group of Tyr in **68** is not exactly a mimic in space of the essential OH groups of the Gal residue in SLe^x. Whether the hydrophobic nature of the aromatic group or the additional amino group contributes to the binding is unclear. Compounds **70** and **71** are more active than SLe^x, perhaps due to the increasing constraint of the hydroxyproline-containing

Scheme 13[a]



[a] Conditions: (a) **92**, HOBt, NMM, EDC, DMF, −20 °C to about rt, 12 h. (b) $BrCH_2COOMe$, NaH, Bu_4NI, DMF, rt, 4 h. (c) H_2 (1 atm), 20% $Pd(OH)_2$ on C, MeOH, rt, 12 h. (d) 0.1 N NaOH, rt, 4 h.

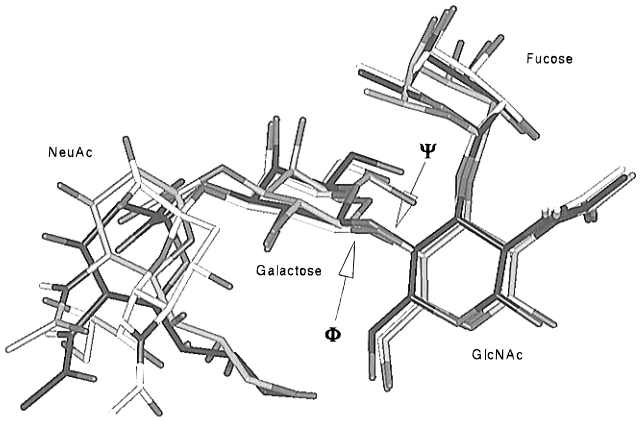


Figure 1. Overlay of three SLe^x conformations and their glycosidic torsion angles (ϕ/ψ for NeuAc-Gal, Gal-GlcNAc, and Fuc-GlcNAc): white, solution conformation determined by NMR[15a] (167/−63, 48/15, 23/30); gray, a predicted conformation based on GESA[15a] (−79/7, 55/7, 48/25); black, bound conformation determined by transfer NOE[15d] (−76/6, 39/12, 38/26).

peptide bonds. Replacement of the Thr component with (1*R*,2*R*)-2-aminocyclohexanol[26] resulted in a significant decrease in activity as shown in **73**. However, replacement of the P^2 residue with a four-carbon acid provides active mimetics (e.g., **72** and **74**). Compounds **69** and **79** are inactive at 3 mM. Perhaps the OH groups equivalent to the Gal residue are too far away from the Fuc residue. It appears that the charge−charge and multi-hydrogen-bonding interactions between E-selectin and SLe^x have to be precisely matched in the mimetic design. Work is in progress to prepare the next generation of SLe^x mimetics with restricted conformation mimicking the bound structure (Figure 1).

In summary, we have investigated the effects of protecting group and stereochemistry[6,33] on the *C*- and *O*-glycosylation reactions using glycosyl phosphites. This method is complementary to other glycosylation methods[6,34] and is of general use[35] except that 2-deoxy-2-azido sugars are not applicable and *N*-protected 2-amino sugars should be used.[3] Some of the sialyl Lewis X mimetics prepared in this study exihit greater inhibitory activities than SLe^x against E-selectin.

(32) The cell free assay was similar to that described in ref 18g except that a synthetic SLe^x polymer instead of HL-60 cells was used: Weitz-Schmidt, G.; Stokmaier, D.; Scheel, G.; Nifant'ev, N. E.; Tuzikov, A. B.; Bovin, N. V. *Ann. Biochem.*, in press.

(33) Feather, M. S.; Harris, J. F. *J. Org. Chem.* **1965**, *30*, 153 and references cited therein. For a recent investigation of the hydrolysis of *n*-pentenyl glycosides, see: Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317.

Experimental Section

Synthesis of Glycosyl Phosphites 2 and 6−12. The syntheses of **2** and **6−12** were carried out according to the reported procedure,[3] and the anomeric mixtures were separated by silica gel column chromatography (hexane:EtOAc:Et_3N = 10:1:0.1).[3,4e] Compound **7**[10] was prepared as described previously.

Compound 6: ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.5 Hz, 3H), 1.89 (s, 3H), 2.00 (s, 3H), 2.16 (s, 3H), 4.21 (q, J = 6.4 Hz, 1H), 4.90 (dd, J = 5.2 and 7.9 Hz, 2H), 4.94 (d, J = 7.4 Hz, 2H), 5.18 (dd, J = 3.4 and 10.8 Hz, 1H), 5.28 (d, J = 3.2 Hz, 1H), 5.39 (dd, J = 3.2 and 10.8 Hz, 1H), 5.76 (dd, J = 3.5 and 8.3 Hz, 1H), 7.26−7.37 (m, 10H).

Compound 8: ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H), 1.93 (s, 3H), 2.00 (s, 3H), 2.14 (s, 3H), 3.98 (dd, J = 6.7 and 11.4 Hz, 1H), 4.06 (dd, J = 6.4 and 11.2 Hz, 1H), 4.34 (t, J = 6.5 Hz, 1H), 4.90 (d, J = 8.0 Hz, 2H), 4.93 (dd, J = 2.2 and 8.0 Hz, 2H), 5.20 (dd, J = 3.4 and 10.8 Hz, 1H), 5.40 (dd, J = 3.3 and 10.8 Hz, 1H), 5.45 (dd, J = 1.2 and 3.2 Hz, 1H), 5.82 (dd, J = 3.4 and 8.3 Hz, 1H), 7.28−7.36 (m, 10H).

Compound 9: ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H), 1.99 (s, 6H), 2.17 (s, 3H), 3.97 (t, J = 6.8 Hz, 1H), 4.12 (dd, J = 7.0 and 11.5 Hz, 1H), 4.16 (dd, J = 6.4 and 11.5 Hz, 1H), 4.84 (dd, J = 7.0 and 12.2 Hz, 1H), 4.92 (d, J = 7.2 Hz, 2H), 4.95 (dd, J = 7.3 and 12.2 Hz, 1H), 5.05 (dd, J = 3.5 and 10.5 Hz, 1H), 5.07 (dd, J = 7.8 and 8.2 Hz, 1H), 5.35 (dd, J = 7.8 and 10.5 Hz, 1H), 5.41 (dd, J = 1.0 and 3.5 Hz, 1H), 7.29−7.37 (m, 10H).

Compound 11 (α:β = 62:38): (for α-anomer) ^{1}H NMR ($CDCl_3$) δ 1.01 (s), 1.87 (s), 2.00 (s), 2.01 (s), 3.57 (dd, J = 1.6 and 9.9 Hz), 3.63 (dd, J = 4.2 and 9.8 Hz), 4.84 (dt, J = 1.5 and 3.5 Hz), 4.90 (d, J = 7.2), 5.16 (dd, J = 3.5 and 10.8 Hz), 5.45 (dd, J = 3.2 and 10.8 Hz), 5.67 (dd, J = 1.1 and 3.2 Hz), 5.75 (dd, J = 3.5 and 8.6 Hz), 7.25−7.39 (m), 7.58−7.61 (m). (for β-anomer) ^{1}H NMR ($CDCl_3$) δ 1.02 (s), 1.90 (s), 2.00 (s), 2.03 (s), 3.65 (dd, J = 4.4 and 8.6 Hz), 3.71 (dd, J = 5.6 and 9.8 Hz), 3.83 (dd, J = 5.8 and 7.5 Hz), 5.07 (dd, J = 3.4 and 10.5 Hz), 5.19 (t, J = 8.2 Hz), 5.30 (dd, J = 7.8 and 10.4 Hz), 5.61 (d, J = 2.6 Hz), 7.58−7.61 (m). HRMS calcd for $C_{42}H_{49}O_{11}$-PSiCs (M + Cs) 921.1836, found 921.1879.

Compound 12 (α:β = 76:24): (for α-anomer) ^{1}H NMR ($CDCl_3$) δ 1.88 (s), 2.00 (s), 2.04 (s), 3.41 (d, J = 6.3 Hz), 4.35 (d, J = 12.1 Hz), 4.37 (t, J = 5.5 Hz), 4.49 (d, J = 12.0 Hz), 4.88 (d, J = 7.9 Hz), 4.93 (dd, J = 1.9 and 7.4 Hz), 5.19 (dd, J = 3.5 and 10.8 Hz), 5.40 (dd, J = 3.3 and 10.8 Hz), 5.53 (dd, J = 1.2 and 3.3 Hz), 5.81 (dd, J = 3.4 and 8.3 Hz), 7.22−7.34 (m). (for β-anomer) ^{1}H NMR ($CDCl_3$) δ 1.90 (s), 1.99 (s), 2.07 (s), 3.48 (dd, J = 6.8 and 9.6 Hz), 3.52 (dd, J = 6.0 and 9.6 Hz), 3.91 (t, J = 6.8 Hz), 4.40 (d, J = 12.0 Hz), 4.53 (d, J = 12.0 Hz), 4.82−4.95 (m), 5.04 (dd, J = 3.5 and 10.8 Hz), 5.05 (t, J = 8.4 Hz), 5.33 (dd, J = 8.4 and 10.8 Hz), 5.49 (dd, J = 1.2 and 3.5 Hz), 7.22−7.34 (m). HRMS calcd for $C_{33}H_{37}O_{11}$PCs (M + Cs) 773.1128, found 773.1130.

A General Procedure for the *C*-Glycosylation with 1,3,5-Trimethoxybenzene. A solution of dibenzyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl phosphite (**8**) (59.2 mg, 0.1 mmol) and 1,3,5-trimethoxybenzene (33.6 mg, 0.2 mmol) dissolved in dry CH_2Cl_2 (2 mL) was stirred in the presence of molecular sieves (3 Å) for 1 h at room temperature, and the mixture was cooled to −15 °C. A solution of 0.1 M TMSOTf in CH_2Cl_2 (0.5 mL, 0.05 mmol) was added to the reaction mixture, and stirring was continued for 1 h at the same temperature. The reaction was quenched by addition of Et_3N (0.5 mL), and the resulting reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$, 10% HCl, and 5% $NaHCO_3$, successively. After drying over $MgSO_4$, the solvent was removed and the residue was purified by flash chromatography (hexane/AcOEt) to give 13 mg of **14** (22%) and 16 mg of **15** (32%) as a viscous oil.

Compound 14: ^{1}H NMR ($CDCl_3$) δ 1.67 (d, J = 10.9 Hz, 3H), 2.068 (s, 3H), 2.074 (s, 3H), 2.10 (s, 3H), 4.14 (m, 2H), 4.29−4.34 (m, 2H), 5.04−5.13 (m, 5H), 5.40 (dd, J = 2.3, 3.3 Hz, 1H), 6.07 (d, J = 4.8 Hz, 1H), 7.35 (br s, 10H); ^{13}C NMR ($CDCl_3$) δ 20.54, 20.74, 22.89, 23.09, 61.49, 65.68, 68.51, 68.94, 72.98, 98.90, 128.00, 128.51, 128.57, 128.69; HRMS calcd for $C_{28}H_{33}O_{12}$PCs (M + Cs) 725.0764, found 725.0794.

Compound 15: ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.20 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 3.98 (ddd, J = 1.0, 6.0, 7.2 Hz, 1H), 4.11 (dd, J = 6.1, 11.2 Hz, 1H), 4.17 (dd, J = 7.6, 11.1 Hz, 1H), 4.97 (d, J = 10.0 Hz, 1H), 5.12 (dd, J = 3.4, 10.0 Hz, 1H), 5.48 (dd, J = 0.9, 3.4 Hz, 1H), 6.07 (d, J = 2.2 Hz, 1H), 6.110 (t, J = 10.0 Hz, 1H), 6.112 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.55, 20.77, 55.20, 56.00, 56.22, 61.78, 67.27, 67.99, 72.16, 73.07, 74.20, 90.66, 91.81; HRMS calcd for $C_{23}H_{30}O_{12}$Cs (M + Cs) 631.0792, found 631,0817.

Compound 22: ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.73 (s, 3H), 2.01 (s, 3H), 2.10 (s, 3H), 3.62 (t, J = 9.3 Hz, 1H), 3.74 (dd, J = 5.2, 9.8 Hz, 1H), 3.76 (s, 6H), 3.81 (s, 3H), 3.87 (dd, J = 5.3, 8.7 Hz, 1H), 4.94 (d, J = 9.9 Hz, 1H), 5.06 (t, J = 9.4 Hz, 1H), 5.17 (dd, J = 3.3, 10.0 Hz, 1H), 5.73 (d, J = 3.2 Hz, 1H), 6.03 (d, J = 2.2 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 6.08 (t, J = 10.0 Hz, 1H), 7.31−7.41 (m, 6H), 7.57−7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.58, 20.75, 20.87, 26.69, 26.73, 55.17, 55.98, 56.16, 61.11, 67.63, 67.80, 72.05, 73.46, 76.87, 76.94, 90.56, 91.70, 127.63, 129.67, 135.64, 135.70; HRMS calcd for $C_{37}H_{46}O_{11}$SiCs (M + Cs) 827.1864, found 827.1895.

Compound 23: ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.99 (s, 3H), 2.10 (s, 3H), 3.44 (dd, J = 7.8, 9.2 Hz, 1H), 3.56 (dd, J = 5.4, 9.2 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 3.92 (ddd, J = 1.0, 5.4, 7.8 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 5.12 (dd, J = 3.4, 10.0 Hz, 1H), 5.58 (dd, J = 0.8, 3.4 Hz, 1H), 5.58 (dd, J = 0.8, 3.4 Hz, 1H), 6.05 (d, J = 2.2 Hz, 1H), 6.085 (t, J = 9.8 Hz, 1H), 6.089 (d, J = 2.2 Hz, 1H), 7.26−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.57, 20.77, 20.81, 55.18, 55.96, 56.19, 67.54, 67.58, 68.46, 72.14, 73.27, 73.41, 75.58, 90.56, 91.75, 127.72, 128.04, 128.36; HRMS calcd for $C_{28}H_{34}O_{11}$Cs (M + Cs) 679.1155, found 679.1186.

Compound 25: ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.3 Hz, 3H), 3.61 (q, J = 6.4 Hz, 1H), 3.65 (dd, J = 3.0, 9.2 Hz, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 4.12 (d, J = 10.6 Hz, 1H), 4.55 (d, J = 10.6 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.75 (t, J = 9.4 Hz, 1H), 4.80 (s, 2H), 4.87 (d, J = 9.7 Hz, 1H), 5.13 (d, J = 11.6 Hz, 1H), 6.09 (d, J = 2.2 Hz, 1H), 6.15 (d, J = 2.2 Hz, 1H), 6.90−6.93 (m, 2H), 7.12−7.16 (m, 3H), 7.25−7.37 (m, 6H), 7.40−7.42 (m, 2H), 7.47−7.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.65, 55.30, 56.00, 56.04, 72.71, 72.94, 74.23, 74.41, 74.62, 76.95, 77.97, 85.52, 90.88, 92.12, 108.40, 126.98, 127.08, 127.17, 127.29, 127.39, 127.51, 127.96, 128.11, 128.31, 138.82, 139.08, 139.71, 159.89, 161.15; HRMS calcd for $C_{36}H_{40}O_7$Cs (M + Cs) 717.1828, found 717.1862.

General Procedure for *O*-Fucosylation. A solution of dibenzyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl phosphite (**2**; 100 mg, 0.13 mmol) and the acceptor alcohol (**26−38**, 0.16 mmol) in CH_2Cl_2 (4 mL) was stirred for 1 h at room temperature in the presence of molecular sieves (4 Å, 100 mg). To the mixture was added 1% TfOH in CH_2Cl_2 solution (100 μL) at −15 °C. After stirring for 1 h at the same temperature, Et_3N (1 mL) was added to quench the reaction, and the mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% $NaHCO_3$, 5% HCl and 5% $NaHCO_3$, successively. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain the desirable fucosides.

Compound 39: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.4 Hz, 3H), 1.28−1.41 (m, 2H), 1.48−1.65 (m, 4H), 1.65 (s, 3H), 2.27−2.32 (m, 2H), 3.31−3.59 (m, 5H), 3.65 (s, 3H), 3.75 (t, J = 10.1 Hz, 1H), 3.79−3.85 (m, 1H), 3.93 (dd, J = 2.7 and 10.2 Hz, 1H), 4.04−4.10 (m, 2H), 4.27−4.35 (m, 2H), 4.58 (d, J = 11.9 Hz, 1H), 4.67 (d, J =

(34) (a) Lemieux, R. U. *Chem. Soc. Rev.* **1978**, *7*, 423. (b) Mukaiyama, T.; Murai, Y.; Shoda, S. I.; *Chem. Lett.* **1981**, 431. (c) Ogawa, T.; Yamamoto, H.; Nukada, T.; Kitajima, T.; Sugimoto, M. *Pure Appl. Chem.* **1984**, *56*, 779. (d) Fugedi, P.; Garegg, P. J.; Lonn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97. (e) Mootoo, D. R.; Konradsson, P.; Udodong, U. Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (f) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (g) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (h) Suzuki, K.; Maeta, H. Matsumoto, T. *Tetrahedron Lett.* **1989**, *36*, 4853. (i) Sinay, P. *Pure Appl. Chem.* **1991**, *63*, 519. (j) Nicolau, K. C.; Caulfield, T. J.; Groneberg, R. D. *Pure Appl. Chem.* **1991**, *63*, 555. (k) Garegg, P. J. *Acc. Chem. Res.* **1992**, *25*, 575. (l) Kanie, O.; Hindsgaul, O. *Curr. Opin. Struct. Biol.* **1992**, *2*, 674. (m) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095.

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11.9 Hz, 1H), 4.74 (s, 2H), 4.88−4.94 (m, 3H), 5.07 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H), 5.74 (d, J = 7.2 Hz, 1H), 7.13−7.47 (m, 20H); HRMS calcd for $C_{49}H_{59}NO_{12}Cs$ (M + Cs) 986.3092, found 986.3090.

Compound 40: ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.5 Hz, 3H), 1.06 (s, 9H), 1.07 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H), 1.24 (s, 9H), 2.04 (s, 3H), 3.44−3.56 (m, 3H), 3.67−3.86 (m, 4H), 3.86−4.21 (m, 8H), 4.42−4.44 (m, 2H), 4.56−4.99 (m, 20H), 5.21 (d, J = 3.5 Hz, 1H), 5.276 (d, J = 3.5 Hz, 1H), 5.283 (d, J = 6.7 Hz, 1H), 7.19−7.40 (m, 61H), 7.64−7.73 (m, 4H); electrospray positive ion mass, *m/z* 2020 $(M + H)^+$.

Compound 41: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 3H), 1.45 (s, 9H), 3.35−3.37 (m, 2H), 3.47 (dd, J = 3.0 and 9.8 Hz, 1H), 3.62 (dd, J = 2.5 and 10.1 Hz, 1H), 3.95 (dd, J = 3.6 and 10.1 Hz, 1H), 4.14 (dd, J = 2.3 and 9.8 Hz, 1H), 4.50−4.53 (m, 1H), 4.60−4.64 (m, 3H), 4.66 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 5.02 (d, J = 12.2 Hz, 1H), 5.26 (d, J = 12.2 Hz, 1H), 5.87 (d, J = 9.2 Hz, 1H), 7.23−7.40 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 54.0, 66.5, 67.0, 69.1, 73.2, 74.7, 76.4, 77.2, 78.8, 79.9, 98.8, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.5, 138.4, 138.5, 138.8, 155.7, 170.4. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 6.3 Hz, 3H), 1.44 (s, 9H), 3.42 (q, J = 6.3 Hz, 1H), 3.47 (dd, J = 2.9 and 9.7 Hz, 1H), 3.54 (d, J = 2.9 Hz, 1H), 3.75 (dd, J = 7.7 and 9.7 Hz, 1H), 4.05 (dd, J = 2.8 and 10.1 Hz, 1H), 4.13 (dd, J = 2.8 and 10.1 Hz, 1H), 4.23 (d, J = 7.7 Hz, 1H), 4.48 (td, J = 2.8 and 9.1 Hz, 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 11.7 Hz, 2H), 4.77 (m, 2H), 4.97 (d, J = 11.7 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 5.75 (d, J = 9.1 Hz, 1H), 7.24−7.36 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 28.3, 54.0, 67.0, 70.6, 73.2, 74.6, 74.9, 75.9, 78.8, 78.9, 82.3, 104.3, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 135.4, 138.3, 138.4, 138.6, 155.6, 170.5. HRMS calcd for $C_{42}H_{49}NO_9Cs$ (M + Cs) 844.2462, found 844.2498.

Compound 42: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, J = 6.5 Hz, 3H), 3.25 (q, J = 6.5 Hz, 1H), 3.28 (br s, 1H), 3.41 (dd, J = 3.1 and 9.8 Hz, 1H), 3.53 (dd, J = 2.7 and 10.1 Hz, 1H), 3.87 (dd, J = 3.6 and 10.1 Hz, 1H), 4.09 (dd, J = 2.5 and 9.8 Hz, 1H), 4.50−4.54 (m, 4H), 4.56 (d, J = 6.5 Hz, 1H), 4.60 (d, J = 6.5 Hz, 1H), 4.69 (d, J = 11.8 Hz, 2H), 4.85 (d, J = 11.8 Hz, 1H), 4.99 (d, J = 12.1 Hz, 1H), 5.07 (d, J = 2.5 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 6.70 (d, J = 9.1 Hz, 1H), 7.17−7.31 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 54.4, 66.5, 67.0, 67.1, 68.9, 73.1, 73.3, 74.6, 76.4, 77.1, 78.8, 98.6, 126.9, 127.5, 127.6, 127.8, 128.1, 128.4, 128.5, 128.6, 135.4, 136.3, 138.4, 138.8, 156.3, 170.1. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, J = 6.3 Hz, 3H), 3.40 (q, J = 6.3 Hz, 1H), 3.46 (dd, J = 2.9 and 9.7 Hz, 1H), 3.53 (d, J = 2.9 Hz, 1H), 3.74 (dd, J = 7.8 and 9.7 Hz, 1H), 4.07 (dd, J = 2.9 and 10.1 Hz, 1H), 4.14 (dd, J = 2.7 and 10.1 Hz, 1H), 4.22 (d, J = 7.7 Hz, 1H), 4.53−4.56 (m, 1H), 4.65 (d, J = 10.7 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.73 (d, J = 10.7 Hz, 1H), 4.77 (d, J = 11.8 Hz, 2H), 4.96 (d, J = 11.8 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.12 (s, 2H), 6.01 (d, J = 8.9 Hz, 1H), 7.20−7.30 (m, 25H). HRMS calcd for $C_{45}H_{47}NO_9Cs$ (M + Cs) 878.2305, found 878.2339.

Compound 43: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J = 6.6 Hz, 3H), 3.28 (q, J = 6.6 Hz, 1H), 3.30 (br s, 1H), 3.43 (dd, J = 2.9 and 10.0 Hz, 1H), 3.56 (dd, J = 2.7 and 10.1 Hz, 1H), 3.89 (dd, J = 3.6 and 10.0 Hz, 1H), 4.11 (dd, J = 2.4 and 10.1 Hz, 1H), 4.13−4.16 (m, 1H), 4.28 (dd, J = 7.3 and 10.6 Hz, 1H), 4.40 (dd, J = 7.0 and 10.6 Hz, 1H), 4.50−4.53 (m, 1H), 4.53 (d, J = 3.6 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.86 (d, J = 11.6 Hz, 1H), 5.00 (d, J = 12.1 Hz, 1H), 5.18 (d, J = 12.1 Hz, 1H), 6.31 (d, J = 9.1 Hz, 1H), 7.13−7.35 (m, 24H), 7.53 (t, J = 6.8 Hz, 2H), 7.66 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 47.1, 54.5, 66.6, 67.2, 69.0, 73.1, 73.4, 74.7, 76.3, 77.1, 78.8, 98.9, 119.9, 125.1, 127.0, 127.5, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 135.4, 138.4, 138.7, 141.2, 143.7, 143.9, 156.4, 170.1. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.3 Hz, 3H), 3.41 (q, J = 6.3 Hz, 1H), 3.48 (dd, J = 2.8 and 9.8 Hz, 1H), 3.55 (d, J = 2.8 Hz, 1H), 3.78 (dd, J = 8.0 and 9.8 Hz, 1H), 4.07 (dd, J = 2.7 and 10.3 Hz, 1H), 4.20 (dd, J = 2.4 and 10.3 Hz, 1H), 4.23−4.25 (m, 2H), 4.34 (dd, J = 7.3 and 10.6 Hz, 1H), 4.42 (dd, J = 7.1 and 10.6 Hz, 1H), 4.54−4.56 (m, 1H), 4.76 (d, J = 10.1 Hz, 1H), 4.78 (d, J = 10.1 Hz, 1H), 4.92−5.14 (m, 4H), 5.18 (d, J = 12.2 Hz, 1H), 6.10 (d, J = 9.0 Hz, 1H), 7.23−7.37 (m, 24H), 7.64 (t, J = 3.5 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H). HRMS calcd for $C_{52}H_{51}NO_9Cs$ (M + Cs) 966.2618, found 966.2660.

Compound 44: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 3H), 1.80 (br s, 2H), 3.44 (d, J = 2.8 Hz, 1H), 3.52 (q, J = 6.6 Hz, 1H), 3.60 (dd, J = 3.6 and 9.7 Hz, 1H), 3.67 (m, 1H), 3.71 (dd, J = 2.8 and 10.1 Hz, 1H), 3.95 (dd, J = 4.5 and 9.7 Hz, 1H), 3.99 (dd, J = 3.7 and 10.1 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 11.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 4.77 (d, J = 3.7 Hz, 1H), 4.82 (d, J = 11.8 Hz, 1H), 4.94 (d, J = 11.6 Hz, 1H), 5.05 (d, J = 12.1 Hz, 1H), 5.19 (d, J = 12.1 Hz, 1H), 7.26−7.33 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 54.7, 66.4, 66.8, 70.0, 73.1, 73.2, 74.7, 76.5, 77.3, 78.9, 98.1, 127.5, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 128.6, 138.5, 138.6, 138.9, 173.4; HRMS calcd for $C_{37}H_{41}NO_9$ (M + H) 612.2961, found 612.2984.

Compound 45: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 6.5 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.38 (s, 9H), 3.47 (dd, J = 3.2 and 10.0 Hz, 1H), 3.52 (br s, 1H), 3.67 (q, J = 6.5 Hz, 1H), 3.75 (dd, J = 2.8 and 10.1 Hz, 1H), 3.94 (dd, J = 3.7 and 10.0 Hz, 1H), 4.05−4.12 (m, 3H), 4.36−4.38 (m, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 3.7 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.9 Hz, 2H), 4.89 (d, J = 11.6 Hz, 1H), 5.76 (d, J = 9.0 Hz, 1H), 7.19−7.32 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.5, 28.3, 53.9, 61.3, 66.6, 69.1, 73.1, 73.2, 74.7, 76.2, 77.4, 79.0, 98.7, 127.5, 127.6, 127.8, 128.1, 128.3, 128.4, 138.4, 138.5, 138.7, 155.7, 170.5. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.5 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 3.44 (q, J = 6.5 Hz, 1H), 3.48 (dd, J = 2.9 and 9.7 Hz, 1H), 3.55 (d, J = 2.9 Hz, 1H), 3.76 (dd, J = 7.7 and 9.7 Hz, 1H), 4.05−4.16 (m, 4H), 4.26 (d, J = 7.7 Hz, 1H), 4.41 (td, J = 2.7 and 9.1 Hz, 1H), 4.68 (d, J = 11.3 Hz, 1H), 4.70 (d, J = 12.3 Hz, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.77 (d, J = 12.3 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.97 (d, J = 11.8 Hz, 1H), 5.68 (d, J = 9.1 Hz, 1H), 7.30−7.37 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.7, 28.3, 53.8, 61.4, 67.2, 70.5, 73.3, 74.6, 74.9, 75.8, 78.8, 82.4, 104.2, 127.5, 127.6, 127.7, 128.1, 128.2, 128.4, 128.7, 138.4, 138.6, 155.6, 170.6. HRMS calcd for $C_{37}H_{47}NO_9Cs$ (M + Cs) 782.2305, found 782.2325.

Compound 46: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, J = 6.5 Hz, 3H), 1.35 (s, 9H), 1.38 (s, 9H), 3.40 (dd, J = 3.1 and 9.8 Hz, 1H), 3.50 (br s, 1H), 3.73−3.76 (m, 2H), 3.97 (dd, J = 3.6 and 9.8 Hz, 1H), 4.04 (dd, J = 2.8 and 9.8 Hz, 1H), 4.27 (td, J = 2.8 and 9.1 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 3.6 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 11.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 4.90 (d, J = 11.7 Hz, 1H), 5.68 (d, J = 9.1 Hz, 1H), 7.19−7.32 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 27.9, 28.3, 54.4, 66.5, 69.3, 73.1, 73.2, 74.8, 76.4, 77.7, 79.0, 98.6, 127.5, 127.6, 127.9, 128.2, 128.4, 138.5, 138.6, 155.7, 169.5. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3H), 1.41 (s, 9H), 1.44 (s, 9H), 3.45 (q, J = 6.5 Hz, 1H), 3.49 (dd, J = 2.9 and 9.7 Hz, 1H), 3.55 (d, J = 2.9 Hz, 1H), 3.76 (dd, J = 7.7 and 9.7 Hz, 1H), 3.98 (dd, J = 3.0 and 10.1 Hz, 1H), 4.10 (dd, J = 3.0 and 10.1 Hz, 1H), 4.27 (d, J = 7.7 Hz, 1H), 4.29 (td, J = 3.0 and 9.1 Hz, 1H), 4.68−4.72 (m, 3H), 4.78 (d, J = 11.9 Hz, 1H), 4.86 (d, J = 11.1 Hz, 1H), 4.97 (d, J = 11.8 Hz, 1H), 5.67 (d, J = 9.1 Hz, 1H), 7.29−7.36 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 28.0, 28.3, 54.3, 70.6, 73.2, 74.6, 74.9, 76.0, 78.8, 81.8, 82.4, 104.1, 127.4, 127.5, 127.6, 128.2, 128.4, 128.6, 138.4, 138.5, 138.6, 155.6, 169.6. HRMS calcd for $C_{39}H_{51}NO_9Cs$ (M + Cs) 810.2618, found 810.2650.

Compound 47: (for α-fucoside) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.48 (s, 9H), 3.42 (d, J = 2.4 Hz, 1H), 3.68 (dd, J = 2.8 and 10.1 Hz, 1H), 3.99 (dd, J = 3.8 and 10.2 Hz, 1H), 4.31 (dq, J = 2.2 and 6.2 Hz, 1H), 4.37 (dd, J = 2.1 and 9.8 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 3.8 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 5.07 (d, J = 12.2 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 5.41 (d, J = 9.8 Hz, 1H), 7.26−7.40 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 16.5, 28.4, 58.5, 66.7, 67.1, 71.9, 73.1, 73.2, 74.7, 76.2, 76.7, 77.3,

78.9, 94.5, 127.5, 127.6, 127.8, 128.1, 128.2, 128.32, 128.35, 128.43, 128.5, 128.6; HRMS calcd for $C_{43}H_{51}NO_9Cs$ (M + Cs) 858.2618, found 858.2657.

Compound 48α: (for α-fucoside) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 6.4 Hz, 3H), 1.20−1.26 (m, 6H), 1.48 (s, 9H), 3.60 (d, J = 2.4 Hz, 1H), 3.69 (q, J = 7.0 Hz, 1H), 3.80 (dd, J = 2.8 and 10.1 Hz, 1H), 3.99−4.32 (m, 5H), 4.60 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 3.8 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 5.34 (d, J = 9.6 Hz, 1H), 7.25−7.40 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 16.6, 28.4, 58.4, 61.5, 66.7, 72.4, 73.0, 73.1, 74.8, 76.1, 77.5, 79.0, 94.8, 127.5, 127.6, 127.8, 128.1, 128.2, 128.3; HRMS calcd for $C_{38}H_{49}NO_9Cs$ (M + Cs) 796.2462, found 796.2485.

Compound 49: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, J = 6.4 Hz, 3H), 1.38 (s, 9H), 3.50 (br s, 1H), 3.63−3.67 (m, 2H), 3.71 (dd, J = 2.6 and 10.2 Hz, 1H), 3.96 (dd, J = 3.7 and 10.2 Hz, 1H), 4.24 (dd, J = 3.3 and 11.5 Hz, 1H), 4.37−4.39 (m, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 3.7 Hz, 1H), 4.64 (d, J = 3.7 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 11.7 Hz, 1H), 4.92 (d, J = 11.5 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 5.91 (d, J = 8.8 Hz, 1H), 7.20−7.36 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 28.3, 54.5, 67.1, 71.2, 73.1, 73.2, 74.8, 76.2, 77.3, 78.9, 79.8, 99.8, 127.4, 127.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.4, 128.5, 135.4, 138.4, 138.5, 138.8, 155.6, 170.4. (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.3 Hz, 3H), 1.41 (s, 9H), 3.41 (q, J = 6.3 Hz, 1H), 3.49 (dd, J = 2.9 and 9.7 Hz, 1H), 3.55 (d, J = 2.9 Hz, 1H), 3.76 (dd, J = 7.7 and 9.7 Hz, 1H), 3.78 (dd, J = 3.3 and 10.4 Hz, 1H), 4.29 (d, J = 7.7 Hz, 1H), 4.36 (dd, J = 3.3 and 10.4 Hz, 1H), 4.49 (td, J = 3.3 and 8.3 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 10.9 Hz, 1H), 4.72 (d, J = 11.9 Hz, 1H), 4.78 (d, J = 11.9 Hz, 1H), 4.81 (d, J = 10.9 Hz, 1H), 4.98 (d, J = 11.6 Hz, 1H), 5.16 (d, J = 12.4 Hz, 1H), 5.22 (d, J = 12.4 Hz, 1H), 5.56 (d, J = 8.3 Hz, 1H), 7.28−7.37 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 28.3, 54.2, 67.2, 69.9, 70.5, 73.1, 74.7, 75.3, 76.3, 79.0, 82.4, 104.2, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 135.4, 138.4, 155.5, 170.2.

Compound 50: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.9 Hz, 3H), 1.40 (s, 9H), 1.27−1.78 (m, 8H), 3.22−3.25 (m, 2H), 3.66 (br s, 1H), 3.94 (dd, J = 2.7 and 10.2 Hz, 1H), 4.04 (dd, J = 3.8 and 10.2 Hz, 1H), 4.05 (q, J = 6.9 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 2.7 Hz, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.47−5.48 (m, 3H), 4.99 (d, J = 11.4 Hz, 1H), 7.28−7.40 (m, 15H). (for β-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.3 Hz, 3H), 1.38 (s, 9H), 1.27−1.78 (m, 6H), 2.01 (br s, 1H), 2.17 (br s, 1H), 3.46 (q, J = 6.3 Hz, 1H), 3.50 (dd, J = 2.9 and 9.7 Hz, 1H), 3.55 (d, J = 2.9 Hz, 1H), 3.55−3.59 (m, 2H), 3.81 (dd, J = 7.7 and 9.7 Hz, 1H), 4.43 (d, J = 7.7 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 4.82−4.88 (m, 2H), 4.95 (d, J = 11.4 Hz, 1H), 4.97 (d, J = 11.4 Hz, 1H), 7.28−7.40 (m, 15H). HRMS calcd for $C_{38}H_{49}NO_7Cs$ (M + Cs) 764.2563, found 764.2575.

Compound 51: (for α-fucoside) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, J = 6.1 Hz, 1H), 1.14−1.28 (m, 4H), 1.67−1.76 (m, 2H), 2.02−2.08 (m, 2H), 3.41−3.47 (m, 2H), 3.71 (br s, 1H), 4.05 (br s, 2H), 4.13 (q, J = 6.1 Hz, 1H), 4.98 (br s, 1H), 4.64−4.99 (m, 6H), 7.25−7.41 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 23.6, 24.1, 29.1, 30.8, 64.5, 66.6, 73.4, 74.8, 75.9, 76.2, 77.8, 79.4, 93.5, 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.5, 136.6; HRMS calcd for $C_{33}H_{39}N_3O_5Cs$ (M + Cs) 580.2787, found 580.2761.

Selective Reduction of 39 for the Synthesis of 52. A mixture of **39** (733 mg, 0.858 mmol), borane−trimethylamine complex (376 mg, 5.15 mmol), and molecular sieves (4 Å) in THF (5 mL) was stirred at room temperature for 30 min. Aluminum trichloride (687 mg, 5.15 mmol) was added, and the mixture was stirred at room temperature for 18 h. The reaction mixture was then filtered, and the filtrate was neutralized with Dowex 50W (H^+), filtered again, and concentrated. The residue was concentrated three times with MeOH, and the product was applied to silica gel column chromatography (hexane:EtOAc = 1:1) to obtain **52** (374 mg, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.4 Hz, 3H), 1.30−1.38 (m, 2H), 1.53−1.66 (m, 4H), 1.61 (s, 3H), 2.29 (t, J = 7.5 Hz, 2H), 3.25−3.35 (m, 1H), 3.40−3.50 (m, 3H), 3.65 (s, 3H), 3.66−3.71 (m, 2H), 3.82 (dd, J = 1.8 and 10.7 Hz, 1H), 3.85−3.91 (m, 2H), 3.95 (dd, J = 2.3 and 10.2 Hz, 1H), 4.07 (dd, J = 3.6 and 10.7 Hz, 1H), 4.10 (m, 1H), 4.17 (br s, 1H), 4.57−4.69 (m, 4H), 4.73−4.85 (d, J = 3.3 Hz, 1H), 5.59 (d, J = 7.1 Hz, 1H), 7.25−7.41 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 23.1, 24.5, 25.5, 29.0, 33.9, 51.4, 56.2, 68.0, 69.2, 69.6, 70.4, 72.8, 73.4, 74.0, 74.8, 74.9, 75.9, 77.2, 79.0, 83.9, 99.0, 99.9, 127.5−128.5, 138.2, 138.4, 170.7, 174.1; HRMS calcd for $C_{49}H_{62}NO_{12}$ (M + H) 856.4272, found 856.4278.

Galactosylation of 52 with 12 for the Synthesis of 53. TMSOTf (14 μL of a 10% solution in CH_2Cl_2, 7.2 μmol) was added to a mixture of **52** (20 mg, 23.4 μmol) and molecular sieves (4 Å) in CH_2Cl_2 at −20 °C under an argon atmosphere. After 10 min, a solution of **12** (61 mg, 94.6 μmol, α:β = 33:67) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred at −20 °C for another 10 min. The temperature was raised to 40 °C, and the stirring was continued for 20 h at that temperature. The reaction was quenched with 10% NH_4Cl (5 mL), and CH_2Cl_2 (10 mL) was added to the reaction mixture. The organic layer was separated, dried with $MgSO_4$, and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:EtOAc = 1:1) to obtain **53** (8.5 mg, 29%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 6.5 Hz, 3H), 1.21−1.33 (m, 2H), 1.48−1.61 (m, 4H), 1.77 (s, 3H), 1.86 (s, 3H), 1.96 (s, 3H), 2.00 (s, 3H), 2.25 (t, J = 7.7 Hz, 2H), 3.31−3.41 (m, 2H), 3.48−3.58 (m, 5H), 3.64 (s, 3H), 3.72−3.79 (m, 2H), 3.85 (dd, J = 2.5 and 10.2 Hz, 1H), 3.93 (t, J = 6.9 Hz, 1H), 4.09 (dd, J = 3.5 and 10.0 Hz, 1H), 4.17 (t, J = 7.0 Hz, 1H), 4.28−4.31 (m, 2H), 4.42 (d, J = 12.3 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.53 (d, J = 8.2 Hz, 1H), 4.62−4.84 (m, 6H), 4.82 (d, J = 6.6 Hz, 1H), 4.84 (dd, J = 3.4 and 10.6 Hz, 1H), 4.94 (d, J = 12.0 Hz, 1H), 5.01 (dd, J = 8.1 and 10.4 Hz, 1H), 5.08 (d, J = 3.4 Hz, 1H), 5.40 (d, J = 3.3 Hz, 1H), 5.95 (d, J = 7.9 Hz, 1H), 7.16−7.19 (m, 2H), 7.24−7.37 (m, 23H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 20.6, 20.7, 23.2, 24.6, 25.4, 28.9, 29.7, 33.9, 51.5, 66.4, 66.6, 68.5, 69.0, 69.2, 70.8, 71.5, 72.9, 83.2, 73.3, 73.4, 73.9, 74.3, 77.2, 79.9, 97.1, 99.5, 127.2−128.5, 137.3, 137.8, 138.6, 138.7, 138.8, 169.5, 169.8, 167.0, 170.2, 174.2; HRMS calcd for $C_{68}H_{83}NO_{20}Cs$ (M + Cs) 1366.4563, found 1366.4622.

***β*-Galactosylation of Benzyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (54)[36] with *β*-Galactosidase from *B. circulans* for the Synthesis of 55.** β-Galactosidase (50 mg, *B. circulans*, Daiwa Kasei) was added to a mixture of lactose monohydrate (3.3 g, 9.16 mmol) and **54** (570 mg, 1.83 mmol) in a mixed solvent prepared from 20 mM phosphate buffer (10 mL, pH 7.0) and MeCN (10 mL). The reaction mixture was stirred under an argon atmosphere for 48 h at room temperature, after which it was concentrated *in vacuo*. The residue was passed through a silica gel column eluted with a mixture of $CHCl_3$, MeOH, and 30% NH_4OH (3:1:0.3) to obtain **55** (107 mg, 59% based on unrecovered **54**): ^{1}H NMR (400 MHz, D_2O) δ 1.94 (s, 3H), 3.53 (dd, J = 7.8 Hz and 9.8 Hz, 1H), 3.65 (dd, J = 3.2 Hz and 9.9 Hz, 1H), 3.68−3.77 (m, 5H), 3.86−3.91 (m, 6H), 4.46 (d, J = 7.8 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 11.9 Hz, 1H), 4.93 (d, J = 1.2 Hz, 1H), 7.38−7.45 (m 5H); ^{13}C NMR (100 MHz, D_2O) δ 22.2, 53.7, 60.3, 61.4, 68.9, 69.9, 70.1, 71.2, 71.4, 73.0, 75.7, 79.2, 96.0, 103.3, 128.8, 128.9, 129.2, 137.3, 174.6; HRMS calcd for $C_{21}H_{31}O_{11}NCs$ (M + Cs) 606.0951, found 606.0926.

Double Silylation of 55 with TBDPSCl for the Synthesis of 56. To a solution of **55** (120 mg, 0.254 mmol) in DMF (5 mL) were added imidazole (38 mg, 0.559 mmol) and TBDPSCl (160 μL, 0.583 mmol) at 0 °C. The mixture was stirred at room temperature for 8 h and poured into water (50 mL). The solution was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:EtOAc = 1:1) to obtain **56** (198 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.04 (s, 9H), 1.92 (s, 3H), 3.31 (d, J = 5.1 Hz, 1H), 3.43−3.46 (m, 1H), 3.56 (t, J = 6.3 Hz, 1H), 3.61 (t, J = 9.2 Hz, 1H), 3.67−3.88 (m, 10H), 3.91 (d, J = 1.8 Hz, 1H), 3.96−4.00 (m, 2H), 4.09 (ddd, J = 3.7, 8.7 and 10.4 Hz, 1H), 4.25 (br s, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.93 (d, J = 3.6 Hz, 1H), 5.75 (d, J = 8.6 Hz, 1H), 7.23−7.41

(36) (a) Paulsen, H.; Kolar, C.; Stenzel, W. *Chem. Ber.* **1978**, *11*, 2370. (b) Flowers, H. M.; Jeanloz, R. W. *J. Org. Chem.* **1963**, *28*, 1377.

(m, 17H), 7.62−7.65 (m, 4H), 7.70−7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 19.2, 23.3, 26.7, 26.8, 31.4, 36.5, 53.2, 62.2, 63.1, 68.1, 69.2, 70.6, 70.9, 71.5, 73.5, 74.9, 80.8, 96.2, 103.5, 127.5−128.1, 128.4, 129.7, 129.8, 135.5−135.8, 170.3; HRMS calcd for $C_{53}H_{67}NO_{11}Si_2Cs$ (M + Cs) 1082.3307, found 1082.3332.

Silylation of 56 for the Synthesis of 27. To a solution of **56** (100 mg, 0.105 mmol) in CH_2Cl_2 (5 mL) were added imidazole (14 mg, 0.206 mmol) and TBDPSCl (60 μL, 0.219 mmol) at 0 °C. The mixture was stirred at room temperature for 8 h, diluted with CH_2Cl_2 (20 mL), and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:EtOAc = 2:1) to obtain **27** (97 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.00 (s, 9H), 1.10 (s, 9H), 1.88 (s, 3H), 3.34 (t, J = 6.5 Hz, 1H), 3.55−3.61 (m, 4H), 3.70−3.84 (m, 8H), 3.88 (dd, J = 4.2 and 11.5 Hz, 1H), 4.05 (ddd, J = 3.6, 8.6 and 10.6 Hz, 1H), 4.21 (d, J = 7.8 Hz, 1H), 4.27 (d, J = 1.2 Hz, 1H), 4.35 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.92 (d, J = 3.6 Hz, 1H), 5.50 (d, J = 8.6 Hz, 1H), 7.22−7.43 (m, 23H), 7.56−7.59 (m, 4H), 7.66−7.71 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 23.4, 26.76, 26.83, 27.0, 53.0, 62.1, 63.4, 68.3, 69.3, 70.6, 70.8, 71.9, 74.5, 82.4, 96.3, 103.9, 127.6, 127.6, 127.7, 127.75, 127.82, 127.9, 128.5, 129.7, 129.8, 130.0, 130.2, 135.5, 135.60, 135.64, 135.7, 135.8, 170.1; electrospray positive ion mass, m/z 1188 $(M + H)^+$.

6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl Dibenzyl Phosphite (57). To a solution of methyl α-D-galactoside (5.82 g, 30 mmol) and benzyl bromide (21 g, 123 mmol) in DMF (60 mL) was added 60% NaH (5.0 g, 125 mmol). The resulting suspension was stirred for 5 h at room temperature, poured into water (300 mL), and extracted with EtOAc. The obtained extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc) to obtain the title compound (12.0 g, 72%) as a colorless syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.52 (s, J = 6.4 Hz, 2H), 3.89 (t, J = 6.5 Hz, 1H), 3.93 (dd, J = 2.9 and 10.9 Hz, 1H), 3.94 (s, 1H), 4.04 (ddd, J = 1.2, 3.4 and 10.9 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.682 (d, J = 3.6 Hz, 1H), 4.684 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 4.83 (d, J = 12.1 Hz, 1H), 4.84 (d, J = 11.8 Hz, 1H), 4.94 (d, J = 11.4 Hz, 1H); HRMS calcd for $C_{35}H_{38}O_6Cs$ (M + Cs) 687.1723, found 687.1753.

To a solution of the above compound (5.54 g, 10 mmol) in Ac_2O (50 mL) was added 98% H_2SO_4 (0.13 mL) at −15 °C, pyridine (10 mL) was added to the mixture, and the resulting solution was stirred for 15 h at room temperature and poured into MeOH (300 mL) cooled on an ice bath. The solvent was removed *in vacuo*, and the residue was dissolved in EtOAc and washed with 10% HCl, 5% $NaHCO_3$, and brine, successively. The solution was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain the 1,6-di-*O*-acetyl derivative (3.68 g, 69%, α:β = 85:15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 3H), 2.11 (s, 3H), 3.87−3.95 (m), 3.96−4.19 (m), 4.19 (dd, J = 3.7 and 7.8 Hz, 1H), 4.63 (d, J = 10.2 Hz, 1H), 4.68 (d, J = 11.4 Hz, 1H), 4.98 (d, J = 11.4 Hz, 1H), 6.40 (d, J = 3.7 Hz, 1H), 7.28−7.39 (m, 15H); HRMS calcd for $C_{31}H_{34}O_8Cs$ (M + Cs) 667.1308, found 667.1329.

To a solution of the above compound (2.67 g, 5 mmol) in THF (50 mL) was added benzylamine (3.0 mL). The mixture was stirred for 6 h at room temperature, and the solvent was removed *in vacuo* at 35 °C. The residue was dissolved in Ac_2O and washed with 10% HCl, 5% $NaHCO_3$, and brine, successively. The solution was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain the C_1-deprotected product (1.40 g, 57%) as a colorless solid, which was used in the next step without characterization.

To a solution of the product (984 mg, 2 mmol) and 1*H*-tetrazole (145 mmol, 2.1 mmol) in THF (10 mL) was added dibenzyl diethylphosphoramidate (DDP). The mixture was stirred for 2 h at room temperature and passed through filter paper. The filterate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/EtOAc/Et_3N) to obtain **57** (1.19 g, 81%, only α) as a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 3.88 (d, J =2.3 Hz, 1H), 3.94 (dd, J = 2.6 and 9.9 Hz, 1H), 4.03−4.14 (m, 4H), 4.62 (d, J = 11.4 Hz, 1H), 4.68 (s, 2H), 4.70 (d, J =11.7 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.83 (d, J = 11.9Hz, 1H), 4.87 (d, J = 7.4 Hz, 2H), 4.98 (d, J = 11.4 Hz, 1H), 5.69 (dd, J = 3.4 and 8.4 Hz, 1H), 7.24−7.52 (m, 25H); HRMS calcd for $C_{43}H_{45}O_9PCs$ (M + Cs) 869.1856, found 869.1891.

Benzyl 3-*O*-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-D-galactopyranosyl)-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (58). A solution of **57** (73.6 mg, 0.1 mmol) and benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactoside (76.2 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature in the presence of molecular sieves (4 Å) and cooled in a dry-ice/ethylene glycol bath (−15 °C). To this solution was added 0.1 M TMSOTf/CH_2Cl_2 solution (0.1 mL, 10 μmol) to start the coupling reaction, and the mixture was stirred for 2 h at −15 °C. Et_3N (1 mL) was added to stop the reaction. The reaction mixture was allowed to warm to room temperature and passed through filter paper. The filterate was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$, 10% HCl, 5% $NaHCO_3$, and brine, successively. After drying over $MgSO_4$, the solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain the title compound (58.8 mg, 58%, α:β = 84:16) as an amorphous colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.91 (s, 3H), 2.32 (d, J =2.2 Hz, 1H), 3.07 (br s, 1H), 3.48−3.55 (m), 3.72−3.78 (m), 3.89−4.13 (m), 4.23 (d, J = 7.8 Hz), 4.23−4.26 (m), 4.60 (d, J =11.9 Hz), 4.61 (d, J = 11.5 Hz), 4.66 (d, J = 11.8 Hz), 4.77 (d, J = 11.8 Hz), 4.82 (d, J = 12.0 Hz), 4.89 (d, J = 11.7 Hz), 4.90 (d, J = 4.6 Hz), 4.96 (d, J = 11.6 Hz), 7.17−7.45 (m), 7.67−7.72 (m); HRMS calcd for $C_{58}H_{66}O_{12}SiCs$ (M + Cs) 1115.3378, found 1115.3342.

Synthesis of Benzyl Monoglutarate (80). A mixture of glutaric anhydride (2.7 g, 23.7 mmol), benzyl alcohol (2.5 mL, 24.2 mmol), pyridine (15 mL), and 4-(dimethylamino)pyridine (10 mg) was stirred in $CHCl_3$ (20 mL) at 50 °C for 15 h. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in Et_2O (30 mL). The Et_2O solution was washed successively with 5% HCl and saturated $CuSO_4$, and extracted with 5% $NaHCO_3$. The extract was acidified with 35% HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to obtain **80** (4.10 g, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (m, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7.5 Hz, 2H), 5.12 (s, 2H), 7.33−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 32.9, 33.1, 66.3, 128.2, 128.3, 128.6, 135.8, 172.7, 179.1; HRMS calcd for $C_{12}H_{14}O_4$ (M + H) 223.0970, found 223.0976.

Synthesis of 81. To a solution of **80** (761 mg, 3.43 mmol), *N*-hydroxysccinimide (395 mg, 3.43 mmol), NEt_3 (0.2 mL), and DMF (0.5 mL) in CH_2Cl_2 (7 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, 660 mg, 3.43 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h and evaporated i*n vacuo*. The residue was dissolved in AcOEt (30 mL) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to obtain **81** (777 mg, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05−2.13 (m, 2H), 2.52 (t, J = 7.5 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.82−2.84 (m, 4H), 5.13 (s, 2H), 7.34−7.37 (m, 5H); HRMS calcd for $C_{16}H_{18}NO_6$ (M + H) 320.1134, found 320.1142.

General Procedure for the Coupling Reaction of 81 with 59 and 60: Synthesis of 82 and 83. Amino acids **59** and **60** were prepared according to the reported procedures.[28,29] To a suspension of amino acid (0.59 mmol) in DMF (5 mL), H_2O (2 mL), Et_3N (0.1 mL), and CH_2Cl_2 (10 mL) was added **81** (230 mg, 0.65 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, and the temperature was allowed to rise to room temperature within 15 h. The solvent was removed *in vacuo*, and the residue was dissolved in AcOEt (20 mL) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography ($CHCl_3$:MeOH = 4:1) to obtain **82** and **83**.

Compound 82: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91−1.95 (m, 2H), 2.20−2.26 (m, 2H), 2.38 (t, J = 5.2 Hz, 2H), 3.58−3.68 (m, 2H), 4.22−4.24 (m, 1H), 4.48 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 5.09 (s, 2H), 6.75 (d, J = 8.2 Hz, 1H), 7.25−7.36 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 33.7, 35.2, 56.1, 66.3, 70.9, 71.1, 73.8, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 135.7, 137.3, 172.1, 173.2, 174.4; HRMS calcd for $C_{23}H_{27}NO_7Na$ (M + Na) 452.1685, found 452.1672.

Compound 83: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (br s, 3H), 1.98 (br s, 4H), 2.45 (br s, 6H), 5.08 (s, 2H), 7.15−7.33 (m, 5H); electrospray negative mass, m/z 338 $(M - H)^-$.

General Procedure for the Coupling Reaction of 82 and 83 with 47 and 48 and the Following Hydrogenation: Synthesis of 65−67. A solution of *N*-Boc-L-threonine esters **47** and **48** (30 μmol) dissolved in 30% TFA in CH_2Cl_2 (2 mL) was allowed to stand for 30 min at room temperature and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1 mL) and neutralized with Et_3N (0.5 mL). To the solution were successively added 1-hydroxybenzotriazole (HOBt, 5.4 mg, 40 μmol), **82** and **83** (40 μmol), and EDC (7.7 mg, 40 μmol) at 0 °C. The solution was stirred for 1 h at 0 °C, and the temperature was allowed to rise to room temperature within 15 h. The reaction mixture was washed with 10% HCl, 5% $NaHCO_3$, and brine, successively, and dried over $MgSO_4$. After evaporation *in vacuo*, the residue was applied to silica gel column chromatography (hexane:EtOAc = 1:2) to obtain the corresponding coupling products, which were dissolved in MeOH (5 mL) and stirred in the presence of 20% $Pd(OH)_2$ on carbon (Degussa type, 1 mg) under an atmosphere of hydrogen (1 atm) for 8 h. After filtration, the filtrate was evaporated *in vacuo* to obtain **65**−**67**.

Compound 65 (Amorphous): ^{1}H NMR (400 MHz, D_2O) δ 1.18−1.30 (m, 9H), 1.79−1.90 (m, 2H), 2.22−2.42 (m, 4H), 3.59−3.86 (m, 5H), 3.98−4.02 (m, 1H), 4.13−4.28 (m, 3H), 4.45 (dd, J = 2.2 and 6.4 Hz, 1H), 4.56 (d, J = 7.2 Hz, 1H), 4.61 (d, J = 2.2 Hz, 1H), 4.98 (d, J = 3.2 Hz, 1H); electrospray negative ion mass, *m/z* 523 (M − H)$^-$.

Compound 66 (Amorphous): ^{1}H NMR (400 MHz, D_2O) δ 1.18 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.77−1.85 (m, 2H), 2.20 (t, J = 7.4 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 3.57−3.86 (m, 5H), 3.94−4.03 (m, 2H), 4.33−4.34 (br s, 1H), 4.40−4.42 (m, 1H), 4.58 (dd, J = 1.1 and 8.3 Hz, 1H), 4.98 (d, J = 3.2 Hz, 1H); electrospray negative ion mass, *m/z* 495 (M − H)$^-$.

Compound 67 (Amorphous): ^{1}H NMR (400 MHz, D_2O) δ 1.13−1.23 (m, 6H), 1.75−1.85 (m, 2H), 2.37−2.43 (m, 4H), 3.63−4.07 (m, 7H), 4.37−4.68 (m, 3H), 4.96 (d, J = 3.2 Hz, 1H); electrospray negative ion mass, *m/z* 495 (M − H)$^-$.

Synthesis of Cbz-L-Asp(α-Bn)-L-Tyr-O^{t}Bu (84). This compound was synthesized in 82% yield according to the procedure for the syntheses of **82** and **83**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.73 (dd, J = 4.2 and 16.2 Hz, 1H), 2.94 (d, J = 4.5 Hz, 2H), 2.95 (dd, J = 4.4 and 16.2 Hz, 1H), 4.60−4.64 (m, 2H), 4.79 (br s, 1H), 5.11 (br s, 2H), 5.19 (s, 2H), 5.98 (d, J = 7.2 Hz, 1H), 6.01 (d, J = 8.9 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.29−7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 36.9, 37.5, 50.7, 53.7, 67.0, 67.4, 82.7, 115.3, 127.6, 128.1, 128.5, 130.6, 135.3, 136.2, 154.7, 156.2, 169.1, 170.5, 171.0; HRMS calcd for $C_{32}H_{37}N_2O_8$ (M + H) 577.2550, found 577.2550.

Coupling of 84 and 47 Followed by Hydrogenation: Synthesis of 68. A solution of **84** (62 mg, 0.11 mmol) dissolved in a mixture of TFA (7 mL) and CH_2Cl_2 (7 mL) was allowed to stand for 3 h at room temperature and evaporated *in vacuo*. The residue was subjected to a coupling reaction with **47** followed by the hydrogenation according to the previous procedure described for the synthesis of **65**−**67** to obtain **68** (28 mg, 48%): ^{1}H NMR (500 MHz, D_2O) δ 0.97 (d, J = 6.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 2.50−2.58 (m, 1H), 2.72−2.81 (m, 2H), 2.99−3.05 (m, 1H), 3.55−3.74 (m, 3H), 3.85 (q, J = 6.5 Hz, 1H), 4.07−4.29 (m, 3H), 4.57 (dd, J = 4.8 and 9.0 Hz, 1H), 4.81 (d, J = 4.0 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H); electrospray negative ion mass, *m/z* 542 (M − H)$^-$.

Synthesis of 85. 3-Deoxy-D-lysoheptulosonic acid (300 mg, 1.35 mmol), which was prepared by enzymatic aldol condensation of D-threose and pyruvate,[30] and Dowex 50W-X8 (H^+) (250 mg) were refluxed for 2 h in MeOH (18 mL). The reaction mixture was passed through Celite and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 9.5:0.5) to give the corresponding methyl glycoside mixture **62** (pyranoside:furanoside = 3:1, 194 mg, 60%). To a solution of **62** (183 mg, 0.78 mmol) in dry DMF (10 mL) were added benzaldehyde dimethyl acetal (0.29 mL, 1.94 mmol) and camphorsulfonic acid (180 mg, 0.78 mmol). The mixture was stirred for 12 h at 60 °C and allowed to stand at room temperature. The solution was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc = 3:7) and dissolved in 4 mL of 0.25 N LiOH in MeOH/H_2O. The mixture was stirred for 2 h at room temperature and diluted with water (2 mL). The solution was adjusted to pH 2 with 0.1 N HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was applied to silica gel column chromatography (CH_2Cl_2:MeOH = 8:2) to afford **85** (117 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (dd, J = 12.0 and 6.0 Hz, 1H), 2.17 (m, 1H), 3.35 (s, 3H), 4.05−4.09 (m, 2H), 4.11−4.39 (m, 3H), 5.9 (s, 1H), 7.53−7.34 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 44.78, 51.76, 72.12, 73.74, 75.51, 75.92, 89.22, 104.40, 126.72, 126.46, 128.38, 129.68, 137.43, 170.1; HRMS calcd for $C_{15}H_{19}O_7$ (M + H) 311.1131, found 311.1139.

Coupling of 85 and 48 for the Synthesis of 86. A solution of **48** (22 mg, 33.6 μmol) dissolved in 30% TFA in CH_2Cl_2 (1.5 mL) was allowed to stand for 10 min at room temperature and evaporated *in vacuo*. The residue was dissolved in dry DMF (0.2 mL), neutralized with 4-methylmorpholine, and stirred for 1 h at room temperature. To the solution were added **85** (12.5 mg, 40 μmol) dissolved in dry DMF (0.2 mL), HOBt (9 mg, 67 μmol), and 4-methylmorpholine (8 μL, 70 μmol), successively, at −20 °C. The resulting mixture was stirred for 20 min at −20 °C followed by addition of EDC (13 mg, 67 μmol). The temperature was allowed to rise to room temperature within 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:EtOAc = 5:5) to afford **86** (13.5 mg, 48%): ^{1}H NMR (400 MHz, CD_3-OD) δ 1.02 (d, J = 6.4 Hz, 3H), 1.19−1.26 (m, 2H), 1.88−2.02 (m, 2H), 2.32 (dd, J = 5.1 and 2.6 Hz, 2H), 2.87−2.92 (m, 3H), 2.94 (s, 3H), 3.21 (s, 3H), 3.50−3.52 (m, 1H), 3.66−3.68 (m, 2H), 3.80−3.83 (m, 2H), 3.91−4.23 (m, 6H), 4.37−4.46 (m, 3H), 4.56−4.90 (m, 6H), 5.55 (s, 1H), 7.12−7.34 (m, 20H); HRMS calcd for $C_{48}H_{57}NO_3Cs$ (M + Cs) 988.2884, found 988.2916.

Sulfation of 86 for the Synthesis of 87. To a solution of **86** (6.3 mg, 73 μmol) in dry pyridine (1.3 mL) was added SO_3·NMe_3 (2.1 mg, 0.15 mmol). The mixture was stirred at room temperature for 6 h and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 9.5:0.5) to yield **87** as a $HNMe_3^+$ salt (5.2 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 6.2 Hz, 3H), 1.04−1.19 (m, 9H), 2.12−2.28 (m, 2H), 3.13 (s, 3H), 3.57−3.63 (m, 5H), 3.87−3.90 (m, 2H), 4.04−4.13 (m, 5H), 4.42 (dd, J = 12.6 Hz and 12.8 Hz, 2H), 4.59−4.87 (m, 6H), 5.51 (s, 1H), 7.16−7.49 (m, 20H); HRMS calcd for $C_{48}H_{56}NO_{16}SCs_2$ (M − H + 2Cs) 1200.1662, found 1200.1671.

Debenzylation of 87 for the Synthesis of 69. To a solution of **87** (5.2 mg, 5 μmol) in MeOH (0.5 mL) was added $Pd(OH)_2$ on carbon (Degussa type, 1 mg). The mixture was stirred for 18 h under hydrogen (1 atm), and the catalyst was removed by filtration with Celite. The filtrate was evaporated *in vacuo*, and the residue was dissolved in water. The resulting solution was stirred for 2 h in the presence of Dowex 50 W-X8 (Na^+). The resin was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was applied to Biogel P-2 chromatography (H_2O) to afford **69** (2.3 mg, 86%): ^{1}H NMR (400 MHz, CD_3-OD) δ 1.08−1.29 (m, 7H), 1.80−1.88 (m, 3H), 2.37−2.43 (m, 4H), 3.69−3.75 (m, 8H), 3.83−3.95 (m, 5H), 4.15−4.20 (m, 3H), 4.50 (d, J = 4.1 Hz, 1H), 3.23 (s, 3H); HRMS calcd for $C_{20}H_{34}O_{16}NSCs_2$ (M − H + 2Cs) 842.9708, found 842.9672; electrospray negative ion mass, *m/z* 576.

Synthesis of Compound 70. A solution of α-**48** (30 μmol) dissolved in 30% TFA in CH_2Cl_2 (2 mL) was allowed to stand for 30 min at room temperature and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1 mL) and neutralized with Et_3N (0.5 mL). To the solution were successively added HOBt (5.4 mg, 40 μmol), *N*-Fmoc-*trans*-4-hydroxy-L-proline (40 μmol), and EDC (7.7 mg, 40 μmol) at 0 °C. The solution was stirred for 1 h at 0 °C, and the temperature was allowed to rise to room temperature within 15 h. The reaction mixture was washed with 10% HCl, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$. After evaporation *in vacuo*, the residue was applied to silica gel column chromatography (hexane:EtOAc = 1:2) to obtain compound **88** (MS *m/z* calcd for $C_{53}H_{58}N_2O_{11}Cs$ (M + Cs) 1031.3095, found 1031.3143) which was used directly in the next step without further characterization.

Reaction of a solution of **88** (258 mg, 0.27 mmol) in 40% $HNEt_2$ in THF (10 mL) was allowed to proceed at room temperature for 2 h, and the solvent was evaporated *in vacuo*. The residue was dissolved

in 4 mL of THF, and then benzyl monoglutarate, HOBt (73 mg, 0.54 mmol), and EDC (104 mg, 0.54 mmol) were added at 0 °C. After the mixture was stirred at 0 °C for 10 h, the solvent was evaporated and the residue was diluted with EtOAc. The resulting organic layer was washed with H_2O (2 × 10 mL), 1 N HCl (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The organic residue was purified by flash column chromatography eluted with toluene/EtOAc (1:1 and then 1:2) to afford product **89** (106 mg, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, J = 6.5 Hz, 3H), 1.24 (q, J = 7.0 Hz, 3H), 1.26 (d, J = 6.5 Hz, 3H), 1.85−1.93 (m, 2H), 1.98−2.10 (m, 3H), 2.19−2.24 (m, 1H), 2.30−2.41 (m, 2H), 3.15−3.17 (m, 1H), 3.42 (dd, J = 11.0, 3.5 Hz, 1H), 3.65−3.70 (m, 2H), 3.78 (dd, J = 10.5, 2.5 Hz, 1H), 3.97−4.05 (m, 1H), 4.07 (dd, J = 10.5, 3.5 Hz, 1H), 4.15−4.21 (m, 1H), 4.36−4.40 (m, 1H), 4.45 (br, 1H), 4.55 (t, J = 8.0 Hz, 1H), 4.61−4.79 (m, 7H), 4.93 (d, J = 3.5 Hz, 1H), 4.94 (d, J = 11.5 Hz, 1H), 5.08 (s, 2H), 7.23−7.40 (m, 20H), 8.26 (d, J = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 14.5, 16.6, 20.0, 33.2, 33.4, 33.5, 37.5, 55.9, 56.4, 58.6, 61.2, 66.1, 66.4, 70.2, 71.0, 72.7, 73.6, 74.8, 76.2, 79.4, 92.9, 127.1, 127.5, 127.7, 128.0, 128.1, 128.2, 128.2, 128.2, 128.3, 128.3, 128.5, 128.5, 137.5, 138.4, 170.6, 171.1, 172.5, 173.2; MS *m*/*z* calcd for $C_{50}H_{60}N_2O_{12}Cs$ (M + Cs) 1013.3201, found 1013.3171.

Compound **89** (16 mg, 15 mmol) was dissolved in ethanol/H_2O (2:1, 2 mL), and then $Pd(OH)_2$ (Degussa type) on carbon was added. Hydrogen was then applied to the mixture through a balloon for 6 h. The mixture was filtered through Celite, concentrated *in vacuo*, and purified by Biogel P-2 (water) to obtain **70** after lyophilization (5.6 mg, 70%): ^{1}H NMR (500 MHz, D_2O) δ 1.05 (d, J = 6.5 Hz, 3H), 1.12−1.15 (m, 6H), 1.68 (t, J = 7.5 Hz, 2H), 1.91−1.97 (m, 1H), 2.11 (t, J = 7.0 Hz, 2H), 2.22−2.33 (m, 3H), 3.52−3.67 (m, 6H), 3.97−4.03 (m, 1H), 4.08−4.14 (m, 1H), 4.33−4.37 (m, 1H), 4.45 (br, 1H), 4.48−4.52 (m, 2H), 4.87 (d, J = 3.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 13.6, 14.5, 15.6, 21.4, 33.9, 36.4, 37.6, 52.5, 55.9, 57.8, 58.8, 63.3, 68.0, 69.7, 70.1, 70.9, 71.9, 94.7, 172.3, 175.3; MS *m*/*z* calcd for negative electrospray $C_{22}H_{35}N_2O_{12}$ (M − H) 519, found 519.

Synthesis of Compound 71. The coupling procedure was the same as that described in Scheme 9. Deprotection of the Cbz group was also the same as described previously.

Compound 90: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 3.43−3.436 (m, 1H), 3.55−3.70 (m, 3H), 3.80−3.82 (m, 1H$_b$), 3.86−3.90 (m, 1H$_a$), 3.98−4.04 (m, 1H$_b$), 4.06 (dd, J = 10.0, 3.2 Hz, 1H$_a$), 4.11−4.25 (m, 2H), 4.33 (q, J = 6.4 Hz, 1H$_a$), 4.44 (br, 1H$_b$), 4.58−4.63 (m, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.69−4.78 (m, 4H), 4.91 (br, 1H$_b$), 4.93 (d, J = 3.2 Hz, 1H$_a$), 4.96 (d, J = 11.6 Hz, 1H), 5.08 (s, 2H), 7.03−7.17 (m, 1H), 7.26−7.43 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.1, 16.4, 16.6, 29.7, 51.5, 51.8, 56.0, 56.2, 61.6, 64.2, 67.0, 67.1, 67.2, 69.9, 70.5, 71.5, 72.7, 74.5, 74.9, 75.0, 76.1, 76.2, 76.3, 79.0, 79.2, 93.4, 127.4, 127.6, 127.7, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3, 128.3, 128.4, 128.5, 128.6, 128.6, 136.4, 137.3, 138.3, 138.3, 155.3, 170.4, 170.9 (rotamers present in NMR); MS *m*/*z* calcd for $C_{46}H_{54}N_2O_{12}Cs$ (M + Cs) 959.2731, found 959.2761.

Compound 91: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.91 (t, J = 7.1 Hz, 2H), 2.22−2.30 (m, 2H), 2.39 (t, J = 7.3 Hz, 2H), 3.43−3.51 (m, 2H), 3.63−3.68 (m, 2H), 3.87−3.92 (m, 2H), 3.99 (dd, J = 10.6, 7.2 Hz, 1H), 4.03−4.06 (m, 2H), 4.18 (dd, J = 10.6, 7.2 Hz, 1H), 4.30 (d, J = 6.3 Hz, 1H), 4.38 (t, J = 7.9 Hz, 1H), 4.59−4.80 (m, 6H), 4.85 (d, J = 3.7 Hz, 1H), 4.94 (d, J = 11.5 Hz, 1H), 5.07 (s, 2H), 7.25−7.43 (m, 20H), 7.58 (d, J = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 16.1, 16.5, 19.8, 20.0, 29.6, 32.7, 33.1, 51.8, 56.3, 61.5, 64.2, 66.0, 66.6, 70.7, 71.5, 72.6, 74.2, 74.8, 76.0, 79.0, 93.7, 127.5, 127.6, 127.8, 128.0, 128.1, 128.1, 128.2, 128.2, 128.4, 128.5, 128.6, 128.6, 135.9, 137.4, 138.3, 138.4, 170.3, 170.4, 172.0, 173.1 (rotamers present in NMR); MS *m*/*z* calcd for $C_{50}H_{60}N_2O_{13}Cs$ (M + Cs) 1029.9406, found 1029.9368.

Compound 71: ^{1}H NMR (500 MHz, D_2O) δ 1.15 (d, J = 5.8 Hz, 3H), 1.19−1.25 (m, 6H), 1.77 (t, J = 7.2 Hz, 2H), 2.27−2.39 (m, 4H), 3.58−3.60 (m, 2H), 3.67−3.73 (m, 4H), 3.81 (dd, J = 11.5, 4.4 Hz, 1H), 4.08−4.13 (m, 1H), 4.17−4.29 (m, 4H), 4.40−4.46 (m, 1H), 4.93 (d, J = 3.4 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 9.4, 10.0, 11.3, 16.3, 28.6, 47.9, 53.4, 59.0, 60.3, 63.0, 63.1, 63.7, 65.5, 66.4, 66.6, 67.7, 70.7, 90.3, 167.8, 168.9, 169.1, 171.0 (rotamers present in NMR); MS *m*/*z* calcd for $C_{22}H_{36}N_2O_{13}Cs$ (M + Cs) 669.1272, found 669.1287.

Synthesis of *N*-Cbz-3,4-dihydroxy-D-proline.[37] The synthesis is described in Scheme 10. To a solution of *cis*-4-hydroxy-D-proline (502 mg 3.8 mmol) in MeOH (7 mL) at 0 °C was added thionyl choride (0.3 mL, 4.25 mmol) dropwise. The reaction was stirred at rt for 1 h before it was heated at reflux for 22 h. The resulting solution was concentrated, and the residue was azeotroped with MeOH. The white product formed was kept under reduced pressure at 0.5 mmHg for 2 h (699 mg, 99% yield). A mixture of methyl *cis*-4-hydroxy-D-prolinate hydrochloride salt (699 mg, 3.83 mmol) was cooled to 0 °C. With efficient stirring, CbzCl (0.6 mL, 4.2 mmol) was added, followed by DIEA (1.6 mL, 9.2 mmol) dropwise and H_2O (3 mL). The reaction was stirred at room temperature for 12 h, and then the organic solvent was evaporated. This aqueous residue was extracted with EtOAc (50 mL), and the organic layer was washed with 5% aqueous HCl (10 mL), 5% aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), filtered, and concetrated. The crude product was purified by flash column chromatography eluting with EtOAc/hexane (3:2) to provide the *N*-protected methyl ester as a viscous oil (897 mg, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12−2.16 (m, 2H), 2.29−2.38 (m, 2H), 3.23 (d, J = 9.3 Hz, 1H), 3.39 (d, J = 9.6 Hz, 1H), 3.62 (s, 3H), 3.58−3.65 (m, 2H), 3.70−3.77 (m, 2H), 3.81 (s, 3H), 4.38−4.42 (m, 3H), 4.45 (dd, J = 9.8, 1.2 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 5.20 (d, J = 12.7 Hz, 2H), 7.27−7.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.7, 38.6, 52.6, 52.9, 55.7, 56.0, 57.7, 58.1, 67.3, 70.2, 71.2, 127.8, 128.0, 128.1, 128.4, 128.5, 136.3, 154.2, 155.0, 174.9, 175.2 (rotamers present in NMR); MS *m*/*z* calcd for $C_{14}H_{17}NO_5Cs$ (M + Cs) 412.0161, found 412.0175.

To a solution of *N*-Cbz-4-hydroxy-D-proline methyl ester (1.23 g, 4.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added Et_3N (0.68 mL, 4.87 mmol) dropwise, followed by mesyl chloride (0.45 mL, 5.76 mmol). A catalytic amount of DMAP was added, and the reaction mixture was stirred at 0 °C to rt for 1.5 h. The mixture was poured into 30 mL of ice/H_2O with stirring. The product was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with 0.1 M HCl, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl, then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography eluting with EtOAc/hexane (2:1) to give the mesylate derivative (1.41 g, 86%) as a clear oil.

Sodium borohydride (26.6 mg, 0.7 mmol) was added in small portions to a solution of diphenyl selenide (109.6 mg, 0.35 mmol) at 0 °C. The mixture was stirred for 5 min until the bright yellow color disappeared. The mixture was added to the previously prepared mesylate (209 mg, 0.59 mmol), followed by refluxing for 2 h, and then the solvent was removed *in vacuo*. The residue was diluted with EtOAc (50 mL), and the organic layer was washed with H_2O. The resulting organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography eluting with EtOAc/hexane (1:4) to afford the phenylselenyl derivative (179 mg, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3H), 2.25−2.38 (m,1.26, t, 7.0, 3), 3.51 (dd, J = 11.0, 7.0 Hz, 1H), 3.59 (dd, J = 11.5, 7.0 Hz, 1H), 3.76−3.82 (m, 2H), 3.95−4.06 (m, 4H), 4.16−4.22 (m, 2H), 4.39 (dd, J = 8.5, 4.5 Hz, 1H), 4.45 (dd, J = 8.5, 4.0 Hz, 1H), 5.04 (d, J = 12.5 Hz, 1H), 5.09 (d, J = 12.5 Hz, 1H), 5.15 (d, J = 8.0 Hz, 1H), 5.18 (d, J = 8.0 Hz, 1H), 7.26−7.38 (m, 16H), 7.52−7.57 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 36.3, 36.8, 36.9, 37.7, 52.8, 53.3, 58.7, 59.0, 61.3, 61.4, 67.2, 127.8, 127.9, 128.0, 128.0, 128.3, 128.4, 128.5, 129.3, 135.1, 135.3, 153.9, 154.5, 172.1, 172.3 (rotamers present in NMR); MS *m*/*z* calcd for $C_{21}H_{25}NO_4Se$ (M + H) 434.0871, found 434.0858.

A mixture of the above (phenylselenyl)proline derivative (146.4 mg, 0.38 mmol) and CH_2Cl_2 (5 mL) was initially cooled to 0 °C in an ice bath. Pyridine was added dropwise to this solution. A solution of 30% H_2O_2 was then gradually added over a 5 min period. The mixture was stirred at rt for 1 h and then diluted with EtOAc (25 mL). The organic layer was washed with 0.1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and saturated aqueous NaCl. The organic phase was then dried over $MgSO_4$, filtered, and concentrated. The resulting residue

(37) (a) Rueger, H.; Benn, M. H. *Can. J. Chem.* **1982**, *60*, 2918. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23* 1973.

was purified by flash column chromatography eluting with EtOAc/hexane (1:4) to afford the dehydro product (76 mg, 73%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (dt, J = 0.7, 7.1 Hz, 3H), 1.27 (dt, J = 0.8, 7.1 Hz, 3H), 4.02−4.10 (m, 2H), 4.21 (dq, J = 0.7, 7.1 Hz, 2H), 4.25−4.38 (m, 4H), 5.03−5.23 (m, 6H), 5.73−5.80 (m, 1H), 5.94−6.01 (m, 1H), 7.26−7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 53.4, 53.8, 61.3, 61.4, 66.4, 66.7, 67.1, 127.7, 127.8, 127.9, 127.9, 128.0, 128.0, 128.4, 128.4, 128.4, 128.5, 129.0, 129.0, 129.1, 129.1, 136.4, 136.5, 153.9, 154.3, 169.9, 170.2 (rotamers present in NMR); MS *m*/*z* calcd for $C_{15}H_{18}NO_4$ (M + H) 276.1236, found 276.1241.

To a mixture of the above compound (405 mg, 1.48 mmol) and H_2O/acetone/*tert*-butyl alcohol (6.25:2.5:1, 4.68 mL) were added *N*-methylmorpholine *N*-oxide (518 mg, 4.43 mmol) and a catalytic amount of K_2OsO_4. The reaction mixture was stirred at 0 °C overnight. To the reaction mixture was added Na_2SO_3 (559 mg, 4.4 mmol), and the mixture was stirred at rt for 1 h. The organic solvent was evaporated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash column chromatography eluting with EtOAc/hexane/MeOH (10:10:1) to afford the title compound ethyl ester (375 mg, 82%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 3.51 (dd, J = 11.4, 4.6 Hz, 1H), 3.60 (dd, J = 11.7, 4.1 Hz, 1H), 3.73−3.78 (m, 2H), 4.00−4.07 (m, 2H), 4.20−4.34 (m, 8H), 5.01 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 2H), 7.27−7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 31.0, 50.8, 51.2, 61.6, 61.7, 64.6, 64.9, 67.4, 69.8, 70.5, 74.7, 75.8, 127.9, 127.9, 128.1, 128.4, 128.5 (rotamers present in NMR); MS *m*/*z* calcd for $C_{15}H_{19}NO_6Na$ 332.1110, found 332.1124.

Alkaline hydrolysis (THF/0.1 N LiOH, 4 h, rt) as usual followed by acidification and extraction gave the title compound which was dried over $MgSO_4$ and used directly for peptide coupling.

Reduction of 51 with PPh_3 for the Synthesis of 92. A solution of **51** (601 mg, 1.08 mmol) was refluxed in a mixture of benzene (25 mL) and water (0.1 mL) for 15 h. The reaction mixture was evaporated *in vacuo*, and the residue was applied to silica gel column chromatography ($CHCl_3$:MeOH = 20:1) to obtain **92** (558 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, J = 6.8 Hz, 3H), 1.21−1.38 (m, 4H), 1.62−2.11 (m, 6H), 2.78−2.85 (m, 1H), 3.34−3.46 (m, 1H), 3.71 (d, J = 1.8 Hz, 1H), 4.00 (dd, J = 1.8 and 10.0 Hz, 1H), 4.02−4.07 (m, 2H), 4.63−4.98 (m, 6H), 5.00 (d, J = 3.5 Hz, 1H), 7.23−7.47 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 24.5, 24.6, 29.2, 54.4, 61.0, 66.6, 73.2, 73.4, 74.8, 76.1, 77.6, 79.4, 80.8, 93.6, 127.4, 127.5, 127.6, 127.1, 128.1, 128.2, 128.3, 128.4; HRMS calcd for $C_{33}H_{41}NO_5$ (M + H) 532.3063, found 532.3040.

Coupling of 92 and *N*-Fmoc-γ-(benzyloxy)threonine for the Synthesis of 93. To a solution of **90** (137 mg, 0.258 mmol) and *N*-Fmoc-γ-(benzyloxy)threonine (105 mg, 0.235 mmol) in CH_2Cl_2 (30 mL) were added HOBt (48 mg, 0.356 mmol) and EDC (59 mg, 0.308 mmol), successively, at 0 °C. The solution was stirred for 20 min at 0 °C and allowed to rise to room temperature within 6 h. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in AcOEt (30 mL). The AcOEt solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:EtOAc = 1:1) to obtain **93** (146 mg, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.21 (m, 2H). 1.12 (d, J = 6.0 Hz, 3H), 1.27−1.42 (m, 2H), 1.53−1.64 (m, 1H), 1.65−1.78 (m, 1H), 1.92−2.05 (m, 2H), 3.34−3.42 (m, 1H), 3.36 (d, J = 6.0 Hz, 1H), 3.52 (dd, J = 6.0 and 10.0 Hz, 1H), 3.64 (dd, J = 6.0 and 10.0 Hz, 1H), 3.66 (br s, 1H), 3.73−3.81 (m, 1H), 3.89 (d, J = 6.0 Hz, 1H), 3.93−4.02 (m, 2H), 4.01 (dd, J = 4.0 and 10.0 Hz, 1H), 4.14 (t, J = 6.5 Hz, 1H), 4.18 (t, J = 7.5 Hz, 1H), 4.21 (dd, J = 7.5 and 10.0 Hz, 1H), 4.41 (dd, J = 7.5 Hz, 1H), 4.48 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.76 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.90 (br s, 1H), 4.91 (d, J = 11.5 Hz, 1H), 5.90 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 7.18−7.42 (m, 24H), 7.51 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.0 Hz, 2H); HRMS calcd for $C_{59}H_{64}N_2O_{10}Cs$ (M + Cs) 1093.3615, found 1093.3649.

Coupling of Deprotected 93 and Succinic Acid Monobenzyl Ester, Glutaric Acid Monobenzyl Ester, or *N*-Boc-Asparatic Acid β-Benzyl Ester for the Syntheses of 94−96. A solution of **93** (146 mg, 0.152 mmol) and diethylamine (0.83 mL) in CH_2Cl_2 was stirred for 7 h at room temperature and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to obtain the corresponding deprotected compound (88.7 mg, 79%). To the solution of this amine (34.6 mg, 46.9 μmol) in CH_2Cl_2 were added succinic acid monobenzyl ester (9.8 mg, 46.9 μmol) or *N*-Boc-asparatic acid β-benzyl ester (15.2 mg, 46.9 μmol), HOBT (10 mg, 74.1 μmol), and EDC (12 mg, 62.6 μmol), successively, at 0 °C. The solution was stirred for 20 min at 0 °C and allowed to rise to room temperature within 9 h. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in AcOEt (10 mL). The AcOEt solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (CH_2Cl_2:AcOEt = 2:1) to obtain **94** (30.5 mg, 70%), **95** (48.5 mg, 55%), or **96** (58.5 mg, 77%).

Compound 94: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07−1.20 (m, 2H), 1.14 (d, J = 6.5 Hz, 3H), 1.26−1.41 (m, 2H), 1.54−1.59 (m, 1H), 1.67−1.75 (m, 1H), 1.93−2.01 (m, 2H), 2.32−2.45 (m, 2H), 2.62−2.77 (m, 2H), 3.43 (dt, J = 4.5 and 9.5 Hz, 1H), 3.53 (dd, J = 6.0 and 10.0 Hz, 1H), 3.66 (dd, J = 5.5 and 10.0 Hz, 1H), 3.69 (br s, 1H), 3.70 (d, J = 6.5 Hz, 1H), 3.75−3.82 (m, 1H), 3.91 (dd, J = 3.0 and 10.0 Hz, 1H), 3.97 (q, J = 6.5 Hz, 1H), 4.01 (dd, J = 4.0 and 10.0 Hz, 1H), 4.00−4.04 (m, 1H), 4.46 (dd, J = 5.5 and 8.0 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.94 (d, J = 3.5 Hz, 1H), 4.96 (d, J = 11.5 Hz, 1H), 5.09 (br s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 7.25−7.39 (m, 20H); HRMS calcd for $C_{55}H_{64}N_2O_{11}Cs$ (M + Cs) 1061.3564, found 1061.3596.

Compound 95: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, J = 6.5 Hz, 3H), 1.20 (m, 4H), 1.54 (m, 1H), 1.70 (m, 1H), 1.93 (m, 4H), 2.20 (m, 3H), 2.36 (t, J = 7.0 Hz, 2H), 3.37 (dd, J = 7.5 and 9.5 Hz, 1H), 3.46 (dd, J = 6.0 and 9.5 Hz, 1H), 3.62 (m, 1H), 3.83 (m, 1H), 3.91 (dd, J = 2.5 and 10.0 Hz, 1H), 3.94 (m, 1H), 4.00 (d, J = 3.5 Hz, 1H), 4.01 (dd, J = 43.5 and 10.0 Hz, 1H), 4.23 (m, 1H), 4.46 (dd, J = 2.0 and 6.0 Hz, 1H), 4.39−5.01 (m, 10H), 4.93 (d, J = 3.5 Hz, 1H), 7.29 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 20.61, 23.2, 29.2, 30.6, 33.1, 35.0, 52.1, 53.1, 66.3, 66.8, 69.0, 69.4, 73.0, 73.1, 73.4, 74.8, 76.0, 77.2, 77.8, 79.1, 94.6, 127.3−128.5 (m), 135.7, 137.5, 138.6, 138.6, 138.9, 170.7, 172.6, 173.0; HRMS calcd for $C_{56}H_{66}N_2O_{11}Cs$ (M + Cs) 1075.3721, found 1075.3760.

Compound 96: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08−1.20 (m, 2H), 1.16 (d, J = 6.5 Hz, 3H), 1.22−1.32 (m, 1H), 1.33−1.41 (m, 1H), 1.44 (s, 9H), 1.52−1.57 (m, 1H), 1.67−1.73 (m, 1H), 1.88−1.97 (m, 2H), 2.76 (dd, J = 5.5 and 17.5 Hz, 1H), 3.05 (dd, J = 5.0 and 17.5 Hz, 1H), 3.41 (dt, J = 4.0 and 9.5 Hz, 1H), 3.51 (d, J = 6.5 Hz, 1H), 3.54 (dd, J = 5.5 and 9.5 Hz, 1H), 3.65 (dd, J = 5.0 and 9.5 Hz, 1H), 3.70−3.78 (m, 1H), 3.76 (br s, 1H), 3.93 (dd, J = 3.0 and 10.5 Hz, 1H), 3.99−4.06 (m, 1H), 4.00 (q, J = 6.5 Hz, 1H), 4.02 (dd, J = 4.0 and 10.5 Hz, 1H), 4.42 (td, J = 5.0 and 7.0 Hz, 1H), 4.45 (dd, J = 5.5 and 7.5 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.5 H, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.90 (d, J = 4.0 Hz, 1H), 4.96 (d, J = 11.5 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 5.44 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 7.5 Hz, 1H), 7.23−7.39 (m, 20H), 7.52 (d, J = 7.0 Hz, 1H); HRMS calcd for $C_{60}H_{73}N_3O_{13}Cs$ (M + Cs) 1176.4198, found 1176.4237.

Deprotection of 94−96 for the Syntheses of 72−74. To the solution of **94**, **95**, or **96** (0.73 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ on carbon (Degussa type E101, 10 mg). The mixture was stirred for 6 h under hydrogen (1 atm), and the catalyst was removed by filtration through Celite. The solvent was evaporated *in vacuo*, and the residue was purified by Biogel P-2 column chromatography (H_2O) to obtain **72**−**74**.

Compound 72: ^{1}H NMR (500 MHz, D_2O) δ 1.09 (d, J = 6.5 Hz, 3H), 1.29 (m, 3H), 1.45 (m, 1H), 1.65 (m, 3H), 2.18 (m, 1H), 2.57 (m, 2H), 2.63 (m, 2H), 3.40 (m, 1H), 3.47 (d, J = 6.5 Hz, 2H), 3.72 (m,

5H), 4.22 (dt, J = 2.0 and 6.5 Hz, 1H), 4.49 (d, J = 2.0 Hz, 1H), 5.03 (d, J = 3.0 Hz, 1H); HRMS calcd for $C_{20}H_{34}N_2O_{11}Cs$ (M + Cs) 611.1217, found 611.1241.

Compound 73: ^{1}H NMR (500 MHz, D_2O) δ 1.11 (d, J = 6.5 Hz, 3H), 1.13−1.28 (m, 4H), 1.67−1.79 (m, 5H), 2.13−2.29 (m, 5H), 3.34−3.38 (m, 1H), 3.47 (dd, J = 6.5 and 12.0 Hz, 1H), 3.54 (dd, J = 3.0 and 10.0 Hz, 1H), 3.56 (t, J = 3.0 Hz, 1H), 3.60 (dd, J = 3.0 and 12.0 Hz, 1H), 3.63 (dd, J = 3.5 and 10.0 Hz, 1H), 3.68−3.78 (m, 2H), 3.83 (q, J = 6.5 Hz, 1H), 4.37 (d, J = 8.0 Hz, 1H), 4.99 (d, J = 3.5 Hz, 1H).

Compound 74: ^{1}H NMR (500 MHz, D_2O) δ 1.12 (d, J = 6.5 Hz, 3H), 1.08−1.26 (m, 4H), 1.39 (s, 9H), 1.65−1.80 (m, 3H), 2.14 (m, 1H), 2.74 (m, 2H), 3.39−3.88 (m, 9H), 4.37 (m, 2H), 4.98 (d, J = 3.5 Hz, 1H); HRMS calcd for $C_{25}H_{43}N_3O_{13}Cs$ (M + Cs) 726.1850, found 726.1832.

Synthesis of 75. To the solution of **96** (40 mg, 38 μmol) in MeOH (2 mL) was added $Pd(OH)_2$ on carbon (Degussa type, 10 mg). The mixture was stirred for 18 h under hydrogen (1 atm), and the catalyst was removed by filtration through Celite. The solvent was evaporated *in vacuo*, and the residue was purified by Biogel P-2 column chromatography (H_2O) to obtain **75** (9.3 mg, 49%): ^{1}H NMR (500 MHz, D_2O) δ 1.15 (d, J = 6.5 Hz, 3H), 1.10−1.40 (m, 4H), 1.66−1.85 (m, 3H), 2.16 (m, 1H), 2.59 (dd, J = 8.5 and 17.5 Hz, 1H), 2.72 (dd, J = 5.0 and 17.5 Hz, 1H), 3.40 (m, 1H), 3.51 (dd, J = 6.0 and 12.0 Hz, 1H), 3.56 (dd, J = 3.5 and 10.0 Hz, 1H), 3.60 (m, 1H), 3.64 (dd, J = 4.0 and 10.0 Hz, 1H), 3.69 (m, 1H), 3.73 (m, 1H), 3.85 (m, 1H), 3.91 (m, 1H), 4.15 (m, 1H), 4.40 (d, J = 7.0 Hz, 1H), 5.00 (d, J = 4.0 Hz, 1H); HRMS calcd for $C_{20}H_{35}N_3O_{11}Na$ (M + Na) 516.2169, found 516.2169.

Synthesis of 97 and 98. These compounds were synthesized by the coupling reactions of *O*-benzyl-Ser with **80** or *N*-Boc-Asp β-benzyl ester according to the procedure for the syntheses of **82** and **83**. Yields: (**97**) 73%, (**98**) 51%.

Compound 97: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.29 (m, 2H), 2.40 (m, 2H), 3.69 (dd, J = 3.5 and 9.5 Hz, 1H), 3.92 (dd, J = 3.0 and 9.5 Hz, 1H), 4.49 (m, 2H), 4.76 (m, 1H), 5.09 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 7.30 (m, 10H); HRMS calcd for $C_{22}H_{25}NO_6Cs$ (M + Cs) 532.0736, found 532.0760.

Compound 98: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.78 (m, 4H), 2.97 (dd, J = 4.5 and 17.5 Hz, 1H), 3.12 (dd, J = 5.0 and 17.5 Hz, 1H), 5.01 (m, 1H), 5.17 (m, 1H), 5.74 (d, J = 9.0 Hz, 1H), 7.35 (m, 5H); HRMS calcd for $C_{20}H_{24}N_2O_8Cs$ (M + Cs) 553.0587, found 553.0573.

Coupling of 97, 98, and 92 Followed by Debenzylation for the Syntheses of 76 and 77. The syntheses of **76** and **77** were carried out according to the procedure for the syntheses of **65**−**67**. Yields: (**76**) 59%, (**77**) 59%.

Compound 76: ^{1}H NMR (500 MHz, D_2O) δ 1.12 (d, J = 6.5 Hz, 3H), 1.18 (m, 5H), 1.66 (m, 3H), 1.77 (m, 2H), 2.15 (t, J = 7.5 Hz, 2H), 2.28 (m, 3H), 3.42 (m, 1H), 3.66 (dd, J = 3.5 and 8.0 Hz, 1H), 3.69 (m, 2H), 3.74 (m, 2H), 3.85 (m, 1H), 4.37 (t, J = 5.5 Hz, 1H), 5.02 (d, J = 3.5 Hz, 1H); HRMS calcd for $C_{20}H_{34}N_2O_{10}Na$ (M + Na) 485.2111, found 485.2127.

Compound 77: ^{1}H NMR (500 MHz, D_2O) δ 1.48 (d, J = 7.0 Hz, 3H), 1.47−1.74 (m, 4H), 1.74 (s, 9H), 2.00−2.11 (m, 3H), 2.47 (m, 1H), 3.64 (s, 1H), 3.76 (m, 1H), 3.97−4.25 (m, 6H), 4.65−4.74 (m, 2H), 5.31 (d, J = 3.5 Hz, 1H); HRMS calcd for $C_{24}H_{41}N_3O_{12}Cs$ (M + Cs) 696.1745, found 696.1717.

Coupling of 92 and 84 Followed by Hydrogenation: Synthesis of 78. Compound **92** (73 mg, 0.14 mmol) was subjected to the previous procedure described for the synthesis of **68** to obtain **78** (31 mg, 42%): ^{1}H NMR (500 MHz, D_2O) δ 1.08 (d, J = 6.8 Hz, 3H), 1.08−1.27 (m, 4H), 1.54−1.71 (m, 3H), 2.12−2.14 (m, 1H), 2.54−2.62 (m, 2H), 2.74−2.86 (m, 2H), 2.96 (dd, J = 6.2 and 10.2 Hz, 1H), 3.15−3.22 (m, 1H), 3.31−3.36 (m, 1H), 3.54−3.68 (m, 2H), 3.83 (q, J = 6.8 Hz, 1H), 3.98 (t, J = 6.4 Hz, 1H), 4.52 (dd, J = 6.2 Hz, 1H), 4.78 (d, J = 3.9 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H); HRMS calcd for $C_{25}H_{37}N_3O_{10}Cs$ (M + Cs) 672.1533, found 672.1546.

Coupling of 85 and 92 for the Synthesis of 99. To a solution of **92** (48 mg, 91 μmol) in dry DMF (1 mL) were added **85** (20 mg, 90 μmol), HOBt (13 mg, 99 μmol), and 4-methylmorpholine (20 μL, 0.18 mmol), successively, at −20 °C. The solution was stirred for 20 min at −20 °C, then EDC (21 mg, 0.11 mmol) was added, and the mixture was allowed to rise to room temperature within 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was applied to silica gel column chromatography (hexane:acetone = 4:1) to obtain **99** (43 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, J = 6.1 Hz), 1.25−1.42 (m, 8H), 1.95−2.12 (m, 2H), 2.24−2.32 (m, 2H), 3.30 (s, 3H), 3.45−3.63 (m, 1H), 3.91−4.26 (m, 9H), 3.91−4.70 (m, 6H), 5.69 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 7.25−7.42 (m, 20H); HRMS calcd for $C_{48}H_{57}O_{11}NCs$ (M + Cs) 956.2986, found 956.2971.

Methoxycarbonylmethylation of 99 for the Synthesis of 100. Compound **99** (14 mg, 17 μmol) was dissolved in dry DMF (0.8 mL), and methyl bromoacetate (2 μL, 22 μmol), NaH (95% suspension in mineral oil, 0.5 mg, 2 μmol), and Bu_4NI (3 mg, 8.5 μmol) were added to the solution successively at 0 °C. The mixture was stirred for 1 h at 0 °C and was allowed to react for 4 h at room temperature. The mixture was then concentrated *in vacuo* and purified by silica gel column chromatography (hexane:EtOAc = 4.5:5.5) to give **100** (7.5 mg, 53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, J = 6.0 Hz, 3H), 1.59 (m, 8H), 1.90−2.22 (m, 2H), 2.45−2.49 (m, 2H), 3.32 (s, 3H), 3.77 (s, 3H), 3.92−4.25 (m, 11H), 4.61−4.90 (m, 6H), 5.70 (s, 1H), 6.8 (d, J = 8.0 Hz, 1H), 7.41−7.25 (m, 20H); HRMS calcd for $C_{51}H_{61}O_{13}NCs$ (M + Cs) 1028.3197, found 1028.3240.

Debenzylation of 100 Followed by Hydrolysis of the Ester for the Synthesis of 79. Compound **100** (7 mg, 7.8 μmol) was dissolved in MeOH (1 mL) and stirred in the presence of 20% $Pd(OH)_2$ on carbon (Degussa type, 1 mg) under an atmosphere of hydrogen (1 atm) for 8 h. The mixture was filtered through Celite and concentrated *in vacuo* to obtain the deprotected product (4 mg, 90%), which was dissolved in 0.1 N NaOH (2 mL) and stirred for 4 h at room temperature. The crude mixture was concentrated *in vacuo* and purified by Biogel P-2 column chromatography (H_2O) to obtain **79** (2.8 mg, 76%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.19 (d, J = 6.0 Hz), 1.24−1.31 (m, 2H), 1.36−1.39 (m, 5H), 1−45−1.48 (m, 1H), 1.73−1.81 (m, 3H), 1.88 (s, 1H), 2.11−2.13 (m, 2H), 2.15−2.18 (m, 1H), 2.31 (dd, J = 4.1 and 7.9 Hz, 2H), 3.25 (s, 3H), 3.62−3.66 (m, 4H), 3.47−3.53 (m, 1H), 3.76−3.92 (m, 4H), 4.12−4.16 (m, 1H), 4.27−4.29 (m, 1H), 4.47−4.53 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 16.9, 19.8, 24.7, 25.7, 29.9, 42.7, 50.0, 50.9, 63.5, 64.5, 67.8, 69.8, 70.2, 70.9, 71.6, 73.6, 76.0, 80.3, 85.8, 95.2, 100.1, 178.1; HRMS calcd for $C_{22}H_{36}O_{13}NNa$ (M + Na) 546.2163, found 546.2186.

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Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **8**, **9**, **11**, **12**, **14**, **15**, **22**, **23**, **25**, **27**, **39**−**53**, **55**, **56**, **65**−**87**, **89**−**94**, **96**, **99**, and **100** (60 pages). See any current masthead page for ordering and Internet access instructions.

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