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Design, synthesis and evaluation of D-galactose-β-cyclodextrin conjugates as drug-carrying molecules

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ABSTRACT

Several kinds of D-galactose-β-cyclodextrin conjugates having a phenyl group in the spacers between the D-galactose and β-cyclodextrin were designed and synthesized as drug-carrying molecules. Their evaluation as drug-carrying molecules was done by measuring the molecular interactions with the anticancer agent, doxorubicin, and with the D-galactose-binding peanut lectin using an SPR optical biosensor. The SPR analyses showed that these conjugates had remarkably high inclusion associations of $10^5 \sim 10^7\ M^{-1}$ levels for the immobilized doxorubicin. Their association constants for immobilized peanut lectin were at the level of $10^4 \sim 10^5\ M^{-1}$, as we expected. These conjugates will be useful drug-carrying models which can site-specifically carry doxorubicin to the cells containing D-galactose-binding lectin.

1. Introduction

Cyclodextrins (CyDs) have the ability to include drug molecules within their cavities. Saccharides are known to be involved in a number of significant biological recognition phenomena on the surfaces of cell membranes. Therefore, the CyD derivatives conjugated with saccharide moieties, which have both the drug-inclusion ability of CyDs and the cell-recognition of saccharides, are expected to carry drug molecules to specific cells. They will be useful for the targeting drug delivery systems (TDDS).[1]

Our recent paper describes the synthesis of glucose-β-CyD conjugates (**1**–**3**) using arbutin. Arbutin is a naturally occurring 4-hydroxyphenyl β-D-glucopyranoside (hydroquinone glucoside). The conjugates **1**–**3** are characterized by the existence of a phenyl group in the spacers between the D-glucose and β-CyD as shown in Figure 1.[2]

They indicated excellent inclusion associations of 10^5–$10^8\ M^{-1}$ for the immobilized doxorubicin (DXR, anthracycline-related anticancer agent) by measurement using an SPR optical biosensor. The NMR analyses of the DXR-inclusion complex from **1** suggested that its phenyl group significantly contributed to the increase in the inclusion associations for DXR. The suggested complexes between the conjugates and DXR are shown in Figure 2. The formation of the stacking complexes by the π–π interactions between the phenyl group and the included DXR seems to enhance the inclusion abilities of **1**–**3** for DXR.[3] These conjugates are promising DXR-related drug-carrying models for the TDDS.

These findings urged us to develop more practicable saccharide-β-CyD conjugate models having spacer structures which are similar to those of **1**–**3** and necessary for the high DXR-inclusion abilities. We designed several D-galactose-β-CyD conjugates (**4**–**7**) with various spacer lengths as shown in Figure 3. Due to D-galactose's high affinity with lectin present on liver cells, these conjugates were expected to selectively carry DXR to hepatic cancer cells. As there were no D-galactoside derivatives having hydroquinone as seen in arbutin, we designed novel spacers ($-O(CH_2CH_2O)_n-CH_2CH_2PhOCH_2CH_2CH_2-$) ($n = 0, 1, 2$). The common part ($-PhOCH_2CH_2CH_2-$), which was also found in the spacers of **1** and **3**, was necessary for the appearance of the high inclusion associations for DXR. The variable part ($-(CH_2CH_2O)_n$) ($n = 0, 1, 2$) made it possible to examine the effect due to the difference in the spacer length.

The synthesized 6^A-mono-D-galactose-β-CyD conjugates (**4**–**6**) and 6^A,6^D-bis-D-galactose-β-CyD conjugate (**7**) were evaluated as drug-carrying molecules. Both the DXR-inclusion abilities and cell-recognition abilities were determined by measuring the molecular interactions with immobilized DXR and with peanut lectin (PNA, D-galactose-binding lectin) using an SPR optical biosensor. This paper describes the synthesis and evaluation of the D-galactose-β-CyD conjugates (**4**–**7**).

2. Results and discussion

2.1. Syntheses of novel D-galactose-β-CyD conjugates (4–7)

The syntheses of the D-galactose-β-CyD conjugates **4**–**7** were investigated as shown in Scheme 1. The spacer precursors **9**, **11**,

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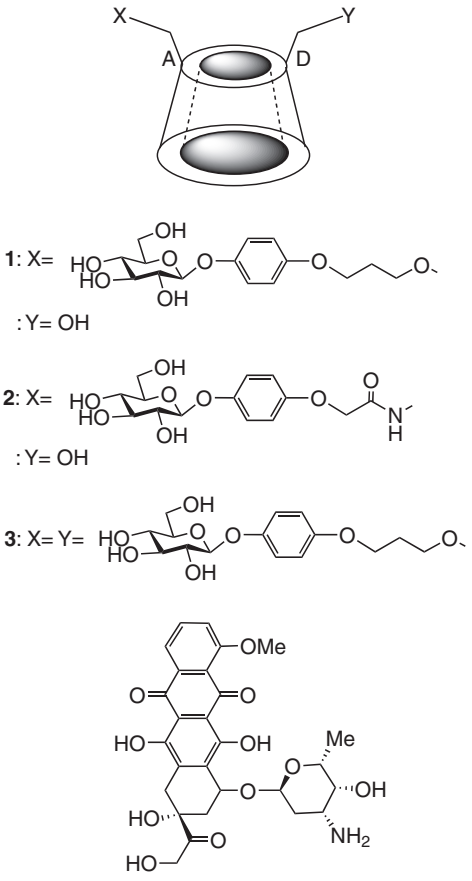


Figure 1. Our reported arbutin-β-CyD conjugates (**1**–**3**) and DXR.

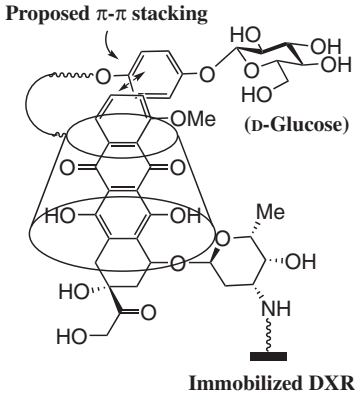


Figure 2. Speculated stacking complexes between arbutin-β-CyD conjugates and DXR.

and **13** were prepared from 4-hydroxyphenyl ethanol **8**. 2-(4-Allyloxyphenyl)ethanol **9** was prepared by the reaction of allyl bromide and the dry sodium salt of **8** in DMF. The reaction of **9** with 2-(1-chloro-3-oxapropane-3-yl)tetrahydro-2*H*-pyran or 2-(1-chloro-3,6-dioxahexane-6-yl)tetrahydro-2*H*-pyran using sodium hydride in DMF gave **10** and **12**. The following acidic hydrolysis using 1 M HCl–THF solution afforded **11** and **13**. The galactosylation from **9**, **11**, and **13** to **14**–**16** was done using penta-*O*-acetyl-β-D-galactopyranose in propionitrile at 0 °C in the presence of boron trifluoride diethyletherate. The deacetylation of **14**–**16** using NaOMe in methanol and the following benzylation using sodium hydride and benzyl bromide in DMF gave **17**–**19**. The hydroboration of **17**–**19** with 9-BBN, followed by hydrolysis using aqueous NaOH and oxidation using aqueous H_2O_2 gave **20**–**22**. The iodonation of **20**–**22** using PPh_3-I_2 afforded **23**–**25**. The reactions of **23**–**25** with the partially benzylated β-CyD **26**[4] using KOH and *n*-Bu_4NI in DMF produced **27**–**30**. The treatment of **27**–**30** with H_2/$Pd(OH)_2$ in DMF gave the desired **4**–**7**. The β-CyD derivative **35** having no D-galactose moiety was prepared by the synthetic procedure as shown in Scheme 2 in order to clarify whether the PNA lectin indicates the non-specific bindings for the conjugates **4**–**7**.

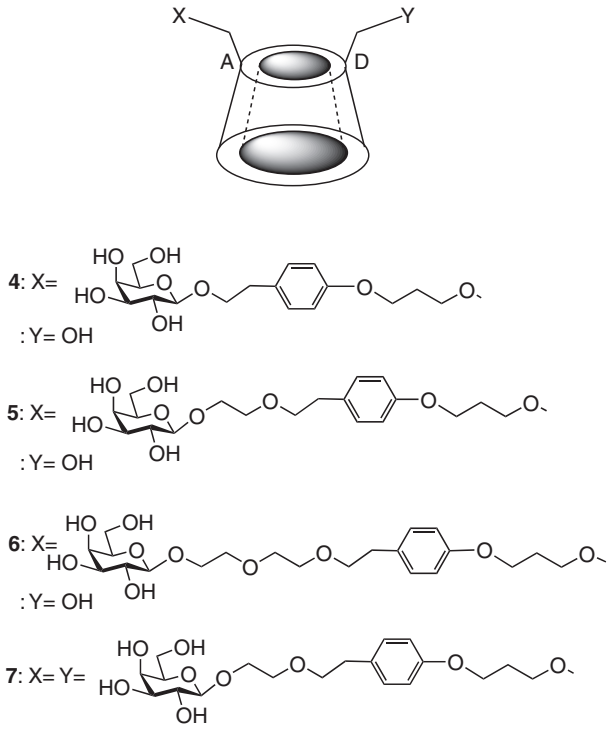


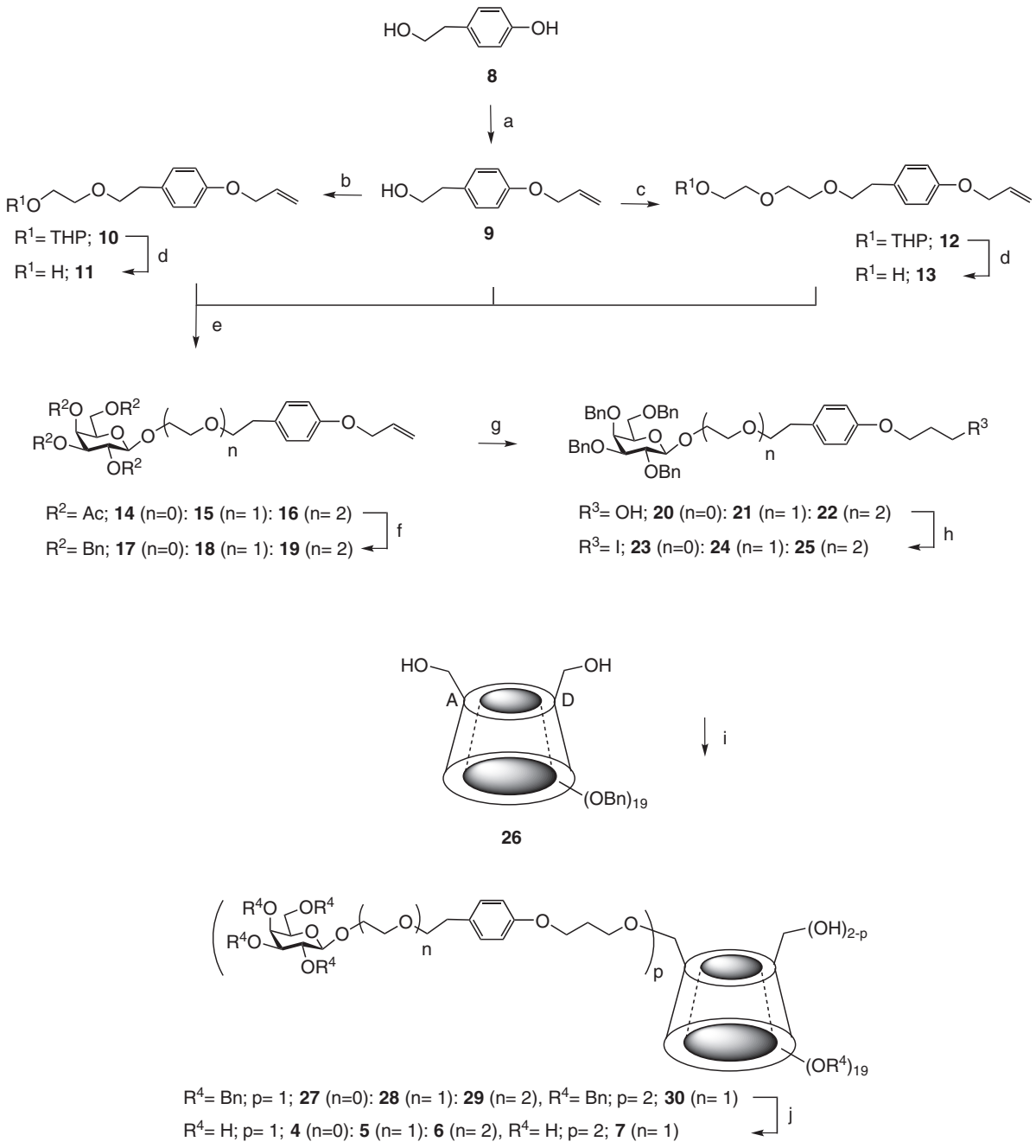
Figure 3. Galactose-β-CyD conjugates (**4**–**7**).

2.2. Molecular interactions

The synthesized conjugates **4**–**7** were evaluated as the drug-carrying molecules. The molecular interactions both with DXR and with the PNA lectin were investigated in order to determine their DXR-inclusion abilities and lectin-association abilities. The association constants of **4**–**7** for the immobilized DXR and for the immobilized PNA lectin were measured using an SPR optical biosensor according to our previously reported methods.[1r] In situ dual molecular interactions of **4** for DXR and the PNA lectin were investigated using an SPR assay for a more practical evaluation of the drug-carrying molecule as shown in Figure 4.

2.2.1. Inclusion associations of 4–7 with immobilized DXR

DXR was immobilized on the sensor cuvette of the optical biosensor and the measurements were carried out under the same conditions as previously reported.[1r] The amount of the immobilized DXR was 0.313 ng/mm^2. The immobilization of DXR was 35% of the aminosilane based on the assumption that the density of the aminosilane was one per 1 nm^2 area. The interactions of **4**–**7** with the immobilized DXR were measured at the concentration of 10^{-5}–10^{-7} M in acetate buffer, pH 5.3, at 25 °C. Figures 5 and 6 indicate the kinetic linear plots of **4**–**7**. Table 1 shows the association rate constants (k_a), dissociation rate constants (k_d),



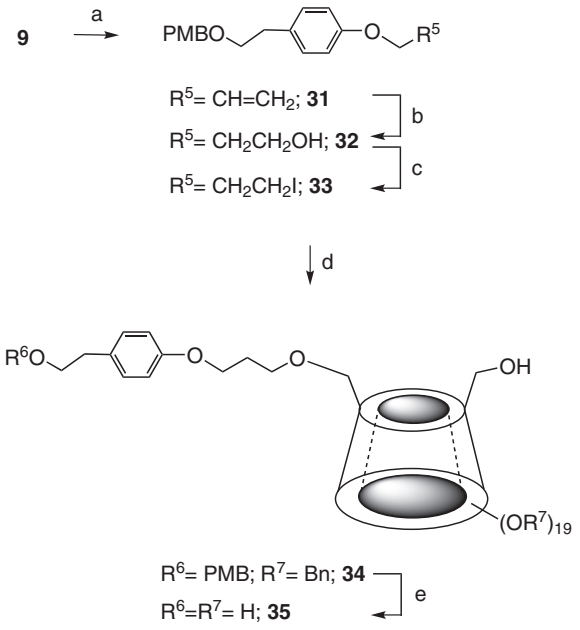
Scheme 1. Synthetic approaches to the galactose-β-CyD conjugates (**4**–**7**). Reagents and conditions: (a) 1—0.5 M NaOH aq, MeOH; 2—AllBr, DMF, 98%; (b) $THPOCH_2CH_2Cl$, NaH, DMF, 62%; (c) $THPOCH_2CH_2OCH_2CH_2Cl$, NaH, DMF, 41%; (d) 1 M HCl aq, THF, 94%; (e) penta-*O*-acetyl-β-D-galactopyranose, $BF_3{\cdot}OEt_2$, CH_3CH_2CN, 0 °C, **14**: 61%, **15**: 65%, **16**: 65%; (f) 1—NaOMe, MeOH; 2—NaH, BnBr, DMF, **17**: 93%, **18**: 84%, **19**: 82%; (g) 1—9-BBN, THF, 2—30% H_2O_2 aq, 0.5 M NaOH aq, **20**: 98%, **21**: 96%, **22**: 82%; (h) Ph_3P, I_2, DMF, 70 °C, **23**: 75%, **24**: 75%, **25**: 82%; (i) **26**, KOH, DMF, *n*-Bu_4NI, **27**: 49%, **28**: 52%, **29**: 72%, **30**: 9%; (j) $Pd(OH)_2$, H_2 gas, DMF, **4**: 92%, **5**: 90%, **6**: 81%, **7**: 83%.

and association constants (K_a) calculated by the relationship, $K_a = k_a/k_d$ of **4**–**7**.

The k_a values of **4**–**6** were 4.0–4.6 × 10^2 M^{-1} s^{-1}, the k_d values were 3.0–3.8 × 10^{-3} s^{-1}, and their K_a values were calculated to be 1.1–1.5 × 10^5 M^{-1}. The conjugates **4**–**6** indicated high inclusion associations for the immobilized DXR as we anticipated. The difference in the spacer lengths of **4**–**6** had almost no influence over their DXR-inclusion abilities. The k_a value of **7** was 1.8 × 10^5 M^{-1} s^{-1}, the k_d value was 12 × 10^{-3} s^{-1}, and its K_a value was calculated to be 1.5 × 10^7 M^{-1}. The conjugate **7** was found to have an excellent inclusion association of 10^7 M^{-1} level for the immobilized DXR. The K_a value of **7** was about 10^2 times higher than those of **4**–**6**. The presence of the two phenyl groups in **7** would strengthen the stacking effect based on π–π interactions by the formation of the inclusion complex whose DXR was interposed into the space between the two phenyl groups. The K_a values of **4**–**7** approximately corresponded to those of **1**–**3**.[2b]

2.2.2. Association constants of 4–7 and 35 with immobilized PNA lectin

The immobilization of the PNA lectin on the sensor cuvette of the optical biosensor was carried out under the same conditions as previously reported.[1r] The amount of the immobilized PNA lectin was 0.523 ng/mm^2. The immobilization of PNA was 30% of the



Scheme 2. Synthetic approaches to the β-CyD conjugate (**35**). Reagents and conditions: (a) NaH, PMBCl, DMF, **31**: 97%; (b) 1—9-BBN, THF; 2—30% H_2O_2 aq, 0.5 M NaOH aq, **32**: 88%; (c) Ph_3P, I_2, DMF, 40 °C, **33**: 87%; (d) **26**, KOH, DMF, *n*-Bu_4NI, **34**: 58%; (e) $Pd(OH)_2$, H_2 gas, DMF, **35**: 64%.

aminosilane based on the assumption that the density of the aminosilane was one per 1 nm^2 area. The molecular interactions of **4**–**7** and **35** were measured at the concentration of 10^{-4}–10^{-6} M in 10 mM acetate buffer, pH 5.3, containing 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 100 mM NaCl at 25 °C. Figure 7 shows the kinetic linear plots of **4**–**7**, and Table 2 summarizes the k_a, k_d, and K_a of **4**–**7**.

The k_a values of **4**–**6** were 1.8–3.4 × 10^2 M^{-1} s^{-1}, and the k_d values of those were 3.3–6.1 × 10^{-3} s^{-1}. Their K_a values were then calculated to be 5.4–9.2 × 10^4 M^{-1}. These K_a values were close to the values predicted from the result of our former research using a lactose conjugated β-CyD,[1k] which indicated the association constant of 8.1 × 10^3 M^{-1} for the immobilized PNA lectin. The K_a values of **4**–**6** suggested that these conjugates maintained the galactose's binding affinity with the PNA lectin. The difference in the spacer lengths of **4**–**6** had almost no influence over the recognition of the PNA lectin. The k_a value of **7** was 11 × 10^2 M^{-1} s^{-1}, the k_d value was 8.0 × 10^{-3} s^{-1}, and its K_a value was calculated to be 1.3 × 10^5 M^{-1}. The K_a value of **7** was about two times higher than that of **5**.

In contrast, the binding of **35** with the immobilized PNA lectin was not observed at the level of an SPR assay. This result indicated that there was no non-specific molecular interaction by the immobilized PNA lectin, that is, the immobilized PNA lectin specifically bound with the D-galactose moieties of **4**–**7**.

2.2.3. In situ dual molecular interactions of 4 for DXR and PNA lectin

The SPR experimental procedure for in situ dual molecular interactions of **4** for DXR and the PNA lectin was as follows. After the formation of the inclusion complex between **4** and the immobilized DXR on the cuvette surface, the association of the complex with the PNA lectin was measured. Figure 8 shows the SPR sensorgram for this experiment. After an increase of 45″ in the SPR signal was observed in the formation process of the inclusion complex between **4** and the immobilized DXR, an increase of 84″ in SPR signal was observed in the association process of the complex with the PNA lectin. The SPR experiment successfully indicated in situ dual molecular interactions of **4** for DXR and the PNA lectin on the cuvette surface.

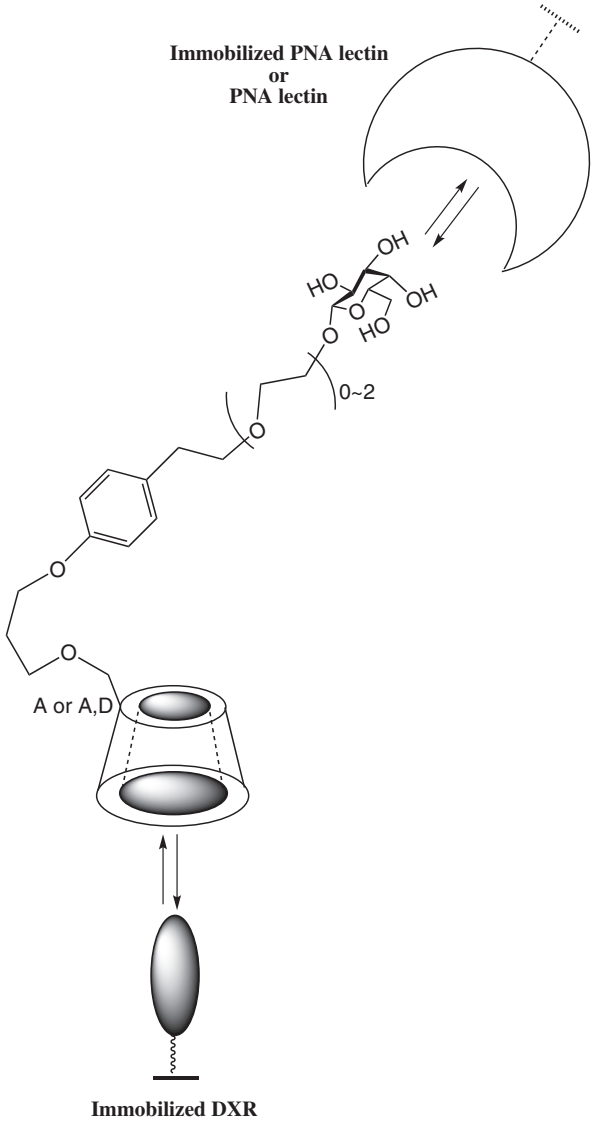


Figure 4. Molecular interactions of **4** for the immobilized DXR and the PNA lectin.

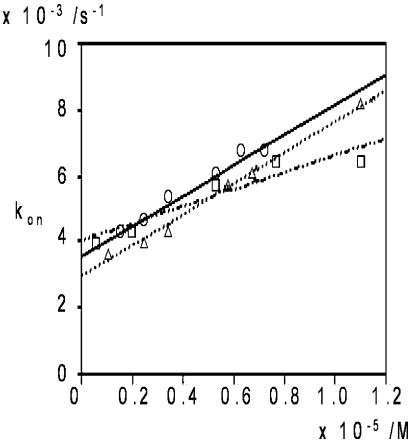


Figure 5. Kinetic linear plots for the immobilized DXR and **4** (○; r = 0.988), **5** (□; r = 0.991), and **6** (△; r = 0.998).

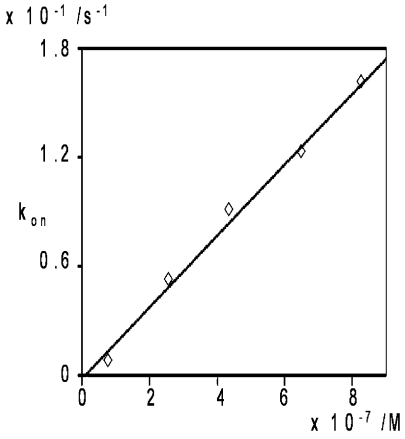


Figure 6. Kinetic linear plots for the immobilized DXR and **7** (◇; $r = 0.995$).

Table 1
Kinetic parameters of conjugates for association with the immobilized DXR

Entry	Conjugate	k_a ($\times 10^2$ M^{-1} s^{-1})	k_d ($\times 10^{-3}$ s^{-1})	K_a ($\times 10^5$ M^{-1})
1	**4**	4.0 ± 0.3	3.8 ± 0.1	1.1 ± 0.1
2	**5**	4.1 ± 0.3	3.5 ± 0.2	1.2 ± 0.2
3	**6**	4.6 ± 0.1	3.0 ± 0.1	1.5 ± 0.1
4	**7**	1800 ± 100	12.0 ± 5.0	150 ± 70

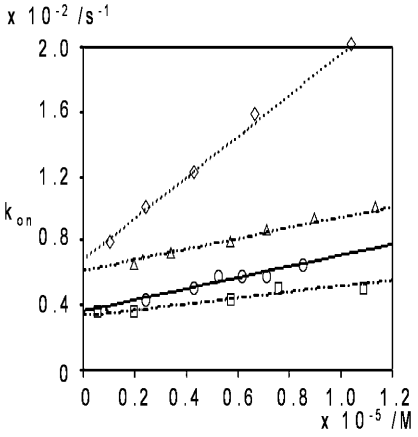


Figure 7. Kinetic linear plots for the immobilized PNA and **4** (○; $r = 0.995$), **5** (□; $r = 0.990$), **6** (△; $r = 0.995$), and **7** (◇; $r = 0.985$).

Table 2
Kinetic parameters of conjugates for association with the immobilized PNA

Entry	Conjugate	k_a ($\times 10^2$ M^{-1} s^{-1})	k_d ($\times 10^{-3}$ s^{-1})	K_a ($\times 10^4$ M^{-1})
1	**4**	3.4 ± 0.2	3.7 ± 0.1	9.2 ± 0.8
2	**5**	1.8 ± 0.1	3.3 ± 0.1	5.5 ± 0.5
3	**6**	3.3 ± 0.2	6.1 ± 0.1	5.4 ± 0.4
4	**7**	11.0 ± 1.0	8.0 ± 0.6	13.0 ± 2.0

3. Conclusions

Several kinds of D-galactose-β-CyD conjugates (**4**–**7**) having a phenyl group in the spacers between the D-galactose and β-CyD were successfully synthesized. Their capabilities as drug-carrying molecules were evaluated by measuring the molecular interactions with the immobilized DXR and peanut lectin using an SPR optical biosensor. They had high inclusion associations of 10^5–10^7 levels for the immobilized DXR and expected association constants of 10^4–10^5 levels for the immobilized peanut lectin. In situ dual molecular interactions of **4** for DXR and the PNA lectin were observed using an SPR technique. These D-galactose-β-CyD conjugates are expected to be useful drug-carrying molecules which can selectively carry DXR to the cells having the D-galactose-binding lectin.

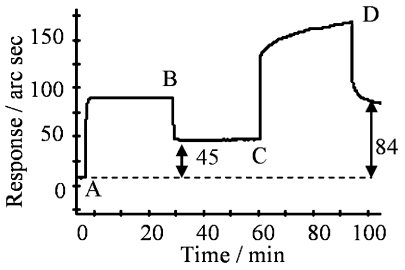


Figure 8. SPR sensorgram for the experimental of in situ dual molecular interactions of **4** for the immobilized DXR and the PNA lectin. (A) Addition of 100 μL of 10^{-4} M **4** in 10 mM acetate buffer to the sensor cuvette surface immobilized with DXR. (B) Washing the sensor cuvette with acetate buffer. (C) Addition of 100 μL of 10^{-6} M PNA lectin in acetate buffer to the sensor cuvette presented the inclusion complex between **4** and immobilized DXR. (D) Washing the sensor cuvette with acetate buffer.

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECA-600 spectrometer in $CDCl_3$ using TMS as the internal standard. The optical rotations were recorded on a JASCO DIP-360 digital polarimeter. The HRMS were obtained using a Mariner spectrometer (PerSeptive Biosystems, Inc.). The MALDI-TOF-MS spectra were recorded by a Voyager DE STR spectrometer. The preparative TLC was performed using Merck 60GF254 silica gel. Column chromatography was conducted using 60 N silica gel (40–50 μm, Kanto Chemical Co., Inc.) All anhydrous solvents were purified according to the standard methods. The balance was used on a METTLER TOLEDO AT261.

4.1.1. 2-(4-Allyloxyphenyl)ethanol (9)

A 0.5 M NaOH aqueous solution (72 mL, 36 mmol) was added to a solution of **8** (5.0 g, 36.2 mmol) in MeOH (30 mL). The resulting mixture was stirred for 1 h, the solvent was evaporated under reduced pressure and the reaction residue was crystallized. The reaction residue was dissolved in DMF (50 mL) and allyl bromide (3.7 mL, 43.7 mmol) was added. The resulting mixture was stirred for 3.5 h. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:3) to give **9** (5.5 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 1H, OH), 2.80 (t, $J = 6.6$ Hz, 2H, CH_2Ph), 3.81 (m, 2H, CH_2CH=CH_2), 4.51 (d, $J = 5.1$ Hz, 2H, HOCH_2), 5.27 (d, $J = 10.5$ Hz, 1H, CH=CH_aH$_b$), 5.40 (d, $J = 17.1$ Hz, 1H, CH=CH$_a$$H_b$), 6.00–6.10 (m, 1H, C$H$=CH$_2$), 6.86 (d, $J = 8.5$ Hz, 2H, Ph), 7.13 (d, $J = 8.3$ Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 38.3 (CH_2Ph), 63.8 (CH_2CH=CH_2), 68.8 (HOCH_2), 114.8 (Ph), 117.6 (CH=CH_2), 129.9 (Ph), 130.5 (Ph), 133.3 (CH=CH$_2$), 157.2 (Ph). HRMS (ESI): *m/z* calcd for $C_{11}H_{14}O_2Na$: 201.0886; found 201.0895.

4.1.2. 2-[6-(4-Allyloxyphenyl)-1,4-dioxahexane-1-yl]tetrahydro-2*H*-pyran (10)

NaH (600 mg, 25 mmol) was added to a solution of **9** (513.6 mg, 2.88 mmol) and 2-(1-chloro-3-oxapropane-3-yl)tetrahydro-2*H*-pyran (1153.7 mg, 7 mmol) in DMF (15 mL) at 0 °C. The resulting mixture was stirred for 164 h at room temperature. The reaction

was then quenched by the addition of a satd NaCl solution (20 mL). The reaction mixture was extracted with CH_2Cl_2. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:4) to give **10** (546.2 mg, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.48–1.62* (m, 4H, H_a-3, H_a-4, H-5), 1.67–1.73 (m, 1H, H_b-3), 1.78–1.86 (m, 1H, H_b-4), 2.83 (t, *J* = 7.2 Hz, 2H, C*H*$_2$Ph), 3.45–3.49 (m, 1H, H_a-6), 3.55–3.67 (m, 5H, C*H*$_2$CH$_2$ or C*H*$_2$CH$_2$Ph), 3.82–3.86 (m, 2H, H_b-6, C*H*$_2$CH$_2$ or C*H*$_2$CH$_2$Ph), 4.48 (d, *J* = 4.8 Hz, 2H, C*H*$_2$CH=CH$_2$), 4.61 (t, *J* = 3.6 Hz, 1H, H-2), 5.25 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H, CH=C*H*$_a$H$_b$), 5.38 (dd, *J* = 1.6 Hz, *J* = 17.2 Hz, 1H, CH=CH$_a$*H*$_b$), 5.98–6.08 (m, 1H, C*H*=CH$_2$), 6.82 (d, *J* = 8.8 Hz, 2H, Ph), 7.12 (d, *J* = 8.8 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 19.4 (C-4), 25.4 (C-5), 30.5 (C-3), 35.3 (*C*H$_2$Ph), 61.9 (C-6), 66.4 (*C*H$_2$CH$_2$ or *C*H$_2$CH$_2$Ph), 68.6 (*C*H$_2$C=CH$_2$), 70.0 (*C*H$_2$CH$_2$ or *C*H$_2$CH$_2$Ph), 72.2 (*C*H$_2$CH$_2$ or *C*H$_2$CH$_2$Ph), 98.6 (C-2), 114.3 (Ph), 117.1 (CH=*C*H$_2$), 129.5 (Ph), 130.9 (Ph), 133.1 (*C*H=CH$_2$), 156.6 (Ph). HRMS (ESI): *m/z* calcd for $C_{18}H_{26}O_4Na$: 329.1723; found: 329.1756.

4.1.3. 6-(4-Allyloxyphenyl)-4-oxahexanol (11)

A 1 M HCl (6 mL, 6 mmol) solution was added to a solution of **10** (501.2 mg, 1.64 mmol) in THF (11 mL). The resulting mixture was stirred for 2 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (15 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, $CHCl_3$/MeOH, 20:1) to give **11** (342 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.84 (t, *J* = 7.6 Hz, 2H, C*H*$_2$Ph), 3.53–3.69 (m, 6H, C*H*$_2$C*H*$_2$OC*H*$_2$CH$_2$Ph), 4.50 (d, *J* = 5.5 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.27 (dd, *J* = 1.4 Hz, *J* = 12.4 Hz, 1H, CH=C*H*$_a$H$_b$), 5.40 (dd, *J* = 2.1 Hz, *J* = 17.2 Hz, 1H, CH=CH$_a$*H*$_b$), 6.00–6.07 (m, 1H, C*H*=CH$_2$), 6.84 (d, *J* = 8.9 Hz, 2H, Ph), 7.12 (d, *J* = 8.9 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.2 (*C*H$_2$Ph), 61.6 (HO*C*H$_2$ or CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$Ph), 68.7 (*C*H$_2$CH=CH$_2$), 71.8 (HO*C*H$_2$ or CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$Ph), 72.2 (HO*C*H$_2$ or CH$_2$*C*H$_2$ or *C*H$_2$CH$_2$Ph), 114.6 (Ph), 117.5 (CH=*C*H$_2$), 129.7 (Ph), 130.9 (Ph), 133.3 (*C*H=CH$_2$), 157.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3Na$: 245.1148; found: 245.1116.

4.1.4. 2-[9-(4-Allyloxyphenyl)-1,4,7-trioxanonane-1-yl]tetrahydro-2*H*-pyran (12)

NaH (564.0 mg, 23.5 mmol) was added to a solution of **9** (1008.8 mg, 5.66 mmol) and 2-(1-chloro-3,6-dioxahexane-6-yl)tetrahydro-2*H*-pyran (1426.7 mg, 6.84 mmol) in DMF (20 mL) at 0 °C. The resulting mixture was stirred for 19 h at room temperature. The reaction was then quenched by the addition of a satd NaCl solution (25 mL). The reaction mixture was extracted with EtOAc. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:3) to give **12** (808.8 mg, 41%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.50–1.54* (m, 2H, H_a-5, H_a-4), 1.56–1.62 (m, 2H, H_a-3, H_b-5), 1.69–1.74 (m, 1H, H_b-3), 1.81–1.84 (m, 1H, H_b-4), 2.84 (t, *J* = 7.6 Hz, 2H, C*H*$_2$Ph), 3.48–3.52 (m, 1H, H_a-6), 3.59–3.68 (m, 9H, C*H*$_2$C*H*$_2$OC*H*$_2$-C*H*$_2$OC*H*$_a$H$_b$CH$_2$Ph), 3.85–3.89 (m, 2H, H_b-6, CH$_a$*H*$_b$CH$_2$Ph), 4.51 (d, 2H, *J* = 4.9 Hz, C*H*$_2$CH=CH$_2$), 4.63 (t, *J* = 3.6 Hz, 1H, H-2), 5.27 (d, 1H, *J* = 1.4 Hz, CH=C*H*$_a$H$_b$), 5.40 (d, *J* = 1.4 Hz, 1H, CH=CH$_a$*H*$_b$), 6.02–6.08 (m, 1H, C*H*=CH$_2$), 6.84 (d, *J* = 8.9 Hz, 2H, Ph), 7.12 (d, *J* = 8.3 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 19.4 (C-4), 25.4 (C-5), 30.5 (C-3), 35.3 (*C*H$_2$Ph), 62.2 (C-6), 66.6 (CH$_2$*C*H$_2$), 68.8 (*C*H$_2$CH=CH$_2$), 70.3 (CH$_2$*C*H$_2$), 70.5 (CH$_2$*C*H$_2$), 70.6 (CH$_2$*C*H$_2$), 72.5 (CH$_2$*C*H$_2$), 98.9 (C-2), 114.6 (Ph), 117.5 (CH=*C*H$_2$), 129.5 (Ph), 131.1 (Ph), 133.4 (*C*H=CH$_2$), 157.0 (Ph). HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_5Na$: 373.1985; found: 373.1942.

4.1.5. 9-(4-Allyloxyphenyl)-4,7-dioxanonanol (13)

A 1 M HCl solution (2.5 mL, 2.5 mmol) was added to a solution of **12** (59 mg, 0.17 mmol) in THF (4 mL). The resulting mixture was stirred for 1 h. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, $CHCl_3$/MeOH, 20:1) to give **13** (41.3 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.85 (t, *J* = 7.6 Hz, 2H, C*H*$_2$Ph), 2.85–3.72 (m, 10H, C*H*$_2$C*H*$_2$OC*H*$_2$-C*H*$_2$OC*H*$_2$CH$_2$Ph), 4.51 (d, *J* = 4.8 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.27 (d, *J* = 9.0 Hz, 1H, CH=C*H*$_a$H$_b$), 5.40 (d, *J* = 17.2 Hz, 1H, CH=CH$_a$*H*$_b$), 6.02–6.08 (m, 1H, C*H*=CH$_2$), 6.84 (d, *J* = 8.9 Hz, 2H, Ph), 7.13 (d, *J* = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.3 (*C*H$_2$Ph), 61.8 (CH$_2$*C*H$_2$), 68.9 (*C*H$_2$CH=CH$_2$), 70.3 (CH$_2$*C*H$_2$), 70.4 (CH$_2$*C*H$_2$), 72.5 (CH$_2$*C*H$_2$), 72.6 (CH$_2$*C*H$_2$), 114.7 (Ph), 117.5 (CH=*C*H$_2$), 129.8 (Ph), 131.0 (Ph), 133.4 (*C*H=CH$_2$), 157.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1364.

4.1.6. 2-(4-Allyloxyphenyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (14)

$BF_3{\cdot}OEt_2$ (99.0 μL, 0.79 mmol) was added to a solution of penta-*O*-acetyl-β-D-galactopyranose (153.8 mg, 0.39 mmol) and **9** (87.1 mg, 0.49 mmol) in CH_3CH_2CN (2 mL) at 0 °C. The resulting mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:3) to give **14** (122.7 mg, 61%) as a colorless oil. $[\alpha]_D^{23}$ +3.83 (*c* 4.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 3H, C*H*$_3$), 1.98 (s, 3H, C*H*$_3$), 2.05 (s, 3H, C*H*$_3$), 2.15 (s, 3H, C*H*$_3$), 2.83–2.85 (m, 2H, C*H*$_2$Ph), 3.63 (dd, *J* = 7.5 Hz, *J* = 15.8 Hz, 1H, C*H*$_a$H$_b$CH$_2$Ph), 3.39 (t, *J* = 6.9 Hz, 1H, H-5), 4.09–4.14 (m, 2H, H_a-6, CH$_a$*H*$_b$CH$_2$Ph), 4.18 (dd, *J* = 6.2 Hz, *J* = 11.0 Hz, 1H, H_b-6), 4.44 (d, *J* = 7.5 Hz, 1H, H-1), 4.50 (dd, *J* = 1.4 Hz, *J* = 5.5 Hz, 2H, C*H*$_2$CH=CH$_2$), 4.98 (dd, *J* = 2.5 Hz, *J* = 9.6 Hz, 1H, H-3), 5.21 (dd, *J* = 8.2 Hz, *J* = 10.3 Hz, 1H, H-2), 5.27 (dt, *J* = 1.4 Hz, *J* = 10.3 Hz, 1H, CH=C*H*$_a$H$_b$), 5.36–5.41 (m, 1H, H-4), 5.40 (dt, *J* = 8.2 Hz, *J* = 10.3 Hz, 1H, CH=CH$_a$*H*$_b$), 6.01–6.07 (m, 1H, C*H*=CH$_2$), 6.83 (d, *J* = 8.3 Hz, 2H, Ph), 7.10 (d, *J* = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.6 (*C*H$_3$), 20.7 (*C*H$_3$ × 3), 35.1 (*C*H$_2$Ph), 61.3 (C-6), 67.1 (C-4), 68.7 (C-2), 68.8 (*C*H$_2$CH=CH$_2$), 70.7 (C-5), 70.9 (*C*H$_2$CH$_2$Ph, C-3), 101.3 (C-1), 114.7 (Ph), 117.6 (CH=*C*H$_2$), 129.9 (Ph), 130.7 (Ph), 133.4 (*C*H=CH$_2$), 157.2 (Ph), 169.4–170.4 (C=O). HRMS (ESI): *m/z* calcd for $C_{25}H_{32}O_{11}Na$: 531.1837; found: 531.1860.

4.1.7. 2-(4-Allyloxyphenyl)ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (17)

A 28% sodium methylate methanol solution (0.3 mL, 0.0016 mmol) was added to a solution of **14** (110.3 mg, 0.22 mmol) in MeOH (20 mL). The resulting mixture was stirred for 16 h. The solvent was evaporated under reduced pressure. The crude product was added to a solution of NaH (146.0 mg, 6.08 mmol) in DMF (15 mL) at 0 °C. After the reaction mixture was stirred for 30 min, benzyl bromide (531.8 μL, 4.48 mmol) was added. The resulting mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of a MeOH solution (15 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:4) to give **17**

(141.6 mg, 93%) as a colorless oil. $[\alpha]_D^{23}$ −2.65 (*c* 3.58, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.89 (d, *J* = 6.6 Hz, 2H, CH_2CH_2Ph), 3.48 (dd, *J* = 2.7 Hz, *J* = 9.5 Hz, 1H, H-5), 3.51 (t, *J* = 8.0 Hz, 1H, H-3), 3.56 (d, *J* = 6.1 Hz, 2H, H-6), 3.67 (q, *J* = 7.8 Hz, 1H, $CH_aH_bCH_2Ph$), 3.79 (t, *J* = 7.2 Hz, 1H, H-2), 3.87 (d, *J* = 1.5 Hz, 1H, H-4), 4.10–4.15 (m, 1H, $CH_aH_bCH_2Ph$), 4.35 (d, *J* = 7.6 Hz, 1H, H-1), 4.39–4.49 (m, 4H, CH_2Ph), 4.61–4.74 (m, 4 H, CH_2Ph), 4.63 (d, *J* = 10.7 Hz, 1H, $CH_aH_bCH{=}CH_2$), 4.93 (d, *J* = 11.7 Hz, 1H, $CH_aH_bCH{=}CH_2$), 5.25 (d, *J* = 10.5 Hz, 1H, $CH{=}CH_aH_b$), 5.38 (d, *J* = 17.2 Hz, 1H, $CH{=}CH_aH_b$), 6.00–6.06 (m, 1H, $CH{=}CH_2$), 6.78 (d, *J* = 8.6 Hz, 2H, Ph), 7.11 (d, *J* = 8.6 Hz, 2H, Ph), 7.22–7.34 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.3 (CH_2CH_2Ph), 68.8 (C-6), 68.9 (CH_2CH_2Ph), 70.8 (CH_2Ph), 73.0 (CH_2Ph), 73.4 (C-4), 73.47 (C-2), 73.52 (CH_2Ph), 74.5 ($CH_2CH{=}CH_2$), 70.8 (CH_2Ph), 79.6 (C-5), 82.1 (C-3), 103.8 (C-1), 114.6 (Ph), 117.5 ($CH{=}CH_2$), 127.4–131.1 (Ph), 133.5 ($CH{=}CH_2$), 137.9–138.8 (Ph). HRMS (ESI): *m/z* calcd for $C_{45}H_{48}O_7Na$: 723.3292; found: 723.3255.

4.1.8. 2-[4-*O*-(3-Hydroxypropyl)phenyl]ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (20)

To a solution of **17** (341 mg, 0.49 mmol) in THF (3 mL) was added a 0.5 M 9-borabicyclo[3.3.1]nonane-THF solution (5.8 mL, 2.9 mmol) at 0 °C. After the reaction mixture was stirred for 24 h at room temperature, a 0.5 M NaOH aqueous solution (2.9 mL, 1.5 mmol) and 30% H_2O_2 aqueous solution (515.6 μL, 4.5 mmol) were added. After the reaction mixture was stirred for 16 h, the reaction was then quenched by adding water (15 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:1) to give **20** (335.8 mg, 98%) as a colorless oil. $[\alpha]_D^{23}$ −4.42 (*c* 5.39, $CHCl_3$). ^1H NMR ($CDCl_3$): δ *1.90–1.93* (m, 2H, CH_2CH_2OH), 2.86–2.91 (m, 2H, CH_2CH_2Ph), 3.49 (dd, *J* = 2.7 Hz, *J* = 9.6 Hz, 1H, H-3), 3.51 (t, *J* = 6.2 Hz, 1H, H-5), 3.57 (dd, *J* = 2.0 Hz, *J* = 6.2 Hz, 2H, H-6), 3.66 (q, *J* = 7.5 Hz, 1H, $CH_aH_bCH_2Ph$), 3.78–3.83 (m, 3H, H-4, CH_2OH), 3.87 (d, *J* = 2.8 Hz, 1H, H-2), 4.01–4.07 (m, 2H, $CH_2CH_2CH_2OH$), 4.08–4.17 (m, 1H, $CH_aH_bCH_2Ph$), 4.35 (d, *J* = 7.5 Hz, 1H, H-1), 4.39 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.43 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.61 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.63 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.68–4.74 (m, 3H, CH_2Ph), 4.93 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 6.77 (d, *J* = 5.2 Hz, 2H, Ph), 7.11 (d, *J* = 8.9 Hz, 2H, Ph), 7.20–7.34 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 32.0 (CH_2CH_2OH), 35.3 (CH_2CH_2Ph), 60.7 (CH_2OH), 65.8 ($CH_2CH_2CH_2OH$), 68.9 (C-6), 70.8 (CH_2CH_2Ph), 73.0 (CH_2Ph), 73.41 (C-4), 73.44 (C-5), 73.5 (CH_2Ph), 74.5 (CH_2Ph), 75.1 (CH_2Ph), 79.6 (C-2), 82.1 (C-3), 103.9 (C-1), 114.4–157.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{45}H_{50}O_8Na$: 741.3398; found: 741.3447.

4.1.9. 2-[4-*O*-(3-Iodopropyl)phenyl]ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (23)

To a solution of **20** (108.9 mg, 0.15 mmol) in DMF (5 mL) was added triphenylphosphine (189.0 mg, 0.72 mmol) and iodine (189.3 mg, 0.75 mmol) at 70 °C under an argon atmosphere. After the reaction mixture was stirred for 24 h, the reaction was then quenched by adding water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:4) to give **23** (96.2 mg, 75%) as a colorless oil. $[\alpha]_D^{23}$ −3.3 (*c* 1.81, $CHCl_3$). ^1H NMR ($CDCl_3$): δ *2.21–2.25* (m, 2H, CH_2CH_2I), 2.87–2.90 (m, 2H, CH_2CH_2Ph), 3.33 (t, *J* = 6.8 Hz, 2H, CH_2I), 3.48–3.52 (m, 2H, H-3, H-5), 3.57 (d, *J* = 6.1 Hz, 2H, H_a-6), 3.57 (t, *J* = 9.6 Hz, 1H, $CH_aH_bCH_2Ph$), 3.79 (t, *J* = 6.8 Hz, 1H, H-2), 3.87 (d, *J* = 2.7 Hz, 1H, H-4), 3.90–3.96 (m, 2H, $CH_2CH_2CH_2I$), 4.12–4.15 (m, 1H, $CH_aH_bCH_2Ph$), 4.35 (d, *J* = 7.6 Hz, 1H, H-1), 4.41–4.94 (m, 8H, CH_2Ph), 6.75–7.34 (m, 24H, Ph); ^{13}C NMR ($CDCl_3$): δ 2.6 (CH_2I), 33.1 (CH_2CH_2I), 35.4 (CH_2CH_2Ph), 67.2 ($CH_2CH_2CH_2I$), 68.9 (C-6), 70.8 (CH_2CH_2Ph), 73.1 (CH_2Ph), 73.4 (C-4), 73.5 (C-5), 73.6 (CH_2Ph), 74.5 (CH_2Ph), 75.1 (CH_2Ph), 79.6 (C-2), 82.1 (C-3), 103.9 (C-1), 114.4–151.2 (Ph). HRMS (ESI): *m/z* calcd for $C_{45}H_{49}O_7INa$: 851.2415; found: 851.2410.

4.1.10. 5-(4-Allyloxyphenyl)-3-oxapentyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (15)

$BF_3{\cdot}OEt_2$ (97.0 μL, 0.77 mmol) was added to a solution of penta-*O*-acetyl-β-D-galactopyranose (150.2 mg, 0.38 mmol) and **11** (114.8 mg, 0.52 mmol) in CH_3CH_2CN (3 mL) at 0 °C. The resulting mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH, 20:1) to give **15** (139.1 mg, 65%) as a colorless oil. $[\alpha]_D^{23}$ −10.3 (*c* 0.73, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.81 (t, *J* = 6.9 Hz, 2H, CH_2Ph), 3.60–3.64 (m, 4H, $CH_2CH_2OCH_2CH_2Ph$), 3.72–3.76 (m, 1H, H_a-6), 3.84 (t, *J* = 6.9 Hz, 1H, H-5), 3.91–3.94 (m, 1H, H_b-6), 4.11–4.18 (m, 1H, $CH_2OCH_2CH_2Ph$), 4.52 (d, *J* = 5.5 Hz, 2H, $CH_2CH{=}CH_2$), 4.55 (d, *J* = 8.3 Hz, 1H, H-1), 5.00 (dd, *J* = 3.4 Hz, *J* = 10.3 Hz, 1H, H-3), 5.21 (dd, *J* = 2.1 Hz, *J* = 10.3 Hz, 1H, H-2), 5.28 (dd, *J* = 1.4 Hz, *J* = 11.0 Hz, 1H, $CH{=}CH_aH_b$), 5.38 (d, *J* = 3.4 Hz, 1H, H-4), 5.41 (dd, *J* = 1.4 Hz, *J* = 17.2 Hz, 1H, $CH{=}CH_aH_b$), 6.02–6.09 (m, 1H, $CH{=}CH_2$), 6.86 (d, *J* = 8.2 Hz, 2H, Ph), 7.12 (d, *J* = 8.3 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.61 (CH_3), 20.67 (CH_3), 20.69 (CH_3), 20.74 (CH_3), 35.4 (CH_2Ph), 61.3 ($CH_2OCH_2CH_2Ph$), 67.1 (C-4), 68.8 (C-2, C-6), 68.9 ($CH_2CH{=}CH_2$), 70.1 (CH_2CH_2Ph), 70.6 (C-5), 70.9 (C-3), 72.5 ($CH_2CH_2OCH_2CH_2Ph$), 101.3 (C-1), 114.7 (Ph), 117.6 ($CH{=}CH_2$), 129.8 (Ph), 131.1 (Ph), 133.5 ($CH{=}CH_2$), 157.2 (Ph), 169.5 (C=O), 170.2 (C=O), 170.3 (C=O), 170.4 (C=O). HRMS (ESI): *m/z* calcd for $C_{27}H_{36}O_{12}Na$: 575.2099; found: 575.2089.

4.1.11. 5-(4-Allyloxyphenyl)-3-oxapentyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (18)

A 28% sodium methylate methanol solution (0.3 mL, 0.0016 mmol) was added to a solution of **15** (132.6 mg, 0.24 mmol) in MeOH (20 mL). The resulting mixture was stirred for 2 h. The solvent was evaporated under reduced pressure. The crude product was added to a solution of NaH (183.0 mg, 7.63 mmol) in DMF (10 mL) at 0 °C. After the reaction mixture was stirred for 30 min, benzyl bromide (239.0 μL, 2.01 mmol) was added. The resulting mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of a MeOH solution (15 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:3) to give **18** (260.6 mg, 84%) as a colorless oil. $[\alpha]_D^{23}$ −9.9 (*c* 0.97, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.79 (t, *J* = 7.6 Hz, 2H, CH_2CH_2Ph), 3.50 (d, *J* = 2.8 Hz, 1H, H-3), 3.52 (d, *J* = 6.9 Hz, 1H, H-5), 3.58 (t, *J* = 6.2 Hz, 1H, H_a-6), 3.61–3.69 (m, 5H, H_b-6, CH_2CH_2Ph), 3.71–3.75 (m, 1H, $CH_aH_bCH_2OCH_2CH_2Ph$), 3.82 (dd, *J* = 2.1 Hz, *J* = 7.5 Hz, 1H, H-2), 3.88 (d, *J* = 2.7 Hz, 1H, H-4), 3.98–4.02 (m, 1H, CH_aH_{b}-$CH_2OCH_2CH_2Ph$), 4.39 (d, *J* = 8.2 Hz, 1H, H-1), 4.41–4.45 (m, 4H, $CH_2OCH_2CH_2Ph$, CH_2Ph), 4.47 (d, *J* = 5.5 Hz, 1H, $CH_aH_bCH{=}CH_2$), 4.61 (d, *J* = 11.7 Hz, 1H, $CH_aH_bCH{=}CH_2$), 4.69–4.77 (m, 4H, CH_2Ph), 4.92–4.96 (m, 2H, CH_2Ph), 5.26 (d, *J* = 9.6 Hz, 1H, $CH{=}CH_aH_b$), 5.38 (dd, *J* = 1.4 Hz, *J* = 17.2 Hz, 1H, $CH{=}CH_aH_b$), 6.00–6.06 (m, 1H, $CH{=}CH_2$), 6.80 (d, *J* = 8.2 Hz, 2H, Ph), 7.07 (d, *J* = 8.2 Hz, 2H, Ph),

7.25–7.38 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.4 (CH_2CH_2Ph), 68.79, 68.80 ($CH_2CH_2OCH_2CH_2Ph$), 68.9 (CH_2CH_2Ph), 70.0 (CH_2Ph), 72.4 (C-6), 73.1 (CH_2Ph), 73.4 (C-5), 73.5 (C-4, CH_2Ph), 74.5 ($CH_2CH{=}CH_2$), 75.0 (CH_2Ph), 79.4 (C-2), 82.1 (C-3), 104.1 (C-1), 114.6 (Ph), 117.5 ($CH{=}CH_2$), 127.4–131.1 (Ph), 133.4 ($CH{=}CH_2$), 137.9–138.9 (Ph), 157.0 (Ph). HRMS (ESI): *m/z* calcd for $C_{47}H_{52}O_8Na$: 767.3554; found: 767.3538.

4.1.12. 5-[4-*O*-(3-Hydroxypropyl)phenyl]-3-oxapentyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (21)

To a solution of **18** (293.8 mg, 0.39 mmol) in THF (2 mL) was added a 0.5 M 9-borabicyclo[3.3.1]nonane-THF solution (4.7 mL, 2.35 mmol) at 0 °C. After the reaction mixture was stirred for 6 h at room temperature, a 0.5 M NaOH aqueous solution (2.4 mL, 1.2 mmol) and 30% H_2O_2 aqueous solution (447.0 μL, 3.94 mmol) were added. After the reaction mixture was stirred for 12 h, the reaction was then quenched by adding water (15 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:1) to give **21** (290.2 mg, 96%) as a colorless oil. $[\alpha]_D^{23}$ −14.9 (*c* 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.58 (s, 1H, OH), 2.01–2.02 (m, 2H, CH_2CH_2OH), 2.78 (t, *J* = 7.5 Hz, 2H, CH_2CH_2Ph), 3.49–3.51 (m, 2H, H-3, H-5), 3.56 (d, *J* = 6.2 Hz, 2 H, CH_2), 3.61–3.74 (m, 5H, H-6, CH_2CH_2, $CH_2CH_aH_b$), 3.80–3.85 (m, 3H, H-2, CH_2OH), 3.88 (d, *J* = 2.7 Hz, 1H, H-4), 3.98–4.01 (m, 1H, $CH_2CH_aH_b$), 4.05 (t, *J* = 5.5 Hz, 2H, $CH_2CH_2CH_2OH$), 4.38 (d, *J* = 7.6 Hz, 1H, H-1), 4.39–4.45 (m, 2H, CH_2Ph), 4.61 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.70–4.77 (m, 3H, CH_2Ph), 4.92–4.96 (m, 2H, CH_2Ph), 6.78 (d, *J* = 8.3 Hz, 2H, Ph), 7.08 (d, *J* = 8.3 Hz, 2H, Ph), 7.26–7.37 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 32.0 (CH_2CH_2OH), 35.4 (CH_2CH_2Ph), 60.7 (CH_2OH), 65.9 ($CH_2CH_2CH_2OH$), 68.85 (CH_2CH_2), 68.89 (CH_2CH_2), 70.0 (CH_2CH_2), 72.4 (C-6), 73.1 (CH_2Ph), 73.4 (C-5), 73.5 (C-4, CH_2Ph), 74.5 (CH_2Ph), 75.0 (CH_2Ph), 79.4 (C-2), 82.1 (C-3), 104.1 (C-1), 114.4 (Ph), 127.5–131.3 (Ph), 137.9–138.9 (Ph), 157.2 (Ph). HRMS (ESI): *m/z* calcd for $C_{47}H_{54}O_9Na$: 785.3660; found: 785.3612.

4.1.13. 5-[4-*O*-(3-Iodopropyl)phenyl]-3-oxapentyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (24)

To a solution of **21** (207.7 mg, 0.27 mmol) in DMF (6 mL) was added triphenylphosphine (298.0 mg, 1.14 mmol) and iodine (290.3 mg, 1.14 mmol) at 70 °C under an argon atmosphere. After the reaction mixture was stirred for 24 h, the reaction was then quenched by adding water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:2) to give **24** (177.3 mg, 75%) as a colorless oil. $[\alpha]_D^{23}$ −9.5 (*c* 1.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ *2.21–2.25* (m, 2H, CH_2CH_2I), 2.79 (t, *J* = 7.6 Hz, 2H, CH_2CH_2Ph), 3.34 (t, *J* = 6.2 Hz, 2H, CH_2I), 3.50–3.52 (m, 2H, H-3, H-5), 3.57–3.74 (m, 8H, H-6, CH_2CH_2), 3.82 (t, *J* = 8.2 Hz, 1H, H-2), 3.88 (d, *J* = 2.0 Hz, 1H, H-4), 3.95–4.02 (m, 4H, CH_2CH_2), 4.39 (t, *J* = 6.9 Hz, 1H, H-1), 4.40–4.45 (m, 2H, CH_2Ph), 4.61 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.70–4.77 (m, 3H, CH_2Ph), 4.93–4.96 (m, 2H, CH_2Ph), 6.77 (d, *J* = 8.2 Hz, 2H, Ph), 7.08 (d, *J* = 8.2 Hz, 2H, Ph), 7.25–7.38 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 2.6 (CH_2I), 33.0 (CH_2CH_2I), 35.4 (CH_2CH_2Ph), 67.2 ($CH_2CH_2CH_2I$), 68.85 (CH_2CH_2), 68.88 (CH_2CH_2), 70.0 (CH_2CH_2), 72.4 (C-6), 73.0 (CH_2Ph), 73.4 (C-5), 73.52 (C-4), 73.53 (CH_2Ph), 74.5 (CH_2Ph), 75.0 (CH_2Ph), 79.4 (C-2), 82.1 (C-3), 104.1 (C-1), 114.4 (Ph), 127.5–131.3 (Ph), 137.9–138.9 (Ph), 157.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{47}H_{53}O_8INa$: 895.2677; found: 895.2664.

4.1.14. 8-(4-Allyloxyphenyl)-3,6-dioxaoctyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (16)

$BF_3{\cdot}OEt_2$ (298.0 μL, 2.37 mmol) was added to a solution of penta-*O*-acetyl-β-D-galactopyranose (463.5 mg, 1.19 mmol) and **13** (379.4 mg, 1.42 mmol) in CH_3CH_2CN (6 mL) at 0 °C. The resulting mixture was stirred for 12 h at room temperature. The reaction was then quenched by the addition of a satd $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on a silica-gel (EtOAc/hexane/allyl alcohol, 1:12:1) to give **16** (458.4 mg, 65%) as a colorless oil. $[\alpha]_D^{23}$ −4.3 (*c* 9.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.05 (s, 6H, CH_3), 2.14 (s, 3H, CH_3), 2.84 (t, *J* = 6.9 Hz, 2H, CH_2Ph), 3.58–3.67 (m, 8H, CH_2CH_2), 3.73–3.77 (m, 1H, H_a-6), 3.90 (t, *J* = 6.9 Hz, 1H, H-5), 3.94–3.97 (m, 1H, H_b-6), 4.14–4.18 (m, 2H, CH_2CH_2), 4.51 (d, *J* = 4.8 Hz, 2H, $CH_2CH{=}CH_2$), 4.57 (d, *J* = 8.2 Hz, 1H, H-1), 5.02 (dd, *J* = 2.7 Hz, *J* = 10.3 Hz, 1H, H-3), 5.21 (dd, *J* = 8.2 Hz, *J* = 10.3 Hz, 1H, H-2), 5.27 (dd, *J* = 2.0 Hz, *J* = 10.3 Hz, 2H, $CH{=}CH_aH_b$), 5.38 (d, *J* = 3.4 Hz, 1H, H-4), 5.42 (d, *J* = 18.5 Hz, 2H, $CH{=}CH_aH_b$), 6.02–6.08 (m, 1H, $CH{=}CH_2$), 6.84 (d, *J* = 8.2 Hz, 2H, Ph), 7.12 (d, *J* = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.5 (CH_3), 20.63 ($CH_3 \times 2$), 20.64 (CH_3), 35.2 (CH_2CH_2), 61.2 (CH_2CH_2), 67.0 (C-4), 68.7 (C-2, C-6), 69.0 ($CH_2CH{=}CH_2$), 70.1 (CH_2CH_2), 70.2 (CH_2CH_2), 70.5 (C-5), 70.6 (CH_2CH_2), 70.8 (C-3), 72.4 (CH_2CH_2), 101.2 (C-1), 114.5 (Ph), 117.4 ($CH{=}CH_2$), 129.6 (Ph), 131.1 (Ph), 133.3 ($CH{=}CH_2$), 157.0 (Ph), 169.3 (C=O), 170.0 (C=O), 170.1 (C=O), 170.2 (C=O). HRMS (ESI): *m/z* calcd for $C_{29}H_{49}O_{13}Na$: 619.2361; found: 619.2354.

4.1.15. 8-(4-Allyloxyphenyl)-3,6-dioxaoctyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (19)

A 28% sodium methylate methanol solution (0.3 mL, 0.0016 mmol) was added to a solution of **16** (106.8 mg, 0.18 mmol) in MeOH (20 mL). The resulting mixture was stirred for 2 h. The solvent was then evaporated under reduced pressure. The crude product was added to a solution of NaH (73.1 mg, 3.05 mmol) in DMF (8 mL) at 0 °C. After the reaction mixture was stirred for 30 min, benzyl bromide (102.2 μL, 0.86 mmol) was added. The resulting mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of a MeOH solution (15 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:2) to give **19** (115.8 mg, 82%) as a colorless oil. $[\alpha]_D^{23}$ −21.7 (*c* 0.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.79 (t, *J* = 7.6 Hz, 2H, CH_2CH_2Ph), 3.50 (d, *J* = 2.7 Hz, 1H, H-3), 3.52–3.54 (m, H-5, 3H, CH_2CH_2), 3.57–3.62 (m, 8H, H-6, CH_2CH_2Ph, CH_2CH_2), 3.67–3.69 (m, 2H, CH_2CH_2), 3.72–3.76 (m, 1H, CH_2CH_2), 3.80–3.83 (dd, *J* = 8.2 Hz, *J* = 9.6 Hz, 1H, H-2), 3.88 (t, *J* = 8.2 Hz, 1H, H-4), 4.00–4.03 (m, 1H, CH_2Ph), 4.40 (d, *J* = 9.6 Hz, 1H, H-1), 4.43–4.49 (m, 3H, CH_2Ph, $CH_aH_bCH{=}CH_2$), 4.61 (d, *J* = 11.7 Hz, 1H, $CH_aH_bCH{=}CH_2$), 4.69–4.78 (m, 2H, CH_2Ph), 4.92–4.96 (m, 2H, CH_2Ph), 5.26 (dd, *J* = 0.69 Hz, *J* = 10.3 Hz, 1H, $CH{=}CH_aH_b$), 5.40 (dd, *J* = 1.4 Hz, *J* = 17.2 Hz, 1H, $CH{=}CH_aH_b$), 6.00–6.06 (m, 1H, $CH{=}CH_2$), 6.80 (d, *J* = 8.2 Hz, 2H, Ph), 7.08 (d, *J* = 8.2 Hz, 2H, Ph), 7.23–7.38 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.4 (CH_2CH_2Ph), 68.78 ($CH_2CH_2 \times 2$), 68.79 (CH_2CH_2), 68.9 (CH_2CH_2), 70.2 (CH_2CH_2 or CH_2Ph), 70.3 (CH_2CH_2 or CH_2Ph), 70.5 (CH_2CH_2 or CH_2Ph), 72.5 (C-6), 73.0 (CH_2Ph), 73.4 (C-5), 73.5 (C-4), 74.4 (CH_2Ph), 75.0 (CH_2Ph), 79.4 (C-2), 82.1 (C-3), 104.1 (C-1), 114.6 (Ph), 117.5 ($CH{=}CH_2$), 127.4–131.1 (Ph), 133.4 ($CH{=}CH_2$), 137.9–138.9 (Ph), 157.0 (Ph). HRMS (ESI): *m/z* calcd for $C_{49}H_{56}O_9Na$: 811.3817; found: 811.3781.

4.1.16. 8-[4-*O*-(3-Hydroxypropyl)phenyl]-3,6-dioxaoctyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (22)

To a solution of **19** (89.4 mg, 0.11 mmol) in THF (2 mL) was added a 0.5 M 9-borabicyclo[3.3.1]nonane–THF solution (1.6 mL, 0.8 mmol) at 0 °C. After the reaction mixture was stirred for 6 h at room temperature, a 0.5 M NaOH aqueous solution (680.0 μL, 0.34 mmol) and 30% H_2O_2 aqueous solution (128.5 μL, 1.13 mmol) were added. After the reaction mixture was stirred for 18 h, the reaction was then quenched by adding water (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:1) to give **22** (75.3 mg, 82%) as a colorless oil. $[\alpha]_D^{23}$ −4.7 (*c* 2.42, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 1H, OH), 1.62–1.65 (m, 2H, CH_2CH_2), 1.87–1.91 (m, 3H, CH_2CH_2), 2.79 (t, *J* = 6.9 Hz, 2H, CH_2CH_2), 3.50–3.74 (m, 10H, H-3, H-5, H-6, CH_2CH_2), 3.82 (dd, *J* = 2.0 Hz, *J* = 7.6 Hz, 1H, H-2), 3.88 (d, *J* = 1.3 Hz, 1H, H-4), 3.90–4.02 (m, 3H, CH_2CH_2), 4.10–4.14 (m, 2H, CH_2CH_2), 4.39 (d, *J* = 7.6 Hz, 1H, H-1), 4.41–4.45 (m, 2H, CH_2Ph), 4.60 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.69–4.76 (m, 3H, CH_2Ph), 4.94 (t, *J* = 12.3 Hz, 2H, CH_2Ph), 6.81 (d, *J* = 8.3 Hz, 2H, Ph), 7.10 (d, *J* = 8.9 Hz, 2H, Ph), 7.25–7.38 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_2CH_2OH), 21.0 (CH_2CH_2), 35.2 (CH_2CH_2Ph), 60.3 (CH_2OH), 68.7 (CH_2CH_2), 68.9 (CH_2CH_2), 70.1 (CH_2CH_2), 70.3 (CH_2CH_2), 70.5 (CH_2CH_2), 73.0 (C-6), 73.3 (C-5), 73.40 (C-4), 73.43 ($CH_2Ph \times 2$), 74.4 (CH_2Ph), 74.9 (CH_2Ph), 79.4 (C-2), 82.0 (C-3), 104.0 (C-1), 114.3 (Ph), 127.4–129.7 (Ph), 137.8–138.8 (Ph), 171.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{49}H_{58}O_{10}Na$: 829.3922; found: 829.3877.

4.1.17. 8-[4-*O*-(3-Iodopropyl)phenyl]-3,6-dioxaoctyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (25)

To a solution of **22** (47.0 mg, 0.058 mmol) in DMF (3 mL) was added triphenylphosphine (93.0 mg, 0.35 mmol) and iodine (90.0 mg, 0.35 mmol) at 70 °C under an argon atmosphere. After the reaction mixture was stirred for 24 h, the reaction was then quenched by adding water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:1) to give **25** (43.8 mg, 82%) as a colorless oil. $[\alpha]_D^{23}$ −4.0 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ *2.23–2.25* (m, 2H, CH_2CH_2I), 2.80 (t, *J* = 7.6 Hz, 2H, CH_2CH_2), 3.35 (t, *J* = 6.9 Hz, 2H, CH_2CH_2), 3.49–3.74 (m, 13H, H-3, H-5, H-6, CH_2CH_2), 3.81 (dd, *J* = 2.1 Hz, *J* = 7.5 Hz, 1H, H-2), 3.88 (d, *J* = 2.8 Hz, 1H, H-4), 3.98–4.03 (m, 3H, CH_2CH_2), 4.39 (d, *J* = 8.2 Hz, 1H, H-1), 4.41–4.45 (m, 2H, CH_2Ph), 4.61 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.69–4.76 (m, 3H, CH_2Ph), 4.92–4.96 (m, 2H, CH_2Ph), 6.80 (d, *J* = 9.0 Hz, 2H, Ph), 7.09 (d, *J* = 8.3 Hz, 2H, Ph), 7.24–7.38 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 2.6 (CH_2I), 33.0 (CH_2CH_2I), 35.3 (CH_2CH_2Ph), 67.2 (CH_2CH_2), 68.8 (CH_2CH_2), 69.0 (CH_2CH_2), 70.2 (CH_2CH_2), 70.4 (CH_2CH_2), 70.6 (CH_2CH_2), 72.5 (C-6), 73.1 (CH_2Ph), 73.49 (C-5), 73.52 (C-4), 73.52 (CH_2Ph), 74.5 (CH_2Ph), 75.0 (CH_2Ph), 79.4 (C-2), 82.1 (C-3), 104.1 (C-1), 114.4 (Ph), 114.4 (Ph), 127.5–131.2 (Ph), 137.9–138.9 (Ph). HRMS (ESI): *m/z* calcd for $C_{49}H_{57}O_9INa$: 939.2939; found: 939.2955.

4.1.18. Heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{A}-*O*-(1-*O*-{4-[1-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)ethyl-2-yl]phenyl}propane-3-yl)-β-cyclodextrin or heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{D}-*O*-(1-*O*-{4-[1-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)ethyl-2-yl]phenyl}propane-3-yl)-β-cyclodextrin (27)

Compound **26** (79.1 mg, 0.028 mmol) was added to a solution of potassium hydrate (193.5 mg, 3.45 mmol) in DMF (2 mL). After the reaction mixture was stirred for 30 min, the mixed sample was added to a solution of **23** (90.9 mg, 0.11 mmol) and tetra-*n*-butylammonium iodide (3.6 mg, 0.0097 mol) in DMF (2 mL). After the reaction mixture was stirred for 48 h, the reaction was then quenched by the addition of water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 2:3) to give **27** (72.0 mg, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.85–1.87* (m, 2H, $CH_2CH_2CH_2$), 2.82–2.83 (m, 2H, CH_2CH_2Ph), 3.44–3.58 (m, 18H), 3.88–4.31 (m, 30H), 4.33–4.75 (m, 50H), 4.83-5.36 (m, 12H), 6.69–6.70 (d, *J* = 8.2 Hz, 2H, Ph), 7.00–7.38 (m, 122H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.3, 29.5, 35.3, 61.5–82.1, 97.9-98.8, 103.9, 114.3, 126.9–129.8, 130.6, 137.8–139.3, 157.3. MALDI-TOF-MS: *m/z* calcd for $C_{227}H_{238}O_{42}Na$: 3658.6; found 3658.2.

4.1.19. 6^{A}-*O*-(1-*O*-{4-[1-*O*-(β-D-Galactopyranside-1-yl)ethyl-2-yl]phenyl}propane-3-yl)-β-cyclodextrin (4)

Compound **27** (92.3 mg, 0.025 mmol) was added to a solution of $Pd(OH)_2$ (117.4 mg, 0.75 mmol) in DMF (15 mL). Hydrogen was bubbled through the solution for 12 h. After the solvent was filtered and evaporated under reduced pressure, the crude product was isolated by adsorbing on LH-20 followed by eluting with methanol to afford **4** (34.5 mg, 92%) as white crystals. ^{1}H NMR (D_2O): δ *1.19–1.20* (m, 2H), 1.77–1.85 (m, 2H, $CH_2CH_2CH_2$), 2.88–2.91 (m, 2H, CH_2Ph), 3.12–4.05 (m, 52H), 4.36 (d, *J* = 7.6 Hz, 1H, H-1), 4.83–4.98 (m, 7H, CyD-1), 6.75 (d, *J* = 8.3 Hz, 2H, Ph), 7.10 (d, *J* = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.6, 29.5, 35.8, 60.4–81.8, 83.0–83.4, 101.5–104.3, 115.7, 130.3, 131.5. MALDI-TOF-MS: *m/z* calcd for $C_{59}H_{94}O_{42}Na$: 1497.5; found 1497.9.

4.1.20. Heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{A}-*O*-(1-*O*-{4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)-1,4-dioxahexane-6-yl]phenyl}propane-3-yl)-β-cyclodextrin or heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{D}-*O*-(1-*O*-{4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)-1,4-dioxahexane-6-yl]phenyl}propane-3-yl)-β-cyclodextrin (28)

Compound **26** (131.8 mg, 0.046 mmol) was added to a solution of potassium hydrate (316.5 mg, 5.64 mmol) in DMF (3 mL). After the reaction mixture was stirred for 30 min, the mixed sample was added to a solution of **24** (152.2 mg, 0.17 mmol) and tetra-*n*-butylammonium iodide (1.8 mg, 0.0049 mmol) in DMF (4 mL). After the reaction mixture was stirred for 48 h, the reaction was then quenched by the addition of water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane/MeOH, 2:12:1) to give **28** (86.4 mg, 52%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.86–1.87* (m, 2H, $CH_2CH_2CH_2$), 2.73–2.80 (m, 2H, CH_2CH_2Ph), 3.38–3.69 (m, 25H), 3.80–4.05 (m, 30H), 4.30–4.49 (m, 30H), 4.59–4.77 (m, 14H), 4.90–5.01 (m, 7H), 5.05–5.20 (m, 4H), 5.25–5.40 (m, 2H), 6.70–6.72 (m, 2H, Ph), 7.00–7.36 (m, 117H, Ph); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.0, 29.1–29.7, 31.9, 35.32, 35.34, 60.3, 60.6, 61.4, 64.56, 64.61, 65.8, 68.0, 68.1–69.9, 71.2–71.7, 72.3–73.4, 74.4–75.8, 78.3–79.7, 80.6–82.0, 98.1–98.6, 104.0, 114.2, 126.7–130.6, 137.7–139.1, 157.1. MALDI-TOF-MS: *m/z* calcd for $C_{229}H_{242}O_{43}$ Na: 3612.6; found 3612.3.

4.1.21. 6^{A}-*O*-(1-*O*-{4-[1-(β-D-Galactopyranside-1-yl)-1,4-dioxahexane-6-yl]phenyl}propane-3-yl)-β-cyclodextrin (5)

Compound **28** (72.5 mg, 0.020 mmol) was added to a solution of $Pd(OH)_2$ (104.9 mg, 0.67 mmol) in DMF (15 mL). Hydrogen was bubbled through the solution for 24 h. After the solvent was fil-

tered and evaporated under reduced pressure, the crude product was isolated by adsorbing on LH-20 followed by eluting with methanol to afford **5** (27.7 mg, 90%) as white crystals. ^{1}H NMR (D_2O): δ *1.77–1.95* (m, 2H, $CH_2CH_2CH_2$), 2.81–2.83 (m, 2H, CH_2Ph), 3.21–4.07 (m, 58H), 4.33 (d, J = 7.6 Hz, 1H, H-1), 4.84–4.98 (m, 7H, CyD-1), 6.74 (d, J = 7.8 Hz, 2H, Ph), 7.09 (d, J = 7.8 Hz, 2H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{61}H_{98}O_{43}Na$: 1541.8; found 1541.5.

4.1.22. Heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{A},6^{D}-bis-*O*-(1-*O*-{4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)-1,4-dioxahexane-6-yl]phenyl}propane-3-yl)-β-cyclodextrin (30)

Compound **26** (131.8 mg, 0.046 mmol) was added to a solution of potassium hydrate (316.5 mg, 5.64 mmol) in DMF (3 mL). After the reaction mixture was stirred for 30 min, the mixed sample was added to a solution of **24** (152.2 mg, 0.17 mmol) and tetra-*n*-butylammonium iodide (1.8 mg, 0.0049 mmol) in DMF (4 mL). After the reaction mixture was stirred for 48 h, the reaction was then quenched by the addition of water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane/MeOH, 2:12:1) to give **30** (18.1 mg, 9%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.85–1.88* (m, 4H, $CH_2CH_2CH_2$), 2.70–2.80 (m, 4H, CH_2CH_2Ph), 3.38–5.40 (m, 137H), 6.69–7.38 (m, 143H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{269}H_{288}O_{51}Na$: 4357.0; found 4356.1.

4.1.23. 6^{A},6^{D}-Bis-*O*-(1-*O*-{4-[1-(β-D-galactopyranside-1-yl)-1,4-dioxahexane-6-yl]phenyl}propane-3-yl)-β-cyclodextrin (7)

Compound **30** (16.1 mg, 0.0037 mmol) was added to a solution of $Pd(OH)_2$ (26.3 mg, 0.17 mmol) in DMF (8 mL). Hydrogen was bubbled through the solution for 24 h. After the solvent was filtered and evaporated under reduced pressure, the crude product was isolated by adsorbing on LH-20 followed by eluting with methanol to afford **7** (5.9 mg, 83%) as white crystals. ^{1}H NMR (D_2O): δ *1.76–1.85* (m, 4H, $CH_2CH_2CH_2$), 2.76 (m, 4H, CH_2Ph), 3.12–3.95 (m, 74H), 4.20 (m, 1H, H-1), 4.30 (m, 1H, H-1'), 4.59–4.96 (m, 7H, CyD-1), 6.63 (m, 2H, Ph), 6.84 (m, 2H, Ph), 7.04–7.14 (m, 4H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{80}H_{126}O_{51}Na$: 1925.7; found 1926.3.

4.1.24. Heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{A}-*O*-(1-*O*-{4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)-1,4,7-trioxanonane-9-yl]phenyl}propane-3-yl)-β-cyclodextrin or heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{D}-*O*-(1-*O*-{4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranside-1-yl)-1,4,7-trioxanonane-9-yl]phenyl}propane-3-yl)-β-cyclodextrin (29)

Compound **26** (9.1 mg, 0.0032 mmol) was added to a solution of potassium hydrate (22.1 mg, 0.39 mmol) in DMF (1 mL). After the reaction mixture was stirred for 30 min, the mixed sample was added to a solution of **25** (11.2 mg, 0.012 mmol) and tetra-*n*-butylammonium iodide (0.3 mg, 0.00081 mmol) in DMF (1.5 mL). After the reaction mixture was stirred for 48 h, the reaction was then quenched by the addition of water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 2:3) to give **29** (8.4 mg, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 2H, $CH_2CH_2CH_2$), 2.72–2.81 (m, 2H, CH_2CH_2Ph), 3.48–5.45 (m, 116H), 6.70–7.38 (m, 96H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{231}H_{246}O_{44}Na$: 3656.6; found 3656.9.

4.1.25. 6^{A}-*O*-(1-*O*-{4-[1-(β-D-Galactopyranside-1-yl)-1,4,7-trioxanonane-9-yl]phenyl}propane-3-yl)-β-cyclodextrin (6)

Compound **29** (8.4 mg, 0.0023 mmol) was added to a solution of $Pd(OH)_2$ (16.2 mg, 0.10 mmol) in DMF (6 mL). Hydrogen was bubbled through the solution for 24 h. After the solvent was filtered and evaporated under reduced pressure, the crude product was isolated by adsorbing on LH-20 followed by eluting with methanol to afford **6** (2.9 mg, 81%) as white crystals. ^{1}H NMR (D_2O): δ *1.08–1.18* (m, 2H), 1.76–1.93 (m, 2H, $CH_2CH_2CH_2$), 2.81 (m, 2H, CH_2Ph), 3.35–3.98 (m, 61H), 4.65–5.25 (m, 7H, CyD-1), 6.72 (d, J = 7.1 Hz, 2H, Ph), 7.07 (d, J = 7.8 Hz, 2H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{63}H_{102}O_{44}Na$: 1585.6; found 1585.9.

4.1.26. 4-Allyloxyphenylethyl 4-methoxybenzyl ether (31)

NaH (206.7 mg, 8.6 mmol) was added to a solution of **9** (337.5 mg, 1.89 mmol) in DMF (20 mL) at 0 °C. After the reaction mixture was stirred for 30 min, 4-methoxybenzyl chloride (310 μL, 2.28 mmol) was added. The resulting mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of a MeOH solution (30 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:10) to give **31** (548.6 mg, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.85 (t, J = 7.6 Hz, 2H, CH_2CH_2Ph), 3.62 (t, J = 7.6 Hz, 2H, CH_2CH_2Ph), 3.80 (s, 3H, CH_3), 4.45 (s, 2H, CH_3OPhCH_2), 4.51 (d, J = 5.5 Hz, 2H, $CH_2CH{=}CH_2$), 5.27 (dd, J = 1.4 Hz, J = 10.3 Hz, 1H, $CH{=}CH_aH_b$), 5.40 (dd, J = 1.4 Hz, J = 17.2 Hz, 1H, $CH{=}CH_aH_b$), 6.02–6.08 (m, 1H, $CH{=}CH_2$), 6.81–6.87 (m, 4H, Ph), 7.12 (d, J = 8.9 Hz, 2H, Ph), 7.23 (d, J = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.5 (CH_2CH_2Ph), 55.3 (CH_3), 68.8 (CH_2CH_2Ph), 71.2 ($CH_2CH{=}CH_2$), 72.6 (CH_3OPhCH_2), 113.8 (Ph), 114.6 (Ph), 117.5 ($CH{=}CH_2$), 129.2-131.2 (Ph), 133.5 ($CH{=}CH_2$), 157.1 (Ph), 159.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_3Na$: 321.1461; found: 321.1413.

4.1.27. [4-(4-Methoxybenzyloxyethyl)phenyl]-1-oxabutane-4-ol (32)

To a solution of **31** (935.9 mg, 3.14 mmol) in THF (10 mL) was added a 0.5 M 9-borabicyclo[3.3.1]nonane-THF solution (12 mL, 6 mmol) at 0 °C. After the reaction mixture was stirred for 21 h at room temperature, a 0.5 M NaOH aqueous solution (18.8 mL, 9.4 mmol) and 30% H_2O_2 aqueous solution (3.5 mL, 30.5 mmol) were added. After the reaction mixture was stirred for 4.5 h, the reaction was then quenched by adding water (50 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane, 1:1) to give **32** (877.6 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.03 (m, 2H, CH_2CH_2OH), 2.85 (t, J = 6.9 Hz, 2H, CH_2CH_2Ph), 3.62 (t, J = 6.9 Hz, CH_2CH_2Ph), 3.80 (s, 3H, CH_3), 3.85 (t, J = 5.5 Hz, 2H, CH_2OH), 4.10 (t, J = 6.2 Hz, 2H, $CH_2CH_2CH_2OH$), 4.44 (s, 2H, CH_3OPhCH_2), 6.83 (dd, J = 2.1 Hz, J = 6.2 Hz, 2H, Ph), 6.86 (dd, J = 2.1 Hz, J = 6.2 Hz, 2H, Ph), 7.12 (d, J = 8.9 Hz, 2H, Ph), 7.23 (d, J = 8.2 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 32.0 (CH_2CH_2OH), 35.4 (CH_2CH_2Ph), 55.2 (CH_3), 60.6 (CH_2OH), 65.9 ($CH_2CH_2CH_2OH$), 71.1 (CH_2CH_2Ph), 72.6 (CH_3OPhCH_2), 113.7 (Ph), 114.3 (Ph), 129.2–131.3 (Ph), 157.2 (Ph), 159.1 (Ph). HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_4Na$: 339.1567; found: 339.1539.

4.1.28. 4-Iodo-[4-(4-methoxybenzyloxyethyl)phenyl]-1-oxabutane (33)

To a solution of **32** (112.7 mg, 0.36 mmol) in DMF (3 mL) was added triphenylphosphine (377.1 mg, 1.44 mmol) and iodine

(399.5 mg, 1.57 mmol) at 40 °C under an argon atmosphere. After the reaction mixture was stirred for 2 h, the reaction was then quenched by adding water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane, 1:10) to give **33** (132.6 mg, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.26 (m, 2H, CH_2CH_2I), 2.85 (t, J = 7.6 Hz, 2H, CH_2CH_2Ph), 3.37 (t, J = 6.9 Hz, 2H, CH_2I), 3.62 (t, J = 6.9 Hz, 2H, CH_2CH_2Ph), 3.80 (s, 3H, CH_3), 4.01 (t, J = 5.5 Hz, 2H, $CH_2CH_2CH_2I$), 4.45 (s, 2H, CH_3OPhCH_2), 6.82 (dd, J = 2.1 Hz, J = 6.9 Hz, 2H, Ph), 6.87 (dd, J = 2.1 Hz, J = 6.9 Hz, 2H, Ph), 7.13 (d, J = 8.2 Hz, 2H, Ph), 7.23 (d, J = 8.9 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 2.6 (CH_2I), 33.0 (CH_2CH_2I), 35.4 (CH_2CH_2Ph), 55.3 (CH_3), 67.3 ($CH_2CH_2CH_2I$), 71.1 (CH_2CH_2Ph), 72.6 (CH_3OPhCH_2), 113.7 (Ph), 114.4 (Ph), 129.2–131.4 (Ph), 157.1 (Ph), 159.1 (Ph). HRMS (ESI): m/z calcd for $C_{19}H_{23}O_3INa$: 449.0584; found: 449.0593.

4.1.29. Heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{A}-*O*-{1-*O*-[4-(4-methoxybenzyloxyethyl)phenyl]-propane-3-yl}-β-cyclodextrin or heptaxis-(2,3-di-*O*-benzyl)-6^{B,C,E,F,G}-penta-*O*-benzyl-6^{D}-*O*-{1-*O*-[4-(4-methoxybenzyloxyethyl)phenyl]-propane-3-yl}-β-cyclodextrin (34)

Compound **26** (129.5 mg, 0.045 mmol) was added to a solution of potassium hydrate (399.2 mg, 7.1 mmol) in DMF (3 mL). After the reaction mixture was stirred for 2 h, the mixed sample was added to a solution of **33** (78.4 mg, 0.18 mmol) and tetra-*n*-butylammonium iodide (8.4 mg, 0.022 mmol) in DMF (3 mL). After the reaction mixture was stirred for 19.5 h, the reaction was then quenched by the addition of water (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/benzene, 1:15) to give **34** (82.4 mg, 58%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ *1.84–1.89* (m, 2H, $CH_2CH_2CH_2$), 2.47 (s, 1H, OH), 2.76–2.81 (m, 2H, CH_2CH_2Ph), 3.35–3.70 (m, 21H), 3.77 (s, 3H, CH_3), 3.79–4.04 (m, 28H), 4.28–5.39 (m, 46H), 6.75 (dd, J = 3.2 Hz, J = 8.0 Hz, 2H, Ph), 6.75 (d, J = 8.8 Hz, 2H, Ph), 7.01–7.25 (m, 99H, Ph); ^{13}C NMR ($CDCl_3$): δ 29.7, 35.5, 55.3, 61.5, 64.7, 68.1, 69.2, 69.3, 71.2–71.8, 72.4–73.3, 74.8–75.9, 77.2, 77.8, 78.6–79.0, 79.5–80.0, 80.7–81.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 113.6, 114.2, 126.8-130.7, 137.8-139.1, 157.0, 158.9. MALDI-TOF-MS: m/z calcd for $C_{194}H_{206}O_{38}Na$: 3166.4; found 3166.5.

4.1.30. 6^{A}-*O*-[1-*O*-(4-Hydroxyethylphenyl)-propane-3-yl]-β-cyclodextrin (35)

Compound **29** (76.6 mg, 0.024 mmol) was added to a solution of $Pd(OH)_2$ (93.7 mg, 0.60 mmol) in DMF (20 mL). Hydrogen was bubbled through the solution for 24 h. After the solvent was filtered and evaporated under reduced pressure, the crude product was isolated by adsorbing on HP-20 followed by eluting with methanol to afford **6** (20.5 mg, 64%) as white crystals. ^{1}H NMR (D_2O): δ *1.91–1.99* (m, 2H, $CH_2CH_2CH_2$), 2.89 (t, J = 7.7 Hz, 2H, CH_2Ph), 3.33–4.16 (m, 48H), 4.98–4.99 (m, 3H, CyD-1), 5.05 (d, J = 3.6 Hz, 1H, CyD-1), 5.06 (d, J = 3.6 Hz, 1H, CyD-1), 5.08 (d, J = 3.6 Hz, 1H, CyD-1), 5.09 (d, J = 3.6 Hz, 1H, CyD-1), 6.87 (d, J = 8.4 Hz, 2H, Ph), 7.22 (d, J = 8.6 Hz, 2H, Ph). MALDI-TOF-MS: m/z calcd for $C_{53}H_{84}O_{37}Na$: 1335.5; found 1335.6.

References and notes

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