

Syntheses of Glucose-Containing Lipid A Analogues and Their LPS-Antagonistic Activities

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Three anomeric pairs of lipid A-type disaccharides containing a glucose on their reducing end were synthesized, and their LPS-antagonistic activities were measured. The inhibitory activities (IC_{50}) on the LPS-induced TNFα production of these six compounds (**16**α, **16**β, **28**α, **28**β, **40**α, and **40**β) toward human whole blood cells were 0.35, 0.42, 2.37, 1.16, 2.89, and 7.70 nM, respectively.

The study of endotoxin, which was named by R. Pfeiffer in 1892,[1] has developed extensively[2] since Shiba and Kusumoto's[3] total synthesis of lipid A, a toxic component of endotoxin (lipopolysaccharide, LPS), existing in the outer surface membrane of Gram-negative bacteria. In an earlier investigation to search for drugs, lipid A-related compounds were investigated as anticancer drugs[2] by stimulating the immune system.[4] Conversely, a nontoxic natural lipid A-related compound (RsDPLA)[5] was recently isolated from *Rhodobacter sphaeroides* by an Eisai group. This compound, unlike lipid A, has a unique structural feature, that is, it contains a *cis*- or *trans*-alkene and a 3-oxoalkanamide in one of its long fatty acid chains, and does not show LPS-agonistic activity toward mouse macrophages.[6] Furthermore, the Eisai group found that many RsDPLA-related compounds having an olefinic double bond in their molecules behave as LPS antagonists toward both human and murine macrophages,[6] and E5564,[7] a compound related to RsDPLA, has been developed as a highly potent anti-septicemia drug.

The active structures of natural RsDPLA and synthetic RsDPLA-related compounds, such as E5564, are constructed with an β(1–6) linked glucosamine–glucosamine disaccharide moiety, and the configuration of the anomeric position of the reducing end is α without exception. Regarding this structure, we addressed two questions: (1) When one of the glucosamine parts or both glucosamine moieties are replaced with a glucose or two glucose molecules, respectively, do these compounds still retain the LPS-antagonistic activity? (2) When the configuration of the anomeric position of these unnatural glucose-containing compounds is β, do they still keep the LPS-antagonistic activity?

To examine these questions, at this time, some compounds in which the non-reducing part was the same glucosamine as that of E5564 and the other reducing end was a glucose were synthesized, and their biological activities as LPS-antagonists were measured. This paper describes the synthesis of six com-

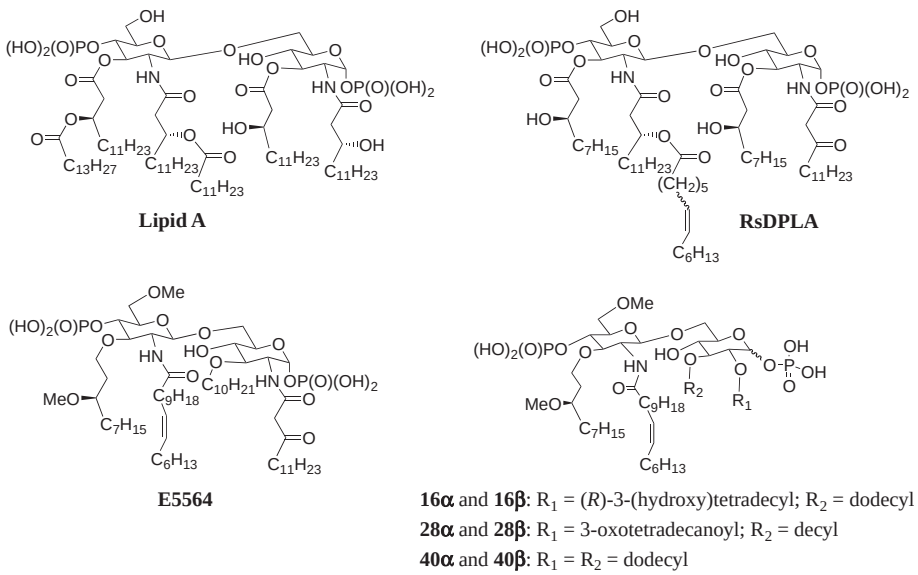

Fig. 1. Structures of Lipid A, RsDPLA, E5564, and six synthetic compounds.

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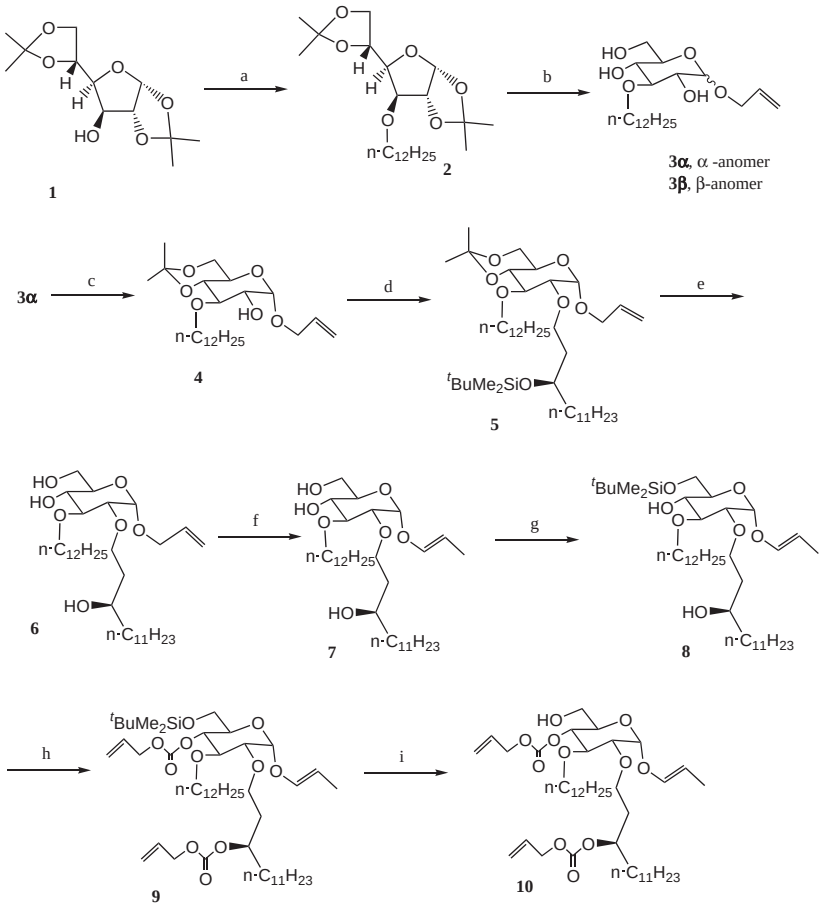
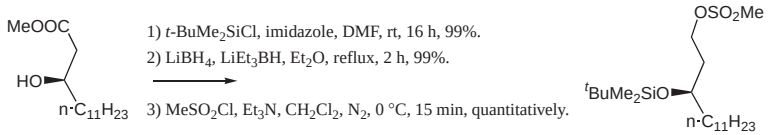
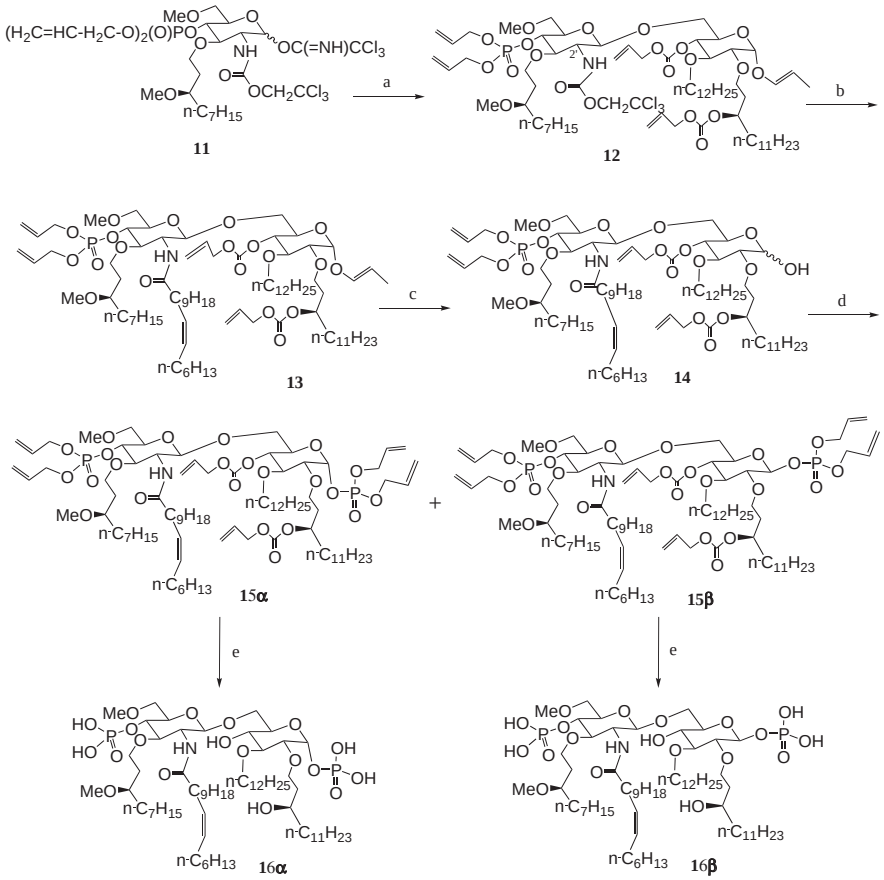


Scheme 1. Reagents and conditions: a) dodecyl methanesulfonate, NaH, DMF, rt, 16 h, 75%: b) allyl alcohol containing 2% HCl, reflux, 20 min, α:β = 10:1, 80% (**3α**), 8% (**3β**); c) 2,2-dimethoxypropane, *p*-TsOH, DMF, rt, 16 h, 81%; d) (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecyl methanesulfonate, NaH, DMF, rt, 16 h, then 50 °C, 1.5 h, 81%; e) *p*-TsOH, MeOH, rt, 1 h; 50%; f) Ir[$(C_8H_{12})(PMePh_2)_2$]PF_6 activated by H_2, THF, rt, 16 h, 100%; g) *t*-$BuMe_2SiCl$, DMAP, CH_2Cl_2, 75%; h) (1) triphosgene, pyridine, toluene, 0 °C, 10 min, then allyl alcohol, 0 °C, 1 h, 100%; i) aq 48% HF, CH_2Cl_2–MeCN (1:2), rt, 30 min, 67%.



pounds (**16α**, **16β**, **28α**, **28β**, **40α**, and **40β**) and their LPS-antagonistic activities toward human whole blood cells,[8] C3H/HeN mice[9] and mouse peritoneal resident macrophages.[10]

Synthesis. Firstly, compounds **16α** and **16β** were synthesized from both compound **10** obtained from diacetone D-glucose **1** and the known compound **11**,[7] reported by an Eisai group. The diacetone D-glucose **1** was alkylated with *n*-dodecyl methanesulfonate in *N*,*N*-dimethylformamide (DMF) using sodium hydride as a base to give dodecyl ether **2**. The furanoside **2** was converted to allyl D-pyranoside **3** as a 10:1 anomeric mixture by heating in allyl alcohol containing hydrochloric acid. The separated α-anomer **3α** chromatographically was used for the synthesis of **10** (Scheme 1). The 4,6-diol part of **3α** was protected with 2,2-dimethoxypropane using *p*-toluenesulfonic acid as a catalyst to yield isopropylidene compound **4**. The C-2 free alcohol of **4** was alkylated with (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecyl methanesulfonate in DMF using sodium hydride as a base to afford **5**. The reagent (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecyl methanesulfonate was obtained from methyl (*R*)-3-hydroxytetradecanoate in three steps: 1) silylation of C-3 alcohol with *tert*-butyldimethylsilyl chloride and imidazole, 2) reduction of methyl ester with $LiBH_4$–$LiEt_3BH$, and finally 3) mesylation of the resulting C-1 alcohol by methanesulfonyl chloride and triethylamine in methylene chloride. Both 4,6-*O*-isopropylidene and the *tert*-butyldimethylsilyl group on the C-2 side chain were deprotected by a treatment with *p*-toluenesulfonic acid in methanol to afford triol **6**. At this stage, the anomeric allyl compound **6** was converted to vinyl ether **7** by a treatment with (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate (Ir[$(C_8H_{12})(PMePh_2)_2$]PF_6) activated by hydrogen in order to distinguish it from the allyloxycarbonyl groups introduced as protecting groups in the latter stage. The primary C-6 alcohol of **7** was reprotected with the *tert*-butyldimethylsilyl group to afford **8**. A treatment of the secondary alcohols of **8** with triphosgene using pyridine as a base,

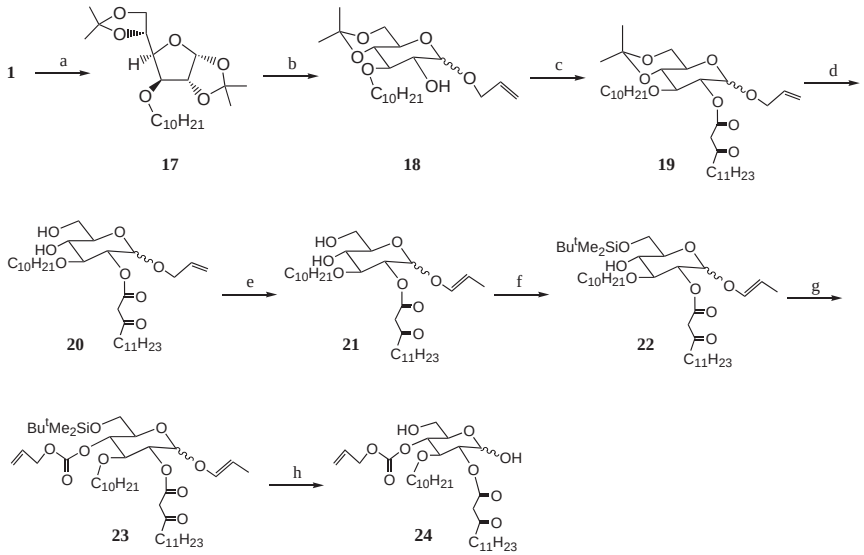


Scheme 2. Reagents and conditions: a) **10**, TMSOTf, AgOTf, MS 4A, CH_2Cl_2, rt, 16 h; b) 1) Zn, AcOH–H_2O (3:2), rt, 3 h, 2) *Z*-11-octadecenoyl chloride, $NaHCO_3$, THF–H_2O (3:1), rt, 2 h, three steps 45%; c) aq 48% HF, CH_2Cl_2–CH_3CN (1:2), rt, 16 h, 67%; d) *i*-$Pr_2NP(OCH_2CH{=}CH_2)_2$, 1*H*-tetrazole, Na_2SO_4, CH_2Cl_2, rt, 30 min, then aq 30% H_2O_2, THF, 0 °C, 45 min, 49% (**15α**), 50% (**15β**); e) $(PPh_3)_4Pd$, PPh_3, Et_3N–HCOOH, THF, under N_2, 55 °C, 16 h, 40% (**16α**), 37% (**16β**).

and then allyl alcohol, afforded di-alloc compound **9**, which was further converted to free C-6 alcohol **10** using aqueous 48% hydrofluoric acid (aq 48% HF).

The treatment of alcohol **10** and imidate **11** with trimethylsilyl trifluoromethanesulfonate and silver trifluoromethanesulfonate in methylene chloride gave β(1–6) disaccharide **12**. The deprotection of the trichloroethoxycarbonyl group from the C-2′ trichloroethoxycarbonylamino group of **12** with Zn–acetic acid and the successive acylation of the resulting amine with (*Z*)-11-octadecenoyl chloride–aq $NaHCO_3$ in tetrahydrofuran (THF)–water gave amide **13**. The treatment of **13** with aq 48% HF afforded an anomeric mixture **14**, which was further converted to an anomeric mixture of phosphates (**15α** and **15β**) through phosphite by the treatment of diallyl diisopropylphosphoramidite and 1*H*-tetrazole, and then aqueous 30% hydrogen peroxide. Both α- and β-anomers, **15α** and **15β**, were separated chromatographically. The treatment of each anomer, **15α** and **15β**, with tetrakis(triphenylphosphine)palladium(0), triphenylphosphine, and triethylamine–formic acid in THF at 55 °C for 16 hours gave **16α** and **16β**, respectively. Compound **16β** was gradually decomposed during long-term storage in a freezer (Scheme 2).

Secondly, compounds **28α** and **28β** were synthesized from both compound **24** obtained from diacetone D-glucose **1** and the known compound **11** reported by an Eisai group.[7] The diacetone D-glucose **1** was alkylated with *n*-decyl methanesulfonate in DMF using sodium hydride as a base to give decyl ether **17**. The furanoside **17** was converted to allyl 4,6-*O*-isopropylidene-D-pyranoside **18** as a 3:1 anomeric mixture by refluxing in allyl alcohol containing hydrochloric acid, and a successive treatment with 2,2-dimethoxypropane using *p*-toluenesulfonic acid as a catalyst. The C-2 free alcohol of an anomeric mixture **18** was acylated with (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecanoic acid in CH_2Cl_2 using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide as a dehydration reagent to give an anomeric mixture **19**. The 4,6-*O*-isopropylidene of **19** was deprotected by a treatment with *p*-toluenesulfonic acid in methanol to afford an anomeric mixture of diol **20**. At this stage, the anomeric allyl compound **20** was converted to an anomeric mixture of vinyl ether **21** by a treatment with $Ir[(C_8H_{12})(PMePh_2)_2]PF_6$ activated by hydrogen in order to distinguish it from the allyloxycarbonyl groups introduced as protecting groups in a latter stage. The primary C-6 alcohol of **21** was reprotected with the *tert*-butyldimethylsilyl group to convert to an anomeric mixture **22**. A treatment of the secondary alcohol of **22** with triphosgene and allyl alcohol using pyridine as a base afforded an anomeric mixture of alloc compound **23**, which was further converted to an anomeric mixture of free C-1 and C-6 alcohol **24** by treating with aq 48% HF at room temperature for 1.5 days. (Scheme 3).



Scheme 3. Reagents and conditions: a) decyl methanesulfonate, NaH, DMF, rt, 16 h, 98%; b) allyl alcohol containing 2% HCl, reflux, 25 min, 80%; c) 3-oxotetradecanoic acid, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, HCl, CH_2Cl_2, rt, 1 h, 80%; d) *p*-TsOH·H_2O, MeOH, rt, 3 h, 59%; e) Ir[$(C_8H_{12})(PMePh_2)_2$]PF_6 activated by H_2, THF, 16 h, 100%; f) ^{t}BuMe$_2$SiCl, DMAP, CH_2Cl_2, 16 h, 100%; g) triphosgene, pyridine, toluene, 0 °C, 15 min, then CH_2=$CHCH_2OH$, 0 °C, 1 h, 68%; h) aq 48% HF, MeCN–CH_2Cl_2 (2:1), rt, 1.5 days, 58%.

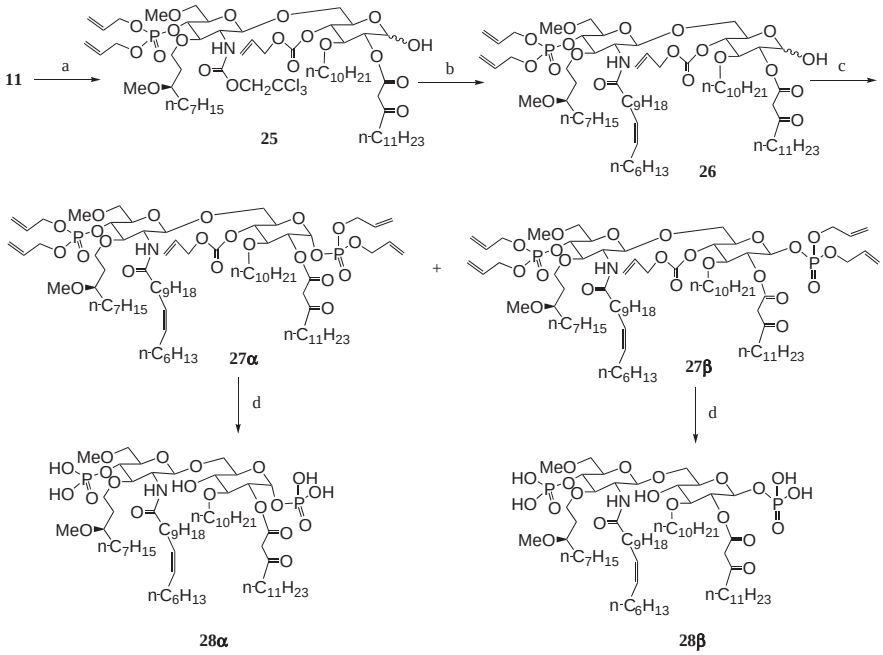
The treatment of alcohol **24** and imidate **11** with trimethylsilyl trifluoromethanesulfonate and silver trifluoromethanesulfonate in methylene chloride gave an anomeric mixture on the reducing end of β(1–6) disaccharide **25** without reacting with the free anomeric position of **24**. Deprotection of the trichloroethoxycarbonyl group of the C-2′ trichloroethoxycarbonylamino group of **25** with Zn–acetic acid and successive acylation of the resulting amine with (*Z*)-11-octadecenoyl chloride–aq $NaHCO_3$ in THF–water gave amide **26** without reacting with the free anomeric position of **25**. The treatment of **26** with diallyl diisopropylphosphoramidite and 1*H*-tetrazole, and then aq 30% hydrogen peroxide afforded an anomeric mixture of phosphates **27**α and **27**β. The mixture of **27**α and **27**β was separated chromatographically. The treatment of each anomer, **27**α and **27**β, with $(PPh_3)_4Pd$, PPh_3, and Et_3N–HCOOH in THF at 55 °C for 16 hours gave **28**α and **28**β, respectively (Scheme 4).

Thirdly, compounds **40**α and **40**β were synthesized from both compound **36**, obtained from allyl α-D-glucoside **29**, and the known compound **11**, reported by an Eisai group.[7] The allyl α-D-glucoside **29**[11] was converted to allyl 4,6-*O*-isopropylidene-α-D-pyranoside **30** by reacting with 2,2-dimethoxypropane using *p*-toluenesulfonic acid as a catalyst. The C-2 and C-3 free alcohols of **30** were alkylated with dodecyl iodide and NaH as a base to afford **31**. The 4,6-*O*-isopropylidene of **31** was deprotected by a treatment with *p*-toluenesulfonic acid in methanol to afford diol **32**. At this stage, the allyl compound **32** was converted to vinyl ether **33** by a treatment with Ir[$(C_8H_{12})(PMePh_2)_2$]PF_6 activated by hydrogen in order to distinguish it from the allyloxycarbonyl groups introduced as protecting groups in a latter stage. The primary C-6 alcohol of **33** was reprotected to be *tert*-butyldimethylsilyl ether **34**. A treatment of the secondary alcohol of **34** with triphosgene and allyl alcohol using pyridine as a base afforded allyloxycarbonyl compound **35**, which was further converted to an anomeric mixture of free C-1 and C-6 alcohols **36** by treating with aq 48% HF at room temperature for 16 hours. (Scheme 5).

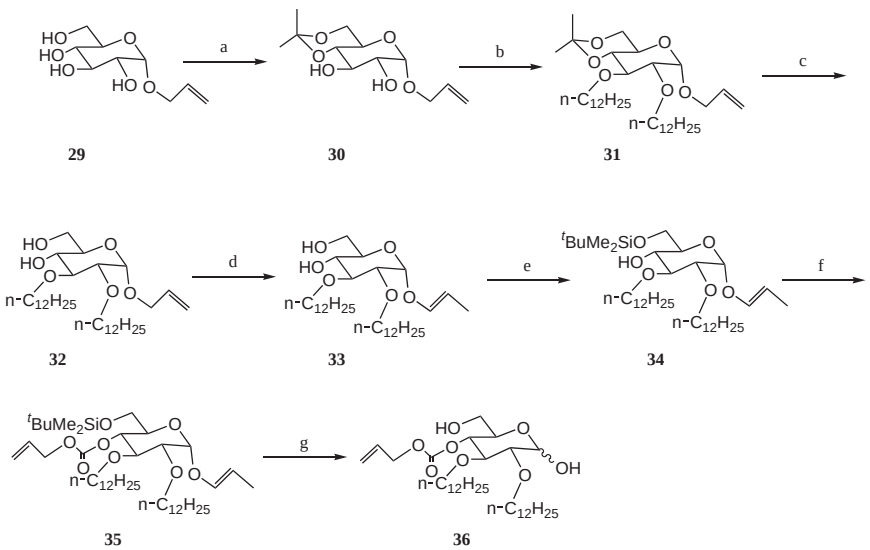
The treatment of alcohol **36** and imidate **11** with trimethylsilyl trifluoromethanesulfonate and silver trifluoromethanesulfonate in methylene chloride gave an anomeric mixture of β(1–6) disaccharide **37** without reacting with the free anomeric position of **36**. Deprotection of the C-2 trichloroethoxycarbonyl group of **37** with Zn–acetic acid, and successive acylation of the resulting amine with (*Z*)-11-octadecenoyl chloride–aqueous $NaHCO_3$ in THF–water gave amide **38** without reacting with the free anomeric position of **37**. The treatment of **38** with diallyl diisopropylphosphoramidite and 1*H*-tetrazole, and then aq 30% hydrogen peroxide converted to an anomeric mixture of phosphates **39**α and **39**β. The mixture of **39**α and **39**β was separated chromatographically. The treatment of each anomer, **39**α and **39**β, with $(PPh_3)_4Pd$, PPh_3, and Et_3N–HCOOH in THF at 55 °C for 16 hours gave **40**α and **40**β, respectively (Scheme 6).

Thus, we could synthesize six disaccharides (**16**α, **16**β, **28**α, **28**β, **40**α, and **40**β).

Biological Activity. The inhibitory activity on LPS-induced TNFα production, LPS-antagonistic activity, of three pairs of synthetic compounds (**16**α and **16**β, **28**α and **28**β, and **40**α and **40**β) was investigated in vitro using human whole blood cells. The IC_{50} values (nM) of these six compounds (**16**α, **16**β, **28**α, **28**β, **40**α, and **40**β) toward human whole blood cells were 0.35, 0.42, 2.37, 1.16, 2.89, and 7.70, respectively. The activities of these compounds were generally strong, except for **40**β. The activity of the unknown type β-anomer **40**β in nature was almost one-third compared with its corresponding α-anomer **40**α. However, astonishingly, the activity of β-anomer **28**β was two-times stronger than that of natural type **28**α, and **16**α and **16**β had almost the same lev-



Scheme 4. Reagents and conditions: a) **24**, TMSOTf, AgOTf, MS 4A, CH_2Cl_2, 24 °C, 97%; b) 1) Zn, AcOH–THF (1:1), rt, 3 h; 2) (*Z*)-11-octadecenoyl chloride, $NaHCO_3$, THF–H_2O (3:1), rt, 2 h, 55%; c) *i*-$Pr_2NP(OCH_2CH{=}CH_2)_2$, 1*H*-tetrazole, Na_2SO_4, CH_2Cl_2, rt, 30 min, then aq 30% H_2O_2, THF, rt, 30 min, 22% (**27*α***), 20% (**27*β***); d) $(PPh_3)_4Pd$, PPh_3, Et_3N–HCOOH, THF, under N_2, 55 °C, 16 h, 59% (**28*α***), 72% (**28*β***).

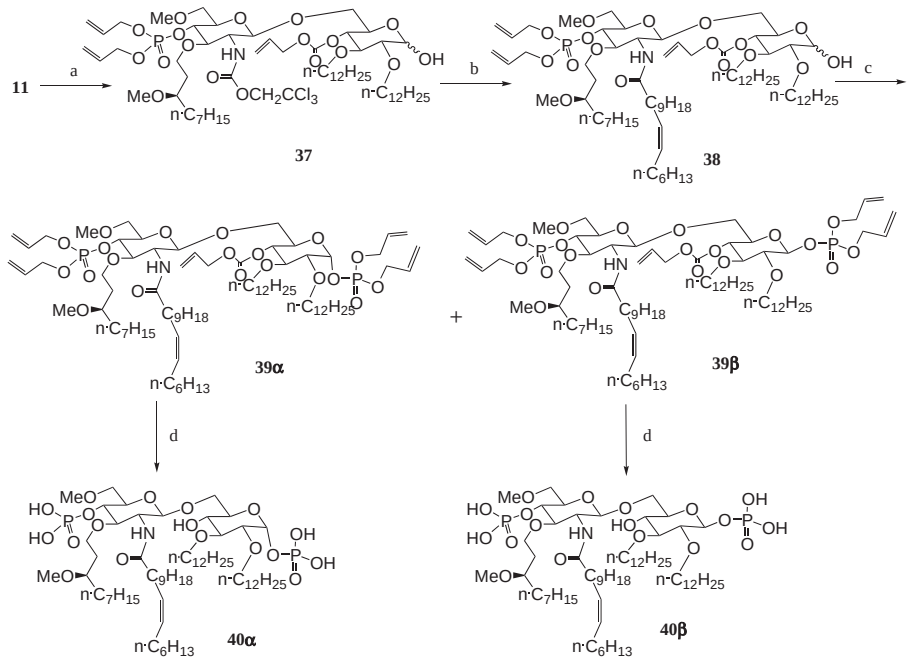


Scheme 5. Reagents and conditions: a) 2,2-dimethoxypropane, *p*-TsOH, DMF, rt, 16 h, 65%; b) dodecyl iodide, NaH, DMF, rt, 16 h, 98%; c) *p*-TsOH, MeOH, rt, 30 min, 54%; d) $Ir[(C_8H_{12})(PMePh_2)_2]PF_6$ activated by H_2, THF, N_2, rt, 16 h, 100%; e) *t*-$BuMe_2SiCl$, DMAP, CH_2Cl_2, 95%; f) triphosgene, pyridine, toluene, 0 °C, 10 min, then allyl alcohol, 0 °C, 1 h, 100%; g) aq 48% HF, CH_2Cl_2–MeCN (1:2), rt, 16 h, 74%.

el of activity.

Also, the inhibitory activity on TNF*α* production toward galactosamine loaded C3H/HeN mice of compounds **28*α*** and **28*β*** was measured, and the activities were sufficiently strong. The values of these compounds were 1.05 and 3.10 nM, respectively. The natural type *α*-anomer was three-times stronger than the unknown type *β*-anomer in nature. Thus, the LPS-antagonistic activity toward human whole blood and the inhibitory activity on TNF*α* production toward galactosamine loaded C3H/HeN mice of compounds **28*α*** and **28*β*** were not in parallel.

Also, the inhibitory activities (IC_{50}) on LPS-induced TNF*α* production of a pair of synthetic compounds, **40*α*** and **40*β***, toward mouse peritoneal resident macrophages were 64 and 58 nM, respectively. The configuration of the anomeric position on the reducing glucose had no influence on the activity.



Scheme 6. Reagents and conditions: a) **36**, TMSOTf, AgOTf, MS 4A, CH_2Cl_2, rt, 16 h, 96%; b) 1) Zn, AcOH–THF (1:1), rt, 2.5 h, 2) (*Z*)-11-octadecenoyl chloride, $NaHCO_3$, THF–H_2O (3:1), rt, 1 h, 65%; c) *i*-$Pr_2NP(OCH_2CH{=}CH_2)_2$, 1*H*-tetrazole, Na_2SO_4, CH_2Cl_2, rt, 30 min, then aq 30% H_2O_2, THF, 0 °C, 20 min, 25% (**39*α***), 26% (**39*β***); d) $(PPh_3)_4Pd$, PPh_3, Et_3N–HCOOH, THF, under N_2, 55 °C, 16 h, 54% (**40*α***), 52% (**40*β***).

As a result, even for un-natural type β-anomers, it may be true that they are still sufficiently active, or even stronger than the corresponding α-anomers in LPS-antagonistic activity toward human whole blood cells, C3H/HeN mice and mouse peritoneal resident macrophages.[12]

Usually, lipid A analogs having six fatty acid chains show LPS-agonistic (endotoxic) activity toward both human U-937 and mouse peritoneal resident macrophages, and lipid IVa[13] having four fatty acid chains shows LPS-antagonistic activity toward human blood cells, and adversely endotoxic activity toward mouse peritoneal resident macrophages. This fact shows, interestingly enough, that a difference exists in molecular recognition between human and mouse LPS receptors.[14] The synthetic compounds (**16*α***, **16*β***, **28*α***, **28*β***, **40*α***, and **40*β***), this time, showed LPS-antagonistic activity toward both human and mouse blood cells, as anticipated from E5564. This tendency was the same activity as that for a nontoxic natural RsDPLA[5] having a cis-double bond in one of the fatty acid chains isolated from *Rhodobacter sphaeroides*.

Experimental

^{1}H NMR spectra were recorded with JEOL-GSX 400 and JNM-ECT 500 spectrometers using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JNM-ECT (500 MHz) at 125 MHz. IR absorption spectra were measured with an IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-700 mass spectrometer. The separation of compounds by column chromatography was done with silica-gel 60 (230–400 mesh ASTM) under a slightly elevated pressure (111–182 kPa) for easy elution. Analytical chromatography was performed on Merck Art 5715 silica-gel 60-F_{245} plates. Commercially available anhydrous THF and dichloromethane were used for the reactions. DMF and pyridine were dried by storage over 4 Å molecular sieves.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)tetradecyl methanesulfonate. (a) To a solution of (*R*)-methyl 3-hydroxytetradecanoate (10.00 g, 38.70 mmol) in DMF (25 mL) were added *tert*-butyldimethylsilyl chloride (9.80 g, 58.05 mmol) and imidazole (6.50 g, 95.48 mmol). The mixture was stirred for 16 h at room temperature, and diluted with EtOAc, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (19:1) gave (*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)tetradecanoate (14.3 g, 99%) as an oil.

(b) To a suspension of $LiBH_4$ (1.76 g, 80.8 mmol) in dry Et_2O (150 mL) was added a solution of the above-obtained (*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)tetradecanoate (25.00 g, 67.1 mmol) in dry Et_2O (50 mL) at room temperature under N_2. To this solution was added a solution of $LiEt_3BH$ (1 M in THF, 6.56 mL). The mixture was refluxed for 2 h. After cooling, the mixture was poured into sat. aq NH_4Cl (150 mL) at ice cooling temperature, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (7:1) gave (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecanol (22.9 g, 99%) as an oil. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.08 (3H, s), 0.09 (3H, s), 0.88 (3H, t, $J = 6.6$ Hz), 0.90 (9H, s), 1.26 (18H, brs), 1.51–1.59 (2H, m), 1.64 (1H, m), 1.82 (1H, m), 2.49 (1H, brs, OH), 3.72 (1H, m), 3.84 (1H, m), 3.92 (1H, m).

(c) To a solution of the above-obtained (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecanol (1.79 g, 5.19 mmol) and Et_3N (630 mg, 6.23 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of methanesulfonyl chloride (720 mg, 6.28 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under nitrogen. After stirring for 15 min, the mixture was diluted with CH_2Cl_2, and washed with H_2O, sat. aq $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered.

The filtrate was concentrated to give the title compound quantitatively. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 0.89 (3H, t, $J = 6.6$ Hz), 1.26 (18H, brs), 1.45–1.48 (2H, m), 1.85 (1H, m), 1.92 (1H, m), 3.00 (3H, s), 3.82 (1H, m), 4.29–4.35 (2H, m). Anal. Calcd for $C_{21}H_{46}O_4SSi$: C, 59.66; H, 10.97; S, 7.59%. Found: C, 59.53; H, 10.61; S, 7.85%.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-dodecyl-α-D-glucofuranose (2). To a solution of **1** (13.02 g, 50.0 mmol) in DMF (50 mL) and dodecyl methanesulfonate (13.20 g, 50.0 mmol) was added NaH (55% oil dispersion, 2.88 g, 60.0 mmol) at 0 °C. After stirring for 15 min, the mixture was stirred for 16 h at room temperature, quenched with MeOH, diluted with EtOAc, which was washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (9:1) gave **2** (15.50 g, 75%) as an oil. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (18H, brs), 1.32 (3H, s), 1.35 (3H, s), 1.43 (3H, s), 1.50 (3H, s), 1.52–1.57 (2H, m), 3.51 (1H, m), 3.59 (1H, m), 3.85 (1H, d, $J = 2.9$ Hz), 3.98 (1H, m), 4.06–4.14 (3H, m), 4.31 (1H, m), 4.52 (1H, d, $J = 3.7$ Hz), 5.88 (1H, d, $J = 3.7$ Hz).

Allyl 3-*O*-dodecyl-α,β-D-glucopyranoside (3α, 3β). A solution of **2** (900 mg, 2.160 mmol) in allyl alcohol (10 mL) containing 2% HCl was refluxed for 20 min. The reaction mixture was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (1:1, then 1:3) gave **3α** (674 mg, 80%) as a solid and **3β** (64 mg, 8%) as an oil. Physical data of **3α**: $R_f = 0.230$ (cyclohexane–EtOAc (1:1)). mp 72–73.5 °C (needles). IR ν_{max} (KBr) 3306, 2920, 2852 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (18H, brs), 1.59–1.64 (2H, m), 2.19 (1H, d, $J = 9.5$ Hz, OH), 2.24 (1H, t, $J = 6.3$ Hz, OH), 2.79 (1H, d, $J = 2.9$ Hz, OH), 3.45 (1H, d, $J = 8.8$ Hz), 3.50–3.61 (2H, m), 3.64–3.71 (2H, m), 3.80–3.86 (2H, m), 3.93 (1H, m), 4.04 (1H, m), 4.23 (1H, m), 4.90 (1H, d, $J = 3.7$ Hz), 5.22–5.34 (2H, m), 5.92 (1H, m). Anal. Calcd for $C_{21}H_{40}O_6$: C, 64.92; H, 10.38%. Found: C, 64.96; H, 10.17%. Physical data of **3β**: $R_f = 0.308$ (cyclohexane–EtOAc (1:1)). 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 7.0$ Hz), 1.26 (18H, brs), 1.50–1.61 (2H, m), 3.46–3.53 (10H, m), 5.07 (1H, d, $J = 5.1$ Hz), 5.21–5.42 (2H, m), 5.93 (1H, m).

Allyl 3-*O*-dodecyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (4). A solution of **3α** (470 mg, 1.210 mmol) in DMF (1 mL) and 2,2-dimethoxypropane (1 mL) containing *p*-TsOH·H_2O (20 mg) was stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (4:1, then 2:1) gave **4** (420 mg, 81%) as an oil. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (18H, brs), 1.41 (3H, s), 1.49 (3H, s), 1.53–1.60 (2H, m), 2.31 (1H, d, $J = 7.3$ Hz, OH), 3.46–3.85 (8H, m), 4.04 (1H, m), 4.21 (1H, m), 4.92 (1H, d, $J = 3.7$ Hz), 5.22–5.34 (2H, m), 5.93 (1H, m).

Allyl 2-*O*-[(*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecyl]-3-*O*-dodecyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (5). To a solution of **4** (4.91 g, 11.45 mmol) in DMF (30 mL) were added (*R*)-3-(*tert*-butyldimethylsilyloxy)dodecyl methanesulfonate (5.37 g, 12.71 mmol) and NaH (55% oil dispersion, 1.50 g, 34.38 mmol). The mixture was stirred for 16 h at room temperature, and then for 1.5 h at 50 °C, and diluted with EtOAc, which was washed with ice water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (9:1) gave **5** (7.01 g, 81%) as an oil. IR ν_{max} (film) 2925, 2856, 1464 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.04 (6H, s), 0.86–0.89 (15H, m, containing 9H, s, at δ 0.88 ppm), 1.26 (38H, brs), 1.40 (3H, s), 1.48 (3H, s), 1.48–1.55 (2H, m), 1.70–1.77 (2H, m), 3.29 (1H, m), 3.45–3.78 (9H, m), 3.84 (1H, m), 4.04 (1H, m), 4.17 (1H, m), 4.91 (1H, d, $J = 3.7$ Hz), 5.20–5.34 (2H, m), 5.92 (1H, m). FABMS (positive-ion) m/z 755 $[M + H]^+$, 777 $[M + Na]^+$ (on addition of NaI). HRFABMS Calcd for $C_{44}H_{86}O_7SiNa$: 777.6040. Found: 777.5994.

Allyl 3-*O*-dodecyl-2-*O*-[(*R*)-3-hydroxytetradecyl]-α-D-glucopyranoside (6). To a solution of **5** (965 mg, 1.287 mmol) in MeOH (20 mL) was added TsOH·H_2O (50 mg, 0.263 mmol). The mixture was stirred for 40 min at room temperature, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (1:1), and then EtOAc gave **6** (386 mg, 50%) as a solid. IR ν_{max} (KBr) 3400–3260, 2920, 2850 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) 0.86–0.89 (6H, m), 1.26 (36H, brs), 1.41–1.73 (6H, m), 2.07 (1H, brs, OH), 2.60 (1H, brs, OH), 2.96 (1H, brs, OH), 3.30 (1H, m), 3.50–3.89 (10H, m), 4.04 (1H, m), 4.20 (1H, m), 5.00 (1H, m), 5.22–5.34 (2H, m), 5.95 (1H, m). FABMS (positive-ion) m/z 599 $[M - H]^+$, 601 $[M + H]^+$, 623 $[M + Na]^+$. HRFABMS Calcd for $C_{35}H_{68}O_7Na$: 623.4862. Found: 623.4861.

(*E*)-1-Propenyl 3-*O*-dodecyl-2-*O*-[(*R*)-3-hydroxytetradecyl]-α-D-glucopyranoside (7). To a solution of **6** (381 mg, 0.634 mmol) in dry THF (5 mL) was added (1,5-cyclooctadiene)bis-(methyldiphenylphosphine)iridium(I) hexafluorophosphate (5 mg). The atmosphere of the flask bottle was replaced with nitrogen, and then hydrogen to activate the iridium complex. After the red iridium complex turned colorless in solution upon stirring for about 10 seconds under a H_2 atmosphere, the hydrogen was replaced again by nitrogen. The solution was stirred for 16 h at room temperature, and concentrated in vacuo to give **7** (381 mg, 100%) as a solid. IR ν_{max} (KBr) 3411 (br), 2920, 2850, 1679 (w), 1468 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (36H, brs), 1.41–1.73 (9H, m), 1.86 (1H, brs, OH), 2.45 (1H, brs, OH), 2.72 (1H, brs, OH), 3.32 (1H, dd, $J = 3.7$, 9.5 Hz), 3.49–3.92 (10H, m), 5.16–5.23 (2H, m), 6.19 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 601 $[M + H]^+$, 623 $[M + Na]^+$. HRFABMS Calcd for $C_{35}H_{68}O_7Na$: 623.4862. Found: 623.4880.

(*E*)-1-Propenyl 6-*O*-*tert*-butyldimethylsilyl-3-*O*-dodecyl-2-*O*-[(*R*)-3-hydroxytetradecyl]-α-D-glucopyranoside (8). To a solution of **7** (747 mg, 1.243 mmol) in CH_2Cl_2 (15 mL) were added *tert*-$BuMe_2SiCl$ (225 mg, 1.492 mmol) and DMAP (182 mg, 1.492 mmol). The solution was stirred for 16 h at room temperature. The mixture was directly chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (9:1, and then 2:1) gave **8** (670 mg, 75%) as a powder. IR ν_{max} (KBr) 3226, 2925, 2853, 1749, 1467 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.88 (3H, t, $J = 6.6$ Hz), 0.90 (9H, s), 1.26 (36H, brs), 1.40–1.73 (7H, m, containing 3H, dd, $J = 1.5$, 6.6 Hz, at δ 1.55 ppm), 2.74 (1H, brs, OH), 2.81 (1H, brs, OH), 3.30 (1H, m), 3.51–3.87 (10H, m), 5.14 (1H, d, $J = 3.7$ Hz). FABMS (positive-ion) m/z 715 $[M + H]^+$, 737 $[M + Na]^+$. HRFABMS Calcd for $C_{41}H_{82}O_7SiNa$: 737.5728. Found: 737.5730.

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-3-*O*-dodecyl-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-α-D-glucopyranoside (9). To a solution of **8** (659 mg, 0.921 mmol) in toluene (20 mL) and pyridine (1.57 g) was added triphosgene (623 mg, 2.099 mmol) at 0 °C. After stirring for 10

min, allyl alcohol (1.88 g) was added to this solution. The mixture was stirred for 1 h at 0 °C, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (14:1) gave **9** (813 mg, 100%) as an oil. IR ν_{max} (film) 2927, 2856, 1749, 1680 (w), 1464, 1371 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.86–0.90 (15H, m, containing 9H, s, at δ 0.88 ppm), 1.25 (36H, brs), 1.46–1.63 (7H, m, containing 3H, dd, $J = 2.2$, 6.6 Hz, at δ 1.54 ppm), 1.88–1.91 (2H, m), 3.35 (1H, m), 3.53 (1H, m), 3.65–3.80 (7H, m), 4.59–4.65 (4H, m), 4.71 (1H, t, $J = 9.9$ Hz), 4.78 (1H, m), 5.09 (1H, d, $J = 3.7$ Hz), 5.18 (1H, m), 5.25–5.39 (4H, m), 5.89–5.98 (2H, m), 6.17 (1H, qd, $J = 2.2$, 12.5 Hz). FABMS (positive-ion) m/z 883 $[M + H]^+$, 905 $[M + Na]^+$. HRFABMS Calcd for $C_{49}H_{90}O_{11}SiNa$: 905.6150. Found: 905.6188.

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-3-*O*-dodecyl-α-D-glucopyranoside (10). To a solution of **9** (840 mg, 0.951 mmol) in CH_2Cl_2 (5 mL) and MeCN (10 mL) were added silica-gel powder (150 mg) and aq 48% HF (100 mg). The mixture was stirred for 13 min at room temperature, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (2:1) gave **10** (485 mg, 67%) as an oil. IR ν_{max} (film) 3527 (br), 2925, 2854, 1747, 1679 (w) cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) 0.88 (6H, t, $J = 6.6$ Hz), 1.25 (36H, brs), 1.50–1.65 (7H, m, containing 3H, dd, $J = 1.5$, 6.6 Hz, at δ 1.55 ppm), 1.87–1.92 (2H, m), 2.33 (1H, brs, OH), 3.37 (1H, dd, $J = 2.9$, 9.5 Hz), 3.55–3.81 (8H, m), 4.60–4.67 (4H, m), 4.72 (1H, m), 4.80 (1H, m), 5.13 (1H, d, $J = 3.7$ Hz), 5.18 (1H, qd, $J = 6.6$, 12.5 Hz), 5.25–5.40 (4H, m), 5.89–5.98 (2H, m), 6.16 (1H, qd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 768 $[M + H]^+$, 791 $[M + Na]^+$. HRFABMS Calcd for $C_{43}H_{76}O_{11}Na$: 791.5286. Found: 791.5281.

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(trichloroethoxycarbonyl)amino]-β-D-glucopyranosyl}-3-*O*-dodecyl-α-D-glucopyranoside (12). A solution of **10** (460 mg, 0.598 mmol) and imidate **11** (606 mg, 0.718 mmol) in CH_2Cl_2 (17 mL) cotaining MS 4A (1.4 g) was stirred for 20 min at room temperature under nitrogen. To this mixture were added AgOTf (310 mg, 1.207 mmol) and TMSOTf (27 mg, 0.121 mmol). This mixture was stirred for 16 h at room temperature under nitrogen, and diluted with CH_2Cl_2, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (2:1) gave **12** (867 mg, 100%) as a gum. IR ν_{max} (film) 3400–3080 (w), 2927, 2856, 1745 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (9H, t, $J = 6.6$ Hz), 1.25–1.30 (48H, m), 1.38–1.75 (9H, m), 1.85–1.90 (2H, m), 3.23–3.80 (22H, m, containing two 3H, s, at δ 3.28 and 3.38 ppm), 4.04 (1H, d, $J = 11.7$ Hz), 4.26 (1H, dd, $J = 9.5$, 18.3 Hz), 4.51–4.85 (12H, m), 5.10 (1H, d, $J = 3.7$ Hz), 5.16 (1H, m), 5.23–5.40 (8H, m), 5.89–5.99 (4H, m), 6.16 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 1470 $[M + Na, {}^{35}Cl]^+$, 1472. HRFABMS Calcd for $C_{70}H_{121}Cl_3NO_{21}PNa$: 1470.7132. Found: 1470.7102.

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-3-*O*-dodecyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-α-D-glucopyranoside (13). To a solution of **12** (895 mg, 0.617 mmol) in THF–AcOH (3:2, 35 mL) was added Zn powder (800 mg, 12.23 m atom). The mixture was stirred vigorously with a magnetic stirrer at 25 °C for 3 h, and filtered. The filtrate was concentrated in vacuo below 30 °C, and diluted with EtOAc, which was washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give amine, which was dissolved in THF (6 mL)–H_2O (2 mL) containing $NaHCO_3$ (220 mg, 2.619 mmol). To this solution was added a solution of *cis*-vaccenyl chloride (250 mg, 0.831 mmol) in THF (4 mL) with vigorous stirring at 25 °C. (This acid chloride was prepared from (*Z*)-11-octadecenoic acid and excess oxalyl chloride in benzene at room temperature for 3 h.) After stirring for 2 h, the reaction mixture was diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (3:1) gave **13** (428 mg, 45%) as an oil. IR ν_{max} (film) 3306 (w), 2926, 2855, 1747, 1678, 1659, 1547, 1465 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) 0.88 (12H, t, $J = 6.6$ Hz), 1.25 (66H, brs), 1.40–1.80 (13H, m, containing 3H, dd, $J = 1.5$, 6.6 Hz, at δ 1.54 ppm), 1.84–1.89 (2H, m), 2.00–2.05 (4H, m), 2.22–2.26 (2H, m), 3.22–3.79 (20H, m, containing two 3H, s, at δ 3.28 and 3.37 ppm), 3.85 (1H, m), 4.04 (1H, m), 4.24 (1H, m), 4.53–4.72 (10H, m), 4.78–4.84 (2H, m), 5.09 (1H, d, $J = 3.7$ Hz), 5.16 (1H, m), 5.22–5.41 (10H, m), 5.88–5.99 (4H, m), 6.05 (1H, d, $J = 8.1$ Hz), 6.13 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 1560 $[M + Na]^+$. HRFABMS Calcd for $C_{85}H_{152}NO_{20}PNa$: 1561.0543. Found: 1561.0560.

4-*O*-Allyloxycarbonyl-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-3-*O*-dodecyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-D-glucopyranose (14). To a solution of **13** (421 mg, 0.274 mmol) in CH_2Cl_2 (7.7 mL) and MeCN (16.8 mL) was added an aq 48% HF solution (5.3 mL). The mixture was stirred vigorously for 16 h at room temperature, and diluted with EtOAc, which was washed with H_2O, sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (1:1, then 1:3) gave an anomeric mixture **14** (274 mg, 67%) as a gum. IR ν_{max} (film) 3300 (w), 2926, 2855, 1748, 1652, 1549, 1465 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.86–0.88 (12H, m), 1.25 (66H, brs), 1.40–1.90 (13H, m, containing OH), 1.92–2.04 (4H, m), 2.16–2.19 (2H, m), 3.08–3.77 (20H, m, containing 3H, s, at δ 3.27 ppm, and 3H, s, at δ 3.38 ppm), 3.85–4.63 (14H, m), 4.82 (1H, m), 5.23–5.40 (11H, m), 5.88–5.98 (4H, m), 6.05 (1H, d, $J = 7.3$ Hz, NH). FABMS (positive-ion) m/z 1520 $[M + Na]^+$. HRFABMS Calcd for $C_{82}H_{148}NO_{20}PNa$: 1521.0230. Found: 1521.0250.

Diallylphosphono 4-*O*-allyloxycarbonyl-3-*O*-dodecyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-α-D-glucopyranoside (15α) and Diallylphosphono 4-*O*-allyloxycarbonyl-3-*O*-dodecyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-[(*R*)-3-(allyloxycarbonyloxy)tetradecyl]-β-D-glucopyranoside (15β). To a solution of **14** (265 mg, 0.177 mmol) in CH_2Cl_2 (10 mL) were added Na_2SO_4 (570

mg), 1*H*-tetrazole (410 mg, 5.853 mmol) and diallyl diisopropylphosphoramidite (450 mg, 1.834 mmol). After stirring for 30 min at room temperature, this reaction mixture was directly charged on a silica-gel column, and elution with cyclohexane–EtOAc (1:1) gave phosphite (304 mg) as an oil. This phosphite was dissolved in THF (25 mL), and an aq 31% H_2O_2 solution (0.60 mL) was added at 0 °C to this solution. The mixture was stirred for 45 min at 0 °C, and diluted with EtOAc, which was washed with aq 10% $Na_2S_2O_3$, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (1:1, then 1:3) gave **15β** (147 mg, 50% yield, $R_f = 0.500$ [cyclohexane–EtOAc (2:3)]) and **15α** (144 mg, 49%, $R_f = 0.357$ [cyclohexane–EtOAc (2:3)]) as a gum. Physical data of **15β**: IR ν_{max} (film) 3309 (w), 2926, 2856, 1748, 1678, 1550, 1462 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.86–0.90 (12H, m), 1.26 (66H, brs), 1.40–2.07 (16H, m), 2.21–2.24 (2H, m), 3.18–3.86 (22H, m, containing two 3H, s, at δ 3.27 and 3.38 ppm), 3.99 (1H, m), 4.25 (1H, dd, $J = 9.5$, 18.3 Hz), 4.43–4.65 (12H, m), 4.70 (1H, d, $J = 8.8$ Hz), 4.78 (1H, m), 4.93 (1H, dd, $J = 5.1$, 8.1 Hz), 5.19–5.43 (14H, m), 5.86–6.00 (6H, m), 7.48 (1H, d, $J = 9.5$ Hz, NH). FABMS (positive-ion) m/z 1680 $[M + Na]^+$. HRFABMS Calcd for $C_{88}H_{157}NO_{23}P_2Na$: 1681.05. Found: 1681.05. Physical data of **15α**: IR ν_{max} (film) 3306 (w), 2926, 2856, 1747, 1660, 1548 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.86–0.90 (12H, m), 1.25 (66H, brs), 1.40–2.05 (16H, m), 2.21–2.25 (2H, m), 3.22–4.06 (23H, m, containing two 3H, s, at δ 3.28 and 3.38 ppm), 4.26 (1H, dd, $J = 9.5$, 18.3 Hz), 4.54–4.62 (12H, m), 4.64–4.73 (2H, m), 4.78 (1H, t, $J = 5.9$ Hz), 5.23–5.43 (14H, m), 5.72 (1H, dd, $J = 3.7$, 6.6 Hz), 5.88–6.01 (6H, m), 6.54 (1H, d, $J = 8.1$ Hz, NH). FABMS (positive-ion) m/z 1680 $[M + Na]^+$.

Phosphono 6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-4-*O*-phosphono-β-D-glucopyranosyl}-3-*O*-dodecyl-2-*O*-[(*R*)-3-(hydroxy)tetradecyl]-α-D-glucopyranoside (16α). To a solution of **15α** (140 mg, 0.084 mmol) in dry THF (8 mL) were added PPh_3 (20 mg, 0.133 mmol), Et_3N (80 mg, 0.791 mmol), HCOOH (73 mg, 1.457 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in this sequence. The solution was stirred for 20 h at 55 °C under nitrogen, and concentrated in vacuo to give a mixture, which was chromatographed on a DEAE-cellulose (Whatman Ion-Exchange cellulose, wet 3 g) column. The column was prepared by preliminary consecutive washing with 30 mL each of 0.5 M HCl, H_2O, 0.5 M NaOH, and H_2O, and 12 mL each of 1 M AcOH and H_2O, and 30 mL of 0.05 M AcO·NH_4, 30 mL each of 2:3:1 $CHCl_3$–MeOH–H_2O, and finally 2:1 $CHCl_3$–MeOH. The column was eluted with 3 mL each of 2:1 $CHCl_3$–MeOH, then 0.05 M AcO·NH_4 in 2:3:1 $CHCl_3$–MeOH–H_2O. The fractions containing **16α** were collected. To this solution were added another volume of $CHCl_3$ and aq 0.15 M HCl to adjust the ratio of $CHCl_3$–H_2O–MeOH to 1:1:1, and the mixture was shaken well. The lower $CHCl_3$ layer was separated, and concentrated in vacuo to give **16α** (45 mg, 40%) as a powder. IR ν_{max} (KBr) 3289 (w), 3077 (w), 2924, 2853, 1627, 1556, 1467 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, 5:1) δ 0.86–0.90 (12H, m), 1.27 (66H, brs), 1.40–1.74 (12H, m), 1.97–2.02 (4H, m), 2.22–2.24 (2H, m), 3.22–4.13 (26H, m, containing two 3H, s, at δ 3.30 and 3.40 ppm), 4.77 (1H, d, $J = 7.3$ Hz), 5.35–5.39 (2H, m), 5.72 (1H, m). 125 MHz ^{13}C NMR ($CDCl_3$–CD_3OD, 1:1) δ 14.3 ($4CH_3$), 23.2 ($4CH_2$), 25.7 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 27.7 ($2CH_2$), 29.5 (CH_2), 29.9–30.4 ($23CH_2$), 31.0 (CH_2), 32.4–32.5 ($4CH_2$), 34.1 (CH_2), 34.4 (CH_2), 38.1 (CH_2), 55.7 (CH), 56.0 (CH_3), 59.3 (CH_3), 68.2 (CH_2), 69.1 (CH_2), 70.2 (CH_2 and CH), 71.3 (CH), 71.9 (CH_2), 74.0 (CH), 74.3 (CH_2), 74.9 (CH), 75.7 (CH), 79.1 (3CH), 81.6 (CH), 94.5 (CH), 101.5 (CH), 130.3 (CH), 130.4 (CH), 176.1 (CO). FABMS (negative-ion) m/z 1328 $[M - H]^-$, 1350 $[M + Na - 2H]^-$. HRFABMS Calcd for $C_{68}H_{132}NO_{19}P_2$: 1328.8871. Found: 1328.8873.

Phosphono 6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-4-*O*-phosphono-β-D-glucopyranosyl}-3-*O*-dodecyl-2-*O*-[(*R*)-3-(hydroxy)tetradecyl]-β-D-glucopyranoside (16β). Compound **15β** (150 mg, 0.090 mmol) was treated as described for the formation of **16α** from **15α** to give **16β** (45 mg, 37%) as a powder. 400 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, 5:1) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (66H, brs), 1.41–1.74 (12H, m), 2.00–2.04 (4H, m), 2.24–2.28 (2H, m), 3.12–4.07 (26H, m, containing two 3H, s, at δ 3.30 and 3.40 ppm), 4.92–4.97 (2H, m), 5.34–5.36 (2H, m). FABMS (negative-ion) m/z 1328 $[M - H]^-$. Anal. Calcd for $C_{68}H_{133}NO_{19}P_2$: C, 61.38; H, 10.07; N, 1.05; P, 4.66%. Found: C, 61.22; H, 9.98; N, 1.10; P, 4.49%.

3-*O*-Decyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (17). To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (17.00 g, 65.31 mmol) and decyl methanesulfonate (15.34 g, 64.90 mmol) in DMF (65 mL) was added NaH (55% oil dispersion, 3.40 g, 77.92 mmol, 1.5 equivalents) under ice-cooling temperature. After stirring for 15 min at 0 °C, the mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with MeOH under ice-cooling temperature, and diluted with EtOAc. The solution was washed with water, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (6:1) gave **17** (22.50 g, 98%) as an oil. IR ν_{max} (film) 2987, 2928, 2857 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.27 (14H, brs), 1.32 (3H, s), 1.36 (3H, s), 1.43 (3H, s), 1.50 (3H, s), 1.55–1.58 (2H, m), 3.52 (1H, m), 3.59 (1H, m), 3.86 (1H, d, $J = 3.7$ Hz), 3.99 (1H, dd, $J = 5.9$, 8.8 Hz), 4.08 (1H, d, $J = 5.9$ Hz), 4.11 (1H, t, $J = 6.6$ Hz), 4.14 (1H, m), 4.31 (1H, m), 4.53 (1H, d, $J = 4.4$ Hz), 5.88 (1H, d, $J = 4.4$ Hz). Anal. Calcd for $C_{22}H_{40}O_6$: C, 65.97; H, 10.07%. Found: C, 65.64; H, 9.94%.

Allyl 3-*O*-decyl-4,6-*O*-isopropylidene-α,β-D-glucopyranoside (18). A solution of **17** (20.60 g, 51.43 mmol) obtained above in allyl alcohol (300 mL) containing 2% HCl was refluxed for 30 min, and concentrated in vacuo to give a mixture, which was dissolved in DMF (30 mL) and 2,2-dimethoxypropane (30 mL). To this solution was added *p*-TsOH·H_2O (500 mg). After stirring for 6 h at room temperature, the reaction mixture was diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (3:1) gave a 3:1 mixture of α- and β-anomer **18** (16.48 g, 80%) as an oil. The mixture was partly separated chromatographically. Physical data of α-anomer: $R_f = 0.460$ (cyclohexane–EtOAc (3:1)); IR ν_{max} (film) 3470 (br), 2994, 2925, 2856 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (14H, brs), 1.41 (3H, s), 1.49 (3H, s), 1.53–1.60 (2H, m), 2.27 (1H, d, $J = 7.3$ Hz, OH), 3.46–3.86 (8H, m), 4.04 (1H, m), 4.21 (1H, m), 4.93 (1H, d, $J = 3.7$ Hz), 5.22–5.35 (2H, m), 5.93 (1H, m). Anal. Calcd for $C_{22}H_{40}O_6$: C, 65.97; H, 10.07%. Found: C, 65.71; H, 9.92%. Physical data of β-anomer: $R_f = 0.540$ (cyclohexane–EtOAc (3:1)); 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz),

1.26 (14H, brs), 1.41 (3H, s), 1.49 (3H, s), 1.55–1.60 (2H, m), 2.29 (1H, d, $J = 2.2$ Hz, OH), 3.25 (1H, m), 3.31 (1H, t, $J = 8.8$ Hz), 3.45 (1H, m), 3.59–3.67 (2H, m), 3.75–3.82 (2H, m), 3.91 (1H, dd, $J = 5.1$, 11.0 Hz), 4.14 (1H, dd, $J = 6.2$, 12.8 Hz), 4.35 (1H, dd, $J = 5.1$, 12.5 Hz), 4.40 (1H, d, $J = 8.1$ Hz), 5.20–5.35 (2H, m), 5.93 (1H, m).

Allyl 3-*O*-decyl-4,6-*O*-isopropylidene-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranoside (19). To a solution of anomeric 3:1 mixture **18** (300 mg, 0.750 mmol) in CH_2Cl_2–THF (2:1, 6 mL) were added 3-oxotetradecanoic acid (242 mg, 1.00 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192 mg, 1.000 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (6:1) gave a 3:1 mixture of α-anomer and β-anomer **19** (375 mg, 80%) as an oil. The mixture was partly separated chromatographically. Physical data of β-anomer: $R_f = 0.536$ (cyclohexane–EtOAc (4:1)); IR ν_{max} (film) 2923, 2853, 1752, 1722, 1636, 1568 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J =$ 6.6 Hz), 1.26 (30H, brs), 1.40 (3H, s), 1.41–1.68 (7H, m, containing 3H, s, at δ 1.49 ppm), 2.56 (2H, t, $J = 6.3$ Hz), 3.23 (1H, m), 3.38–3.56 (3H, m), 3.92 (1H, m), 4.05 (1H, m), 4.30 (1H, m), 4.47 (1H, d, $J = 8.1$ Hz), 4.95 (1H, m), 5.15–5.27 (2H, m), 5.84 (1H, m). FABMS (positive-ion) m/z 623 $[M - H]^+$, 647 $[M + Na]^+$.

Allyl 3-*O*-decyl-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranoside (20). A solution of anomeric 3:1 mixture **19** (2.37 g, 3.793 mmol) in MeOH (35 mL) containing *p*-toluenesulfonic acid monohydrate (200 mg) was stirred at room temperature for 2 h, and concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (3:2) gave a 3:1 mixture of α-anomer and β-anomer **20** (1.31 g, 59%) as an amorphous substance. The mixture was partly separated chromatographically. Physical data of α-anomer: $R_f = 0.346$ (cyclohexane–EtOAc (3:2)); 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (30H, brs), 1.51–1.60 (4H, m), 2.05 (2H, m, OH), 2.53 (2H, dt, $J = 1.5$, 6.6 Hz), 3.48 (2H, s), 3.59–3.87 (7H, m), 4.01 (1H, m), 4.18 (1H, m), 4.74 (1H, dd, $J = 3.7$, 10.3 Hz), 5.08 (1H, d, $J = 3.7$ Hz, anomeric H), 5.19–5.32 (2H, m), 5.89 (1H, m). Physical data of β-anomer: $R_f =$ 0.269 (cyclohexane–EtOAc (3:2)); IR ν_{max} (film) 3284 (br), 2921, 2852, 2596–2400 (w), 1752, 1720, 1649, 1632 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (30H, brs), 1.51–1.63 (4H, m), 2.07 (1H, m, OH), 2.52–2.57 (2H, m), 3.20 (1H, d, $J = 2.9$ Hz), 3.45 (1H, s), 3.35–3.41 (2H, m), 3.58–3.68 (3H, m), 3.80 (1H, m), 3.91 (1H, m), 4.07 (1H, m), 4.31 (1H, m), 4.46 (1H, d, $J = 8.1$ Hz), 4.94 (1H, m), 5.16–5.28 (2H, m), 5.86 (1H, m). FABMS (positive-ion) m/z 583 $[M - H]^+$, 607 $[M + Na]^+$.

(*E*)-1-Propenyl 3-*O*-decyl-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranoside (21). To a solution of anomeric 3:1 mixture **20** (1.15 g, 1.966 mmol) in dry THF (40 mL) was added $Ir[C_8H_{12}(MePh_2P)_2]PF_6$ (25 mg). The atmospheric air in the reaction flask was replaced with nitrogen, then hydrogen to activate the iridium complex. After the red iridium complex turned colorless (ca. 30 sec) in solution, hydrogen was replaced with nitrogen. After stirring for 6 h under nitrogen at room temperature, the reaction mixture was concentrated in vacuo to give anomeric 3:1 mixture **21** (1.15 g, 100%), which was employed for the next reaction without purification. The mixture was partly separated chromatographically. Elution with cyclohexane–EtOAc (3:2) gave the α-anomer ($R_f = 0.459$) as an amorphous compound and the β-anomer ($R_f = 0.324$) as a wax. Physical data of α-anomer: IR ν_{max} (KBr) 3408 (br), 2923, 2853, 1740, 1681 (w), 1659 (w) cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (30H, brs), 1.54–1.60 (7H, m, containing 3H, dd, $J = 1.5$, 6.6 Hz, at δ 1.55 ppm), 2.00 (1H, m, OH), 2.51–2.55 (2H, m), 3.48 (2H, s), 3.60–3.76 (5H, m), 3.80–3.83 (2H, m), 4.76 (1H, dd, $J = 3.7$, 9.5 Hz), 5.16 (1H, dd, $J = 6.6$, 12.5 Hz), 5.23 (1H, d, $J = 3.7$ Hz), 6.11 (1H, dd, $J = 1.5$, 12.5 Hz). Physical data of β-anomer: IR ν_{max} (film) 3500–3200 (br), 2922, 2853, 1745, 1720, 1682, 1648 (w), 1630 (w) cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.26 (30H, brs), 1.51–1.62 (7H, m, containing 3H, d, $J = 5.9$ Hz at δ 1.54 ppm), 2.02 (1H, brs, OH), 2.52–2.58 (2H, m), 3.19 (1H, d, $J = 10.3$ Hz), 3.36–3.48 (3H, m, containing 2H, s, at δ 3.45 ppm), 3.57–3.70 (3H, m), 3.81 (1H, m), 3.93 (1H, m), 4.62 (1H, d, $J = 8.1$ Hz), 4.99 (1H, m), 5.10 (1H, m), 6.16 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 607 $[M + Na]^+$.

(*E*)-1-Propenyl 6-*O*-*tert*-butyldimethylsilyl-3-*O*-decyl-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranoside (22). To a solution of anomeric 3:1 mixture **21** (2.89 g, 4.942 mmol) in CH_2Cl_2 (40 mL) were added *tert*-$BuMe_2SiCl$ (800 mg, 5.315 mmol) and DMAP (650 mg, 5.315 mmol) for 16 h at room temperature. The reaction mixture was applied directly to a silica-gel column. Elution with cyclohexane–EtOAc (6:1) gave an anomeric 3:1 mixture **22** (3.45 g, 100%) as an oil. The mixture was partly separated chromatographically. Physical data of β-anomer: $R_f = 0.565$ (cylohexane/EtOAc = 4/1); IR ν_{max} (film) 3507 (br), 2927, 2856, 1754, 1721, 1682, 1663, 1621, 1465 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.08 (6H, m), 0.86–0.91 (15H, m, containing 9H, s, at δ 0.90 ppm), 1.25 (30H, brs), 1.50–1.61 (5H, m), 2.55–2.58 (2H, m), 3.12–3.20 (1H, m), 3.36–3.46 (3H, m), 3.54–3.73 (3H, m), 3.83–3.93 (2H, m), 4.57 (1H, d, $J = 8.8$ Hz), 4.98 (1H, m), 5.08 (1H, m), 6.14 (1H, d, $J = 10.7$ Hz). FABMS (positive-ion) m/z 697 $[M - H]^+$, 721 $[M + Na]^+$ (on addition of NaI).

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-3-*O*-decyl-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranoside (23). To a solution of anomeric 3:1 mixture **22** (3.45 g, 4.935 mmol) in toluene (60 mL) were added pyridine (4.00 g, 50.569 mmol) and triphosgene (2.20 g, 7.414 mmol) 0 °C. After stirring for 15 min at 0 °C, allyl alcohol (6.90 g, 118.8 mmol) was added to this mixture. This solution was stirred for 1 h at 0 °C, and diluted with EtOAc. The solution was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (9:1) gave an anomeric 3:1 mixture **23** (2.63 g, 68%) as an oil. The mixture was partly separated chromatographically. Physical data of β-anomer: $R_f = 0.368$ (cylohexane/EtOAc = 9/1); IR ν_{max} (film) 2927, 2856, 1758, 1722, 1682 (w), 1664 (w), 1628 (w), 1464 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.04 (6H, s), 0.86–0.90 (15H, m, containing 9H, s, at 0.88 ppm), 1.26 (30H, brs), 1.42–1.60 (7H, m, containing 3H, d, $J = 7.3$ Hz, at 1.52 ppm), 2.54 (2H, t, $J = 7.3$ Hz), 3.19 (1H, d, $J = 8.8$ Hz), 3.43 (1H, s), 3.47–3.57 (4H, m), 3.72–3.73 (2H, m), 4.57 (1H, d, $J = 8.1$ Hz), 4.61–4.65 (2H, m), 4.78 (1H, t, $J = 9.5$ Hz), 4.97–5.14 (2H, m), 5.27–5.39 (2H, m), 5.92 (1H, m), 6.16 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 805 $[M + Na]^+$.

4-*O*-Allyloxycarbonyl-3-*O*-decyl-2-*O*-(3-oxotetradecanoyl)-α,β-D-glucopyranose (24). To a solution of anomeric 3:1 mix-

ture **23** (2.20 g, 4.935 mmol) in CH_2Cl_2 (30 mL) and MeCN (60 mL) was added an aq 48% HF solution (20 mL). The mixture was stirred vigorously for 1.5 days at room temperature, and diluted with EtOAc, which was washed with H_2O, sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (2:3) gave an anomeric mixture **24** (1.02 g, 58%) as an oil. IR ν_{max} (film) 3430, 2925, 2855, 1754, 1719, 1650 (w), 1466 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (30H, brs), 1.45–1.70 (4H, m), 2.50–2.57 (2H, m), 3.47–3.80 (7H, m), 3.90 (1H, t, $J = 9.5$ Hz), 4.02 (1H, m), 4.66 (2H, d, $J = 5.9$ Hz), 4.76–4.88 (1.5H, m), 5.29–5.40 (2H, m), 5.49 (0.5H, brs), 5.93 (1H, m). FABMS (positive-ion) m/z 369, 611, 651 $[M + Na]^+$. HRFABMS Calcd for $C_{34}H_{60}O_{10}Na$: 651.4085. Found: 651.4052.

4-*O*-Allyloxycarbonyl-3-*O*-decyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(trichloroethoxycarbonyl)amino]-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-D-glucopyranose (25). Compound **24** (641 mg, 1.019 mmol) and imidate **11** (877 mg, 1.040 mmol) were treated as described for the formation of **12** from **10** and **11** to give **25** (1.300 g, 97%) as a gum. IR ν_{max} (film) 3500–3200, 2927, 2856, 1753, 1737, 1721 (shoulder) cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) 0.88 (9H, t, $J = 6.6$ Hz), 1.26 (40H, brs), 1.40–1.50 (4H, m), 1.57–1.63 (2H, m), 1.70–1.78 (2H, m), 2.51–2.55 (2H, m), 3.35–3.88 (24H, m, containing two 3H, s, at δ 3.27 and 3.39 ppm), 4.18–4.30 (2H, m), 4.55 (0.5H, m), 5.25–5.43 (6.5H, m), 5.89–5.99 (3H, m), 6.65 (1H, br). FABMS (positive-ion) m/z 1330 $[M + Na, {}^{35}Cl]^+$, 1332. HRFABMS Calcd for $C_{61}H_{105}{}^{35}Cl_3NO_{20}PNa$: 1330.5931. Found: 1330.5928.

4-*O*-Allyloxycarbonyl-3-*O*-decyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-D-glucopyranose (26). To a solution of **25** (1.290 g, 0.985 mmol) in THF–AcOH (1:1, 20 mL) was added Zn dust (2.00 g, 30.595 m atom). The mixture was stirred vigorously with a magnetic stirrer at 25 °C for 3 h, and filtered. The filtrate was concentrated in vacuo below 30 °C, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give amine, which was dissolved in THF (6 mL)–H_2O (2 mL) containing $NaHCO_3$ (250 mg, 2.976 mmol). To this solution was added a solution of *cis*-vaccenyl chloride (356 mg, 1.186 mmol, 1.2 equivalents) in THF (2 mL) with vigorous stirring at 25 °C. (This acid chloride was prepared from (*Z*)-11-octadecenoic acid and excess oxalyl chloride in benzene at room temperature for 3 h). After stirring for 2 h, the reaction mixture was diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a mixture, which was chromatographed on a silica-gel column. Elution with EtOAc–hexane (3:1) gave **26** (756 mg, 55%) as an oil. IR ν_{max} (film) 3305 (br), 2926, 2856, 1755, 1652, 1543, 1465 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (12H, m), 1.26 (60H, brs), 1.40–1.80 (10H, m), 2.01–2.02 (4H, m), 2.16–2.22 (2H, m), 2.52–2.59 (2H, m), 3.04–4.37 (25H, m, containing two 3H, s, at δ 3.27 and 3.39 ppm), 4.54–4.78 (7H, m), 5.00 (0.5H, s), 5.23–5.52 (8.5H, m), 5.86–5.98 (3H, m), 6.09 (1H, d, $J = 7.3$ Hz, NH). FABMS (positive-ion) m/z 1420 $[M + Na]^+$. HRFABMS Calcd for $C_{76}H_{136}NO_{19}PNa$: 1420.9342. Found: 1420.9347.

Diallylphosphono 4-*O*-allyloxycarbonyl-3-*O*-decyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-α-D-glucopyranoside (27α) and Diallylphosphono 4-*O*-allyloxycarbonyl-3-*O*-decyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-β-D-glucopyranoside (27β). The above-obtained anomeric mixture **26** (743 mg, 0.531 mmol) was treated as described for the formation of **15β** and **15α** from **14** to give **27β** (166 mg, 20%) [$R_f = 0.448$, cyclohexane–EtOAc (1:2)] and **27α** (185 mg, 22%) [$R_f = 0.299$, cyclohexane–EtOAc (1:2)] as an oil. Physical data of **27β**: IR ν_{max} (film) 3309, 3086 (w), 2926, 2856, 1759, 1722, 1669, 1550 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (60H, brs), 1.38–1.70 (10H, m), 2.00–2.04 (4H, m), 2.21–2.23 (2H, m), 2.53 (2H, t, $J = 7.4$ Hz), 3.21–3.79 (21H, m, containing two 3H, s, at δ 3.27 and 3.38 ppm), 3.98 (1H, m), 4.27 (1H, m), 4.46–4.72 (12H, m), 5.00–5.09 (2H, m), 5.23–5.42 (12H, m), 5.85–5.98 (5H, m), 7.35 (1H, d, $J = 9.5$ Hz, NH). FABMS (positive-ion) m/z 1580 $[M + Na]^+$. HRFABMS Calcd for $C_{82}H_{145}NO_{22}P_2Na$: 1580.9632. Found: 1580.9650. Physical data of **27α**: IR ν_{max} (film) 3306, 3086 (w), 2926, 2856, 1759, 1721, 1666, 1548 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (60H, brs), 1.46–1.73 (10H, m), 2.00–2.05 (4H, m), 2.21–2.24 (2H, m), 2.53 (2H, t, $J = 7.7$ Hz), 3.24–3.79 (19H, m, containing two 3H, s, at δ 3.28 and 3.38 ppm), 3.88–3.98 (2H, m), 4.08 (1H, m), 4.27 (1H, m), 4.54–4.65 (11H, m), 4.75–4.83 (2H, m), 5.24–5.42 (12H, m), 5.80 (1H, dd, $J = 3.7$, 6.6 Hz), 5.89–5.99 (5H, m), 6.54 (1H, d, $J = 7.3$ Hz, NH). FABMS (positive-ion) m/z 1558 $[M + H]^+$, 1580 $[M + Na]^+$. HRFABMS Calcd for $C_{82}H_{145}NO_{22}P_2Na$: 1580.9632. Found: 1580.9617.

Phosphono 3-*O*-decyl-6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-4-*O*-phosphono-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-α-D-glucopyranoside (28α). Compound **27α** (178 mg, 0.114 mmol) was treated as described for the formation of **16α** from **15α** to give **28α** (89 mg, 59%) as a powder. IR ν_{max} (KBr) 3286 (br), 2925, 2854, 1747, 1717, 1630, 1551, 1466 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$–CD_3OD, 5:1) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.27 (60H, brs), 1.40–1.75 (10H, m), 2.00–2.04 (4H, m), 2.22–2.25 (2H, m), 2.58 (2H, t, $J = 7.3$ Hz), 3.24–4.10 (24H, m), 4.69 (1H, m), 4.76 (1H, d, $J = 8.1$ Hz), 5.33–5.36 (2H, m), 5.67 (1H, m). 125 MHz ^{13}C NMR ($CDCl_3$–CD_3OD, 1:1) δ 14.3 ($4CH_3$), 23.2 ($4CH_2$), 24.0 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 27.7 ($2CH_2$), 29.5–30.4 ($21CH_2$), 30.9 (CH_2), 32.3 (CH_2), 32.4 (CH_2), 32.5 ($2CH_2$), 34.1 (CH_2), 34.4 (CH_2), 37.1 (CH_2), 43.5 (CH_2), 55.8 (CH), 56.0 (CH_3), 59.3 (CH_3), 68.1 (CH_2), 70.2 (CH and CH_2), 71.8 (CH_2), 73.9 (CH), 74.1 (CH_2), 74.8 (CH), 75.7 (CH), 79.1 (3CH), 81.4 (CH), 93.5 (CH), 101.5 (CH), 130.3 (CH), 130.4 (CH), 167.7 (CO), 176.2 (CO), 204.1 (CO). FABMS (negative-ion) m/z 1312 $[M - H]^-$. Anal. Calcd for $C_{66}H_{125}NO_{20}P_2$: C, 60.30; H, 9.58; N, 1.07; P, 4.71%. Found: C, 60.20; H, 9.49; N, 1.20; P, 4.69%.

Phosphono 3-*O*-decyl-6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-4-*O*-phosphono-β-D-glucopyranosyl}-2-*O*-(3-oxotetradecanoyl)-β-D-glucopyranoside (28β). Compound **27β** (160 mg, 0.103 mmol) was treated as described for the formation of **16α** from **15α** to give **28β** (97 mg, 72%) as a powder. IR ν_{max} (KBr) 3287 (br), 2925, 2854, 1746, 1717, 1629, 1554, 1466 cm^{-1}. 400 MHz ^1H NMR ($CDCl_3$–CD_3OD, 5:1) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (60H, brs), 1.40–1.73 (10H, m), 2.01–2.02 (4H, m), 2.23–2.27 (2H, m), 2.58 (2H, t, $J = 7.3$ Hz), 3.30–3.82 (21H, m, containing two 3H,

s, at 3.30 and 3.41 ppm), 4.01–4.05 (3H, m), 4.88–4.94 (2H, m), 5.05 (1H, m), 5.33–5.36 (2H, m). 125 MHz ^{13}C NMR ($CDCl_3$–CD_3OD, 1:1) δ 14.3 ($4CH_3$), 23.1 ($4CH_2$), 23.9 (CH_2), 25.6 (CH_2), 26.5 (CH_2), 27.6 (CH_2), 27.7 ($2CH_2$), 29.4–30.3 ($21CH_2$), 30.7 (CH_2), 32.3 ($2CH_2$), 32.4 ($2CH_2$), 34.0 (CH_2), 34.3 (CH_2), 36.9 (CH_2), 43.5 (CH_2), 55.2 (CH), 55.9 (CH_3), 59.2 (CH_3), 67.7 (CH_2), 70.1 (CH_2), 70.6 (CH), 71.8 (CH_2), 73.8 (CH_2), 74.5 (CH), 75.6 (CH), 79.0 (CH), 79.2 (3CH), 82.7 (CH), 96.6 (CH), 101.6 (CH), 130.2 (CH), 130.3 (CH), 166.8 (CO), 175.9 (CO), 204.0 (CO). FABMS (negative-ion) m/z 1312 $[M-H]^-$. Anal. Calcd for $C_{66}H_{125}NO_{20}P_2$: C, 60.30; H, 9.58; N, 1.07; P, 4.71%. Found: C, 60.18; H, 9.74; N, 1.11; P, 4.58%.

Allyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (30). A solution of **29** (5.00 g, 22.7 mmol) in DMF (10 mL) and 2,2-dimethoxypropane (15 mL) containing *p*-TsOH·H_2O (200 mg) was stirred for 16 h at room temperature. The reaction mixture was diluted with EtOAc, which was washed with a small amount of sat. aq $NaHCO_3$–brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give **30** (3.84 g, 65%) as an oil. IR ν_{max} (film) 3434 (br) cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, s), 1.52 (3H, s), 2.30 (1H, d, $J = 10.3$ Hz, OH), 2.79 (1H, d, $J = 2.2$ Hz, OH), 3.51–3.88 (6H, m), 4.03 (1H, m), 4.23 (1H, m), 4.92 (1H, d, $J = 3.7$ Hz), 5.23–5.34 (2H, m), 5.91 (1H, m).

Allyl 2,3-di-*O*-dodecyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (31). To a solution of **30** (2.90 g, 11.14 mmol) and dodecyl iodide (8.00 g, 27.00 mmol) in DMF (29 mL) was added NaH (55% oil dispersion, 2.36 g, 54.00 mmol) at room temperature, and the mixture was stirred for 16 h at room temperature. The reaction mixture was poured into ice water, and extracted with EtOAc, which was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to give a mixture, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (9:1) gave **31** (6.49 g, 98%) as an oil. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (36H, brs), 1.41 (3H, s), 1.48 (3H, s), 1.50–1.60 (4H, m), 3.30 (1H, m), 3.49–3.74 (8H, m), 3.83 (1H, m), 4.08 (1H, dd, $J = 6.6$, 13.3 Hz), 4.18 (1H, dd, $J = 5.1$, 13.3 Hz), 4.90 (1H, d, $J = 3.7$ Hz), 5.22 (1H, m), 5.32 (1H, m), 5.92 (1H, m).

Allyl 2,3-di-*O*-dodecyl-α-D-glucopyranoside (32). To a solution of **31** (6.40 g, 10.72 mmol) in MeOH (50 mL) was added TsOH·H_2O (300 mg, 1.58 mmol). The mixture was stirred for 40 min at room temperature, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (1:1) gave **32** (3.23 g, 54%) as a solid. IR ν_{max} (KBr) 3364 (br), 2919, 2850, 1467 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (36H, brs), 1.54–1.60 (4H, m), 1.95 (1H, t, $J = 5.7$ Hz, OH), 2.46 (1H, d, $J = 2.9$ Hz, OH), 3.28 (1H, m), 3.46–3.90 (8H, m), 3.93 (1H, m), 4.07 (1H, dd, $J = 6.6$, 13.2 Hz), 4.20 (1H, dd, $J = 5.1$, 13.2 Hz), 4.96 (1H, d, $J = 3.7$ Hz), 5.21–5.35 (2H, m), 5.93 (1H, m). FABMS (positive-ion) m/z 555 $[M-H]^+$, 579 $[M+Na]^+$. HRFABMS Calcd for $C_{33}H_{64}O_6Na$: 579.4600. Found: 579.4581.

(*E*)-1-Propenyl 2,3-di-*O*-dodecyl-α-D-glucopyranoside (33). To a solution of **32** (2.602 g, 4.672 mmol) in dry THF (40 mL) was added (1,5-cyclooctadiene)bis(methyldiphenylphosphine)-iridium(I) hexafluorophosphate (50 mg). The atmosphere was replaced with nitrogen, and then hydrogen to activate the iridium complex. After the red iridium complex turned colorless in solution by stirring for about 10 sec under a hydrogen atmosphere, the hydrogen was replaced again by nitrogen. The solution was stirred for 16 h at room temperature, and concentrated in vacuo to give **33** (quantitatively) as a solid. IR ν_{max} (KBr) 3341 (br), 2919, 2851, 1678 (w), 1468 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (36H, brs), 1.55–1.60 (9H, m), 1.89 (1H, brs, OH), 2.50 (1H, brs, OH), 3.30 (1H, dd, $J = 3.7$, 8.8 Hz), 3.46–3.78 (6H, m), 3.70–3.84 (2H, m), 3.93 (1H, m), 5.12 (1H, d, $J = 3.7$ Hz), 5.19 (1H, qd, $J = 6.6$, 12.5 Hz), 6.18 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 555 $[M-H]^+$, 579 $[M+Na]^+$.

(*E*)-1-Propenyl 6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-dodecyl-α-D-glucopyranoside (34). To a solution of **33** (2.700 g, 4.848 mmol) in CH_2Cl_2 (50 mL) were added *tert*-$BuMe_2SiCl$ (880 mg, 5.838 mmol) and DMAP (713 mg, 5.838 mmol). The solution was stirred for 16 h at room temperature. The mixture was directly chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (7:1, and then 2:1) gave **34** (3.105 g, 95%) as an oil. IR ν_{max} (film) 3504 (br), 2926, 2855, 1680 (w), 1659 (w), 1464 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.88 (15H, m, containing 9H, s, at δ 0.90 ppm), 1.26 (36H, brs), 1.58–1.65 (7H, m), 2.71 (1H, d, $J = 2.2$ Hz, OH), 3.28 (1H, dd, $J = 2.7$, 9.5 Hz), 3.52–3.90 (9H, m), 5.10 (1H, d, $J = 3.7$ Hz), 5.19 (1H, m), 6.19 (1H, dd, $J = 2.2$, 12.5 Hz). FABMS (positive-ion) m/z 671 $[M+H]^+$, 693 $[M+Na]^+$ (on addition of NaI). HRFABMS Calcd for $C_{39}H_{78}O_6Si$: 693.5466. Found: 693.5469.

(*E*)-1-Propenyl 4-*O*-allyloxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-dodecyl-α-D-glucopyranoside (35). To a solution of **34** (3.10 g, 4.619 mmol) in toluene (45 mL) and pyridine (3.5 mL, 3.423 g) was added triphosgene (1.60 g, 5.392 mmol) at 0 °C. After stirring for 10 min, allyl alcohol (6.00 g) was added to this solution. The mixture was stirred for 1 h at 0 °C, and diluted with EtOAc, which was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with cyclohexane–EtOAc (14:1) gave **35** (3.49 g, 100%) as an oil. IR ν_{max} (film) 2926, 2856, 1758, 1680 (w), 1661 (w), 1464 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.88 (9H, s), 0.88 (6H, t, $J = 6.6$ Hz), 1.25 (36H, brs), 1.51–1.57 (7H, m), 3.35 (1H, dd, $J = 3.7$, 9.7 Hz), 3.51–3.83 (8H, m), 4.62–4.65 (2H, m), 4.72 (1H, t, $J = 9.5$ Hz), 5.19 (1H, d, $J = 3.7$ Hz), 6.19 (1H, m), 5.26–5.39 (2H, m), 5.94 (1H, m), 6.18 (1H, dd, $J = 1.5$, 12.5 Hz). FABMS (positive-ion) m/z 753 $[M-H]^+$, 777 $[M+Na]^+$ (on addition of NaI). HRFABMS Calcd for $C_{43}H_{82}O_8SiNa$: 777.5677. Found: 777.5641.

4-*O*-Allyloxycarbonyl-2,3-di-*O*-dodecyl-D-glucopyranose (36). To a solution of **35** (3.60 g, 4.767 mmol) in CH_2Cl_2 (10 mL) and MeCN (20 mL) was added aq 48% HF solution (3 mL). The mixture was stirred for 16 h at room temperature, and diluted with EtOAc, which was washed with H_2O, sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica-gel column. Elution with EtOAc gave an anomeric mixture **36** (2.12 g, 74%) as an oil. IR ν_{max} (film) 3446 (br), 2920, 2851, 1754, 1724, 1468 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, $J = 6.6$ Hz), 1.26 (32H, brs), 1.43–1.58 (2H, m), 1.69 (1H, brs, OH), 3.12–3.98 (7H, m), 4.65–4.72 (3H, m), 5.28–5.40 (2H, m), 5.93 (1H, m). FABMS (positive-ion) m/z 583 $[M+Na]^+$. HRFABMS Calcd for $C_{34}H_{64}O_8Na$: 623.4499. Found: 623.4490.

4-*O*-Allyloxycarbonyl-2,3-di-*O*-dodecyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(2,2,2-trichloroethoxycarbonyl)amino]-β-D-glucopyranosyl}-D-glucopyranose (37). Compound **36** (1.82 g, 3.112 mmol) and imidate **11** (2.65 g, 3.142 mmol) were treated as described for the formation of **12** from **10** and **11** to give an anomeric mixture **37** (3.86 g, 96%) as a gum. IR ν_{max} (film) 3500–3100, 2926, 2856, 1753, 1736, 1542, 1465 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) 0.88 (9H, t, $J = 6.6$ Hz), 1.26 (48H, brs), 1.43–1.75 (6H, m), 3.11–3.90 (24H, m), 4.13–4.40 (2H, m), 4.55–4.85 (10H, m), 5.24–5.39 (6H, m), 5.89–5.97 (3H, m). FABMS (positive-ion) m/z 1304, 1302 $[M + Na, {}^{35}Cl]^+$, 1332. HRFABMS Calcd for $C_{61}H_{109}{}^{35}Cl_3NO_{18}Na$: 1302.6346. Found: 1302.6333.

4-*O*-Allyloxycarbonyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2,3-di-*O*-dodecyl-D-glucopyranose (38). Compound **37** (1.90 g, 1.482 mmol) was treated as described for the formation of **26** from **25** to give **38** (1.32 g, 65%) as an oil. IR ν_{max} (film) 3302 (br), 2926, 2855, 1754, 1652, 1549, 1465 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (12H, m), 1.26 (66H, brs), 1.40–1.80 (10H, m), 1.99–2.02 (4H, m), 2.17–2.33 (2H, m), 3.10–4.10 (25H, m), 4.24–4.63 (8H, m), 5.21–5.32 (8H, m), 5.87–5.98 (3H, m), 6.12 (1H, m, NH). FABMS (positive-ion) m/z 1392 $[M + Na]^+$. HRFABMS Calcd for $C_{76}H_{140}NO_{17}PNa$: 1392.9756. Found: 1392.9774.

Diallylphosphono 4-*O*-allyloxycarbonyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2,3-di-*O*-dodecyl-α-D-glucopyranoside (39α) and Diallylphosphono 4-*O*-allyloxycarbonyl-6-*O*-{2-deoxy-4-*O*-diallylphosphono-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methyl-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2,3-di-*O*-dodecyl-β-D-glucopyranoside (39β). The above-obtained anomeric mixture **38** (1.32 g, 0.963 mmol) was treated as described for the formation of **15β** and **15α** from **14** to give **39β** (378 mg, 26%, $R_f = 0.380$ [cyclohexane–EtOAc (1:1)]) as an oil and **39α** (356 mg, 25%, $R_f = 0.240$ (cyclohexane–EtOAc (1:1)) as an oil. Physical data of **39β**: IR ν_{max} (film) 3310 (w), 3086 (w), 2926, 2855, 1757, 1668, 1549, 1465 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (66H, brs), 1.40–1.75 (10H, m), 2.00–2.02 (4H, m), 2.10–2.25 (2H, m), 3.18–3.75 (22H, m, containing two 3H, s, at δ 3.27 and 3.38 ppm), 4.00 (1H, m), 4.25 (1H, m), 4.47–4.63 (11H, m), 4.70 (1H, d, $J = 8.8$ Hz), 4.95 (1H, dd, $J = 5.1$, 8.1 Hz), 5.23–5.43 (12H, m), 5.86–5.97 (5H, m), 7.48 (1H, d, $J = 9.5$ Hz, NH). FABMS (positive-ion) m/z 1552 $[M + Na]^+$. HRFABMS Calcd for $C_{82}H_{149}NO_{20}P_2Na$: 1553.0046. Found: 1553.0040. Physical data of **39α**: IR ν_{max} (film) 3310, 3085, 2926, 2855, 1757, 1665, 1548, 1465 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.26 (66H, brs), 1.40–1.75 (10H, m), 1.99–2.01 (4H, m), 2.21–2.25 (2H, m), 3.21–3.83 (22H, m, containing two 3H, s, at δ 3.28 and 3.38 ppm), 3.96–4.02 (2H, m), 4.26 (1H, dd, $J = 9.5$, 18.3 Hz), 4.52–4.73 (11H, m), 5.23–5.42 (12H, m), 5.73 (1H, dd, $J = 3.3$, 6.3 Hz), 5.87–6.01 (5H, m), 6.53 (1H, d, $J = 8.1$ Hz, NH). FABMS (positive-ion) m/z 1552 $[M + Na]^+$. HRFABMS Calcd for $C_{82}H_{149}NO_{20}P_2Na$: 1553.0046. Found: 1553.0041.

Phosphono 6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methy-4-*O*-phosphono-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2,3-di-*O*-dodecyl-α-D-glucopyranoside (40α). Compound **39α** (153 mg, 0.100 mmol) was treated as described for the formation of **16α** from **15α** to give **40α** (70 mg, 54%) as a powder. IR ν_{max} (KBr) 3292 (br), 2924, 2853, 1630, 1551, 1467, 1377 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, 5:1) δ 0.88 (12H, t, $J = 6.6$ Hz), 1.27 (66H, brs), 1.40–1.76 (10H, m), 1.96–2.04 (4H, m), 2.22–2.26 (2H, m), 3.23–4.10 (25H, m, containing two 3H, s, at δ 3.30 and 3.40 ppm), 4.74 (1H, d, $J = 8.3$ Hz), 5.34–5.39 (2H, m), 5.64 (1H, m). FABMS (negative-ion) m/z 1284 $[M - H]^-$. HRFABMS Calcd for $C_{66}H_{128}NO_{18}P_2$: 1284.8607. Found: 1284.8601. Anal. Calcd for $C_{66}H_{129}NO_{18}P_2$: C, 61.61; H, 10.11; N, 1.09; P, 4.81%. Found: C, 61.77; H, 9.96; N, 1.10; P, 4.73%.

Phosphono 6-*O*-{2-deoxy-3-*O*-[(*R*)-3-(methoxy)decyl]-6-*O*-methy-4-*O*-phosphono-2-[(*Z*)-11-(octadecenoyl)amino]-β-D-glucopyranosyl}-2,3-di-*O*-dodecyl-β-D-glucopyranoside (40β). Compound **39β** (185 mg, 0.1210 mmol) was treated as described for the formation of **16α** from **15α** to give **40β** (106 mg, 68%) as a powder. IR ν_{max} (KBr) 3387, 3299, 2924, 2853, 1631, 1552, 1467, 1377 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, 4:1) δ 0.89 (12H, t, $J = 6.6$ Hz), 1.27 (66H, brs), 1.40–1.76 (10H, m), 2.00–2.04 (4H, m), 2.25–2.29 (2H, m), 3.11–3.89 (23H, m, containing two 3H, s, at δ 3.31 and 3.41 ppm), 4.00–4.05 (2H, m), 4.94–4.98 (2H, m), 5.32–5.37 (2H, m). FABMS (negative-ion) m/z 1284 $[M - H]^-$. HRFABMS Calcd for $C_{66}H_{128}NO_{18}P_2$: 1284.8607. Found: 1284.8601.

Methods for Measurement of Biological Activity. The sources of the materials used in the study were as follows: lipopolysaccharide (LPS) from *E. coli* serotype 026:B6 and 12-*O*-tetradecanoylphorbol acetate (TPA) were from Sigma, St. Louis, MO; RPMI-1640 medium, fetal bovine serum (FBS), and newborn calf serum (NBCS) were from Gibco, Grand Island, NY; and human TNFα ELISA kit and mouse TNFα ELISA kit were from Genzyme-Techne, Minneapolis, MN.

Production of TNFα by Human Whole Blood.[9] **Materials:** Lipopolysaccharide (LPS, lot 50K4117, *E. coli* 026:B6), human tumor necrosis factor alpha (TNFα) immunoassay kit and 96-well assay plates were purchased from Sigma, BioSource International, Inc. and Corning Inc. (Cat. No. 3956), respectively.

Whole Blood TNFα Production: Fresh blood was collected aseptically in the presence of heparin by venipuncture from healthy adult volunteers. The subjects did not have any apparent inflammatory conditions and had taken no drugs for at least 7 days prior to blood collection. Written informed consent was obtained from all volunteers before the experiment. In each well of the plates, 360 μL aliquots of blood were mixed with 20 μL of LPS solution (200 ng/mL) dissolved in PBS in the presence (for test sample) or absence (for positive control sample) of test compounds solution (dissolved in 10% DMSO/PBS solution). For the negative control samples, the same amount of blood was cultured without either LPS or a test compound solution. After 6 h of incubation at 37 °C, the plates were centrifuged at 490 × *g* for 15 min, and the plasma was collected and stored at −20 °C. The concentrations of TNFα in the plasma were measured with commercially available immunoassay kits.

Statistical Analysis: The percentage of inhibition of TNFα production was calculated by the following formula: [1 − (concentration of TNFα in the test sample − concentration of TNFα in the negative control sample)/(concentration of TNFα in the positive control sample − concentration of TNFα in the negative control sample)] × 100. The suppressive activities of test compounds are expressed as the fifty percent inhibitory concentration (IC_{50}) of the test compound, the concentration at which the test compound suppresses TNFα production by 50%. The IC_{50} was calculated from the percentage of inhibition using the SAS System for Windows (version 5). The results are expressed as the mean

IC_{50} of triplicate experiments.

Production of TNFα by Galactosamine Loaded C3H/HeN Mice.[10] **Materials; Animals:** Male C3H/HeN mice were purchased from Charles River Japan (Tokyo, Japan). All mice were used at the age of 7 weeks, and housed at Sankyo Laboratories (Tokyo, Japan) with free access to standard rodent chow diet.

Reagents: Lipopolysaccharide (LPS, from *Escherichia coli* O26:B6) and D-Galactosamine (GalN) were purchased from Sigma (St. Louis, MO). Enzyme-linked immunosorbent assay (ELISA) kits of murine TNFα were from R&D Systems (Minneapolis, MN).

TNFα Production: Naïve C3H/HeN mice (five per group) were intravenously injected with the test compound solution (10 mL/kg; dissolved in 0.1% triethylamine/saline solution), and immediately after, were intravenously injected with a mixture of LPS (0.05 mg/10 mL saline/kg) and GalN (1 g/10 mL saline/kg). Mice were injected with vehicle (0.1% triethylamine/saline solution) and saline for negative control samples, and with vehicle and LPS/GalN for positive control samples. One hour after injection, venous blood was collected under ether anesthesia with heparinized syringes fitted with 23-gauge needles from the abdominal vena, and was centrifuged at 4 °C for 3 min at 13230 × *g* to obtain the plasma. Plasma was stored at −30 °C before measuring the TNFα levels by ELISA. The concentrations of TNFα of mouse plasma were measured using ELISA analysis according to the manufacturer's instructions.

Statistical Analysis: The percentage of inhibition of TNFα production was calculated by the following formula: [1 − (concentration of TNFα in the test sample − concentration of TNFα in the negative control sample)/(concentration of TNFα in the positive control sample − concentration of TNFα in the negative control sample)] × 100. The suppressive activities of test compounds are expressed as the fifty percent inhibitory concentration (IC_{50}) of the test compound, the concentration at which the test compound suppresses TNFα production by 50%. The IC_{50} was calculated from the percentage of inhibition using the SAS System for Windows (version 5). The results are expressed as the mean IC_{50} of triplicate experiments.

Production of TNFα by Mouse Peritoneal Macrophage.[11] C57BL/6 female mice (6–7 weeks old) were obtained from Charles River Japan, Inc., Yokohama, Japan. Peritoneal resident macrophages were collected by peritoneal lavage with ice-cold saline. After washing, cells were resuspended in the RPMI-1640 medium supplemented with 10% NBCS, 100 U/mL of penicillin and 100 μg/mL of streptomycin, and were plated in 96-well plates (5×10^4/100 μL/well). After incubation overnight at 37 °C, nonadherent cells were removed by washing three times with RPMI-1640 medium containing 10% NBCS, and adherent cells were incubated in 100 μL of the same medium, in the absence or presence of 10 ng/mL of LPS, with graded concentrations of the compounds in a humidified atmosphere of 5% CO_2 for 4.5 h at 37 °C. After incubation, the amount of TNFα produced in the culture supernatants was determined using the mouse TNFα ELISA kits. The IC_{50} of the compounds was calculated as described above.

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