Pergamon

Tetrahedron 54 (1998) 4033–4050

TETRAHEDRON

Divergent Synthesis and Biological Activities of Lipid A Analogues of Shorter Acyl Chains

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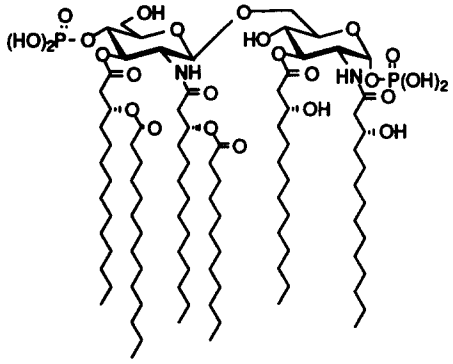
Abstract: Novel lipid A analogues which possess four (*R*)-3-hydroxyacyl moieties of shorter chain length were synthesized via a new divergent synthetic route in order to clarify the effect of the chain length of acyl groups to the biological activity: a disaccharide 4'-phosphate was first constructed as a common synthetic intermediate and all acyl moieties were then introduced step by step to the respective positions. The hydroxy group in acyl moieties was protected with a benzyl group by novel 1-pot reductive alkylation using benzaldehyde, TMS_2O, TMSOTf, and Et_3SiH. Both the glycosyl donor and acceptor were synthesized by using the new method recently reported by ourselves for the regioselective reductive opening of 4,6-*O*-benzylidene glucosamine derivatives with BH_3•Me_2NH and BF_3•OEt_2. In this reaction, a 3-*O*-allyloxycarbonylated 4,6-*O*-benzylidene compound in CH_3CN afforded the 6-*O*-benzylated product selectively, which was then converted to a glycosyl trichloroacetimidate used as the donor. The 4-*O*-benzylated acceptor was synthesized by the same reductive opening of a 3-*O*-p-methoxybenzylated compound in CH_2Cl_2. A disaccharide 4'-phosphate was synthesized by coupling of the imidate donor and the acceptor using TMSOTf as a catalyst. (*R*)-3-Benzyloxyacyl groups were then introduced to the 3, 3', 2 and 2' positions followed by 1-*O*-phosphorylation and subsequent deprotection by Pd/H_2 afforded the desired lipid A analogues. The present divergent route opens an efficient way toward the synthesis of lipid A libraries. Biological tests (inhibition of IL-6 induction) clearly showed the critical importance of the chain length of the acyl moieties in lipid A to the activity.

Lipopolysaccharide (LPS), a cell surface glycoconjugate characteristic of Gram-negative bacteria, has been well-known as endotoxin. LPS stimulates immunocompetent cells such as macrophages, monocytes, endothelial cells to produce powerful mediators such as cytokines, oxygen free radicals, and lipids. When moderate amounts of mediators are produced, the immune system is appropriately stimulated to exhibit beneficial activities such as antitumor activity. On the other hand, overproduced mediators cause endotoxin-related symptoms such as high fever, hypotension, and, in severe cases, lethal shock.[1,2] LPS consists of a glycolipid component termed lipid A covalently bound to a polysaccharide portion. In our previous study, we have clearly demonstrated by means of the total synthesis of *Escherichia coli* lipid A **1** that lipid A is the chemical entity responsible for the biological activities of LPS.[3,4] Lipid A of various bacterial origin were shown to be structurally closely related and to consist of: 1) β(1→6) disaccharide of two D-glucosamines, 2) phosphono groups at the reducing end and the 4-position of the non-reducing sugar, and 3) long-chain acyl groups bound at 2, 2', 3, and 3' positions. Many structural variations of lipid A, however, have been reported mainly in terms of the acyl moieties: their types, numbers, and locations on the hydrophilic sugar backbone. It has been shown that both phosphono groups at the 1- and 4'-positions and acyl groups are crucial for the biological activities of lipid A.[5,6,7,8]

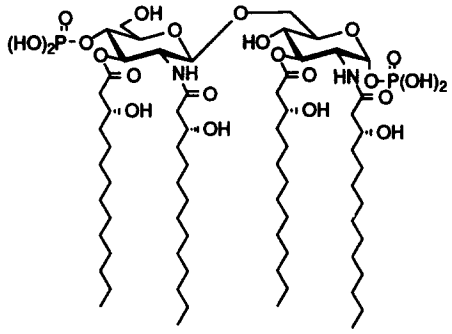
The tetraacyl analogue **2** which lacks the dodecanoyl and tetradecanoyl moieties of **1** was isolated and characterized as a biosynthetic precursor of LPS.[9,10,11] The biosynthetic precursor **2** shows weaker but

0040-4020/98/$19.00
PII: S0040-4020(98)00133-1

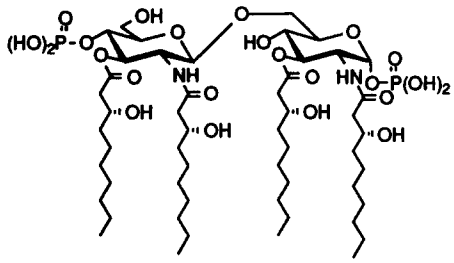
definite endotoxic activity against mice. Quite interestingly, however, **2** act as an antagonist to LPS or lipid A **1** in human systems.[5] Other studies of lipid A analogues also demonstrated the importance of acyl groups on the biological activities.[5,6,7] The acyl moieties probably play an important role in holding the overall conformation of the hydrophilic part which would bind to the receptor on the macrophages. However, the precise structure-activity relationship as well as the role of acyl moieties have not been systematically elucidated. We thus planned to synthesize analogues that possess various types of fatty acyl moieties to investigate these issues.



1 : Lipid A from *Escherichia coli*



2 : Biosynthetic precursor of lipid A



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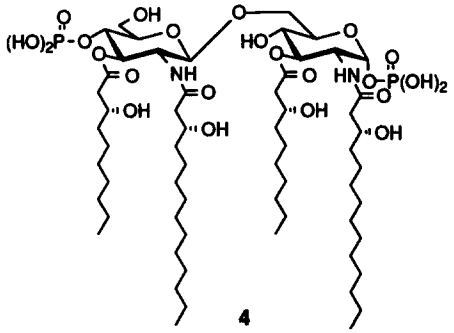

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Recently, we synthesized two unnatural analogues of lipid A via an improved efficient route.[12] They have the same acylation pattern as *E. coli* lipid A and its biosynthetic precursor, respectively, but contain only (*S*)-3-hydroxytetradecanoyl groups in place of the natural (*R*)-isomer. The (*S*)-acyl analogue of lipid A exhibited slightly stronger interleukin-6 inducing activity than the corresponding natural lipid A, and the (*S*)-acyl analogue of biosynthetic precursor was far more active than the natural precursor in inhibiting the induction of interleukin-6 by LPS.[12a,c] These results showed that the (*R*)-configuration of the 3-hydroxytetradecanoyl groups in lipid As is not necessarily required for the activity.

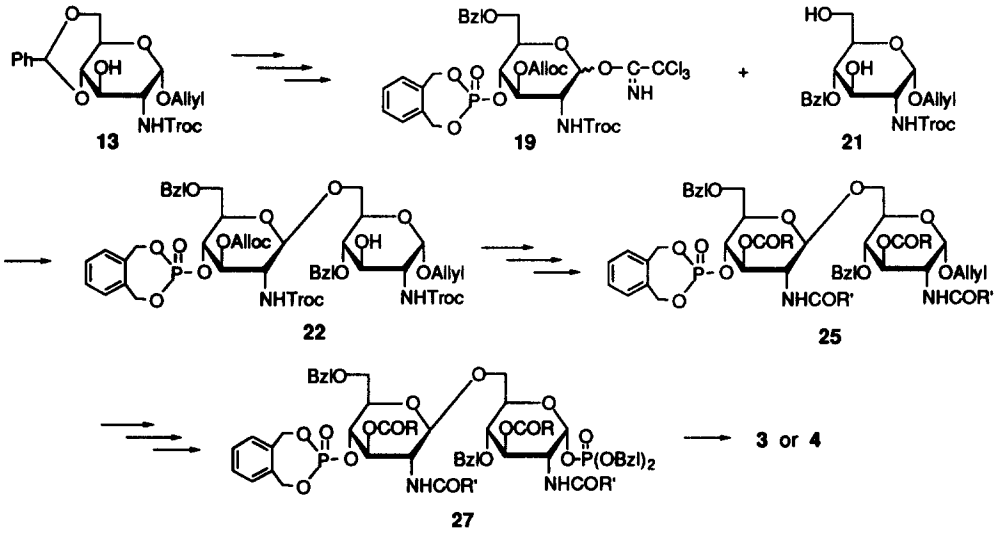
For further investigation of the biological importance of acyl groups, the present study was focused on the effect of the chain length of the acyl groups. We hence synthesized precursor-type analogues which possess four (*R*)-3-hydroxyalkanoyl moieties of shorter chains, i.e., **3** which possesses four (*R*)-3-hydroxydecanoic acids at 2, 2', 3, and 3' positions and **4** which possesses two (*R*)-3-hydroxytetradecanoic acids at 2- and 2'-N positions and two (*R*)-3-hydroxydecanoic acids at 3- and 3'-O positions. In order to construct structurally

diverse lipid A analogues having various types of acyl groups, we have established a new divergent synthetic route where compounds were prepared from a common synthetic intermediate.

Results and Discussion

Synthetic Plan. The new divergent synthetic route is outlined in Scheme 1. A β(1→6) disaccharide 4'-phosphate **22** was first constructed in good yield as a common key synthetic intermediate by the coupling of the two monosaccharides by the use of a glycosyl trichloroacetimidate **19** as a donor. The method of glycosidation and the basic protecting strategy, except for the use of the allyloxycarbonyl (Alloc) group, were same as in our recent work.[12] All acyl moieties were then introduced step by step to the respective positions. After the cleavage of the allyl glycoside, the 1-hydroxy group was phosphorylated to give the lipid A analogues **27** in the fully protected form. Removal of all benzyl-type protecting groups by catalytic hydrogenolysis afforded the desired lipid A analogues **3** and **4**.

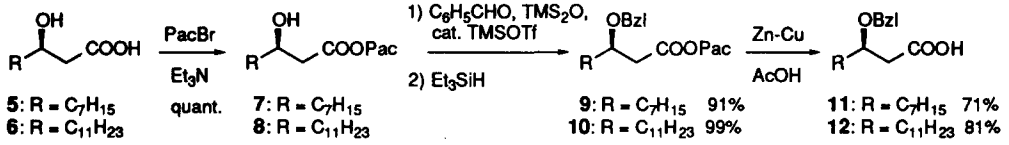
Successful selective deprotection and acylation at 2, 2', 3, and 3' positions are crucial for the present divergent synthesis. Both 2- and 2'-amino groups were protected with the trichloroethoxycarbonyl (Troc) group since the same acyl group was introduced at the 2 and 2' positions in the present study. The Alloc group was employed for the protection of the 3'-hydroxy group whereas the 3-hydroxy group was not protected. The acylation reaction was thus carried out in the following order: 3-*O*-acylation, 3'-*O*-acylation, 2 and 2'-*N*-acylation. In addition to the reactive 6'-hydroxy group, the 4-hydroxy group also had to be protected with a benzyl group since we previously observed the 4-hydroxy group was readily acylated under *O*-acylation conditions though it remained inert during the disaccharide formation. Both the 6'-*O*-benzylated glycosyl donor **19** and the 4-*O*-benzylated glycosyl acceptor **21** were prepared from the common compound **13** via our novel method for regioselective reductive opening of the benzylidene function by using BH_3•Me_2NH and BF_3•OEt_2.[13]



Scheme 1.

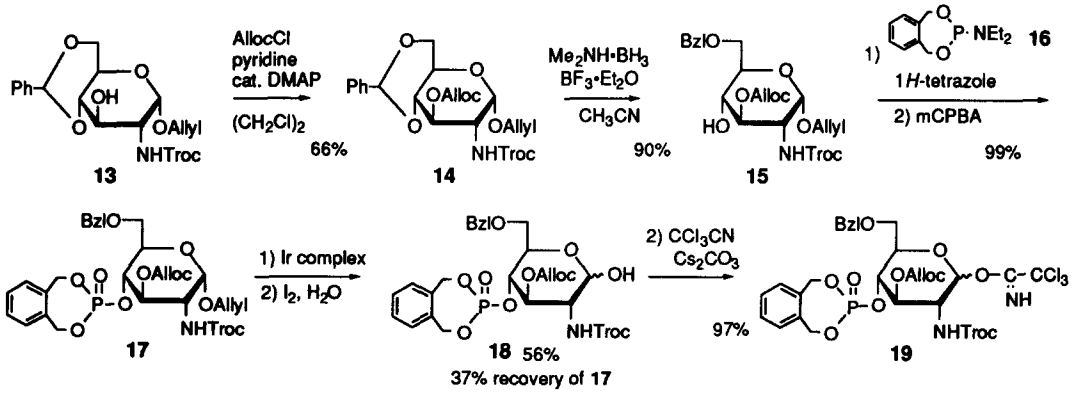
Protection of (*R*)-3-Hydroxyfatty Acids by a New One-Pot Reductive Benzylation Reaction: ROH, Benzaldehyde, TMS_2O, TMSOTf, and Et_3SiH. Optically pure (*R*)-3-

hydroxydecanoic acid (**5**) and (*R*)-3-hydroxytetradecanoic acid (**6**) were prepared according to the literature.[14,15] Phenacylation of **5** or **6** gave the corresponding phenacyl esters **7** and **8**, respectively. For the protection of the 3-hydroxy group, we devised a new one-pot reductive benzylation reaction by improvement of Nishizawa's method,[16] in which the hydroxy group was once trimethylsilylated and then benzylated by treatment with benzaldehyde, TMSOTf, and Et_3SiH.[17] However, the yield of benzylation of **7** did not exceed 70 % because of partial cleavage of the 3-*O*-TMS group prior to the benzylation reaction: no benzylation proceeded on the free hydroxy group. We then applied *in situ* trimethylsylilation of the hydroxy group by addition of TMS_2O. The benzylation of both **7** and **8** with a free hydroxy group was effected by means of a new one-pot procedure by using benzaldehyde, TMS_2O, TMSOTf, and Et_3SiH to afford the corresponding 3-(benzyloxy)alkanoates in good yields [phenacyl (*R*)-3-(benzyloxy)decanoate (**9**): 91%, phenacyl (*R*)-3-(benzyloxy)tetradecanoate (**10**): 99%]. Cleavage of the phenacyl group of **9** and **10** by Zn-Cu / AcOH gave free *O*-benzylated acids **11** and **12**, respectively.



Scheme 2.

Syntheses of the Glycosyl Donors and Acceptors via a Novel Method for Reductive Opening of Benzylidene Function with BH_3•Me_2NH and BF_3•OEt_2. We recently described a novel method for the regioselective reductive opening of 4,6-*O*-benzylidene glucose and glucosamine derivatives with BH_3•Me_2NH and BF_3•OEt_2.[13] The procedure is operationally simple by the use of a non-hygroscopic solid reagent, BH_3•Me_2NH, under ambient atmosphere. There scarcely occurred the undesired hydrolysis of the benzylidene acetal. The glycosyl donors and acceptors for the disaccharide synthesis were thus synthesized by using this novel method.

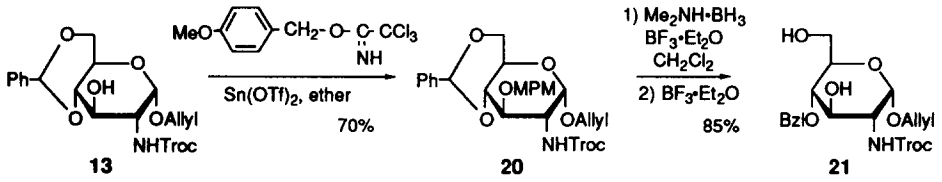


Scheme 3.

Synthesis of the glycosyl donor from the known compound **13**[12] is summarized in Scheme 3. After 3-*O*-

allyloxycarbonylation of **13**, the product **14** was subjected to the reductive benzylidene-ring opening by using BH_3•Me_2NH and BF_3•OEt_2 in CH_3CN to give the 6-*O*-benzylated **15** in good yields with high regioselectivity. The free 4-hydroxy group was phosphitylated by Watanabe's reagent **16**[18] and 1H-tetrazole, and successive oxidation with m-chloroperbenzoic acid (mCPBA) furnished the phosphate **17** in 99% yield. The *o*-xylidene group employed for the protection of the 4-phosphono group of **17** can be readily removed at the final stage of the synthesis by catalytic hydrogenolysis using Pd-black. The allyl group of **17** was deprotected by isomerization to the 1-propenyl group using an iridium complex ($[Ir(cod)(MePh_2P)_2]$-PF_6) followed by cleavage with iodine and water. The rate of the allyl to 1-propenyl isomerization in **17** was much lower than the corresponding reaction substrate which lacks an Alloc group. Since prolonged reaction caused partial cleavage of the Alloc group, we had to stop the isomerization reaction before its completion. Compound **18** was thus obtained in 56% yield with 37% recovery of **17**. Compound **18** was then allowed to react with trichloroacetonitrile in the presence of Cs_2CO_3 as the catalyst to give trichloroacetimidate **19** in good yield.

The glycosyl acceptor was also prepared from the same benzylidene derivative **13** (Scheme 4). The 3-hydroxy group in **13** was p-methoxybenzylated by the imidate method to give **20**, which was then subjected to reduction with BH_3•Me_2NH and BF_3•OEt_2 in CH_2Cl_2. The reaction proceeded smoothly to form the desired 4-*O*-benzylated glucosamine derivative. Since the 3-*O*-MPM group was already partially cleaved during the reduction by the action of BF_3•OEt_2, excess BF_3•OEt_2 was then added to complete the cleavage. The desired 4-*O*-benzylated acceptor **21** with the free 3- and 6-hydroxy groups was thus obtained in 85% yield from **20**.

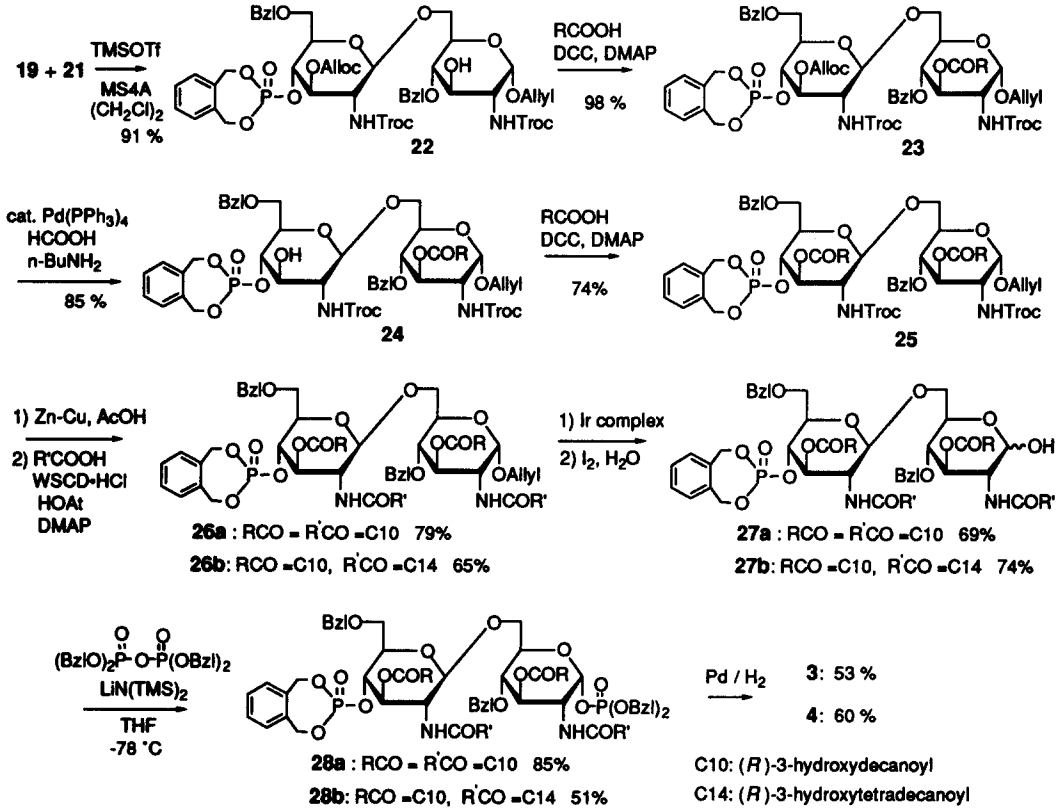


Scheme 4.

Disaccharide Formation and the Synthesis of the Precursor-type Analogues of Shorter Acyl Chains. Coupling of the imidate **19** with **21** was carried out in dichloroethane at -20°C by the use of trimethylsilyl triflate (TMSOTf) as a catalyst to give the desired β-disaccharide **22** in 91% yield. We then introduced acyl groups to the disaccharide. Acylation to the 3-position of **22** with (*R*)-3-(benzyloxy)decanoic acid (**11**) proceeded smoothly with the aid of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to give **23**, the Alloc group of which was readily removed with $Pd(PPh_3)_4$, HCOOH, and butylamine.[19] The 3'-hydroxy group of the product **24** was then acylated with **11** (DCC, DMAP). Deprotection of the *N*-Troc groups at the 2 and 2'-positions of **25** (aqueous AcOH and zinc-copper couple) was followed by *N*-acylation with (*R*)-3-(benzyloxy)decanoic acid (**11**) or (*R*)-3-(benzyloxy)tetradecanoic acid (**12**) by using [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCD•HCl) and 1-hydroxy-7-azabenzotriazole (HOAt)] to give the fully acylated disaccharides **26a** or **26b**, respectively. The 1-*O*-allyl group of **26a** and **26b** was then removed by treatment with the iridium complex and then with iodine to yield 1-hydroxy disaccharide **27a** and **27b**, respectively.

Finally, the 1-*O*-α-phosphorylation was carried out via 1-*O*-lithiation and subsequent treatment with tetrabenzyl diphosphate in THF at -78°C → r.t. In the present study, we used lithium hexamethyldisylazide for

1-*O*-lithiation in place of butyllithium which had been used in our previous work.[3,4,12] The lithium silazide reagent is much easier to handle and this modification rendered the reaction more reproducible. The protected 1,4'-bisphosphate **28a** or **28b** thus obtained was purified by silica-gel column chromatography. Owing to the acid-susceptibility of the glycosyl phosphate moiety, a part of the 1-phosphate group, particularly of **28b**, was cleaved during the silica-gel chromatography. Subsequently, all the protecting groups of **28a** or **28b** were removed by hydrogenolysis (7 kg cm^{-2} of H_2) with Pd-black in one-step. Efficient purification of lipid A and their analogues by simple chromatography had been difficult because of their amphiphilic character and poor solubility in both organic and aqueous media. Centrifugal partition chromatography (CPC) is very useful for the separation of amphiphilic glycoconjugates such as lipid A and LPS since these molecules dissolve in a two-phase solvent system, e.g., $CHCl_3$-MeOH-H_2O and BuOH-THF-H_2O, and are distributed between the two phases.[12,20] We recently found liquid-liquid partition column chromatography using Sephadex® LH-20 is also effective and even more convenient than CPC for the purification of lipid A analogues.[12a] The present crude final products were thus purified by this partition column chromatography furnishing the desired free precursor-type analogues of shorter acyl chains **3** or **4**, respectively, in moderate yields.



Inhibition Assay of Interleukin-6 Induction. The biological activity of **3** or **4** was examined by testing inhibition of the induction of interleukin-6 (IL-6) by LPS.[21] A mixture consisting of test sample, LPS (*E. coli* 0111:B4; Sigma Chemicals Co.), and heparinized human peripheral whole-blood collected from an

adult volunteer in RPMI 1640 medium (Flow Laboratories, Irvine, Scotland) was incubated at 37°C in 5% CO_2 for 24 h. The levels of induced IL-6 were measured by means of enzyme-linked immunosorbent assay (ELISA). LPS (100 pg/mL dose) alone induced 2.0 ng/mL of IL-6. Biosynthetic precursor **2** inhibited the induction of IL-6 by LPS completely at 10 ng/mL of **2**. A new analogue **4**, which possesses two (*R*)-3-hydroxytetradecanoic acids and two (*R*)-3-hydroxydecanoic acids, also showed almost complete inhibition of IL-6 induction at 100 ng/mL of **4** (Fig. 1). Thus, in a rough estimation, **4** is ca. 10~100 times less potent than the natural-type **2** in inhibiting the IL-6 induction of LPS. The other analogue **3** which possesses four (*R*)-3-hydroxydecanoic acids did not show inhibiting activity (Fig. 1). These results clearly indicate hydrophobic acyl moieties play an important role in the bioactivity and a certain level of hydrophobicity is certainly essential for expression of the bioactivity.

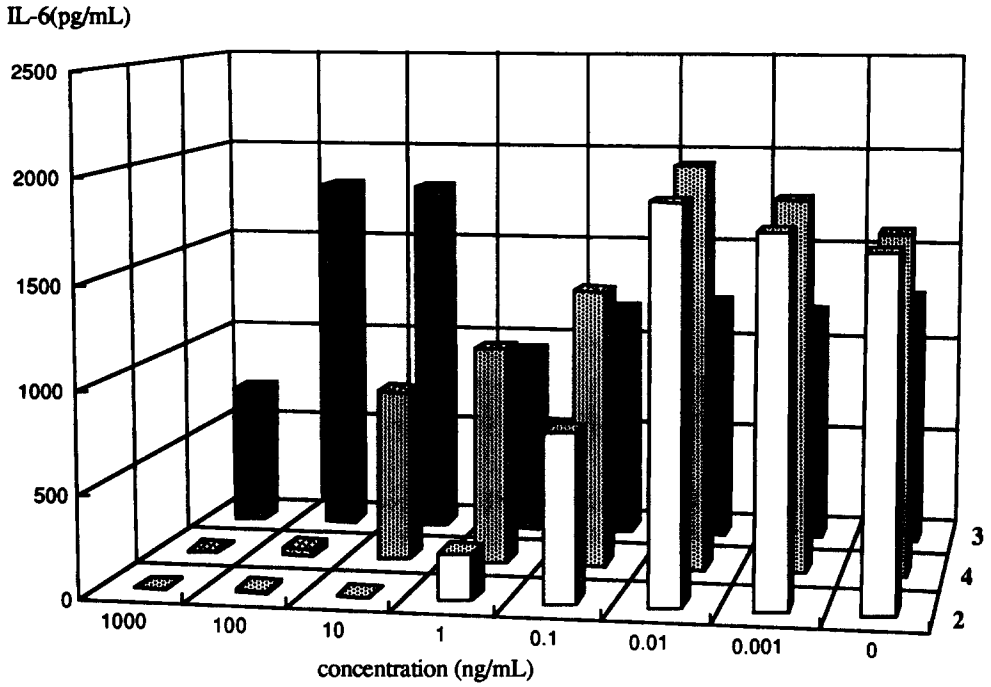


Fig. 1. Inhibitory activity by **2** and **4** against IL-6 induction by LPS (100 pg/mL)

Conclusions

We unequivocally proved for the first time by the use of synthetic compounds that the biological activity of lipid A analogues varied dramatically depending on the chain length of acyl groups. The results coincide our assumption that hydrophobic interaction between acyl chains might hold the disaccharide backbone to a particular conformation that would be recognized by receptors. To further substantiate this idea, precise analysis is necessary of the conformational behavior of various analogues in relation to their acylation patterns as well as biological activities. We have already started the conformational study of the biosynthetic precursor **2** and its analogues by NMR and the results will be reported in due course.

We established a divergent route for the synthesis of lipid A analogues in solution phase and applied it to the

synthesis of two analogues **3** and **4**. The present work opens an efficient way toward the synthesis of lipid A libraries possessing various kinds of acyl moieties. By means of such a divergent synthetic methodology, combinatorial chemistry is expected to be applicable to synthesis of a library of complex natural products and elucidation of their structure-activity relationships.

Experimental

All melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were measured with a JEOL JNM-LA 500 spectrometers for $CDCl_3$ solutions unless otherwise noted. The chemical shifts are given in δ values from tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained on a JEOL JMS-SX 102 mass spectrometer and a Perkin Elmer SCIEX API III Mass spectrometer. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Silica-gel column chromatography was carried out using Kieselgel 60 (E. Merck, 0.040 - 0,063 mm) at medium-pressure (2 - 4 kg cm^{-2}). Organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo* unless otherwise noted.

Phenacyl (*R*)-3-Hydroxydecanoate (7). To a solution of (*R*)-3-hydroxydecanoic acid (**5**) (8.98 g, 47.8 mmol) in ethyl acetate (150 mL) were added phenacyl bromide (10.5 g, 52.5 mmol) and triethylamine (8.30 mL, 59.7 mmol) at 0°C. The mixture was stirred overnight at room temperature. After the precipitate was filtered off, the filtrate was washed with water and brine and worked up as usual. The residue was purified by silica-gel column chromatography (480 g, toluene/EtOAc = 15:1) to give **7** as a yellow solid. (12.6 g, 87%). $[\alpha]_D^{28}$ = -6.5 (c 1.16, $CHCl_3$). Found: C, 70.23; H, 8.75%. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55%. ^1H NMR (500 MHz) δ = 7.93-7.91 (m, 2H, meta COPh), 7.65-7.61 (m, 1H, para COPh), 7.52-7.49 (m, 2H, ortho COPh), 5.48 (d, *J* = 16.5 Hz, 1H, CH_2COPh), 5.35 (d, *J* = 16.5 Hz, 1H, CH_2COPh), 4.13 (m, 1H, β-CH), 3.40 (d,*J* = 3.5 Hz, 1H, β-OH), 2.68 (dd, *J* = 14.9, 3.0 Hz, 1H, α-CH_2), 2.56 (dd, *J* = 14.9, 8.9 Hz, 1H, α-CH_2), 1.62-1.48 (m, 2H, $CH_3(CH_2)_5CH_2$), 1.44-1.26 (m, 10H, $CH_3(CH_2)_5$), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3).

Phenacyl (*R*)-3-Hydroxytetradecanoate (8). The reaction was carried out by using (*R*)-3-hydroxytetradecanoic acid (**6**) (24.1 g, 98.6 mmol) in a manner similar to the preparation of **7** to give compound **8** as a yellow solid (36.0 g, quant.). $[\alpha]_D^{28}$ = -5.5 (c 1.13, $CHCl_3$). ^1H NMR (500 MHz) δ = 7.93-7.91 (m, 2H, meta COPh), 7.60-7.61 (m, 1H, para COPh), 7.52-7.48 (m, 2H, ortho COPh), 5.48 (d, *J* = 16.4 Hz, 1H, CH_2COPh), 5.37 (d, *J* = 16.4 Hz, 1H, CH_2COPh), 4.15-4.11 (m, 1H, β-CH), 2.79 (dd, *J* = 15.1, 3.0 Hz, 1H, α-CH_2), 2.57 (dd, *J* = 15.1, 9.3 Hz, 1H, α-CH_2), 1.64-1.45 (m, 2H, $CH_3(CH_2)_9CH_2$), 1.44-1.26 (m, 18H, $CH_3(CH_2)_9$), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3).

Phenacyl (*R*)-3-(Benzyloxy)decanoate (9). To a solution of **7** (276 mg, 0.902 mmol) and benzaldehyde (275 μl, 2.71 mmol) in anhydrous THF (7 mL) were added hexamethyldisiloxane (1.15 mL, 5.41 mmol) and TMSOTf (85 μL, 0.44 mmol) at 0 °C. After the mixture was stirred for 10 min, triethylsilane (510 μL, 3.19 mmol) was added and stirring was continued for another 2 h. The solution was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The EtOAc solution was worked up as usual. The residue was purified by silica-gel column chromatography (45 g, hexane/EtOAc = 15:1) to give **9** as a yellow oil (323 mg, 91%). $[\alpha]_D^{28}$ = -13.2 (c 1.02, $CHCl_3$). ^1H NMR (500 MHz) δ = 7.92-7.90 (m, 2H, meta COPh), 7.62-7.59 (m, 1H, para COPh), 7.50-7.47 (m, 2H, ortho COPh), 7.36-7.25 (m, 5H, CH_2Ph), 5.36 (d, *J* = 16.3 Hz, 1H, CH_2COPh), 5.30 (d, *J* = 16.3 Hz, 1H, CH_2COPh), 4.61 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.55 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 3.95 (m, 1H, β-CH), 2.81 (dd, *J* = 15.3, 7.1 Hz, 1H, α-CH_2), 2.67 (dd,

J = 15.1, 5.4 Hz, 1H, α-C$\underline{H}_2$), 1.69-1.58 (m, 2H, $CH_3(CH_2)_5C\underline{H}_2$), 1.44-1.24 (m, 10H, $CH_3(C\underline{H}_2)_5$), 0.88 (t, J = 6.9 Hz, 3H, C$\underline{H}_3$).

Phenacyl (*R*)-3-(Benzyloxy)tetradecanoate (10). The benzylation was carried out by using **8** (213 mg, 0.588 mmol) in a manner similar to the preparation of **9** to give compound **10** as a yellow solid (261 mg, 99%). $[\alpha]_D^{28}$ = -8.4 (c 1.22, $CHCl_3$). ^{1}H NMR (500 MHz) δ = 7.90-7.88 (m, 2H, meta CO$\underline{Ph}$), 7.60-7.57 (m, 1H, para CO$\underline{Ph}$), 7.48-7.45 (m, 2H, ortho CO$\underline{Ph}$), 7.34-7.23 (m, 5H, $CH_2\underline{Ph}$), 5.33 (d, J = 16.2 Hz, 1H, C$\underline{H}_2$COPh), 5.28 (d, J = 16.2 Hz, 1H, C$\underline{H}_2$COPh), 4.59 (d, J = 11.5 Hz, 1H, C$\underline{H}_2$Ph), 4.52 (d, J = 11.5 Hz, 1H, C$\underline{H}_2$Ph), 3.97-3.91 (m, 1H, β-C$\underline{H}$), 2.78 (dd, J = 15.3, 8.2 Hz, 1H, α-C$\underline{H}_2$), 2.66 (dd, J = 15.3, 5.5 Hz, 1H, α-C$\underline{H}_2$), 1.69-1.54 (m, 2H, $CH_3(CH_2)_9C\underline{H}_2$), 1.44-1.24 (m, 18H, $CH_3(C\underline{H}_2)_9$), 0.88 (t, J = 7.0 Hz, 3H, C$\underline{H}_3$).

(*R*)-3-(Benzyloxy)decanoic acid (11). To a solution of **9** (11.1 g, 27.9 mmol) in AcOH (160 mL) was added zinc-copper couple (20 g), and the mixture was stirred at room temperature for 2 h. The insoluble material was filtered off, the filtrate was concentrated *in vacuo*, and the residual solvent coevaporated with toluene three times. The residue was purified by silica-gel column chromatography (480 g, $CHCl_3$/Acetone = 100:1) to give **11** as a pale yellow oil (5.49 g, 71%). $[\alpha]_D^{28}$ = -4.5 (c 1.19, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.26 (m, 5H, $CH_2\underline{Ph}$), 4.57 (s, 2H, C$\underline{H}_2$Ph), 3.87 (m, 1H, β-C$\underline{H}$), 2.63 (dd, J = 15.3, 7.1 Hz, 1H, α-C$\underline{H}_2$), 2.55 (dd, J = 15.6, 5.3 Hz, 1H, α-C$\underline{H}_2$), 1.69-1.50 (m, 2H, $CH_3(CH_2)_5C\underline{H}_2$), 1.41-1.26 (m, 10H, $CH_3(C\underline{H}_2)_5$), 0.88 (t, J = 6.9 Hz, 3H, C$\underline{H}_3$).

(*R*)-3-(Benzyloxy)tetradecanoic acid (12)

In a manner similar to the synthesis of **11**, **10** (519 mg, 1.15 mmol) was deprotected to yield **12** as a pale yellow oil (310 mg, 81%). $[\alpha]_D^{24}$ = -4.8 (c 1.08, $CHCl_3$). Found: C, 75.31; H, 10.39%. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37-7.27 (m, 5H, $CH_2\underline{Ph}$), 4.57 (s, 2H, C$\underline{H}_2$Ph), 3.89-3.84 (m, 1H, β-C$\underline{H}$), 2.63 (dd, J = 15.4, 7.0 Hz, 1H, α-C$\underline{H}_2$), 2.56 (dd, J = 15.4, 5.2 Hz, 1H, α-C$\underline{H}_2$), 1.70-1.50 (m, 2H, $CH_3(CH_2)_9C\underline{H}_2$), 1.39-1.26 (m, 18H, $CH_3(C\underline{H}_2)_9$), 0.88 (t, J = 6.9 Hz, 3H, C$\underline{H}_3$).

Allyl 3-*O*-Allyloxycarbonyl-4,6-*O*-benzylidene-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (14). To a solution of allyl 3-*O*-allyloxycarbonyl-4,6-*O*-benzylidene-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (**13**)[12] (11.5 g, 23.9 mmol) in anhydrous 1,2-dichloroethane (90 mL) at 0 °C was added pyridine (3.85 mL, 47.8 mmol), DMAP (0.58 g, 4.75 mmol) and allyl chloroformate (5.10 mL, 47.8 mmol). After stirring at room temperature for 90 min, the reaction mixture was quenched with water, extracted with EtOAc, and worked up as usual. The residue was purified by silica-gel column chromatography (300 g, hexane/EtOAc = 5:1) to give **14** as a colorless oil (8.95 g, 66%) with recovery of **13** as colorless powder (4.10 g, 34%). $[\alpha]_D^{20}$ = +41.8 (c 1.01, $CHCl_3$). Found: C, 48.57; H, 4.60; N, 2.44%. Calcd. for $C_{23}H_{26}Cl_3NO_9$: C, 48.74; H, 4.62; N, 2.47%. FAB-MS (positive): m/z 566.0 [$(M+H)^+$]. ^{1}H NMR (500 MHz) δ = 7.47-7.45 (m, 2H, meta $\underline{Ph}$-CH), 7.36-7.34 (m, 2H, ortho and para $\underline{Ph}$-CH), 5.94-5.84 (m, 2H, $OCH_2C\underline{H}$=CH_2 × 2), 5.53 (s, 1H, Ph-C$\underline{H}$), 5.39 (d, J = 9.7 Hz, 1H, N$\underline{H}$), 5.32 (dd, J = 17.2, 1.4 Hz, 2H, OCH_2CH=C$\underline{H}_2$), 5.25 (dd, J = 10.3, 1.2 Hz, 2H, OCH_2CH=C$\underline{H}_2$), 5.18 (t, J = 10.1 Hz, 1H, H-3), 4.94 (d, J = 3.7 Hz, 1H, H-1), 4.79 (d, J = 12.2 Hz, 1H, C$\underline{H}_2$ of Troc), 4.67 (d, J = 12.1 Hz, 1H, C$\underline{H}_2$ of Troc), 4.60 (d, J = 5.7 Hz, 2H, O$\underline{CH}_2CH$=CH_2 of Alloc), 4.30 (dd, J = 10.3, 4.9 Hz, 1H, H-6a), 4.22 (dd, J = 12.6, 5.5 Hz, 1H, O$\underline{CH}_2CH$=CH_2 of allyl glycoside), 4.12 (td, J = 10.1, 3.4 Hz, 1H, H-2), 4.03 (dd, J = 12.8, 6.4 Hz, 1H, O$\underline{CH}_2CH$=CH_2 of allyl glycoside),

3.95 (td, J = 9.9, 4.9 Hz, 1H, H-6b), 3.80-3.73 (m, 2H, H-4 and H-5).

Allyl 3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (15). To a solution of **14** (471 mg, 0.830 mmol) and BH_3•Me_2NH (245 mg, 4.16 mmol) in anhydrous CH_3CN (10 mL) were added BF_3•Et_2O (510 μL, 4.15 mmol). After stirring for 90 min at 0 °C, the solution was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, and worked up as usual. The residue was purified by silica-gel column chromatography (50 g, hexane/AcOEt = 5:1) to give **15** as a colorless oil (422 mg, 90%). $[\alpha]_D^{21}$ = +52.2 (c 1.12, $CHCl_3$). Found: C, 47.08; H, 4.80; N, 2.46%. Calcd. for $C_{23}H_{28}Cl_3NO_9 \cdot 0.8H_2O$: C, 47.36; H, 5.12; N, 2.40%. FAB-MS (positive): m/z 568.0 [$(M+H)^+$]. ^{1}H NMR (500 MHz) δ = 7.37-7.27 (m, 5H, Ph-CH_2), 5.94-5.84 (m, 2H, OCH_2CH=CH_2 × 2), 5.38-5.21 (m, 5H, NH and OCH_2CH=CH_2 × 2), 4.99 (t, J = 8.8 Hz, 1H, H-3), 4.92 (d, J = 3.4 Hz, 1H, H-1), 4.82 (d, J = 12.1 Hz, 1H, CH_2 of Troc), 4.65-4.55 (m, 5H, Ph-CH_2, CH_2 of Troc and OCH_2CH=CH_2 of Alloc), 4.20 (dd, J = 12.6, 5.3 Hz, 1H, OCH_2CH=CH_2 of allyl glycoside), 4.06-3.99 (m, 2H, H-2 and OCH_2CH=CH_2 of allyl glycoside), 3.88-3.79 (m, 3H, H-4, H-5 and H-6a), 3.72 (dd, J = 10.5, 3.4 Hz, 1H, H-6b), 2.89 (d, J = 3.4 Hz, 1H, C_4-OH).

Allyl 3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (17). To a solution of **15** (2.49 g, 4.37 mmol) in anhydrous 1,2-dichloroethane (40 mL) were added *N,N*-diethyl-1,5-dihyro-3H-2,4,3-benzodioxaphosphepin-3-amine (**16**) (2.62 g, 10.9 mmol) and 1H-tetrazole (1.53 g, 21.8 mmol). After the mixture was stirred at room temperature for 15 min and then at -20 °C for 10 min, mCPBA (3.77 g, 21.8 mmol) was added and stirring was continued for another 20 min. The solution was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, and worked up as usual. The residue was purified by silica-gel column chromatography (180 g, hexane/EtOAc = 1:1) to give **17** as colorless crystals (3.24 g, 99%). Mp 51.0-52.0 °C. $[\alpha]_D^{20}$ = +38.9 (c 0.94, $CHCl_3$). Found: C, 49.38; H, 4.65; N, 1.91%. Calcd. for $C_{31}H_{35}Cl_3NO_{12}P$: C, 49.58; H, 4.70; N, 1.87%. FAB-MS (positive): m/z 750.3 [$(M+H)^+$]. ^{1}H NMR (500 MHz) δ = 7.38-7.26 (m, 5H, Ph-CH_2), 7.21-7.17 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 5.93-5.84 (m, 2H, OCH_2CH=CH_2 × 2), 5.36-5.28 (m, 3H, NH and OCH_2CH=CH_2), 5.23 (d, J = 10.5 Hz, 2H, OCH_2CH=CH_2), 5.19 (t, J = 9.4 Hz, 1H, H-3), 5.16-5.03 (m, 4H, *o* -$C_6H_4(CH_2O)_2P$), 4.95 (d, J = 3.7 Hz, 1H, H-1), 4.83 (d, J = 12.6 Hz, 1H, CH_2 of Troc), 4.74 (dd, J = 18.6, 9.2 Hz, 1H, H-4), 4.67-4.57 (m, 5H, Ph-CH_2, CH_2 of Troc and OCH_2CH=CH_2 of Alloc), 4.21 (dd, J = 12.6, 5.3 Hz, 1H, OCH_2CH=CH_2 of allyl glycoside), 4.11 (td, J = 11.2, 4.1 Hz, 1H, H-2), 4.03 (dd, J = 13.1, 6.4 Hz, 1H, OCH_2CH=CH_2 of allyl glycoside), 4.03-3.99 (m, 1H, H-5), 3.83 (dd, J = 8.9, 2.4 Hz, 1H, H-6a), 3.78 (dd, J = 11.3, 4.8 Hz, 1H, H-6b).

3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranose (18). To a degassed solution of **17** (911 mg, 1.21 mmol) in anhydrous THF (15 mL) was added [bis(methyldiphenylphosphine)](1,5-cyclooctadiene)iridium(I) hexafluorophosphate (103 mg, 0.122 mmol). After activation of the iridium catalyst with hydrogen three times (each 30 sec), the mixture was stirred under nitrogen atmosphere at room temperature for 14 h. Then iodine (610 mg, 3.40 mmol) and water (20 mL) were added and the reaction mixture was stirred for additional 1 h. To the mixture was added 5% aqueous $Na_2S_2O_3$ and the solution was extracted with EtOAc. The extract was washed with 5% aqueous $Na_2S_2O_3$ and brine and worked up as usual. The crude product was purified by silica-gel column chromatography (50 g,

hexane/EtOAc = 1:1) to give **18** (α:β =1:1) as pale yellow crystals (482 mg, 56%) with recovery of **17** (333 mg, 37%). Mp 68.5-70.0 °C. $[\alpha]_D^{23}$ = +19.7 (c 1.14, $CHCl_3$). Found: C, 46.47; H, 4.30; N, 1.96%. Calcd. for $C_{28}H_{31}Cl_3NO_{12}P\cdot 0.7H_2O$: C, 46.48; H, 4.51; N, 1.94%. FAB-MS (positive): m/z 711.3 $[(M+H)^+]$. ^1H NMR (500 MHz) δ = 7.38-7.26 (m, 5H, Ph-CH_2), 7.21-7.17 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 5.92-5.84 (m, 1H, $OCH_2CH=CH_2$), 5.37 (d, *J* = 10.6 Hz, 1H, $OCH_2CH=CH_2$), 5.33-5.30 (m, 2H, NH and H-1), 5.24 (d, *J* = 10.6 Hz, 1H, $OCH_2CH=CH_2$), 5.23 (t, *J* = 8.9 Hz, 1H, H-3), 5.18-5.05 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 4.82 (d, *J* = 12.1 Hz, 1H, CH_2 of Troc), 4.69-4.56 (m, 6H, H-4, Ph-CH_2, $OCH_2CH=CH_2$ and CH_2 of Troc), 4.26-4.23 (m, 1H, H-5), 4.08 (td, *J* = 12.2, 7.4 Hz, 1H, H-2), 3.83 (dd, *J* = 8.9, 1.9 Hz, 1H, H-6a), 3.75 (dd, *J* = 10.8, 5.7 Hz, 1H, H-6b), 3.40 (s, 1H, C_1-OH).

3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl Trichloroacetimidate (19). To a solution of **18** (495 mg, 0.696 mmol) in anhydrous 1,2-dichloroethane (10 mL) at room temperature were added molecular sieves 4A (2.11 g), trichloroacetonitrile (700 μL, 6.98 mmol) and Cs_2CO_3 (115 mg, 0.353 mmol). After stirring for 30 min, another portion of Cs_2CO_3 (230 mg, 0.705 mmol) was added and the reaction mixture was stirred for additional 45 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. After removal of molecular sieves by filtration, the mixture was extracted with EtOAc. The extract was worked up as usual to give **19** as a pale yellow solid (575 mg, 97%), which was used for the subsequent glycosidation without further purification.

Allyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(4-methoxyphenylmethyl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (20). To a solution of **13** (500 mg, 1.04 mmol) and 4-methoxyphenylmethyl trichloroacetimidate (585 mg, 2.07 mmol) in ether was added $Sn(OTf)_2$ (43 mg, 0.10 mmol) at -20°C. The solution was stirred at 0 °C for 2 h and quenched with saturated aqueous $NaHCO_3$. The organic layer was worked up as usual to give **20** as a pale yellow solid (437 mg, 70%)

Allyl 4-*O*-Benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (21). To a solution of **20** (500 mg, 0.83 mmol) and $BH_3\cdot Me_2NH$ (244 mg, 4.15 mmol) in anhydrous dichloromethane (10 mL) was added $BF_3\cdot Et_2O$ (510 μL, 4.15 mmol) at -40 °C. After stirring for 2 h at 0 °C, the solution was quenched with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, and worked up as usual. The residue was dissolved in CH_2Cl_2 (5 mL) and $BF_3\cdot Et_2O$ (135 μl, 1.1 mmol) was added at 0 °C. After stirring for 1 h at 0 °C, the solution was quenched with saturated aqueous $NaHCO_3$ and worked up as usual. The residue was purified by silica-gel column chromatography ($CHCl_3$/Acetone = 35:1) to give **21** as white powder (325 mg, 81%). Mp 106.5-107.0 °C. $[\alpha]_D^{19}$ = +61.4 (c 0.93, $CHCl_3$). Found: C, 46.26; H, 5.07; N, 2.98%. Calcd. for $C_{19}H_{24}Cl_3NO_7P\cdot 0.5H_2O$: C, 46.22; H, 5.10; N, 2.84%. FAB-MS (positive): m/z 484.1 $[(M+H)^+]$. ^1H NMR (500 MHz) δ = 7.37-7.30 (m, 5H, Ph-CH_2), 5.91-5.83 (m, 1H, $OCH_2CH=CH_2$), 5.28 (dd, *J* = 17.2, 1.6 Hz, 1H, $OCH_2CH=CH_2$), 5.21 (dd, *J* = 10.5, 1.2 Hz, 1H, $OCH_2CH=CH_2$), 5.28-5.26 (m, 1H, NH), 4.90 (d, *J* = 3.4 Hz, 1H, H-1), 4.85 (d, *J* = 11.2 Hz, 1H, CH_2 of Troc), 4.77-4.75 (m, 3H, CH_2 of Troc and Ph-CH_2), 4.16 (ddt, *J* = 12.9, 5.3, 1.4 Hz, 1H, $OCH_2CH=CH_2$), 3.98 (dd, *J* = 12.8, 6.2 Hz, 1H, $OCH_2CH=CH_2$), 3.90 (t, *J* = 10.1 Hz, 1H, H-3), 3.88-3.86 (m, 1H, H-2), 3.87-3.79 (m, 2H, H-6), 3.70 (ddd, *J* = 9.9, 3.4, 3.4 Hz, 1H, H-5), 3.53 (t, *J* = 9.0 Hz, 1H, H-4), 2.40 (s, 1H, C_3-OH), 1.77 (s, 1H, C_6-OH).

Allyl 6-*O*-[3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-gluco-

pyranosyl]-4-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-gluco-pyranoside (22). The imidate **19** (238 mg, 0.278 mmol), the acceptor **21** (112 mg, 0.232 mmol), and the molecular sieves 4A (2.50 g) in anhydrous 1,2-dichloroethane (10 mL) were stirred at -20 °C for 10 min. To this mixture was added TMSOTf (10 μL, 0.05 mmol) and the mixture was stirred at -20 °C for 30 min. After removal of molecular sieves by filtration, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with EtOAc, and worked up as usual. The residue was purified by silica-gel column chromatography (24 g, $CHCl_3$/Acetone = 10:1) to give **22** as a colorless solid (249 mg, 91%). Mp 65.0-65.5 °C. $[\alpha]_D^{23}$ = +23.4 (c 1.19, $CHCl_3$). Found: C, 47.97; H, 4.55; N, 2.37%. Calcd. for $C_{47}H_{53}Cl_6N_2O_{18}P$: C, 47.94; H, 4.54; N, 2.38%. FAB-MS (positive): m/z 1197.5 $[(M+Na)^+]$. ^1H NMR (500 MHz) δ = 7.36-7.26 (m, 12H, Ph-CH_2 × 2 and *o*-$C_6H_4(CH_2O)_2P$), 7.20-7.16 (m, 2H, *o*-$C_6H_4(CH_2O)_2P$), 5.93-5.83 (m, 2H, $OCH_2CH=CH_2$ × 2), 5.35 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H, $OCH_2CH=CH_2$ of Alloc), 5.30 (d, *J* = 15.4 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 5.34-5.28 (m, 1H, H-3'), 5.28-5.25 (m, 1H, NH), 5.24 (dd, *J* = 10.5, 1.4 Hz, 1H, $OCH_2CH=CH_2$ of Alloc), 5.20 (d, *J* = 10.6 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 5.21-5.18 (m, 1H, NH'), 5.16-5.04 (m, 4H, *o* -$C_6H_4(CH_2O)_2P$), 4.89 (d, *J* = 2.8 Hz, 1H, H-1), 4.83 (d, *J* = 11.2 Hz, 1H, CH_2 of Troc), 4.74 (d, *J* = 7.4 Hz, 1H, CH_2 of Troc), 4.70 (d, *J* = 14.1 Hz, 1H, H-1'), 4.67 (d, *J* = 11.5 Hz, 1H, CH_2 of Troc), 4.63-4.58 (m, 1H, H-4'), 4.58-4.56 (m, 3H, CH_2 of Troc and $OCH_2CH=CH_2$ of Alloc), 4.62-4.48 (m, 4H, Ph-CH_2 × 2), 4.15 (dd, *J* = 12.6, 6.3 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 4.17-4.13 (m, 1H, H-6a), 3.95 (dd, *J* = 12.6, 6.2 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 3.91-3.87 (m, 4H, H-2, H-3 and H-6'), 3.79-3.76 (m, 2H, H-5 and H-6b), 3.76-3.72 (m, 1H, H-5'), 3.58 (dd, *J* = 17.9, 8.3 Hz, 1H, H-2'), 3.51 (t, *J* = 8.7 Hz, 1H, H-4), 2.53 (d, *J* =3.0 Hz, 1H, C_3-OH).

Allyl 6-*O*-[3-*O*-Allyloxycarbonyl-6-*O*-benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-gluco-pyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-deoxy-2-(2,2,2-trichloroethoxy-carbonylamino)-α-D-glucopyranoside (23). To a solution of disaccharide **22** (71.0 mg, 60.3 μmol) in anhydrous 1,2-dichloroethane (3 mL) were added (*R*)-3-(benzyloxy)decanoic acid (**11**) (20.0 mg, 71.8 μmol), DCC (20.0 mg, 96.9 μmol), and DMAP (1.0 mg, 8.2 μmol). The mixture was stirred at room temperature for 1h. Then MeOH (50 μL) and AcOH (10 μL) were added, and the mixture was stirred for 10 min. After the insoluble materials were filtered off, the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc and worked up as usual. The residue was purified by silica-gel column chromatography (20 g, $CHCl_3$/Acetone = 15:1) to give **23** as a colorless solid (85.3 mg, 98%). $[\alpha]_D^{23}$ = +26.7 (c 1.00, $CHCl_3$). Found: C, 53.83; H, 5.41; N, 2.07%. Calcd. for $C_{64}H_{77}Cl_6N_2O_{20}P$: C, 53.46; H, 5.40; N, 1.95%. FAB-MS (positive): m/z 1457.0 $[(M+Na)^+]$. ^1H NMR (500 MHz) δ = 7.36-7.26 (m, 15H, Ph-CH_2 × 5), 7.23-7.18 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 5.92-5.85 (m, 2H, $OCH_2CH=CH_2$ × 2), 5.39 (t, *J* = 9.4 Hz, 1H, H-3), 5.36 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H, $OCH_2CH=CH_2$ of Alloc), 5.29 (dd, *J* = 5.3, 3.9 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 5.30-5.28 (m, 1H, NH), 5.25 (dd, *J* = 10.3, 1.2 Hz, 1H, $OCH_2CH=CH_2$ of Alloc), 5.26-5.22 (m, 1H, H-3'), 5.20 (dd, *J* = 10.3, 1.4 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 5.17-5.12 (m, 1H, NH'), 5.13-5.03 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 4.89 (d, *J* = 3.4 Hz, 1H, H-1), 4.68 (d, *J* = 11.9 Hz, 1H, CH_2 of Troc), 4.63-4.53 (m, 8H, H-1', Ph-CH_2 × 2, $OCH_2CH=CH_2$ of Alloc and H-4'), 4.53-4.44 (m, 4H, Ph-CH_2 and CH_2 of Troc), 4.15 (ddt, *J* = 11.5, 5.3, 1.4 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 4.09 (d, J = 9.4 Hz, 1H, H-6a), 3.96 (dd, *J* = 12.6, 6.2 Hz, 1H, $OCH_2CH=CH_2$ of allyl glycoside), 3.92 (dd, *J* = 10.9, 4.1 Hz, H-2), 3.86 (dd, *J* = 10.5, 9.2 Hz, 2H, H-6'), 3.86-3.83 (m, 1H, β-CH of *O*-acyl), 3.75-3.67 (m, 4H, H-

4, H-5, H-6b and H-5'), 3.57 (dd, J = 17.9, 8.3 Hz, 1H, H-2'), 2.57 (dd, J = 16.0, 7.3 Hz, 1H, α-CH_2 of *O*-acyl), 2.42 (dd, J = 16.0, 5.1 Hz, 1H, α-CH_2 of *O*-acyl), 1.71-1.64 (m, 2H, CH_2), 1.39-1.18 (m, 10H, $CH_2 \times 5$), 0.88 (t, J = 6.9 Hz, CH_3).

Allyl 6-*O*-[6-*O*-Benzyl-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (24). To a solution of **23** (98.5 mg, 68.5 μmol) in anhydrous THF (3 mL) were added n-$BuNH_2$ (13.5 μL, 137 μmol), HCOOH (5.2 μL, 138 μmol), and tetrakis(triphenylphosphine)palladium(0) (4.0 mg, 3.5 μmol). After the mixture was stirred at room temperature for 1 h, EtOAc was added. The organic layer was washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine and worked up as usual. The residue was purified by silica-gel column chromatography (21 g, $CHCl_3$/Acetone = 7:1) to give **24** as a colorless solid (78.8 mg, 85%). $[\alpha]_D^{23}$ = +27.6 (c 1.09, $CHCl_3$). Found: C, 53.73; H, 5.64; N, 2.55%. Calcd. for $C_{60}H_{73}Cl_6N_2O_{18}P$: C, 53.23; H, 5.43; N, 2.07%. FAB-MS (positive): m/z 1373.9 [(M+Na)$^+$]. ^{1}H NMR (500 MHz) δ = 7.53 (dd, J = 14.3, 7.2 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 7.50 (dtd, J = 42.9, 8.6, 3.5 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 7.28-7.26 (m, 2H, *o*-$C_6H_4(CH_2O)_2P$), 7.26-7.24 (m, 15H, Ph-$CH_2 \times 3$), 5.89-5.83 (m, 1H, $OCH_2CH{=}CH_2$), 5.40 (t, J = 10.5 Hz, 1H, H-3), 5.30 (d, J = 9.4 Hz, 1H, $OCH_2CH{=}CH_2$), 5.31-5.29 (m, 1H, NH), 5.20 (d, J = 11.0 Hz, 1H, $OCH_2CH{=}CH_2$), 5.21-5.19 (m, 1H, NH'), 5.17-4.98 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 4.90 (d, J = 3.7 Hz, 1H, H-1), 4.67 (dd, J = 17.2, 11.9 Hz, 2H, CH_2 of Troc), 4.60-4.56 (m, 1H, H-1'), 4.61-4.50 (m, 6H, Ph-$CH_2 \times 3$), 4.45 (d, J = 11.5 Hz, 2H, CH_2 of Troc), 4.36 (dd, J = 16.1, 8.7 Hz, 1H, H-4'), 4.17 (dd, J = 12.8, 5.3 Hz, 1H, $OCH_2CH{=}CH_2$), 4.12-4.08 (m, 2H, H-6a and H-3'), 3.99 (dd, J = 13.5, 7.3 Hz, 1H, $OCH_2CH{=}CH_2$), 3.94 (dd, J = 11.0, 4.4 Hz, 1H, H-2), 3.88-3.84 (m, 1H, β-CH of *O*-acyl), 3.78-3.70 (m, 5H, H-4, H-5, H-6b and H-6'), 3.63-3.60 (m, 1H, H-5'), 3.40 (dd, J = 19.6, 8.7 Hz, 1H, H-2'), 2.58 (dd, J = 16.3, 7.6 Hz, 1H, α-CH_2 of *O*-acyl), 2.42 (dd, J = 16.1, 4.8 Hz, 1H, α-CH_2 of *O*-acyl), 1.70 (dt, J = 13.8, 3.7 Hz, 2H, CH_2), 1.39-1.19 (m, 10H, $CH_2 \times 5$), 0.88 (t, J = 6.9 Hz, 3H, CH_3).

Allyl 6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (25). To a solution of **24** (77.9 mg, 57.5 μmol) in anhydrous 1,2-dichloroethane (3 mL) were added (*R*)-3-(benzyloxy)decanoic acid (**11**) (25.0 mg, 89.8 μmol), DCC (20.0 mg, 96.9 μmol), and DMAP (1.0 mg, 8.2 μmol). The mixture was stirred at room temperature for 3 h and worked up as described in the preparation of **23**. The residue was purified by silica-gel column chromatography (21 g, $CHCl_3$/Acetone = 20:1) to give **25** as a colorless solid (68.6 mg, 74%). $[\alpha]_D^{23}$ = +23.0 (c 0.83, $CHCl_3$). Found: C, 57.62; H, 6.00; N, 1.68%. Calcd. for $C_{77}H_{97}Cl_6N_2O_{20}P$: C, 57.29; H, 6.16; N, 1.74%. FAB-MS (positive): m/z 1611.4 [(M+H)$^+$]. ^{1}H NMR (500 MHz) δ = 7.37-7.21 (m, 22H, *o*-$C_6H_4(CH_2O)_2P$ and Ph-$CH_2 \times 4$), 7.13 (d, J = 7.1 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 6.88 (d, J = 7.2 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 5.90-5.82 (m, 1H, $OCH_2CH{=}CH_2$), 5.43 (t, J = 10.1 Hz, 1H, H-3'), 5.40 (dd, J = 10.6, 9.4 Hz, 1H, H-3), 5.28 (dd, J = 9.0 Hz, 1H, NH), 5.28 (dd, J = 17.7, 1.6 Hz, 1H, $OCH_2CH{=}CH_2$), 5.20 (dd, J = 10.3, 1.2 Hz, 1H, $OCH_2CH{=}CH_2$), 5.08-4.90 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 4.92 (d, J = 7.4 Hz, 1H, NH'), 4.89 (d, J = 3.5 Hz, 1H, H-1), 4.69 (d, J = 12.2 Hz, 1H, CH_2 of Troc), 4.65-4.45 (m, 12H, H-1', H-4', Ph-$CH_2 \times 4$ and CH_2 of Troc), 4.38 (d, J = 12.1 Hz, 1H, CH_2 of Troc), 4.15 (dd, J = 12.6, 5.1

Hz, 1H, $OCH_2CH=CH_2$), 4.08 (d, J = 9.6 Hz, 1H, H-6a), 3.96 (dd, J = 12.8, 6.7 Hz, 1H, $OCH_2CH=CH_2$), 3.94 (dd, J = 16.7, 3.5 Hz, 1H, H-2), 3.88-3.83 (m, 4H, H-6' and β-CH of *O*-acyl × 2), 3.75-3.66 (m, 4H, H-4, H-5, H-6b and H-5'), 3.37 (dd, J = 18.4, 8.3 Hz, 1H, H-2'), 2.66 (t, J = 6.2 Hz, 2H, α-CH_2 of $C_{3'}$-*O*-acyl), 2.59 (dd, J = 16.0, 7.3 Hz, 1H, α-CH_2 of C_3-*O*-acyl), 2.44 (dd, J = 16.0, 5.0 Hz, 1H, α-CH_2 of C_3-*O*-acyl), 1.64-1.47 (m, 4H, CH_2 × 2), 1.37-1.24 (m, 20H, CH_2 × 10), 0.90-0.86 (m, 6H, CH_3 × 2).

Allyl 6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)-decanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)decanoylamino]-2-deoxy-α-D-glucopyranoside (26a).

To a solution of **25** (38.4 mg, 23.8 μmol) in AcOH (4 mL) was added zinc-copper couple (500 mg), and the mixture was stirred at room temperature for 1 h. After the insoluble material was filtered off, the filtrate was concentrated *in vacuo*, and the residual solvent coevaporated with toluene three times. The crude product was dissolved in EtOAc and worked up as usual to give the *N*-deprotected product (32.0 mg, quant.).

The crude amine thus obtained was dissolved in anhydrous $CHCl_3$ (2mL). To this solution were added (*R*)-3-(benzyloxy)decanoic acid (**11**) (30.0 mg, 108 μmol), HOAt (10.0 mg, 73.5 μmol), and WSCD•HCl (20.0 mg, 104 μmol). The mixture was stirred at room temperature for 13 h, and then added **11** (25.0 mg, 89.8 μmol) and WSCD•HCl (15.0 mg, 92.8 μmol). After the solution was stirred for additional 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and worked up as usual. The residue was purified by preparative TLC ($CHCl_3$/Acetone = 10:1) to give **26a** as a colorless solid (33.3 mg, 79 %). FAB-MS (positive): m/z 1784.0 $[(M+H)^+]$. ^1H NMR (500 MHz) δ = 7.35-7.18 (m, 32H, *o*-$C_6H_4(CH_2O)_2P$ and Ph-CH_2 × 6), 7.12 (d, J = 7.1 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 6.77 (d, J = 7.2 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 6.28 (d, J = 8.3 Hz, 1H, NH'), 6.19 (d, J = 9.4 Hz, 1H, NH), 5.71-5.65 (m, 1H, $OCH_2CH=CH_2$), 5.50 (dd, J = 10.3, 8.9 Hz, 1H, H-3'), 5.35 (dd, J = 10.8, 9.2 Hz, 1H, H-3), 5.16 (ddd, J = 15.6, 1.6, 1.4 Hz, 1H, $OCH_2CH=CH_2$), 5.05 (dd, J = 10.3, 1.4 Hz, 1H, $OCH_2CH=CH_2$), 5.02-4.91 (m, 4H, *o*-$C_6H_4(CH_2O)_2P$), 4.74 (d, J = 3.5 Hz, 1H, H-1), 4.72 (d, J = 8.2 Hz, 1H, H-1'), 4.63-4.58 (m, 1H, H-4'), 4.63-4.41 (m, 12H, Ph-CH_2 × 6), 4.29 (ddd, J = 9.7, 3.4, 1.4 Hz, 1H, H-2), 3.99 (ddd, J = 14.2, 5.3, 1.6 Hz, 1H, $OCH_2CH=CH_2$), 3.97 (dd, J = 8.9, 1.6 Hz, 1H, H-6a), 3.87-3.79 (m, 5H, H-6', β-CH of *O*-acyl × 2 and β-CH of *N*-acyl), 3.73-3.68 (m, 3H, $OCH_2CH=CH_2$, H-6b and H-5'), 3.66-3.56 (m, 4H, H-4, H-5, H-2' and β-CH of *N*-acyl), 2.71 (dd, J = 16.7, 7.4 Hz, 1H, α-CH_2 of $C_{3'}$-*O*-acyl), 2.56-2.52 (m, 2H, α-CH_2 of *O*-acyl), 2.38 (dd, J = 16.0, 5.5 Hz, 1H, α-CH_2 of C_3-*O*-acyl), 2.28 (d, J = 1.6 Hz, 1H, α-CH_2 of *N*-acyl), 2.25 (dd, J = 16.7, 8.5 Hz, 2H, α-CH_2 of *N*-acyl), 2.16 (dd, J = 15.3, 4.1 Hz, 2H, α-CH_2 of *N*-acyl), 1.60-1.21 (m, 48H, CH_2 × 24), 0.89-0.85 (m, 12H, CH_3 × 4).

Allyl 6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)tetradecanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)tetradecanoylamino]-2-deoxy-α-D-glucopyranoside (26b). In a manner similar to the preparation of **26a**, **25** (93.0 mg, 57.6 μmol) was deprotected and acylated with (*R*)-3-(benzyloxy)-tetradecanoic acid to yield **26b** as a colorless solid (70.6 mg, 65%). $[\alpha]_D^{20}$ = +11.7 (c 0.52, $CHCl_3$). Found: C, 70.55; H, 8.23; N, 1.50%. Calcd. for $C_{113}H_{159}N_2O_{20}P•1.5H_2O$: C, 70.56; H, 8.49; N, 1.46%. ESI-MS (positive): m/z 1997.1 $[(M+Et_3NH)^+]$. ^1H NMR (500 MHz) δ = 7.35-7.19 (m, 32H, *o*-$C_6H_4(CH_2O)_2P$ and Ph-CH_2 × 6), 7.11 (d, J = 7.4 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$), 6.77 (d, J = 7.6 Hz, 1H, *o*-$C_6H_4(CH_2O)_2P$),

6.25 (d, J = 8.3 Hz, 1H, NH'), 6.18 (d, J = 9.4 Hz, 1H, NH), 5.71-5.65 (m, 1H, $OCH_2CH{=}CH_2$), 5.49 (t, J = 9.2 Hz, 1H, H-3'), 5.35 (t, J = 10.5 Hz, 1H, H-3), 5.16 (d, J = 18.1 Hz, 1H, $OCH_2CH{=}CH_2$), 5.05 (d, J = 10.3 Hz, 1H, $OCH_2CH{=}CH_2$), 5.02-4.88 (m, 4H, o-$C_6H_4(CH_2O)_2P$), 4.74 (d, J = 3.7 Hz, 1H, H-1), 4.70 (d, J = 8.3 Hz, 1H, H-1'), 4.62-4.56 (m, 1H, H-4'), 4.59-4.41 (m, 12H, Ph-CH_2 × 6), 4.29 (ddd, J = 11.0, 3.4, 1.4 Hz, 1H, H-2), 4.01-3.95 (m, 2H, H-6a and $OCH_2CH{=}CH_2$), 3.88-3.79 (m, 5H, H-6', β-CH of O-acyl × 2 and β-CH of N-acyl), 3.73-3.68 (m, 3H, $OCH_2CH{=}CH_2$, H-6b and H-5'), 3.66-3.55 (m, 4H, H-4, H-5, H-2' and β-CH of N-acyl), 2.70 (dd, J = 16.7, 7.4 Hz, 1H, α-CH_2 of C_3'-O-acyl), 2.58-2.52 (m, 2H, α-CH_2 of O-acyl), 2.38 (dd, J = 15.8, 5.3 Hz, 1H, α-CH_2 of C_3-O-acyl), 2.24 (dd, J = 15.8, 7.6 Hz, 3H, α-CH_2 of N-acyl), 2.16 (dd, J = 15.3, 4.1 Hz, 1H, α-CH_2 of N-acyl), 1.56-1.24 (m, 64H, CH_2 × 32), 0.88 (ddd, J = 6.7, 5.7, 5.7 Hz, 12H, CH_3 × 4).

6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)decanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)-decanoylamino]-2-deoxy-α-D-glucopyranose (27a).

To a degassed solution of **26a** (47.0 mg, 26.3 μmol) in anhydrous THF (3 mL) was added [bis(methyldiphenylphosphine)](1,5-cyclooctadiene)iridium(I) hexafluorophosphate (5.0 mg, 5.9 μmol). After activation of the iridium catalyst with hydrogen three times (each 15 sec), the mixture was stirred under nitrogen atmosphere at room temperature for 50 min. Then iodine (15.0 mg, 59.1 μmol) and water (4.0 mL) were added and the reaction mixture was stirred for additional 20 min. To the mixture was added 5% aqueous $Na_2S_2O_3$ and the solution was extracted with EtOAc. The extract was washed with 5% aqueous $Na_2S_2O_3$ and brine and worked up as usual. The crude product was purified by silica-gel column chromatography (20 g, $CHCl_3$/Acetone = 10:1) to give **27a** (α:β =1:1) as a white solid (30.9 mg, 69%). FAB-MS (positive): m/z 1744.0 [(M+H)$^+$]. ^{1}H NMR (500 MHz) δ = 7.37-7.11 (m, 33H, o-$C_6H_4(CH_2O)_2P$ and Ph-CH_2 × 6), 6.77 (d, J = 7.4 Hz, 1H, o-$C_6H_4(CH_2O)_2P$), 6.28 (d, J = 8.3 Hz, 1H, NH'), 6.19 (d, J = 9.4 Hz, 1H, NH), 5.47 (dd, J = 10.3, 9.2 Hz, 1H, H-3'), 5.32 (dd, J = 10.5, 9.2 Hz, 1H, H-3), 5.12 (d, J = 8.2 Hz, 1H, H-1'), 5.04-4.88 (m, 5H, H-1 and o-$C_6H_4(CH_2O)_2P$), 4.81 (s, 1H, C_1-OH), 4.64-4.59 (m, 1H, H-4'), 4.64-4.37 (m, 12H, Ph-CH_2 × 6), 4.14 (ddd, J = 9.7, 3.4, 1.4 Hz, 1H, H-2), 3.96-3.90 (m, 2H, H-5 and H-6a), 3.89-3.79 (m, 5H, H-6', β-CH of O-acyl × 2 and β-CH of N-acyl), 3.73-3.69 (m, 2H, H-5' and β-CH of N-acyl), 3.58 (dd, J = 12.2, 8.7 Hz, 1H, H-6b), 3.41 (ddd, J = 18.3, 10.3, 8.0 Hz, 1H, H-2'), 3.27 (t, J = 9.9 Hz, 1H, H-4), 2.70 (dd, J = 16.8, 7.4 Hz, 1H, α-CH_2 of C_3'-O-acyl), 2.61-2.54 (m, 2H, α-CH_2 of O-acyl), 2.39 (dd, J = 16.0, 5.3 Hz, 1H, α-CH_2 of C_3-O-acyl), 2.31 (dd, J = 14.9, 7.8 Hz, 1H, α-CH_2 of N-acyl), 2.25 (ddd, J = 14.7, 7.6, 4.1 Hz, 2H, α-CH_2 of N-acyl), 2.16 (dd, J = 15.6, 7.8 Hz, 1H, α-CH_2 of N-acyl), 1.59-1.22 (m, 48H, CH_2 × 24), 0.89-0.85 (m, 12H, CH_3 × 4).

6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)tetradecanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)tetradecanoylamino]-2-deoxy-α-D-glucopyranose (27b). In a manner similar to the synthesis of **27a**, compound **27b** was obtained from **26b** (38.1 mg, 20.1 μmol) as a pale yellow solid (27.4 mg, 74%). ESI-MS (positive): m/z 1957.4 [(M+Et_3NH)$^+$]. ^{1}H NMR (500 MHz) δ = 7.38-7.11 (m, 33H, o-$C_6H_4(CH_2O)_2P$ and Ph-CH_2 × 6), 6.77 (d, J = 7.6 Hz, 1H, o-$C_6H_4(CH_2O)_2P$), 6.31 (d, J = 8.3 Hz, 1H, NH'), 6.20 (d, J = 9.4 Hz, 1H, NH), 5.47 (t, J = 10.3 Hz, 1H, H-3'), 5.31 (t, J = 10.6 Hz, 1H, H-3), 5.13 (d, J = 8.3 Hz, 1H,

H-1'), 5.04-4.84 (m, 5H, H-1 and *o*-$C_6H_4(CH_2O)_2P$), 4.73 (s, 1H, C_1-OH), 4.64-4.58 (m, 1H, H-4'), 4.64-4.38 (m, 12H, Ph-CH_2 × 6), 4.14 (ddd, *J* = 12.8, 3.4, 1.4 Hz, 1H, H-2), 3.96-3.91 (m, 2H, H-5 and H-6a), 3.87-3.79 (m, 5H, H-6', β-CH of *O*-acyl × 2 and β-CH of *N*-acyl), 3.72-3.70 (m, 2H, H-5' and β-CH of *N*-acyl), 3.59 (dd, *J* = 11.9, 8.5 Hz, 1H, H-6b), 3.40 (dd, *J* = 17.9, 8.0 Hz, 1H, H-2'), 3.27 (t, *J* = 9.9 Hz, 1H, H-4), 2.70 (dd, *J* = 17.0, 7.4 Hz, 1H, α-CH_2 of C_3'-*O*-acyl), 2.58-2.54 (m, 2H, α-CH_2 of *O*-acyl), 2.39 (dd, *J* = 16.1, 5.5 Hz, 1H, α-CH_2 of C_3-*O*-acyl), 2.33-2.22 (m, 3H, α-CH_2 of *N*-acyl), 2.16 (dd, *J* = 15.6, 7.8 Hz, 1H, α-CH_2 of *N*-acyl), 1.58-1.22 (m, 64H, CH_2 × 32), 0.89-0.85 (m, 12H, CH_3 × 4).

6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)decanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-benzyloxydecanoyl]-2-[(*R*)-3-(benzyloxy)decanoylamino]-1-*O*-bis(benzyloxy)phosphoryl-2-deoxy-α-D-glucopyranose (28a). To a solution of **27a** (28.6 mg, 16.4 μmol) and tetrabenzyl diphosphate (12.0 mg, 22.3 μmol) in anhydrous THF (4 mL) was added lithium bis(trimethylsilyl)amide in THF (1.0 M, 23 mL, 23 μmol) at -78 °C. The mixture was stirred at that temperature for 90 min. The mixture was then allowed to warm gradually to room temperature, neutralized with saturated aqueous $NaHCO_3$, extracted with EtOAc, and worked up as usual. The residue was purified by silica-gel column chromatography (20 g, $CHCl_3$/acetone/Et_3N = 10:1:0.02%) to give **28a** as a pale yellow oil (27.9 mg, 85%).

6-*O*-[6-*O*-Benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)tetradecanoylamino]-2-deoxy-4-*O*-(1,5-dihydro-3-oxo-3λ^5-3H-2,4,3-benzodioxaphosphepin-3-yl)-β-D-glucopyranosyl]-4-*O*-benzyl-3-*O*-[(*R*)-3-(benzyloxy)decanoyl]-2-[(*R*)-3-(benzyloxy)-tetradecanoylamino]-1-*O*-bis(benzyloxy)phosphoryl-2-deoxy-α-D-glucopyranose (28b). In a manner similar to the synthesis of **28a**, **27b** (34.3 mg, 18.5 μmol) was phosphorylated to yield **28b** as a colorless solid (19.8 mg, 51%).

2-Deoxy-6-*O*-[2-deoxy-3-*O*-[(*R*)-3-hydroxydecanoyl]-2-*O*-[(*R*)-3-hydroxydecanoylamino]-α-D-glucopyranosyl]-3-*O*-[(*R*)-3-hydroxydecanoyl]-2-*O*-[(*R*)-3-hydroxydecanoylamino]-α-D-glucopyranose 1,4'-Bisphosphate (3).

To a solution of **28a** (27.9 mg, 13.9 μmol) in anhydrous THF (3 mL) was added Pd-black (37.1 mg). The mixture was stirred under 7 kg cm^{-2} of hydrogen at room temperature for 19 h. Then another Pd-black (35.9 mg) was added, and the reaction mixture was stirred for additional 19 h. The mixture was then neutralized with Et_3N in THF (10%, 60 μL). After removal of the Pd catalyst by filtration, the solvent was evaporated *in vacuo*. The crude product was purified by liquid-liquid partition column chromatography (15 g of Sephadex® LH-20, $CHCl_3$/MeOH/^{i}PrOH/H_2O/Et_3N = 20:20:2.5:22.5:0.001). The organic layer was the stationary phase, and the aqueous layer was the mobile phase in this chromatography. After removal of the solvent *in vacuo* followed by lyophilization, **3** was obtained as triethylammonium salt (colorless solid, 8.7 mg, 53%). ESI-MS (negative): m/z 1179.7 [(M-H)$^-$], 589.1 [(M-2H)$^{2-}$].

2-Deoxy-6-*O*-[2-deoxy-3-*O*-[(*R*)-3-hydroxydecanoyl]-2-*O*-[(*R*)-3-hydroxytetradecanoylamino]-α-D-glucopyranosyl]-3-*O*-[(*R*)-3-hydroxydecanoyl]-2-*O*-[(*R*)-3-hydroxytetradecanoylamino]-α-D-glucopyranose 1,4'-Bisphosphate (4). In a manner similar to the synthesis of **3**, **28b** (15.0 mg, 7.09 μmol) was deprotected to yield **4** as triethylammonium salt (white powder, 5.5 mg, 60%). ESI-MS (negative): m/z 1291.6 [(M-H)$^-$], 645.3 [(M-2H)$^{2-}$].

Acknowledgments: This work was supported in part by Grant-in-Aid for Scientific Research on Priority Areas No. 06240105, No 08245229, and No. 09231228 and Grant-in-Aid for International Scientific Research No. 09044086 from the Ministry of Education, Science and Culture, Japan, by "Research for the Future" Program No. 97L00502 from the Japan Society for the Promotion of Science, and by a research fund from Kyowa Hakko Kogyo Co., Ltd.

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