Zinc Triflate-Promoted Glycosidation: Synthesis of Lipid A Disaccharide Intermediates

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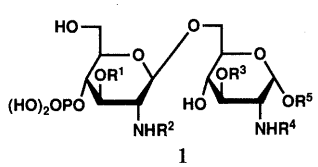
Zinc triflate was found to be superior to the heavy metal salts as a promoter in the Koenigs–Knorr type glycosidation reaction in the synthesis of lipid A disaccharide intermediates. It readily promoted the reaction of a complex glycosyl bromide with a reducing sugar moiety and gave the disaccharide with β-selectivity in good yield. This method would be suitable for the bulk preparation of lipid A disaccharide intermediates.

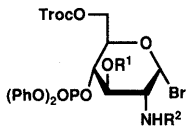
Keywords glycosidation; Lewis acid; zinc triflate; zinc halide; glycosyl bromide; Koenigs–Knorr reaction; heavy metal salt; lipid A; disaccharide

In our study of the synthesis of lipid A derivatives, we have employed the Koenigs–Knorr method[1] using $Hg(CN)_2$ as a promoter in the glycosidation step.[2] This method, however, is not suitable for bulk preparation, because of the use of a toxic reagent. An alternative reagent was therefore required for this key reaction in the preparation of lipid A derivatives.

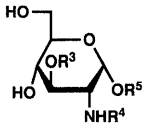


1

	R^1	R^2	R^3	R^4	R^5
1	$GlyC_{12}$	C_{14}	$GlyC_{12}$	C_{14}	$CH(CH_2CO_2H)_2$



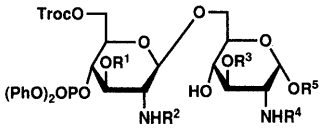
2–4



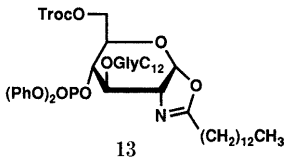
5–7

	R^1	R^2
2	$GlyC_{12}$	Troc
3	$C_{14}OC_{14}$	Troc
4	$GlyC_{12}$	C_{14}

	R^3	R^4	R^5
5	$GlyC_{12}$	Troc	$CH_2CH_2OPO(OPh)_2$
6	$C_{14}OBn$	$C_{14}OBn$	allyl
7	$GlyC_{12}$	C_{14}	$CH(CH_2CO_2Bn)_2$



8–12



13

	R^1	R^2	R^3	R^4	R^5
8	$GlyC_{12}$	Troc	$GlyC_{12}$	Troc	$CH_2CH_2OPO(OPh)_2$
9	$C_{14}OC_{14}$	Troc	$C_{14}OBn$	$C_{14}OH$	allyl
10	$C_{14}OC_{14}$	Troc	$C_{14}OH$	$C_{14}OBn$	allyl
11	$C_{14}OC_{14}$	Troc	$C_{14}OBn$	$C_{14}OBn$	allyl
12	$GlyC_{12}$	C_{14}	$GlyC_{12}$	C_{14}	$CH(CH_2CO_2Bn)_2$

Bn: CH_2Ph

C_{14}: $CO(CH_2)_{12}CH_3$

$C_{14}OH$: $COCH_2\underset{\underset{OH}{|}}{\overset{(R)}{C}}H(CH_2)_{10}CH_3$

$C_{14}OBn$: $COCH_2\underset{\underset{OBn}{|}}{\overset{(R)}{C}}H(CH_2)_{10}CH_3$

$C_{14}OC_{14}$: $COCH_2\underset{\underset{OCO(CH_2)_{12}CH_3}{|}}{\overset{(R)}{C}}H(CH_2)_{13}CH_3$

$GlyC_{12}$: $COCH_2NHCO(CH_2)_{10}CH_3$

Troc: $COOCH_2CCl_3$

Fig. 1

We reported that in the case of the coupling reaction of simple alcohols with glycosyl bromides, the combined use of trityl chloride (TrCl) and $ZnCl_2$ proved to be effective as a catalyst for β-selective glycosidation, while zinc halide alone was suitable for α-selective glycosidation.[3a] We applied this methodology to the β (1→6) disaccharide formation of lipid A derivatives.

Firstly, combinations of TrCl and Lewis acid were examined in the reaction of the glycosyl bromide **2**[2c] with the reducing sugar moiety **5** (Fig. 1). The results are shown in Table I (reaction A).

Among these Lewis acids in combination with TrCl, $ZnCl_2$ was the best reagent and gave a β-glycoside **8** selectively (Table I, runs 1—8). Then we studied the glycosidation using Lewis acid alone to ascertain how the stereoselectivity would change. When ZnX_2 was used alone, the β-glycoside **8** was afforded selectively as well (Table I, runs 9—11). The highest yield and shortest reaction time were achieved with $Zn(OTf)_2$ (Table I, run 11).

As described in our previous report,[3] the use of ZnX_2 alone gave an α-glycoside selectively in the case of coupling reaction of simple alcohols and glycosyl bromides; however, this disaccharide formation resulted in the selective production of a β-glycoside. The α-selectivity in the former reaction was attributed to anomerization of β-glycoside, a kinetically favored isomer, by HBr–ZnX_2 complex.[3b] When β-glycoside **8** was exposed to the anomerization reaction

TABLE I. Comparison of Promoter Activity in the Koenigs–Knorr Type Glycosidation Reaction for the Synthesis of Lipid A Disaccharide Derivatives

Run	Reaction	Promoter[a]	Temperature[b]	Time (h)	Product (yield[c] %)
1	A	$TrBF_4$	Reflux	8	—
2	A	TrCl, $AlCl_3$	Reflux	8	—
3	A	TrCl, $MgBr_2$	Reflux	10	—
4	A	TrCl, $BF_3 \cdot OEt_2$	Reflux	8	—
5	A	TrCl, $SnCl_2$	Reflux	24	**8** (18)
6	A	TrCl, $SnCl_4$	Reflux	10	**8** (40)
7	A	TrCl, $ZnCl_2$	Reflux	8	**8** (73)
8	A	TrCl, $ZnCl_2$	r.t.	20	**8** (49)
9	A	$ZnCl_2$	Reflux	10	**8** (82)
10	A	$ZnBr_2$	Reflux	10	**8** (93)
11	A	$Zn(OTf)_2$	Reflux	3	**8** (96)
12	B	$ZnBr_2$	Reflux	7	**9** or **10** (79), **11** (0)
13	B	$Zn(OTf)_2$	Reflux	3	**9** or **10** (51), **11** (32)
14	B	$Zn(OTf)_2$, TMU[d]	Reflux	2	**9** or **10** (0), **11** (89)

a) One mol eq of the reagent was used in each case. *b*) All reactions were carried out in CH_2Cl_2. *c*) Isolated yield. *d*) TMU: 1,1,3,3-tetramethylurea.

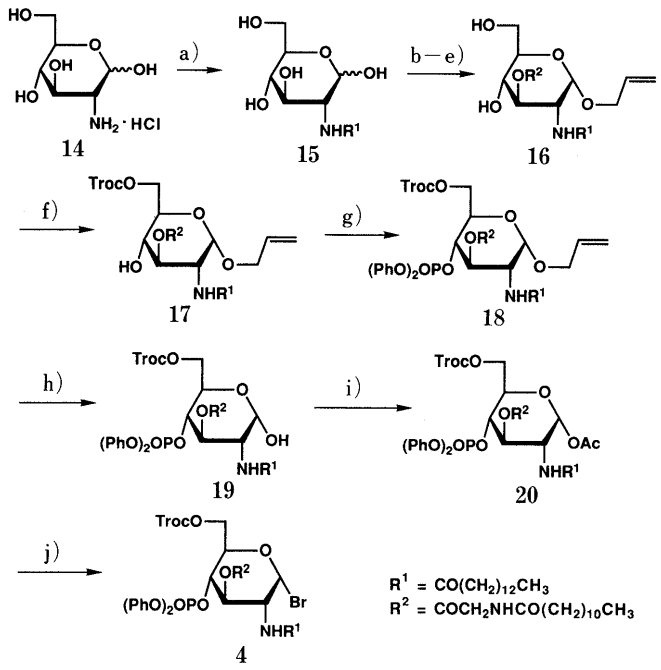


Chart 1

using trimethylsilyl bromide (TMSBr) and $ZnBr_2$,[3b] compound **8** was recovered without anomerization along with a small amount of the glycosyl bromide **2** and the reducing sugar moiety **5**. These results would indicate the disaccharide **8** to be not only the kinetically presumably favored isomer, but also the thermodynamically more stable one, because of the inductive effect, which reduced the anomeric effect, of the oxygen functional groups on the reducing end component.

We next applied this method for the synthesis of a natural *E. coli*-type lipid A disaccharide intermediate (**11**). The results of the reaction of **3** and **6** (reaction B) are shown in Table I. When $ZnBr_2$ was used, the coupling reaction proceeded; however, one of the benzyl group in the fatty acyl moiety at the C2 or C3 position was removed (Table I, run 12). It is not clear which benzyl group is cleaved. With Zn $(OTf)_2$, the same debenzylation product (**9** or **10**) was produced in 51% yield; however, the desired product **11** was obtained in 32% yield (Table I, run 13). As we previously reported,[3b,c] an active complex would be produced with HBr and ZnX_2 which would cause this debenzylation. We therefore added 1,1,3,3-tetramethylurea (TMU) as an acid scavenger, which resulted in a marked increase in the yield of the disaccharide **11** (Table I, run 14). We thus found Zn $(OTf)_2$ to be a useful promoter for Koenigs–Knorr type glycosidation. So, we finally investigated the application of this method to the synthesis of a more complicated lipid A disaccharide to compare the promoter activity of ZnX_2 and that of heavy metal salts.

In the synthesis of compound **1**,[2c] a novel lipid A analog with low toxicity, compound **2** was used as a donor having a 2,2,2-trichloroethoxycarbonyl (Troc) group as a protective group of the amino function at the C2 position. If compound **4**, which has a tetradecanoyl group at the amino function, can be used in the disaccharide formation, the synthesis of **1** would be more straightforward. Compound **4** was synthesized as shown in Chart 1.

Table II. Comparison of Promoter Activity between Heavy Metal Salts and ZnX_2 in the Reaction of **4** and **7**

Run	Promoter[a]	Temperature[b]	Time (h)	Yield of **12** (%)[c]
1	$Hg(CN)_2$	Reflux	4	0[d]
2	$AgClO_4$	0 °C	0.5	0[e]
3	$ZnBr_2$	Reflux	12	0[f]
4	$Zn(OTf)_2$	r.t.	30	71

a) One mol eq of the reagent was used in each case. *b*) All reactions were carried out in CH_2Cl_2. *c*) Isolated yield. *d*) The oxazoline derivative (**13**) was obtained in 41% yield. *e*) Decomposition of the donor (**4**) occurred. *f*) No reaction occurred.

Firstly, D-glucosamine was *N*-acylated with tetradecanoyl chloride, and the anomeric hydroxy group was protected with an allyl group by Fischer's glycosidation. After protection of the 4,6-dihydroxy group with an isopropylidene group, condensation of the 3-hydroxy group with *N*-dodecanoylglycine by the dicyclohexylcarbodiimide (DCC) method, followed by removal of the isopropylidene group by acid-catalyzed solvolysis, afforded **16**. After the 6-hydroxy group was protected with the Troc group, the diphenylphosphono group was introduced at the 4-hydroxy group. Selective deprotection of the 1-*O*-allyl group was carried out with Pd $(PPh_3)_4$–acetic acid,[4] and the resulting 1-hydroxy group was acetylated. Finally, the acetate **20** was converted into the glycosyl bromide **4** with HBr–acetic acid.

The results of the reaction of **4** and **7**[2c] are shown in Table II. With $Hg(CN)_2$, the oxazoline derivative **13** only was produced in 41% yield (Table II, run 1), while the use of a more active heavy metal salt ($AgClO_4$) resulted in a complex mixture arising from decomposition of the donor (Table II, run 2). Using $ZnBr_2$ resulted in no reaction but did not cause decomposition of the bromide **4** (Table II, run 3). When Zn $(OTf)_2$ was used, the reaction proceeded smoothly and produced a reasonable yield of the desired disaccharide **12** (Table II, run 4).

In conclusion, we have found that heavy metal salts can be replaced by ZnX_2, which would be applicable to a large-scale synthesis, for the Koenigs–Knorr reaction in the synthesis of lipid A disaccharide intermediates. Zn $(OTf)_2$ was the most reliable reagent and its promoter activity was higher than that of heavy metal salts.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in deuteriochloroform on a JEOL GSX 500 spectrometer (500 MHz). Chemical shifts are reported in parts per million relative to tetramethylsilane (δ units) as an internal standard. Optical rotations were measured with a Horiba SEDA 200 polarimeter at 25 °C. Mass spectra (MS) were obtained on a JMS-HX 110 instrument. Column chromatography was performed with Merck Silica gel 60 (70—230 mesh). Preparative thin-layer chromatography (preparative TLC) was performed by using precoated silica gel (150 A 1.0 mm thickness; PLK5F Whatman).

2-(Diphenylphosphonooxy)ethyl 2-Deoxy-3-*O*-(*N*-dodecanoylglycyl)-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (5) DCC (290

mg, 1.43 mmol) was added to a solution of 2-(diphenylphosphonooxy)ethyl 2-deoxy-4,6-*O*-isopropylidene-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside[2c] (800 mg, 1.19 mmol), *N*-dodecanoylglycine (370 mg, 1.43 mmol), and 4-dimethylaminopyridine (DMAP) (70 mg) in CH_2Cl_2 (20 ml) under ice-cooling, and the solution was stirred for 16 h at room temperature. The insoluble material was filtered off, and the filtrate was washed with 1 M HCl and brine, then dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in 90% AcOH, and the solution was heated at 90 °C for 20 min. After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 19 : 1) to afford **5** (980 mg, 94%) as an oil. $[\alpha]_D$ +40.7° (c = 1.3, $CHCl_3$). *Anal.* Calcd for $C_{37}H_{52}Cl_3N_2O_{13}P$: C, 51.07; H, 6.02; N, 3.22. Found: C, 50.87; H, 6.38; N, 3.06. ^{1}H-NMR δ: 0.88 (3H, t, J = 7.3 Hz, CH_3), 1.25 (br, CH_2), 1.63 (2H, m, $C\underline{H}_2CH_2CO$), 2.24 (2H, t, J = 7.3 Hz, CH_2CO), 3.66—4.02 (8H, m, H-4, $OC\underline{H}_2CH_2OP$, H-5, $COC\underline{H}_2NH$, H-6), 4.43 (2H, m, $OCH_2C\underline{H}_2OP$), 4.56 (1H, d, J = 12.2 Hz, CH_2CCl_3), 4.80 (1H, d, J = 12.2 Hz, CH_2CCl_3), 4.86 (1H, d, J = 3.4 Hz, H-1), 5.16 (1H, t, J = 8.8 Hz, H-3), 5.88 (1H, d, J = 8.8 Hz, NH), 6.18 (1H, m, NH), 7.2—7.4 (10H, m, arom. H).

General Procedure of Glycosidation Using ZnX_2 (Synthesis of Compound 8) Zinc bromide (20 mg, 0.094 mmol) was added to a solution of **2** (100 mg, 0.094 mmol), **5** (80 mg, 0.094 mmol) and $CaSO_4$ (50 mg) in CH_2Cl_2 (4 ml). The reaction mixture was refluxed for 10 h then diluted with AcOEt. This solution was washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20 : 1) to afford **8** (162 mg, 93%) as an oil. $[\alpha]_D$ +24.0° (c = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{75}H_{99}Cl_9N_4O_{26}P_2$: C, 48.60; H, 5.38; N, 3.02. Found: C, 48.78; H, 5.56; N, 3.01. ^{1}H-NMR δ: 0.88 (6H, t, J = 7.3 Hz, CH_3), 1.25 (br), 1.55 (2H, m), 1.63 (2H, m), 2.09 (2H, t, J = 7.3 Hz, CH_2CO), 2.24 (2H, t, J = 7.3 Hz, CH_2CO), 3.30 (1H, m, H-2′), 3.56 (1H, m, H-4), 3.6—4.0 (m), 4.14 (1H, d, J = 10.1 Hz), 4.31 (1H, dd, J = 11.9, 3.7 Hz), 4.42 (1H, m), 4.46 (1H, d, J = 11.9 Hz), 4.53 (1H, d, J = 11.9 Hz, CH_2CCl_3), 4.55 (1H, d, J = 11.9 Hz, CH_2CCl_3), 4.64 (1H, q, J = 9.2 Hz, H-4′), 4.70 (1H, d, J = 11.9 Hz, CH_2CCl_3), 4.80 (4H, m), 4.97 (1H, d, J = 8.3 Hz, H-1′), 5.11 (1H, t, J = 9.2 Hz, H-3), 5.66 (1H, t, J = 9.2 Hz, H-3′), 5.72 (1H, d, J = 9.2 Hz, NH), 6.14 (1H, m, NH), 6.20 (1H, m, NH), 6.39 (1H, d, J = 7.3 Hz, NH), 7.1—7.4 (20H, m, arom. H).

Reaction of 3 and 6 Using $ZnBr_2$ Zinc bromide (11 mg, 0.049 mmol) was added to a solution of **3** (64 mg, 0.051 mmol), **6** (43 mg, 0.051 mmol) and $CaSO_4$ (100 mg) in CH_2Cl_2 (2 ml). The mixture was refluxed for 3 h, then diluted with AcOEt. This solution was washed with saturated $NaHCO_3$ aqueous solution and brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by preparative TLC using $CHCl_3$–MeOH (100 : 3) as an eluant to give a monodebenzylated disaccharide derivative (**9** or **10**) (78 mg, 79%) as an oil. $[\alpha]_D$ +24.0° (c = 0.4, $CHCl_3$). FD-MS: m/z 1938 (M^+). ^{1}H-NMR δ: 0.88 (12H, t, J = 7.3 Hz), 1.26 (br), 1.43 (br), 1.57 (br), 1.68 (br), 2.17—2.48 (m), 2.66 (1H, dd), 3.10 (2H, br), 3.36 (1H, m), 3.43 (1H, m), 3.65—3.84 (m), 4.0—4.1 (m), 4.25—4.34 (m), 4.45—4.55 (m), 4.62—4.80 (m), 5.01 (1H, d, J = 8.3 Hz, H-1′), 5.11—5.21 (m), 5.55 (2H, m), 5.72 (2H, m), 5.81 (1H, br), 5.94 (1H, br), 6.26 (1H, d, J = 9.2 Hz), 6.38 (1H, d, J = 9.2 Hz), 7.13—7.34 (15H, m, arom. H).

Reaction of 3 and 6 Using $Zn(OTf)_2$ in the Presence of TMU Zinc triflate (32 mg, 0.087 mmol) was added to a solution of **3** (110 mg, 0.087 mmol), **6** (74 mg, 0.087 mmol), TMU (10 μl, 0.087 mmol) and $CaSO_4$ (10 mg) in CH_2Cl_2 (2 ml). The mixture was refluxed for 2 h, then diluted with AcOEt. This solution was washed with saturated $NaHCO_3$ aqueous solution and brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by preparative TLC using $CHCl_3$–MeOH (20 : 1) as an eluant to give **11** (157 mg, 89%) as an oil. The ^{1}H-NMR of this compound was identical with that of the authentic compound.[2d]

2-Deoxy-2-tetradecanoylamino-α-D-glucopyranose (15) Tetradecanoyl chloride (60 g, 0.24 mol) was added to a solution of D-glucosamine hydrochloride (30 g, 0.14 mol) and $NaHCO_3$ (30 g, 0.36 mol) in H_2O (350 ml) at 0 °C. The solution was stirred for 2 h at room temperature. The precipitated solid was collected and washed with H_2O. This solid was suspended in 10% citric acid aqueous solution and the solid was again collected, washed with *n*-hexane, and dried to give **15** (25.8 g, 47%) as a colorless powder. mp 191—195 °C (dec.). *Anal.* Calcd for $C_{20}H_{39}NO_6$: C, 61.67; H, 10.09; N, 3.60. Found: C, 61.79; H, 9.91; N, 3.72. IR (KBr): 3394, 2926, 2854, 1647, 1554, 1473 cm^{-1}.

Allyl 2-Deoxy-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-α-D-glucopyranoside (16) Compound **15** (2.0 g, 5.13 mmol) was suspended in allyl alcohol (15 ml). Then 4 M HCl/1,4-dioxane (2 ml) was added to the suspension and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure to give an oil. This oil was dissolved in acetone (20 ml) and 2,2-dimethoxypropane (5 ml), followed by the addition of D-camphor-10-sulfonic acid (CSA) (200 mg) and $MgSO_4$ (2 g). The reaction mixture was stirred for 10 min, and triethylamine (2 ml) was added. The insoluble material was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt, and washed with saturated $NaHCO_3$ aqueous solution and brine. After drying over $MgSO_4$, the organic layer was evaporated under reduced pressure to give an oil (1.42 g). This material was dissolved in CH_2Cl_2 (20 ml), and *N*-dodecanoylglycine (970 mg, 3.77 mmol), DMAP (80 mg), and DCC (770 mg, 3.77 mmol) were added consecutively to the solution under ice-cooling. The mixture was stirred for 2 h. The insoluble urea was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in MeOH (50 ml), followed by the addition of CSA (200 mg). The mixture was stirred for 3 h at room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in AcOEt. The solution was washed with H_2O, saturated $NaHCO_3$ aqueous solution and brine, then dried ($MgSO_4$). Evaporation of the solvent gave an oil. This was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20 : 1) to give **16** (918 mg, 44%) as a powder. mp 122—124 °C. $[\alpha]_D$ +53.5° (c = 0.9, $CHCl_3$). *Anal.* Calcd for $C_{37}H_{68}N_2O_8$: C, 66.43; H, 10.25; N, 4.19. Found: C, 66.36; H, 10.20; N, 4.14. IR (KBr): 3292, 2926, 2854, 1755, 1656, 1551, 1470, 1401, 1206 cm^{-1}. ^{1}H-NMR δ: 0.88 (6H, t, J = 7.3 Hz, CH_3), 1.26 (36H, br, CH_2), 1.55 (2H, m, CH_2), 1.64 (2H, m, CH_2), 1.71 (2H, m, CH_2), 2.14 (2H, t J = 7.3 Hz, CH_2CO), 2.24 (2H, t, J = 7.3 Hz, CH_2CO), 2.42 (1H, m), 3.74 (1H, m, H-4), 3.86 (2H, m, H-5, $C\underline{H}_2NH$), 3.98 (2H, q, J = 6.4 Hz, $C\underline{H}_2CH=CH_2$), 4.06 (1H, d, J = 5.5 Hz, $C\underline{H}_2NH$), 4.08 (1H, d, J = 5.5 Hz, H-6), 4.20 (1H, dd, J = 12.8, 5.5 Hz, H-6), 4.25 (1H, td, J = 10.1, 3.7 Hz, H-2), 4.85 (1H, d, J = 3.7 Hz, H-1), 5.15 (1H, m, H-3), 5.23 (1H, d, J = 11.9 Hz, $CH_2CH=C\underline{H}_2$), 5.30 (1H, dd, J = 11.9, 1.8 Hz, $CH_2CH=C\underline{H}_2$), 5.79 (1H, d, J = 10.1 Hz, NH), 5.88 (1H, m, $CH_2C\underline{H}=CH_2$), 6.30 (1H, br, NH).

Allyl 2-Deoxy-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranoside (17) 2,2,2-Trichloroethyl chloroformate (0.10 ml, 0.73 mmol) was added to a solution of **16** (500 mg, 0.75 mmol) in pyridine (5 ml) under ice-cooling. The mixture was stirred for 10 min at the same temperature. Then 1 M HCl (30 ml) was added, and the mixture was extracted with AcOEt. The organic layer was washed with brine and then dried ($MgSO_4$). Evaporation of the solvent gave an oil. This oil was purified by silica gel column chromatography ($CHCl_3$–acetone, 20 : 1) to give **17** (580 mg, 92%) as a colorless powder. mp 99—102 °C. $[\alpha]_D$ +44.4° (c = 1.2, $CHCl_3$). IR (KBr): 3304, 2926, 2854, 1755, 1656, 1548, 1470, 1380, 1338 cm^{-1}. ^{1}H-NMR δ: 0.88 (6H, t, J = 7.3 Hz, CH_3), 1.26 (36H, br, CH_2), 1.56 (4H, m, $C\underline{H}_2CH_2CO$), 2.13 (2H, m, CH_2CO), 2.25 (2H, t, J = 7.3 Hz, CH_2CO), 3.66 (1H, td, J = 9.6, 3.7 Hz, H-4), 3.82 (1H, dd, J = 18.3, 5.5 Hz, $C\underline{H}_2NH$), 3.93 (1H, m, H-5), 4.02 (2H, m, $C\underline{H}_2NH$, $C\underline{H}_2CH=CH_2$), 4.20 (1H, dd, J = 12.8, 5.5 Hz, $C\underline{H}_2CH=CH_2$), 4.29 (1H, td, J = 10.1, 3.7 Hz, H-2), 4.49 (1H, dd, J = 11.9, 5.5 Hz, H-6), 4.56 (1H, dd, J = 11.9, 1.8 Hz, H-6), 4.78 (2H, ABq, J = 11.9 Hz, CH_2CCl_3), 4.84 (1H, d, J = 3.7 Hz, H-1), 5.14 (1H, dd, J = 11.0, 9.2 Hz, H-3), 5.24 (1H, d, J = 10.1 Hz, $CH_2CH=C\underline{H}_2$), 5.30 (1H, d, J = 10.1 Hz, $CH_2CH=C\underline{H}_2$), 5.71 (1H, d, J = 10.1 Hz, NH), 5.88 (1H, m, $CH_2C\underline{H}=CH_2$), 6.13 (1H, br, NH).

Allyl 2-Deoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranoside (18) Diphenyl phosphorochloridate (0.15 ml, 0.72 mmol) was added to a solution of **17** (500 mg, 0.592 mmol), DMAP (7 mg) and pyridine (1 ml) in CH_2Cl_2 (10 ml) at room temperature. The mixture was stirred for 30 min, then diluted with AcOEt. This solution was washed with 1 M HCl and brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$–acetone, 10 : 1) to give **18** (479 mg, 75%) as a wax. $[\alpha]_D$ +45.3° (c = 0.3, $CHCl_3$). *Anal.* Calcd for $C_{52}H_{78}Cl_3N_2O_{13}P$: C, 58.02; H, 7.30; N, 2.60. Found: C, 58.02; H, 7.36; N, 2.59. IR (KBr): 3316, 3076, 2932, 2854, 1764, 1653, 1548, 1494, 1395 cm^{-1}. ^{1}H-NMR δ: 0.88 (6H, t, J = 7.3 Hz, CH_3), 1.26 (36H, br, CH_2), 1.55 (4H, br, $C\underline{H}_2CH_2CO$), 2.06—2.17 (4H, m, $C\underline{H}_2CO$), 3.75 (1H, dd, J = 18.3, 4.6 Hz, $C\underline{H}_2NH$), 3.93 (1H, dd, J = 18.3, 5.5 Hz, $C\underline{H}_2NH$), 4.02 (1H, dd, J = 12.8, 6.4 Hz, $C\underline{H}_2CH=CH_2$), 4.07 (1H, m, H-5), 4.20 (1H, dd, J = 12.8, 5.5 Hz, $C\underline{H}_2CH=CH_2$), 4.31 (1H, dd, J = 11.9, 3.8 Hz, H-6), 4.36 (1H, m, H-2), 4.45 (1H, dd, J = 11.9, 1.8 Hz, H-6), 4.59 (1H, d, J = 11.0 Hz, CH_2CCl_3), 4.70 (1H, d, J = 11.9 Hz, CH_2CCl_3), 4.76 (1H, q, J = 9.2 Hz, H-4), 4.92 (1H, d, J = 2.8 Hz, H-1), 5.26 (2H, m, $CH_2CH=C\underline{H}_2$), 5.41 (1H, t, J = 9.2 Hz, H-3), 5.66 (1H, d, J = 9.2 Hz, NH), 5.88 (1H, m, $CH_2C\underline{H}=CH_2$), 6.33 (1H, m, NH), 7.20—7.38 (10H, m,

arom. H).

2-Deoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranose (19) $Pd(PPh_3)_4$ (100 mg, 0.087 mmol) was added to a solution of **18** (310 mg, 0.29 mmol) in acetic acid (5 ml) under a nitrogen atmosphere at room temperature, and the mixture heated (80 °C) for 1 h. The solvent was removed by azeotropic evaporation with toluene, and the residue was purified by silica gel column chromatography ($CHCl_3$–acetone, 10 : 1) to give **19** (254 mg, 85%) as a wax. $[\alpha]_D$ +19.5° (c=1.3, $CHCl_3$). *Anal.* Calcd for $C_{49}H_{74}Cl_3N_2O_{13}P$: C, 56.78; H, 7.20; N, 2.70. Found: C, 56.61; H, 7.10; N, 2.98. ^{1}H-NMR δ: 0.88 (6H, t, J=7.3 Hz, CH_3), 1.25 (br), 1.55 (4H, br, $C\underline{H}_2CH_2CO\times2$), 2.09—2.30 (4H, m, CH_2CO), 3.62 (1H, dd, J=18.1, 4.4 Hz), 3.72 (1H, dd, J=18.1, 4.9 Hz), 3.93 (1H, dd, J=18.1, 5.4 Hz), 4.0—4.3 (m), 4.48 (1H, m), 4.54 (1H, d, J=11.7 Hz, CH_2CCl_3), 4.58 (1H, m), 4.68 (1H, d, J=11.7 Hz, CH_2CCl_3), 4.70 (1H, m), 4.76 (1H, q, J=9.3 Hz, H-4), 5.31 (1H, d, J=3.9 Hz, H-1), 5.53 (1H, t, J=9.3 Hz, H-3), 5.88 (1H, br), 6.25 (1H, br, NH), 6.43 (1H, br, NH), 7.1—7.4 (10H, m, arom. H).

1-*O*-Acetyl-2-deoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranose (20) Compound **19** (250 mg, 0.24 mmol) was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) at room temperature, and the mixture was stirred for 1 h. The solvent was evaporated *in vacuo* and the residue was dissolved in AcOEt. This solution was washed with 1 M HCl, saturated $NaHCO_3$ aqueous solution and brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$–acetone, 10 : 1) to give **20** (253 mg, 97%) as a powder. mp 59—63 °C. $[\alpha]_D$ +35.3° (c=0.4, $CHCl_3$). *Anal.* Calcd for $C_{51}H_{76}Cl_3N_2O_{14}P$: C, 56.80; H, 7.10; N, 2.60. Found: C, 57.29; H, 7.33; N, 2.64. IR (KBr): 3407, 3286, 3064, 2923, 2852, 2360, 1762, 1716, 1675, 1591, 1558, 1540, 1521, 1490 cm^{-1}. ^{1}H-NMR δ: 0.88 (6H, t, J=7.3 Hz, CH_3), 1.25 (36H, br, CH_2), 1.54 (4H, br, CH_2CO), 2.07—2.18 (4H, m, CH_2CO), 2.20 (3H, s, $OCOCH_3$), 3.73 (1H, dd, J=18.3, 4.8 Hz, $C\underline{H}_2NH$), 3.98 (1H, dd, J=18.3, 5.6 Hz, $C\underline{H}_2NH$), 4.08 (1H, m, H-5), 4.27 (1H, dd, J=11.9, 3.2 Hz, H-6), 4.44 (1H, dd, J=11.9, 2.4 Hz, H-6), 4.50 (1H, m, H-2), 4.55 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.68 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.86 (1H, q, J=9.5 Hz, H-4), 5.42 (1H, dd, J=11.1, 8.7 Hz, H-3), 5.57 (1H, m, NH), 6.23 (1H, d, J=3.2 Hz, H-1), 6.37 (1H, m, NH), 7.1—7.4 (10H, m, arom. H).

2-Deoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranosyl Bromide (4) Compound **20** (130 mg, 0.12 mmol) was dissolved in 25% HBr–acetic acid (1 ml), and the mixture was stirred for 23 h at room temperature. After dilution with AcOEt, the solution was washed with saturated $NaHCO_3$ aqueous solution and brine, then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$–acetone, 100 : 1) to give **4** as a colorless oil (125 mg, 95%). $[\alpha]_D$+78.5° (c=0.3, $CHCl_3$). ^{1}H-NMR δ: 0.88 (6H, t, J=7.1 Hz, CH_3), 1.25 (br, CH_2), 1.5—1.7 (br, CH_2), 2.08 (2H, td, J=7.9, 3.2 Hz, CH_2CO), 2.19 (2H, m, CH_2CO), 3.72 (1H, dd, J=17.8, 4.8 Hz, $COC\underline{H}_2NH$), 3.98 (1H, dd, J=17.9, 6.4 Hz, $COC\underline{H}_2NH$), 4.28—4.38 (3H, m, H-2, H-5, H-6), 4.50 (1H, d, J=10.3 Hz, H-6), 4.55 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.57 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.90 (1H, q, J=9.5 Hz, H-4), 5.50 (1H, dd, J=10.7, 9.1 Hz, H-3), 5.79 (1H, d, J=7.9 Hz, NH), 6.35 (1H, m, NH), 6.55 (1H, d, J=4.0 Hz, H-1), 7.14—7.40 (10H, m, arom. H).

2-Tridecyl-[1,2-dideoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-6-*O*-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyrano]-[2,1-*d*]-2-oxazoline (13) $Hg(CN)_2$ (7.4 mg, 0.03 mmol) was added to a solution of **4** (15 mg, 0.014 mmol), **7** (13 mg, 0.014 mmol) and $CaSO_4$ (10 mg) in CH_2Cl_2 (2 ml). The mixture was refluxed for 4 h, then diluted with AcOEt. This solution was washed with 5% KI aqueous solution, then brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by preparative TLC using $CHCl_3$–MeOH (20 : 1) as an eluant to afford **13** (6.2 mg, 41%) as an oil. $[\alpha]_D$ +5.7° (c=0.7, $CHCl_3$). *Anal.* Calcd for $C_{49}H_{72}Cl_3N_2O_{12}P$: C, 57.79; H, 7.13; N, 2.75. Found: C, 57.85; H, 7.40; N, 2.61. ^{1}H-NMR δ: 0.88 (6H, t, J=7.2 Hz, CH_3), 1.28 (br, CH_2), 1.61 (br, CH_2), 2.19 (2H, t, J=7.2 Hz), 2.33 (2H, t, J=7.5 Hz), 3.72 (1H, m, H-5), 3.96 (1H, dd, J=18.3, 4.8 Hz, $COC\underline{H}_2NH$), 4.09 (1H, dd, J=18.3, 5.6 Hz, $COC\underline{H}_2NH$), 4.20 (1H, m, H-2), 4.30 (1H, dd, J=11.9, 4.8 Hz, H-6), 4.43 (1H, dd, J=11.9, 1.6 Hz, H-6), 4.67 (1H, d, J=11.6 Hz, CH_2CCl_3), 4.72 (1H, td, J=8.7, 3.2 Hz, H-4), 4.76 (1H, d, J=11.6 Hz, CH_2CCl_3), 5.53 (1H, t, J=3.2 Hz, H-3), 5.96 (1H, d, J=7.2 Hz, H-1), 5.97 (1H, m, NH), 7.20—7.36 (10H, m, arom. H).

Bis(benzyloxycarbonylmethyl)methyl 2-Deoxy-6-*O*-[2-deoxy-4-*O*-diphenylphosphono-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-6-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranosyl]-3-*O*-(*N*-dodecanoylglycyl)-2-tetradecanoylamino-α-D-glucopyranoside (12) Zinc triflate (40 mg, 0.11 mmol) was added to a solution of **4** (120 mg, 0.11 mmol), **7** (102 mg, 0.11 mmol) and $CaSO_4$ (500 mg) in CH_2Cl_2 (2 ml) under a nitrogen atmosphere at room temperature. The mixture was stirred for 30 h, then diluted with AcOEt. This solution was washed with saturated $NaHCO_3$ aqueous solution and brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel chromatography ($CHCl_3$–MeOH, 50 : 1) to afford **12** (150.8 mg, 71%) as an oil. $[\alpha]_D$ +25.3° (c=0.3, $CHCl_3$). *Anal.* Calcd for $C_{102}H_{154}Cl_3N_4O_{24}P$: C, 62.58; H, 7.93; N, 2.86. Found: C, 62.59; H, 8.18; N, 2.98. ^{1}H-NMR δ: 0.88 (12H, t, J=6.9 Hz, CH_3), 1.25 (br, CH_2), 1.55—1.73 (m), 2.12 (6H, m, $C\underline{H}_2CO$), 2.24 (2H, t, J=7.3 Hz, $C\underline{H}_2CO$), 2.62 (1H, dd, J=16.5, 7.3 Hz, $OCHC\underline{H}_2$), 2.68 (2H, m, $OCHC\underline{H}_2$), 2.91 (1H, dd, J=16.0, 5.0 Hz, $OCHC\underline{H}_2$), 3.16 (1H, m, H-2), 3.57 (1H, t, J=10.1 Hz, H-4), 3.63 (1H, dd, J=17.4, 5.5 Hz, $COC\underline{H}_2NH$), 3.73 (1H, dd, J=11.0, 4.6 Hz, H-6), 3.82 (2H, m, H-5, H-5′), 3.85 (1H, t, J=5.5 Hz, $COC\underline{H}_2NH$), 3.89 (1H, t, J=5.5 Hz, $COC\underline{H}_2NH$), 4.08 (2H, m, $COC\underline{H}_2NH$, H-6), 4.21 (1H, m, H-2′), 4.30 (1H, dd, J=11.9, 4.6 Hz, H-6′), 4.37 (1H, m, $OC\underline{H}CH_2$), 4.45 (1H, d, J=11.9 Hz, H-6′), 4.53 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.63 (1H, q, J=9.2 Hz, H-4′), 4.67 (1H, d, J=11.9 Hz, CH_2CCl_3), 4.89 (1H, d, J=3.7 Hz, H-1), 5.03 (1H, t, J=10.1 Hz, H-3), 5.11 (2H, s, CH_2Ph), 5.12 (2H, s, CH_2Ph), 5.41 (1H, d, J=7.3 Hz, H-1′), 5.74 (1H, t, J=10.1 Hz, H-3′), 6.24 (1H, t, J=5.5 Hz, NH), 6.28 (1H, t, J=5.5 Hz, NH), 6.49 (2H, m, NH), 7.10—7.35 (20H, m, arom. H).

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