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SYNTHESIS OF CARBOCYCLIC ANALOGUES OF LIPID X

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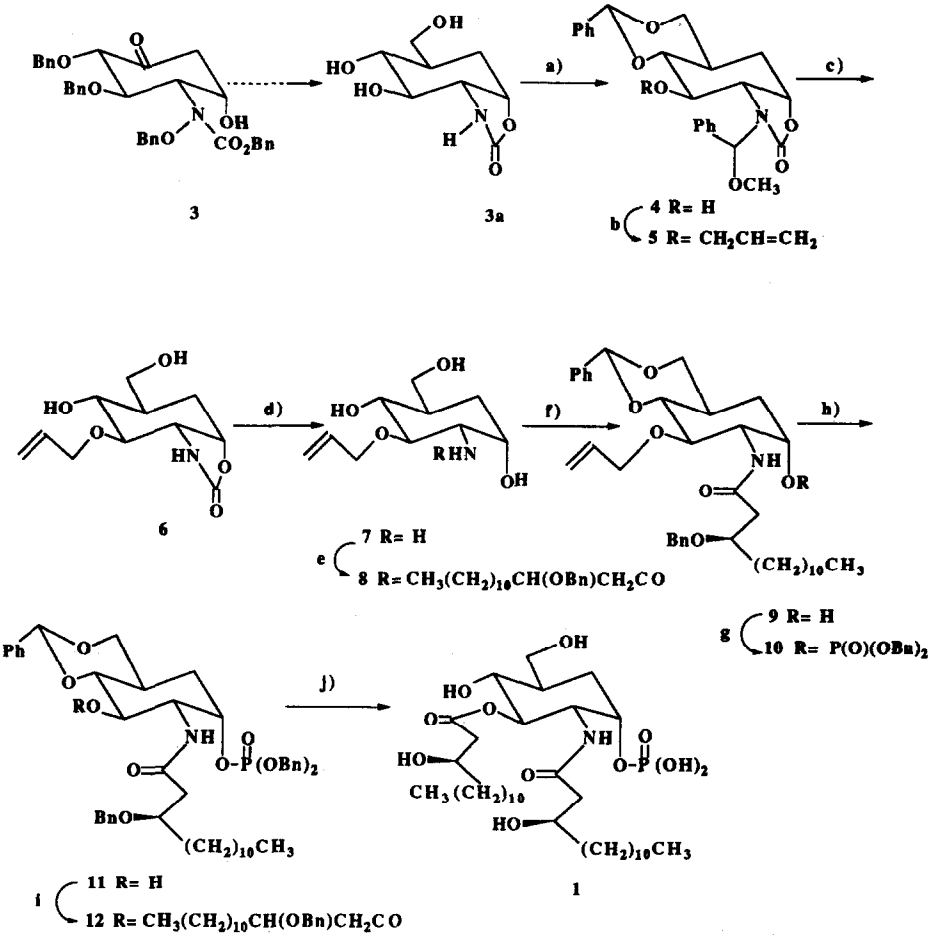
ABSTRACT *- Carbocyclic analogues of lipid X and nor-lipid X (1 and 2) are synthesized respectively from amino-inososes 3 and 16a, readily prepared from exocyclic olefins by Ferrier rearrangement*

Résumé- *La synthèse d'analogues carbocycliques du lipide X et du nor-lipide X (1 et 2) a été réalisée respectivement à partir des amino-inososes 3 and 16a, préparées aisément par un rearrangement de Ferrier des oléfines exocycliques correspondantes.*

Lipid A,[1] the hydrophobic portion of lipopolysaccharide (LPS) of Gram-negative bacteria, first synthesized by Shiba *et al* ,[2] is of considerable biological and pharmacological interest, because it is responsible for many physiological effects of Gram-negative bacteria; endotoxicity, adjuvancity, immunostimulating properties. Lipid A is believed to be associated with endotoxin induced septic shock. Due to their toxicity, LPS and lipid A could not be used clinically.

Monophosphoryl lipid A (MLA)[3] and a monosaccharide lipid X (N^2,O^3-diacylglucosamine-1-phosphate)[4] have been isolated from bacterial lipopolysaccharides. In contrast to LPS and lipid A, they are nontoxic to animals. MLA possesses immunostimulant and potent adjuvant properties and enhances immunoresponsiveness and nonspecific resistance to bacterial infections.[5] Until now, lipid X, synthesized in an efficient way by Macher,[6] exhibited, albeit weakly, most of the activity of lipid A. Very recently[7] in 1990, synthetic lipid X highly purified by gel filtration over Sephadex LH20, was re-examined for endotoxin like biological activities and was found to be virtually devoid of immunostimulant properties. It displays, however, anti-viral and anti-endotoxic activities. In addition, lipid X can also inhibit protein kinase C in human platelets.[8]

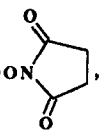


a) $C_6H_5CH(OCH_3)_2$, PTSA, DMF, 40°C

b) CH_2=CH-CH_2Br, NaH, DMF

c) AcOH, H_2O

d) LiOH, MeOH-H_2O

e) $CH_3(CH_2)_{10}CH(OBn)CH_2COON$  , DMF , 20°C.

f) PhCHO, $ZnCl_2$

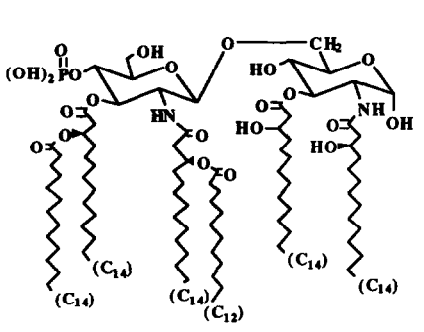
g)  $P(OBn)_2$, tetrazole, tBuOOH

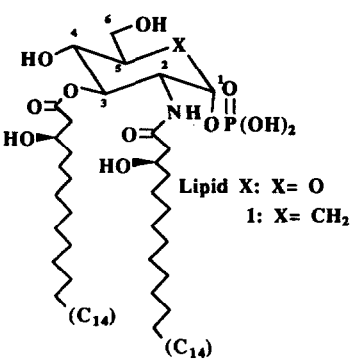
h) SeO_2 , AcOH

i) $CH_3(CH_2)_{10}CH(OBn)CH_2COOH$, DCC, DMAP, CH_2Cl_2, 20°C

j) H_2, Pd/C, THF

Scheme 1





As part of a larger synthetic program, we are interested in replacing the *D*-glucosamine moiety of simple or complex natural products by *pseudo-D*-glucosamine, where the ring oxygen of the *D*-glucosamine has been changed to a methylene group.[9] This nominally simple modification might give rise to isosteres with novel and interesting biological activity.[10] Towards this objective, we initiated a synthetic program to prepare carbocyclic analogues of lipid X.

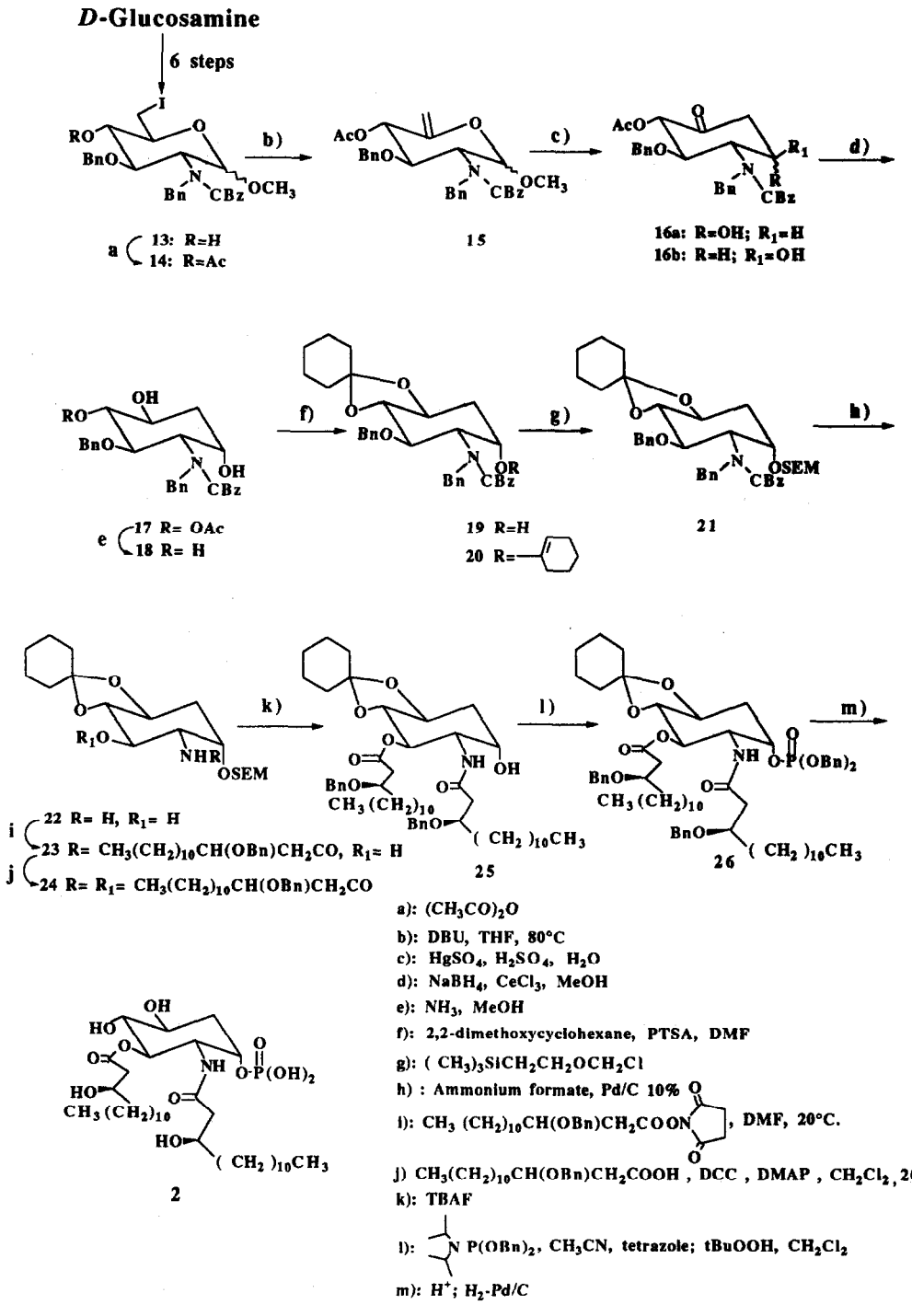
We describe in this paper the synthesis of carbocyclic lipid X **1** and a carbocyclic nor-analogue of lipid X.[11] These two compounds are devoid of immunostimulant activity but, like lipid X, antagonize LPS toxicity. The carbocyclic lipid X is able to inhibit the capacity of LPS (*S. thyphimurium*) to induce procoagulant activity and did not induce tumor necrosis factor (TNF).

Recently a paper[12] was published on the synthesis of Carbocyclic Analogue of lipid X. The *pseudo*-lipid X has been described in two Ph. D. theses,[11] presented at the University of Paris XI.

Synthesis of the Carbocyclic Analogue of Lipid X 1 (Scheme 1).

The synthesis of the carbocyclic analogue of Lipid X **1** uses a carbamate derivative of *pseudo-D*-glucosamine **3a** as key intermediate.[9b] The preparation of **1** was realised in 10 steps in 6% overall yield (Scheme 1).

4,6-*O*-Benzylidenation of **3** to yield **4** (54%) was performed by transacetalation with benzaldehyde dimethyl acetal in *N,N*-dimethylformamide at 60°C under vacuum (18 mmHg) in the presence of toluene-*p*-sulfonic acid as catalyst. Under these conditions, we also observed the simultaneous formation of an aminal group. The alcohol **4** was transformed to the 3-*O*-allyl derivative **5** by treatment with allyl bromide and sodium hydride in *N,N*-dimethylformamide (71%). The benzylidene and aminal groups were removed by acid hydrolysis to afford the diol **6** (95%). Cleavage of the oxazolidinone ring under basic conditions afforded the 3-*O*-allyl-*pseudo-D*-glucosamine **7**. *N*-Acylation of **7** by *N*-(R)-3-benzyloxytetradecanoyloxysuccinimide[13] in *N,N*-dimethylformamide was followed by 4,6-*O*-benzylidenation to give **9** (86%). This latter was converted to the 1-dibenzylphosphono derivative **10** by treatment with *N,N*-ethyldiisopropyldibenzylphosphoramidite[14] in the presence of tetrazole in acetonitrile, followed by oxidation of the phosphite by *t*-butylhydroperoxide (73%). Cleavage of the allyl group of **10** was achieved with selenium dioxide[15] to afford the alcohol **11** (62%). Acylation of **11** by (R)-3-benzyloxytetradecanoic acid,[6] dicyclohexylcarbodiimide in the presence of 4-


D-Glucosamine
6 steps
a) 13: R=H; 14: R=Ac
b)
c)
d)
15
16a: R=OH; R1=H
16b: R=H; R1=OH
e) 17 R= OAc; 18 R= H
f)
g)
h)
19 R=H
20 R=
21
i) 22 R= H, R1= H
j) 23 R= CH3(CH2)10CH(OBn)CH2CO, R1= H
24 R= R1= CH3(CH2)10CH(OBn)CH2CO
k)
l)
m)
25
26
2
a): (CH3CO)2O
b): DBU, THF, 80°C
c): HgSO4, H2SO4, H2O
d): NaBH4, CeCl3, MeOH
e): NH3, MeOH
f): 2,2-dimethoxycyclohexane, PTSA, DMF
g): (CH3)3SiCH2CH2OCH2Cl
h) : Ammonium formate, Pd/C 10%
l): CH3 (CH2)10CH(OBn)CH2COON, DMF, 20°C.
j) CH3(CH2)10CH(OBn)CH2COOH , DCC , DMAP , CH2Cl2 , 20°C
k): TBAF
l): N P(OBn)2, CH3CN, tetrazole; tBuOOH, CH2Cl2
m): H+; H2-Pd/C

Scheme 2

dimethylaminopyridine in dichloromethane furnished **12** (52%).The benzyl and benzylidene groups of **12** were removed by catalytic hydrogenation to yield **1** (85%).

Synthesis of the nor Analogue of Lipid X (Scheme 2)

The synthesis of the carbocyclic nor-analogue of Lipid X **2** was achieved from amino-inosose **16a** available from *D*-glucosamine.

The iodo compound **13** prepared in 6 steps from *D*-glucosamine as previously described[9b] was acetylated and converted to the exocyclic olefin **15** by treatment with DBU in tetrahydrofuran at 80°C. In the presence of a catalytic amount of mercuric sulfate in dioxane with aqueous sulfuric acid at 80°C, the olefin **15** was transformed to the ketones **16a** and **16b** with a good stereoselectivity (7:2 respectively). The ketone **16a** was reduced with sodium borohydride in the presence of cerium chloride[16] in ethanol to afford exclusively the equatorial alcohol **17**. Hydrolysis of the acetate group of **17** with ammonia followed by treatment of **18** with 2,2-dimethoxycyclohexane and toluene-*p*-sulfonic acid in *N,N*-dimethylformamide gave the cyclohexylidene acetal **19** together with the side product **20** which, by hydrolysis in the presence of toluene-*p*-sulfonic acid, was transformed to the desired derivative **19**. Treatment of the latter with SEM chloride in the presence of *N*-ethyldiisopropylamine afforded **21**. Catalytic hydrogenolysis of **21** was achieved with ammonium formate as proton source and palladium on charcoal 10% in methanol to yield **22**. *N*-Acylation of **22** with *N*-(R)-benzyloxy-tetradecanoyloxysuccinimide (13) in *N,N*-dimethylformamide gave **23** (61%). *O*-Acylation of **23** was carried out by treatment with (R)-3-benzyloxytetradecanoic acid in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine in dichloromethane to afford **24** (84%). Removal of the SEM blocking group of **24** was achieved according to the method described by Paquette[17] which involved heating **24** in solvent-free melted tetra-*n*-butylammonium fluoride under a vacuum of 2 mmHg to yield **25**. Phosphorylation of **25** at positon 1 with *N,N*-ethyldiisopropyldibenzylphosphoramidite in the presence of tetrazole in acetonitrile, followed by oxydation of the phosphite by *t*-butylhydroperoxide furnished **26** (71%). Hydrolysis of the acetal group followed by catalytic hydrogenolysis of the benzyl groups yielded the carbocyclic nor-analogue **2** of Lipid X.

EXPERIMENTAL SECTION

Microanalyses were performed by the Analytical Department, C.N.R.S., Gif-sur-Yvette. Melting points were determined on a Reichert apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer polarimeter 141. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometers: WP 80 (80 MHz), WP 200 (200 MHz, 50 MHz ^{13}C), WM 400 (400 MHz). Mass spectra were recorded on AEI MS 50 (EI), AEI MS 9 (IC) and Kratos MS 80 (FAB) spectrometers. Chromagel 60 A CC (230-400 mesh) SDS was used for column chromatography. HPLC chromatography was carried out on a silica gel column (Si 60 5µ). Chromatography was done using the flash column technique.

1-*D*-(1,2,4/3,5)-4,7-*O*-Benzylidene-2-*N*-(methoxymethylphenyl)-aminal-1,2-*N,O*-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 4. A solution of 1*D*-(1,2,4/2,5)-3,4-Di-*O*-benzyl-2-benzylamino-1,2-*N,O*-carbonyl-5-hydroxymethyl-1,3,4-cyclohexanetriol[9b] (0.5 g, 1.057 mmol) in dry tetrahydrofuran (5 mL) was added to a blue solution of Li metal in liquid NH_3 (30 mL, dried over Na) at -78°C. Small amounts of Li were added in alternation with the benzyl derivative to maintain the blue color. After 30 min tert-butyl alcohol (3 mL) was added dropwise in three portions and then ethanol until the solution turned white. The mixture was diluted with tetrahydrofuran and treated with a resin CG 50 H^+. This mixture was filtered off and concentrated to give the crude triol **3a**. To this latter (0.214 g, 1.05 mmol) in *N,N*-dimethylformamide (1 ml) was added benzaldehyde dimethyl acetal (2 ml) and a catalytic amount of toluene-*p*-sulfonic acid. The mixture was stirred at 60°C under vacuum (18 mm Hg) for 3 h and concentrated. The residue was diluted with dichloromethane, washed with water and the organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Column chromatography (ethyl acetate-hexane, 1:2) of the residue gave **4** as

a colorless oil (0.233g, 54%). Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H. 6.12. Found: C, 67.25; H, 6.08. $[\alpha]_D^{20}$= -62° (c= 6.29, CH_2Cl_2). MS (EI. m/z): 411 $(M)^{+\cdot}$. ^1H NMR δ (200 MHz, $CDCl_3$): 1.38 (m, 1H, H6); 2.17 (m, 2H, H5, H6'); 3.28 (t, 1H, H2, $J_{1,2}$= $J_{2,3}$= 7 Hz); 3.43 (t, 1H, H4, $J_{4,5}$= 10 Hz) ; 3.62 (t, 1H, H7, $J_{5,7}$= $J_{7,7'}$= $J_{5,7'}$= 11 Hz); 3.72 (s, 3H, OCH_3); 3.90 (t, 1H, H3, $J_{3,4}$= 10 Hz); 4.27 (dd, 1H, H7'); 4.52 (m, 1H, H1); 5.57 (s. 1H, OCHO); 6.25 (s, 1H, OCHN); 7.32-7.62 (m, 10H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 26.4 (C_6); 31.5 (C_5); 57.8 (OCH_3); 60.5 (C_2); 70.7 (C_7); 74.7 (C_3); 75.1(C_1); 79.6 (C_4); 85.2 (OCN); 101.6 (OCHO); 126.2-137.9 (Ph); 157.7 (CO).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-4,7-*O*-benzylidene-1,2-*N*,*O*-carbonyl-5-C-hydroxymethyl-2-*N*-(methoxymethylphenyl)-aminal-1,3,4-cyclohexanetriol 5. To a stirred suspension of sodium hydride (50% in oil) (0.143 g, 3.11 mmol) in *N*,*N*-dimethylformamide (4 ml) was added dropwise at 0°C, under argon a solution of alcohol **4** (0.85 g, 2.07 mmol) in *N*,*N*-dimethylformamide (1 ml) and allyl bromide (0.269 ml, 3.11 mmol). The mixture was stirred at 20°C for 2 h and diluted with tetrahydrofuran (20 ml), neutralized with a resin IRN-77 H^+ at 0°C and then filtered. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (ethyl acetate-hexane, 1:2) to yield **5** (0.66 g, 71%) as a colorless oil. Anal. Calcd. for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47. Found: C, 69.19; H, 6.71. $[\alpha]_D^{20}$= -62° (c= 0.81, CH_2Cl_2). MS (CI, m/z): 452 $(MH)^{+\cdot}$. ^1H NMR δ (200 MHz, $CDCl_3$): 1.17 (m, 1H, H6); 2.08 (m, 2H, H5, H6'); 3.35 (t, 1H, H2); 3.53 (m, 2H, H4, H7); 3.68 (m, 4H, H7', OCH_3); 4.20 (m, 2H, O$\underline{C}H_2$CH=CH_2); 4.40 (t, 1H, H3); 4.50 (m, 1H, H1); 5.50 (m, 3H, $\underline{CH_2}$=CHCH_2O, $\underline{CH}$Ph); 6.14 (m, 2H, OCHN, CH_2=$\underline{CH}$-CH_2O); 7.40 (m, 10 H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 26. 5 (C6); 30.4 (C5); 56.9 (C2); 58.3 ($\underline{OCH_3}$); 70.7 (C7); 74.4 (O$\underline{C}H_2$CH=CH_2); 74.9 (C3); 83.1 (C1); 83.4 (C4); 86.3 (OCHN); 101.3 (OCHO); 116.5 (CH=$\underline{C}H_2$); 125.9-129.0 (Ph); 135.3 ($\underline{C}$H=CH_2); 136.8 (Ph); 138.1 (Ph).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-2-amino-1,2-N,*O*-carbonyl-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 6. A suspension of **5** (0.452 g, 1 mmol) in water/acetic acid (3 ml, 1:2) was stirred for 24 h at room temperature and then concentrated. Column chromatography (dichloromethane-methanol, 7:1) gave the crystalline diol **6** (0.23 g, 95%). Anal. Calcd. for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04. Found: C, 54.28; H, 7.09. $[\alpha]_D^{20}$= +62° (c= 1, CH_3OH). Mp: 141°C ($CHCl_3$). MS (CI, m/z): 244 $(MH)^+$.^1H NMR δ (200 MHz, $CDCl_3$): 1.63 (m, 2H, H6, H5); 2.13 (d, 1H, H6'); 3.30 (m, 1H, H4, H7); 3.63 (m, H2, H3, H7); 4.38 (dd, 2H, CH_2=CH-$\underline{CH_2}$O); 4.76 (m, 1H, H1); 5.23 (m, 2H, $\underline{CH_2}$=CH-); 6.08 (m, 1H, CH_2=$\underline{CH}$-). ^{13}C NMR δ (50 MHz, $CDCl_3$): 28.6 (C6); 40.2 (C5); 58.8 (C2); 64.0 (C7); 73.1 (C1); 74.2 (O$\underline{C}H_2$-CH=CH_2); 76.3 (C3); 86.7 (C4); 117.2 ($\underline{CH_2}$=CH-); 136.5 (CH_2=$\underline{C}$H-).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-2-amino-5-C-hydroxymethyl-1,3,4-cyclohexanetriol (3-O-Allyl-*pseudo*-*D*-glucosamine) 7. To a solution of lithium hydroxide (0.88 g, 20 mmol) in water methanol (10 ml, 6:4) was added **6** (0.15 g, 0.61 mmol). The mixture was heated at 90°C overnight. The solution was then cooled, diluted with water (10 ml) and neutralized with a resin IRN-77 H^+ and filtered. The resin was washed with methanol and ammonium hydroxide 10 N (2x10 ml). The solvent was evaporated to give **7** (0.125 g, 93%). MS (FAB, m/z): 218 $(MH)^+$. ^1H NMR δ (200 MHz, CD_3OD): 1.74 (m, 2H, H6', H5); 2.33 (d, 1H, H6); 3.24 (m, 3H, H2, H4, H7); 3.60 (m, 2H, H3, H7'); 3.93 (s, 1H, H1); 4.14 (dd, 1H, CH_2=CH-$\underline{CH_2}$-O); 4.45 (dd, 1H, CH_2=CH-$\underline{CH_2}$O); 5.15 (m, 2H, $\underline{CH_2}$=CH-); 6.10 (m, 1H, CH_2=$\underline{CH}$-CH_2). ^{13}C NMR δ (50 MHz, CD_3OD): 33.8 (C6); 40.5 (C5); 57.7 (C2); 64.7 (C7); 69.6 (C1); 75.1 (O$\underline{C}H_2$-CH=CH_2); 76.5 (C3); 85.9 (C4); 116.8 ($\underline{CH_2}$=CH-); 137.0 (CH_2=$\underline{C}$H-).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-2-[(R)-3-benzyloxytetradecanoyl-amido]-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 8 A mixture of **7** (0.15 g, 0.69 mmol) and (R)-3-benzyloxy-tetradecanoylsuccinimide (0.3 g, 0.71 mmol) in dry *N*,*N*-dimethylformamide (2 ml) was stirred at room temperature overnight under argon and then concentrated. The residue was chromatographed on a silica gel column (dichloromethane-methanol, 7:1) to give crystalline **8** (0.288 g, 78%). Anal. Calcd. for $C_{31}H_{51}NO_6$: C, 69.76; H, 9.63. Found: C,69.60; H, 9.58. $[\alpha]_D^{20}$= +33° (c= 1.81, CH_3OH). Mp: 112-117°C ($CHCl_3$). MS (FAB, m/z): 534 $(MH)^+$. ^1H NMR δ (200 MHz, $CDCl_3$): 0.72, 1.30, 1.65, 2.47, 2.60 (m, 28 H, H6, H6', H5, CH_3-CH_2-chain); 3.50 (m, 2H, H4, H7); 3.67 (m, 2H, H7', H2); 3.97 (m, 3H, H1, H3, $\underline{CH}OCH_2Ph$); 4.13 (m, 2H, CH_2=CH-$\underline{CH_2}$O); 4.57 (q, 2H, $\underline{CH_2}$Ph); 5.20 (m, 2H, $\underline{CH_2}$=CH-CH_2O); 5.90 (m, 1H, CH_2=$\underline{CH}$-CH_2O); 6.95 (d, 1H, NH); 7.50 (m, 5H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.1 (CH_3); 22.6, 25.2, 25.4, 29.3, 29.6, 42.0 (CH_2-chain); 34.1 (C6); 38.1 (C5); 54.8 (C2); 66.0 (C7); 68.5 (C1); 71.8 ($\underline{C}H_2$Ph); 72.8 (CH_2=CH-$\underline{C}H_2$O); 76.4 (C3); 76.6 ($\underline{C}HOCH_2Ph$); 81.2 (C4); 116.9 ($\underline{C}H_2$=CH-); 127.9, 128.0, 128.5 (Ph); 135.1 (CH_2=$\underline{C}$H-); 171.9 (CO).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-4,7-*O*-benzylidene-2-[(R)-3-benzyloxytetradecanoyl-amido]-5-C-hydroxy-methyl-1,3,4-cyclohexanetriol 9. A mixture of zinc chloride (0.08 g, 0.587 mmol), benzaldehyde (1.5 ml) and triol **8** (0.11 g, 0.206 mmol) was stirred under argon at room temperature for 30 min and then diluted with dichloromethane. The solution was neutralized with a resin IRA-68 and filtered. The filtrate was washed with water, dried ($MgSO_4$), then filtered and evaporated to dryness. Column chromatography (ethyl acetate) yielded **9** as an oil (0.11 g, 86%). Anal. Calcd. for $C_{38}H_{55}NO_6$: C, 73.40; H, 8.92. Found: C, 73.48; H, 8.87. $[\alpha]_D^{20}$= +3° (c= 5.53, $CHCl_3$). MS (CI, m/z): 622 (MH)+. ^1H NMR δ

(200 MHz, $CDCl_3$): 0.88, 1.25, 1.63, 2.40 (m, 28 H, H6, H6', H5, CH_3-CH_2-chain); 3.60-4.20 (m, 8H, H2, H3, H4, H1, CHOCH$_2$Ph, CH_2=CH-CH_2O, H7, H7'); 4.42 (dd, 1H, CH_2=CH-CH_2O); 4.60 (q, 2H, CH_2Ph); 5.23 (m, 2H, CH_2=CH-CH_2O); 5.63 (s, 1H, OCHO); 5.90 (m, 1H, CH_2=CH-CH_2O); 6.65 (d, 1H, NH); 7.50 (m, 10H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.1 (CH_3); 22.7, 25.3, 29.4, 29.7, 31.9, 42.0 (CH_2-chain); 34.1 (C6); 55.8 (C2); 68.0 (C1); 71.3 (C7); 71.7 (CH_2Ph); 73.6 (CH_2=CH-CH_2O); 77.1 (CHOCH$_2$Ph); 77.4 (C3); 85.1 (C4); 101.8 (C8); 116.5 (CH_2=CH-); 126.1, 128.7 (Ph); 135.5 (CH_2=CH-); 138.5, 138.6 (Ph); 171.9 (CO).

1-*D*-(1,2,4/3,5)-3-*O*-Allyl-4,7-*O*-benzylidene-2-[(R)-3-benzyloxytetradecanoylamido]-1-*O*-dibenzyl-phosphono-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 10. To a solution of alcohol **9** (0.15 g, 0.242 mmol) in dry acetonitrile (1 ml) was added at room temperature, under argon, sublimed tetrazole (0.054 g, 0.793 mmol) and *N,N*-ethyldiisopropyldibenzylphosphoramidite (0.12 ml, 0.348 mmol). The mixture was stirred at room temperature for 30 min and diluted with dichloromethane (10 ml), then *t*-butylhydroperoxide (0.2 ml) was added. After 2 h, a solution of sodium thiosulfate was added and then the mixture was extracted with dichloromethane. The organic layer was dried, filtered ($MgSO_4$) and evaporated to dryness. Column chromatography on a silica gel column (ethyl acetate-heptane, 3:1) yielded the phosphate **10** as an oil (0.155 g, 73%). Anal. Calcd. for C_{52} H_{68} N O_9P: C, 70.08; H, 7.77. Found: C, 70.01; H, 8.03. $[\alpha]_D^{20}$= +17° (c= 4.30, CH_2Cl_2). MS (FAB, m/z): 883 $(MH)^+$. ^{1}H NMR δ (200 MHz, $CDCl_3$): 1.00, 1.33, 1.60, 1.90, 2.20, 2.42 (m, 28 H, H6, H6', H5, CH_3-CH_2-chain); 3.47-3.85 (m, 4H, H7, H7', H4, H2); 3.96 (dd, 1H, CH_2=CH-CH_2O,); 4.17 (m, 2H, H3, CHOCH$_2$Ph); 4.37 (dd, 1H, CH_2=CH-CH_2O); 4.57 (q, 2H, CHOCH_2Ph); 4.91 (m, 1H, H1); 5.17 (m, 6H, POCH_2Ph, CH_2=CH-CH_2O); 5.70 (s, 1H,CHPh); 5.92 (m, 1H,CH_2=CH-CH_2O); 6.91 (d, 1H, NH); 7.53 (m, 20H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.1 (CH_3); 22.7, 25.4, 29.0, 29.4, 29.7, 32.0 (CH_2-chain); 33.8 (C6); 32.5 (C5); 53.6 (C2); 69.7, 69.8, 70.9 (CH_2Ph); 71.1 (C7); 73.7 (CH_2=CH-CH_2O); 76.5 (CHOCH$_2$Ph); 77.1 (C3); 84.7 (C4); 101.3 (C8); 116.6 (CH_2=CH-); 126.0, 128.8 (Ph); 135.2 (CH_2=CH-); 136.1, 138.4, 138.5 (Ph); 171.9 (CO).

1-*D*-(1,2,4/3,5)-4,7-*O*-Benzylidene-2-[(R)-3-benzyloxytetradecanoylamido]-1-*O*-dibenzyl-phosphono-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 11. To a solution of **10** (0.051 g, 0.058 mmol) and selenium oxide (IV) (0.0065 g, 0.059 mmol) in dry dioxane (2 ml) was added under argon acetic acid (0.045 ml, 0.075 mmol). The mixture was heated at 100°C for 2 h. The solvent was evaporated under reduced pressure. Column chromatography of the residue gave **11** as an oil (0.030 g, 62%). Anal. Calcd. for C_{49} H_{64} N O_9P: C, 69.90; H, 7.66. Found: C, 69.71; H, 7.58. $[\alpha]_D^{20}$= +9° (c= 7.40, CH_2Cl_2). MS (FAB, m/z): 842 (MH)+. ^{1}H NMR δ (200 MHz, $CDCl_3$): 0.90, 1.30, 1.82, 2.13, 2.43 (m, 28 H, H6, H6', H5, CH_3-CH_2-chain); 3.44-4.17 (m, 6H, H2, H3, H4, H7, H7', CHOCH$_2$Ph); 4.58 (m, 2H, CH_2Ph); 4.81 (m, 1H, H1); 5.07 (m, 4H, CH_2Ph); 5.64 (s, 1H, CHPh); 7.01 (d, 1H, NH); 7.42 (m, 20H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.1 (CH_3); 22.7, 25.4, 28.2, 29.1, 29.4, 29.7, 32.0, 41.2 (CH_2-chain); 31.9 (C5); 34.0 (C6); 54.9 (C2); 69.7, 70.0, 70.9 (CH_2Ph); 71.1 (C1); 71.2 (C7); 76.1 (C3); 76.2 (CHOCH$_2$Ph); 84.1 (C4); 102.0 (OCHO); 126.2- 138.8 (Ph); 172.2 (CO).

1-*D*-(1,2,4/3,5)-4,7-O-Benzylidene-3-*O*-[(R)-3-benzyloxytetradecanoyl]-2-[(R)-3-benzyl-oxytetradecanoylamido]-1-*O*-dibenzylphosphono-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 12. To a solution of **11** (0.074g, 0.088 mmol), (R)-3-benzyloxytetradecanoic acid (13) (0.035 g, 0.70 mmol) and a catalytic amount of 4-dimethylaminopyridine in dry dichloromethane (1 ml) was added under argon dicyclohexylcarbodiimide (0.022 g, 0.105 mmol). The mixture was kept at room temperature for 24 h and then evaporated under reduced pressure. The residue was chromatographed on a silica gel column (ethyl acetate-hexane, 2:1) to give **12** as a syrup (0.053 g, 52%). Anal. Calcd. for C_{70} H_{96} N $O_{11}P$: C, 72.58; H, 8.35. Found: C, 72.14; H, 8.03. $[\alpha]_D^{20}$= +19° (c= 4.70, CH_2Cl_2). MS (FAB, m/z): 1158 $(MH)^+$. ^{1}H NMR δ (200 MHz, $CDCl_3$): 0.88, 1.23, 1.92, 2.17, 2.52 (m, 53 H, H6, H6', H5, CH_3-CH_2-chain); 3.47-3.84 (m, 4H, H2, H4, H7, H7'); 4.02 (m, 1H, H3); 4.30 (m, 2H, 2 CHOCH_2Ph); 4.45 (m, 4H, CH_2Ph); 4.77 (m, 1H, H1); 5.05 (m, 4H, 2 CH_2Ph); 5.48 (s, 1H, CHPh); 6.61 (d, 1H, NH); 7.42 (m, 25H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.1 (CH_3); 22.8, 25.1, 25.2, 25.5, 25.8, 29.2, 29.4, 29.7, 30.1, 34.1, 34.3, 34.8, 40.0, 41.4 (CH_2-chain); 32.0 (C6); 32.3 (C5); 53.4 (C2); 69.9, 70.8 (CH_2Ph); 71.2 (C7); 75.7 (C3); 76.1 (C3); 76.0 , 76.6 (CHOCH$_2$Ph); 81.3 (C4); 101.6 (OCHO); 126.3-139 (Ph); 171.0 (COO); 171.8 (NCO).

1-*D*-(1,2,4/3,5)-3-*O*-[(R)-3-Hydroxytetradecanoyl]-2-[(R)-3-hydroxytetradecanoyl-amido]-1-*O*-phosphono-5-C-hydroxymethyl-1,3,4-cyclohexanetriol 1. A solution of **12** (0.115 g, 0.099 mmol) in a mixture of tetrahydrofuran/water (30 ml, 9:1) was hydrogenated for 5 h at 25°C and 10^5 Pa over 10% Pd/C (0.1 g) and then filtered. The tetrahydrofuran was evaporated and the aqueous suspension was lyophilised. The lyophilisate (0.07 g) was washed with ether and dried to give **1** (0.06 g, 85%). MS (FAB, m/z): 710 $(MH)^+$; 732 $(M+Na)^+$. Anal. Calcd. for $C_{35}H_{68}NO_{11}P$. H_2O: C, 57.75; H, 9.69; N, 1.92; P, 4.26. Found: C, 58.01; H, 9.31; N, 1.94; P, 4.09.

Methyl-4-*O*-acetyl-3-*O*-benzyl-2-(*N*-benzyl-*N*-benzyloxycarbonylamino)-2,6-dideoxy-6-iodo-α,*D*-glucopyranoside 14. To a solution of **13** (23 g, 37.3 mmol) in dry dichloromethane was added at 0°C acetic anhydride (4.6 ml, 48.7 mmol), triethylamine (7.87 ml, 56.0 mmol) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at 20°C for 30 min and extracted with water. The organic layer

was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was crystallized from ethyl acetate to yield **14** (23.2 g, 92%). Anal. Calcd. for $C_{31}H_{34}INO_7$: C, 56.45; H, 5.20; N, 2.12. Found: C, 56.38; H, 5.31; N, 2.01. $[\alpha]_D^{20}$= +76° (c= 1.49, CH_2Cl_2). Mp= 152°C (ethyl acetate). MS (EI, m/z): 659 $(M)^{+\cdot}$. ^1H NMR δ (200 MHz, $CDCl_3$): 2.00 (s, 3H, $COCH_3$); 2.95 (s, 3H, OCH_3); 3.10 (m, 1H, H6); 3.20 (m, 1H, H6'); 3.70 (td, 1H, H2); 4.35 (m, 2H, H3, H5); 4.45 (m, 3H, H4, Ph$\underline{C}H_2$N); 4.70 (m, 2H, Ph$\underline{C}H_2$O); 5.05 (m, 2H, Ph$\underline{C}H_2$O); 5.15 (m, 1H, H1); 7.00-7.40 (m, 15H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 4.3 (C6); 20.9 ($CO\underline{C}H_3$); 47.5 ($N\underline{C}H_2Ph$); 55.2 (C2); 67.6 ($O\underline{C}H_2Ph$); 69.9 (C5); 74.2, 74.8 (C3, C4); 99.6 (C1); 125.9-139.6 (Ph); 157.2 ($\underline{C}O_2CH_2Ph$); 169.6 ($\underline{C}OCH_3$).

Methyl-4-*O*-acetyl-3-*O*-benzyl-2-(*N*-benzyl-*N*-benzyloxycarbonylamino)-2-deoxy-α,*D*-*xylo*-hex-enopyranoside 15. To a solution of **14** (5 g, 7.4 mmol) in dry tetrahydrofuran (50 mL) was added diazabicyclo-(1,8)-(5,4,0)undec-7-ene (DBU) (12.5 ml, 84 mmol). The mixture was heated at 80°C for 24 h. The cooled mixture was diluted with dichloromethane, washed with water and the organic layer was dried ($MgSO_4$), filtered, then evaporated to dryness. Column chromatography of the residue (ethyl acetate-hexane, 1:4) gave the crystalline **15** (3.3 g, 82%). Anal. Calcd. for $C_{31}H_{32}NO_7$: C, 70.04; H, 6.26; N, 2.63. Found: C, 69.98; H, 6.39; N, 2.58. $[\alpha]_D^{20}$= +57° (c= 0.79, CH_2Cl_2). Mp= 126°C (ethyl acetate-hexane); MS (EI, m/z): 531 $(M)^{+\cdot}$. ^1H NMR δ (200 MHz, $CDCl_3$): 2.05 (s, 3H, $COCH_3$); 2.90 (s, 3H, OCH_3); 4.10 (t, 1H, H2); 4.25 (d, 1H, H3); 4.45 (s, 2H, $\underline{C}H_2Ph$); 4.57 (s, 1H, H6); 4.64 (s, 2H, $\underline{C}H_2Ph$); 4.70 (s, 1H, H6'); 4.85 (m, 1H, H1); 5.10 (d, 2H, $\underline{C}H_2Ph$); 5.55 (m, 1H, H4): 7.00-7.40 (m, 15H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 20.1 ($CO\underline{C}H_3$); 47.4 ($N\underline{C}H_2Ph$); 55.1 (OCH_3); 52.8 (C2); 67.8 ($O\underline{C}H_2Ph$); 72.0 (C3); 74.6 (C4); 96.5 (C6); 100.4 (C1); 125.9-139.7 (Ph); 151.6 (C5); 157.3 ($\underline{C}O_2CH_2Ph$); 169.4 ($\underline{C}OCH_3$).

2-*L*-(2,4,5/3)-2-*O*-Acetoxy-3-*O*-benzyloxy-4-*N*-benzyl-*N*-benzyloxycarbonylamino-5-hydroxy-cyclohexanone 16a. A solution of alkene **15** (2 g, 3.8 mmol) and mercuric (II) sulfate (0.02 g) in dioxane-aqueous H_2SO_4 5 mM (45 ml, 2:1) was heated at 80°C for 2 h. The cooled mixture was extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate-hexane, 2:1) to afford α -isomer **16a** (1 g, 52%). Anal. Calcd. for $C_{30}H_{31}NO_7$: C, 69.62; H, 6.04; N, 2.71. Found: C, 69.38; H, 6.21; N, 2.43. $[\alpha]_D^{20}$= +23° (c= 1.41, CH_2Cl_2). MS (CI, m/z): 518 $(MH)^+$.^1H NMR δ (200 MHz, $CDCl_3$): 2.07 (s, 3H, $COCH_3$); 2.30 (m, 1H, H6); 2.55 (dd, 1H, H6'); 3.55 (m, 1H, OH); 4.05 (t, 1H, H3); 4.18 (m, 1H, H4); 4.45 (s, 2H, $\underline{C}H_2Ph$); 4.57 (d, 2H, $\underline{C}H_2Ph$); 4.80 (s, 1H, H5); 5.20 (d, 2H, $\underline{C}H_2Ph$); 5.27 (d, 1H, H2): 7.10-7.50 (m, 15H, Ph). ^{13}C NMR δ (50 MHz, $CDCl_3$): 20.2 ($CO\underline{C}H_3$); 45.7 (C6); 47.5 ($N\underline{C}H_2Ph$); 66.0 (C5); 68.5 ($O\underline{C}H_2Ph$); 69.4 (C4); 75.3 ($\underline{C}H_2Ph$); 76.0 (C3); 81.6 (C2); 159.4 ($\underline{C}O_2CH_2Ph$); 170.6 ($\underline{C}OCH_3$); 204.2 (C-1).

1-*D*- (1,2,4/3,5)- 4-*O*-acetoxy-3-*O*-benzyloxy- 2-*N*-benzyl- *N*- benzyloxycarbonylamino-1,3,4,5-cyclohexatetrol 17. To a solution of **16a** (3.3, 6.36 mmol) in methanol (50 ml) was added Cerium (III) chloride heptahydrate (2.56 g, 6.87 mmol). The mixture was stirred until the solution became homogenous and then a suspension of sodium borohydride in ethanol (24 ml) was added dropwise at -78°C. After 90 min, the mixture was treated at 0°C with acetic acid to remove the excess of sodium borohydride and filtered through a silica gel cake. The filtrate was evaporated under reduced pressure to give **17** as a colorless oil (2.65 g, 80%). Anal. Calcd. for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.48; H, 6.33; N, 2.58. $[\alpha]_D^{20}$= +8° (c= 1.57, CH_2Cl_2). MS (EI, m/z): 519 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 20.4 ($CO\underline{C}H_3$); 33.6 (C6); 67.8 ($COO\underline{C}H_2Ph$); 69.1 (C1); 72.8 (C5); 73.0 (C3); 74.8 ($O\underline{C}H_2Ph$); 79.0 (C4); 158.5 ($N\underline{C}OO$); 170.2 ($\underline{C}OCH_3$).

1-*D*-(1,2,4/3,5)-3-*O*-Benzyloxy-2-*N*-benzyl-*N*-benzyloxycarbonylamino-4,5-*O*-cyclohexylidene-1,3,4,5-cyclohexanetetrol 19. Compound **17** (3 g, 5.78 mmol) was dissolved in dry methanol (70 ml) and ammonia was bubbled through over 2h 30 at 0°C. The solution was evaporated to dryness to give the crude **18** which was used without futher purification for the next step.

To a solution of the crude triol **18** (2.76 g, 5.78 mmol) in *N,N*-dimethylformamide (5 ml) was added 2,2-dimethoxycyclohexane (8 ml, 55.56 mmol) and a catalytic amount of toluene-*p*-sulfonic acid. The mixture was heated at 100°C under vacuum (18 mmHg) and then evaporated to dryness. Column chromatography (ethyl acetate-hexane: 2-5) gave **19** as an oil (2.32 g, 72% from **17**) and **20** which was recycled into **19** by hydrolysis in the presence of a catalytic amount of p-toluene sulfonic pyridinium salt in tetrahydrofuran-water at 50°C for 3 h.

Compound **19**: Anal. Calcd. for $C_{34}H_{39}NO_6$: C, 73.23; H, 7.05; N, 2.51. Found: C, 73.28; H, 7.02; N, 2.53. $[\alpha]_D^{20}$= -13° (c= 1.12, CH_2Cl_2). MS (EI, m/z): 557 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 23.2, 23.6, 24.5, 34.7, 38.0 (CH_2); 31.8 (C6); 67.3 ($COO\underline{C}H_2Ph$); 70.7 (C1); 72.5 ($O\underline{C}H_2Ph$); 74.4 (C3); 76.1 (C5); 82.3 (C4); 110.1 (OCO); 126.7-139.9 (Ph); 158.0 ($N\underline{C}OO$).

Compound **20**: SM (EI, m/z): 637 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 22.4, 23.3, 23.6, 24.0, 25.0, 27.3, 35.2, 38.2, (CH_2, C6); 47.2 ($N\underline{C}H_2Ph$); 57.6 (C2); 67.0 ($CO_2\underline{C}H_2Ph$); 71.8 (C1); 72.2 ($O\underline{C}H_2Ph$); 72.9 (C3); 75.6 (C4); 81.8 (C5); 94.1 (OC=$\underline{C}$H-); 109.1 (OCO); 127.1-139.7 (Ph); 151.6 (O-$\underline{C}$=CH); 157.6 (OCON).

1-*D*-(1,2,4/3,5)-3-*O*-Benzyloxy-2-*N*-benzyl-*N*-benzyloxy-carbonyl-amino-4,5-*O*-cyclohexylidene-1-[(trimethylsilyl)-2'-ethoxy-methoxy]-1,3,4,5-cyclohexanetetrol 21. To a solution of **19** (0.1 g, 0.18 mmol) in dry dichloromethane (1 ml) was added *N,N*-diisopropylethylamine (0.2 ml, 1.17 mmol) and 2-(trimethylsilyl)-ethoxymethyl chloride (SEM-Cl). The mixture was stirred at 40°C under argon for 3 h and diluted with dichloromethane, then washed with water. The organic layer was dried ($MgSO_4$) filtered and evaporated to dryness to afford **21** as a colorless oil (0.115 g, 93%). Anal. Calcd. for $C_{40}H_{53}NO_7Si$: C, 69.84; H, 7.77; N, 2.04. Found: C, 69.70; H, 7.63; N, 2.06. $[\alpha]_D^{20}$= +4° (c= 1.20, CH_2Cl_2). MS (EI, m/z): 687 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): -1.5 (CH_3Si); 17.9 (CH_2-CH_2Si); 23.7, 24.1, 25.0, 35.2, 38.2 (CH_2); 30.6 (C6); 47.3 (NCH_2Ph); 58.4 (C2); 65.1 (OCH_2CH_2); 67.1 ($COOCH_2Ph$); 72.2 (OCH_2Ph); 73.0 (C1); 75.4 (C3); 76.5 (C4); 82.0 (C5); 94.7 (OCH_2O); 109.2 (OCO); 125.8-139.9 (Ph); 157.6 (NCOO).

1-*D*- (1,2,4/3,5) -2-[(R)-3-Benzyloxytetradecanoylamido]- 4,5- *O*- cyclohexylidene- 1 -[(trimethylsilyl)-2'-ethoxy-methoxy]-cyclohexanetetrol 23. A mixture of **21** (0.75 g, 1.09 mmol), ammonium formate (0.45 g, 9.57 mmol), palladium 10% on charcoal (0.75 g) in dry methanol (15 ml) was refluxed under argon for 2 h. The mixture was filtered through a silica gel cake. The filtrate was evaporated to dryness to yield a white solid (0.4 g) which was used for the next step without futher purification.

The crude **22** was dissolved in *N,N*-dimethylformamide (2 ml) and treated with *N*-(R)- 3-benzyloxytetradecanoyloxysuccinimide (0.45.g, 1.07 mmol). The mixture was stirred overnight at room temperature under argon and evaporated to dryness. The residue was chromatographed on a silica gel column (ethyl acetate-hexane, 1:1) to yield the *N*-acyl compound **23** as a colorless oil (0.458 g, 61%). Anal. Calcd. for $C_{39}H_{67}NO_7Si$: C, 67.88; H, 9.79; N, 2.03. Found: C, 67.76; H, 9.63; N, 2.03. $[\alpha]_D^{20}$= -12° (c= 2.02, CH_2Cl_2). MS (EI, m/z): 689 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): -1.4 (CH_3Si); 14.1 (CH_3); 18.1 (CH_2-CH_2Si); 22.6, 25.3, 29.3, 29.6; 33.9, 41.8 (CH_2-chain); 23.6, 24.0, 25.0, 35.2 38.3 (CH_2); 31.9 (C6); 52.9 (C2); 65.3 (OCH_2CH_2); 71.4 (OCH_2Ph); 71.4 ($CHOCH_2Ph$); 72.5 (C1); 74.2 (C3); 76.4 (C4); 80.1 (C5); 94.4 (OCH_2O; 109.5 (OCO); 127.4-138.5 (Ph); 172.2 (NCO).

1*D*-(1,2,4/3,5)-3-*O*-[(R)-3-Benzyloxytetradecanoyl]-2-[(R)-3-benzyloxytetradecanoylamido]-4,5-*O*-cyclohexylidene-1-[(trimethylsilyl)-2'-ethoxy-methoxy]-1,3,4,5-cyclohexanetetrol 24. To a solution of **23** (0.551 g, 0.8 mmol), (R)-3-benzyloxytetradecanoic acid (13) (0.269 g, 0.81 mmol) and a catalytic amount of 4-dimethylaminopyridine in dry dichloromethane (2 ml) was added under argon dicyclohexylcarbodiimide (0.167 g, 0.81 mmol). The mixture was kept at room temperature for 24 h and filtered. The filtrate was then evaporated under reduced pressure. The residue was chromatographed on a silica gel column (ethyl acetate-hexane, 1:3) to give **24** as a colorless oil (0.675 g, 84%). Anal. Calcd. for $C_{60}H_{99}NO_9Si$: C, 71.60; H, 9.91; N,1.39. Found: C, 71.50; H, 9.82; N, 1.42. $[\alpha]_D^{20}$= -7° (c= 1.23, CH_2Cl_2). MS (EI, m/z): 1005 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 3.6 (CH_3Si); 19.1 (CH_3); 23.0 (CH_2-CH_2Si); 27.7, 30.3, 34.6, 39.1, 47.0 (CH_2-N-acyl-chain); 27.7, 30.3, 34.6, 39.1, 47.0 (CHO-acyl-chain); 28.7, 28.9, 30.0, 40.5, 43.0 (CH_2); 36.9 (C6); 56.2 (C2); 70.6 (OCH_2CH_2Si); 76.3 (OCH_2Ph); 77.1 (C1); 77.8 (C3); 80.9, 81.0 ($HCOCH_2Ph$); 81.4 (C4); 82.5 (C5); 100 (OCH_2O); 114.9 (OCO); 132.4-143.8 (Ph); 175.8 (COO); 176.8 (NCOO).

1*D*-(1,2,4/3,5)-3-*O*-[(R)-3-Benzyloxytetradecanoyl]-2-(R)-3-benzyloxytetadecanoylamido-4,5-*O*-cyclohexylidene-1,3,4,5-cyclohexatetrol 25. In a round-bottom two-neck flask, tetrabutylammonium fluoride trihydrate (1g, 1.59 mmol) was dried at 90°C under vacuum (0.1 mmHg). After 3 h, a solution of **24** (0.5 g, 0.50 mmol) in dry tetrahydrofuran (1 ml) was added at room temperature. The mixture was stirred at 60°C for 20 h under vacuum (0.1 mmHg). Cooled water (10 ml) was added and the solution was extracted with dichloromethane. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Column chromatography of the residue (ethyl acetate-hexane, 1:1) gave **25** (0.178 g, 41%) and **23** (0.153 g, 44%) which can be recycled. Compound **25**: Anal. Calcd. for $C_{54}H_{85}NO_8$: C, 74.02; H, 9.77; N, 1.60. Found: C, 74.01; H, 9.70; N, 1.58. $[[\alpha]_D^{20}$= -14° (c= 0.51, CH_2Cl_2). MS (EI, m/z): 875 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.2 (CH_3); 22.8, 25.4, 29.8, 34.0, 42.1 (CH_2-N-acyl-chain); 22.8, 25.4, 29.8, 34.2, 40.0 (CH_2-O-acyl-chain); 24.0, 25.0, 25.3, 35.3, 38.2 (CH_2); 32.0 (C6); 52.8 (C2); 65.6 (C1); 71.5 (OCH_2Ph); 73.0 (C3); 74.2, 76.0 ($HCOCH_2Ph$); 76.4 (C4); 77.8 (C5); 109.9 (OCO); 127.0-138.8 (Ph); 171.0 (COO); 171.5 (NCO).

1*D*-(1,2,4/3,5)-3-*O*-[(R)-3-Benzyloxytetradecanoyl]-2-(R)-3-benzyloxytetradecanoylamido-1-*O*-dibenzylphosphono-4,5-*O*-cyclohexylidene-cyclohexanetetrol 26. To a solution of alcohol **25** (0.175 g, 0.2 mmol) in dry acetonitrile (1 ml) was added at room temperature and under argon sublimed tetrazole (0.045 g, 0.64 mmol) and *N,N*-ethyldiisopropyldibenzylphosphoramidite (0.1 ml, 0.29 mmol). The mixture was stirred for 25 min at room temperature and then diluted with dichloromethane (2 ml) and *t*-butylhydroperoxide (0.16 ml, 1.07 mmol) was added. After 1.5 h , the mixture was washed with a saturated sodium thiosulfate solution and then extracted with dichloromethane. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (ethyl acetate-heptane, 1:1) to yield the phosphate **26** as a colorless oil (0.162 g, 71%). Anal. Calcd. for $C_{68}H_{98}NO_{11}P$: C, 71.86; H, 8.69; N, 1.23. Found: C, 71.98; H, 8.50; N, 1.22. $[\alpha]_D^{20}$= -0.3° (c= 4.90, CH_2Cl_2). MS (EI, m/z): 1136 $(M)^{+\cdot}$. ^{13}C NMR δ (50 MHz, $CDCl_3$): 14.0 (CH_3); 22.5, 25.2, 29.2, 29.5, 34.4, 39.6 (CH_2-O-

acyl-chain); 22.5, 25.2, 29.2, 29.5, 33.9, 40.9, ($\underline{C}H_2$-N-acyl-chain); 23.6, 23.8, 24.9, 35.2, 37.9 ($\underline{C}H_2$); 31.8 (C6); 51.0 (C2); 69.2, 69.3 (PO$\underline{C}H_2$Ph); 70.8, 71.3 (O$\underline{C}H_2$Ph); 70.9 (C1); 72.3 (C3); 75.4, 75.6, 75.7 (C4, $\underline{C}OCH_2$Ph); 77.0 (C5); 110.0 (O$\underline{C}$O); 127.3-138.6 (Ph); 171.1 (COO); 171.8 (N$\underline{C}$O).

1-*D*-(1,2,4/3,5)-3-*O*-[(R)-3-Hydroxy-tetradecanoyl]-2-[(R)-3-hydroxytetradecanoylamido]-1-*O*-phosphono-cyclohexanetetrol 2. A solution of **26** (0.07 g, 0.062 mmol) in tetrahydrofuran (20 ml) was hydrogenolyzed over palladium (10%) on charcoal (0.03 g) at room temperature for 4 h then filtered. Pyrogen-free water (2 ml) and Dowex AG 50W-X8 in H^+ form (1g) was added. The mixture was kept at 60°C for 1 h. The resin was filtered off, the tetrahydrofuran was evaporated and the aqueous suspension was lyophilised to give **2** (0.018 g, 46%).This latter was dissolved in 5 ml of a mixture of 1:1 tetrahydrofuran-water (pyrogen-free) and the pH was adjusted to 7 by addition of a 0.1 M solution of tris(hydroxymethyl)aminomethane in pyrogen-free water. The tetrahydrofuran was evaporated and the aqueous suspension was lyophilised. The lyophilisate (0.025 g) was dissolved in methanol (10 mg/ml) and chromatographed over Sephadex LH-20, using methanol as eluent to give TRIS salt of **2** (0.007 g, 14%). Anal. Calcd. for $C_{38}H_{77}N_2O_{14}P$: P, 3.79. Found 3.47. ^1H NMR spectrum shows that all protecting groups are removed.

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