Synthesis of Glycolipid Clusters with Pentaerythritol Cores and Different Ethyleneoxy-Spaced Mannose Residues as Terminal Carbohydrates

Matthias Schmidt,[a] Bodo Dobner,[a] and Peter Nuhn*[a]

Keywords: Alkylation / Cluster compounds / Glycolipids / Glycosidation

We describe the synthesis of polyantennary glycolipid clusters with pentaerythritol cores. A known protecting group strategy permits the introduction of different hydrophobic moieties and the selective coupling with ethyleneoxy spacers of different lengths. After glycosidation, substances with one, two or three mannose residues as terminal carbohydrate headgroups were isolated. These polyantennary mannosides can be used as attractive tools for targeting of liposomes towards the macrophage mannose receptor.

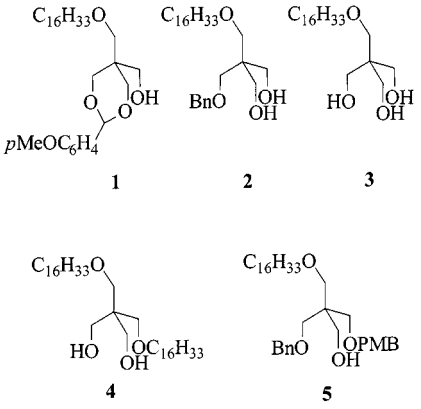
Complex carbohydrate structures are one of the basic constituents of biological membranes besides phospholipids. The importance of the carbohydrate domains in the context of glycoproteins and glycolipids as elements of all surface recognition is manifested by their role in cellular adhesion. Investigations into the interaction of natural glycoconjugates indicate that the structures of the terminal carbohydrate headgroups in the hydrophilic moiety and the different distances between the hydrophobic and the recognition domains are responsible for the efficiency of ligand coupling to the receptor. Because of the complexity of the total retrosynthesis of natural oligosaccharides (Sialyl-Lewis^X, for example),[1] interest in simply structured model substances is growing.

On one hand, the development of neoglycoconjugates with two, three or more sugar compounds in the hydrophilic moiety evidence the cluster effect and hence a logarithmic increase of the binding affinity. On the other hand, studies of glycomimics with different ethyleneoxy spacers demonstrate a relationship between the spacer length and adhesion effects of the corresponding receptor.

There are actually two possible means to simulate effective ligand−receptor binding with carbohydrate-clustered glycoconjugates. Beside the glycodendrimers,[2−5] highly branched, complex and symmetrical macromolecules with a core substance and multiple terminal sugar residues,[6,7] which can be applied in, for example, antiadhesion therapy,[8] the incorporation of neocluster glycolipids in large unilamellar liposomes, as first reported by Lee et al.,[9] promises to be a possible target strategy.

In continuation of our work on the study of cellular response towards liposomes, we have developed a synthetic strategy[10] that allows different carbohydrates with suitable distances to be introduced within the molecule in place of the former cluster glycolipids with equal sugar domains or spacer lengths.[11] In this case we have synthesized mono-, di- and trimannosylated glycolipids. The molecules differ in the number of lipid anchors, in the length and number of the ethyleneoxy spacers used in place of natural oligosaccharides, and in the variety of terminal carbohydrate headgroups. As the sugar domain we chose mannose, because of our investigation into mannosylated liposomes as attractive tools for targeting towards the macrophage mannose receptor.

The core substance of our neoglycoconjugates is pentaerythritol [2,2-bis(hydroxymethyl)propane-1,3-diol], of which diverse functional derivatives are known.[12,13] The lipid anchor starting materials used in this work, *O*-hexadecyl-*O′*,*O′′*-(*p*-methoxybenzylidene)pentaerythritol (**1**), *O*-benzyl-*O′*-hexadecylpentaerythritol (**2**), *O*-hexadecylpentaerythritol (**3**), di-*O*,*O′*-hexadecylpentaerythritol (**4**) and *O*-benzyl-*O′*-hexadecyl-*O′′*-(*p*-methoxybenzyl)pentaerythritol (**5**),[10] are shown in Scheme 1.



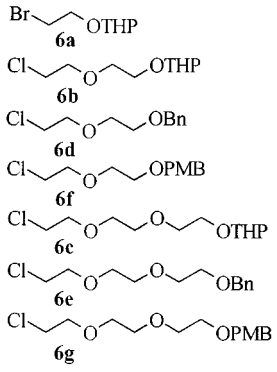
Scheme 1. Different functionalized *O*-hexadecylpentaerythritol derivatives **1**−**5**

[a] Institute of Pharmaceutical Chemistry, Martin Luther University,
Wolfgang-Langenbeck-Str. 4, 06120 Halle/Saale, Germany
E-mail: nuhn@pharmazie.uni-halle.de

The substances are characterized by different numbers of hexadecyl residues as a lipid anchor that can of course be exchanged for other long alkyl chains – with branching, for example[10] – to achieve efficient and variable hydrophilic–lipophilic balance (HLB) values as possible membrane components.

The selective protection of the hydroxy groups permits the introduction of various headgroups with different monosaccharides, such as D-glucose, D-galactose[10] or, in this work, coupling with ethyleneoxy spacers of different lengths to simulate a variety of binding epitopes. It should be mentioned that the introduction of the spacer into the core substances **3** and **4** can also be achieved without the need for a protecting group strategy. The result of this reaction is certainly a mixture of products, separation of which is a problem because of the similarity of, for example, the R_f values of mono- and dialkylated products.

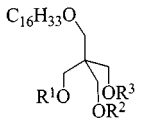
As spacer material we chose the often used ethyleneoxy derivatives,[14,15] the advantages of which are their uncomplicated chemical properties and their greater flexibility in comparison to natural oligosaccharides. In Scheme 2 a number of ethyleneoxy spacer derivatives are shown.



Scheme 2. Halogenated ethyleneoxy derivatives **6a**–**6g** of different lengths with protecting groups as spacer material

The introduction of the halogenated ethylene glycol derivatives **6** into the hydrophobic core substances (Scheme 1) was achieved by simple *O*-alkylation. The terminal hydroxy group was blocked by different protecting groups. The THP protecting group can be selectively removed by catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS)[16] and the *p*-methoxybenzyl (PMB) group by treatment with ceric ammonium nitrate (CAN),[17] while the *O*-benzyl ether can be reduced to the free hydroxy group by palladium-catalysed hydrogenolysis.[18,19] With this selective deprotection, the introduction of various carbohydrate headgroups is possible.

According to this procedure, a range of amphiphilic molecules characterized by one or two hexadecyl chains and ethyleneoxy spacers of different lengths was achieved in good yield (Scheme 3). With the possibility of varying the structures of the hydrophobic and spacer core substance between small/short terminal binding domains and polyantennary/voluminous ligands we can synthesize a host of synthons that promise to find neoglycoconjugates for optimal ligand–receptor binding.



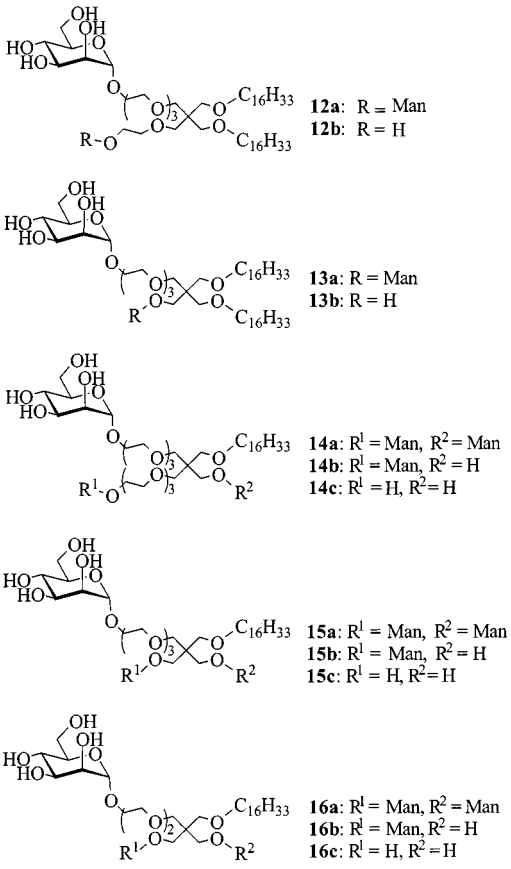
7: $R^1 = (CH_2CH_2O)_3H$, $R^2 = H$, $R^3 = C_{16}H_{33}$
8: $R^1 = (CH_2CH_2O)_3H$, $R^2 = CH_2CH_2OH$, $R^3 = C_{16}H_{33}$
9: $R^1 = R^2 = (CH_2CH_2O)_3H$, $R^3 = H$
10: $R^1 = (CH_2CH_2O)_3H$, $R^2 = R^3 = H$
11: $R^1 = (CH_2CH_2O)_2H$, $R^2 = R^3 = H$

Scheme 3. Hydrophobic pentaerythritol derivatives **7**–**11** with different numbers and lengths of ethylene glycol spacers

Experience has shown that the main problem in the synthesis of glycolipid clusters is the introduction of the terminal carbohydrate headgroups into the molecule, because of the relatively low yields of glycosidation reactions. Investigations in our group into the effectivities of the triflate method, the Koenigs–Knorr method and the imidate method for the synthesis of cluster glycolipids demonstrated that the triflate method afforded the best results with the highest yields and anomeric purities.[20] Nevertheless, in the reactions of the intermediates **7**–**11**, mixtures of the expected mono-, di- and (in the cases of **9**–**11**) also triglycosidated products were obtained. Certainly, separation of the acetylated intermediate glycolipids could not be achieved with conventional methods such as column or flash chromatography. Therefore, prior deprotection of the acetylated sugar compounds and subsequent separation of the unprotected final compounds by use of a preparative, centrifugally accelerated, radial, thin layer chromatograph (Chromatotron, Harrison Research) afforded a range of glycolipids with different numbers of terminal mannose headgroups and various spacer lengths (Scheme 4).

All compounds were fully characterized by ^{1}H NMR and ESI-MS. The final products **12**–**16** had to be reacetylated for final structure elucidation for the reasons given.

Initial biochemical investigation has shown that these polyantennary mannosides can be used as attractive tools for liposome-targeting toward the macrophage mannose receptor. The neoglycolipids were asymmetrically incorporated into liposomes and subsequently investigated in detail by flow cytometry. It was shown that the degree of mannosylation and the linkage moiety between the acyl chain and the headgroups resulted in increases in macrophage binding and uptake, respectively. This suggests that molecular recognition of mannose residues by the mannose-specific 175KDa receptor may occur prior to endocytosis which enables it's use as target device for therapeutic reason.[21] Further biochemical investigations will follow soon.



Scheme 4. Different glycosidated mannosides **12**−**16** with variation in the hydrophobic and spacer moieties

Experimental Section

General: ^{1}H NMR spectra were recorded with a Bruker AC 500 spectrometer at a frequency of 400 MHz with TMS as internal standard. Mass spectra were obtained with a Finnigan MAT 710 spectrometer. The ionization was effected at 4.5 kV both in negative and positive modes. Elemental analyses were performed with a CHNS-932 apparatus (LECO Corporation). Column chromatography was carried out with silica gel 60 (0.04−0.2 mm; Merck) and preparative, centrifugally accelerated, radial, thin layer chromatography with a Chromatotron (Harrison Research). All reactions were performed under argon. Solvents were dried before use. All chemicals were purchased from Aldrich and Fluka.

Synthesis of the Starting Materials: Di-*O*,*O*′-hexadecylpentaerythritol (**4**)[22] and *O*-benzyl-*O*′-(*p*-methoxybenzyl)-*O*′′-hexadecylpentaerythritol (**5**)[10] were synthesized according to the literature.

***O*-Hexadecyl-*O*′,*O*′′-(*p*-methoxybenzylidene)pentaerythritol (1):** Compound **1** was synthesized according to ref.[1] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84−0.88 (t, 3 H, −C*H*$_3$), 1.24−1.28 (s, 26 H, −C*H*$_2$−), 1.54−1.58 (m, 2 H, −OCH$_2$C*H*$_2$−), 2.81 (s, 1 H, −O*H*), 3.25 (s, 2 H, −OC*H*$_2$C−), 3.35−3.38 (t, 2 H, −OC*H*$_2$CH$_2$−), 3.38−3.50 (d, 2 H, −CC*H*$_2$OCH−), 3.72−3.74 (d, 2 H, $J_{eq,ax}$ = 11.8 Hz, −CC*H*$_2$OCH−), 3.78 (s, 3 H, −OC*H*$_3$), 4.11−4.13 (d, 2 H, −CC*H*$_2$OH), 5.36 (s, 1 H, −C*H*−), 6.85−6.89 (m, 2 H, −C$_6$*H*$_4$OCH$_3$), 7.38−7.40 (m, 2 H, −C$_6$*H*$_4$OCH$_3$). MS (ES, positive ions): *m*/*z* = 501.70 [M + 23]$^+$. R_f ($CHCl_3$/Et_2O, 8:2) = 0.59. Yield 56%; m.p. 55−57 °C (heptane). $C_{29}H_{50}O_5$ (478.71): calcd. C 72.76, H 10.53; found C 72.73, H 10.59.

***O*-Benzyl-*O*′-hexadecylpentaerythritol (2):** Compound **2** was synthesized according to ref[1]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84−0.87 (t, 3 H, −C*H*$_3$), 1.23−1.28 (s, 26 H, −C*H*$_2$−), 1.50−1.56 (m, 2 H, −OCH$_2$C*H*$_2$−), 2.64 (t, 2 H, −O*H*), 3.36−3.40 (t, 2 H, −OC*H*$_2$CH$_2$−), 3.49 (s, 2 H, −CC*H*$_2$O−), 3.53 (s, 2 H, −CC*H*$_2$OBn), 3.64 (d, 2 H, HOC*H*$_2$C−), 3.66 (d, 2 H, HOC*H*$_2$C−), 4.49 (s, 2 H, −OC*H*$_2$C$_6$H$_5$), 7.27−7.33 (m, 5 H, −C$_6$*H*$_5$). MS (ES, positive ions): *m*/*z* = 473.69 [M + 23]$^+$. R_f ($CHCl_3$/Et_2O, 8:2) = 0.26. Yield 28%. $C_{28}H_{50}O_4$ (450.70): calcd. C 74.62, H 11.18; found C 74.58, H 11.29.

***O*-Hexadecylpentaerythritol (3):** Concentrated HCl (50 mL) was added dropwise to a solution of **1** (0.1 mol) in 500 mL of EtOH. The mixture was heated at 80 °C for 3 h and neutralized with NaOH while still warm. After cooling, the mixture was repeatedly partitioned with ethyl acetate. The organic phases were dried with Na_2SO_4 and the solvents were evaporated under reduced pressure. The oily residue was resuspended in heptane/diethyl ether (90:10) to provide **3** as a pure crystalline material (28.1 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84−0.86 (t, 3 H, −C*H*$_3$), 1.23−1.26 (s, 26 H, −C*H*$_2$−), 1.50−1.55 (m, 2 H, −OCH$_2$C*H*$_2$−), 2.53 (s, 3 H, −O*H*), 3.38−3.42 (t, 2 H, −OC*H*$_2$CH$_2$−), 3.45 (s, 2 H, −OC*H*$_2$C−), 3.69 (s, 6 H, −C*H*$_2$OH). MS (ES, positive ions): *m*/*z* = 383.57 [M + 23]$^+$. R_f ($CHCl_3$/MeOH 8:2) = 0.68; m.p. 71 °C. $C_{21}H_{44}O_4$ (360.57): calcd. C 69.95, H 12.30; found C 69.83, H 12.38.

Synthesis of the Spacers: 2-Bromo-1-(tetrahydro-2*H*-pyran-2-yloxy)ethane (**6a**),[23] 5-chloro-1-(tetrahydro-2*H*-pyran-2-yloxy)-3-oxapentane (**6b**),[24] 8-chloro-1-(tetrahydro-2*H*-pyran-2-yloxy)-3,6-dioxaoctane (**6c**),[25] 1-chloro-7-phenyl-3,6-dioxaheptane (**6d**)[26] and 1-chloro-10-phenyl-3,6,9-trioxadecane (**6e**)[27] were synthesized according to the literature. 5-Chloro-3-oxapentanol (0.1 mol) or 8-chloro-3,6-dioxaoctanol (0.1 mol) were dissolved together with *p*-methoxybenzyl bromide (0.1 mol) in THF (100 mL), and *t*BuOK (0.1 mol) was added at 0 °C. The mixture was stirred for 24 h, the solid was filtered off and the organic phase was concentrated. The oily residue was purified by flash chromatography (petroleum ether/EtO_2) to obtain **6f** or **6g**, respectively, in good yields.

1-Chloro-7-(*p*-methoxyphenyl)-3,6-dioxaheptane (6f): MS (ES, positive ions): *m*/*z* = 267.72 [M + 23]$^+$. R_f ($CHCl_3$) = 0.65. Yield 74%. $C_{12}H_{17}ClO_3$ (244.72): calcd. C 58.90, H 7.00; found C 58.86, H 6.95.

1-Chloro-10-(*p*-methoxyphenyl)-3,6,9-trioxadecane (6g): MS (ES, positive ions): *m*/*z* = 311.77 [M + 23]$^+$. R_f ($CHCl_3$) = 0.57. Yield 68%. $C_{14}H_{21}ClO_4$ (288.77): calcd. C 58.23, H 7.33; found C 58.75, H 7.18.

Introduction of the Spacers into the Hydrophobic Core Substances

***O*,*O*′-Dihexadecyl-*O*′′-(8-hydroxy-3,6-dioxaoctyl)pentaerythritol (7):** Compound **6e** (0.01 mol), dissolved in THF (10 mL), was added dropwise to a solution of **4** (0.01 mol), *t*BuOK (0.011 mol) and catalytic amounts of tetrabutylammonium iodide (TBAI) in 50 mL of THF. The mixture was heated at 65 °C for 24 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$. The organic phase was washed with water and dried with Na_2SO_4, and the solvents were evaporated. The intermediate **7**/**I** was dissolved in 20 mL of EtOH and removal of the *O*-benzyl group was achieved by palladium-catalysed hydrogenolysis for 12 h. After filtration, the

solvents were evaporated and the residue was purified by flash chromatography (petroleum ether/$CHCl_3$) to provide the mono-*O*-alkylated product **7** (3.01 g, 42%). MS (ES, positive ions): *m*/*z* = 740.16 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.89. $C_{43}H_{88}O_7$ (717.16): calcd. C 72.02, H 12.37; found C 71.95, H 12.46.

***O,O′*-Dihexadecyl-*O′′*-(8-hydroxy-3,6-dioxaoctyl)-*O′′′*-(2-hydroxyethyl)pentaerythritol (8):** The intermediate **7/I** (0.01 mol), isolated by flash chromatography (petroleum ether/$CHCl_3$), *t*BuOK (0.011 mol) and catalytic amounts of TBAI were dissolved in 50 mL of THF. A solution of **6a** (0.01 mol), dissolved in 10 mL of THF was added dropwise to this mixture, which was heated at 65 °C for 24 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$. The organic phase was washed with water and dried with Na_2SO_4, and the solvents were evaporated. The residue was dissolved in 20 mL of EtOH and removal of the *O*-benzyl group was achieved by palladium-catalysed hydrogenolysis for 12 h. After filtration, the mixture was stirred with catalytic amounts of PPTS for 4 h. After concentration, the residue was purified by flash chromatography (petroleum ether/EtO_2) to provide compound **8** (2.74 g, 36%). MS (ES, positive ions): *m*/*z* = 784.22 $[M + 23]^+$. R_f ($CHCl_3$/MeOH 8:2) = 0.83. $C_{45}H_{92}O_8$ (761.22): calcd. C 71.00, H 12.18; found C 70.89, H 12.27.

***O*-Hexadecyl-*O′,O′′*-bis(8-hydroxy-3,6-dioxaoctyl)pentaerythritol (9):** Compound **6e** (0.025 mol), dissolved in THF (10 mL), was added dropwise to a solution of **2** (0.01 mol), *t*BuOK (0.025 mol) and catalytic amounts of TBAI in THF (50 mL). The mixture was heated at 65 °C for 24 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$. The organic phase was washed with water and dried with Na_2SO_4, and the solvents were evaporated. The intermediate **9/I** was dissolved in 20 mL of EtOH and removal of the *O*-benzyl group was achieved by palladium-catalysed hydrogenolysis for 12 h. After filtration, the solvents were evaporated and the residue was purified by flash chromatography (petroleum ether/$CHCl_3$) to provide the bis-*O*-alkylated product **9** (2.93 g, 47%). MS (ES, positive ions): *m*/*z* = 647.89 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.81. $C_{33}H_{68}O_{10}$ (624.89): calcd. C 63.43, H 10.97; found C 63.37, H 11.04.

***O*-Hexadecyl-*O′*-(8-hydroxy-3,6-dioxaoctyl)pentaerythritol (10):** Compound **6c** (0.012 mol), dissolved in THF (10 mL), was added dropwise to a solution of **1** (0.01 mol), *t*BuOK (0.012 mol) and catalytic amounts of TBAI in THF (50 mL). The mixture was heated for 24 h at 65 °C. After cooling to room temperature, the mixture was diluted with $CHCl_3$. The organic phase was washed with water and dried with Na_2SO_4, and the solvents were evaporated. The intermediate **10/I** was dissolved in 100 mL of EtOH (100 mL) and removal of the *O*-(*p*-methoxybenzylidene) and THP groups was achieved by heating the mixture with HCl (2 M, 10 mL) for 3 h. After cooling to room temperature, the mixture was neutralized and diluted with water and $CHCl_3$. The organic phase was separated and dried with Na_2SO_4. After concentration, the residue was purified by flash chromatography (petroleum ether/$CHCl_3$) to provide the mono-*O*-alkylated product **10** (2.21 g, 45%). MS (ES, positive ions): *m*/*z* = 515.73 $[M + 23]^+$. R_f ($CHCl_3$/MeOH 8:2) = 0.86. $C_{27}H_{56}O_7$ (492.73): calcd. C 65.82, H 11.46; found C 65.73, H 11.56.

***O*-Hexadecyl-*O′*-(5-hydroxy-3-oxapentyl)pentaerythritol (11):** Compound **11** was synthesized like compound **10** by use of **6b** as spacer derivative. MS (ES, positive ions): *m*/*z* = 471.68 $[M + 23]^+$. R_f ($CHCl_3$/MeOH 8:2) = 0.87. Yield 51%. $C_{25}H_{52}O_6$ (448.68): calcd. C 66.92, H 11.68; found C 66.85, H 11.76.

Synthesis of the Final Compounds

General Method for the Synthesis of Compounds 12−16 by Transglycosidation with TMS Triflate: TMS triflate was added to a solution of penta-*O*-acetyl-D-mannopyranose in dry CH_2Cl_2 and molecular sieves and the mixture was stirred for 4 h at 20 °C under argon. The glycosyl acceptors **7**−**11** were added and the mixture was stirred for 8 h at room temperature (the TMS triflate/glycosyl donor/glycosyl acceptor ratio was 2.2:2.2:1 in the cases of **7** and **8** and 3.3:3.3:1 in the cases of **9**, **10** and **11**). The mixture was neutralized with triethylamine (TEA), filtered and washed with water, and the organic phase was dried with Na_2SO_4. After concentration, the residue was dissolved in MeOH and a catalytic amount of NaOMe was added. The mixture was stirred for 12 h and then the solvent was removed. The residue was purified by preparative, centrifugally accelerated, radial, thin layer chromatograph (Chromatotron) to separate the mono-, di- and particularly triglycosylated final compounds **12**−**16**.

***O,O′*-Dihexadecyl-*O′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]-*O′′′*-[2-(α-D-mannopyranosidoyloxy)ethyl]pentaerythritol (12a):** MS (ES, positive ions): *m*/*z* = 1108.50 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.32. Yield 16%. $[\alpha]_D^{20}$ = +14.9 (*c* = 1.8, MeOH). $C_{57}H_{112}O_{18}$ (1085.50): calcd. C 63.07, H 10.40; found C 63.02, H 10.48.

***O,O′*-Dihexadecyl-*O′′*-(2-hydroxyethyl)-*O′′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (12b):** MS (ES, positive ions): *m*/*z* = 946.36 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.54. Yield 19%. $[\alpha]_D^{20}$ = +15.2 (*c* = 2.1, MeOH). $C_{51}H_{102}O_{13}$ (923.36): calcd. C 66.34, H 11.13; found C 66.31, H 11.16.

***O,O′*-Dihexadecyl-*O′′*-(α-D-mannopyranosidoyl)-*O′′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (13a):** MS (ES, positive ions): *m*/*z* = 1064.45 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.34. yield 18%. $[\alpha]_D^{20}$ = +12.7 (*c* = 2.7, MeOH). $C_{55}H_{108}O_{17}$ (1041.45): calcd. C 63.43, H 10.45; found C 63.31, H 10.52.

***O,O′*-Dihexadecyl-*O′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (13b):** MS (ES, positive ions): *m*/*z* = 902.30 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.57. Yield 21%. $[\alpha]_D^{20}$ = +11.3 (*c* = 2.1, MeOH). $C_{49}H_{98}O_{12}$ (879.30): calcd. C 66.93, H 11.23; found C 66.86, H 11.26.

***O*-Hexadecyl-*O′*-(α-D-mannopyranosidoyl)-*O′′,O′′′*-bis[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (14a):** MS (ES, positive ions): *m*/*z* = 1134.32 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.07. Yield 11%. $[\alpha]_D^{20}$ = +26.4 (*c* = 3.1, MeOH). $C_{51}H_{98}O_{25}$ (1111.32): calcd. C 55.12, H 8.89; found C 55.07, H 8.93.

***O*-Hexadecyl-*O′,O′′*-bis[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (14b):** MS (ES, positive ions): *m*/*z* = 972.18 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.16. Yield 14%. $[\alpha]_D^{20}$ = +17.8 (*c* = 2.5, MeOH). $C_{45}H_{88}O_{20}$ (949.18): calcd. C 56.94, H 9.34; found C 56.85, H 9.42.

***rac*-*O*-Hexadecyl-*O′*-(8-hydroxy-3,6-dioxaoctyl)-*O′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (14c):** MS (ES, positive ions): *m*/*z* = 810.03 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.47. Yield 18%. $[\alpha]_D^{20}$ = +4.9 (*c* = 1.9, MeOH). $C_{39}H_{78}O_{15}$ (787.03): calcd. C 59.52, H 9.99; found C 59.47, H 10.03.

***O*-Hexadecyl-*O′,O′′*-bis(α-D-mannopyranosidoyl)-*O′′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (15a):** MS (ES, positive ions): *m*/*z* = 1002.16 $[M + 23]^+$. R_f ($CHCl_3$/MeOH, 8:2) = 0.09. Yield 12%. $[\alpha]_D^{20}$ = +22.6 (*c* = 2.4, MeOH). $C_{45}H_{86}O_{22}$ (979.16): calcd. C 55.20, H 8.85; found C 55.16, H 8.91.

***rac*-*O*-Hexadecyl-*O′*-α-D-mannopyranosidoyl-*O′′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]pentaerythritol (15b):** MS (ES, positive ions): *m/z* = 840.02 [M + 23]$^+$. R_f (CHCl$_3$/MeOH, 8:2) = 0.19. Yield 16%. $[\alpha]_D^{20}$ = +6.1 (*c* = 3.3, MeOH). $C_{39}H_{76}O_{17}$ (817.02): calcd. C 57.33, H 9.38; found C 57.28, H 9.42.

***O*-Hexadecyl-*O′*-[8-(α-D-mannopyranosidoyloxy)-3,6-dioxaoctyl]-pentaerythritol (15c):** MS (ES, positive ions): *m/z* = 677.87 [M + 23]$^+$. R_f (CHCl$_3$/MeOH, 8:2) = 0.52. Yield 20%. $[\alpha]_D^{20}$ = +13.8 (*c* = 2.7, MeOH). $C_{33}H_{66}O_{12}$ (654.87): calcd. C 60.52, H 10.16; found C 60.49, H 10.17.

***O*-Hexadecyl-*O′*,*O′′*-bis(α-D-mannopyranosidoyl)-*O′′′*-[5-(α-D-mannopyranosidoyloxy)-3-oxapentyl]pentaerythritol (16a):** MS (ES, positive ions): *m/z* = 958.11 [M + 23]$^+$. R_f (CHCl$_3$/MeOH, 8:2) = 0.09. Yield 11%. $[\alpha]_D^{20}$ = +24.5 (*c* = 2.5, MeOH). $C_{43}H_{82}O_{21}$ (935.11): calcd. C 55.23, H 8.84; found C 55.24, H 8.81.

***rac*-*O*-Hexadecyl-*O′*-(α-D-mannopyranosidoyl)-*O′′*-[5-(α-D-mannopyranosidoyloxy)-3-oxapentyl]pentaerythritol (16b):** MS (ES, positive ions): *m/z* = 795.96 [M + 23]$^+$. R_f (CHCl$_3$/MeOH, 8:2) = 0.20. Yield 15%. $[\alpha]_D^{20}$ = +3.7 (*c* = 1.9, MeOH). $C_{37}H_{72}O_{16}$ (772.96): calcd. C 57.49, H 9.39; found C 57.47, H 9.44.

***O*-Hexadecyl-*O′*-[5-(α-D-mannopyranosidoyloxy)-3-oxapentyl]-pentaerythritol (16c):** MS (ES, positive ions): *m/z* = 633.82 [M + 23]$^+$. R_f (CHCl$_3$/MeOH, 8:2) = 0.55. Yield 19%. $[\alpha]_D^{20}$ = +16.1 (*c* = 3.2, MeOH). $C_{31}H_{62}O_{11}$ (610.82): calcd. C 60.96, H 10.23; found C 61.00, H 10.21.

Analytical Data for the Reacetylated Glycolipids

***O*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′*-[2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxyethyl]-*O′′*,*O′′′*-dihexadecylpentaerythritol (17a):** MS (ES, positive ions): *m/z* = 1444.80 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.84−0.87 (t, 6 H, −C*H*$_3$), 1.23−1.27 (s, 52 H, −C*H*$_2$−), 1.54−1.58 (m, 4 H, −OCH$_2$C*H*$_2$−), 1.94−2.14 (4 s, 24 H, 8 COC*H*$_3$), 3.41−3.87 (m, 28 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.05−4.10 (dd, *J* = 2.2 and 12.2 Hz, 2 H, 6-H), 4.15−4.19 (m, 2 H, 5-H), 4.24−4.29 (dd, *J* = 5.3 and 12.2 Hz, 2 H, 6′-H), 4.87 (d, *J* = 1.8 Hz, 2 H, 1-Hα), 5.23−5.37 (m, 6 H, 2-H, 4-H, 3-H).

***O*-(Acetoxyethyl)-*O′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′*,*O′′′*-dihexadecylpentaerythritol (17b):** MS (ES, positive ions): *m/z* = 1156.54 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.83−0.87 (t, 6 H, −C*H*$_3$), 1.24−1.28 (s, 52 H, −C*H*$_2$−), 1.51−1.57 (m, 4 H, −OCH$_2$C*H*$_2$−), 1.92−2.11 (5 s, 15 H, 5 COC*H*$_3$), 3.37−3.79 (m, 28 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.07−4.10 (dd, *J* = 2.3 and 12.2 Hz, 1 H, 6-H), 4.14−4.19 (m, 1 H, 5-H), 4.24−4.29 (dd, *J* = 5.2 and 12.2 Hz, 1 H, 6′-H), 4.84 (d, *J* = 1.8 Hz, 1 H, 1-Hα), 5.22−5.35 (m, 3 H, 2-H, 4-H, 3-H).

***O*-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyl)-*O′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′*,*O′′′*-dihexadecylpentaerythritol (18a):** MS (ES, positive ions): *m/z* = 1400.75 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.84−0.88 (t, 6 H, −C*H*$_3$), 1.25−1.29 (s, 52 H, −C*H*$_2$−), 1.52−1.58 (m, 4 H, −OCH$_2$C*H*$_2$−), 1.89−2.09 (4 s, 24 H, 8 COC*H*$_3$), 3.42−3.87 (m, 24 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.04−4.11 (dd, *J* = 2.2 and 12.2 Hz, 2 H, 6-H), 4.15−4.20 (m, 2 H, 5-H), 4.24−4.29 (dd, *J* = 5.3 and 12.1 Hz, 2 H, 6′-H), 4.74 (d, *J* = 1.7 Hz, 2 H, 1-Hα), 5.25−5.43 (m, 6 H, 2-H, 4-H, 3-H).

***O*-Acetyl-*O′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)3′′,6′′-dioxaoctyl]-*O′′*,*O′′′*-dihexadecylpentaerythritol (18b):** MS (ES, positive ions): *m/z* = 1112.49 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.81−0.88 (t, 6 H, −C*H*$_3$), 1.24−1.27 (s, 52 H, −C*H*$_2$−), 1.53−1.57 (m, 4 H, −OCH$_2$C*H*$_2$−), 1.99−2.15 (5 s, 15 H, 5 COC*H*$_3$), 3.37−3.88 (m, 24 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.07−4.11 (dd, *J* = 2.1 and 12.2 Hz, 1 H, 6-H), 4.14−4.19 (m, 1 H, 5-H), 4.24−4.27 (dd, *J* = 5.2 and 12.2 Hz, 1 H, 6′-H), 4.69 (d, *J* = 1.6 Hz, 1 H, 1-Hα), 5.21−5.37 (m, 3 H, 2-H, 4-H, 3-H).

***O*-(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-mannopyranosidoyl)-*O′*,*O′′*-bis-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′′*-hexadecylpentaerythritol (19a):** MS (ES, positive ions): *m/z* = 1638.77 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.83−0.88 (t, 3 H, −C*H*$_3$), 1.24−1.27 (s, 26 H, −C*H*$_2$−), 1.53−1.58 (m, 2 H, −OCH$_2$C*H*$_2$−), 1.97−2.14 (4 s, 36 H, 12 COC*H*$_3$), 3.39−3.87 (m, 34 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.10−4.12 (dd, *J* = 2.3 and 12.2 Hz, 3 H, 6-H), 4.15−4.19 (m, 3 H, 5-H), 4.23−4.29 (dd, *J* = 5.3 and 12.2 Hz, 3 H, 6′-H), 4.77 (d, *J* = 1.7 Hz, 3 H, 1-Hα), 5.21−5.34 (m, 9 H, 2-H, 4-H, 3-H).

***O*-Acetyl-*O′*,*O′′*-bis[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′′*-hexadecylpentaerythritol (19b):** MS (ES, positive ions): *m/z* = 1350.51 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.85−0.88 (t, 3 H, −C*H*$_3$), 1.24−1.28 (s, 26 H, −C*H*$_2$−), 1.53−1.59 (m, 2 H, −OCH$_2$C*H*$_2$−), 1.89−2.11 (5 s, 27 H, 9 COC*H*$_3$), 3.42−3.85 (m, 34 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.03−4.08 (dd, *J* = 2.2 and 12.2 Hz, 2 H, 6-H), 4.12−4.17 (m, 2 H, 5-H), 4.23−4.28 (dd, *J* = 5.3 and 12.1 Hz, 2 H, 6′-H), 4.76 (d, *J* = 1.7 Hz, 2 H, 1-Hα), 5.20−5.37 (m, 6 H, 2-H, 4-H, 3-H).

***rac*-*O*-(8′-Acetoxy-3′,6′-dioxaoctyl)-*O′*-acetyl-*O′′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′′*-hexadecylpentaerythritol (19c):** MS (ES, positive ions): *m/z* = 1062.26 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.84−0.90 (t, 3 H, −C*H*$_3$), 1.24−1.28 (s, 26 H, −C*H*$_2$−), 1.54−1.58 (m, 2 H, −OCH$_2$C*H*$_2$−), 1.93−2.15 (6 s, 18 H, 6 COC*H*$_3$), 3.39−3.87 (m, 34 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.06−4.09 (dd, *J* = 2.3 and 12.2 Hz, 1 H, 6-H), 4.15−4.19 (m, 1 H, 5-H), 4.24−4.27 (dd, *J* = 5.1 and 12.2 Hz, 1 H, 6′-H), 4.76 (d, *J* = 1.8 Hz, 1 H, 1-Hα), 5.24−5.37 (m, 3 H, 2-H, 4-H, 3-H).

***O*,*O′*-Bis(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyl)-*O′′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′′*-hexadecylpentaerythritol (20a):** MS (ES, positive ions): *m/z* = 1506.61 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.83−0.89 (t, 3 H, −C*H*$_3$), 1.23−1.27 (s, 26 H, −C*H*$_2$−), 1.54−1.58 (m, 2 H, −OCH$_2$C*H*$_2$−), 1.98−2.12 (4 s, 36 H, 12 COC*H*$_3$), 3.38−3.79 (m, 22 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.03−4.10 (dd, *J* = 2.3 and 12.2 Hz, 3 H, 6-H), 4.13−4.19 (m, 3 H, 5-H), 4.22−4.27 (dd, *J* = 5.2 and 12.2 Hz, 3 H, 6′-H), 4.67 (d, *J* = 1.8 Hz, 3 H, 1-Hα), 5.23−5.37 (m, 9 H, 2-H, 4-H, 3-H).

***rac*-*O*-Acetyl-*O′*-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyl)-*O′′*-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O′′′*-hexadecylpentaerythritol (20b):** MS (ES, positive ions): *m/z* = 1118.35 [M + 23]$^+$. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.84−0.88 (t, 3 H, −C*H*$_3$), 1.24−1.29 (s, 26 H, −C*H*$_2$−), 1.52−1.58 (m, 2 H, −OCH$_2$C*H*$_2$−), 1.92−2.11 (5 s, 27 H, 9 COC*H*$_3$), 3.38−3.85 (m, 22 H, −OC*H*$_2$CH$_2$−, −OC*H*$_2$C−, −OC*H*$_2$C*H*$_2$O−), 4.07−4.11 (dd, *J* = 2.1 and 12.3 Hz, 2 H, 6-H), 4.15−4.19 (m, 2 H, 5-H), 4.22−4.27 (dd, *J* = 5.3 and 12.2 Hz, 2

H, 6′-H), 4.81 (d, J = 1.7 Hz, 2 H, 1-Hα), 5.21−5.41 (m, 6 H, 2-H, 4-H, 3-H).

***O*,*O*′-Diacetyl-*O*′′-[8′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′,6′′-dioxaoctyl]-*O*′′′-hexadecylpentaerythritol (20c):** MS (ES, positive ions): m/z = 930.10 $[M + 23]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82−0.89 (t, 3 H, $-CH_3$), 1.24−1.27 (s, 26 H, $-CH_2-$), 1.53−1.61 (m, 2 H, $-OCH_2CH_2-$), 1.95−2.09 (5 s, 18 H, 6 $COCH_3$), 3.43−3.88 (m, 22 H, $-OCH_2CH_2-$, $-OCH_2C-$, $-OCH_2CH_2O-$), 4.05−4.10 (dd, J = 2.2 and 12.2 Hz, 1 H, 6-H), 4.15−4.19 (m, 1 H, 5-H), 4.26−4.29 (dd, J = 5.2 and 12.2 Hz, 1 H, 6′-H), 4.84 (d, J = 1.8 Hz, 1 H, 1-Hα), 5.20−5.37 (m, 3 H, 2-H, 4-H, 3-H).

***O*-Hexadecyl-*O*′-[5′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′-oxapentyl)]-*O*′′,*O*′′′-bis(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyl)pentaerythritol (21a):** MS (ES, positive ions): m/z = 1462.55 $[M + 23]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84−0.88 (t, 3 H, $-CH_3$), 1.24−1.29 (s, 26 H, $-CH_2-$), 1.53−1.57 (m, 2 H, $-OCH_2CH_2-$), 1.98−2.11 (4 s, 36 H, 12 $COCH_3$), 3.41−3.87 (m, 18 H, $-OCH_2CH_2-$, $-OCH_2C-$, $-OCH_2CH_2O-$), 4.08−4.11 (dd, J = 2.3 and 12.3 Hz, 3 H, 6-H), 4.15−4.21 (m, 3 H, 5-H), 4.26−4.31 (dd, J = 5.3 and 12.1 Hz, 3 H, 6′-H), 4.81 (d, J = 1.8 Hz, 3 H, 1-Hα), 5.19−5.35 (m, 9 H, 2-H, 4-H, 3-H).

***rac*-*O*-Acetyl-*O*′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyl)-*O*′′-[5′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyllxoxy)-3′′-oxapentyl]-*O*′′′-hexadecylpentaerythritol (21b):** MS (ES, positive ions): m/z = 1174.30 $[M + 23]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82−0.87 (t, 3 H, $-CH_3$), 1.24−1.28 (s, 26 H, $-CH_2-$), 1.52−1.58 (m, 2 H, $-OCH_2CH_2-$), 1.93−2.14 (5 s, 27 H, 9 $COCH_3$), 3.37−3.85 (m, 18 H, $-OCH_2CH_2-$, $-OCH_2C-$, $-OCH_2CH_2O-$), 4.07−4.11 (dd, J = 2.2 and 12.3 Hz, 2 H, 6-H), 4.14−4.19 (m, 2 H, 5-H), 4.23−4.28 (dd, J = 5.1 and 12.2 Hz, 2 H, 6′-H), 4.69 (d, J = 1.8 Hz, 2 H, 1-Hα), 5.26−5.42 (m, 6 H, 2-H, 4-H, 3-H).

***O*,*O*′-Diacetyl-*O*′′-[5′′-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosidoyloxy)-3′′-oxapentyl]-*O*′′′-hexadecylpentaerythritol (21c):** MS (ES, positive ions): m/z = 886.05 $[M + 23]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84−0.87 (t, 3 H, $-CH_3$), 1.24−1.28 (s, 26 H, $-CH_2-$), 1.51−1.57 (m, 2 H, $-OCH_2CH_2-$), 1.94−2.12 (5 s, 18 H, 6 $COCH_3$), 3.40−3.88 (m, 18 H, $-OCH_2CH_2-$, $-OCH_2C-$, $-OCH_2CH_2O-$), 4.04−4.08 (dd, J = 2.3 and 12.2 Hz, 1 H, 6-H), 4.13−4.18 (m, 1 H, 5-H), 4.26−4.29 (dd, J = 5.3 and 12.3 Hz, 1 H, 6′-H), 4.75 (d, J = 1.7 Hz, 1 H, 1-Hα), 5.21−5.38 (m, 3 H, 2-H, 4-H, 3-H).

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 197).

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Received August 29, 2001
[O01418]