Tetrahedron Vol. 46, No. 15, pp. 5145-5154, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

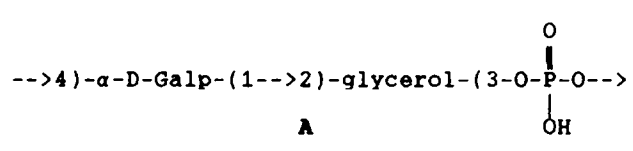
SYNTHESIS OF THE REPEATING UNIT OF THE CAPSULAR ANTIGEN OF *NEISSERIA MENINGITIDIS* SEROGROUP H

KARL-HEINZ METTEN and PETER WELZEL*
Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum (FRG)

(*Received in Germany 27 March* 1990)

Abstract- **9c** and **10b** (one of which represents the repeating unit of the *N. meningitidis* capsular polysaccharide **A**) have been synthesized via the common intermediate **6**, commencing from D-mannitol.

Chiral glycerol derivatives play an important role (i) for the synthesis of cell wall and cell membrane constituents and (ii) as highly functionalized C_3 synthons for the EPC synthesis of many types of natural products and pharmacologically important compounds.[1] Many different ways of preparing optically active glycerol starting materials have been reported,[2] but apparently, the capacity of quite a few of these procedures has yet to be demonstrated. Their synthetic merits may be judged by the efficiency of handling the protective group chemistry and the ease of providing both enantiomeric series.[3] Recently, within the context of platelet activating factor synthetic studies, use of 1,3(R):4,6(R)-bis-O-(4-methoxy-benzylidene)-D-mannitol (**2a**) as precursor of such glycerol compounds has been shown to be very promising in terms of both above mentioned requirements.[4] It appeared to us that the synthesis of the repeating unit of the *Neisseria meningitidis* serogroup H capsular polysaccharide would be a good further test for the efficiency of our method.



A

N. meningitidis is a *Gram-negative* organism that has been classified serologically into a number of groups. Almost each group produces a unique capsular polysaccharide that is the antigen responsible for group specificity.[5] Some time ago, structure **A** (partially O-acetylated in the 2'- and

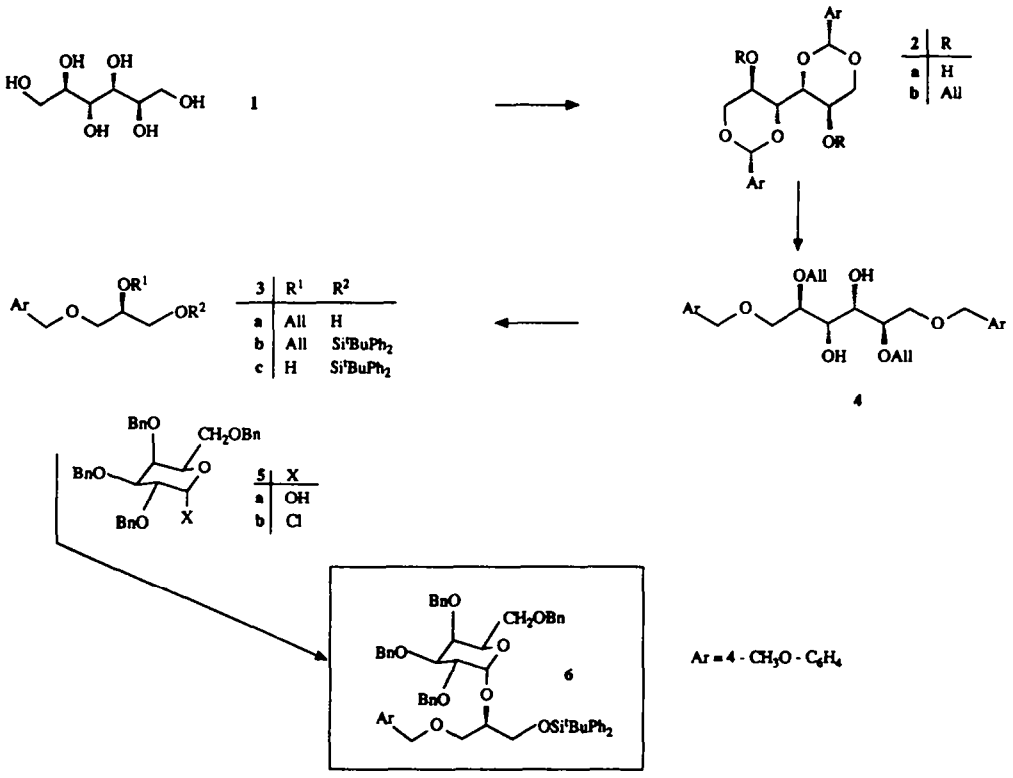
---

Dedicated with appreciation to Professor Wolfgang R. Roth on the occasion of his 60th birthday.

the 3'-position, respectively) has been established for the capsular antigen of serogroup H. The configuration at C-2 of the glycerol moiety remained, however, undetermined.[6,7] If O-acetylation in the D-galactose part is neglected, the repeating unit of **A** has either structure **9c** or **10b**. It is the purpose of this article to outline an approach to both **9c** and **10b** via central intermediate **6** that may be of general applicability.[8,9]

The synthesis commenced from D-mannitol (**1**) which was converted into bis-acetal **2a** by reaction with 4-methoxybenzaldehyde-H_2SO_4-trimethyl orthoformate.[4] Although **2a** is now reproducibly available in 48% yield and the other reaction products (5-membered ring and mixed acetals) can, in principle, be recycled, there seems to be room for further improvements. Alkylation of **2a** with allyl bromide under phase transfer conditions[10] furnished **2b** in 95% yield. Reductive opening of the acetal groupings (**2b**-->**4**, 86%), and periodate cleavage, followed by sodium borhydride reduction (**4**-->**3a**, 92%) were performed as described previously.[4] Protection of the free OH group (**3a**-->**3b**, 79%) using the Hernandez procedure[11] and Pd^{2+}-mediated deallylation[12] (**3b**-->**3c**, 88%) proceeded uneventfully. Stereoselective α-galactosidation of **3c** turned out to be the most difficult step of the synthesis. After much experimentation[13] best results were obtained using α-chloride **5b** (prepared from tetra-O-benzyl-D-galactopyranose (**5a**) on reaction with the Vilsmeier reagent[14]) as glycosyl donor and silver triflate as catalyst for the in-situ anomerisation-glycoside formation.[15] α-Galactoside **6** was obtained in 58% yield alongside with 27% of the ß-isomer.[13c,16] From **6** the p-methoxybenzyl protecting group was selectively removed by oxidation with ceric ammonium nitrate in acetonitrile-water to give **7** (81%).[17] For the phosphorylation the phosphite methodology[18] was employed. **7** was treated with N,N-diethyl dibenzyl phosphoramidite[18a,b] in the presence of 1H-tetrazole, and the intermediate phosphorous acid triester was oxidized with tert-butyl hydroperoxide to give phosphoric acid triester **9a** in 85% yield. Deblocking of **9a** was found to be critical. The benzyl groups have to be removed prior to cleavage of the silyl ether in order to avoid phosphate group migration.[13a] Thus, hydrogenolysis of **9a** gave **9b** (86%) from which the silyl protecting group was cleaved off by treatment with potassium fluoride in methanol[13a,19] whereupon the desired compound **9c** was obtained in 96% yield. For the preparation of **10b** the silyl ether bond in **6** was broken with tetra-n-butylammonium fluoride to provide **8** (99%).[20] Phosphorylation was performed as described above and led to **10a** in 92% yield. Finally, simple hydrogenolytic removal of all protecting groups of **10a** gave **10b** in quantitative yield.

9c and **10b** exhibit very similar spectroscopic and chromatographic properties (see Experimental). Nevertheless, a differentiation between them is possible. On TLC (methanol-$CHCl_3$-water-acetic acid 15:10:3:0.1) **10b** is the faster moving compound. The phosphate resonance in the ^{31}P NMR


1
2 | R
a | H
b | All
3 | R1 | R2
a | All | H
b | All | Si tBuPh2
c | H | Si tBuPh2
4
5 | X
a | OH
b | Cl
6
Ar = 4 - CH3O - C6H4
7
8
9 | R1 | R2 | R3
a | Bn | PO(OBn)2 | Si tBuPh2
b | H | PO3H2 | Si tBuPh2
c | H | PO3H2 | H
10 | R1 | R2 | R3
a | Bn | ArCH2 | PO(OBn)2
b | H | H | PO3H2

spectrum of **10b** appears at δ = 3.67 and that of **9c** at δ = 3.48 (external standard: conc. H_3PO_4). The specific rotation of **9c** is +107 and that of **10b** +97 (in H_2O).

From these values the configuration of **A** at C-2 of the glycerol part should be obvious as soon as a sample of the repeating unit becomes available by degradation. In this respect it is of interest to mention that these compounds are not configurationally stable: A pure specimen of **10b** equilibrated to a 1:1 mixture of **9c** and **10b** on storage.

Experimental

General

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminium caps with open top and Teflon-faced septum (Aldrich). Usual work-up means partitioning the reaction mixture between water and an organic solvent (given in parenthesis), evaporating the combined organic solutions in vacuo at 40°C using a rotatory evaporator. Solvents were purified by standard techniques. Molecular sieves were activated at 320°C and 13 Pa for 14 h. The instrumentation used was: Melting point (corrected): Kofler hot-stage apparatus (Reichelt); ^1H NMR: WP 80 (Bruker), AM 400 (Bruker); ^{13}C NMR: AM 400 (Bruker); ^{31}P NMR: WM 250 (Bruker), proton broad band decoupled, the samples were passed through an ion exchange resin column (Dowex 50-H^+) prior to recording the spectra; IR: Perkin Elmer 1310; EI MS: MAT CH7 (Varian); FAB MS: MAT 731 (Varian); $[\alpha]_D$: Perkin-Elmer 141, 10 cm cell, 22°C; preparative gravitational LC: silica gel (ICN Biomedicals Silica 63-100); MPLC (medium-pressure liquid chromatography): 40.0 cm x 4.5 cm (column C) or 31.0 cm x 2.5 cm (column B) glass tubes, 50 µm silica gel (Amicon), Duramat pump (CfG), Thomachrom UV detector (Reichelt); analytical TLC: Merck precoated silica gel 60 F_{254} plates (0.2 mm), spots were identified under a UV lamp (Camag 29 200) and by spraying with a 2.22M H_2SO_4-solution which contained $Ce(SO_4)_2 \cdot 4H_2O$ (10 g/l) and $H_3[PO_4(Mo_3O_9)_4] \cdot xH_2O$ (25 g/l) and heating at 140°C; lyophilization: Leybold-Heraeus GT2.

The position numbers in the sugar part are dashed in this publication.

1,3(R):4,6(R)-Bis-O-(4-methoxy-benzylidene)-D-mannitol (2a).[4]

To a solution of D-mannitol (2.14 g, 11.73 mmol) in DMF (13.5 ml) were successively added 4-methoxybenzaldehyde (1.90 ml, 15.62 mmol), conc. H_2SO_4 (0.43 ml, within 10 min), and trimethyl orthoformate (3.20 ml, 29.26 mmol). The mixture was stirred at 20°C for 17 h. A second portion of 4-methoxybenzaldehyde (2.00 ml, 16.44 mmol) was added and the mixture was warmed to 60°C for 4 h. Then stirring was continued at 20°C, 14 h at ca.

$3x10^2$ Pa, 1.5 h at normal pressure, and again 2 h at ca. $3x10^2$ Pa. The reaction mixture was then poured into an ice-cold K_2CO_3 solution (120 ml). Usual work-up (ethyl acetate) and MPLC (C column, hexanes-ethyl acetate 1:2) provided **2a** (2.36 g, 48%). For spectral data, see ref.[4]

2,5-Di-O-allyl-1,3(R):4,6(R)-bis-O-(4-methoxy-benzylidene)-D-mannitol (**2b**).[4]

A two-phase system consisting of (i) a solution of **2a** (6.28 g, 15.00 mmol), allyl bromide (32.6 ml, 376.70 mmol) and tetra-n-butylammonium hydrogensulfate (3.17 g, 9.34 mmol) in toluene (47 ml) and (ii) a solution of NaOH (21 g) in water (54 ml) was vigorously stirred at 60°C for 2.5 h. The organic layer was then separated, washed with water, and dried (Na_2SO_4). Solvent evaporation and LC (hexanes-ethyl acetate 5:1) gave **2b** (7.07 g, 95%). For spectral data, see ref.[4]

(R)-2-Allyloxy-1-tert-butyl-diphenyl-silyloxy-3-(4-methoxy-benzyloxy)-propane (**3b**).

To a solution of **3a**[4] (50.0 mg, 0.198 mmol) in CH_2Cl_2 (3.0 ml) were added triethylamine (31 µl, 0.222 mmol), 4-dimethylaminopyridine (0.9 mg, 0.007 mmol), dissolved in CH_2Cl_2 (0.80 ml), and $^tBuPh_2SiCl$ (110 µl, 0.423 mmol), and the reaction mixture was stirred at 20°C for 5 d. Solvent evaporation and MPLC (B column, hexanes-acetone 40:1) furnished **3b** (77.0 mg, 79%).- $[\alpha]_D$ = +1.43 (c 1.4, $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.00 (s, 9H, $C(CH_3)_3$), 3.40-3.76 (m, 5H), 3.78 (s, 3H, OCH_3), 3.98-4.16 (2H, $CH_2(CHCH_2)$), 4.45 (s, 2H, benzyl. H's), 5.00-5.38 (2H, $CH_2(CHCH_2)$), 5.60-6.16 (1H, $CH_2(CHCH_2)$), 6.72-7.81 (14H, aromat. H's).- MS: m/z (%)= 491 (0.1), 463 (0.15), 239 (1.1), 211 (1.2), 178 (20), 71 (30), 57 (56), 44 (100).- (Found: C, 73.63; H, 7.96. $C_{30}H_{38}O_4Si$ (490.7^{21a}; 490.3^{21b}) requires C, 73.43; H, 7.81).

(R)-1-tert-Butyl-diphenyl-silyloxy-3-(4-methoxy-benzyloxy)-propan-2-ol (**3c**).

A suspension of **3b** (3.31 g, 6.75 mmol) and $PdCl_2$ (3.85 mg, 21.51 mmol) in 0.1M NaOAc in 20:1 acetic acid-water (110 ml) was stirred at 20°C for 7 h. Then $CHCl_3$ (250 ml) and water (350 ml) were added. After filtration the layers were separated. The organic phase was washed with water (2x), with saturated aq. $NaHCO_3$, and dried (Na_2SO_4). MPLC (C column, hexanes-isopropanol-ethyl acetate 120:2:1 --> 100:2:1) gave **3c** (2.69 g, 88%).- $[\alpha]_D$ = +3.6 (c 1.0, $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.03 (s, 9H, $C(CH_3)_3$), 2.80 (br s, 1H, OH), 3.44-3.90 (8H), 3.78 (s, 3H, OCH_3), 4.45 (s, 2H, benzyl. H's), 6.88-7.74 (14H, aromat. H's).- IR ($CHCl_3$): 3580 (OH), 1615 (C=C), 1590 and 1510 cm^{-1} (C=C, aromat.).- MS: m/z (%)= 241 (5), 225 (4), 199 (100), 181 (7), 163 (12), 152 (7), 135 (25), 121 (39), 105 (6), 91 (7), 77 (21), 45 (12).- (Found: C, 71.53; H, 7.89. $C_{27}H_{34}O_4Si$ (450.6^{21a}; 450.2^{21b}) requires C, 71.96; H, 7.60).

[(R)-1-(tert-Butyl-diphenyl-silyloxy-methyl)-2-(4-methoxy-benzyloxy)-ethyl] [tetra-O-benzyl-α-D-galactopyranoside] (6).

A mixture, obtained from a solution of silver triflate (810.0 mg, 3.136 mmol), and 2,4,6-trimethylpyridine (700.0 µl, 5.394 mmol) in CH_2Cl_2 (6.0 ml), 4Å molecular sieves (1.9 g), and a solution of **3c** (389.3 mg, 0.864 mmol) in CH_2Cl_2 (5.0 ml) was stirred in the dark at 20°C for 1.5 h. Then a solution of freshly prepared tetra-O-benzyl-α-D-galactopyranosyl chloride[14] (**5b**, 1.633 g, 2.927 mmol) in CH_2Cl_2 (6.0 ml) was added at -60°C. The reaction mixture was kept at this temperature for 1 h, at -30°C for 1 h, and was then allowed to reach 20°C within 1.5 h. CH_2Cl_2 was added and the mixture was filtered through a short column (5 g SiO_2, eluent: CH_2Cl_2). Concentration of the eluate and LC (CH_2Cl_2-ethyl acetate 120:1 + 0.1% triethylamine) gave **6** (484.8 mg, 58%) and the β-isomer[13c] (230.7 mg, 27%).- $[\alpha]_D$ = +41.7 (c 1.5, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9H, $C(CH_3)_3$), 3.47 (1H, 6'$_a$-H), 3.53 (1H, 6'$_b$-H), 3.55 (dd, 1H, 1$_a$-H), 3.64 (dd, 1H, 1$_b$-H), 3.72 (s, 3H, OCH_3), 3.74 (m, 2H, $ArCH_2OC\underline{H}_2$-), 3.91 (dd, 1H, 3'-H), 3.95 (1H, 2-H), 3.97 (m, 1H, 4'-H), 3.98 (dd, 1H, 2'-H), 4.21 (m, 1H, 5'-H), 4.31-4.93 (10H, benzyl. H's), 5.04 (d, 1H, 1'-H), 6.75-7.66 (34H, aromat. H's), $J_{1',2'}$=3.6 Hz, $J_{2',3'}$=10.2 Hz, $J_{3',4'}$=2.8 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'a}$=5.6 Hz, $J_{5',6'b}$=7.6 Hz, $|J_{6'a,6'b}|$=9.0 Hz, $J_{1a,2}$=6.1 Hz, $J_{1b,2}$=4.0 Hz, $|J_{1a,1b}|$=10.2 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = (C_q signals) 158.96, 138.91, 138.74, 138.41, 138.13, 133.32, 133.15, 130.41, 19.13; (CH signals) 135.57, 135.48, 129.67-127.32 (15 signals), 113.60, 96.94 (C-1'), 78.95, 76.41, 76.38, 75.09, 68.98; (CH_2 signals) 74.77, 73.24, 73.07, 72.97, 72.60, 69.84, 68.70, 63.23; (CH_3 signals) 55.16, 26.79.- FAB MS (triethyl citrate): m/z 974 = $[M+H]^+$.- (Found: C, 75.24; H, 6.84. $C_{61}H_{68}O_9Si$ (973.3[21a]; 972.5[21b]) requires C, 75.28; H, 7.04).

(R)-3-(tert-Butyl-diphenyl-silyloxy)-2-(tetra-O-benzyl-α-D-galacto-pyranosyloxy)-propan-1-ol (7).

To a solution of **6** (36.2 mg, 0.07 mmol) in 9:1 acetonitrile-water (2.5 ml) were added pyridine (13 µl) and ceric ammonium nitrate (86.4 mg, 0.158 mmol). The mixture was stirred at 20°C for 4.3 h. Addition of CH_2Cl_2 (2.5 ml), washing with water, saturated aq. Na_2SO_3 and $NaHCO_3$, drying (Na_2SO_4), solvent evaporation, and LC (hexanes-acetone 5:1 + 0.1% triethylamine) gave **7** (25.5 mg, 81%).- $[\alpha]_D$ = +33.1 (c 1.5, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$, H,C COSY): δ = 1.05 (s, 9H, $C(CH_3)_3$), 3.04 (br s, 1H, OH), 3.33 (1H) and 3.51 (1H; AB part of an ABX system, 6'$_a$-H and 6'$_b$-H), 3.66-3.83 (4H, 3'-H or 2'-H, 1$_a$-H, CH_2-3), 3.85 (m, 1H, 4'-H), 3.87-3.92 (2H, 1$_b$-H, 2-H), 4.00 (m, 1H, 2'-H or 3'-H), 4.11 (m, 1H, 5'-H), 4.37-4.91 (8H, benzyl. H's), 4.93 (d, 1H, 1'-H), 7.12-7.71 (30H, aromat. H's), $J_{1',2'}$=3.7 Hz, $J_{2',3'}$=10.9 Hz, $J_{5',6'a}$=5.0 Hz, $J_{5',6'b}$=7.3 Hz, $|J_{6'a,6'b}|$=9.6 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = (C_q signals) 138.69, 138.36, 137.62, 133.30, 133.16, 19.17; (CH signals) 135.60, 135.52, 129.73-127.41 (15

signals), 97.86 (C-1'), 81.57 (C-3' or C-2'), 78.90 (C-2), 76.42 (C-2' or C-3'), 74.95 (C-4'), 70.04 (C-5'); (CH_2 signals) 74.56, 73.50, 73.24, 73.18, 69.48 (C-6'), 63.48 and 63.37 (C-1, C-3); (CH_3 signal) 26.79.- (Found: C, 74.49; H, 7.18. $C_{53}H_{60}O_8Si$ (853.1[21a]) requires C, 74.62; H, 7.09).

(S)-3-(4-Methoxy-benzyloxy)-2-(tetra-O-benzyl-α-D-galactopyranosyloxy)-propan-1-ol (8).

A solution of **6** (9.4 mg, 0.0096 mmol) and tetra-n-butylammonium fluoride (1M in THF, 26 µl, 0.026 mmol) in THF (0.5 ml) was stirred at 20°C for 3.7 h. Solvent evaporation and LC (hexanes-ethyl acetate 2:1) provided **8** (7.0 mg, 99%).- $[\alpha]_D$ = +31.7 (c 1.5, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ = 3.26 (br s, 1H, OH), 3.42-3.65 (5H), 3.70 (m, 1H), 3.77 (s, 3H, OCH_3), 3.83 (m, 1H, 2-H), 3.97 (dd, 1H, 3'-H), 4.00 (m, 1H), 4.05 (dd, 1H, 2'-H), 4.12 (m, 1H, 5'-H), 4.32-4.96 (10H, benzyl. H's), 5.01 (d, 1H, 1'-H), 6.81-7.42 (24H, aromat. H's), $J_{1',2'}$=3.7 Hz, $J_{2',3'}$=9.7 Hz, $J_{3',4'}$=2.7 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'}$≈6.5 Hz.- FAB MS (triethyl citrate): m/z 735 = $[M+H]^+$.- (Found: C, 73.47; H, 6.92. $C_{45}H_{50}O_9$ (734.9[21a]; 734.3[21b]) requires C, 73.55; H, 6.86).

Dibenzyl [(S)-3-(tert-butyl-diphenyl-silyloxy)-2-(tetra-O-benzyl-α-D-galactopyranosyloxy)-propyl] phosphate (9a).

A solution of N,N-diethyl dibenzyl phosphoramidite[18a,b] (69.2 mg, 0.216 mmol) and **7** (79.8 mg, 0.093 mmol) and 1H-tetrazole (21.1 mg, 0.300 mmol) in THF (3.0 ml) was stirred at 20°C for 2 h. At -30°C tert-butyl hydroperoxide (80%, 61 µl, 0.488 mmol) was added and the mixture was stirred for 15 min at this temperature and for 45 min at 20°C. After addition of CH_2Cl_2 (2 ml) the mixture was washed with saturated aq. Na_2SO_3, saturated aq. $NaHCO_3$, and water, then dried (Na_2SO_4). LC (hexanes-ethyl acetate 6:1 + 0.1% triethylamine) furnished **9a** (88.2 mg, 85 %).- $[\alpha]_D$ = +33.7 (1.5, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9H, $C(CH_3)_3$), 3.51 (1H) and 3.54 (1H; AB part of an ABX system, $6'_a$-H and $6'_b$-H), 3.72 (m, 2H, CH_2-3), 3.87 (dd, 1H, 3'-H), 3.89 (m, 1H, 4'-H), 3.92 (m, 1H, 5'-H), 3.98 (dd, 1H, 2'-H), 4.13-4.22 (2H, 1_a-H, 2-H), 4.32-4.39 (1H, 1_b-H), 4.32-4.91 (8H, benzyl. H's), 4.93 (d, 1H, 1'-H), 4.95-5.05 (4H, $OPO(OCH_2C_6H_5)_2$), 7.05-7.69 (40H, aromat. H's), $J_{1',2'}$=3.7 Hz, $J_{2',3'}$=10.0 Hz, $J_{3',4'}$=2.8 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'_a}$=7.2 Hz, $J_{5',6'_b}$=6.2 Hz, $|J_{6'_a,6'_b}|$=8.8 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = (C_q signals) 138.80, 138.63, 138.29, 138.16, 135.90, 135.80, 132.99, 132.83, 19.10; (CH signals) 135.51, 135.44, 129.81-127.23 (16 signals), 97.11 (C-1'), 78.87, 76.23, 75.85 (d, C-2, $J_{2,P}$=7.4 Hz), 74.89, 69.39; (CH_2 signals) 74.70, 73.28, 73.13, 72.96, 69.11 (d, $OPO(OCH_2C_6H_5)_2$, $J_{C,P}$=6.0 Hz), 69.06 (d, $OPO(OCH_2C_6H_5)_2$), $J_{C,P}$=5.8 Hz), 68.74, 67.41 (d, C-1, $J_{1,P}$=5.7 Hz), 61.88; (CH_3 signal) 26.75.- (Found: C, 72.30; H, 6.60. $C_{67}H_{73}O_{11}PSi$ (1113.4[21a]) requires C, 72.28; H, 6.61).

[(S)-3-(tert-Butyl-diphenyl-silyloxy)-2-(α-D-galactopyranosyl)-propyl] phosphate (9b).

A solution of **9a** (86.2 mg, 0.077 mmol) in ethanol (22.0 ml) was hydrogenated over 10% Pd/C (187.5 mg) at 20°C and atmospheric pressure for 17 h. After filtration and solvent evaporation the residue was dissolved in water and lyophilized. LC ($CHCl_3$-methanol-water 5:5:1) gave **9b** (37.6 mg, 86%).- m.p. 165-167°C.- $[\alpha]_D$ = +74.6 (c 1.5, MeOH).- ^1H NMR (400 MHz, CD_3OD): δ = 1.03 (s, 9H, $C(CH_3)_3$), 3.60-3.86 (m, 6H), 3.92 (1H)*, 3.97 (1H)*, 4.05 (1H)*, 4.14 (1H)*, 4.28 (1H)*, 5.03 (d, 1H, 1'-H), 7.33-7.46 (6H, aromat. H's), 7.63-7.73 (4H, aromat. H's), $J_{1',2'}$=3.4 Hz; *broad unresolved signals.- ^{13}C NMR (100.6 MHz, CD_3OD, DEPT): (C_q signals) 134.30, 19.95; (CH signals) 136.70, 130.91, 128.87, 99.74 (C-1'), 78.31 (d, C-2), 72.10, 71.54, 70.95, 70.42; (CH_2 signals) 66.51 (C-1 or C-3), 64.44 (C-6'), 62.63 (C-3 or C-1); (CH_3 signal) 27.32.- $C_{25}H_{37}O_{11}PSi$ (572.6[21a]; 572.2[21b]), FAB MS (DMSO-glycerol): m/z (%)= 573 ([M+H]$^+$, 7.0), 411 ([$C_{19}H_{27}O_6PSi$+H]$^+$, 4.5).

[(S)-2-(α-D-Galactopyranosyloxy)-3-hydroxy-propyl] phosphate (9c).

A solution of **9b** (9.6 mg, 0.017 mmol) and KF (10.2 mg, 0.175 mmol) in 5:1 water-methanol (1.3 ml) was stirred at 20°C for 6 d, then diluted with methanol and filtered through a short column (0.5 g SiO_2, eluent: methanol). After solvent evaporation the residue was dissolved in water and lyophilized. LC (methanol-$CHCl_3$-water 10:5:1) gave **9c** (5.4 mg, 96 %).- $[\alpha]_D$ = +107 (c 0.7, H_2O).- ^1H NMR (400 MHz, D_2O, H,H COSY): δ = 3.50-3.59 (2H, CH_2-6'), 3.53-3.67 (2H, CH_2-3), 3.63 (dd, 1H, 2'-H), 3.73 (dd, 1H, 3'-H), 3.78 (1H, 2-H), 3.81 (m, 1H, 4'-H), 3.85-3.93 (2H, CH_2-1), 4.00 (m, 1H, 5'-H), 4.96 (d, 1H, 1'-H), $J_{1',2'}$=3.9 Hz, $J_{2',3'}$=10.4 Hz, $J_{3',4'}$=3.4 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'}\approx$6.4 Hz.- ^{13}C NMR (100.6 MHz, D_2O, DEPT): δ = (CH signals) 100.46 (C-1'), 79.38 (d, C-2, $J_{2,P}$=7.7 Hz), 73.37, 71.76, 71.64, 70.90; (CH_2 signals) 67.63 (d, C-1, $J_{1,P}$=4.5 Hz), 63.56 and 62.53 (C-3, C-6').- ^{31}P NMR (101.3 MHz, D_2O): δ = 3.48.- $C_9H_{19}O_{11}P$ (334.2[21a]; 334.1[21b]), FAB MS (DMSO-glycerol): m/z 335 = [M+H]$^+$.- R_F = 0.43 (methanol-$CHCl_3$-water-acetic acid 15:10:3:0.1, 3x developed).

Dibenzyl [(R)-2-(tetra-O-benzyl-α-D-galactopyranosyloxy)-3-(4-methoxy-benzyloxy)-propyl] phosphate (10a).

A solution of N,N-diethyl dibenzyl phosphoramidite (42.2 mg, 0.133 mmol) and **8** (28.0 mg, 0.038 mmol) and 1H-tetrazole (9.9 mg, 0.141 mmol) in THF (0.5 ml) was stirred at 20°C for 1 h. At -30°C tert-butyl hydroperoxide (80%, 10 µl, 0.080 mmol) was added and the mixture was stirred for 1 h at this temperature and for 20 min at 20°C. After addition of aq. $NaHCO_3$ (5%, 2 ml) and CH_2Cl_2 (5 ml) the phases were separated and the organic layer was washed with aq. Na_2SO_3 (10%, 5 ml), aq. $NaHCO_3$ (5%, 6 ml), then dried (Na_2SO_4). MPLC (B column, hexanes-acetone 7:2 + 0.1% triethylamine) furnished **10a** (34.4 mg, 92 %).- $[\alpha]_D$ = +27.5 (c 1.5, $CHCl_3$).- ^1H NMR (400 MHz, $CDCl_3$, H,C COSY): δ = 3.44-3.54 (4H, CH_2-3, CH_2-6'), 3.72 (s, 3H, OCH_3), 3.88 (dd, 1H, 3'-H), 3.93 (m, 1H, 4'-H), 3.96 (m, 1H, 5'-H), 4.01

(dd, 1H, 2'-H), 4.08 (1H, 1_a-H), 4.09 (1H, 2-H), 4.19 (1H, 1_b-H), 4.25-4.93 (10H, benzyl. H's), 4.94-5.04 (4H, OPO($OCH_2C_6H_5$)$_2$), 5.06 (d, 1H, 1'-H), 6.76-7.35 (34H, aromat. H's), $J_{1',2'}$=3.6 Hz, $J_{2',3'}$=10.4 Hz, $J_{3',4'}$=2.9 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'}$≈6.3 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = (C_q signals) 159.10, 138.85, 138.66, 138.48, 138.03, 135.79, 135.72, 130.06; (CH signals) 129.22-127.33 (15 signals), 113.69, 97.45 (C-1'), 78.79 (C-3'), 76.32 (C-2'), 75.09 and 75.03 (C-4', C-5'), 69.45 (C-2); (CH_2 signals) 74.73, 73.37, 73.15, 72.80 (benzyl. C's), overlapping signals at 69.31, 69.28 and 69.24 (OPO($OCH_2C_6H_5$)$_2$), 69.04 and 68.98 (C-6', C-3), 66.89 (d, C-1, $J_{1,P}$=5.8 Hz); (CH_3 signal) 55.20.- (Found: C, 71.21; H, 6.35. $C_{59}H_{63}O_{12}P$ (995.1[21a]) requires C, 71.21; H, 6.38).

[(R)-2-(α-D-Galactopyranosyloxy)-3-hydroxy-propyl] phosphate (**10b**).
A solution of **10a** (39.0 mg, 0.039 mmol) in methanol (10.9 ml) was hydrogenated over 10% Pd/C (94.8 mg) at 20°C and atmospheric pressure for 30 h. After filtration and solvent evaporation the residue was dissolved in water and lyophilized. LC ($CHCl_3$-methanol-water 5:5:1) gave **10b** (13.0 mg, 100%).- $[\alpha]_D$ = +97 (c 0.7, H_2O).- ^{1}H NMR (400 MHz, D_2O, H,H COSY): δ = 3.56 (2H, AB part of an ABX system, CH_2-6'), 3.57-3.61 (2H, CH_2-3), 3.62 (dd, 1H, 2'-H), 3.71 (dd, 1H, 3'-H), 3.75-3.88 (4H, 4'-H, CH_2-1, 2-H), 3.90 (m, 1H, 5'-H), 5.01 (d, 1H, 1'-H), $J_{1',2'}$=3.9 Hz, $J_{2',3'}$=10.4 Hz, $J_{3',4'}$=3.4 Hz, $J_{4',5'}$<1 Hz, $J_{5',6'}$≈6.4 Hz, $|J_{6'a,6'b}|$ very small.- ^{13}C NMR (100.6 MHz, D_2O, DEPT): δ = (CH signals) 100.54 (C-1'), 79.46 (d, C-2, $J_{2,P}$=7.5 Hz), 73.51 (C-5'), 71.72 and 71.67 (C-3', C-4'), 70.85 (C-2'); (CH_2 signals) 66.20 (d, C-1, $J_{1,P}$=5.5 Hz), 63.70 and 63.59 (C-3, C-6').- ^{31}P NMR (101.3 MHz, D_2O): δ = 3.67.- $C_9H_{19}O_{11}P$ (334.2[21a]; 334.1[21b]), FAB MS (DMSO-glycerol): m/z 357 = $[M+Na]^+$, 335 = $[M+H]^+$.- R_F = 0.39 (methanol-$CHCl_3$-water-acetic acid 15:10:3:0.1, 3x developed).

We wish to thank Dr.U.Peters for performing the initial experiments of this project, Dr.D.Müller, Dr.W.Dietrich, and their colleagues, and Dr.T.Mischo for the MS and NMR spectra. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

1 Reviews: a) Mulzer,J. *Nachr.Chem.Tech.Lab.***1984**,*32*,146-149; b) Jurczak,J.;Pikul,S.;Bauer,T. *Tetrahedron* **1986**,*42*,447-488; c) Takano,S. *Pure Appl.Chem.***1987**,*59*,353-362; d) Golding,B.T. *Chem.Ind.***1988**,617-621; for recent work, see Webb II,R.R.; Wos,J.A.;Bronson,J.J.;Martin,J.C. *Tetrahedron Lett.***1988**,*29*,5475-5478; Veeneman,G.H.;Brugghe,H.F.;Hoogerhout,P.;van der Marel,G.A.;van Boom,J.H. *Recl.Trav.Chim.Pays-Bas* **1988**,*107*,610-612; Bhatia,S.K.; Hajdu,J. *J.Org.Chem.***1988**,*53*,5034-5039; Elie,C.J.J.;Dreef,C.E.; Verduyn,R.;van der Marel,G.A.;van Boom,J.H. *Tetrahedron* **1989**,*45*,3477-3486; Burgos,C.E.;Ayer,D.E.;Johnson,R.A. *J.Org.Chem.***1987**,*52*,4973-4977; Takano,S.;Shimazaki,Y.;Sekiguchi,Y.;Ogasawara,K. *Synthesis* **1989**,539-541; Takano,S.;Sekiguchi,Y.;Ogasawara,K. *Heterocycles* **1989**, *29*,445-448; Guivisdalsky,P.N.;Bittman,R. *J.Org.Chem.***1989**,*54*,4637-4642; Guivisdalsky,P.N.;Bittman,R. *J.Org.Chem.***1989**,*54*,4643-4648; Takano,S.;Iwabuchi,Y.;Ogasawara,K. *J.Chem.Soc.,Chem.Commun.***1989**,1371-

1372; Kang,S.H.;Kim,W.J. *Tetrahedron Lett.***1989**,*30*,5915-5918; Nagaoka,H.;Iwashima,M.;Abe,H.;Yamada,Y. *Tetrahedron Lett.***1989**,*30*,5911-5914, and references therein.

[2] Review: Altenbach,H.J. *Nachr.Chem.Tech.Lab.***1988**,*36*,33-38; for recent work, see Suemune,H.;Mizuhara,Y.;Akita,H.;Sakai,K. *Chem.Pharm.Bull.* **1986**,*34*,3440-3444; Terao,Y.;Murata,M.;Achiwa,K.;Nishio,T.;Akamtsu,M.; Kamimura,M. *Tetrahedron Lett.***1988**,*29*,5173-5176; Jäger,V.;Wehner,V. *Angew.Chem.***1989**,*101*,512-513, *Angew.Chem.Int.Ed.Engl.***1989**,*28*,469; Byun,H.-S.;Bittman,R. *Tetrahedron Lett.***1989**,*30*,2751-2754; Leftheris,K.;Goodman,M. *Synthesis* **1989**,564-565; de Witt,P.;Misiti,D.; Zappia,G. *Tetrahedron Lett.***1989**,*30*,5505-5506, and references therein.

[3] For a discussion of this point, see ref.[4,10b]

[4] Peters,U.;Bankova,W.;Welzel,P. *Tetrahedron* **1987**,*43*,3803-3816.

[5] Review: Jennings,H.J. *Adv.Carbohydr.Chem.Biochem.***1983**,*41*,155-208.

[6] Michon,F.;Roy,R.;Jennings,H.J. *Can.J.Chem.***1984**,*62*,1519-1524.

[7] van der Kaaden,A.;van Doorn-van Wakeren,J.I.M.;Kamerling,J.P.; Vliegenthart,J.F.G.;Tiesjema,R.H. *Eur.J.Biochem.***1984**,*141*,513-519.

[8] For the more complex but structurally related capsular polymer of *Actinobacillus pleuropneumoniae* serotype 6, see Altman,E.;Brisson, J.-R.;Perry,M.B. *Carbohydr.Res.***1988**,*183*,321-331.

[9] For preliminary results, see ref.[13a,13b]

[10] a) Dehmlow,E.V.;Dehmlow,S.S. *Phase Transfer Catalysis*,Verlag Chemie, Weinheim,2nd Ed.,**1983**,
b) Schubert,T.;Kunisch,F.;Welzel,P. *Tetrahedron* **1983**,*39*,2211-2217.

[11] Chaudhary,S.K.;Hernandez,O. *Tetrahedron Lett.***1979**,99-102.

[12] a) Ogawa,T.;Nakabayashi,S. *Carbohydr.Res.***1981**,*93*,C1-C5,
b) Kloosterman,M.;van Boom,J.H.;Chatelard,P.;Boullanger,P.; Descotes,G. *Tetrahedron Lett.***1985**,*26*,5045-5048.

[13] Using the bromide and the fluoride, respectively, instead of chloride **5b**. For details, see
a) Peters,U. Dissertation, Ruhr-Universität Bochum (1988),
b) Peters,U. Diplomarbeit, Ruhr-Universität Bochum (1985),
c) Metten,K.-H. Dissertation, Ruhr-Universität Bochum, in preparation,
d) Metten,K.-H. Diplomarbeit, Ruhr-Universität Bochum (1988).

[14] Iversen,T.;Bundle,D.R. *Carbohydr.Res.***1982**,*103*,29-40.

[15] a) Lemieux,R.U.;Hendriks,K.B.;Stick,R.V.;James,K. *J.Am.Chem.Soc.***1975**, *97*,4056-4062,
b) Paulsen,H. *Angew.Chem.***1982**,*94*,184-201, *Angew.Chem.Int.Ed.Engl.* **1982**,*21*,155,
c) Paulsen,H. *Chem.Soc.Rev.***1984**,*13*,15-45,
d) Paulsen,H.;Kolár,C. *Chem.Ber.***1979**,*112*,3190-3202,
e) Paulsen,H.;Heitmann,A.C. *Liebigs Ann.Chem.***1989**,655-663.

[16] Removal of all protecting groups from **6** would lead to floridoside; see, Meng,J.;Rosell,K.-G.;Srivastava,L.M. *Carbohydr.Res.***1987**,*161*, 171-180, and references therein.

[17] a) Classon,B.;Garegg,P.J.;Samuelsson,B. *Acta Chem.Scand.,Ser.B* **1984**,*38*,419-422,
b) Masaki,Y.;Iwata,I.;Mukai,I.;Oda,H.;Nagashima,H. *Chem.Lett.***1989**,659-662.

[18] a) Perich,J.W.;Johns,R.B. *Synthesis* **1988**,142-144,
b) Perich,J.W.;Johns,R.B. *Tetrahedron Lett.***1987**,*28*,101-102,
c) de Bont,H.B.A.;Veeneman,G.H.;van Boom,J.H.;Liskamp,R.M.J. *Recl.Trav.Chim.Pays-Bas* **1987**,*106*,641-642,
d) Dreef,C.E.;Elie,C.J.J.;Hoogerhout,P.;van der Marel,G.A.;van Boom,J.H. *Tetrahedron Lett.***1988**,*29*,6513-6516,
e) Bannwarth,W.;Trzeciak,A. *Helv.Chim.Acta* **1987**,*70*,175-186, and references therein.

[19] Review: Lalonde,M.;Chan,T.H. *Synthesis* **1985**,817-845.

[20] Hanessian,S.;Lavallee,P. *Can.J.Chem.***1975**,*53*,2975-2977.

[21] Calculated a) using the International Atomic Masses, b) for ^{12}C, ^{1}H, ^{16}O, ^{28}Si, ^{31}P (mono-isotopic mass).