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Synthesis of fragments of the capsular polysaccharide of *Haemophilus influenzae* type b
Part I. Preparation of suitably protected 1-*O*-β-D-ribofuranosyl-D-ribitol building blocks

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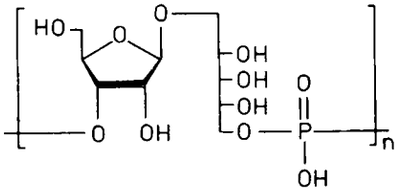
Abstract. The synthesis of the protected ribosylribitol derivatives **15** and **17**, which are building blocks for the preparation of fragments of the *H. influenzae* type b polysaccharide, is presented. Starting from D-ribonolactone (**1**), 5-*O*-allyl-2,3,4-tri-*O*-benzyl-D-ribitol (**8**) was prepared in seven steps (Scheme 1). Coupling of **8** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) in the presence of trimethylsilyl trifluoromethanesulfonate gave the ribosylribitol derivative **10** (Scheme 2), which was debenzoylated to afford compound **11**. The C-3′- and C-5′-hydroxyl functions of the ribose moiety of **11** were protected with the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group and the C-2′ position with the benzyloxymethyl group. Compound **13** thus obtained was converted into its 5-*O*-*trans*-1-propenyl isomer **14**.
Cleavage of the propenyl group from **14** gave compound **15**, which can be phosphorylated at O-5 of the ribitol. On the other hand, removal of the 3′,5′-protection from **14** and subsequent blocking of the primary hydroxyl function yielded ribosylribitol derivative **17** having a 3′-hydroxyl function available for phosphorylation.

Introduction

Six types (a–f) of the bacterium *Haemophilus influenzae* produce type-specific antigens in the form of extracellular capsular polysaccharides[1,2]. The capsules of types a, b, c and f are polymers in which oligosaccharides are joined through phosphodiester bonds. In the case of *Haemophilus influenzae* type b (Hib**), 1-*O*-β-D-ribitol units are linked from O-3′ of ribose to O-5 of ribitol (Fig.)[3,4].
Hib is known as a major cause of endemic meningitis and other invasive infectious diseases in children. Since it is generally agreed that a vaccine against these diseases can be prepared using the capsular polysaccharide antigen[5], the synthesis of fragments of this antigen is of great importance. The synthesis of a single repeating unit of the Hib polysaccharide, that is of 1-*O*-β-D-ribofuranosyl-D-ribitol 5-phosphate and the spacer containing derivative 4-aminophenyl β-D-ribofuranoside 3-(D-ribit-5-yl phosphate), has been described by *Garegg* et al.[6,7].



⟶ 3)-β-D-Rib f-(1⟶1)-D-ribitol-5-(PO$_4$⟶

Fig. 1. Structure of the repeating unit of the capsular polysaccharide of Haemophilus influenzae *type b.*

Based on our experience with the synthesis of cell-wall teichoic acids, for example of *Bacillus subtilis*[8], *Staphylococcus aureus*[9], *Staphylococcus lactis*[10] and *Bacillus licheniformis*[11], we also undertook the synthesis of larger fragments of the Hib capsular polysaccharide[12].
In this paper we wish to present full experimental details of the preparation of two ribosylribitol derivatives (**15** and **17**, Scheme 2), which can be used as building blocks for the synthesis of Hib oligosaccharides.

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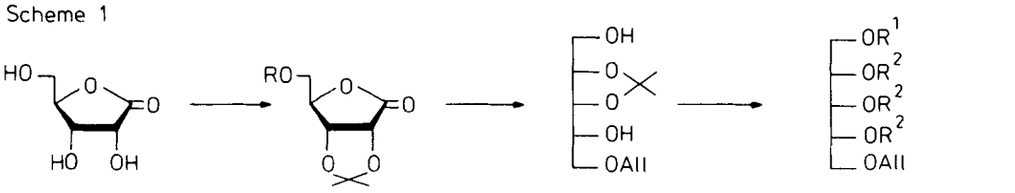
** Abbreviations: Ac, acetyl; All, allyl; BOM, benzyloxymethyl; Bz, benzoyl; Bzl, benzyl; Hib, *Haemophilus influenzae* type b; Prop, *trans*-1-propenyl; TIPS, 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl; Trt, triphenylmethyl (trityl).

Scheme 1



1 2 R=H 3 R=All-O-CO- 4 R=All 5 6 R^1=Trt, R^2=H 7 R^1=Trt, R^2=Bzl 8 R^1=H, R^2=Bzl

All = allyl ; Bzl = benzyl ; Trt = triphenylmethyl (trityl)

Scheme 1

Results and discussion

A general strategy for preparing fragments of the Hib polysaccharide requires the availability of a protected 1-*O*-β-D--ribosyl-D-ribitol derivative, which can be selectively deprotected and subsequently phosphorylated at either O-3′ of the ribose or at O-5 of the ribitol moiety. For the time being, however, we adopted a sequential strategy[12] using two building blocks, a "terminal unit" with a free 5-hydroxyl group (*e.g.* **15**, Scheme 2) and an "elongation unit" with a free 3′-OH and the *trans*-1-propenyl group temporarily blocking the O-5 position (*e.g.* **17**). Both compounds have been prepared from the intermediate **14**.

The first part of the synthesis of 1-*O*-β-D-ribofuranosyl--D-ribitol dimers concerns the preparation of suitably protected D-ribitol derivatives. Obviously, such compounds are most conveniently prepared from a chiral precursor such as D-ribose or D-ribonolactone[13]. We selected the latter compound (**1**, Scheme 1) to prepare 5-*O*-allyl-2,3,4-tri-*O*--benzyl-1-*O*-(triphenylmethyl)-D-ribitol (**7**) and 5-*O*-allyl--2,3,4-tri-*O*-benzyl-D-ribitol (**8**). Ether-type protection was chosen to avoid problems involving intramolecular protecting group migration.

D-Ribonolactone (**1**) was converted into the 2,3-*O*-isopropylidene derivative **2**[14] (95%). Direct allylation by reaction of **2** with allyl bromide in *N,N*-dimethylformamide, in the presence of silver oxide, in analogy with the preparation of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone[15], gave poor yields of **4** (30–40%). This is possibly caused by the instability of the lactone ring under basic conditions or by the rather high acidity of the proton at C-2 in compound **2**. A two-step introduction of the allyl group via intermediate **3**, containing 5-*O*-(allyloxycarbonyl), proved to be advantageous. Thus, **2** was treated with two equivalents of allyl chloroformate in a mixture of tetrahydrofuran and pyridine at 0°C[16,17] to give, after work-up and crystallization, compound **3** (85%). This compound was also conveniently prepared from **1** without isolation of intermediate **2**, albeit in lower over-all yield (60%). Compound **4** was then obtained in a quantitative yield by decarboxylation of **3** using a catalytic amount of *tetrakis*(triphenylphosphine)-palladium[16,17] in boiling dioxane.

Next, the lactone ring of **4** was opened reductively. Although various methods for the reduction of aldonolactones are known[18,19], we preferred a procedure which was originally recommended for the reduction of amino acid or peptide alkyl esters[20]. Thus, dry methanol was slowly added to a mixture of **4** and excess sodium borohydride in dry tetrahydrofuran at 55°C. After the usual work-up and silicagel chromatography, the ribitol derivative **5** was obtained in 80% yield. The isopropylidene function was then removed from **5** by hydrolysis with aqueous acetic acid at 50°C to give 5-*O*-allyl-D-ribitol, which was not isolated but immediately treated with a slight excess of triphenylmethyl chloride in pyridine. Purification by short-column chromatography gave the 1,5-protected ribitol **6** in 75% yield.

In the following step, the secondary hydroxyl functions of **6** were benzylated using a standard procedure (86%). Finally, the 1-*O*-trityl group of **7** was removed with aqueous acetic acid at 80°C to give 5-*O*-allyl-2,3,4-tri-*O*-benzyl-D-ribitol **8** (90%). Compounds **7** and **8** were purified by chromatography over silica gel. However, as shown by thin-layer chromatography, **8** was still contaminated with a small amount of triphenylmethanol.

The investigation was now focused on the introduction of a β-linkage between a ribosyl donor and the ribitol derivatives **7** and **8**.

Firstly, a coupling of 1,2-*O*-(cyanoethylidene)-3,5-di-*O*--acetyl-α-D-ribofuranose [which was prepared from tetra--*O*-acetyl-β-D-ribofuranose and cyanotrimethylsilane, catalyzed by tin(II) chloride[21]] with **7** in the presence of triphenylmethyl perchlorate was attempted. However, in this case, the cyanoethylidene coupling method, which has proven its value in carbohydrate chemistry[22], was not successful.

Secondly, glycosylation of **8** with 2,3,5-tri-*O*-benzoyl-α/β--D-ribofuranosyl bromide[23,24] was investigated. This labile bromide was prepared by treatment of 2,3,5-tri-*O*-benzoyl--1-*O*-(4-nitrobenzoyl)-β-D-ribofuranose with hydrogen bromide in dichloromethane[23]. Unfortunately, its reaction with **8** using either silver carbonate or silver trifluoromethanesulfonate as a catalyst[25] afforded **10** in very poor yield (<20%). The possible use of less reactive ribosyl chlorides[23,26] as glycosyl donors was not investigated.

Finally, we concentrated on the glycosylation of the ribitol **8** with peracylated β-D-ribofuranoses in the presence of trimethylsilyl trifluoromethanesulfonate[27]. Reaction of tetra--*O*-acetyl-β-D-riboranose and **8** resulted in predominant formation of 1-*O*-acetyl-5-*O*-allyl-2,3,4-tri-*O*-benzyl-D-ribitol, most likely via an ortho ester intermediate[28,29]. This type of undesirable acylation of **8** could be circumvented by using 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose (**9**, Scheme 2) as the glycon. Thus, coupling of commercially available **9** with ribitol **8** in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate (0.05–0.15 eq.) and molecular sieves 4 Å at room temperature gave the fully protected ribosylribitol **10**, which was obtained in 85% yield after short-column chromatography. The chemical shift observed for C′-1 in the ^{13}C NMR spectrum (105.1 ppm) is in accordance with the β-glucosidic structure.

In principle, a ribosylribitol derivative with a free 5-OH on the ribitol (a "terminal unit") is easily accessible from **10**.

The allyl protecting group may either be selectively removed using palladium chloride[30] or it may be isomerized into a *trans*-1-propenyl group, which can be removed under very mild conditions (see below, preparation of **14** and **15**). However, transformation of **10** into a compound with only a free 3'-OH on the ribose moiety (or – more general – with orthogonal protection of the 3'- and 5-OH) requires several steps. Furthermore, it must be noted that 2'-*O*-acyl type protection of the ribose, which was very convenient for formation of the β-glycosidic linkage in **10** (due to neighbouring-group participation), has now become highly undesirable, since acyl migration in a *cis*-diol configuration may easily occur[31]. Therefore, ether-type protecting groups were again selected.

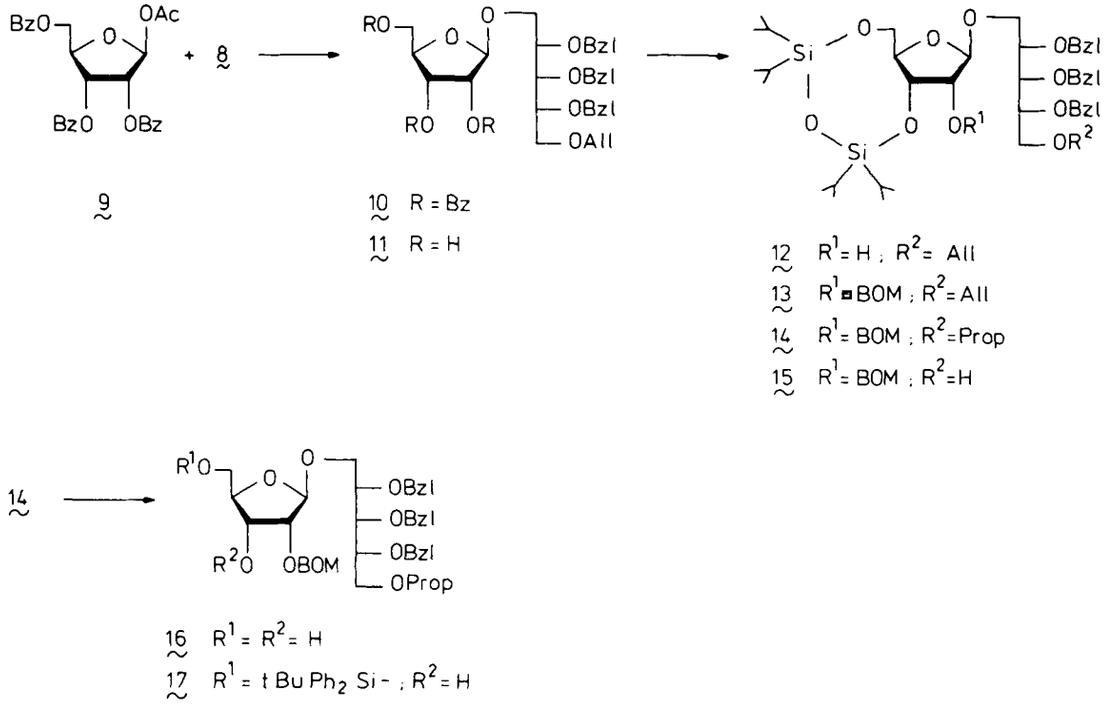
The benzoyl groups were removed from **10** using sodium methoxide in a mixture of methanol and dioxane to give compound **11** (88%). The 3'- and 5'-hydroxyl functions of **11** were simultaneously protected with the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group, which is frequently used for 3',5'-protection of ribonucleosides[32-34] and also for diol protection in carbohydrates[35-40]. Compound **12** was obtained in 67% yield by reaction of **11** with a slight excess of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine.

Protection of the remaining 2'-OH function of **12** was rather difficult. Unexpectedly, the introduction of a tetrahydropyranyl ether with dihydropyran under acidic conditions[41] (anhydrous 4-toluenesulfonic acid) failed completely. Attempted protection of the 2'-OH with a benzyl or 4-methoxybenzyl ether by reaction with (4-methoxy) benzyl trifluoromethanesulfonate[42] also failed. Fortunately, the introduction of a 2'-*O*-benzyloxymethyl (BOM) group was more successful. For the protection of sterically hindered alcohols, the use of benzyloxymethyl bromide in the presence of *N,N,N',N'*-tetramethylurea was recommended[43]. More reactive alcohols can be alkylated with benzyloxymethyl chloride (BOM-Cl). The reaction of **12** with BOM-Cl was tested in several solvents (dichloromethane, acetonitrile, *N,N*-dimethylformamide) using *N,N,N',N'*-tetramethylurea or diisopropylethylamine as a base. Optimal conditions, with respect to the yield and suppression of side-reactions, seemed to be the use of excess BOM-Cl (3 eq.) and diisopropylethylamine (4 eq.) in acetonitrile at 50°C, which gave **13** in 85% yield. All BOM-containing compounds show a characteristic ^{13}C NMR resonance at 94–95 ppm for the acetal-type methylene group.

In the next step, compound **13** was converted into its 5-*O*-*trans*-1-propenyl isomer **14** by treatment with the homogeneous catalyst (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium hexafluorophosphate[44,45] in tetrahydrofuran. Since the iridium catalyst is easily poisoned, the starting compound **13** must be very pure. A quantitative allyl-into-propenyl isomerization was clearly indicated by NMR spectroscopy, as well as by thin-layer chromatography.

Compounds **15** and **17** were now prepared from intermediate **14**. Direct cleavage of the propenyl group with mercury chloride/mercury oxide in acetone/water[46] gave the protected ribosylribitol **15** in 84% yield. On the other hand, the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group was removed from **14** with tetra-*n*-butylammonium fluoride[47] in dioxane. The primary hydroxyl function of **16** was selectively protected by reaction with *tert*-butyldiphenylsilyl chloride[48] in pyridine to give **17** (68% from **14**). The ribosylribitol derivatives **11–17** were purified by chromatography over silica gel, except for **14** which was used without further purification.

The structural integrity of **15** and **17** was firmly established by homo[49]- and hetero-nuclear[50] correlated NMR spectroscopy. The compounds were successfully applied as building blocks for the synthesis of fragments of the Hib capsular polysaccharide, comprising two or three repeating units, by using a phosphotriester approach[12]. Full experimental details of this work will be presented in forthcoming publication.



Scheme 2 Ac = acetyl ; All = allyl ; BOM = benzyloxymethyl ; Bz = benzoyl ; Bzl = benzyl ; Prop = propen-1-yl.

Experimental

Materials and methods

Dry acetonitrile, 1,2-dichloroethane, dichloromethane, *N,N*-dimethylformamide, dioxane, pyridine, tetrahydrofuran and toluene were obtained by heating under reflux with calcium hydride (5 g/l) and then distilled. *N,N*-Diisopropylethylamine and triethylamine were distilled from sodium hydroxide. Dry methanol was prepared using magnesium, activated by iodine and distilled. 1,2-Dichloroethane was redistilled from lithium aluminium hydride. The solvents and reagents were stored over molecular sieves 4 Å (methanol 3 Å). Sodium hydride (85% suspension in oil) was washed with dry diethyl ether and pentane and dried under a stream of nitrogen.
1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) was purchased from Sigma Chemical Company, St. Louis, USA. Benzyloxymethyl chloride was prepared from benzyl alcohol and paraformaldehyde according to a general procedure for the preparation of chloromethyl ethers[51]. A standard solution of tetra-*n*-butylammonium fluoride in dioxane was prepared according to ref. 52.
All evaporations were carried out at low temperature (30–35°C) under diminished pressure. Organic layers, obtained after extractions, were always dried with magnesium sulfate. Thin-layer chromatograms (TLC) were run on silica gel F 1500, L 254 (Schleicher & Schull, G.F.R.). Compounds were detected under UV light and by spraying with 20% sulfuric acid in methanol or a solution of potassium permanganate (1% w/v) in aqueous sodium carbonate (2% w/v), Column chromatography was performed on Kieselgel 60, 230–400 mesh (Merck).
Optical rotations were measured using a Perkin-Elmer 141 polarimeter.
A Jeol JNM-FX-200 spectrometer was used for recording ^1H and ^{13}C (APT ^1H decoupled) NMR spectra at 200 and 50.1 MHz, respectively. A Bruker WM 300 spectrometer was used for recording 300-MHz ^1H NMR spectra, 75.5-MHz ^{13}C (^1H decoupled) NMR spectra and homo[47]- and hetero-nuclear (^1H, ^{13}C)[48] chemical-shift-correlated 2D spectra (compounds **15** and **17**). The compounds were dissolved in $CDCl_3$ and ^1H and ^{13}C chemical shifts are given in ppm relative to internal tetramethylsilane (δ 0 ppm).

5-O-(Allyloxycarbonyl)-2,3-O-isopropylidene-D-ribonolactone (**3**)

a. A solution of 2,3-*O*-isopropylidene-D-ribonolactone (**2**)[14] (4.0 g, 21.2 mmol) and dry pyridine (3.5 ml, 43 mmol) in dry acetonitrile (10 ml) was cooled to 0°C and allyl chloroformate (4.5 ml, 42.4 mmol) in dry acetonitrile (10 ml) was added dropwise over 45 min. Stirring at 0°C was continued for 1 h. Excess chloroformate was destroyed by addition of ice. The reaction mixture was diluted with diethyl ether (100 ml) and washed with water (3 × 50 ml). The organic layer was dried and concentrated. The residue was dissolved in dichloromethane (10 ml) and filtered over a small column of Kieselgel 60 (6 g). The column was washed with 40 ml of dichloromethane and the combined filtrate and washings were concentrated to give a syrup which was crystallized from diethyl ether/diisopropyl ether. Yield 4.9 g (85%). M.p. 55–56°C. Anal. $C_{12}H_{16}O_7$ (272.25) calcd.: C 52.94, H 5.92; found: C 53.38, H 6.08. TLC (hexane/acetone 3/1, v/v): R_f 0.43. $[\alpha]_D$ −50.7° (*c* 1.0, $CHCl_3$). 200-MHz ^1H NMR: δ 4.30 (dd, 1H, *J* 12.1 and 2.2 Hz); 4.48 (dd, 1H, *J* 12.1 and 2.6 Hz); 4.60–4.65 (m, 2H); 4.72–4.86 (m, 3H); 5.27–5.42 (m, CH_2=); 5.82–5.97 (m, =CH−). ^{13}C NMR: 25.6, 26.8 (2 × CH_3); 66.8, 69.1 (2 × CH_2); 75.2, 77.2, 79.5 (3 × CH); 113.6 (Cq isopropylidene); 119.5 (CH_2=); 131.2 (=CH−); 154.1 (−O−CO−O−); 173.7 (C1).

b. Compound **3** was also prepared on a larger scale from D-ribonolactone (**1**), without isolation of **2**.
Thus, **1** (25 g) was treated with acetone (1 l) and concentrated hydrochloric acid (10 ml) for 24 h at room temperature. The reaction mixture was neutralized with pyridine and concentrated. The residue was coevaporated with dry acetonitrile and further processed (with proportional scaling-up) as described above. A single crystallization of the product from diethyl ether/diisopropyl ether 1/1 (250 ml) gave 28 g of **3** (60%, based on **1**).

5-O-Allyl-2,3-O-isopropylidene-D-ribonolactone (**4**)

a. Allylation of 2,3-O-isopropylidene-D-ribonolactone (**2**). This reaction was carried out in a similar way as described for the preparation of 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone[15]. Compound **2** (25 g, 0.13 mol) was dissolved in dry *N,N*-dimethylformamide (50 ml), and silver oxide (25 g, 0.11 mol) and allyl bromide (22 ml, 0.25 mol) were added. The mixture was shaken in the dark for 48 h. Solid material was removed by filtration and washed with *N,N*-dimethylformamide. The combined filtrate and washings were concentrated. The residue was taken up in dichloromethane (250 ml), washed with water (3 × 100 ml) and dried. Evaporation of the solvent gave an oil which was purified in two portions by chromatography on 12.5 × 6-cm columns. Elution was effected with dichloromethane. From the appropriate fractions compound **4** was obtained as an oil in variable yields (30–40%). TLC (hexane/acetone 3/1, v/v): R_f 0.52. $[\alpha]_D$ −61.3° (*c* 2.1, $CHCl_3$). 200-MHz ^1H NMR: δ 1.38 (s, CH_3); 1.47 (s, CH_3); 3.68 (d, 2H, *J* 2 Hz); 3.98 (dd, 2H, *J* 5.5 and 1 Hz); 4.65 (t, 1H, *J* 2 Hz); 4.72–4.80 (dd, 2H, *J* 11 and 5.5 Hz); 5.18–5.31 (m, CH_2=); 5.72–5.92 (m, =CH−). ^{13}C NMR: δ 25.2, 26.5 (2 × CH_3); 68.6 (C5); 72.2 (−CH_2−, allyl); 75.3, 78.1, 80.7 (3 × CH); 112.6 (Cq, isopropylidene); 117.4 (CH_2=); 133.4 (=CH−); 174.1 (C1).

b. Decarboxylation of 5-O-(allyloxycarbonyl)-2,3-O-isopropylidene-D-ribonolactone (**3**). A degassed solution of compound **3** (5.0 g, 18.4 mmol) in dioxane (20 ml, freshly distilled from $LiAlH_4$) was placed under a helium atmosphere. Tetrakis(triphenylphosphine)palladium (15 mg) was added and the solution was refluxed for 15 min. TLC (hexane/acetone 3/1, v/v) showed complete conversion of **3** (R_f 0.43) into **4** (R_f 0.52). The reaction mixture was concentrated and compound **4**, thus obtained, was used in the next step without further purification.

5-O-Allyl-2,3-O-isopropylidene-D-ribitol (**5**)

A stirred mixture of compound **4** (8.6 g, 38 mmol), sodium borohydride (3.5 g, 93 mmol) and dry tetrahydrofuran (150 ml) was heated to 55°C. Dry methanol (30 ml) was added dropwise over 45 min and stirring at 55°C was continued for 1 h[20]. After a short period of cooling, the reaction mixture was concentrated. The residue was coevaporated with dry methanol (3 × 50 ml), taken up in dichloromethane (100 ml) and washed with a 90% saturated solution of ammonium chloride in water (100 ml). The aqueous layer was extracted with dichloromethane (2 × 100 ml). The combined organic layers were dried and concentrated. The residue was purified by chromatography on a 9 × 6-cm column. Elution was effected with dichloromethane/methanol, 100/0–95/5, v/v. From the appropriate fractions **5** was obtained as a syrup. Yield 7.0 g (80%). TLC (CH_2Cl_2/MeOH, 95/5, v/v): R_f 0.41. $[\alpha]_D$ +35.2° (*c* 2, $CHCl_3$). 200-MHz ^1H NMR: δ 1.34 (s, CH_3); 1.40 (s, CH_3); 3.4 (br, 2H, OH); 3.52 (dd, 1H, *J* 10 and 6.5 Hz); 3.72 (dd, 1H, *J* 10 and 2.5 Hz); 3.7–4.13 (m, 6H); 4.31–4.40 (m, 1H); 5.17–5.35 (m, CH_2=); 5.82–6.02 (m, =CH−). ^{13}C NMR: δ 25.3 (CH_3); 27.9 (CH_3); 60.6 (CH_2); 68.6 (CH); 71.8 (CH_2); 72.4 (CH_2); 76.7 (CH); 77.4 (CH); 108.5 (Cq, isopropylidene); 117.4 (CH_2=); 134.4 (=CH−).

5-O-Allyl-1-O-trityl-D-ribitol (**6**)

Compound **5** (6.2 g, 27 mmol) was dissolved in acetic acid (100 ml) and water (40 ml) was added. The solution was stirred at 50°C for 4 h. TLC analysis (CH_2Cl_2/MeOH, 95/5, v/v) showed complete removal of the isopropylidene group (**5**, R_f 0.41; product R_f 0). The reaction mixture was concentrated. The residue was coevaporated with dry toluene (3 × 25 ml) and dry pyridine (3 × 25 ml) and redissolved in pyridine (40 ml). Trityl chloride (7.5 g, 27 mmol) was added and the olution was stirred overnight at room temperature. After addition of methanol (5 ml), the reaction mixture was concentrated. The residue was coevaporated with toluene (3 × 25 ml), taken up in dichloromethane (150 ml) and washed with 1 M sodium bicarbonate solution (150 ml) and water (150 ml). The organic layer was dried and concentrated. The product was purified by chromatography on a 10.5 × 6 cm column. Elution was effected with dichloromethane/methanol 100/0–95/5, v/v. From the appropriate fractions **6** was obtained as a syrup. Yield 8.7 g (75%). TLC CH_2Cl_2/MeOH, 95/5, v/v): R_f 0.51. $[\alpha]_D$ 0° (*c* 2.0, $CHCl_3$). 200-MHz ^1H NMR: δ 3.2–3.9 (m, 10H); 3.96–4.01 (m, 2H);

5.13–5.30 (m, CH_2=); 5.76–5.96 (m, =CH–); 7.0–7.5 (15 arom. H). ^{13}C NMR: δ 65.2 (CH_2); 71.1 (CH); 71.3 (CH_2); 71.7 (CH); 72.1 (CH_2); 73.1 (CH); 87.0 (Cq, trityl); 117.2 (CH_2=); 134.1 (=CH–); 123–149 (atom. C).

5-O-Allyl-2,3,4-tri-O-benzyl-1-O-trityl-D-ribitol (**7**)

Compound **6** (7.3 g, 17 mmol) was dissolved in dry *N,N*-dimethylformamide (40 ml) and sodium hydride (2.0 g, 83 mmol) was added in small portions. The stirred reaction mixture was cooled to 0°C and benzyl bromide (6.2 ml, 52 mmol) in dry *N,N*-dimethylformamide (10 ml) was added dropwise over approximately 30 min. Stirring was continued for 30 min at 0°C and, thereafter, overnight at room temperature. Dry methanol (10 ml) was added slowly in order to destroy the excess sodium hydride. The reaction mixture was then concentrated. The residue was taken up in diethyl ether (150 ml) and washed with water (3 × 50 ml). The organic layer was dried and concentrated. The oil thus obtained was purified by chromatography on a 9 × 6-cm column. Elution: hexane/dichloromethane 2/1 (400 ml) and 1/1 (400 ml), v/v, followed by pure dichloromethane. After evaporation of the appropriate fractions, pure **7** (10.2 g, 86%) was obtained as a syrup. TLC (CH_2Cl_2/MeOH, 95/5, v/v): R_f 0.74. $[\alpha]_D$ +18.1° (*c* 2.1, $CHCl_3$). 200-MHz ^{1}H NMR: δ 3.42 (m, 2H); 3.65 (m, 2H); 3.91 (m, 5H); 4.49–4.82 (m, 6H); 5.08–5.27 (m, CH_2=); 5.79–5.93 (m, =CH–); 7.0–7.5 (30 arom. H). ^{13}C NMR: δ 63.9, 70.3, 72.0, 72.4, 72.5, 73.5 (6 × CH_2); 78.6, 78.7, 78.9 (3 × CH); 86.6 (Cq, trityl); 116.5 (CH_2=); 34.8 (=CH–); 126–144 (arom. C).

5-O-Allyl-2,3,4-tri-O-benzyl-D-ribitol (**8**)

Compound **7** (8.5 g, 12 mmol) was dissolved in acetic acid (135 ml) and water (15 ml) and heated at 80°C for 90 min. TLC analysis (CH_2Cl_2) indicated complete removal of the trityl group (**7**, R_f 0.46; trityl alcohol, R_f 0.39; product, R_f 0). The solution was concentrated and the residue was taken up in diethyl ether and washed with water (50 ml) and 1-M sodium bicarbonate solution (2 × 50 ml). The organic layer was dried and concentrated. The residue was triturated with dichloromethane/hexane, 1/1, v/v (10 ml), thus partly precipitating the trityl alcohol, which was removed by filtration. The filtrate was applied to a 9 × 6-cm column and eluted with chloroform/hexane, 1/1, v/v (400 ml), dichloromethane (400 ml) and, finally, with dichloromethane/methanol, 98/2, v/v. Compound **8** (5.0 g, 90%), contaminated with a small amount of triphenylmethanol, was obtained as an oil. TLC (CH_2Cl_2/MeOH, 99/1, v/v): R_f 0.42 + trace R_f 0.63 (Trt-OH). $[\alpha]_D$ −15.0° (*c* 2.0, $CHCl_3$). 200-MHz ^{1}H NMR: δ 2.3 (br, OH); 3.60–3.97 (m, 9H); 4.58–4.76 (m, 6H); 5.12–5.31 (m, CH_2=); 5.78–5.99 (m, =CH–); 7.17–7.36 (15 arom. H). ^{13}C NMR: δ 61.1, 69.5, 71.7, 72.0, 72.2, 73.8 (6 × CH_2); 78.0, 78.6, 78.8 (3 × CH); 116.7 (CH_2=); 134.6 (=CH–); 127–138 (arom. C). Analysis of a small sample, after a second purification by column chromatography: $C_{29}H_{34}O_5$ (462.56) calcd.: C 75.30, H 7.41; found: C 75.31, H 7.34%.

5-O-Allyl-1-O-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-2,3,4-tri-O-benzyl-D-ribitol (**10**)

A mixture of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**, 3.4 g, 6.7 mmol) and compound **8** (3.1 g, 6.7 mmol) was dried by coevaporation with dioxane (3 × 50 ml) and, thereafter, dissolved in dry 1,2-dichloroethane (50 ml). Molecular sieves 4 Å (10 g of activated pellets) were added and the mixture was stirred at room temperature for 90 min under a stream of dry nitrogen. A syringe was used for adding trimethylsilyl trifluoromethanesulfonate at t = 0, 1 h and 2 h (each time 30 μl)[27]. Samples were drawn from the reaction mixture at regular intervals and analyzed by TLC (toluene/acetone, 95/5, v/v). Within 3 h, the starting compounds **8** (R_f 0.27) and **9** (R_f 0.43) had almost disappeared, while a single product (R_f 0.56) had formed. (Note: depending on the quality of the trimethylsilyl trifluoromethanesulfonate used, extra – or larger – additions of this catalyst and somewhat longer reaction times may be required). The reaction was quenched by addition of triethylamine (0.1 ml). The molecular sieves were removed by filtration and washed with chloroform and toluene. The combined filtrate and washings were concentrated and the residue thus obtained was purified by chromatography on a 8 × 6-cm column. Elution was effected with toluene/acetone, 100/0–98/2, v/v. From the appropriate fractions, **10**, contaminated with a trace of **9** as judged by TLC, was obtained as a syrup. Yield 5.2 g (85%). $[\alpha]_D$ +53.5° (*c* 2.1, $CHCl_3$). 200-MHz ^{1}H NMR: δ 3.63–3.97 (m, 9H); 4.55–4.71 (m, 9H); 5.17–5.30 (m + s, 3H); 5.64–5.97 (m, 3H); 7.2–8.0 (m, 30 arom. H). ^{13}C NMR: δ 65.1, 67.3, 69.6, 72.0, 72.2 (two overlapping signals) (6 × CH_2); 72.7 (CH); 73.6 (CH_2); 75.3, 77.9, 78.0, 78.3, 78.7 (5 × CH); 105.1 (C1, Rib*f*); 116.6 (CH_2=); 134.7 (=CH–); 127–138 (arom. C); 165.0, 165.1, 165.9 (3 × C=O).

5-O-Allyl-2,3,4-tri-O-benzyl-1-O-(β-D-ribofuranosyl)-D-ribitol (**11**)

The fully protected dimer **10** (5.0 g, 5.5 mmol) was dissolved in dry dioxane (25 ml). Dry methanol (25 ml) and 1-M sodium methoxide in methanol (1.25 ml) were added. The reaction mixture was stirred at room temperature for 4 h. A second portion of sodium methoxide solution (0.25 ml) was added and stirring was continued for 1 h. Neutralization was effected by addition of Dowex 50W X4 (H^+ form, 1.25 g). After 30 min. the ion-exchange resin was removed by filtration and washed with methanol and chloroform. The combined filtrate and washings were concentrated. The product was purified by chromatography on a 8 × 4.5-cm column. Elution: dichloromethane/methanol, 100/0–95/5, v/v. From the appropriate fractions pure **11** was obtained as a syrup. Yield 3.0 g (88%). TLC (CH_2Cl_2/MeOH, 95/5, v/v): R_f 0.23. $[\alpha]_D$ −30.7° (*c* 2.0, $CHCl_3$). 200-MHz ^{1}H NMR: δ 3.0–3.4 (br, 3H, OH); 3.5–4.1 (m, 13H); 4.35 (br, t, 1H); 4.55–4.75 (m, 6H); 4.84 (s, 1H); 5.1–5.3 (CH_2=); 5.7–6.0 (m, =CH–); 7.2–7.4 (m, 15 arom. H). ^{13}C NMR: δ 62.7, 67.7, 69.5 (3 × CH_2); 70.7 (CH); 72.1 (three overlapping signals, CH_2); 73.6 (CH_2); 75.4, 77.7, 77.9, 78.1, 84.0 (5 × CH); 107.2 (Cl, Rib*f*); 116.9 (CH_2=); 134.6 (=CH–); 127–138 (arom. C).

5-O-Allyl-2,3,4-tri-O-benzyl-1-O-[3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-D-ribitol (**12**)

Compound **11** (2.4 g, 4.0 mmol) was concentrated from dry pyridine (20 ml) twice and redissolved in pyridine (20 ml). The solution thus obtained was stirred under a nitrogen atmosphere at 0°C and 1,3-dichloro-1,1,3,3-tetra-isopropyldisiloxane (1.4 ml, 4.4 mmol) was added dropwise over 15 min[32-40]. Stirring was continued for a further 60 min at room temperature, during which time a pyridine hydrochloride precipitate formed. The reaction mixture was concentrated and coevaporated with toluene (3 × 20 ml). The residue was taken up in diethyl ether (75 ml) and washed with 1-M KH_2PO_4 (3 × 50 ml) and 1-M $NaHCO_3$ (50 ml). The organic layer was dried and concentrated. The product was purified by chromatography on a 5 × 4.5-cm column. Elution: dichloromethane/acetone, 100/0–98/2, v/v. Pure **12** (2.3 g, 67%) was obtained as a syrup. TLC (CH_2Cl_2/MeOH, 98/2, v/v and CH_2Cl_2/acetone, 98/2, v/v): R_f 0.71 and 0.29, respectively. $[\alpha]_D$ −39.9° (*c* 2.1, $CHCl_3$). 200-MHz ^{1}H NMR: δ 1.0–1.2 (br, 28H, TIPS); 3.07 (s, 1H, OH); 3.69–4.13 (m, 13H); 4.57–4.83 (m, 7H); 4.98 (s, 1H); 5.20–5.37 (m, CH_2=); 5.89–6.03 (m, =CH–); 7.2–7.4 (m, 15 arom. H). ^{13}C NMR: δ 12.4–17.4 (TIPS); 66.0, 67.1, 69.8, 72.0, 72.1, 72.3, 73.7 (7 × CH_2); 75.0, 75.8, 77.7, 78.1, 78.5, 85.6 (6 × CH); 106.1 (Cl, Rib*f*); 116.6 (CH_2=); 134.8 (=CH–); 127–138 (arom. C).

5-O-Allyl-2,3,4-tri-O-benzyl-1-O-[2'-O-(benzyloxymethyl)-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-D-ribitol (**13**)

Compound **12** (1.49 g, 1.78 mmol) was concentrated from dry acetonitrile (5 ml) twice and redissolved in 4.5 ml acetonitrile. The solution was stirred under a nitrogen atmosphere at 50°C and dry *N,N*-diisopropylethylamine (1.35 ml, 7.7 mmol) and benzyloxymethyl chloride 10.50 ml, 3.8 mmol) were added successively. After 2 h, extra benzyloxymethyl chloride (0.25 ml) was added and stirring was continued for 1 h. TLC analysis (hexane/ethyl acetate, 9/1, v/v) showed complete conversion of **12** (R_f 0.12) into a more lypophilic compound. The excess chloromethyl ether was destroyed by reaction with dry methanol (2 ml) at 50°C. After some cooling, the reaction mixture was concentrated. The residue was taken up in diethyl ether (40 ml), washed with 1-M KH_2PO_4 (3 × 20 ml) and 1-M $NaHCO_3$ (20 ml) and dried. Evaporation of the solvent gave a product which was purified by chromatography on a 5 × 3 cm column. Elution: hexane/ethyl acetate, 10/0–9/1, v/v. Pure **13** (1.46 g, 85%) was obtained as a syrup. TLC (hexane/ethyl acetate, 9/1, v/v): R_f 0.34. $[\alpha]_D$ −40.0° (*c* 2.1, $CHCl_3$). 200-MHz ^{1}H NMR: δ 1.0–1.2 (br, 28H, TIPS); 3.6–4.2 (m, 13H); 4.5–5.5 (m, 12H);

5.10–5.32 (m, CH_2=); 5.77–5.94 (m, =CH–); 7.2–7.4 (20 arom. H). ^{13}C NMR: δ 12.6–17.4 (TIPS); 64.5, 67.2, 69.3, 70.0, 72.1 (two overlapping signals), 72.3, 73.7 (8 × CH_2); 74.1, 77.8, 78.3, 78.6, 79.4, 81.1 (6 × CH); 94.0 (–O–CH_2–O–, BOM); 105.1 (Cl, Rib*f*); 116.6 (CH_2=); 134.8 (=CH–); 127–139 (arom. C).

2,3,4-Tri-O-*benzyl-1*-O-*[2'*-O-*(benzyloxymethyl)-3',5'*-O-*-(tetraisopropyldisiloxane-1,3-diyl)*-β-D-*ribofuranosyl]-5*-O-*-(*trans-*propen-1-yl)*-D-*ribitol* (**14**)

Compound **13** (1.32 g, 1.38 mmol) was dissolved in tetrahydrofuran (4 ml, freshly distilled from $LiAlH_4$). The solution was alternatingly degassed and placed under helium (3 ×). (1,5-Cyclooctadiene)-bis(methyldiphenylphosphine)iridium hexafluorophosphate (2–3 mg)[44,45] was added and again the solution was degassed and placed under helium (3 ×). The catalyst was activated by passing a stream of hydrogen for 2 min. Once again the reaction mixture was degassed and, thereafter, left under a gentle stream of helium for 4 h. TLC (hexane/ethyl acetate, 9/1, v/v) showed complete conversion of **13** (R_f 0.34) into **14** (R_f 0.38). The reaction mixture was concentrated and syrupy **14** thus obtained was used in further reactions without purification. $[\alpha]_D$ –38.9° (*c* 1.0, $CHCl_3$). 300-MHz ^{1}H NMR: signals of the *trans*-1-propenyl group δ 1.53 (dd, –CH=CH–CH_3); 4.72 (dq, –O–CH=CH–CH_3, $J_{2,3}$ 6.5 Hz); 6.20 (dq, –O–CH=CH–CH_3, $J_{1,2}$ 12 Hz, $J_{1,3}$ 1.5 Hz). The signal at 4.72 ppm is located in a highly complicated region of the spectrum. The assignment was made unambiguously by using a differential plot of the standard spectrum and a CH_3-decoupled spectrum. ^{13}C NMR: δ 12.5–17.5 (TIPS + CH_3, Prop); 64.5, 67.1, 68.7, 69.5, 72.2, 72.4, 73.8 (7 × CH_2); 74.0, 77.7 (two overlapping signals), 78.4, 79.5, 81.2 (6 × CH); 94.1 (–O–CH_2–O–, BOM); 98.4 (–O–CH=CH–); 105.2 (Cl, Rib*f*); 127–138 (arom. C); 146.6 (–O–CH=CH–). The NMR spectra confirmed a quantitative allyl-into-propenyl isomerization (no trace of **13** was detected).

2,3,4-Tri-O-*benzyl-1*-O-*[2'*-O-*(benzyloxymethyl)-3',5'*-O-*-(tetraisopropyldisiloxane-1,3-diyl)*-β-D-*ribofuranosyl]*-D-*ribitol* (**15**)

Compound **14** (1.20 g, 1.31 mmol) was dissolved in acetone (15 ml) and water (1 ml). HgO (300 mg, 1.39 mmol) and $HgCl_2$ (375 mg, 1.38 mmol) were added and the suspension was stirred at room temperature for 30 min[46]. HgO was temoved by filtration and washed with acetone. The combined filtrate and washings were concentrated. The residue was taken up in diethyl ether (75 ml), washed with 50% saturated KI solution (3 × 40 ml), 1% $NaHSO_3$ solution (40 ml) and 1 M $NaHCO_3$ (30 ml) and dried. The solvent was removed and the product was purified by chromatography on a 6 × 3 cm column. Elution: hexane/ethyl acetate 9/1–7/3, v/v. Pure **15** (0.97 g, 84%) was obtained as a syrup. Anal. $C_{51}H_{72}O_{11}Si_2$ (917.29) calcd.: C 66.78, H 7.91; found: C 67.01, H 7.85%. TLC (hexane/ethyl acetate, 7/3, v/v): R_f 0.34. $[\alpha]_D$ +39° (*c* 1.0, $CHCl_3$). 300-MHz ^{1}H NMR: δ 1.0–1.1 (28H, TIPS); 2.22 (t, OH, *J* 6.0 Hz); 3.64–3.74 (m, 4H, H1a ribitol, H5a,b ribitol, CH ribitol); 3.78–3.92 (m, 4H, H5a Rib*f*, H1b ribitol, 2 × CH ribitol); 3.99–4.05 (m, 2H, H4 Rib*f*, H5b Rib*f*); 4.14 (d, H2 Rib*f*, $J_{2,3}$ 4.4 Hz); 4.53 (dd, H3 Rib*f*, $J_{3,4}$ 7.4 Hz); 4.55–4.72 (m, 8H, 4 × –O–CH_2–Ph); 4.84 (s, H1 Rib*f*); 4.87 (d, –O–CH_2a–O–, BOM, *J* 6.9 Hz); 4.95 (d, –O–CH_2b–O–, BOM); 7.25–7.33 (20 arom. H). 75.5-MHz ^{13}C NMR: δ 12.7–17.3 (TIPS); 61.2 (C5, ribitol); 64.2 (C5 Rib*f*); 66.8 (C1, ribitol); 69.4, 71.7, 72.2 (3 × –O–CH_2–O–Ph); 73.7 (C3, Rib*f*); 73.9 –O–CH_2–O–Ph); 77.6, 78.7, 78.9 (3 × CH, ribitol); 79.4 (C2, Rib*f*); 81.1 (C4, Rib*f*); 94.0 (–O–CH_2–O–, BOM); 105.2 (C1, Rib*f*); 127–138 (arom. C).

2,3,4-Tri-O-*benzyl-1*-O-*(2'*-O-*(benzyloxymethyl)*-β-D-*ribofuranosyl)-5*-O-*(*trans-*1-propenyl)*-D-*ribitol* (**16**)

Compound **14** (425 mg, 0.44 mmol) was concentrated from dry dioxane (2 ml) twice and redissolved in 2.2 ml 0.5-M tetra-*n*-butylammonium fluoride in dioxane[47]. After reaction at room temperature for 30 min, the solvent was removed by evaporation. 1-M $NaHCO_3$ (25 ml) was added to the residue and the heterogeneous mixture thus obtained was extracted with dichloromethane (3 × 25 ml). The combined extracts were dried and concentrated. The product was purified by chromatography on a 3 × 2 cm column. Elution: dichloromethane/methanol, 100/0–98/2, v/v. Fractions containing **16** were pooled and concentrated. The product (239 mg) was homogeneous on TLC (dichloromethane/methanol, 98/2, v/v): R_f 0.21. However, as judged by NMR spectroscopy, about 0.5 equivalent of 1,3-difluoro-1,1,3,3-tetraisopropyldisiloxane (TIPS–F_2) was present. (Note: in **14** the CH_3 as well as the CH groups of the TIPS group are not equivalent, giving rise to two pairs of four NMR signals. In this case, however, in both ^{1}H and ^{13}C NMR, only two sharp signals were detected). Therefore, the 239 mg of product contained about 200 mg of **16** (63% yield from **14**). 200-MHz ^{1}H NMR: δ 1.01 (s) and 1.04 (s): contaminating TIPS-F_2; 1.53 (dd, –CH=CH–CH_3, *J* 7 and 1.5 Hz); 2.84 (br, t, OH); 3.10 (br, d, OH); 3.5–4.03 and 4.47–4.48 (2 × m, 21H); 4.82 (s, 2H); 4.97 (s, 1H); 6.20 (m, –O–CH=CH–); 7.2–7.4 (20 arom. H). ^{13}C NMR: δ 13.3 (CH) and 17.3 (CH_3): contaminating TIPS-F_2; 12.6 (=CH–CH_3); 62.8, 67.7, 68.5, 70.0 (4 × CH_2); 70.7 (CH); 72.3 (two overlapping signals, 2 × CH_2); 73.8 (CH_2); 77.4, 77.8, 78.2, 81.5, 84.6 (5 × CH); 94.9 (–O|CH_2–O–, BOM); 98.6 (–O–CH=CH–); 105.7 (C1, Rib*f*); 127–138 (arom. C); 146.6 (–O–CH=CH–).

2,3,4-Tri-O-*benzyl-1*-O-*(2'*-O-*(benzyloxymethyl)-5'*-O-*(*tert-*butyldiphenylsilyl)*-β-D-*ribofuranosyl)-5*-O-*(*trans-*1-propenyl)*-D-*ribitol* (**17**)

The 239 mg of product, which was obtained in the previous step, containing 200 mg (0.28 mmol) of **16**, was concentrated from dry pyridine (2.5 ml) twice and redissolved in pyridine (1.0 ml). *tert*-Butyldiphenylsilyl chloride (90 µl, 0.35 mmol)[48] was added and the reaction mixture was stirred at room temperature. TLC analysis (dichloromethane/acetone, 99/1, v/v) after 5 h indicated complete conversion of **16** (R_f 0.08) into a more lypophilic compound (R_f 0.45). Dry methanol (0.5 ml) was added and, thereafter, the solvents were evaporated. The residue was taken up in diethyl ether (25 ml) and washed with 1-M KH_2PO_4 (3 × 10 ml) and 1-M $NaHCO_3$ (10 ml). The organic layer was dried and concentrated. The product was purified by chromatography on a 3 × 2 cm cm column. Elution: hexane/ethyl acetate, 10/0–7/3, v/v. Pure **17** (254 mg, 95%) was obtained as a stiff syrup which slowly solidified. (Starting from 2.6 g of **14**, compound **17** was obtained in 68% over-all yield). Anal. $C_{58}H_{68}O_{10}Si$ (953.25) calcd.: C 73.08, H 7.19; found: C 72.79, H 7.22%. TLC (hexane/ethyl acetate, 7/3, v/v): R_f 0.41. $[\alpha]_D$ –24.8° (*c* 1.0, $CHCl_3$). 300-MHz ^{1}H NMR: δ 1.04 (s, 9H, –C(CH_3)$_3$); 1.52 (dd, =CH–CH_3, *J* 6.7 and 1.5 Hz); 2.56 (d, OH, *J* 7.6 Hz); 3.69–3.91 (m, 9H, H5a,b Rib*f* and all 7H of ribitol); 3.99–4.05 (m, 2H, H2 Rib*f*, H4 Rib*f*); 4.20–4.27 (m, H3 Rib*f*); 4.45–4.65 (m, 8H, 4 × –O–CH_2–Ph); 4.69 (dq, –CH=CH–CH_3); 4.81 (d, –O–CH_2a–O–, BOM, *J* 6.8 Hz); 4.83 (d, –O–C_2b–O–, BOM); 5.04 (d, H1 Rib*f*, $J_{1,2}$ 1.5 Hz); 6.19 (dq, –O–CH=CH–, *J* 12.5 and 1.5 Hz); 7.2–7.7 (30 arom. H). 75.5-MHz ^{13}C NMR: δ 12.5 (=CH–CH_3); 19.2 [–C(CH_3)$_3$]; 26.8 [–C(CH_3)$_3$]; 65.3 (C5, Rib*f*); 67.4 (C1 ribitol); 68.6 (C5 ribitol); 70.0 (–O–CH_2–Ph); 71.8 (C3 Rib*f*); 72.1, 72.3, 73.7 (3 × –O–CH_2–Ph); 77.7 (2 × CH ribitol, overlapping); 78.3 (CH ribitol); 81.1 (C2 Rib*f*); 84.1 (C4 Rib*f*); 94.6 (–O–CH_2–O–, BOM); 98.4 (–CH=CH–CH_3); 105.6 (C1 Rib*f*); 127–138 (arom. C); 146.5 (–O–CH=CH–).

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References

[1] *W. Egan, R. Schneerson, K. E. Werner* and *G. Zon*, J. Am. Chem. Soc. **104**, 2998 (1982).
[2] *L. Kenne* and *B. Lindberg* in "The polysaccharides", *G. O. Aspinall*, ed., Academic Press Inc., 1983, Vol. 2, pp. 287–363.
[3] *R. M. Crisel, R. S. Baker* and *D. E. Dorman*, J. Biol. Chem. **250**, 4926 (1975).
[4] *P. Branefors-Helander, C. Erbing, L. Kenne* and *B. Lindberg*, Acta Chem. Scand. Ser. B. **30**, 276 (1976).

[5] *D. M. Granoff* and *R. S. Munson*, J. Infect. Dis. **153**, 448 (1986).
[6] *P. J. Garegg* and *B. Samuelsson*, Carbohydr. Res. **86**, 293 (1980).
[7] *P. J. Garegg, R. Johansson, I. Lindh* and *B. Samuelsson*, Carbohydr. Res. **150**, 285 (1985).
[8] *C. A. A. van Boeckel, G. M. Visser, J. P. G. Hermans* and *J. H. van Boom*, Recl. Trav. Chim. Pays-Bas **102**, 526 (1983).
[9] *J. J. Oltvoort, C. A. A. van Boeckel, J. H. de Koning* and *J. H. van Boom*, Recl. Trav. Chim. Pays-Bas **101**, 87 (1982).
[10] *P. Westerduin, G. H. Veeneman, G. A. van der Marel* and *J. H. van Boom*, Tetrahedron Lett. **27**, 6271 (1986).
[11] *P. Westerduin, G. H. Veeneman, Y. Pennings, G. A. van der Marel* and *J. H. van Boom*, Tetrahedron Lett. **28**, 1557 (1987).
[12] Preliminary communication: *P. Hoogerhout, D. Evenberg, C. A. A. van Boeckel, J. T. Poolman, E. C. Beuvery, G. A. van der Marel* and *J. H. van Boom*, Tetrahedron Lett. **28**, 1553 (1987).
[13] For a review of the use of D-ribonolactone as a chiral template in organic synthesis *cf. K. L. Bhat, S. Y. Chen* and *M. M. Joullié*, Heterocycles **23**, 691 (1985).
[14] *L. Hough, J. K. N. Jones* and *D. L. Mitchell*, Can. J. Chem. **36**, 1720 (1958).
[15] *J. Baddiley, J. G. Buchanan* and *F. E. Hardy*, J. Chem. Soc. 2180 (1961).
[16] *F. Guibe* and *Y. Saint M'Leux*, Tetrahedron Lett. **22**, 3591 (1981).
[17] *P. Boullanger, P. Chatelard, G. Descotes, M. Kloosterman* and *J. H. van Boom*, J. Carbohydr. Chem. **5**, 541 (1986).
[18] *M. L. Wolfrom* and *A. Thompson* in "Methods Carbohydr. Chem.", *R. L. Whistler* and *M. L. Wolfrom*, eds., Academic Press Inc., 1963, Vol. 2, pp. 65–68.
[19] *B. A. Lewis, F. Smith* and *A. M. Stephen* in "Methods Carbohydr. Chem.", *R. L. Whistler* and *M. L. Wolfrom*, eds., Academic Press Inc., 1963, Vol. 2, pp. 68–77.
[20] *K. Soai, H. Oyamada* and *M. Takase*, Bull. Chem. Soc. Jpn. **57**, 2357 (1984).
[21] *K. Utimoto* and *T. Horiie*, Tetrahedron Lett. **23**, 237 (1982).
[22] *V. I. Betanelli, M. V. Ovchinnikov, L. V. Backinowski* and *N. K. Kochetkov*, Carbohydr. Res. **76**, 252 (1979).
[23] *R. K. Ness* and H. G. Fletcher, Carbohydr. Res. **19**, 423 (1971).
[24] *S. Hanessian* and *A. Pernet*, Can. J. Chem. **52**, 1280 (1974).
[25] *P. Kosma, G. Schulz* and *F. M. Unger*, Carbohydr. Res. **132**, 261 (1984).
[26] *R. S. Klein, H. Ohrui* and *J. J. Fox*, J. Carbohydrates Nucleosides, Nucleotides **1**, 265 (1974).
[27] *T. Ogawa, K. Beppu* and *S. Nakabayashi*, Carbohydr. Res. **93**, C6 (1981).
[28] *J. Banoub* and *D. R. Bundle*, Can. J. Chem. **57**, 2085 (1979).
[29] *J. Banoub* and *D. R. Bundle*, Can. J. Chem. **57**, 2091 (1979).
[30] *T. Ogawa*, Carbohydr. Res. **93**, C1 (1981).
[31] *C. B. Reese*, Tetrahedron **34**, 3143 (1978).
[32] *W. T. Markiewicz* and *Wiewiorowsky*, Nucl. Acids Res. Special Report no. **5**, 3185 (1978).
[33] *W. T. Markiewicz*, J. Chem. Res. (S) 24 (1979).
[34] *W. T. Markiewicz, N. S. Padyukova, Z. Samek* and *J. Smrt*, Coll. Czech. Chem. Commun. **45**, 1860 (1980).
[35] *C. H. M. Verdegaal, P. L. Jansse, J. F. M. de Rooij* and *J. H. van Boom*, Tetrahedron Lett. 1571 (1980).
[36] *C. A. A. van Boeckel* and *J. H. van Boom*, Tetrahedron **41**, 4545 (1985).
[37] *C. A. A. van Boeckel, G. M. Visser* and *J. H. van Boom*, Tetrahedron **41**, 4557 (1985).
[38] *C. A. A. van Boeckel* and *J. H. van Boom*, Tetrahedron **41**, 4567 (1985).
[39] *J. J. Oltvoort, M. Kloosterman* and *J. H. van Boom*, Recl. Trav. Chim. Pays-Bas **102**, 501 (1983).
[40] *H. Paulsen, M. Stiem* and *F. M. Unger*, Tetrahedron Lett. **27**, 1135 (1986).
[41] *B. E. Griffin, M. Jarman* and *C. B. Reese*, Tetrahedron **24**, 639 (1968).
[42] *J. M. Berry* and *L. D. Hall*, Carbohydr. Res. **47**, 307 (1976).
[43] *O. Hindsgaul, T. Norberg, J. Le Pendu* and *R. U. Lemieux*, Carbohydr. Res. **109**, 109 (1982).
[44] *L. M. Haines* and *E. Singleton*, J. Chem. Soc. Dalton Trans. 1891 (1972).
[45] *J. J. Oltvoort, C. A. A. van Boeckel, J. H. de Koning* and *J. H. van Boom*, Synthesis 305 (1981).
[46] *R. Gigg* and *C. D. Warren*, J. Chem. Soc. (C) 1903 (1968).
[47] *E. J. Corey* and *A Venkateswarlu*, J. Am. Chem. Soc. **94**, 6190 (1972).
[48] *S. Hanessian* and *P. Lavallee*, Can. J. Chem. **53**, 2975 (1975).
[49] *W. P. Aue, E. Bartholdi* and *R. R. Ernst*, J. Chem. Phys. **64**, 2229 (1976).
[50] *A. Bax* and *G. A. Morris*, J. Magn. Res. **42**, 501 (1981).
[51] *L. Brandsma*, "Preparative acetylenic chemistry", Elsevier, Amsterdam, 1971, p. 190.
[52] *J. H. van Boom* and *C. T. J. Wreesmann* in "Oligonucleotide synthesis: a practical approach", *M. J. Gait*, ed., I.R.L. Press, Oxford, U.K., 1984, pp. 153–183.