Efficient Blockwise Synthesis of Pyruvated Di- and Trisaccharide Fragments Related to Klebsiella K26 Capsular Polysaccharides

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Abstract. Pyruvated di- and trisaccharide fragments representing the immunodominant side chains of *Klebsiella* K26 capsular polysaccharides are prepared. Phenyl 4',6'-*O*-benzylidene-1-thio-β-D-lactoside (**1**) is converted in 4 steps into the corresponding pyruvated 1-thio-lactoside (**2**) and transformed into the imidate (**4**). Coupling of the latter with Z-protected 5-aminopentanol gives the pyruvated disaccharide fragment (**6**) upon deblocking. Similarly, imidate (**4**) is coupled to allyl 2,3-di-*O*-benzoyl-3-*O*-(1-fluoro-1,1,3,3-tetra-isopropyl-1,3-disiloxane-3-yl)-α-D-glucopyranoside (**8**) to give the corresponding trisaccharide fragment upon deblocking.

Ongoing studies toward the synthesis of immunologically relevant pyruvated bacterial saccharides prompted us to turn our interest to the structurally divers capsular polysaccharides of *Klebsiella* species. Enterobacteriae of the genus *Klebsiella* are ubiquitous gram negative bacteria that can cause pulmonary infections or opportunistic infections of the urinary tract [1]. More than 80 species of *Klebsiella* are identified so far and are most commonly classified by serological differences of their capsular polysaccharides (K-antigens) [2]. 29 of these K-antigenic saccharide structures are found to contain pyruvic acetals at different positions of the sugar chain, either at intracatenal sugar residues or at residues of side chains (up to 3 monosaccharides long) of the respective polysaccharide backbone. These immunodominat pyruvated sugar residues [3] of *Klebsiella* capsuls have been thought to be responsible for cross-reactivities found during serotyping [4] and are therefore interesting targets for synthetic studies.

The hexasaccharide repeating unit of the capsular polysaccharide of *Klebsiella* serovar K26 (Figure 1) contains a trisaccharide side chain having a 4',6'-pyru-

→3)-β-D-Gal*p*-(1→2)-α-D-Glc*Ap*-(1→3)-α-D-Man*p*-(1→
                              4
                              ↑
                              1
β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*
    6 4
    X_COOH

Fig. 1 Repeating unit of the capsular polysaccharide of *Klebsiella* K26 (the pyruvic acid acetal has the (*R*) configuration) [5].

vated β-D-lactosyl residue (1→6)-linked to an α-D-glucopyranosyl residue [5]. A pyruvated lactosyl residue is unique for *Klebsiella* and for almost all other pyruvated saccharides. Solely the aggregation factor of the marine sponge *Microciona prolifera* is known to contain such a residue [6]. In contrast, 4,6-pyruvated galactosyl residues are relatively common upon *Klebsiella* capsular polysaccharides [7]. Therefore, an efficient synthesis of pyruvated saccharide fragments related to *Klebsiella* K26 that should be useful for immunological studies is presented here.

Recently, the crystalline pyruvated lactosyl block **2** was efficiently prepared in 4 steps and 58% overall yield on a multigram scale from phenyl 4',6'-*O*-benzylidene-1-thio-β-D-lactoside **1** [8] and applied as an intermediate for the synthesis of a trisaccharide fragment related to the aggregation factor of *Microciona prolifera* [9]. It could be used as a disaccharide donor either by itself or *via* subsequent conversion into the respective pyruvated lactosyl bromide [9]. Here, the synthetic flexibility of lactosyl block **2** was further demonstrated by its conversion into the trichloroacetimidate **4**. Thus, 1-thiolactoside **2** was treated with Br₂ in a mixture of dichloromethane and water to give directly the corresponding 1-OH derivative **3** (88%). The latter was subsequently converted into the α-trichloroacetimidate **4** (82%). The imidate **4** was chosen here as a disaccharide donor since it has previously been shown that pyruvated glycosyl trichloroacetimidates are superior glycosyl donors for oligosaccharide syntheses [10].

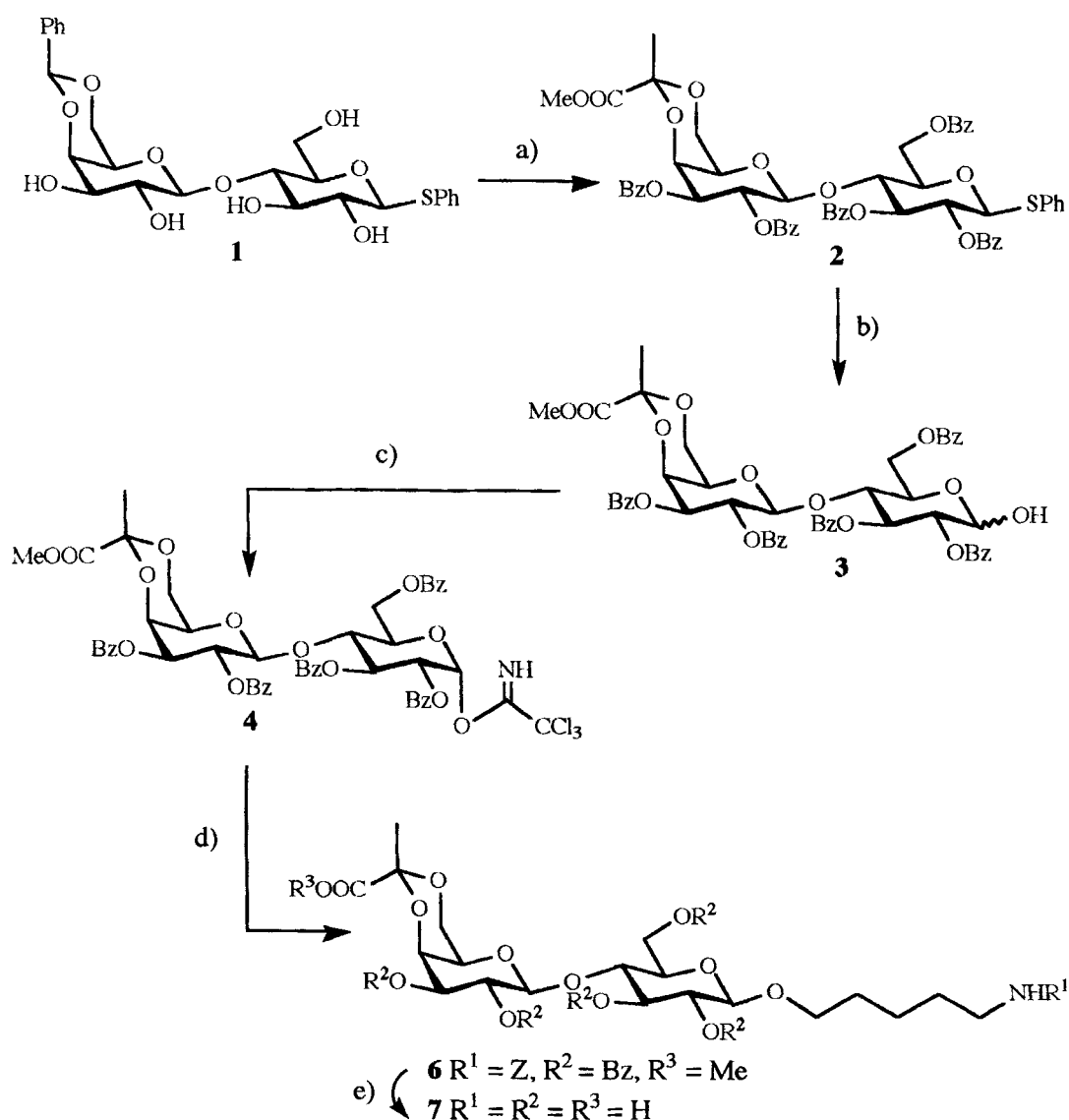For the efficient construction of a disaccharide fragment that could be later used for conjugation with a

suitable carrier, Z-protected 5-aminopentanol 5 [11] was chosen as the acceptor. 5-Aminopentyl residues have previously been demonstrated to be excellent aglycons for pyruvated saccharides since the NH_2 function can easily be coupled to proteins or solid carriers in order to obtain the desired glycoconjugates for immunological studies or affinity purification of proteins that bind pyruvated sugars [10]. Thus, 4 and 5 were condensed by the promotion of BF_3 diethylether to give the corresponding fully blocked disaccharide aminopentyl glycoside 6 in 72% yield. The β-configuration of the formed anomeric bond was evident from the NMR spectra of 6 that showed a vicinal coupling constant of 8.3 Hz and a

chemical shift for C-1 of 100.7 ppm. Sequential deblocking of disaccharide 6 by removing the benzoyl groups (Zemplén) followed by saponification of the methyl pyruvate residue and hydrogenolysis of the Z group then afforded the disaccharide fragment 7 (68%).

For the efficient preparation of a *Klebsiella* K26 related trisaccharide fragment a strategy related to the glycodesilylation method [12] was applied here. This method uses tetraisopropyl disiloxane-protected glycosides as acceptors and glycosyl fluorides as donors and is preferencially applied to the synthesis of pyruvated oligosaccharides [13]. Alternatively, 4,6-O-tetraisopropyl disiloxane-protected glycosides can be opened regioselec-

Scheme 1   a) ref. [9]; b) 2 (1 eq.), Br_2 (2 eq.), CCl_4/H_2O (5:1), 45 min., 25 °C, 88%; c) 3 (1 eq.), Cl_3CCN (5 eq.), K_2CO_3 (9.2 eq.), CH_2Cl_2, 24 h, 25 °C, 82%; d) 4 (1 eq.), $HO(CH_2)_5NHZ$ (5, 1.7 eq.), $BF_3 \cdot Et_2O$ (1.3 eq.), CH_2Cl_2, 20 min., –10 °C, 72%; e) 1) 6 (1 eq.), cat. NaOMe, MeOH, 24 h, 25 °C; 2) NaOH (5.4 eq.), $MeOH/H_2O$ (1:1), 24 h, 25 °C; 3) cat. Pd/C (10%), H_2 (100 kPa), $MeOH/H_2O$ (1:1), 24 h, 25 °C, 68% (3 steps).
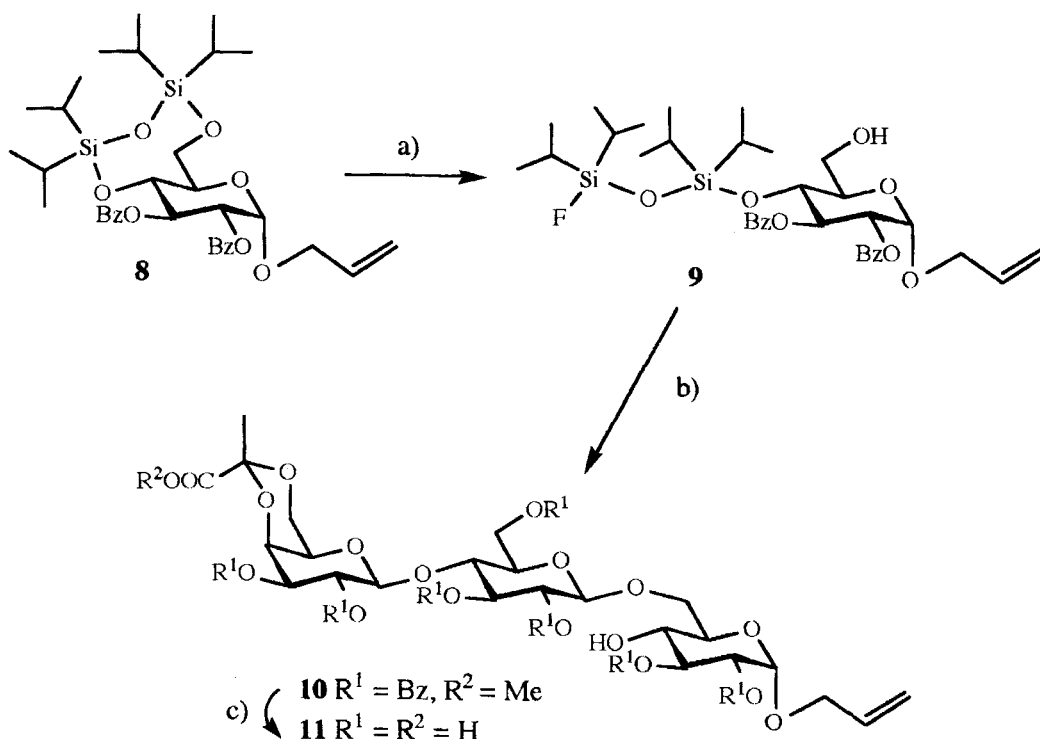
Scheme 2 a) **8** (1 eq.), excess HF-pyridine (70%), CH_2Cl_2, 15 min., 25 °C, 99%; b) 1) **4** (1 eq.), **9** (1.15 eq.), TMSOTf (0.12 eq.), CH_2Cl_2, 15 min., –12 °C; 2) cat. $Bu_4NF·3 H_2O$, THF, 2 h, 25 °C, 76% (2 steps); c) 1) **10** (1 eq.), cat. NaOMe, MeOH, 24 h, 25 °C; 2) NaOH (5 eq.), $MeOH/H_2O$ (1:1), 24 h, 25 °C, 95% (2 steps).

tively in high yield and applied as acceptors in combination with trichloroacetimidates as donors [12]. In order to demonstrate the practicability of that approach for the synthesis of the desired trisaccharide, the disiloxandiyl group of allyl 2,3-di-O-benzoyl-4,6-O-(1,1,3,3-tetraisopropyl-1,3-disiloxan-1,3-diyl)-α-D-glucopyranoside **8** [14] was first opened regioselectively with HF-pyridine complex, to give the nucleophile **9** (99%). The presence of a 6-OH group in **9** was shown by a significant low-field-shift of C-6 compared to the silylated position 6 in compound **8** [13]. Condensation of **9** with disaccharide imidate **4** followed by fluoride catalyzed desilylation of the intermediate coupling product then afforded the crystalline trisaccharide **10** in 76% yield. In its NMR spectra the geminal H,H-coupling constant $J_{1',2'}$ of 7.7 Hz proved a β-selective coupling and the low-field shift of C-6 compared to that of compound **9**, unambiguously showed a (1→6)-coupling. Debenzoylation and saponification of **10** as described for disaccharide **6** finally gave the desired trisaccharide allyl glycoside **11** (95%).

The preparation of glycoconjugates from oligosaccharide ω-aminoalkyl and allyl glycosides, respectively is well documented [15] and will be published elsewhere for **7** and **11**.

Experimental

General Methods. NMR data were extracted from spectra measured in solutions of $CDCl_3$ (with TMS as an internal standard) for blocked compounds and D_2O (with MeOH as an internal standard) for fully deblocked compounds at 25 °C with a Bruker AC 250F spectrometer. Protonsignal assignments were made by first order analysis of the spectra. Of the two magnetically non-equivalent geminal protons at C-6, the one resonating at lower field was designated 6-Ha and the one resonating at higher field was designated 6-Hb. Carbonsignal assignments were made by mutual comparison of the spectra and by comparison with spectra of related compounds. Optical rotations were measured at 25 °C with a Perkin-Elmer automatic polarimeter, Model 241. Melting points were measured with a Büchi apparatus, Model SMP-20. Thin-layer chromatography (TLC) was performed on precoated plastic sheets, Polygram SIL UV_{254}, 40 × 80 mm (Macherey-Nagel) using appropriately adjusted mixtures of carbon tetrachloride-acetone for the developing. Detection was effected with UV light, where applicable and by charring with 5% sulfuric acid in ethanol. Preparative chromatography was performed by elution from columns of Silica Gel 60 (Merck) using carbon

tetrachloride–acetone mixtures as solvent. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 2 kPa, ≤40 °C.

O-{2,3-Di-O-benzoyl-4,6-O-[(R)-1-methoxycarbonyl(ethylidene)]-β-D-galacto-pyranosyl}-(1→4)-2,3,6-tri-O-benzoyl-D-glucopyranose (3)

A solution of Br_2 (1 N in CCl_4, 6 ml, 6 mmol) was added at room temperature to a suspension of compound 2 [9] (3.12 g, 3 mmol) and H_2O (1 ml) in CCl_4–CH_2Cl_2 (5:1, 85 ml). The mixture was stirred until TLC indicated the complete formation of two slower moving products (45 min.). The suspension was sucessively washed with aqueous $NaHCO_3$ and $Na_2S_2O_3$ solution, dried and concentrated. Crystallization of the residue from CCl_4 afforded 3 (2.5 g, 88%). M. p. 210–215 °C with softening at 200 °C; $[\alpha]_D$ = +67.1 (c = 1.1, pyridine); ^{13}C-NMR (significant signals): δ = 101.3 (C-1'), 98.5 (C_{acetal}), 90.2 (C-1), 52.2 (OMe), 25.4 (CH_3).

$C_{51}H_{46}O_{18}$ (946.9)   Calcd.:   C 64.69; H 4.90
                                Found: C 64.69; H 4.95

O-{2,3-Di-O-benzoyl-4,6-O-[(R)-1-methoxycarbonyl(ethylidene)]-β-D-galactopyranosyl}-(1→4)-2,3,6-tri-O-benzoyl-α-D-glucopyranosyl trichloroacetimidate (4)

A suspension of compound 3 (1.5 g, 1.58 mmol), trichloroacetonitril (1.14 g, 7.9 mmol) and K_2CO_3 (2 g, 14.5 mmol) in CH_2Cl_2 (10 ml) was stirred until TLC indicated the complete formation of a faster moving product (24 h). The suspension was filtered through a layer of Celite, and the filtrate was concentrated. Chromatography of the residue afforded 4 (1.42 g, 82%) as a colorless foam. $[\alpha]_D$ = +144.9 (c = 0.8, $CHCl_3$); ^1H-NMR: δ = 6.67 (d, 1 H, $J_{1,2}$ = 3.8 Hz, 1-H), 6.27 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 8.6 Hz, 3-H), 5.78 (dd, 1 H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 10.4 Hz, 2'-H), 5.40 (dd, 1 H, 2-H), 5.30 (dd, 1 H, $J_{3',4'}$ = 3.6 Hz, 3'-H), 4.87 (d, 1 H, 1'-H), 4.66 (br. d, 1 H, 6a'-H), 4.39–4.28 (m, 5 H, 4, 5, 6a, 5', 6b'-H), 4.25 (br.d, 1 H, $J_{4',5'}$ < 1 Hz, 4'-H), 3.77–3.43 (m, 1 H, 6b-H), 3.56 (s, 3 H, OMe), 1.42 (CH_3); ^{13}C-NMR: δ = 101.6 (C-1'), 98.5 (C_{acetal}), 93.0 (C-1), 90.7 (CCl_3), 76.2 (C-4), 72.7 (C-2',4'), 71.1 (C-3,5), 69.3 (C-2), 68.5 (C-3'), 65.9 (C-5'), 64.1 (C-6'), 61.8 (C-6), 52.3 (OMe), 24.4 (CH_3).

$C_{53}H_{46}Cl_3NO_{18}$ (1091.3) Calcd.: C 58.33; H 4.25; N 1.28
                                     Found: C 58.25; H 4.27; N 1.26

5-[(Benzyloxycarbonyl)amino]pentyl O-{2,3-Di-O-benzoyl-4,6-O-[(R)-1-methoxy-carbonyl(ethylidene)]-β-D-galactopyranosyl}-(1→4)-2,3,6-tri-O-benzoyl-β-D-glucopyranoside (6)

$BF_3·Et_2O$ (50 μl, 0.4 mmol) was added under Ar at −10°C to a solution of compound 5 [11] (120 mg, 0.5 mmol) and compound 4 (330 mg, 0.3 mmol) in CH_2Cl_2 (5 ml), and the mixture was stirred until TLC indicated the complete formation of a slower moving product (20 min.). The mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ solution, dried and concentrated. The residue was redissolved in THF (10 ml) and stirred at room temperature with a catalytic amount of $Bu_4NF·3 H_2O$ until TLC indicated the complete conversion of the educt (2 h). The mixture was concentrated, the residue

was redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ solution, dried and concentrated. Chromatography of the residue afforded 6 (251 mg, 72%), as a colorless foam. $[\alpha]_D$ = +87.9 (c = 0.8, $CHCl_3$); ^1H-NMR: δ = 5.86 (t, 1 H, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 9.1 Hz, 3-H), 5.75 (dd, 1 H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 10.1 Hz, 2'-H), 5.32 (br. d, 1 H, $J_{1,2}$ = 8.3 Hz, 2-H), 5.05 (s, 2 H, OCH$_2$Ph), 5.04 (dd, 1 H, $J_{3',4'}$ = 3.3 Hz, 3'-H), 4.79–4.65 (m, 4 H, 6a, 6b, 6a', 6b'-H), 4.28–4.20 (m, 2 H, 5,5'-H), 4.25 (br. d, 1 H, $J_{4',5'}$ < 1.0 Hz, 4'-H), 4.24 (br. t, 1 H, $J_{4,5}$ = 9.0 Hz, 4-H), 3.54 (s, 3 H, OMe), 1.38 (s, 3 H, CH_3); ^{13}C-NMR: δ = 101.2 (C-1'), 100.7 (C-1), 98.4 (C_{acetal}), 76.6 (C-4), 73.9 (C-3), 72.7, 72.5, 72.3 (C-5, 2', 4'), 69.7 (OCH$_2$), 69.3 (C-2), 68.4 (C-3'), 66.3 (OCH$_2$Ph), 65.6 (C-5'), 64.0 (C-6'), 62.2 (C-6), 52.3 (OMe), 40.8 (CH_2N), 25.4 (CH_3).

$C_{64}H_{63}NO_{20}$ (1166.2) Calcd.: C 65.92; H 5.45; N 1.20
                                 Found: C 66.19; H 5.08; N 1.49.

5-Aminopentyl O-{4,6-O-[(R)-1-Carboxyethylidene]-β-D-galactopyranosyl}-(1→4)-β-D-glucopyranoside (7)

A solution of compound 6 (215.9 mg, 0.185 mmol) and a catalytic amount of NaOMe in MeOH (15 ml) was stirred at room temperature until TLC indicated complete formation of a slower moving product (24 h). The solution was neutralized by addition of ion exchange resin (Dowex 1 X 8, H^+), filtered and concentrated. The residue was redissolved in MeOH–H_2O (1:1, 15 ml), and aqueous NaOH solution (1 N, 1 ml) was added. The mixture was stirred at room temperature until TLC indicated complete formation of a slower moving product (24 h), neutralized by addition of ion exchange resin (Dowex 1 X 8, H^+) and filtered. A catalytic amount of Pd (10% on charcoal) was added to the filtrate, the mixture was treated with H_2 (100 kPa) for 24 h, filtered and concentrated. Chromatography of the residue with H_2O on Bio gel P2 and lyophilisation of the carbohydrate-containing fractions afforded 7 (62.3 mg, 68%). $[\alpha]_D$ = −22.9 (c = 0.4, H_2O); ^{13}C-NMR: δ = 105.4 (C-1'), 104.9 (C-1), 103.5 (C_{acetal}), 81.5 (C-4), 77.7, 77.2 (C-2,3), 75.6 (C-5), 74.2, 73.8, 73.2 (C-2', 3' 4'), 72.9 (OCH$_2$), 68.9 (C-5'), 67.9 (C-6'), 62.8 (C-6), 42.2 (NCH$_2$), 27.9 (CH_3).
FAB-MS (pos.) Calcd. for $C_{20}H_{35}NO_{13}$: 497.2. Found: 498 (M+H^+).

Allyl 2,3-Di-O-benzoyl-4-O-(3-fluoro-1,1,3,3-tetraisopropyl-1,3-disiloxan-1-yl)-α-D-glucopyranoside (9)

HF-pyridine complex (70%, 0.2 ml) was added at room temperature to a solution of compound 8 [14] (0.5 g, 0.745 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred until TLC indicated complete formation of a slower moving product (15 min.). The mixture was washed with aqueous $NaHCO_3$ solution, dried and concentrated. Chromatography of the residue gave 9 (0.51 g, 99%), as a colorless foam. $[\alpha]_D$ = +93.2 (c = 0.3, $CHCl_3$); ^1H-NMR: δ = 5.95 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 9.1 Hz, 3-H), 5.28 (d, 1 H, $J_{1,2}$ = 3.7 Hz, 1-H), 5.06 (dd, 1 H, 2-H), 4.30–4.20 (m, 3 H, 4, 5, 6a-H), 4.00–3.70 (m, 1 H, 6b-H); ^{13}C-NMR: δ = 95.0 (C-1), 73.2, 72.5, 72.3 (C-2,3,4), 69.4 (C-5), 68.7 (OCH$_2$), 61.5 (C-6).

$C_{35}H_{51}FO_9Si_2$ (691.0)   Calcd.: C 60.84; H 7.44
                                  Found: C 60.80; H 7.31

Allyl O-{2,3-Di-O-benzoyl-4,6-O-[(R)-1-methoxycarbo-nyl(ethylidene)]-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzoyl-β-D-glucopyranosyl}-(1→6)-2,3-di-O-benzoyl-α-D-glucopyranoside (**10**)

Trimethylsilyl trifluoromethanesulfonate (12.8 µl, 70 µmol) was added at –20 °C under Ar to a solution of compound **9** (477 mg, 0.69 mmol) in CH_2Cl_2 (8 ml) followed by the addition of a solution of compound **4** (655 mg, 0.6 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred until TLC indicated complete formation of a slower moving product (15 min.). Pyridine (2 drops) was added, the mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ solution, dried and concentrated. The residue was dissolved in THF (10 ml) and treated with a catalytic amount of $Bu_4NF·3 H_2O$ and worked up as described for the preparation of compound **6**. Recrystallization from MeOH afforded **10** (620 mg, 76%). M. p. 195–198 °C; $[\alpha]_D = +110.1$ (c = 1.1, $CHCl_3$); ^{1}H-NMR (significant signals): $\delta = 5.04$ (d, 1 H, $J_{1,2} = 3.4$ Hz, 1-H), 4.84 (d, 1 H, $J_{1',2'} = 7.7$ Hz, 1'-H), 4.82 (d, 1 H, $J_{1'',2''} = 8.0$ Hz, 1''-H), 3.54 (s, 3 H, OMe), 1.38 (s, 3 H, CH_3); ^{13}C-NMR: $\delta = 101.3$, 101.2 (C-1',1''), 98.4 (C_{acetal}), 94.8 (C-1), 76.3 (C-4'), 74.2 (C-3'), 73.7 (C-5), 72.9 (C-2''), 72.5, 72.3 (C-5',4''), 71.2, 70.7 (C-2,4), 69.4 (C-3), 69.2 (C-2'), 68.5 (C-3''), 68.4 (C-6), 68.0 (OCH_2), 65.6 (C-5''), 64.0 (C-6''), 62.0 (C-6'), 52.2 (OMe), 24.3 (CH_3). $C_{74}H_{68}O_{25}$ (1357.3)　　Calcd.: C 65.48; H 5.05

　　　　　　　　　　　Found: C 65.46; H 4.96

Allyl O-{4,6-O-[(R)-1-Carboxyethylidene]-β-D-galacto-pyranosyl-(1→4)-β-D-glucopyranosyl}-(1→6)-α-D-glucop-yranoside (**11**)

A solution of compound **10** (485.6 mg, 0.36 mmol) and a catalytic amount of NaOMe in MeOH (15 ml) was stirred at room temperature until TLC indicated complete formation of a slower moving product (24 h). The solution was neutralized by addition of ion exchange resin (Dowex 1 X 8, H^+), filtered and concentrated. The residue was redissolved in MeOH–H_2O (1:1, 15 ml) and aqueous NaOH solution (1 N, 1 ml) was added. The mixture was stirred at room temperature until TLC indicated complete formation of a slower moving product (24 h), neutralized by addition of ion exchange resin (Dowex 1 X 8, H^+), filtered and concentrated. Chromatography of the residue with H_2O on Bio gel P2 and lyophilisation of the carbohydrate-containing fractions afforded **11** (209.3 mg, 95%). $[\alpha]_D = +27.9$ (c = 0.6, H_2O); ^{13}C-NMR: $\delta = 105.7$ (C-1'), 105.4 (C-1''), 103.6 (C_{acetal}), 100.2 (C-1), 81.5 (C-4'), 77.7 (C-3'), 77.1 (C-2'), 75.8, 75.6 (C-3,5'), 74.2, 74.0, 73.8, 73.7 (C-2, 2'', 3'', 4''), 73.2 (C-4), 72.1 (C-5), 71.5 (C-6), 71.2 (OCH_2), 68.9 (C-5''), 67.9 (C-6''), 62.8 (C-6'), 27.9 (CH_3). FAB-MS (pos.) Calcd. for $C_{24}H_{38}O_{18}$: 614.2. Found: 615 ($M+H^+$).

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