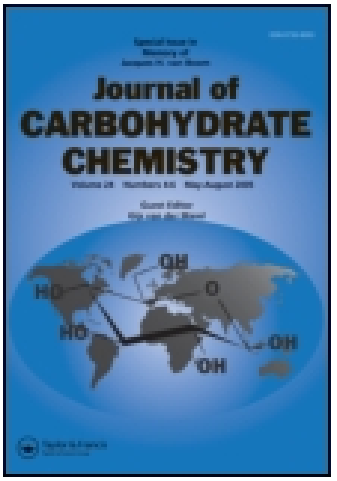

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Laurence A. Mulard & Joël Ughetto-Monfrin
[a] Unité de Chimie Organique, BGM, Institut Pasteur , 28 rue du Dr. Roux, 75724 Paris Cedex 15, France E-mail:
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LINEAR SYNTHESIS OF THE METHYL GLYCOSIDES OF TRI-, TETRA-, AND PENTASACCHARIDE FRAGMENTS OF THE *Shigella flexneri* SEROTYPE 5a *O*-ANTIGEN[1]

Laurence A. Mulard* and Joël Ughetto-Monfrin

Unité de Chimie Organique, BGM, Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris Cedex 15, France. E-mail: lmulard@pasteur.fr

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ABSTRACT

The stepwise synthesis of methyl α-D-glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (**EBC-OMe, 1**), methyl α-L-rhamnopyranosyl-(1→2)-[α-D-glucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (**A(E)BC-OMe, 2**), and methyl 2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-[α-D-glucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (**DA(E)BC-OMe, 3**) is described. Compounds **1**, **2** and **3** constitute the methyl glycosides of fragments of the *O*-specific polysaccharide of *Shigella flexneri* serotype 5a. Methyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside was an appropriate **BC** precursor for the synthesis of **1**. For the synthesis of the branched targets **2** and **3**, a benzyl group was best suited at position 2 of rhamnose **C**. Thus, methyl 4-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside was the key intermediate to the **BC** portion. In all cases, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride was a convenient **E** precursor, when used in combination with titanium tetrafluoride. All along, attention was paid to steric hindrance as a factor of major impact on the condensation steps outcome. Therefore, based on previous experience, 2-*O*-acetyl-3,4-di-*O*-allyl-α-L-rhamnopyranosyl trichloroacetimidate and 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl trichloroacetimidate were used as donors. Both suited all requirements when used as key precursors for residues **A** and **D** in the synthesis of **3**, respectively.

INTRODUCTION

A program to develop a possible substitute approach to the use of *O*-specific polysaccharide (*O*-SP):protein conjugates as human anti-bacterial vaccines is in progress on the model bacterium *Shigella flexneri* serotype 5a. Our approach focuses on the use of multivalent constructs involving immunogenic mimics, whether carbohydrate derived or not, of the antigenic polysaccharide. The design of potentially optimal constructs is supported by the investigation at the molecular level of the complementarity between the *O*-SP and homologous protective antibodies. Such an *O*-antigen:antibodies interaction study requires that ligands representative of the major structural features of the *O*-SP of *Shigella flexneri* serotype 5a be available in rather large amounts.

A **B** **C** **D**

→2)-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*-(1→

(1↑3)

E α-D-Glc*p* **I**

A **B** **C** **D**

→2)-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*-(1→

II

The repeating unit of the *O*-SP of *S. flexneri* serotype 5a is the branched pentasaccharide[2,3] **I**, composed of α-linked L-rhamnoses, β-linked 2-acetamido-2-deoxy-D-glucose, and α-D-glucose branches. It comprises the linear tetrasaccharide **II**, which defines the repeating unit of *Shigella flexneri* variant Y *O*-SP.[4-6] The latter has been studied in great detail in D. R. Bundle's group,[7,8] while a lot of work on the *S. flexneri* serotype 5a *O*-antigen has been reported by N. K. Kochetkov's group.[9,10]

α-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-OMe

EBC-OMe **1**

α-L-Rha*p*-(1→2)-[α-D-Glc*p*-(1→3)]-α-L-Rha*p*-(1→3)-α-L-Rha*p*-OMe

A(E)BC-OMe **2**

β-D-GlcNAc*p*-(1→2)-α-L-Rha*p*-(1→2)-[α-D-Glc*p*-(1→3)]-α-L-Rha*p*-(1→3)-α-L-Rha*p*-OMe.

DA(E)BC-OMe **3**

In spite of the large amount of work reported previously in the literature, the preparation of the required synthetic haptens was undertaken.[11,12] In this paper we describe

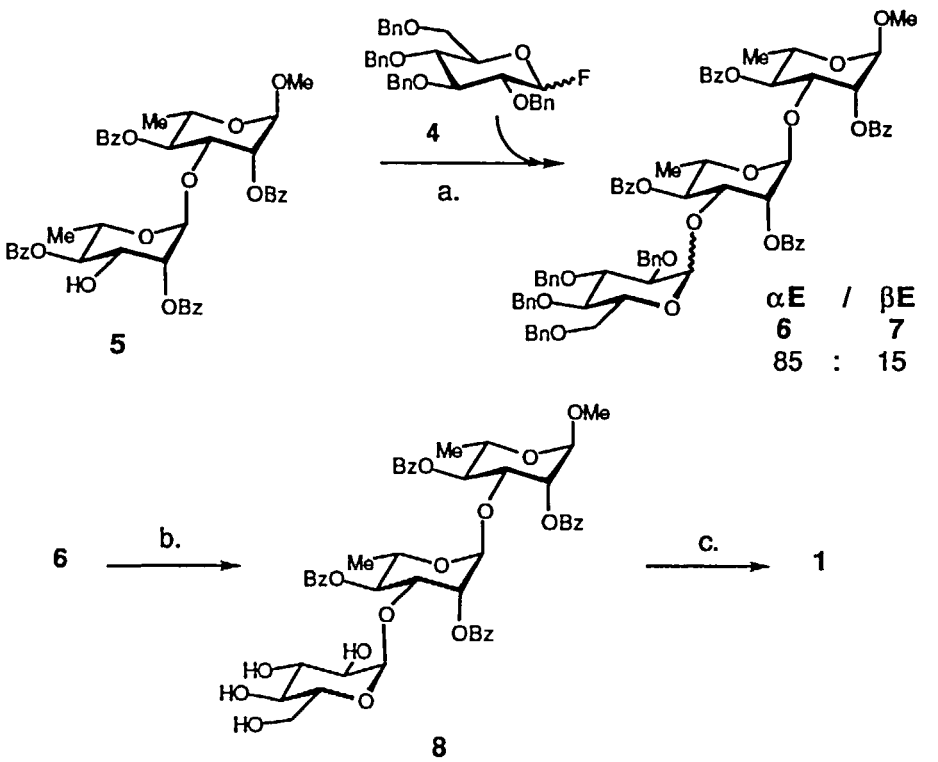
a revised synthesis of the known methyl glycosides of the linear trisaccharide **EBC (1)**,[10] and the branched tetrasaccharide **A(E)BC (2)**.[10] Besides, the synthesis of the previously unknown methyl glycoside of the branched pentasaccharide **DA(E)BC (3)** is also reported. As was the case for the precedent home-made ligands, the target compounds were synthesised as their methyl glycosides to allow binding studies in solution and structural analysis.

RESULTS AND DISCUSSION

A retrosynthetic analysis showed that, as opposed to the blockwise approach, a linear strategy was best suited for the preparation of targets **1**, **2**, and **3**. In that respect, the general strategy to **1** and **2** resembles that described earlier.[10] Anyhow, the choice of the appropriate heterofunctional monosaccharides to be combined, was based on previous experience gained in the laboratory.[11,12] Consequently, synthons involved in the following preparations differ from those used by others.

Synthesis of trisaccharide EBC (1).

The glucosyl fluoride **4** has been used on several occasions as an efficient donor in the construction of 1,2-*cis*-α-D-glucopyranosyl linkages.[13,14] Besides, earlier work in the laboratory[11] showed that, among others, donor **4** was a suitable precursor to residue **E** in the construction of the **EB** linkage. It was prepared, as described,[15] in one step from the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and used in the syntheses described in the following. The easiest access to the target **1** we envisaged was using 2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside **(5)** as a conveniently functionalised key precursor to the **BC** moiety. This known tetra-*O*-benzoyl rhamnobioside was prepared as described previously.[16] Thus (Scheme 1), acceptor **5** was glycosylated with the fluoride donor **4** using anhydrous diethyl ether as the solvent and titanium tetrafluoride (TiF_4) as the Lewis acid promoter[17] in the presence of MS 4Å, to give the fully protected αE- **(6)** and βE- **(7)** trisaccharides as an 85:15 mixture (84%). Separation of the anomers at this stage resulted in pure **6** (60%) together with a slight amount of **7** (10%) and a 5:1 α/β mixture (14%). The anomeric identity of **6** and **7** was assessed based on the measurement of the $^1J_{C,H}$ coupling constants.[18,19] Compound **6** had $^1J_{C,H}$ equal to 167 Hz, 168 Hz, and 172 Hz, while the minor condensation product **7** had $^1J_{C,H}$ equal to 160 Hz, 175 Hz, and 171 Hz for residues **E**, **B**, and **C**, respectively. It should be noted that the α:β ratio obtained here (5.5:1) was slightly better than that obtained for the construction of the **EB** linkage using identical experimental conditions, at the disaccharide level (α/β, 3.7:1).[11] Similarly, the 5.5:1 α/β ratio obtained here was found



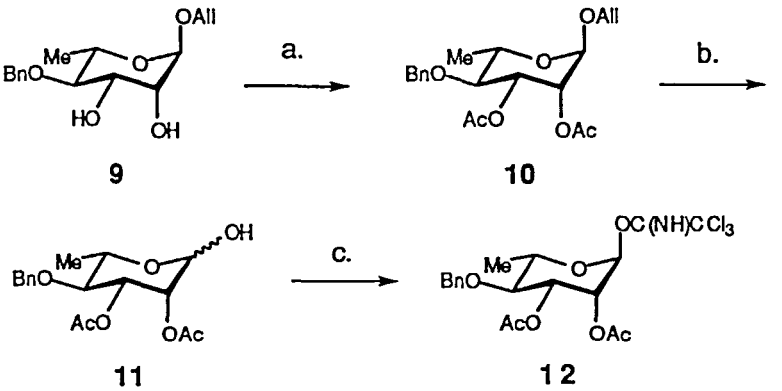
(a) TiF_4, MS 4Å, Et_2O; (b) H_2, Pd/C; (c) MeONa, MeOH.

Scheme 1

acceptable when compared to the 3:1 α/β ratio reported previously in the construction of a closely related trisaccharide using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide as the donor.[10] Next, compound **6** was fully deprotected by (i) hydrogenolysis using Pd-C as the catalyst to give the tetraol **8** (81%), and (ii) Zemplén transesterification which resulted in the target trisaccharide **1** (91%).

The known[20] allyl 4-*O*-benzyl-α-L-rhamnopyranoside (**9**) has a permanent protecting group at position 4 and a temporary blocking group at the anomeric position. It is well suited as a potential rhamnosyl donor allowing subsequent chain extension at positions 2 and 3. Thus, prepared from L-rhamnose in four steps as described,[21] diol **9** was chosen as the key precursor to residue **B**. Conventional acetylation of **9** gave the fully protected **10** (98%) (Scheme 2). The latter was selectively deallylated using palladium(II) chloride as the promoter to afford the hemiacetal **11** (86%) as a 4:1 α/β mixture, as seen on the ^1H NMR

Synthesis of tetrasaccharide A(E)BC (2).



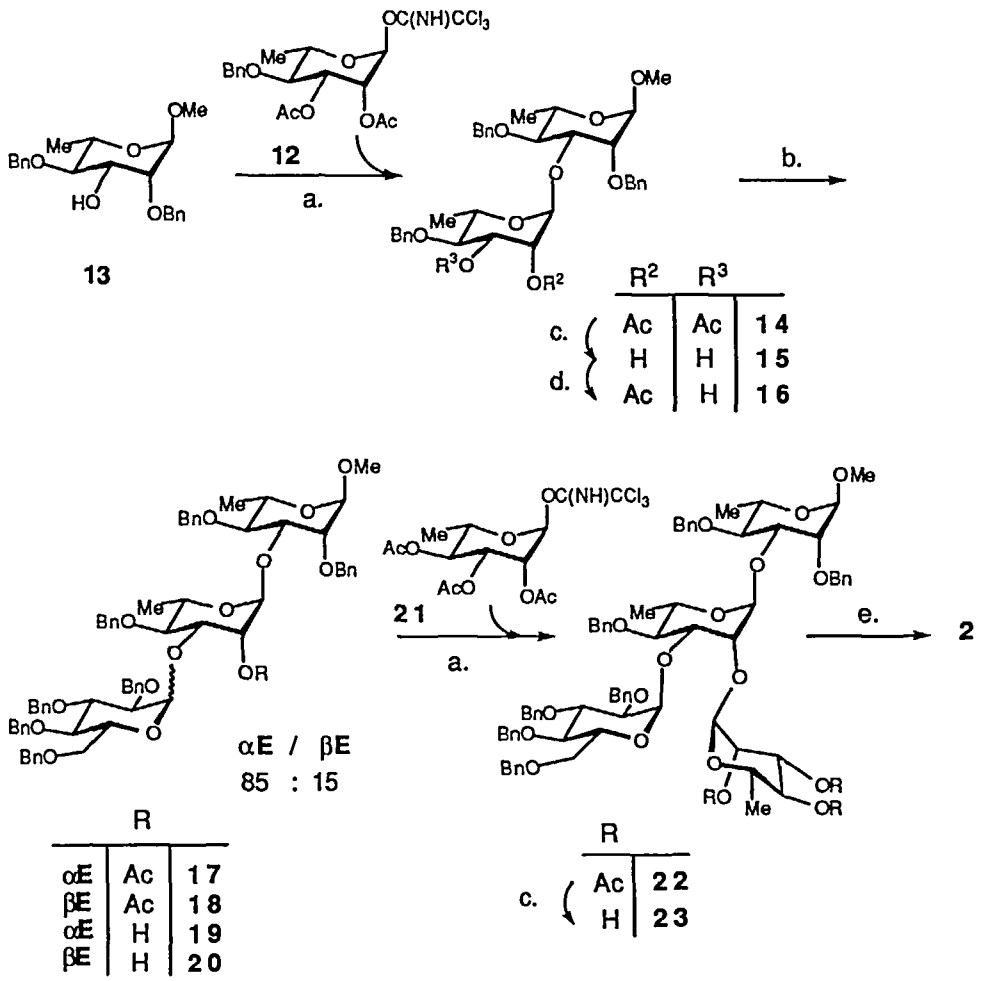
(a) Ac_2O, Pyridine; (b) i. Ir(I) cationic complex, THF; ii. HgO, $HgBr_2$, acetone/water; (c) CCl_3CN, DBU.

Scheme 2

spectrum. Treatment of **11** with trichloroacetonitrile in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the activated intermediate **12** (97%).

Chemoselective *O*-deacetylation of an *O*-benzoylated compound is a well-known process and several procedures have been described in the literature to perform such a transformation. Conditions previously recommended include mildly basic medium using $Mg(OMe)_2$ in methanol,[22] DBU in methanol[23] or methanolic ammonia,[24] as well as acid catalysed methanolysis using methanolic hydrogen chloride in dichloromethane[25,26] or HBF_4 in a mixture of diethyl ether and methanol.[27] Nevertheless, previous work in our laboratory (C. Costachel, unpublished results) showed that, in the *S. flexneri* series, optimisation of such a selective deprotection step was not an easy task. For that reason, the strategy described in the following to prepare target **2** was designed so as to avoid any chemoselective deacylation step. Consequently, the known methyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside[28] (**13**), having non-interfering protecting groups at position 2 and 4, was chosen as the key precursor to residue **C**.

As a result (Scheme 3), acceptor **13** was glycosylated with the trichloroacetimidate donor **12** in anhydrous diethyl ether using TMSOTf as the catalyst to give the rhamnobioside **14** (70%), which was deacetylated under Zemplén conditions[29] into diol **15** (98%). Treatment of the latter with trimethyl orthoacetate under acid catalysis resulted in the 2,3-*O*-orthoacetate intermediate, which was opened regioselectively (80% aq AcOH) to give the corresponding axial acetate **16** quantitatively. Condensation of mono-hydroxylated **16** to donor **4** was achieved under the conditions described for the preparation of **6**. As earlier,



(a)TMSOTf, Et_2O; (b) **4**, TiF_4, MS 4Å, Et_2O; (c) MeONa, MeOH; (d) i. $MeC(OMe)_3$, ii. AcOH 80%; (e) H_2, Pd/C.

Scheme 3

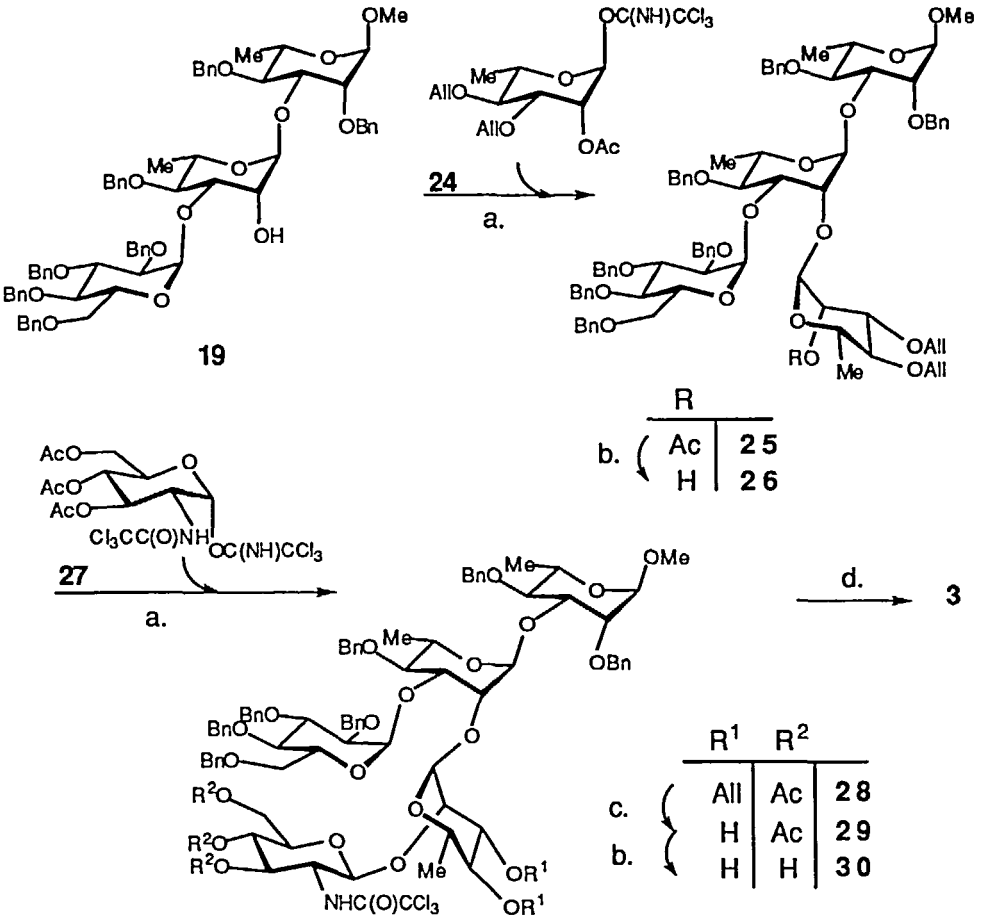
a mixture of αE- (**17**) and βE- (**18**) condensation products was obtained, again in an 85:15 ratio, from which pure **17** could not be isolated. Thus, transesterification (MeONa-MeOH) was performed on the mixture of **17** and **18**. As observed previously,[11] the presence of the tetra-*O*-benzyl-α-D-glucopyranosyl moiety at position 3 of rhamnose **B** renders position 2 of the same residue so hindered that the deacetylation step required 72 h when sodium methoxide was used in stoichiometric amount. Again, the βE anomer **18** proved less hindered than its αE counterpart **17**, resulting in a faster kinetics of deprotection of the former. Repeated chromatography of the deacetylated mixture resulted in the

isolation of the required α-anomer **19** (45%) together with a small amount of the β-anomer **20** (8.7%). The anomeric conformity of the condensation products was ascertained by measuring their $^1J_{C,H}$ coupling constants. Compound **19** had $^1J_{C,H}$ equal to 168 Hz, 170 Hz, and 168 Hz while compound **20** had $^1J_{C,H}$ equal to 160 Hz, 170 Hz, and 167 Hz, for residue **E**, **B**, and **C**, respectively. In this case, the resulting α/β ratio (5.2:1) was comparable to that obtained for the preparation of **6** and **7**, but the yield was much lower. These data support the general idea that the outcome of α-D-glucosylation, as that of other glycosylation reactions, is case-specific. Other coupling conditions may be required in the future for the preparation of new sequences in the series.

In the previous report[10] on the synthesis of the tetrasaccharide **2**, the construction of the **AB** linkage was based on the condensation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→ 3)-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→ 3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside and acetobromorhamnose. Although the condensation was attempted in the presence of a large variety of promoters, it proved really sluggish. This outcome was attributed for the most part to the lack of reactivity of the bromide donor. In the following, condensation of the trisaccharide acceptor **19** and the easily accessible chain terminator[30] **21**, in association with a catalytic amount of TMSOTf promoter, proceeded satisfactorily in diethyl ether to give the fully protected tetrasaccharide **22** in 75% yield. Thus, the former drawback was partly overcome when using the trichloroacetimidate methodology. Zemplén deacetylation of **22** gave the triol **23** (98%), which was further hydrogenolyzed into the free tetrasaccharide **2** (77%).

Synthesis of pentasaccharide DA(E)BC (3).

Previous results[11] have shown that a suitable precursor to residue **A** in the synthesis of the target **3** should fulfil two requirements: (i) bear an orthogonal protecting group at position 2, which should act as a participating group, and (ii) have blocking groups of low bulk at positions 3 and 4. Previous work in this series has shown that the introduction of allyl protecting groups at these positions was a satisfactory answer to this second requirement. Thus, the known[11] 2-*O*-acetyl-3,4-di-*O*-allyl-α-L-rhamnopyranosyl trichloroacetimidate (**24**), allowing regioselective chain elongation at position 2, was chosen as an appropriate precursor to residue **A**. In a similar way, the choice of the key precursor to residue **D** was based on previous work from our laboratory. In fact, among several known glucosaminyl donors tested, the trichloroacetimidate precursor bearing an *N*-trichloroacetyl protecting group was found the best one in terms of accessibility, condensation yield and deprotection facilities.[11] Therefore, 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl trichloroacetimidate,[31] (**27**) was used in the following synthesis, as well.



(a) TMSOTf, Et_2O; (b) MeONa, MeOH; (c) i. Ir(I) cationic complex, THF; ii. HgO, $HgBr_2$, acetone/water; (d) i. H_2, Pd/C, AcOH/EtOH, ii. H_2, Pd/C, Et_3N, EtOH.

Scheme 4

Consequently (Scheme 4), the trisaccharide acceptor **19** was condensed to the trichloroacetimidate donor **24** in anhydrous diethyl ether, using TMSOTf as the promoter. Next, the resulting fully protected tetrasaccharide **25** (94%) was deacetylated smoothly under Zemplén conditions into the mono-hydroxylated **26** (98%). Glycosylation of the latter with the glucosaminyl trichloroacetimidate donor **27**, performed in anhydrous acetonitrile in the presence of a catalytic amount of TMSOTf, proceeded satisfactorily to give the fully protected pentasaccharide **28** (81%), which was next deprotected sequentially. Deallylation of **28** was performed first, accordingly to the cationic iridium based two-step process, (i) isomerisation of the allyl group under catalysis with 1,5-

cyclooctadiene-bis(methyldiphenylphosphine)iridium hexafluorophosphate complex,[32] and (ii) subsequent hydrolysis of the resulting prop-1-enyl ether.[20] The resulting diol **29** (79%) was *O*-deacylated under careful control (MeONa-MeOH) into the pentaol **30** (95%). Lastly, the intermediate **30** was fully deprotected into the target **3** (74%) *via* a two-step hydrogenolysis using Pd-C as the catalyst. First, removal of the benzyl groups was conducted in an acidic medium, and second, reduction of the trichoroacetyl group was completed in a slightly basic medium.

The reaction products were characterised by fully assigned ^{1}H and ^{13}C NMR spectra. Assignment of the ^{1}H NMR spectra was made possible by analysis of the experimental subspectra generated when running selective TOCSY experiments[33] to identify sets of signals attributed to individual rings, followed by unambiguous identification of one of the signals for each residue in one particular compound. Next, the assignment of the ^{13}C NMR spectra, the assignment of the $^{13}C\{^{1}H\}$ NMR signals followed directly from the analysis of the ^{13}C-^{1}H chemical shift correlated spectrum. As observed earlier for several synthetic intermediates used in the construction of the methyl glycosides of the **DA(E)B** and **CDA(E)B** fragments,[11,12] signal distortion was apparent in the spectrum of some of the above described intermediates. Carbons associated to these distorted signals were C-3_C, C-4_B and C-1_B, but contrary to previous observations, in the **DA(E)BC** series, distortion was only minor. This was rather unexpected considering the close resemblance of the involved intermediates. Such an observation suggests that residue **C** has a strong favourable impact on the overall conformation of the oligosaccharides, whether protected or not, when involved in the **BC** linkage. Further NMR studies on several sequences representative of the *O*-SP of *S. flexneri* are in progress. They may help our understanding of the conformational behaviour of the polysaccharide.

EXPERIMENTAL

General Methods. General experimental methods not referred to in this section were as described previously.[12] TLC on precoated slides of Silica Gel 60 F_{254} (Merck) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A*, dichloromethane-methanol; *B*, cyclohexane-ethyl acetate, *C*, cyclohexane-acetone, *D*, cyclohexane-diethyl ether, *E*, toluene-ethyl acetate, *F*, dichloromethane-diethyl ether, *G*, water-acetonitrile, *H*, *iso*-propyl alcohol-ammonia-water. Detection was effected when applicable, with UV light, and/or by charring with orcinol (35 mM) in 4N aq H_2SO_4. In the NMR spectra, of the two magnetically non-equivalent geminal protons at C-6, the one resonating at lower field is denoted H-6a and the one at higher field is denoted H-6b. Interchangeable assignments in the ^{13}C NMR spectra are marked with an asterisk in listing

of signal assignments. Sugar residues in oligosaccharides are serially lettered according to the lettering of the repeating unit of the *O*-SP and identified by a subscript in listing of signal assignments. Low-resolution mass spectra were obtained by either chemical ionisation (CIMS) using NH_3 as the ionising gas, by electrospray mass spectrometry (ESMS), or by fast atom bombardment mass spectrometry (FABMS).

Methyl (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→ 3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (6) and Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-(1→ 3)-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→ 3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (7). A solution of the tetra-*O*-benzoyl acceptor[16] **5** (1.20 g, 1.62 mmol), the fluoride donor[15,34] **4** (1.76 g, 3.25 mmol), and MS 4Å (4.0 g) in anhydrous Et_2O (25 mL) was stirred at 0 °C for 20 min. Titanium tetrafluoride (TiF_4, 1.83 g, 14.7 mmol) was added, and the mixture was stirred for 16 h at 0 °C. As no starting material could be detected (solvent *E*, 94:6), the reaction mixture was filtered over a bed of Celite. The organic phase was washed successively with satd aq $NaHCO_3$, water, and satd aq NaCl, then dried and concentrated to dryness. Column chromatography of the crude material (solvent *E*, 96:4) gave the β-anomer **7** (205 mg, 10%) as the first eluting product and the α-anomer **6** (1.22 g, 60%) as the slower moving product, together with a 5:1 α/β mixture (286 mg, 14%). Compound **6**, isolated as a colourless foam, had $[\alpha]_D$ +94° (*c* 1.0); ^{1}H NMR: δ 8.23-6.89 (m, 40H, Ph), 5.61 (dd, 1H, $J_{3,4}$ = 9.9, $J_{4,5}$ = 9.9 Hz, H-4$_C$), 5.52 (dd, 1H, $J_{1,2}$ = 1.6, $J_{2,3}$ = 3.3 Hz, H-2$_C$), 5.39 (dd, 1H, $J_{3,4}$ = 9.7, $J_{4,5}$ = 9.7 Hz, H-4$_B$), 5.25 (s, 1H, H-1$_B$), 5.14 (dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 3.2 Hz, H-2$_B$), 4.90 (d, 1H, H-1$_C$), 4.56 (d, 1H, J = 11.2 Hz, OCH_2), 4.51 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1$_E$), 4.49 (dd, 1H, $J_{3,4}$ = 10.5 Hz, H-3$_C$), 4.38-4.28 (m, 3H, 3 OCH_2), 4.22 (d, 1H, J = 11.2 Hz, OCH_2), 4.14-3.93 (m, 6H, 3 OCH_2, H-5$_C$, 3$_B$, 5$_B$), 3.55 (dd, 1H, $J_{3,4}$ = 8.7 Hz, H-3$_E$), 3.48 (s, 3H, OCH_3), 3.41 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4$_E$), 3.38 (m, 1H, H-5$_E$), 3.15 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2$_E$), 3.08 (dd, 1H, $J_{5,6a}$ = 1.6, $J_{6a,6b}$ = 10.9 Hz, H-6a$_E$), 2.83 (d, 1H, H-6b$_E$), 1.38 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6$_C$), and 1.15 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6$_B$); ^{13}C NMR: δ 165.1, 166.0, 165.6, 165.4 (C=O), 133.4-125.2 (Ph), 99.4 (C-1$_B$, $J_{C,H}$ = 168 Hz), 98.3 (C-1$_C$, $J_{C,H}$ = 172 Hz), 95.8 (C-1$_E$, $J_{C,H}$ = 167 Hz), 81.3 (C-3$_E$), 78.4 (C-2$_E$), 76.7 (C-4$_E$), 76.1 (C-3$_C$), 75.0, 74.2 (2C, 2 OCH_2), 73.2 (2C, OCH_2, C-3$_B$), 73.2 (C-4$_C$), 72.3 (2C, C-2$_C$, 4$_B$), 72.0 (OCH_2), 70.7 (C-5$_E$), 69.8 (C-2$_B$), 67.4 (C-6$_E$), 67.3 (C-5$_B$), 66.7 (C-5$_C$), 55.2 (OCH_3), 17.7 (C-6$_C$), and 17.4 (C-6$_B$); CIMS for $C_{75}H_{74}O_{18}$ (M, 1262.5) *m/z* 1280.7 $[M+NH_4]^+$.

Anal. Calcd for $C_{68}H_{76}O_{14}$: C, 71.30; H, 5.90%. Found: C, 71.46; H, 6.02%.

Compound **7**, isolated as a colourless foam, had $[\alpha]_D$ +84° (*c* 1.0); ^{1}H NMR: δ 8.45-6.87 (m, 40H, Ph), 5.65 (dd, 1H, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8 Hz, H-4$_C$), 5.57 (dd, 1H,

$J_{1,2}$ = 1.6, $J_{2,3}$ = 3.3 Hz, H-2_C), 5.51 (dd, 1H, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8 Hz, H-4_B), 5.26 (s, 2H, H-2_B, 1_B), 4.93 (s, 1H, H-1_C), 4.68-4.57 (m, 3H, OCH_2), 4.52-4.43 (m, 3H, H-3_C, 2 OCH_2), 4.30 (d, 1H, J = 10.5 Hz, OCH_2), 4.25 (m, 2H, OCH_2, H-3_B), 4.16 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1_E), 4.10 (dq, 1H, H-5_C), 4.01 (m, 2H, OCH_2, H-5_B), 3.55 (dd, partially overlapped, 1H, H-4_E), 3.49 (s, 3H, OCH_3), 3.43 (dd, 1H, $J_{5,6a}$ = 2.4, $J_{6a,6b}$ = 11.5 Hz, H-$6a_E$), 3.29 (dd, 1H, $J_{3,4}$ = 9.1, $J_{2,3}$ = 9.1 Hz, H-3_E), 3.19 (dd, 1H, H-2_E), 3.03 (d, 1H, H-$6b_E$), 2.64 (m, 1H, H-5_E), 1.39 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_C), and 1.10 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_B); ^{13}C NMR: δ 166.0, 165.9, 165.6, 165.4 (4C, C=O), 138.7-127.0 (Ph), 104.6 (C-1_E, $J_{C,H}$ = 160 Hz), 99.0 (C-1_B, $J_{C,H}$ = 175 Hz), 98.4 (C-1_C, $J_{C,H}$ = 171 Hz), 84.1 (C-3_E), 81.4 (C-2_E), 76.9 (C-4_E), 76.4 (C-3_C), 75.8 (C-3_B), 75.3 (OCH_2), 74.7 (C-5_E), 74.6, 74.1, 73.2 (3C, 3 OCH_2), 73.0 (C-4_C), 72.6 (C-4_B), 72.3 (2C, C-2_B, 2_C), 68.1 (C-6_E), 67.6 (C-5_B), 66.5 (C-5_C), 55.3 (OCH_3), 17.8 (C-6_C), and 17.4 (C-6_B); CIMS for $C_{75}H_{74}O_{18}$ (M, 1262.5) *m/z* 1280.7 $[M+NH_4]^+$.

Anal. Calcd for $C_{75}H_{74}O_{18}$: C, 71.30; H, 5.90%. Found: C, 71.46; H, 5.92%.

Methyl α-D-Glucopyranosyl-(1→3)-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (8). A suspension of Pd-C catalyst (200 mg) in a 4:1 mixture of ethanol and acetic acid (10 mL) containing the fully protected **6** (280 mg, 0.22 mmol) was stirred for 72 h under a hydrogen atmosphere. The suspension was filtered on a bed of Celite, and volatiles were concentrated by repeated coevaporation with cyclohexane. To remove any residual trace of catalyst, the residue was purified on a short column of silica gel (solvent *A*, 97:3) to give the tetraol **8** (160 mg, 81%) as a colourless foam: $[\alpha]_D$ +137° (*c* 1.0); ^1H NMR: δ 8.24-7.19 (m, 20H, Ph), 5.57 (dd, 1H, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8 Hz, H-4_C), 5.50 (bs, 1H, H-2_C), 5.20 (dd, 1H, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8 Hz, H-4_B), 5.11 (s, 1H, H-1_B), 5.06 (bs, 1H, H-2_B), 4.90 (bs, 1H, H-1_C), 4.48 (bs, 1H, H-1_E), 4.38 (dd, 1H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.8 Hz, H-3_C), 4.25 (dd, 1H, $J_{2,3}$ = 2.7, $J_{3,4}$ = 9.8 Hz, H-3_B); 4.08 (dq, 1H, H-5_C), 3.99 (dq, 1H, H-5_B), 3.46 (s, 3H, OCH_3), 3.42 (m, 2H, H-$6a_E$, $6b_E$), 3.21 (m, 1H, H-5_E), 3.03 (m, 3H, H-2_E, 3_E, 4_E), 1.35 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_C), and 1.05 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6_B); ^{13}C NMR: δ 166.2, 166.0, 165.7 (4C, 4 C=O), 133.6-128.5 (Ph), 99.0 (C-1_B), 98.3 (C-1_C), 94.8 (C-1_E), 76.9 (C-3_C), 74.2 (C-3_E*), 73.1 (C-4_C), 72.2 (C-5_E), 72.1 (2C, C-2_C, 4_B), 71.9 (C-2_E*), 71.2 (C-3_B), 69.9 (C-4_E), 68.3 (C-2_B), 67.6 (C-5_B), 66.3 (C-5_C), 62.2 (C-6_E), 55.4 (OCH_3), 17.6 (C-6_C), and 17.3 (C-6_B); CIMS for $C_{47}H_{50}O_{18}$ (M, 902.3) m/z 920.5 $[M+NH_4]^+$.

The compound could not be obtained solvent-free (containing 0.5 H_2O per mol according to C,H analysis) and was further characterised as deprotected compound **1**.

Methyl α-D-Glucopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (1). 1M methanolic sodium methoxide (200 μL) was added to a

solution of **8** (270 mg, 0.3 mmol) in methanol (3 mL) and the solution was stirred at rt for 24 h. After neutralisation with Amberlite IR-120 (H^+); filtration and evaporation of the solvent, the oily residue was solubilised in a mixture of water and dichloromethane and extracted with dichloromethane. The aq phase was lyophilised and the residue was purified by reverse phase chromatography (solvent *G*, gradient 100:0 → 97:3) to give, after lyophilisation, the target trisaccharide **1** as an amorphous powder (133 mg, 91%); $[\alpha]_D$ +17° (*c* 0.9, methanol), lit.[10] $[\alpha]_D$ +15° (*c* 1.1, methanol); ^1H NMR: δ 5.08 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1_E), 5.06 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1_B), 4.65 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1_C), 4.25 (dd, 1H, H-2_B), 4.00 (dd, partially overlapped, 1H, $J_{2,3}$ = 3.2 Hz, H-2_C), 3.97 (ddd, 1H, $J_{5,6a}$ = 2.9, $J_{5,6b}$ = 3.6 Hz, H-5_E), 3.90 (dd, 1H, $J_{2,3}$ = 3.1, $J_{3,4}$ = 9.8 Hz, H-3_B), 3.83 (dq, partially overlapped, 1H, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2 Hz, H-5_B), 3.80-3.73 (m, 4H, H-3_C, 3_E, $6a_E$, $6b_E$), 3.69 (dq, 1H, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.3 Hz, H-5_C), 3.57 (m, 2H, H-2_E, 4_B), 3.51 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-4_C), 3.45 (dd, 1H, $J_{3,4}$ = 9.6, $J_{4,5}$ = 10.1 Hz, H-4_E), 3.39 (s, 3H, OCH_3), and 1.29 (d, 6H, H-6_B, 6_C). The ^{13}C NMR spectrum was identical to that described.[10] CIMS for $C_{19}H_{34}O_{14}$ (M, 486.2) *m/z* 504.3 $[M+NH_4]^+$.

Allyl 2,3-Di-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranoside (10). Acetic anhydride (29 mL, 310 mmol) was added dropwise, at 0 °C, to a solution of diol[20,21] **9** (30.75 g, 104.6 mmol) in pyridine (150 mL). The mixture was stirred overnight at rt. Methanol (30 mL) was added, and stirring was continued for 2 h. Solvents were evaporated and the residue, taken up in CH_2Cl_2, was washed successively with 5% aq HCl, water, 5% $NaHCO_3$, water, and satd aq NaCl. Chromatography of the crude mixture (solvent *B*, 80:20) gave di-*O*-acetylated **10** (38.26 g, 98%) as a colourless oil: $[\alpha]_D$ –51° (*c* 1.0); ^1H NMR: δ 7.38-7.27 (m, 5H, Ph), 5.86 (m, 1H, C*H*=CH_2), 5.35 (dd, partially overlapped, 1H, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.7 Hz, H-3), 5.29 (m, 1H, CH=CH_2), 5.27 (dd, partially overlapped, 1H, H-2), 5.20 (m, 1H, CH=CH_2), 4.74 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 4.70 (d, 1H, OCH_2), 4.16 (m, 1H, CH_2CH), 3.98 (m, 1H, CH_2CH), 3.87 (dq, 1H, $J_{4,5}$ = 9.5 Hz, H-5), 3.51 (dd, 1H, H-4), 2.15 (s, 3H, C(=O)CH_3), 1.99 (s, 3H, C(=O)CH_3), and 1.35 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR: δ 170.0, 169.8 (2C, C=O), 138.0-127.8 (Ph), 117.8 (CH=CH_2), 96.4 (C-1), 78.9 (C-4), 75.1 (OCH_2), 71.7 (C-3), 70.5 (C-2), 68.1 (OCH_2), 67.7 (C-5), 21.8, 21.7 (2C, C(=O)CH_3), and 17.7 (C-6); CIMS for $C_{20}H_{26}O_7$ (M, 378.2) *m/z* 396 $[M+NH_4]^+$.

Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93%. Found: C, 63.31; H, 7.20%.

2,3-Di-*O*-acetyl-4-*O*-benzyl-α/β-L-rhamnopyranose (11). 59% Palladium (II) chloride (10.52 g, 33.2 mmol) was added to a mixture of **10** (10.24 g, 27.5 mmol) and sodium acetate (16.83 g, 123.7 mmol) in acetic acid (58 mL) containing water (6.5 mL). The mixture was stirred in the dark for 10 h at rt. Et_3N was added and solvents were evaporated. The residue, taken up in ethyl acetate, was washed 3 times with satd aq

$NaHCO_3$, then with satd aq NaCl. Chromatography of the crude mixture (solvent *B*, 75:25 → 60:40, containing 0.1% Et_3N) gave hemiacetal **11** (7.99 g, 86%) as a colourless foam. Compound **11** was isolated as a 4:1 α/β mixture as seen on the ^1H NMR spectrum. ^1H NMR: δ (α-anomer) 7.37-7.27 (m, 5H, Ph), 5.37 (dd, 1H, $J_{2,3}$ = 3.3, $J_{3,4}$ = 9.8 Hz, H-3), 5.25 (dd, 1H, $J_{1,2}$ = 1.8 Hz, H-2), 5.07 (dd, 1H, $J_{1,OH}$ = 3.9 Hz, H-1), 4.70 (d, 1H, J = 10.7 Hz, OCH_2), 4.64 (d, 1H, OCH_2), 4.10 (d, overlapped, 1H, OH-1), 4.09 (dq, partially overlapped, 1H, H-5), 3.51 (dd, 1H, H-4), 2.19 (s, 3H, $C(=O)CH_3$), 1.97 (s, 3H, $C(=O)CH_3$), and 1.33 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR: δ (α-anomer) 170.2, 170.0 (2C, C=O), 138.0-127.7 (Ph), 92.1 (C-1), 78.7 (C-4), 75.0 (OCH_2), 71.4 (C-3), 70.7 (C-2), 67.8 (C-5), 20.8 (2C, $C(=O)CH_3$), and 17.8 (C-6); ^{13}C-NMR: δ (β-anomer) 170.7, 163.6 (2C, C=O), 137.9-127.6 (Ph), 92.5 (C-1), 78.0 (C-4), 75.2 (OCH_2), 73.7 (C-5), 71.9 (C-3), 70.9 (C-2), 20.8 (2C, $C(=O)CH_3$), and 17.7 (C-6); CIMS for $C_{17}H_{22}O_7$ (M, 338.4) *m/z* 356 $[M+NH_4]^+$.

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55%. Found: C, 60.18; H, 6.55%.

2,3-Di-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl trichloroacetimidate (12). DBU (250 μL, 1.7 mmol) was added to a solution of hemiacetal **11** (3.09 g, 9.1 mmol) in a mixture of anhydrous CH_2Cl_2 (10 mL) and trichloroacetonitrile (5 mL, 50 mmol), and the solution was stirred at rt, under an inert atmosphere, for 30 min. Volatiles were evaporated, and the residue was coevaporated twice with toluene. The crude mixture was flash-chromatographed (solvent *B*, 70:30, containing Et_3N 0.1%) to give **12** (4.85 g, 97%). Crystallisation of an analytical sample in a mixture of isopropyl ether and petroleum ether gave **12** as highly hygroscopic white needles (mp could not be measured); $[\alpha]_D$ –47° (*c* 1.0); ^1H NMR: δ 8.68 (s, 1H, NH), 7.37-7.17 (m, 5H, Ph), 6.17 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 5.47 (dd, 1H, H-2), 5.39 (dd, 1H, $J_{2,3}$ = 3.4, $J_{3,4}$ = 9.6 Hz, H-4), 4.74 (d, 1H, J = 11.1 Hz, OCH_2), 4.66 (d, 1H, OCH_2), 4.07 (dq, 1H, $J_{4,5}$ = 9.4 Hz, H-1_E), 3.61 (dd, 1H, H-4), 2.19 (s, 3H, $(C=O)CH_3$), 2.01 (s, 3H, $(C(=O)CH_3)$, 1.39 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR: δ 169.7 (2C, 2 C=O), 160.1 (C=NH) 137.6-125.2 (Ph), 94.8 (C-1), 90.6 (CCl_3), 78.1 (C-4), 75.3 (CH_2), 71.3 (C-3), 70.7 (C-2), 68.7 (C-5), 20.7 (2C, 2 $C(=O)CH_3$), and 17.9 (C-6).

Anal. Calcd for $C_{19}H_{22}Cl_3NO_7$: C, 47.27; H, 4.59; N, 2.90%. Found: C, 47.90; H, 4.93; N, 3.07%.

Methyl (2,3-Di-*O*-acetyl-4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→ 3)-2, 4-di-*O*-benzyl-α-L-rhamnopyranoside (14). A solution of the rhamnopyranoside acceptor[35] **13** (7.40 g, 20.67 mmol) and the trichloroacetimidate donor **12** (12.97 g, 26.87 mmol) in anhydrous Et_2O (100 mL) was stirred at -78 °C for 30 min. TMSOTf (280 μL, 0.07 eq) was added, and the mixture was stirred for 15 h while slowly warming up to rt. As no starting material could be detected (solvent *F*, 9:1), Et_3N (500 μL) was added and the

solvent was evaporated. Chromatography of the crude mixture (solvent *C*, 89:11) gave the fully protected disaccharide **14** (9.84 g, 70%) as a colourless glass which crystallised on standing. A sample was recrystallised for analytical purpose; mp 77-78 °C (isopropyl ether-petroleum ether); $[\alpha]_D$ –53° (*c* 1.0); ^{1}H NMR: δ 7.44-7.22 (m, 15H, Ph), 5.43 (dd, partially overlapped, 1H, $J_{2,3}$ = 3.4 Hz, H-3_B), 5.41 (bs, overlapped, 1H, H-2_B), 5.06 (bs, 1H, H-1_B), 4.82 (d, 1H, J = 11.1 Hz, OCH_2), 4.76 (d, 2H, OCH_2), 4.70 (d, 1H, J = 11.4 Hz, OCH_2), 4.67 (bs, 1H, H-1_C), 4.62 (d, 1H, J = 11.1 Hz, OCH_2), 4.06 (m, 1H, H-3_C), 3.88 (dq, 1H, $J_{4,5}$ = 9.4 Hz, H-5_B), 3.71 (dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 2.9 Hz, H-2_C), 3.66 (m, 2H, H-4_C, 5_C), 3.48 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-4_B), 3.32 (s, 3H, OCH_3), 2.06 (s, 3H, C(=O)CH_3), 1.99 (s, 3H, C(=O)CH_3), 1.32 (d, 3H, $J_{5,6}$ = 5.6 Hz, H-6_C), and 1.27 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_B); ^{13}C NMR: δ 169.8, 169.7 (2C, C=O), 138.3-127.6 (Ph), 99.2 (C-1_B), 98.6 (C-1_C), 80.9 (C-4_C), 78.8 (C-4_B), 77.9 (C-3_C), 77.6 (C-2_C), 75.3, 74.8, 72.8 (3C, 3 OCH_2), 71.7 (C-3_B), 70.4 (C-2_B), 68.2 (C-5_B), 68.0 (C-5_C), 54.7 (OCH_3), 20.9, 20.8 (2C, C(=O)CH_3), and 18.0 (2C, C-6_B, 6_C); ESMS of $C_{38}H_{46}O_{11}$ (M, 678.3) *m/z* 679.3 $[M+H]^+$.

Anal. Calcd for $C_{38}H_{46}O_{11}$: C, 67.24; H, 6.83%. Found: C, 67.14; H, 6.85%.

Methyl (4-*O*-Benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (15). 1N Methanolic sodium methoxide was added dropwise to a solution of the fully protected disaccharide **14** (8.56 g, 12.6 mmol) in a mixture of methanol and dichloromethane (9:1, 50 mL) until pH 10 was reached. The mixture was stirred at rt for 15 h, neutralised with resin IR 120 (H^+), filtered, and concentrated. The crude material was column chromatographed (solvent *C*, 85:15) to give the diol **15** (7.35 g, 98%) as a colourless glass, $[\alpha]_D$ –44° (*c* 1.0); ^{1}H NMR: δ 7.41-7.23 (m, 15H, Ph), 5.08 (bs, 1H, H-1_B), 4.77-4.69 (m, 6H, 6 OCH_2), 4.66 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1_C), 4.04 (dd, 1H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.2 Hz, H-3_C), 3.92 (m, partially overlapped, 1H, H-3_B), 4.89 (m, overlapped, 1H, H-2_B), 3.81 (dq, 1H, $J_{4,5}$ = 9.4 Hz, H-5_B), 3.70 (dd, 1H, H-2_C), 3.64 (m, partially overlapped, 1H, H-5_C), 3.59 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4_C), 3.32 (m, 4H, H-4_B, OCH_3), 2.28 (d, 1H, $J_{OH,3}$ = 5.2 Hz, OH-3_B), 2.06 (d, 1H, $J_{OH,2}$ = 3.7 Hz, OH-2_B), 1.34 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_C), and 1.28 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6_B); ^{13}C NMR: δ 128.6-127.7 (Ph), 101.2 (C-1_C), 98.6 (C-1_B), 81.6 (C-4_B), 81.3 (C-4_C), 77.9 (C-3_C), 77.8 (C-2_C), 75.3, 74.8, 72.7 (3C, 3 OCH_2), 71.5 (C-3_B*), 71.3 (C-2_B*), 68.0 (C-5_C), 67.8 (C-5_B), 54.7 (OCH_3) and 18.0 (2C, C-6_B, 6_C); ESMS of $C_{34}H_{42}O_9$ (M, 594.3) *m/z* 595.3 $[M+H]^+$.

Anal. Calcd for $C_{34}H_{42}O_9$: C, 68.67; H, 7.12%. Found: C, 68.52; H, 7.24%.

Methyl (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1 → 3)-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (19) and Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-(4-

***O*-benzyl-α-L-rhamnopyranosyl)-(1→ 3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (20).** *p*TsOH (40 mg, 0.2 mmol) was added to a solution of the diol **15** (6.36 g, 10.7 mmol) in a mixture of trimethyl orthoacetate (6.5 mL, 50.9 mmol) and anhydrous acetonitrile (25 mL). The reaction mixture was stirred at rt for 1.5 h, after which TLC (solvent *C*, 6:1) showed that no starting material remained. The reaction mixture was cooled to 0 °C and 80% aq acetic acid was added. Stirring was continued for 1.25 h at this temperature. Water (330 mL) was added, and the aq phase was extracted with CH_2Cl_2. Concentration of the organic phase gave the crude monoacetate **16**, isolated as a colourless oil, in quantitative yield. Compound **16** had ^{1}H NMR: δ 7.43-7.24 (m, 15H, Ph), 5.26 (dd, 1H, $J_{1,2}$ = 1.6 Hz, H-2_B), 5.07 (d, 1H, H-1_B), 4.84 (d, 1H, J = 11.3 Hz, OCH_2), 4.82 (d, 1H, J = 11.0 Hz, OCH_2), 4.72 (bs, 2H, OCH_2), 4.69 (d, 1H, J = 9.0 Hz, OCH_2), 4.66 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1_C), 4.62 (d, 1H, J = 11.1 Hz, OCH_2), 4.14 (dd, 1H, $J_{2,3}$ = 3.5, $J_{3,4}$ = 9.4 Hz, H-3_B), 4.05 (dd, 1H, $J_{2,3}$ = 3.1, $J_{4,5}$ = 8.9 Hz, H-3_C), 3.83 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-5_B), 3.69 (dd, 1H, H-2_C), 3.66 (m, partially overlapped, 1H, H-5_C), 3.64 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4_C), 3.35 (dd, 1H, H-4_B), 3.31 (s, 3H, OCH_3), 2.09 (s, 3H, C(=O)CH_3), 1.30 (d, 3H, $J_{5,6}$ = 5.7 Hz, H-6_C), and 1.29 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_B); ^{13}C NMR: δ 170.7 (C=O), 138.3-127.6 (Ph), 99.1 (C-1_B), 98.5 (C-1_C), 81.5 (C-4_B), 81.0 (C-4_C), 77.7 (C-2_C*), 77.6 (C-3_C*), 75.2, 75.0 (2C, 2 OCH_2), 72.7 (2C, C-2_B, OCH_2), 70.33 (C-3_B), 68.0 (2C, C-5_B, 5_C), 54.7 (OCH_3), 20.6 (C(=O)CH_3), and 17.9 (2C, C-6_B, 6_C).

A solution of the crude disaccharide **16** (from **15**, 6.36 g, 10.7 mmol), donor **5** (8.8 g, 16.2 mmol), and MS 4Å (20 g) in anhydrous Et_2O (250 mL) was stirred at -78 °C for 30 min. TiF_4 (6.63 g, 53.5 mmol) was added, and the mixture was stirred for 15 h while slowly warming up to rt. As hardly any starting material could be detected (solvent *B*, 3.2:1), the reaction mixture was filtered over a bed of Celite and worked up as described for the preparation of trisaccharides **6** and **7**. Chromatography of the crude material (solvent *C*, 88:12) gave a mixture (16.5 g) of, among others, the fully protected condensation products **17** and **18**, which could not be separated at this stage. The residue was then solubilized in a methanol:CH_2Cl_2 (1:1, 160 mL) solution, and methanolic 1N sodium methoxide (66 mL) was added at rt. Stirring was continued for 72 h, after which TLC (solvent *D*, 96:4; solvent *B*, 3:1) showed that no starting material remained. Neutralisation with resin IR 120 (H^+) was followed by filtration and concentration to dryness of the organic phase. Repeated column chromatography of the residue (solvent *E*, gradient; solvent *B*, gradient) gave the α-anomer **19** (5.37 g, 45% from **15**) as the first eluting product and the β-anomer **20** (950 mg, 8% from **15**) as the slower moving product, together with a 1:1 α/β mixture (225 mg, 1.8% from **15**).

Compound **19**, isolated as a colourless glass, had $[\alpha]_D$ +22° (*c* 1.0); ^{1}H NMR: δ 7.40-7.13 (m, 35H, Ph), 5.31 (bs, 1H, H-1_B), 4.97-4.45 (m, 13H, OCH_2), 4.90 (d,

partially overlapped, 1H, H-1_E), 4.65 (bs, 1H, partially overlapped, H-1_C), 4.26 (d, 1H, J = 12.0 Hz, OCH_2), 4.15-4.02 (m, 4H, H-3_C, 3_B, 2_B, 3_E), 3.94 (m, 1H, H-5_E), 3.84 (dq, 1H, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.0 Hz, H-5_B), 3.73 (dd, 1H, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.3 Hz, H-4_E), 3.70 (bd, 1H, H-2_C), 3.66 (m, partially overlapped, 1H, H-5_C), 3.60 (dd, partially overlapped, 1H, $J_{4,5}$ = 9.1 Hz, H-4_C), 3.58 (dd, 1H, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.7 Hz, H-2_E), 3.51 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-4_B), 3.43 (dd, 1H, $J_{5,6a}$ = 2.4, $J_{6a,6b}$ = 11.0 Hz, H-$6a_E$), 3.32 (s, 3H, OCH_3), 3.30 (m, partially overlapped, 1H, H-$6b_E$), 1.33 (d, 3H, $J_{5,6}$ = 5.8 Hz, H-6_C), and 1.31 (d, 3H, H-6_B); ^{13}C NMR: δ 138.6-127.5 (Ph), 101.0 (C-1_B, $J_{C,H}$ = 170 Hz), 98.5 (C-1_C, $J_{C,H}$ = 168 Hz), 93.8 (C-1_E, $J_{C,H}$ = 168 Hz), 82.4 (C-3_E), 81.0 (C-4_C), 79.3 (C-4_B), 78.9 (C-2_E), 77.8 (C-3_B*), 77.7 (C-4_E), 77.5 (C-2_C), 76.4 (C-3_C*), 75.6, 75.4, 74.9, 74.2, 73.4, 72.5 (7C, 7 OCH_2), 70.7 (C-5_E), 68.0 (C-5_C), 67.9 (C-6_E), 67.7 (C-5_B), 67.6 (C-2_B), 54.7 (OCH_3), and 18.1 (2C, C-6_B, 6_C); ESMS for $C_{68}H_{76}O_{14}$ (M, 1116.5) *m/z* 1117.5 $[M+H]^+$.

Anal. Calcd for $C_{68}H_{76}O_{14}$: C, 73.10; H, 6.86%. Found: C, 73.15; H, 7.00%.

Compound **20**, isolated as a colourless glass, had $[\alpha]_D$ –8° (*c* 1.0); ^1H NMR: δ 7.42-7.13 (m, 35H, Ph), 5.20 (bs, 1H, H-1_B), 4.97-4.33 (m, 14H, 14 OCH_2), 4.75 (bs, overlapped, 1H, H-1_C), 4.68 (d, overlapped, 1H, H-1_E), 4.17 (bd, 1H, H-2_B), 4.15 (m, partially overlapped, 1H, H-3_B), 4.07 (dd, 1H, $J_{3,4}$ = 9.2, $J_{2,3}$ = 3.1 Hz, H-3_C), 3.89 (dq, 1H, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.2 Hz, H-5_B), 3.75 (dd, 1H, $J_{1,2}$ = 1.8, $J_{2,3}$ = 3.0 Hz, H-2_C), 3.66 (dq, partially overlapped, H-5_C), 3.64-3.51 (m, 7H, H-4_E, 3_E, 4_C, 4_B, 2_E, $6a_E$, $6b_E$), 3.32 (m, 4H, H-5_E, OCH_3), 3.25 (d, 1H, OH-2_B), 1.31 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_C), and 1.26 (d, 3H, H-6_B); ^{13}C NMR: δ 138.3-127.2 (Ph), 102.6 (C-1_E, $J_{C,H}$ = 159 Hz), 101.4 (C-1_B, $J_{C,H}$ = 170 Hz), 98.5 (C-1_C, $J_{C,H}$ = 167 Hz), 84.7 (C-3_E*), 92.0 (C-2_E), 80.9 (C-3_B), 80.8 (C-4_B), 80.1 (C-4_C), 78.3 (C-3_C), 77.8 (C-2_C), 77.4 (C-4_E*), 75.6, 75.2, 74.9, 74.8, 74.7 (5C, OCH_2), 74.4 (C-5_E), 73.5, 73.3 (2C, OCH_2), 70.2 (C-2_B), 68.5 (C-6_E), 68.0 (C-5_B), 67.9 (C-5_C), 54.7 (OCH_3), 18.0 (2C, C-6_B, 6_C), ESMS for $C_{68}H_{76}O_{14}$ (M, 1116.5) *m/z* 1117.6 $[M+H]^+$.

Anal. Calcd for $C_{68}H_{76}O_{14}$: C, 73.10; H, 6.86%. Found: C, 73.10; H, 6.94%.

Methyl (2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (22). A mixture of trisaccharide **19** (1.85 g, 1.66 mmol) and trichloroacetimidate[30] **21** (1.44 g, 3.32 mmol) was stirred under an inert atmosphere, for 15 min in anhydrous Et_2O (15 mL) at –78 °C. TMSOTf (32 μL, 0.1 eq) was added, and the mixture was stirred overnight, slowly warming up to rt. As no starting material remained (solvent *F*, 95:5), Et_3N (100 μL) was added, and volatiles were evaporated. Column chromatography of the residue (solvent *F*, 98:2) afforded the fully protected tetrasaccharide **22** (1.72 g, 75%). Compound **22**,

isolated as a colourless foam, had $[\alpha]_D$ –17° (*c* 1.0); ^{1}H NMR: δ 7.40-7.04 (m, 35H, Ph), 5.56 (m, 2H, H-2_A, 1_A), 5.36 (dd, 1H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 10.1 Hz, H-3_A), 5.11 (bs, 1H, H-1_B), 5.05 (dd, 1H, $J_{4,5}$ = 9.9 Hz, H-4_A), 4.86 (m, 1H, H-1_E), 4.69 (bs, 1H, H-1_C), 5.11-4.62 (m, 9H, OCH_2), 4.53 (d, 1H, J = 11.3 Hz, OCH_2), 4.52 (d, 1H, J = 12.2 Hz, OCH_2), 4.41 (d, 1H, J = 11.9 Hz, OCH_2), 4.35 (d, 1H, J = 11.0 Hz, OCH_2), 4.18 (m, partially overlapped, 1H, H-3_B), 4.16 (bs, 1H, H-2_B), 4.11 (d, 1H, J = 12.0 Hz, OCH_2), 4.06 (dd, 1H, $J_{2,3}$ = 3.0, $J_{3,4}$ = 9.3 Hz, H-3_C), 4.00-3.92 (m, 3H, H-5_A, 5_E, 3_E), 3.88 (dq, 1H, $J_{4,5}$ = 9.3, H-5_B), 3.73 (bd, 1H, H-2_C), 3.69-3.62 (m, 3H, H-4_E, 5_C, 4_B), 3.57 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4_C), 3.48 (dd, 1H, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.8 Hz, H-2_E), 3.32 (s, 3H, OCH_3), 3.26 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, H-$6a_E$), 3.16 (dd, 1H, H-$6b_E$), 2.06, 1.98, 1.85 (3s, 9H, 3 C(=O)CH_3), 1.36 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_B), 1.25 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_C), and 1.20 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_A); ^{13}C NMR: δ 170.1, 170.0, 169.7 (3C, C=O), 138.9-127.3 (Ph), 101.1 (C-1_B, $J_{C,H}$ = 171 Hz), 98.4 (C-1_C, $J_{C,H}$ = 172 Hz), 98.3 (C-1_A, $J_{C,H}$ = 172 Hz), 95.6 (C-1_E, $J_{C,H}$ = 168 Hz), 82.0 (C-3_E), 80.4 (C-4_C), 79.5 (C-4_B), 79.2 (C-3_C), 78.9 (C-2_E), 77.8 (C-2_C), 77.7 (C-4_E), 76.6 (C-3_B), 75.5, 75.3, 75.2, 74.8 (4C, 4 OCH_2), 74.2 (C-2_B), 73.5, 73.3, 72.5 (3C, 3 OCH_2), 71.2 (C-4_A), 70.4 (C-5_E), 69.4 (C-5_B), 69.3 (2C, C-3_A, 2_A), 68.0 (C-5_C), 67.8 (C-6_E), 66.8 (C-5_A), 54.7 (OCH_3), 20.9, 20.8, 20.7 (3C, C(=O)CH_3), 18.0 (C-6_B), 17.9 (C-6_C), and 17.5 (C-6_A); ESMS for $C_{80}H_{92}O_{21}$ (M, 1388.6) *m/z* 1389.8 $[M+H]^+$.

Anal. Calcd for $C_{80}H_{82}O_{21}$: C, 69.15; H, 6.67%. Found: C, 69.10; H, 6.83%.

Methyl α-L-Rhamnopyranosyl-(1→ 2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (23). 1N Methanolic sodium methoxide was added dropwise to a solution of triacetate **22** (1.67 g, 1.20 mmol) in a 1:1 mixture of dichloromethane and methanol until pH 10 was reached, and the reaction was stirred for 7 h at rt. After neutralisation with Amberlite IR-120 (H^+) and evaporation of the volatiles, the crude mixture was chromatographed from a column of silica gel (solvent *A*, 98:2) to give triol **23** (1.52 g, 98%). Compound **23**, isolated as a colourless foam, had $[\alpha]_D$ -9° (*c* 1.0); ^{1}H NMR: δ 7.38-7.07 (m, 35H, Ph), 5.14 (bs, 1H, H-1_B), 5.10 (bs, 1H, H-1_A), 4.94 (m, overlapped, 1H, H-1_E), 4.65 (bs, 1H, H-1_C), 4.98-4.53 (m, 11H, OCH_2), 4.43 (d, 1H, J = 12.0 Hz, OCH_2), 4.41 (d, 1H, J = 10.9 Hz, OCH_2), 4.18 (dd, 1H, $J_{2,3}$ = 2.3 Hz, H-3_B), 4.14 (d, 1H, J = 12.2 Hz, OCH_2), 4.06-3.99 (m, 5H, H-3_E, 2_B, 5_E, 3_C, 2_A), 3.86 (m, 1H, $J_{4,5}$ = 9.2 Hz, H-5_B), 3.77-3.68 (m, 4H, H-5_A, 4_E, 3_A, 2_C), 3.65 (m, 1H, partially overlapped, $J_{4,5}$ = 9.4 Hz, H-5_C), 3.60-3.54 (m, 2H, H-4_C, 2_E), 3.50 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-4_B), 3.36 (dd, 1H, partially overlapped, $J_{5,6a}$ = 2.3 Hz, H-$6a_E$), 3.35 (m, overlapped, 1H, H-4_A), 3.31 (s, 3H, OCH_3), 3.24 (d, 1H, $J_{6a,6b}$ = 10.5 Hz, H-$6b_E$), 1.32 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6_B), 1.24 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_A), and 1.21 (d, 3H,

$J_{5,6}$ = 6.2 Hz, H-6_C); ^{13}C NMR: δ 138.6-127.5 (Ph), 101.4 (C-1_A), 101.0 (C-1_B), 98.4 (C-1_C), 94.6 (C-1_E), 82.1 (C-3_E), 80.4 (C-4_C), 79.9 (C-4_B), 79.4 (C-2_E), 79.1 (C-3_C), 77.9 (C-4_E), 77.7 (C-2_C), 75.6 (C-3_B), 75.5, 75.2 (3C, 3 OCH_2), 75.0 (C-2_B), 74.9, 73.9 (2C, 2 OCH_2), 73.6 (C-4_A), 73.3, 72.6 (2C, 2 OCH_2), 71.6 (C-3_A), 70.7 (C-2_A), 70.3 (C-5_E), 68.9 (C-5_B), 68.4 (C-5_A), 68.0 (C-5_C), 67.9 (C-6_E), 54.7 (OCH_3), 19.2 (C-6_B), 18.0 (C-6_C), and 17.6 (C-6_A); ESMS for $C_{74}H_{86}O_{18}$ (M, 1262.6) *m/z* 1263.6 $[M+H]^+$.

Anal. Calcd for $C_{74}H_{86}O_{18}$: C, 70.35; H, 6.86%. Found: C, 70.24; H, 6.88%.

Methyl α-L-Rhamnopyranosyl-(1→2)-[α-D-glucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (2). A suspension of 10% Pd-C catalyst (500 mg) in a 4:1 mixture of methanol and acetic acid (30 mL) containing the triol **23** (1.26 g, 0.99 mmol) was stirred at rt for 72 h under a hydrogen atmosphere. The suspension was filtered on a bed of Celite and the filtrate was concentrated by repeated coevaporation with methanol and cyclohexane. Only one product could be detected (solvent *H*, 7:1:2) and the suspension was filtered on a bed of Celite. Volatiles were evaporated and the residue was purified by reverse-phase chromatography (solvent *G*, gradient) to give the target tetrasaccharide **2** (486 mg, 77%) after lyophilisation. Compound **2**, isolated as an amorphous solid, had $[\alpha]_D$ -12° (*c* 1.0, methanol), lit.[10] $[\alpha]_D$ –11° (*c* 1.0, methanol), lit.[10] $[\alpha]_D$ –5° (*c* 0.8, water); ^1H NMR (D_2O): δ 5.18 (bs, 1H, H-1_B), 5.09 (bs, overlapped, 1H, H-1_A), 5.08 (d, partially overlapped, 1H, H-1_E), 4.65 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1_C), 4.26 (dd, 1H, H-2_B), 4.04 (dd, 1H, $J_{1,2}$ = 1.6, $J_{2,3}$ = 3.3 Hz, H-2_A), 4.00-3.96 (m, 2H, H-3_B, 2_C), 3.92 (m, 1H, $J_{5,6}$ = 2.6, $J_{4,5}$ = 10.1 Hz, H-5_E), 3.82 (m, 1H, H-5_B), 3.78-3.71 (m, 5H, H-$6a_E$, $6b_E$, 3_A, 3_C, 3_E), 3.69 (m, partially overlapped, 1H, H-5_C), 3.65 (m, partially overlapped, 1H, H-5_A), 3.62 (m, 2H, H-4_B, 2_E), 3.53 (dd, 1H, $J_{3,4}$ = 9.6, $J_{4,5}$ = 9.6 Hz, H-4_C), 3.41 (m, 2H, H-4_A, 4_E), 3.39 (s, 3H, OCH_3), 1.31 (d, partially overlapped, 3H, $J_{5,6}$ = 5.5 Hz, H-6_B), 1.29 (d, partially overlapped, 3H, $J_{5,6}$ = 5.7 Hz, H-6_C), and 1.24 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_A); ^{13}C NMR[10] (D_2O): δ 102.5 (C-1_A, $J_{C,H}$ = 171 Hz), 101.6 (C-1_B, $J_{C,H}$ = 170 Hz), 101.5 (C-1_C, $J_{C,H}$ = 170 Hz), 96.0 (C-1_E, $J_{C,H}$ = 168 Hz), 78.0 (C-3_C), 75.4 (C-3_B), 74.2 (C-2_B), 73.6 (C-3_E), 72.8 (C-4_A), 72.5 (C-4_C), 72.4 (C-5_E), 71.8 (C-2_E), 71.2 (C-4_B), 70.8 (2C, C-3_A, 2_A), 70.6 (C-2_C), 70.2 (C-4_E), 70.0 (C-5_B), 69.9 (C-5_A), 69.2 (C-5_C), 61.1 (C-6_E), 55.5 (OCH_3), 17.5 (C-6_B), 17.4 (C-6_A*), and 17.3 (C-6_C*); FABMS for $C_{25}H_{44}O_{18}$ (M, 632.2) *m/z* 633.5 $[M+H]^+$, 655.5 $[M+Na]^+$, 671.4 $[M+K]^+$.

The compound (containing 2.5 H_2O per mol according to C,H analysis) could not be obtained solvent-free.

Methyl (2-*O*-Acetyl-3,4-di-*O*-allyl-α-L-rhamnopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→ 3)]-(4-*O*-benzyl-α-L-rham-

nopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (25). TMSOTf (35 μL, 0.08 eq) was added, at -78 °C, to a solution of acceptor **19** (2.40 g, 2.15 mmol) and trichloroacetimidate[11] **24** (1.85 g, 4.3 mmol) in anhydrous Et_2O (100 mL), and the mixture was processed as described for the preparation of **22**. After 24 h, the acidic medium was neutralised by addition of Et_3N (100 μL), and volatiles were evaporated. Chromatography of the residue (solvent *B*, 88:12 → 86:14) gave **25** (2.81 g, 94%) as a colourless foam. Compound **25** had $[\alpha]_D$ -13° (*c* 1.0); ^1H NMR: δ 7.39-7.03 (m, 35H, Ph), 6.00-5.85 (m, 2H, C*H*=CH_2), 5.51 (bs, 1H, H-1_A), 5.47 (dd, 1H, $J_{2,3}$ = 3.2 Hz, H-2_A), 5.29 (m, 2H, CH=CH_2), 5.20 (m, 2H, CH=CH_2), 5.51 (bs, 1H, H-1_B), 4.90 (d, partially overlapped, 1H, H-1_E), 4.67 (bs, 1H, H-1_C), 4.95-4.63 (m, 9H, OCH_2), 4.42 (d, 1H, J = 12.3 Hz, OCH_2), 4.51 (d, 1H, J = 11.4 Hz, OCH_2), 4.43 (d, 1H, J = 12.1 Hz, OCH_2), 4.37 (d, 1H, J = 10.9 Hz, OCH_2), 4.36 (d, 1H, OCH_2), 4.21-3.97 (m, 9H, H-3_C, 3_B, 2_B, 3_E, 5_E, 4 OCH_2), 3.89 (dq, 1H, $J_{4,5}$ = 9.9, $J_{5,6}$ = 6.3 Hz, H-5_B), 3.82 (dd, 1H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.3 Hz, H-3_A), 3.77 (dq, 1H, H-5_A), 3.73 (bd, 1H, H-2_C), 3.69-3.51 (m, 4H, H-4_E, 5_C, 4_B, 4_C), 3.51 (dd, 1H, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.8 Hz, H-2_E), 3.32 (s, 3H, OCH_3), 3.30 (bd, 1H, H-$6a_E$), 3.23 (dd, 1H, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5 Hz, H-4_A), 3.18 (bd, 1H, H-$6b_E$), 1.31 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_B), 1.22 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_A*), and 1.20 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6_C*); ^{13}C NMR: δ 169.8 (C=O), 139.1-127.2 (Ph), 116.9-116.5 (CH=*C*H_2), 101.1 (C-1_B, $J_{C,H}$ = 172 Hz), 98.4 (C-1_C, $J_{C,H}$ = 165 Hz), 98.2 (C-1_A, $J_{C,H}$ = 172 Hz), 95.2 (C-1_E, $J_{C,H}$ = 169 Hz), 82.0 (C-3_E), 80.2 (C-4_C), 80.0 (C-4_A), 79.6 (bs, C-4_B), 79.4 (bs, C-3_C), 79.0 (C-2_E), 77.9 (C-2_C), 77.7 (C-4_E), 77.2 (C-3_A), 76.5 (C-3_B), 75.4, 75.3, 74.8, 74.2, 73.3 (7C, 7 OCH_2), 73.0 (C-2_B), 72.5, 70.7 (2C, OCH_2), 70.4 (C-5_E), 69.2 (C-5_B), 69.0 (C-2_A), 68.2 (C-5_A), 68.0 (C-5_C), 67.9 (C-6_E), 54.7 (OCH_3), 20.9 (C(=O)CH_3), and 18.2, 18.1, 17.9 (3C, C-6_A, 6_B, 6_C); ESMS for $C_{82}H_{96}O_{19}$ (M, 1384.6) *m/z* 1385.6 $[M+H]^+$.

Anal. Calcd for $C_{82}H_{96}O_{19}$: C, 71.08; H, 6.98%. Found: C, 70.97; H, 7.17%.

Methyl (3,4-Di-*O*-allyl-α-L-rhamnopyranosyl)-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→ 3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (26). A solution of compound **25** (2.66 g, 1.92 mmol) in a 1:1 dichloromethane:methanol mixture was processed as described for the preparation of **23**. The residue was eluted from a column of silica gel (solvent *B*, 85:15) to give mono-hydroxylated **26** (3.03 g, 98%) as a highly hygroscopic amorphous solid: $[\alpha]_D$ -4° (*c* 1.0); ^1H NMR: δ 7.38-7.06 (m, 35H, Ph), 6.00-5.87 (m, 2H, CH=CH_2), 5.34-5.14 (m, 6H, CH=CH_2, H-1_A, 1_B), 4.97 (d, 1H, J = 11.0 Hz, OCH_2), 4.91 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1_E), 4.90-4.78 (m, 4H, 4 OCH_2), 4.72-4.66 (m, 4H, 4 OCH_2), 4.63 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1_C), 4.57 (d, 1H, J = 10.5 Hz, OCH_2), 4.51 (d, 1H, J = 11.4 Hz, OCH_2), 4.36-4.21 (m, 3H, 3 OCH_2), 4.20-3.98 (m, 10H, H-

3_B, 2_A, 3_E, 2_B, 3_C, 5_E, 4 OCH_2), 3.85 (dq, 1H, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.0 Hz, H-5_B), 3.79 (dq, 1H, $J_{4,5}$ = 9.1, $J_{5,6}$ = 6.0 Hz, H-5_A), 3.73-3.52 (m, 6H, H-4_E, 2_C, 3_A, 5_C, 2_E, 4_C), 3.49 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-4_B), 3.40 (dd, 1H, H-$6a_E$), 3.30 (s, 3H, OCH_3), 3.28 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-4_A), 3.23 (d, 1H, $J_{6a,6b}$ = 12.8 Hz, H-$6b_E$), 2.13 (d, 1H, $J_{OH,2}$ = 2.3 Hz, OH-2), 1.30 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6_B), and 1.20 (d, 6H, H-6_A, 6_C); ^{13}C NMR: δ 135.1-127.4 (Ph), 116.9, 116.8 ($CH=CH_2$), 101.2 (bs, C-1_B), 101.0 (C-1_C), 98.5 (C-1_A), 94.7 (C-1_E), 82.3 (C-3_E), 80.5 (C-4_C*), 79.9 (2C, C-4_B, 4_A), 79.1 (bs, C-3_C), 79.0 (C-3_A), 78.7 (C-2_E *), 77.8 (C-4_E), 77.7 (C-2_C), 75.6, 75.5, 75.3 (3C, 3 OCH_2), 75.1 (2C, C-2_B, 2_A), 74.9, 74.1, 73.9, 73.3, 72.5, 71.1 (6C, 6 OCH_2), 70.3 (C-5_E), 68.9 (C-3_B), 68.7 (C-5_B), 68.0 (2C, C-5_C, 5_A), 67.9 (C-6_E), 54.6 (OCH_3), 18.2 (C-6_B), and 17.8 (2C, C-6_A, 6_C); ESMS for $C_{80}H_{94}O_{18}$ (M, 1342.6) *m/z* 1343.8 $[M+H]^+$, 1355.6 $[M+Na]^+$.

Anal. Calcd for $C_{80}H_{94}O_{18}$: C, 71.51; H, 7.05%. Found: C, 71.45; H, 7.25%.

Methyl (3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→ 2)-(3,4-di-*O*-allyl-α-L-rhamnopyranosyl)-(1→ 2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (28). A solution of tetrasaccharide **26** (2.39 g, 1.78 mmol) and the glucosaminyl donor[31] **27** (1.93 g, 3.27 mmol) in anhydrous acetonitrile was cooled to –25 °C. TMSOTf (37 μL) was added, and the mixture was stirred overnight while the cooling bath was slowly coming back to rt. As only very little starting remained (TLC, solvent *B*, 76:24), Et_3N (150 μL) was added, and volatiles were evaporated. Column chromatography of the residue (solvent *B*, 80:20 → 75:25) resulted in the fully protected pentasaccharide **28** (2.56 g, 81%): glassy solid, $[\alpha]_D$ –11° (*c* 1.0); ^1H NMR: δ 7.36-7.06 (m, 35H, Ph), 6.78 (d, 1H, $J_{NH,2}$ = 8.5 Hz, NH), 6.03-5.85 (m, 2H, C*H*=CH_2), 5.37-5.08 (m, 7H, 4 CH=CH_2, H-1_A, 1_B, 3_D), 4.99-4.76 (m, 7H, H-1_E, 4_D, 1_D, 4 OCH_2), 4.72-4.58 (m, 6H, H-1_C, 5 OCH_2), 4.50 (d, 1H, J = 11.5 Hz, OCH_2), 4.41 (d, 1H, J = 11.0 Hz, OCH_2), 4.37 (d, 1H, J = 12.1 Hz, OCH_2), 4.32-4.20 (m, 5H, H-3_B, 2_A, 3 OCH_2), 4.16-3.83 (m, 10H, H-$6a_D$, 2_B, 3_E, 5_E, 3_C, $6b_D$, 5_B, 2_D, 2 OCH_2), 3.80-3.48 (m, 8H, H-5_C, 3_A, 5_A, 2_C, 4_E, 2_E, 4_B, 4_C), 3.42 (m, 2H, H-5_D, $6a_E$), 3.30 (s, 3H, OCH_3), 3.26 (m, 2H, H-4_A, $6b_E$), 2.01, 2.00, 1.83 (3s, 9H, C(=O)CH_3), 1.32 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_B), 1.20 (d, 3H, $J_{5,6}$ = 5.9 Hz, H-6_C), and 1.16 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_A); ^{13}C NMR: δ 170.7, 170.4, 169.3 (3C, O(C=O)), 161.6 (NC(=O)), 138.7-127.5 (Ph), 117.4, 116.5 ($CH=CH_2$), 100.5 (bs, C-1_B, $J_{C,H}$ = 173 Hz), 100.0 (C-1_D, $J_{C,H}$ = 164 Hz), 99.7 (C-1_A, $J_{C,H}$ = 171 Hz), 98.6 (C-1_C, $J_{C,H}$ = 168 Hz), 93.3 (C-1_E, $J_{C,H}$ = 172 Hz), 92.3 (CCl_3), 82.1(C-3_E), 80.9 (C-4_A), 80.4 (C-4_C), 79.8 (bs, C-4_B), 79.5 (C-3_A), 79.2 (bs, C-3_C), 78.4 (C-2_E), 77.6 (2C, C-2_C, 4_E), 75.7, 75.4, 75.3 (3C, 3 OCH_2), 75.0 (C-2_A), 74.9 (OCH_2), 74.2 (C-3_B), 74.1

(OCH_2), 73.7 (C-2_B), 73.2, 72.6, 72.3, 72.2 (4C, 4 OCH_2), 72.1 (bs, C-5_D), 72.0 (C-3_D), 70.1 (C-5_E), 68.8 (C-5_B), 68.7 (C-5_A), 68.2 (C-4_D), 68.0 (C-6_E), 68.0 (C-5_C), 61.8 (C-6_D), 56.1 (C-2_D), 54.6 (OCH_3), 20.6, 20.5 (3C, C(=O)CH_3), 18.2 (C-6_C), and 17.9 (2C, C-6_A, 6_B); ESMS for $C_{94}H_{110}Cl_3NO_{26}$ (M, 1773.6) *m/z* 1774.7 $[M+H]^+$.

Anal. Calcd for $C_{94}H_{110}Cl_3NO_{26}$: C, 63.56; H, 6.24; N, 0.79%. Found: C, 63.51; H, 6.40; 0.74%.

Methyl (3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→2)-α-L-rhamnopyranosyl-(1→2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→ 3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1→ 3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (29). Compound **28** (2.19 g, 1.23 mmol) was dissolved in anhydrous THF (20 mL). The solution was degassed and placed under Ar. 1,5-Cyclooctadiene-bis(methyldiphenylphosphine)iridium hexafluorophosphate (50 mg, 59 μmol) was added, and the solution was degassed again. The catalyst was activated by passing over a stream of hydrogen until the solution had turned yellow (ca. 3 min). The reaction mixture was degassed and stirred under an Ar atmosphere for 17 h, then concentrated to dryness. The residue was dissolved in acetone (54 mL), then water (6 mL), mercuric bromide (755 mg, 2.09 mmol), and mercuric oxide (536 mg, 2.49 mmol), were added successively. The mixture, protected from light, was stirred at rt for 3 h, and acetone was evaporated. The resulting suspension was taken up in CH_2Cl_2, washed twice with 50% aq KI, water and satd aq NaCl, dried and concentrated. Purification of the crude material was effected by silica gel column chromatography (solvent *A*, 80:20) to furnish diol **29** (1.64 g, 79%) as a colourless foam: $[\alpha]_D$ –8° (*c* 1.0); ^1H NMR: δ 7.45-7.06 (m, 35H, Ph), 6.96 (d, 1H, $J_{NH,2}$ = 8.5 Hz, NH), 5.30 (bs, 1H, H-1_B), 5.10 (bs, 1H, H-1_A), 5.06 (d, 1H, $J_{1,2}$ = 6.0 Hz, H-1_E), 5.00-4.92 (m, 4H, H-3_D, 4_D, 2 OCH_2), 4.87-4.67 (m, 6H, 6 OCH_2), 4.60 (m, 2H, H-1_C, OCH_2), 4.51 (d, 1H, J = 11.5 Hz, OCH_2), 4.43 (d, 2H, H-1_D, OCH_2), 4.41 (d, 1H, J = 11.3 Hz, OCH_2), 4.39 (d, 1H, J = 12.0 Hz, OCH_2), 4.28 (dd, 1H, $J_{3,4}$ = 9.4, $J_{2,3}$ = 2.3 Hz, H-3_B), 4.17-3.99 (m, 8H, H-3_E, 2_B, 2_A, $6a_D$, 5_E, 3_C, 2_D, OCH_2), 3.95-3.85 (m, 3H, H-3_A, $6b_D$, 5_B), 3.75 (m, 2H, H-5_A, 4_E), 3.67 (dd, 1H, $J_{1,2}$ = 2.0 Hz, H-2_C), 3.62 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2_E), 3.60-3.52 (m, 3H, H-5_C, 4_C, 4_B), 3.44 (m, 2H, H-$6a_E$, 4_A), 3.35 (m, 1H, H-5_D), 3.29 (s, 3H, OCH_3), 3.27 (bd, 1H, H-$6b_E$), 2.41 (bd, 1H, OH-3_A), 2.18 (m, 1H, OH-4_A), 2.02, 2.01, 1.83 (3s, 9H, C(=O)CH_3), 1.32 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_B), 1.20 (d, 3H, $J_{5,6}$ = 5.9 Hz, H-6_C), and 1.16 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6_A); ^{13}C NMR: δ 170.9, 170.4, 169.2 (3C, O(C=O)), 161.9 (NC(=O)), 138.6-127.4 (Ph), 101.3 (C-1_D), 100.0 (bs, C-1_B), 100.0 (C-1_A), 98.7 (C-1_C), 92.9 (C-1_E), 92.3 (CCl_3), 81.9 (C-3_E), 80.6 (C-4_C), 79.8 (bs, C-4_B), 78.7 (2C, C-3_C, 2_E), 78.3 (C-2_A), 77.7 (C-4_E), 77.3 (C-2_C), 75.9, 75.4, 75.2, 74.9 (4C, 4 OCH_2), 74.7 (C-2_B), 73.7 (C-3_B), 73.2 (2C, C-4_A, OCH_2), 72.6 (OCH_2), 72.3 (C-3_D),

72.1 (OCH_2), 72.0 (2C, C-3_A, 5_D), 70.1 (C-5_E), 68.7 (2C, C-5_A, 5_B), 68.0 (2C, C-6_E, 5_C), 67.9 (C-4_D), 61.6 (C-6_D), 55.8 (C-2_D), 54.6 (OCH_3), 20.6, 20.5 (3C, $C(=O)CH_3$), 18.3 (C-6_B), 17.9 (C-6_C), and 17.3 (C-6_A); FABMS for $C_{88}H_{102}Cl_3NO_{26}$ (M, 1693.6) *m/z* 1716.2 $[M+Na]^+$.

Anal. Calcd for $C_{88}H_{102}Cl_3NO_{26}$: C, 62.32; H, 6.06; N, 0.83%. Found: C, 62.38; H, 6.16; N, 0.71%.

Methyl (2-Deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→2)-α-L-rhamnopyranosyl-(1 → 2)-[(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1 → 3)]-(4-*O*-benzyl-α-L-rhamnopyranosyl)-(1 → 3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (30). A solution of diol **29** (1.32 g, 0.78 mmol) in a mixture of methanol:CH_2Cl_2 (25 mL, 4:1) was treated with 1N methanolic sodium methoxide, as described for the preparation of compound **23**. Column chromatography of the residue (solvent *A*, 96:4) gave **30** (1.16 g, 95%) as a colourless foam: $[\alpha]_D$ –22° (*c* 1.0); ^1H NMR: δ 7.75 (d, 1H, $J_{NH,2}$ = 4.6 Hz, NH), 7.41-7.00 (m, 35H, Ph), 5.70 (bs, 1H, H-1_B), 5.15 (d, 1H, $J_{1,2}$ = 3.1 Hz, H-1_E), 5.10 (bs, 1H, H-1_A), 5.04-4.83 (m, 5H, 5 OCH_2), 4.71 (m, 2H, OCH_2, H-1_D), 4.74-4.53 (m, 5H, 4 OCH_2, H-1_C), 4.38 (m, 2H, OCH_2), 4.33 (bd, 1H, H-3_A), 4.31 (bs, 1H, H-2_A), 4.12-3.99 (m, 5H, OCH_2, H-3_E, 2_B, 3_C, 5_E), 3.93-3.82 (m, 3H, H-5_A, 3_B, $6a_D$), 3.72-3.58 (m, 8H, H-4_E, 2_C, 3_D, 4_A, 5_C, $6b_D$, 4_C, 2_E), 3.54 (m, 1H, H-2_D), 3.47 (m, 4H, H-4_B, 5_D, 5_B, $6a_E$), 3.29 (s, 3H, OCH_3), 3.25 (m, 2H, H-$6b_E$, 4_D), 1.35 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_A), 1.19 (d, 3H, $J_{5,6}$ = 5.6 Hz, H-6_C), and 1.06 (d, 3H, $J_{5,6}$ = 5.1 Hz, H-6_B); ^{13}C NMR: δ 164.4 (NC(=O)), 139.0-127.4 (Ph), 102.1 (C-1_D), 101.1 (C-1_A), 98.7 (C-1_C), 98.2 (C-1_B), 92.6 (C-1_E), 92.4 (CCl_3), 81.7 (C-3_E), 80.3 (C-4_C), 79.5 (C-4_A), 79.4 (C-2_B), 78.6 (C-3_C), 78.2 (C-4_E), 77.7 (C-2_E), 77.3 (C-2_C), 76.0 (2C, OCH_2, 3_D), 75.7 (C-4_B), 74.9, 74.8, 74.7 (3C, OCH_2), 74.5 (C-3_A), 73.3 (C-5_B*), 73.2, 73.0, 72.7 (3C, OCH_2), 71.9 (C-4_D), 71.3 (C-3_B), 69.9 (C-5_E), 69.4 (C-5_A), 68.7 (C-5_D*), 68.1 (C-2_A), 68.0 (2C, C-6_E, 5_C), 62.0 (C-6_D), 59.1 (C-2_D), 54.7 (OCH_3), 18.1 (C-6_A), 17.8 (C-6_C), and 17.4 (C-6_B); FABMS for $C_{82}H_{96}Cl_3NO_{23}$ (M, 1567.5) *m/z* 1590.2 $[M+K]^+$.

Anal. Calcd for $C_{82}H_{96}Cl_3NO_{23}$: C, 62.73; H, 6.16. N, 0.89%. Found: C, 62.65; H, 6.10, N, 0.72%.

Methyl (2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→2)-α-L-rhamnopyranosyl-(1→ 2)-[α-D-glucopyranosyl-(1→ 3)]-α-L-rhamnopyranosyl-(1 → 3)-α-L-rhamnopyranoside (3). A suspension of 10% Pd-C catalyst (500 mg) in a 4:1 mixture of methanol and acetic acid (25 mL) containing the pentaol **30** (546 mg, 0.35 mmol) was stirred at rt for 48 h under a hydrogen atmosphere. The suspension was filtered, and the filtrate was concentrated by repeated coevaporation with methanol and cyclohexane. Methanol (15 mL), Et_3N (500 μL), and Pd-C catalyst (200 mg) were added, and the

suspension was stirred at rt for 24 h. Only one product could be detected (solvent *H*, 7:1:2), and the suspension was filtered over a bed of Celite. Volatiles were evaporated and the residue was purified by reverse-phase chromatography (solvent *G*, gradient) to give the target pentasaccharide **3** (216 mg, 74%) after lyophilisation. Compound **3**, isolated as an amorphous solid, had $[\alpha]_D$ +1° (*c* 1.0, methanol); ^{1}H NMR (D_2O): δ 5.25 (bs, 1H, H-1_B), 5.11 (bs, 1H, H-1_A), 5.09 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1_E), 4.72 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1_D), 4.66 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1_C), 4.27 (bd, 1H, H-2_A), 4.14 (bd, 1H, H-2_B), 4.02-3.81 (m, 6H, H-3_B, 2_C, 5_E, 3_A, 5_B, $6a_D$), 3.79-3.65 (m, 8H, H-$6a_E$, $6b_E$, 3_E, 3_C, 2_D, $6b_D$, 5_C, 5_A), 3.62-3.51 (m, 4H, H-2_E, 4_B, 4_C, 3_D), 3.50-3.29 (m, 7H, H-5_D, 4_E, 4_D, 4_A, OCH_3), 2.04 (s, 3H, $(C{=}O)CH_3$), 1.31 (d, 3H, $J_{5,6}$ = 5.9 Hz, H-6_B), 1.29 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6_C), and 1.23 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6_A); ^{13}C NMR (D_2O): δ 175.6 (NC(=O)), 103.2 (C-1_D, $J_{C,H}$ = 163 Hz), 101.9 (C-1_A, $J_{C,H}$ = 171 Hz), 101.5 (C-1_C, $J_{C,H}$ = 171 Hz), 101.3 (C-1_B, $J_{C,H}$ = 174 Hz), 95.1 (C-1_E, $J_{C,H}$ = 171 Hz), 79.2 (C-2_A), 77.8 (C-3_C), 76.7 (C-5_D), 75.3 (C-2_B), 74.3 (C-3_D), 74.0 (C-3_B), 73.7 (C-3_E), 73.1 (C-4_A), 72.6 (C-4_C), 72.4 (C-5_E), 71.8 (C-4_B), 71.1 (C-2_E), 70.7 (C-4_D), 70.6 (2C, C-3_A, 2_C), 70.2 (C-4_E), 70.0 (C-5_A), 69.8 (C-5_B), 69.2 (C-5_C), 61.6 (C-6_D), 61.2 (C-6_E), 56.6 (C-2_D), 55.5 (OCH_3), 23.1 ($C(=O)CH_3$), 17.6 (C-6_B), 17.4 (C-6_C*), and 17.3 (C-6_A*); FABMS for $C_{33}H_{57}NO_{23}$ (M, 835.3) *m/z* 836.5 $[M+H]^+$, 842.5 $[M+Li]^+$, 858.5 $[M+Na]^+$, 874.5 $[M+K]^+$.

The compound (containing 3 H_2O per mol according to C,H,N analysis) could not be obtained solvent-free.

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