Achiral Cyclodextrin Analogues**

Peter R. Ashton, Stuart J. Cantrill, Giuseppe Gattuso, Stephan Menzer, Sergey A. Nepogodiev, Andrew N. Shipway, J. Fraser Stoddart,* and David J. Williams

Abstract: The synthesis of a new family of cyclodextrin (CD) analogues is described. This family consists of novel cyclic oligosaccharides built from monosaccharides that possess the same relative but opposite absolute (D- and L-) configurations. The alternation of such D- and L-residues—specifically, D- and L-rhamnose or D- and L-mannose—in a macrocyclic structure results in S_n-type symmetry and, consequently, optical inactivity. The synthesis of these cyclic oligosaccharides was achieved by an economical polycondensation/cycloglycosylation approach that relies on an appropriately-derivatized disaccharide monomer and that avoids the time-consuming, and often low-yielding, stepwise growth of long linear oligosaccharide precursors. In the cases reported, the key precursors are the disaccharide monomers **1-RR** and **1-MM**, which bear both a glycosyl donor (cyanoethylidene function) and a glycosyl acceptor (trityloxy group). These compounds are able to undergo Tr^+-catalyzed polycondensation which, under appropriate dilution conditions, can be terminated by cycloglycosylation. Thus, compound **1-RR** was converted into a range of protected cyclic rhamnooligosaccharides **15**–**19** in 64% overall yield. All these products, including the unique cyclic dodeca- and tetradecasaccharides **18** and **19**, have been isolated by preparative HPLC. Unexpectedly, treatment of the *manno* analogue of the disaccharide **1-RR** (compound **1-MM**) under the same conditions produced only the cyclic hexasaccharide **28** and numerous apparently linear oligomers. Removal of the protecting groups from **16**–**19** afforded the free cyclic oligosaccharides **21**–**24**, which exhibited the predicted zero optical rotation and very simple NMR spectra, indicating highly symmetrical structures. X-ray crystallography reveals that in the solid state the cyclooctaoside **21** possesses a C_2 symmetric structure, on account of a slight deformation of its cylindrical shape. The channel-type crystal packing of molecules of **21** forms nanotubes with an internal diameter of around 1 nm. Conversely, the cyclic hexasaccharide **29** possesses a C_i symmetric solid-state structure and its molecules pack to form a parquet-like superstructure.

Keywords
carbohydrates · cyclodextrin analogues · cyclooligomerizations · glycosylations · nanostructures

Introduction

Cyclodextrins (CDs), which are composed of (1→4)-linked α-D-glucose residues, are the most well-known family of compounds in the class of cyclic oligosaccharides. They have been studied extensively[1] as a result of their unique ability to form inclusion complexes with a very broad range of guest molecules. Along with CDs, a limited number of examples of naturally produced cyclic oligosaccharides are known: either they are formed as a result of enzymatic degradation of polysaccharides[2] or they are produced by microorganisms.[3] Therefore, it appears that total chemical synthesis is the only feasible method for the production of cyclic oligosaccharides with different structural and chemical properties. The chemical synthesis of α-CD and γ-CD was a remarkable achievement[4] as it was the first successful attempt at the total synthesis of cyclic oligosaccharides. However, CDs themselves do not represent extremely interesting synthetic targets as they can be easily obtained from enzymatic action on a low-cost natural raw material, that is, starch. Unnatural cyclic oligosaccharides are obviously more attractive synthetic targets, and numerous studies on the synthesis of both α-(1→4)-linked CD analogues[5] and compounds with different interglycosidic linkages[6] have been reported during the past decade. In order to develop a practical route to the preparation of complex cyclic oligosaccharides, we have employed[7] a polycondensation/cyclization approach that uses a small saccharide precursor for the synchronous preparation of a series of cyclic oligosaccharides composed of different numbers of repeating units (Figure 1). The basic structural requirement for the pre-

[*] Prof. J. F. Stoddart, Dr G. Gattuso, Dr. S. A. Nepogodiev, Dr A. N. Shipway, P. R. Ashton, S. J. Cantrill
School of Chemistry, University of Birmingham
Edgbaston, Birmingham, B152TT (UK)
Fax: Int. code +(121)414-3531
Prof. D. J. Williams, Dr. S. Menzer
Chemical Crystallography Laboratory, Department of Chemistry, Imperial College
South Kensington, London, SW72AY (UK)
Fax: Int. code +(171)594-5804

[**] Part 2 of a series on Synthetic Cyclic Oligosaccharides. For Part 1, see: P. R. Ashton, C. L. Brown, S. Menzer, S. A. Nepogodiev, J. F. Stoddart, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 580–591.

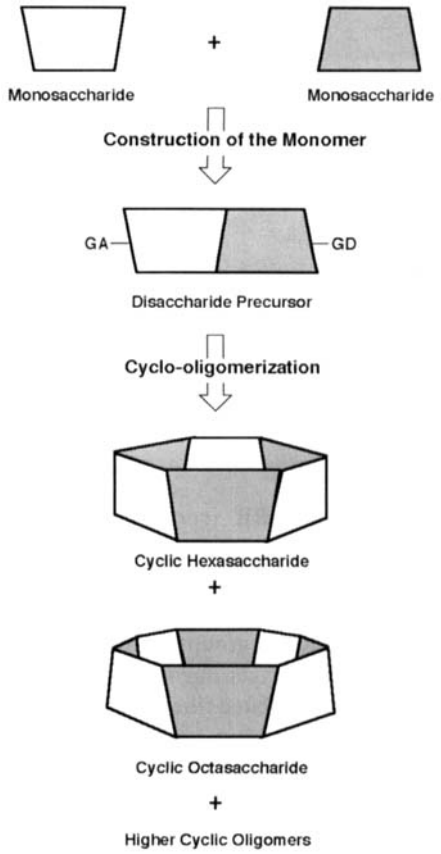


Figure 1. Cartoon representation of the approach to the synthesis of cyclic oligosaccharides by the cyclooligomerization of a disaccharide monomer; GA = glycosyl acceptor function, GD = glycosyl donor function

cursor is the presence of a glycosyl donor function at one end of the molecule and a glycosyl acceptor function at the other end. There are several types of glycosyl donor groups that might be useful for this purpose, for example F,[8] MeS,[9] or *n*-C_5H_{11}.[10] For our studies we chose the trityl (triphenylmethyl)–cyanoethylidene condensation method,[11] because it is currently the only procedure for the chemical synthesis of polysaccharides that has been investigated extensively. Recently, we demonstrated the efficiency of the aforementioned strategy by synthesizing[7] two cyclic oligosaccharides composed of alternating L-rhamnose and D-mannose units.

The next stage of our research program involved using the polycondensation/cyclization methodology for the construction of CD analogues possessing a very high degree of symmetry. In order to achieve our goal, we decided to prepare cyclic oligosaccharides composed of alternating residues with opposite absolute configurations—namely, D- and L-rhamnose and D- and L-mannose (Figure 2). This design leads to achiral compounds that possess S_n symmetry—where n is equal to the number of monosaccharide units—and consequently to loss in optical activity of the oligosaccharide molecules. Moreover, in contrast to CDs, which possess two constitutionally different rims lined with either primary or secondary OH groups, the cyclic oligosaccharides schematically depicted in Figure 2 have enantiotopic rims, which may be distinguished only by the directionality of the glycosidic linkages.

The preparations of the cyclic D-*manno*- and L-*rhamno*-oligosaccharides, described by the groups of Ogawa[12] and

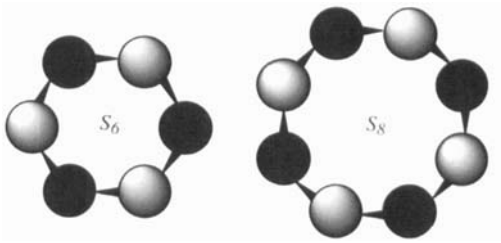
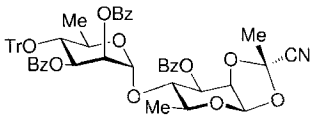


Figure 2. Schematic representation of D/L-alternating hexasaccharide (left) and octasaccharide (right) possessing S_n-type symmetry.

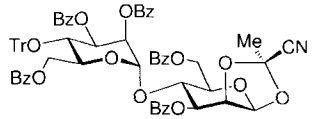
Nishizawa,[13] are two of the most efficient processes reported on the synthesis of cyclic oligosaccharides. Our target molecules differ markedly from these C_n symmetric structures as they incorporate both enantiomers of the monosaccharide residues at the same time, giving rise to the already mentioned S_n symmetry. Furthermore, a different, relatively short, and economical synthetic strategy has been employed for their preparation. In this paper, we report the synthesis and characterization of a series of homologous cyclic oligosaccharides, composed of alternating D-rhamnose and L-rhamnose, which possess the structural features already described. The same synthetic methodology was applied subsequently to the preparation of the analogous *manno*-oligosaccharide series and these results are also described in this paper.

Results and Discussion

Synthetic Strategy: The trityl–cyanoethylidene condensation method[11] was used as the basic glycosylation reaction in the polycondensation/cyclization process that led to the formation of a series of cyclic oligosaccharides. The key intermediates for the assembly of the target D/L alternating *rhamno*- and *manno*-oligosaccharides were the disaccharide derivatives **1-RR** and **1-MM** (Figure 3). As a consequence of their structural similarities, these compounds can be prepared by following a common synthetic pathway (Scheme 1), which is based on the methodology we reported previously.[7] This generic scheme involves six steps, starting from the cyanoethylidene derivatives **2** together with the glycosyl bromides **5**, the preparation of which obviously requires some additional effort. The synthesis of cyanoethylidene derivatives of L-rhamnose and D-mannose is well documented,[14] which prompted us to employ these particular residues at the reducing ends of compounds **1-RR** and **1-MM**, leaving D-rhamnosyl and L-mannosyl residues, respectively, to be introduced at the nonreducing ends of the derivatives. This outcome may be achieved by coupling D-rhamnose and L-mannose (as their glycosyl bromides **5**) with the glycosyl acceptors **4**, constructed from L-rhamnose and D-



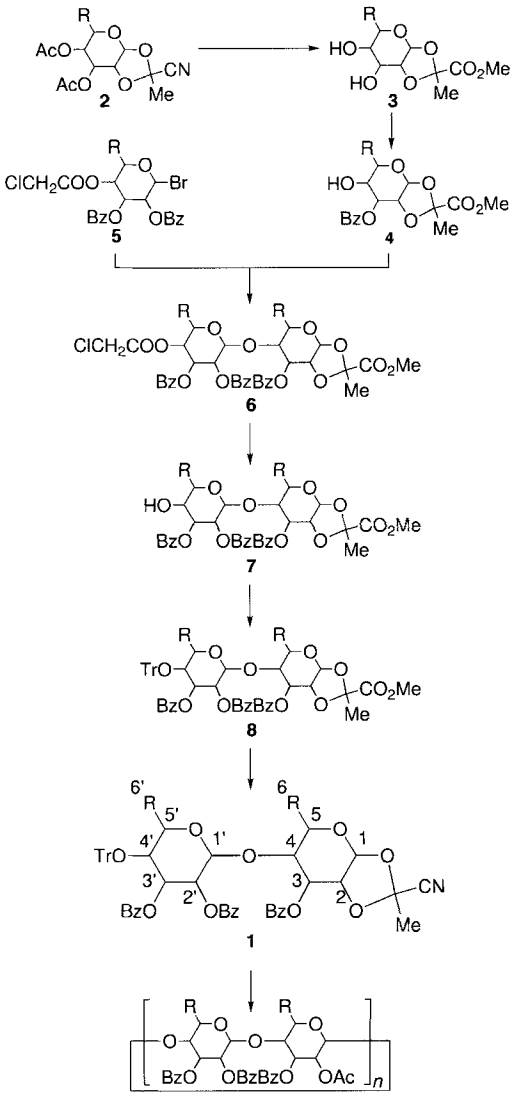
1-RR



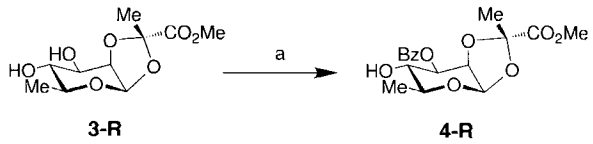
1-MM

Figure 3. Structure of disaccharide precursors **1-RR** and **1-MM** for *rhamno*- and *manno*-oligosaccharides.

0947-6539/97/0308-1300 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8



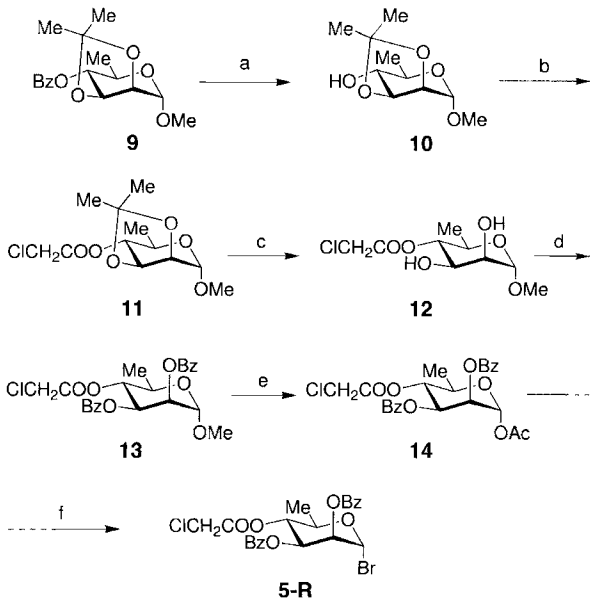
Scheme 1. General scheme for the synthesis of trityl–cyanoethylidene-functionalized disaccharides suitable for cyclooligomerizations aimed at the preparation of (1 → 4)-linked cyclic oligosaccharides. The configurations of chiral centers are not shown.



Scheme 2. Synthesis of the L-rhamnose glycosyl acceptor **4-R**. Reagents and conditions: a) $BzCN/C_5H_5N/CH_2Cl_2$, 20 °C, 18 h, 58%.

zoate, from which the 3-*O*-benzoate was separated by fractional crystallization in 58% yield.

The synthesis of the glycosyl bromide **5-R** was performed starting from the methyl 2,3-*O*-isopropylidene-4-*O*-benzoyl-α-D-rhamnopyranoside **9** (Scheme 3), which was, in turn, prepared in five steps by following the literature procedure,[17]

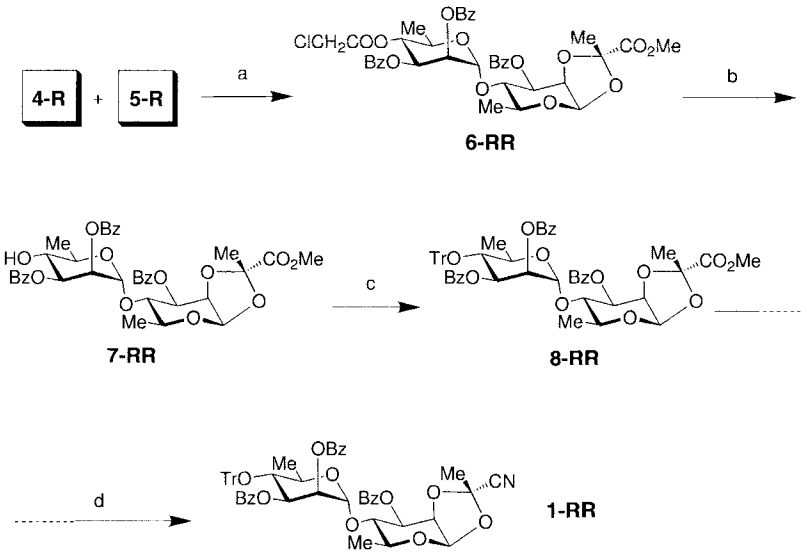


Scheme 3. Synthesis of the D-rhamnose glycosyl donor **5-R**. Reagents and conditions: a) NaOMe/MeOH, 20 °C, 6 h, quantitative; b) $ClCH_2COCl/C_5H_5N/CH_2Cl_2$, 20 °C, 18 h, 77%; c) $CF_3CO_2H/H_2O/CHCl_3$, 20 °C, 6 h, 96%; d) $BzCl/C_5H_5N/CH_2Cl_2$, 20 °C, 24 h, 82%; e) $Ac_2O/H_2SO_4/CH_2Cl_2$, 20 °C, 2 h, 86%; f) $AcBr/MeOH/CH_2Cl_2$, 20 °C, 2 h, 99%.

mannose, respectively. The resulting disaccharides **6** can then be converted into the desired precursors **1** by dechloroacetylation, tritylation, and two-step transformations[15] of the CO_2Me group into a CN function. During the transformations outlined in Scheme 1, the cyano function was converted into a methoxycarbonyl group; the latter, in contrast to the former,[16] is stable during the reactions employed in the synthesis of **1-RR** and **1-MM**. The details of the synthesis of **1-RR** and **1-MM** and the results of their cyclooligomerization are outlined in the following sections.

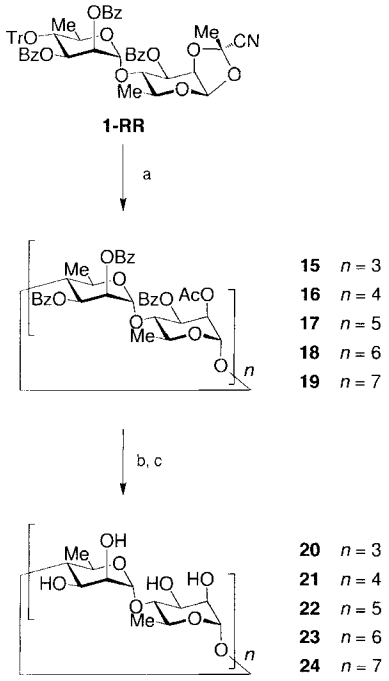
The D-Rhamnosyl-L-Rhamnose Monomer 1-RR and its Cyclooligomerization: In order to prepare the disaccharide monomer **1-RR** it is necessary to synthesize the methoxycarbonyl derivative **4-R** and the rhamnosyl bromide **5-R**. The monobenzoate **4-R** was prepared by treatment of the known[17] diol **3-R** with a mild benzoylating agent, namely BzCN in the presence of pyridine (Scheme 2). The reaction afforded a 4:1 mixture of the desired 3-*O*-benzoate and the isomeric 4-*O*-benzoate starting from methyl α-D-mannoside, since D-rhamnose is not commercially available. Removal of the benzoyl protecting group ($MeONa/MeOH/CH_2Cl_2$) from the known benzoate **9**,[15c] followed by chloroacetylation ($ClCH_2COCl/C_6H_5N$) of **10**, afforded the chloroacetyl derivative **11** in 77% yield. Replacement of the isopropylidene protecting group with benzoyl groups in compound **11** was achieved by successive deacetonation ($CF_3CO_2H/H_2O/CHCl_3$, 96%) and benzoylation ($BzCl/C_6H_5N/CH_2Cl_2$, 82%). The resulting acylated derivative **13** was subjected to acetolysis (1% H_2SO_4 in Ac_2O) to give the 1-acetate **14** in 86% yield, which was finally converted quantitatively into the glycosyl bromide **5-R** by treatment of **14** with HBr in CH_2Cl_2.

The glycosyl donor **5-R** and acceptor **4-R** underwent reaction in the presence of AgOTf/collidine to afford exclusively the α-linked disaccharide **6-RR** (65% yield), which was then dechloroacetylated selectively at the 4′-position by treatment of **6-RR** with thiourea (Scheme 4). The resulting alcohol **7-RR**



Scheme 4. Synthesis of the D-rhamnosyl-L-rhamnose disaccharide monomer **1-RR** from the glycosyl donor **5-R** and the glycosyl acceptor **4-R**. Reagents and conditions: a) AgOTf/collidine/CH_2Cl_2, -30 °C, 1 h, 65%; b) $(H_2N)_2CS$/MeCN/H_2O, 20 °C, 40 h, 91%; c) $TrClO_4$/collidine/CH_2Cl_2, 20 °C, 4 h, 84%; d) i) NH_3/MeOH/CH_2Cl_2, -5 to 20 °C, 18 h, ii) $BzCl/C_5H_5N$, 20 °C, 18 h, 87%.

(91% yield) was treated with $TrClO_4$ and collidine to afford the trityl ether **8-RR** (84%). The conversion of **8-RR** into the disaccharide monomer **1-RR** was achieved by ammonolysis (NH_3/MeOH/CH_2Cl_2) of the CO_2Me group of **8-RR** and then by treatment of the resulting mixture of products—partially debenzoylated amides—with $BzCl/C_6H_5N$. This procedure afforded, after column chromatography, the target D-rhamnosyl-L-rhamnose monomer **1-RR** in 87% yield.



Scheme 5. Polycondensation/cycloglycosylation of the disaccharide monomer **1-RR** and deprotection of the resulting cyclic oligosaccharides. Reagents and conditions: a) $TrClO_4$/CH_2Cl_2, 20 °C, 48 h; b) i) NaOMe/MeOH, ii) H_2O, 20 °C, 24 h; c) NaOMe/MeOH/CH_2Cl_2, 20 °C, 24 h, 73% (**21**), 80% (**22**), 86% (**23**), 29% (**24**).

The disaccharide **1-RR** served as a monomer in the crucial step of the synthesis, the cyclooligomerization. This reaction was performed by the treatment of **1-RR** with $TrClO_4$ as a catalyst at 25 °C in a CH_2Cl_2 solution, using a high-vacuum apparatus for the preparation of both the reagents and the solvent (Scheme 5). Special precautions to eliminate moisture were necessary, since traces of H_2O can quickly destroy the catalyst and terminate the growth of the oligosaccharide chains. The reactions were carried out under moderately dilute conditions (ca. 0.01 M), in contrast to earlier polycondensation experiments,[18] where a concentration greater than 0.1 M was employed. The catalyst was used in an equimolar amount with respect to the monomers in order to increase the rate of reaction.

The reaction mixture, resulting from the cyclooligomerization of the D-rhamnosyl-L-rhamnose monomer **1-RR**, was investigated by MALDI-TOF mass spectrometry.[18] After the reaction had proceeded for 48 h this analysis revealed that, in the region of 2000–5000 Daltons, there were no peaks that could be assigned to linear oligosaccharides (Figure 4): instead, a series

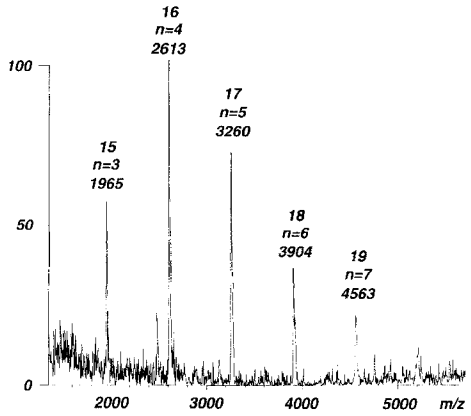


Figure 4. Partial MALDI-TOF mass spectrum of the reaction mixture arising from the polycondensation/cycloglycosylation of the D-rhamnosyl-L-rhamnose monomer **1-RR**. The peaks refer to $[M+Na]^+$.

of compounds with molecular weights corresponding to the protected cyclic hexa-, octa-, deca-, dodeca-, and even tetradecasaccharides were identified. In the first instance, these compounds were isolated as a mixture from the low molecular weight, trityl-containing products by means of conventional column chromatography on silica gel. Thereafter, the mixture of the cyclic oligosaccharides was subjected to reverse phase HPLC on a C-18 column using MeCN as the eluent.[20] In this manner, the aforementioned protected cyclic oligosaccharides, composed of alternating D-rhamnose and L-rhamnose residues, were isolated successfully and characterized as the cyclic trimer **15** (14%), tetramer **16** (17%), pentamer **17** (15%), hexamer **18** (10%), and heptamer **19** (7.5%) with reference to the number of disaccharide repeating units.

The deprotection of the cyclic oligosaccharides **15**–**19** was performed by treating them with NaOMe in a mixture of MeOH/CH_2Cl_2 followed, in the case of **15**, by further exposure to an aqueous NaOH solution, since the partially deprotected forms of this cyclic hexasaccharide were found to precipitate out of the reaction mixture. The free cyclic oligosaccharides **20**–**24** (Figure 5) were purified by reverse phase HPLC (C-18 column, H_2O/MeCN).

Amongst the five homologous cyclic oligosaccharides **20**–**24**, only the hexasaccharide **20** was poorly soluble in H_2O. Thus, for characterization purposes, it was exhaustively acetylated with Ac_2O/C_6H_5N (Scheme 6) and characterized as the peracetate **25**.

0947-6539/97/0308-1302 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

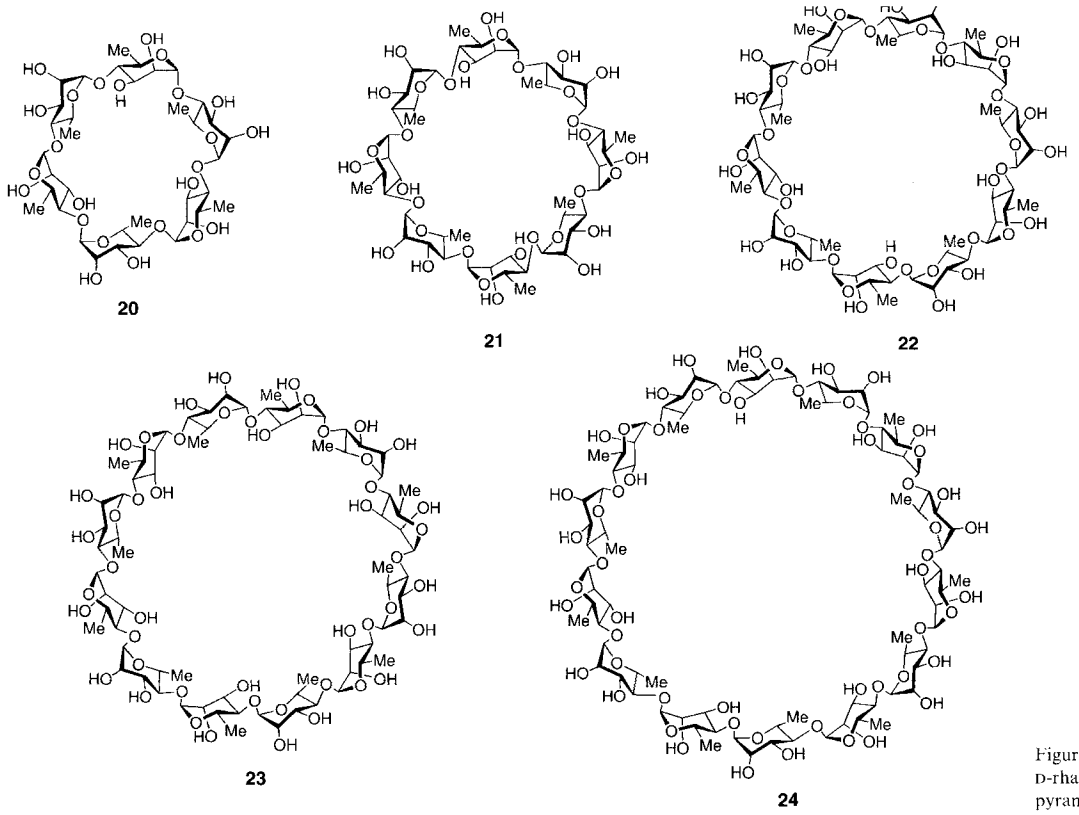
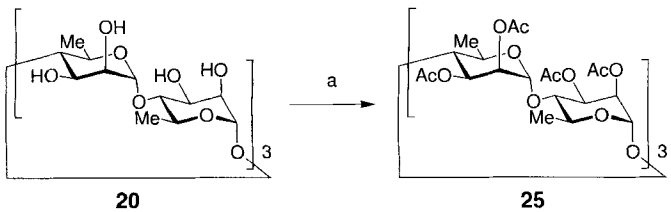


Figure 5. Structure of cyclic [(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranoso)-oligosaccharides **20**–**24**.

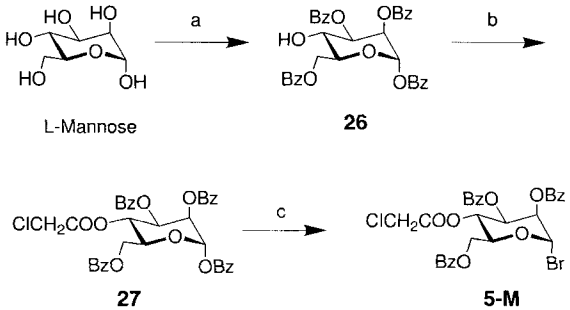
Synthesis of L-Mannosyl-D-Mannose Monomer 1-MM and its Cyclooligomerization: The disaccharide monomer **1-MM** was also prepared by following the general strategy that was employed in the synthesis of D-rhamnosyl-L-rhamnose analogue **1-RR** (Scheme 1). The previously reported[7] methoxycarbonyl derivative **4-M** was used as the glycosyl acceptor for the construction of the disaccharide monomer **1-MM**. To create the L-mannosyl donor, we applied a simple and efficient procedure for selective benzoylation developed[21] for the preparation of 1,2,3,6-tetra-*O*-benzoyl-D-mannose (4 equiv. $BzCl/C_6H_5N$, −40 °C), which, in the case of L-mannose, led to the tetrabenzoate **26** in 35% yield (Scheme 7). Chloroacetylation of **26** with $ClCH_2COCl/C_6H_5N/CH_2Cl_2$ proceeded in 96% yield, affording the chloroacetyl derivative **27**, which was treated finally with HBr/AcOH to give the mannosyl bromide **5-M** quantitatively.

Next, the L-mannosyl bromide **5-M** was coupled with the glycosyl acceptor **4-M** under the same conditions as those described for the synthesis of **6-RR** to afford the desired disaccharide **6-MM** in 67% yield (Scheme 8). The next four steps, 1) dechloroacetylation ($(NH_2)_2CS/MeCN/H_2O$), 2) tritylation ($TrClO_4$/collidine/CH_2Cl_2), and conversion of the CO_2Me group into a CN function by 3) ammonolysis (NH_3/MeOH), and 4) dehydration ($BzCl/C_5H_5N$) of the intermediate amide, were carried out under the same conditions as described for the conversion of **6-RR** into **1-RR**. The disaccharide derivatives **7-MM** and **8-MM**, and the target L-mannosyl-D-mannose monomer **1-MM** were obtained in 87, 84, and 74% yield, respectively.

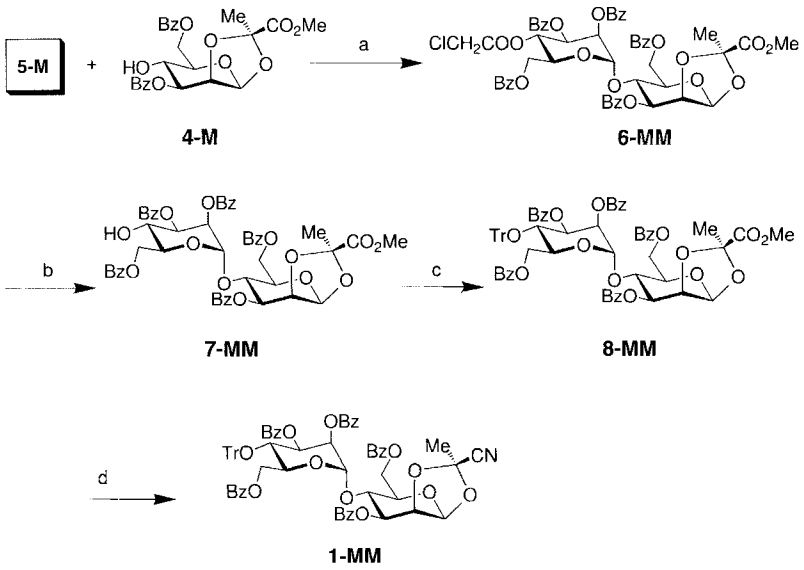
The attempt at the cyclooligomerization of the L-mannosyl-D-mannose monomer **1-MM** afforded, after 60 h, a reaction mixture with a noticeably different composition of products compared with the results of the analogous reaction carried out on **1-RR**. In this case, MALDI-TOFMS analysis revealed a highly complex mixture of products. The majority of peaks in the spectrum could not be assigned to the desired cyclic oligosaccharides. Nevertheless, one cyclic product, the hexasaccharide **28** (Scheme 9), was isolated from the reaction mixture by preparative reverse-phase HPLC. The acyl protecting groups were re-



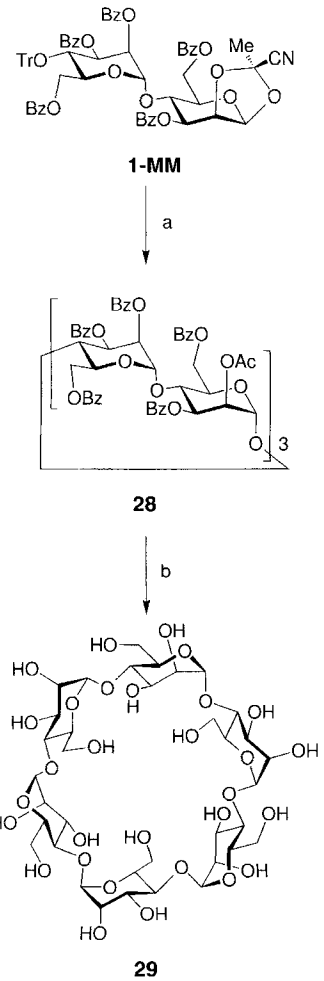
Scheme 6. Acetylation of the D-rhamnose-L-rhamnose cyclic hexasaccharide **20**. Reagents and conditions: a) Ac_2O/C_5H_5N, 20 °C, 48 h, 12%.



Scheme 7. Synthesis of the L-mannosyl donor **5-M**. Reagents and conditions: a) $BzCl/C_5H_5N$, −40 to 20 °C, 24 h, 35%; b) $ClCH_2COCl/C_5H_5N/CH_2Cl_2$, 20 °C, 4 h, 96%; c) $AcBr/H_2O/AcOH/CH_2Cl_2$, 20 °C, 18 h, quantitative.



Scheme 8. Synthesis of the L-mannosyl-D-mannose disaccharide monomer **1-MM** from the glycosyl donor **5-M** and the glycosyl acceptor **4-M**. Reagents and conditions: a) AgOTf/collidine/CH_2Cl_2, $-30\,^{\circ}C$, 1 h, 67%; b) $(H_2N)_2CS/MeCN/H_2O$, 48 h, $20\,^{\circ}C$, 87%; c) $TrClO_4$/collidine/CH_2Cl_2, $20\,^{\circ}C$, 4 h, 84%; d) i) NH_3/MeOH/CH_2Cl_2, -5 to $20\,^{\circ}C$, 18 h, ii) $BzCl/C_5H_5N$, $20\,^{\circ}C$, 18 h, 74%.



Scheme 9. Formation of cyclic hexasaccharide **28** by cyclooligomerization of **1-MM** and deprotection of **28** to **29**. Reagents and conditions: a) $TrClO_4$/CH_2Cl_2, $20\,^{\circ}C$, 60 h, 8%; b) i) NaOMe/MeOH, ii) H_2O, $20\,^{\circ}C$, 24 h, 93%.

moved successfully from **28** (by successive treatment with NaOMe/MeOH/CH_2Cl_2 and NaOH/H_2O) to afford the free cyclic hexasaccharide **29**.

Three similar disaccharide monomers have been investigated as precursors for the preparation of cyclic oligosaccharides using the polycondensation/cycloglycosylation procedure — namely, derivatives **1-RR** and **1-MM**, and the previously reported **1-RM**[7] (Figure 6). The monomer **1-MM** shows by far the lowest tendency toward the formation of cyclic oligosaccharides (Table 1). Conversely, under the same reaction conditions, the monomers **1-RR** and **1-RM**, bearing a rhamnose residue with D- and L-configuration, respectively, at the nonreducing end of the disaccharide structure, were converted efficiently into mixtures of cyclic oligosaccharides. Consequently, it is tempting to propose that the presence of the benzoate group at C-6′ is responsible for the low efficiency of the macrocyclization process. The "deactivating" effect of the benzoyl group at O-6′ may be ascribed to 1) the different reactivity of the 4-*O*-Tr group as glycosyl acceptor in benzoylated rhamnose and mannose residues[22] or 2) the additional steric encumbrance of the large benzoyl group on the 6′-position, which simultaneously reduces the accessibility of the 4-*O*-Tr group and makes the macrocyclization less favorable than the linear growth of the oligosaccharide chain. Especially under the dilution conditions employed, the reduced reactivity of the glycosyl acceptor function favors chain-breaking reactions associated with side reactions of the activated glycosyl donor function. The compositions of the mixture of cyclic products, formed in the reactions of the monomers **1-RM** and **1-RR**, were also different; trimerization and tetramerization were the predominant processes in the case of the reaction of **1-RM**, whereas the linear polycondensation is a more efficient process in the case of cyclooligomerization of **1-RR**, giving rise to comparable yields of five cyclic oligosaccharides of different size. Despite the moderate yields obtained in the synthesis of compounds **15**–**19**, the relatively short procedure involving cyclooligomerization of the disaccharide monomer **1-RR** is, undoubtedly, more convenient than the alternative step-by-step preparation of long-chain linear precursors such as hexa-, octa-, deca-, dodeca-, and tetradecasaccharides followed by cyclization as independent events.

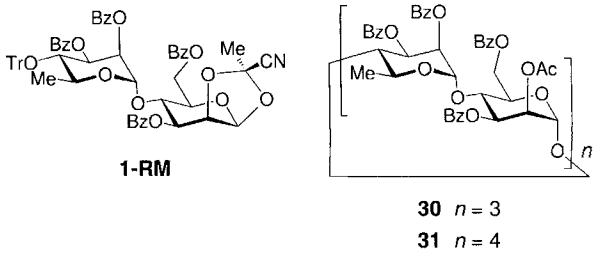
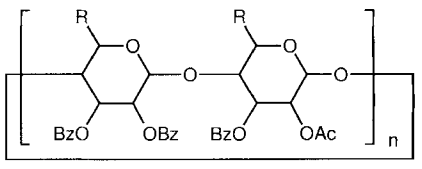


Figure 6. Structure of cyclic [(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranoso)-oligosaccharides **30** and **31** and their synthetic precursor **1-RM** (ref. [7]).

Table 1. Yield of cyclic oligosaccharides in polycondensation/cycloglycosylation of disaccharide monomers **1-RR**, **1-MM**, and **1-RM** [a]. *n* is the number of disaccharide repeating units in the cyclic oligosaccharide.



Disaccharide precursor	*n* = 3	4	5	6	7
1-RR	**15** (14%)	**16** (17%)	**17** (15%)	**18** (10%)	**19** (7.5%)
1-RM	**30** (34%)	**31** (31%)			
1-MM	**28** (9%)				

[a] For **1-RM** the results are taken from ref. [7].

0947-6539/97/0308-1304 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

Structural Characterization of Protected and Free Cyclic Oligosaccharides: In order to prove the macrocyclic character of an oligomeric compound, two preliminary pieces of evidence are sufficient. They are the fact that 1) high molecular symmetry (C_n or S_n) can be deduced from NMR spectroscopy and 2) the precise molecular masses can be measured by mass spectrometry. Both these pieces of evidence have been obtained for the cyclic oligosaccharides presented in this paper.

^1H NMR and ^{13}C NMR Spectroscopy: All the disaccharide repeating units in the cyclic oligosaccharides **15**–**19** and **28** are equivalent on the NMR timescale and consequently relatively simple spectra relating to disaccharide residues were obtained, whether ^1H or ^{13}C probes were employed. In the ^1H NMR spectra (Figure 7) of **15**–**19** and **28**, signals for protons H-1/H-1′, H-2/H-2′, and H-3/H-3′ resonate as three pairs of peaks with different chemical shifts—a consequence of the different substituents (OAc and OBz) at C-2 of the D- and L-residues. The H-4/H-4′, H-5/H-5′, and H-6/H-6′ protons, which are more remote from the C-2 position, give rise to resonances that are hardly distinguishable for the D- and L-residues.

The ^{13}C NMR spectra (see Experimental Section) of the cyclic oligosaccharides **15**–**19** and **28** are also very distinctive and characteristic. Indeed, each of these spectra contained no more than thirteen signals in the chemical shift region below $\delta = 100$: one of them ($\delta = 20.9$) belongs to the acetyl group and the remainder to the two sets of C-1–C-6 atoms. In these portions of the spectra, the peaks for C-1/C-1′ ($\delta = 98.5$–98.9), C-4/C-4′ ($\delta = 77.7$–81.4 for rhamnose and $\delta = 75.2$ for mannose), and C-6/C-6′ ($\delta = 17.8$–18.4 for rhamnose and $\delta = 62.1$ for mannose) could be assigned, whereas the numerous signals in the region $\delta = 67$–71.6, corresponding to C-2/C-2′, C-3/C-3′, and C-5/C-5′, have not been assigned.

After removal of the protecting groups from the synthetic cyclic oligosaccharides **15**–**19** and **28**, their D- and L-monosaccharide residues became indistinguishable, and their comparable nuclei magnetically equivalent. As a result, the NMR spectra of the cyclic D/L-rhamno-oligosaccharides **20**–**24** appear as if they were the spectra of single monosaccharide residues (Figure 8 and Table 2). This result confirms unequivocally the assumption that the compounds **21**–**24** possess S_n symmetry. Furthermore, the specific optical rotations of **21**–**24**, which were measured in water, were equal to zero, as expected for these achiral compounds.[23]

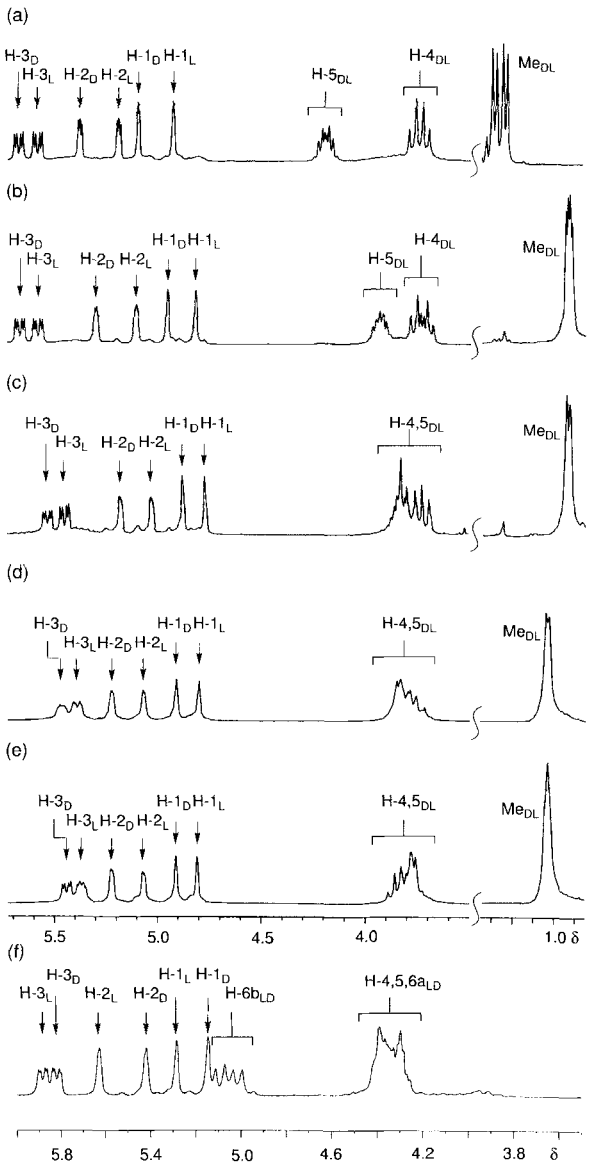


Figure 7. Partial ^1H NMR spectra (300 MHz, $CDCl_3$) showing the ring protons of the protected cyclic oligosaccharides: a) hexasaccharide **15**, b) octasaccharide **16**, c) decasaccharide **17**, d) dodecasaccharide **18**, e) tetradecasaccharide **19**, and f) hexasaccharide **28**.

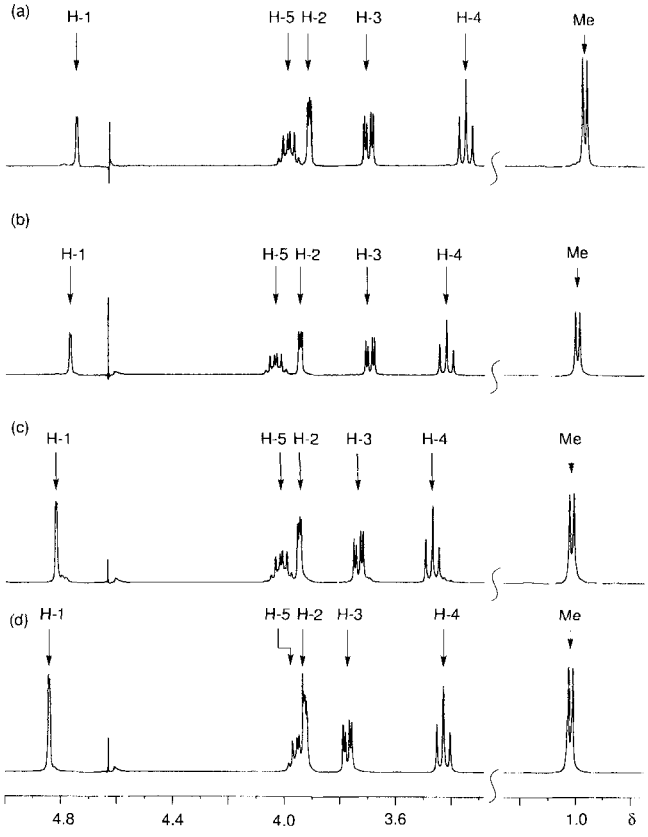


Figure 8. ^1H NMR Spectra (400 MHz, D_2O, HOD suppressed) of the free cyclic D-rhamnosyl-L-rhamno-oligosaccharides: a) octasaccharide **21**, b) decasaccharide **22**, c) dodecasaccharide **22**, d) tetradecasaccharide **24**. The intensity of the peaks in the region between $\delta = 3.50$ and 5.00 has been doubled.

Table 2. Chemical shifts in ^{13}C MNR spectra (75.5 MHz, D_2O, 25 °C) of free cyclic oligosaccharides **20**–**24** and **29**.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
21	104.4	73.4	71.8	85.2	70.6	19.0
22	104.3	73.4	71.6	83.6	71.0	19.0
23	103.9	73.5	71.7	82.8	71.2	19.4
24	103.5	73.2	71.6	84.4	70.6	19.4
29	103.7	74.3	72.6	81.1	72.2	63.3

Also, in the case of the D/L-manno-oligosaccharide **29** only six signals are present in the ^1H NMR spectrum (Figure 9) as well as in the ^{13}C NMR spectrum (Table 2). It was possible to assign all peaks in the ^1H NMR spectrum of **29**, thus confirming its structure with S_6 symmetry. This spectrum was very similar to, but not coincident with, the spectrum reported in the literature[12a] for the cyclic (1 → 4)-α-D-manno-hexaoside.

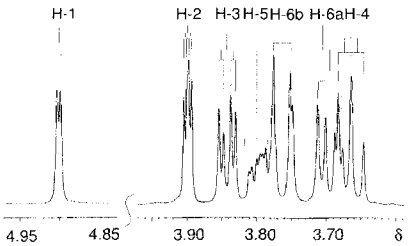


Figure 9. ^1H NMR spectrum (500 MHz, D_2O, HOD suppressed) of the cyclic hexasaccharide **29**.

Mass Spectrometry: The molecular mass of the cyclic oligosaccharides was determined by MALDI-TOFMS (Table 3). This technique is extremely useful, not only for the protected cyclic oligosaccharides **15**–**19** and **28**, but also for free cyclic oligosaccharides **20**–**24** and **29**, which were not amenable to LSIMS. It helped greatly in assigning structures to the cyclic oligosaccharides. The protected cyclic oligosaccharides **15**–**19** and **28** were also characterized in a convincing manner by high-resolution LSIMS.

Table 3. Mass spectrometric data for the protected cyclic oligosaccharides **15**–**19**, **28**, and free cyclic oligosaccharides **20**–**24** and **29**.

Compound	Predicted *m/z*	Observed *m/z*	
	M^+	$[M+Na]^+$ LSIMS [a]	$[M+Na]^+$ MALDI-TOFMS
15	1939.9	1963	1963
16	2586.5	2609	2610
17	3233.1	3255	3255
18	3879.8	3902	3903
19	4526.4	4549	4549
20	876.8	–	899
21	1169.1	–	1192
22	1461.4	–	1485
23	1753.7	–	1777
24	2046.0	–	2071
28	2660.5	2683	2682
29	972.8	–	995

[a] NaOAc was added to the probes to promote ionization.

*X-Ray Crystal Structure of the Cyclic Octasaccharide **21**:* Single crystals of the cyclic octasaccharide **21** suitable for X-ray crystallography were obtained by vapor diffusion of Me_2CO into an aqueous solution of **21**. The X-ray analysis of the cyclic octasaccharide revealed a solid-state structure that departs from ideal S_8 symmetry (Figure 10). The crystallographic symmetry is C_2 and the radii of the polygon formed by the eight glycosidic oxygen atoms range between 5.35 and 5.90 Å (Figure 11). The planes of the four independent alternating (1→4)-linked α-D-

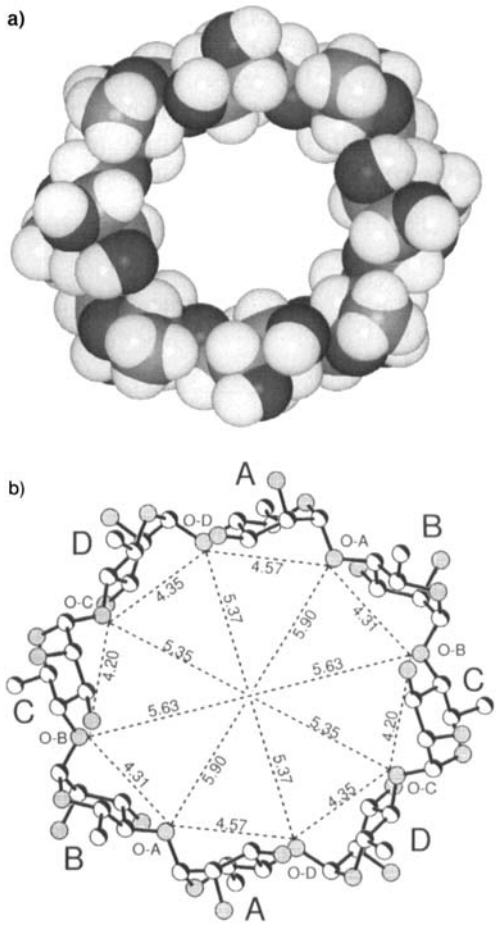


Figure 10. a) Space-filling and b) ball-and-stick representations of the C_2-symmetric solid-state structure of the cyclic octasaccharide **21**. The glycosidic C-O-C bond angles are: 116° at O-A and O-D and 118° at O-B and O-C. The numbers displayed beside the dashed lines indicate the distances (in Å) between adjacent pairs of glycosydic oxygen atoms and their radial distances from the center of the cyclic octasaccharide. a) Dark grey = oxygen atoms; light grey = carbon atoms; white = hydrogen atoms. b) Speckled grey = oxygen atoms; white = carbon atoms.

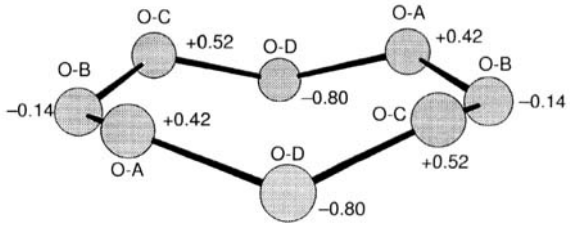


Figure 11. The polygon formed by the eight glycosidic oxygen atoms of the cyclic octasaccharide **21**. The distances (in Å) from the mean plane of this ring are shown beside each oxygen atom. The speckled grey balls represent the eight glycosidic oxygen atoms.

0947-6539/97/0308-1306 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

and α-L-rhamnopyranose residues A, B, C, and D (as defined by C-2/C-3/C-5/ring-O) are inclined by 88°, 98°, 68°, and 93°, respectively, to the mean plane of the eight-oxygen polygon. All four independent rhamnopyranose residues have conventional chair conformations. The absence of molecular rotation–reflection symmetry, coupled with a slight folding of the plane of the macroring, results in the formation of diastereotopic faces for the cyclic octasaccharide. This "polarity" is reflected in the mode of both the packing and the stacking of the macrorings. Molecules are stacked head-to-tail to form polar channels that extend down the crystallographic C_2 axis with an intermolecular translation of ca. 8 Å (Figure 12). The molecules within each

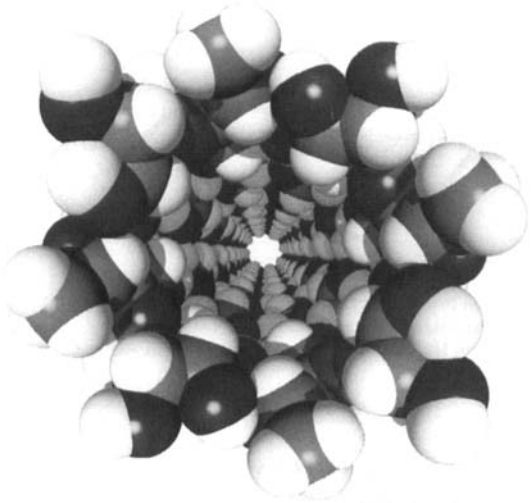


Figure 12. The discrete nanotubular stack of **21** in the solid state seen looking down one of the stacks. Dark grey = oxygen atoms; light grey = carbon atoms; white = hydrogen atoms.

stack are positioned perfectly in register with respect to each other and hence form large open channels, very similar to those reported[7] for the related cyclic octasaccharide **31**, and reminiscent of the hydrogen-bonded nanotubes described by Ghadiri and coworkers[24] for cyclic peptides incorporating alternating D- and L-amino acids. However, there is no indication of the presence of intermolecular hydrogen bonding within the stacks of **21**. In one direction, the crystallographic *a* direction, adjacent stacks are of the same polarity, whereas those in the crystallographic *c* direction alternate in terms of their polarity and are enantiomeric (Figure 13). Adjacent stacks in the *a* direction are offset by half a ring thickness and are cross-linked by [O–H···O] hydrogen bonds, whereas those in the *c* direction are almost in register but have no cross-linking intermolecular hydrogen bonds (Figure 14).

*Investigation of the Binding Abilities of the Cyclic Octasaccharide **21**:* In order to gain some insight into the binding capabilities of the D-rhamnose-L-rhamnose cyclic oligosaccharide **21**, liquid secondary ion mass spectrometry (LSIMS) experiments[25] were carried out as follows. Two solutions were prepared, the first containing a 1:1 mixture of **21** and the sodium salt of anthraquinone-2-sulfonic acid[26] (ASANA)—a possible guest for **21**, which is known[26] to form inclusion complexes with γ-CD, the naturally-occurring cyclic oligosaccharide of a corresponding size—and the second containing a 1:1 mixture of γ-CD and ASANA as a reference standard. When the reference solution was subjected to LSIMS (Figure 15a), a peak at $m/z = 1629$ corresponding to the mass of the complex γ-CD:ASANA was observed along with a peak at $m/z = 1319$ for γ-CD plus Na^+ ions. Similarly, when the solution containing the cyclic oligosaccharide **21** and ASANA was subjected to LSIMS (Figure 15b), a peak at $m/z = 1501$ for the complex **21**:ASANA was observed—once again, together with the peak at $m/z = 1191$ for **21** plus Na^+ ions. This evidence suggests strongly that the cyclic oligosaccharide **21** has binding abilities similar to those exhibited by γ-CD.

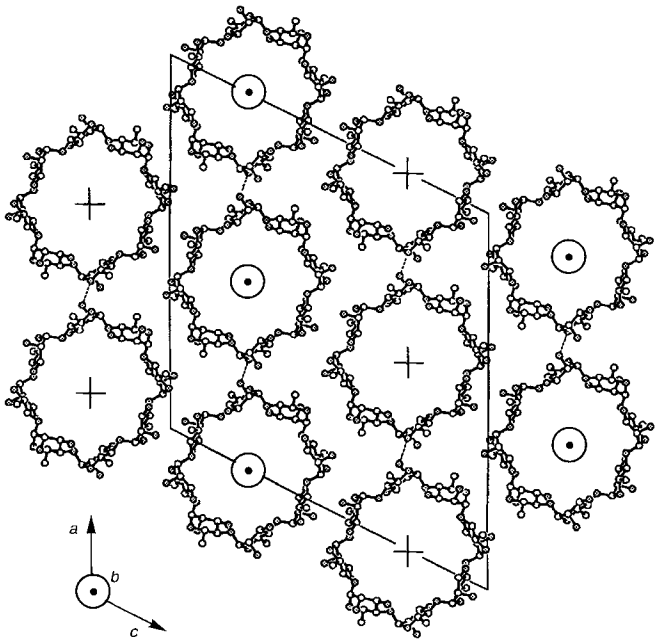


Figure 13. The near close-packed hexagonal array of molecules of **21**. Interstack hydrogen bonds are shown. The circle-and-dot and the cross symbols show the respective polarities of the stacks.

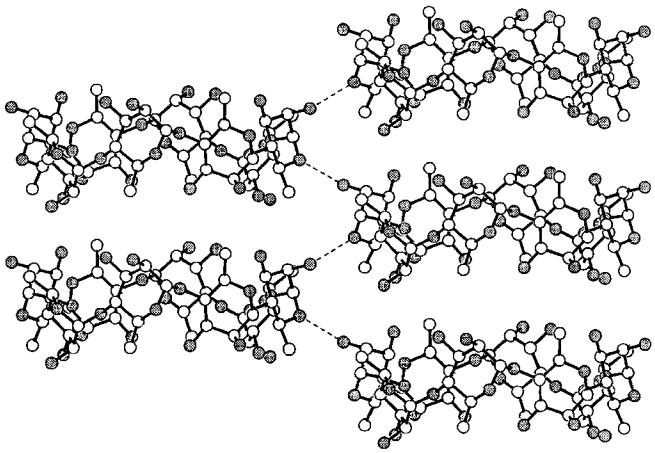


Figure 14. Ladder-like hydrogen bonds between stepped adjacent stacks of molecules of **21**. The [O···O] distance is 2.73 Å. Speckled grey circles = oxygen atoms; open circles = carbon atoms.

*X-Ray Crystal Structure of the Cyclic Hexasaccharide **29**:* Single crystals suitable for X-ray crystallography were obtained by

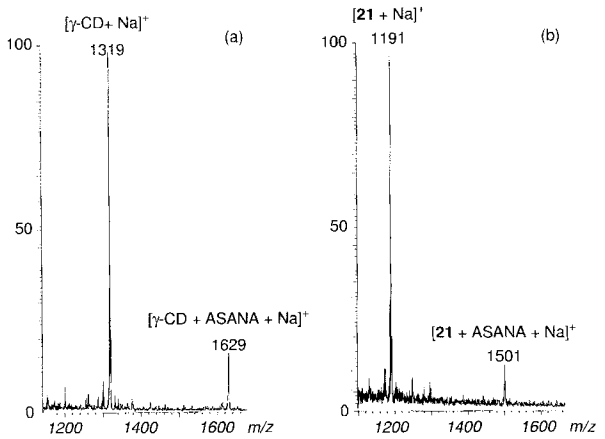


Figure 15. LSIMS spectra of a) an aqueous solution containing a 1:1 mixture of γ-CD and ASANA; b) an aqueous solution containing a 1:1 mixture of the octasaccharide **21** and ASANA.

cooling a D_2O solution of **29**. The X-ray analysis of **29** reveals a solid-state structure that exhibits marked departures from ideal S_6 symmetry (Figure 16). The cyclic hexasaccharide has crystallographic C_i symmetry and the radii of the polygon formed by the six glycosidic oxygen atoms (which adopt the chair-like arrangement shown in Figure 17) range between 4.01 and 4.51 Å. The alternating (1→4)-linked α-D- and α-L-mannopyranosyl residues (ABCĀB̄C̄) have conventional $^4C_1$ and $^1C_4$ conformations. The planes of the three independent pyranose rings A, B, and C (as defined by C-2/C-3/C-5/ring-O) are inclined by 107°, 81°, and 92°, respectively, to the mean plane of the O_6 polygon (Figure 17). Further departures from S_6 symmetry are observed in the relative orientations of the hydroxymethyl groups, the O–C-5–C-6–O-6 torsional angles being +71°, −64°, and −65° for residues A, B, and C, respectively.

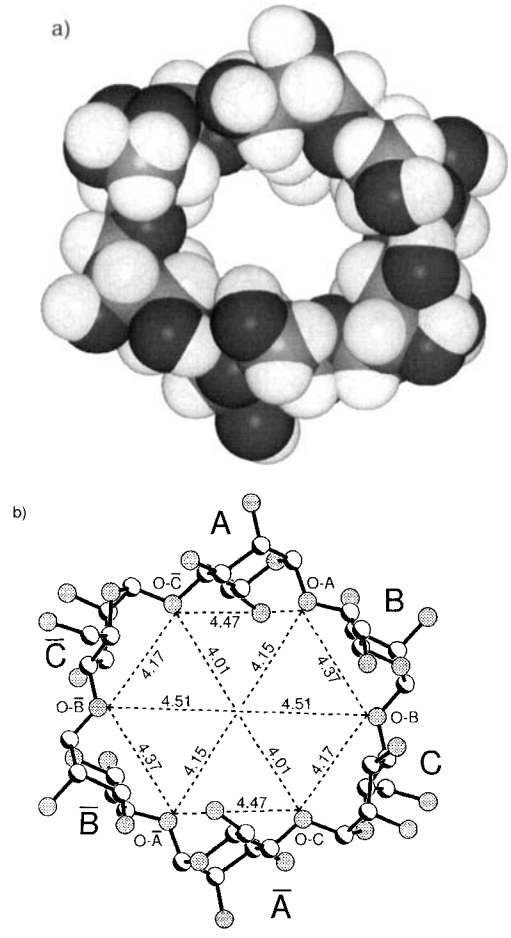


Figure 16. a) Space-filling and b) ball-and-stick representations of the C_i symmetric solid-state structure of the cyclic hexasaccharide **29**. The glycosidic C-O-C bond angles are: 117° at O-A and O-C and 119° at O-B. The numbers displayed beside the dashed lines indicate the distances (in Å) between adjacent pairs of glycosydic oxygen atoms and their radial distances from the center of the cyclic hexasaccharide. a) Dark grey = oxygen atoms; light grey = carbon atoms; white = hydrogen atoms. b) Speckled grey = oxygen atoms; white = carbon atoms.

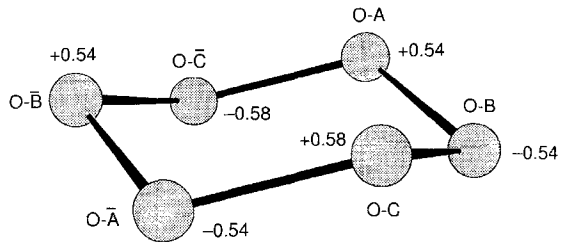


Figure 17. The polygon formed by the six glycosidic oxygen atoms of the cyclic hexasaccharide **29**. The distances (Å) from the mean plane of this ring are shown beside each oxygen atom. The speckled grey balls represent the six glycosidic oxygen atoms.

Inspection of the packing of **29** reveals an interlocked parquet-like pattern with no free pathways through the superstructure (Figure 18). The overall assemblage is stabilized by both intermacroring and intermolecular hydrogen bonding (involving some of the nine D_2O molecules per cyclic hexasaccharide). These hydrogen bonds are present both within and between the parquet-like sheet arrangements.

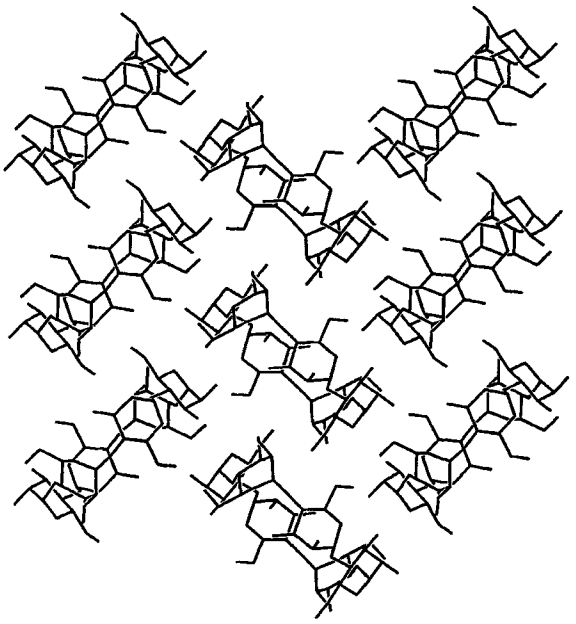


Figure 18. The parquet-like packing of the molecules of the cyclic hexasaccharide **29**.

© VCH Verlagsgesellschaft mbH, D-69451 Weinheim, 1997 0947-6539/97/0308-1308 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

Conclusion

The polycondensation/cyclooligomerization approach to the preparation of cyclic oligosaccharides has been applied successfully to the preparation of cyclotris- (**20**), cyclotetrakis- (**21**), cyclopentakis- (**22**), cyclohexakis- (**23**), and cycloheptakis-[(1→4)-α-D-rhamnopyranosyl-(1→4)-α-L-rhamnopyranosyl] (**24**), and cyclotris[(1→4)-α-L-mannopyranosyl-(1→4)-α-D-mannopyranosyl] (**29**). These unique compounds possess two enantiotopic rims and, as a consequence of the S_n symmetry, they are achiral. The synthetic approach relies upon the rational design of suitable disaccharide precursors, namely, the so-called disaccharide monomers **1-RR** and **1-MM**. The efficient formation of the D-rhamnose-L-rhamnose cyclic oligosaccharides from the monomer **1-RR** can be accounted for by the high reactivity of both the rhamnose-derived glycosyl donor and acceptor functions and the preorganization of the growing oligosaccharide chains. The axial orientation of the C-1/O-1 bond and the equatorial orientation of the C-4/O-4 bond on the pyranosyl rings determines the helical conformation of the linear oligosaccharides. In the case of the L-mannose-D-mannose monomer **1-MM**, the polycondensation/cyclooligomerization reaction lacks the high efficiency observed in the D-rhamnose-L-rhamnose series and, indeed, in the previously reported[7] L-rhamnose-D-mannose situation. This result is probably a consequence of the increased steric hindrance of the BzO group on the C-6′ position of the monomer and the concomitant decrease in nucleophilicity of the oxygen atom in the 4′-position of the disaccharide monomer **1-MM**.

In the solid state, it has been shown that the cyclic octasaccharide **21** composed of alternating D- and L-rhamnopyranosyl residues assembles to form nanotubules of ca. 1 nm diameter, not too dissimilar from those reported[7] for the L-rhamnose-D-mannose octasaccharide **31**, but contrasting with the tight paquet-like solid-state superstructure constructed by molecules of the cyclic hexasaccharide **29** composed of alternating D- and L-mannopyranosyl residues. It is conceivable that these new families of cyclic oligosaccharides could become interesting candidates for research in the area of interfacial science, taking into account the evidence presented that these novel compounds can act as molecular receptors toward appropriately structured substrates in a similar manner to the CDs, the most well-known of the cyclic oligosaccharides.

Experimental Section

General Techniques: Chemicals, including monosaccharides, were purchased from Aldrich, Sigma, or Lancaster. $TrClO_4$ was prepared according to a literature procedure.[27] Solvents were dried as recommended in the literature.[28] Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Kieselgel 60 F 254 (Merck). The plates were inspected by UV light and developed with 5% H_2SO_4 in EtOH at 120 °C. Column chromatography was performed on silica gel 60 F (Merck 9385, 230–400 mesh). High performance liquid chromatography (HPLC) was carried out on Dynamax C-18 reverse phase columns (Anachem) with a Gilson 714 system. Fractions were monitored using a variable UV detector or a Knauer Differential Refractometer. Melting points were determined on an Electrothermal 9200 apparatus. Optical rotations were measured at 22±2 °C on Perkin–Elmer 457 polarimeter. ^{1}H NMR spectra were recorded on either a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX400 (400 MHz) spectrometer or Bruker 500 (500 MHz) spectrometer with the solvent reference as internal standards. ^{13}C NMR spectra were recorded on a Bruker AC300 (75.5 MHz) spectrometer or a Bruker AMX400 (100.6 MHz) spectrometer using the JMOD pulse sequence. Low-resolution mass spectra (EIMS and CIMS) were obtained on either a Kratos Profile or a VG Prospec mass spectrometer. Fast atom bombardment mass spectra (FABMS) were recorded on a Kratos MS80RF spectrometer using a Krypton primary atom beam at 8 eV and a nitrobenzyl alcohol matrix. Liquid secondary ion mass spectra (LSIMS) were recorded on a VG Zapspec mass spectrometer equipped with a cesium gun operating at ≈30 keV. Matrix-assisted laser desorption ionization/time-of-flight mass spectra (MALDI-TOFMS) were recorded on a Kratos Kompact MALDI III instrument using a gentisic acid matrix or a indolacrylic acid matrix. Microanalyses were performed by the University of North London Microanalytical Service.

3-*O*-Benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-L-rhamnopyranose (4-R): 1,2-*O*-[1-(*exo*-Methoxycarbonyl)ethylidene]-β-L-rhamnopyranose[15b] (**3-R**) (9.89 g, 39.8 mmol) was dissolved in C_5H_5N (100 mL), and BzCN (4.75 g, 39.8 mmol) was added at 0 °C. The reaction mixture was stirred under nitrogen overnight. MeOH (10 mL) was added and the mixture was then diluted with CH_2Cl_2 (150 mL). The solution was washed with H_2O (100 mL) and aqueous $NaHCO_3$ solution (3 × 100 mL), before being dried and concentrated. The mixture was subjected to column chromatography (SiO_2:$CHCl_3$/EtOAc, 80:20 to 70:30) to give a mixture of mono- and dibenzoylated compounds. Crystallization from hot MeOH afforded the benzoate **4-R** (8.13 g, 23.1 mmol, 58%); R_f = 0.39 ($CHCl_3$/EtOAc, 80:20); $[\alpha]_D$ −18.6 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37 (d, $J_{5,6}$ = 6.2 Hz, 3H; H-6), 1.73 (s, 3H; CCH_3), 2.33 (d, $J_{4,OH}$ = 4.8 Hz, 1H; OH), 4.78 (m, 1H; H-5), 3.70 (s, 3H; CO_2CH_3), 4.13 (ddd, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, $J_{4,OH}$ = 4.8 Hz, 1H; H-4), 4.68 (dd, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 4.0 Hz, 1H; H-2), 5.21 (dd, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 9.2 Hz, 1H; H-3), 5.42 (d, $J_{1,2}$ = 2.2 Hz, 1H; H-1), 7.42–7.63 and 8.06–8.12 (m, 5H; C_6H_5CO); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.8 (C-6), 23.6 (CH_3C), 52.7 (OCH_3), 70.6, 71.7, 74.1, 78.4 (C-2, C-3, C-4, C-5), 97.4 (C-1), 107.7 (CH_3C), 128.6, 129.4, 130.2, 133.6 (C_6H_5), 166.8 (C_6H_5CO), 169.3 (CO_2CH_3); FABMS: m/z = 375 $[M+Na]^+$; $C_{17}H_{20}O_8$ (352.34): calcd C 57.95, H 5.72; found C 57.83, H 5.65.

Methyl 4-*O*-Chloroacetyl-2,3-*O*-isopropylidene-α-D-rhamnopyranoside (11): Methyl 4-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-rhamnopyranoside[16c] (**9**, 19.06 g, 59.1 mmol) was dissolved in a mixture of dry MeOH (250 mL) and dry CH_2Cl_2 (50 mL), and 1 M NaOMe/MeOH (70 mL) was added. The removal of the benzoyl group was monitored by TLC (SiO_2, PhMe/EtOAc, 90:10). After 4 h, the debenzoylation was complete; the solution was neutralized with 1 M HCl and concentrated to give alcohol **10** as a colorless syrup. The syrup was dissolved in CH_2Cl_2 (150 mL), and chloroacetyl chloride (4.41 mL, 55.5 mmol) and C_5H_5N (4.48 mL, 55.5 mmol) were added under nitrogen while cooling to 0 °C. The resulting reaction mixture was stirred overnight at room temperature. Addition of MeOH (10 mL), followed by a standard aqueous workup procedure, afforded a crude compound, which was purified by column chromatography (SiO_2, PhMe/EtOAc, 90:10) to give the chloroacetate **11** (10.46 g, 42.7 mmol, 77%); R_f = 0.49 (PhMe/EtOAc, 90:10); $[\alpha]_D$ +16.0 (c = 2.42 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (d, $J_{5,6}$ = 6.3 Hz, 3H; H-6), 1.31 (s, 3H; $C(CH_3)_2$), 1.54 (s, 3H; $C(CH_3)_2$), 3.36 (s, 3H; OCH_3), 3.73 (dq, 1H; H-5), 4.07 (s, 2H; $ClCH_2CO$), 4.09–4.17 (m, 2H; H-2, H-3), 4.84–4.09 (m, 2H; H-1, H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.9 (C-6), 26.4, 27.7 ($C(CH_3)_2$), 40.9 ($ClCH_2CO$), 55.0 (OCH_3), 63.5 (C-5), 76.6, 77.0, 77.5 (C-2, C-3, C-4), 98.0 (C-1), 110.0 ($C(CH_3)_2$), 166.7 (C=O); FABMS: m/z = 295 $[M+H]^+$, 317 $[M+Na]^+$; $C_{12}H_{19}ClO_6$ (294.73): calcd C 48.97, H 6.51; found C 48.82, H 6.67.

Methyl 4-*O*-Chloroacetyl-α-D-rhamnopyranoside (12): The chloroacetate **11** (10.4 g, 35.4 mmol) was dissolved in $CHCl_3$ and the isopropylidene group was removed by treatment with a 10% solution of CF_3COOH in H_2O (10 mL) for 6 h at room temperature. Removal of the solvents gave the diol **12** (8.62 g, 34.0 mmol, 96%); R_f = 0.28 ($CHCl_3$/MeOH, 90:10); m.p. 108–109 °C; $[\alpha]_D$ +78.1 (c = 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.22 (d, $J_{5,6}$ = 6.2 Hz, 3H; H-6), 3.37 (s, 3H; OCH_3), 3.77 (dq, 1H; H-5), 3.86 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 10.0 Hz, 1H; H-3), 3.93 (dd, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.5 Hz, 1H; H-2), 4.12 (m, 2H; $COCH_2Cl$), 4.70 (d, 1H; H-1), 3.79 (pt, $J_{4,5}$ = 10.0 Hz, 1H; H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.3 (C-6), 40.8 ($COCH_2Cl$), 55.1 (OCH_3), 65.4 (C-5), 69.8, 71.0

(C-2, C-3) 76.7 (C-4), 100.7 (C-1), 167.9 (C=O); FABMS: $m/z = 277$ $[M+Na]^+$; $C_9H_{15}ClO_6$ (254.67): calcd C 42.45, H 5.94; found C 42.85, H 5.60.

Methyl 2,3-Di-*O*-Benzoyl-4-*O*-chloroacetyl-α-D-rhamnopyranoside (13): A solution of the diol **12** (8.58 g, 33.8 mmol) in CH_2Cl_2 (100 mL) containing C_5H_5N (6.48 mL, 81.1 mmol) was treated with BzCl (8.63 mL, 74.3 mmol) at 0–5 °C and the reaction mixture was stirred for 24 h at room temperature. The mixture was treated with MeOH (10 mL), diluted with CH_2Cl_2 (200 mL), and washed with H_2O (2 × 100 mL), aqueous $NaHCO_3$ solution (2 × 100 mL), and H_2O (100 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was subjected to chromatography (SiO_2:PhMe/EtOAc, 98:2 to 95:5), affording a colorless syrup, which was characterized as the dibenzoate **13** (12.8 g, 27.7 mmol, 82%); $R_f = 0.63$ (PhMe/EtOAc, 96:4); $[\alpha]_D$ −102 ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.35$ (d, $J_{5,6} = 6.3$ Hz, 3H; H-6), 3.47 (s, 3H; OCH_3), 3.96 (m, 2H; $COCH_2Cl$), 4.07 (dq, 1H; H-5), 4.81 (d, $J_{1,2} = 1.7$ Hz, 1H; H-1), 5.46 (pt, $J_{3,4} = J_{4,5} = 10.0$ Hz, 1H; H-4), 5.61 (dd, $J_{1,2} = 1.7$ Hz, $J_{2,3} = 3.4$ Hz, 1H; H-2), 5.66 (dd, $J_{2,3} = 3.4$ Hz, $J_{3,4} = 10.0$ Hz, 1H; H-3), 7.30–8.10 (m, 10H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.6$ (C-6), 40.5 ($COCH_2Cl$), 55.4 (OCH_3), 66.0 (C-5), 69.9, 70.7, 73.3 (C-2, C-3, C-4), 98.5 (C-1), 128.5–133.5 (C_6H_5), 165.4, 165.5 (C_6H_5CO), 166.8 ($COCH_2Cl$); FABMS: $m/z = 485$ $[M+Na]^+$, 463 $[M+H]^+$; $C_{23}H_{23}ClO_8$ (462.88): calcd C 59.68, H 5.01; found C 59.87, H 5.04.

1-*O*-Acetyl-2,3-di-*O*-benzoyl-4-*O*-chloroacetyl-α-D-rhamnopyranoside (14): The dibenzoate **13** (12.0 g, 26.0 mmol) was dissolved in Ac_2O (50 mL) and treated with conc. H_2SO_4 (0.5 mL). The reaction mixture was allowed to stand for 2 h at room temperature. NaOAc (1.7 g) was added and the mixture was poured into ice (300 g) and stirred overnight. The product was extracted with $CHCl_3$ (3 × 80 mL), the combined organic layers were washed with H_2O (100 mL) and an aqueous $NaHCO_3$ solution (3 × 100 mL), dried ($MgSO_4$), and concentrated. Following column chromatography (SiO_2:EtOAc/hexane, 90:10) the product was isolated as the acetate **14** (10.95 g, 22.3 mmol, 86%); $R_f = 0.59$ (PhMe/EtOAc, 96:4); m.p. 105–106 °C; $[\alpha]_D$ −81.6 ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.36$ (d, $J_{5,6} = 6.3$ Hz, 3H; H-6), 2.23 (s, 3H; $COCH_3$), 3.98 (m, 2H; $COCH_2Cl$), 4.17 (dq, 1H; H-5), 5.50 (pt, $J_{3,4} = J_{4,5} = 10.0$ Hz, 1H; H-4), 5.62 (dd, $J_{1,2} = 1.9$ Hz, $J_{2,3} = 3.5$ Hz, 1H; H-2), 5.69 (dd, $J_{2,3} = 3.5$ Hz, $J_{3,4} = 10.0$ Hz, 1H; H-3), 6.26 (s, 1H; H-1) 7.31–8.09 (m, 10H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.5$ (C-6), 20.8 ($COCH_3$), 40.5 ($COCH_2Cl$), 68.4 (C-5), 69.5, 69.6 (C-2, C-3), 72.6 (C-4), 90.6 (C-1), 128.5–133.5 (C_6H_5), 165.2, 165.4 (C_6H_5CO), 166.6 ($COCH_2Cl$), 168.3 (CH_3CO); FABMS: $m/z = 513$ $[M+Na]^+$; $C_{24}H_{23}ClO_9$ (490.90): calcd C 58.72, H 4.72, found C 58.95, H 4.79.

2,3-Di-*O*-benzoyl-4-*O*-chloroacetyl-α-D-rhamnopyranosyl bromide (5-R): A solution of the acetate **14** (9.00 g, 18.36 mmol) and AcBr (7.92 mL, 108 mmol) in CH_2Cl_2 (80 mL) was treated while cooling with MeOH (3.82 mL, 98.4 mmol) in CH_2Cl_2 (20 mL). The solution was maintained at room temperature for 2 h before being poured into a separating funnel filled with crushed ice (200 g). The crude product was separated by extraction with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with H_2O (100 mL), aqueous $NaHCO_3$ solution (2 × 100 mL), dried ($MgSO_4$), and concentrated. The product, which was identified as the bromide **5-R** (9.23 g, 99%), was used immediately for the glycosylation reaction without further purification; $R_f = 0.72$ (PhMe/EtOAc, 95:5); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.40$ (d, $J_{5,6} = 6.3$ Hz, 3H; H-6), 4.01 (m, 2H; $COCH_2Cl$), 4.33 (dq, $J_{4,5} = 10.0$ Hz, $J_{5,6} = 6.3$ Hz, 1H; H-5), 5.55 (pt, $J_{3,4} = J_{4,5} = 10.0$ Hz, 1H; H-4), 5.83 (dd, $J_{1,2} = 1.4$ Hz, $J_{2,3} = 3.5$ Hz, 1H; H-2), 6.01 (dd, $J_{2,3} = 3.5$ Hz, $J_{3,4} = 10.0$ Hz, 1H; H-3), 6.50 (d, $J_{1,2} = 1.4$ Hz, 1H; H-1), 7.32–8.07 (m, 10H, C_6H_5); CIMS: $m/z = 431$ $[M-Br]^+$.

4-*O*-(4-*O*-Chloroacetyl-2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl)-3-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-L-rhamnopyranose (6-RR): A solution of the glycosyl acceptor **4-R** (2.28 g, 6.48 mmol), the glycosyl donor **5-R** (3.31 g, 6.48 mmol), and collidine (0.69 mL, 5.18 mmol) in dry CH_2Cl_2 (5 mL) was added under argon to a cooled (−30 °C) suspension of AgOTf (2.00 g, 7.77 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was allowed to warm up to room temperature. C_5H_5N (1 mL) was added and the suspension was diluted with CH_2Cl_2 (100 mL). The suspension was filtered through a layer of Celite and washed with CH_2Cl_2 (100 mL). The filtrates were combined and washed successively with H_2O (100 mL), aqueous $Na_2S_2O_3$ solution (2 × 100 mL), and H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated. The product was isolated by column chromatography (SiO_2:PhMe/EtOAc, 90:10 to 95:5) to give the title compound **6-RR** (3.30 g, 65%); $R_f = 0.24$ (PhMe/EtOAc, 95:5); m.p. 96–97 °C; $[\alpha]_D$ −25.8 ($c = 1.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.85$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.54 (d, $J_{5,6} = 6.2$ Hz, 3H; H-6), 1.77 (s, 3H; CCH_3), 3.62–3.70 (m, 1H, H-5), 3.71 (s, 3H; OCH_3), 3.83 (s, 2H; $COCH_2Cl$), 3.92 (dq, $J_{4,5} = 9.2$ Hz, $J_{5,6} = 6.2$ Hz, 1H, H-5'), 4.02 (dd, $J_{3,4} \approx J_{4,5} = 9.2$ Hz, 1H; H-4), 4.71 (dd, $J_{1,2} = 2.2$ Hz, $J_{2,3} = 4.1$ Hz, 1H; H-2), 5.20 (s, 1H; H-1'), 5.30 (dd, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4'), 5.46–5.57 (m, 4H, H-1, H-3, H-2', H-3'), 7.13–7.63 and 7.85–8.16 (m, 15H; C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.1$, 18.3 (C-6, C-6'), 23.6 (CCH_3), 40.4 (CH_2Cl), 52.7 (OCH_3), 66.8, 69.4, 70.8, 70.9, 71.6, 72.8, 78.4, 78.6 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', C-5'), 97.1, 98.4 (C-1, C-1'), 107.6 ($CH_3CCO_2CH_3$), 128.4–133.7 (C_6H_5), 165.4, 165.7, 165.9, 166.6 (C_6H_5CO, $ClCH_2CO$), 169.2 (CCO_2CH_3); FABMS: $m/z = 805$ $[M+Na]^+$; $C_{39}H_{39}ClO_{15}$ (782.34) calcd C 59.81, H 5.02; found C 60.01, H 5.09.

3-*O*-Benzoyl-4-*O*-(2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-L-rhamnopyranose (7-RR): A solution of **6-RR** (3.22 g, 4.11 mmol) and $(NH_2)_2CS$ (1.6 g) in a mixture of MeCN/H_2O (110 mL, 10:1) was allowed to stand for 40 h at 20 °C, before the reaction was concentrated, and the residue purified by column chromatography (SiO_2:CH_2Cl_2/EtOAc, 95:5) to give the title compound **7-RR** (2.65 g, 91%); $R_f = 0.48$ (PhMe:EtOAc, 95:5); m.p. 112–113 °C; $[\alpha]_D$ +0.6 ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.92$ (d, $J_{5,6} = 5.9$ Hz, 3H; H-6'), 0.92 (d, $J_{5,6} = 6.2$ Hz, 3H; H-6), 1.73 (s, 3H; CH_3CCO_2), 3.57–3.80 (m, 3H, H-5, H-4', H-5'), 3.69 (s, 3H; OCH_3), 3.97 (dd, $J_{3,4} \approx J_{4,5} = 9.2$ Hz, 1H; H-4), 4.68 (dd, $J_{1,2} = 2.2$ Hz, $J_{2,3} = 4.0$ Hz, 1H; H-2), 5.12 (d, $J_{1,2} = 1.8$ Hz, 1H; H-1'), 5.35 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9.2$ Hz, 1H; H-3'), 5.42–5.50 (m, 3H; H-1, H-3, H-2'), 7.32–7.66 and 7.90–8.18 (m, 15H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.3$, 18.3 (C-6, C-6'), 23.5 (CCH_3), 52.6 (OCH_3), 69.5, 70.8, 71.2, 71.5, 71.6, 72.4, 78.3, 78.4 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', C-5'), 97.0, 98.7 (C-1, C-1'), 107.4 ($CH_3CCCO_2CH_3$), 128.4–133.5 (C_6H_5), 165.7, 165.9, 166.7 (C_6H_5CO), 169.1 (CCO_2CH_3); FABMS: $m/z = 729$ $[M+Na]^+$; $C_{37}H_{38}O_{14}$ (705.86): calcd C 62.88, H 5.42; found C 62.97, H 5.30.

3-*O*-Benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4-*O*-trityl-α-D-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-L-rhamnopyranose (8-RR): $TrClO_4$ (2.78 g, 8.10 mmol) was added in portions during ca. 2 h to a stirred solution of the alcohol **7-RR** (2.49 g, 3.52 mmol) in CH_2Cl_2 (30 mL) containing collidine (1.0 mL, 8.1 mmol) and the reaction mixture was allowed to stand for another 2 h. The mixture was then diluted with CH_2Cl_2 (200 mL), before being washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and concentrated. Successive column chromatography (SiO_2:*n*-hexane/EtOAc, 80:20 to 60:40; then PhMe/Me_2CO, 97:3) of the residue afforded the trityl ether **8-RR** (2.79 g, 84%); $R_f = 0.17$ (*n*-hexane/EtOAc, 80:20); m.p. 143–145 °C; $[\alpha]_D$ +44.0 ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.61$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.45 (d, $J_{5,6} = 6.2$ Hz, 3H; H-6), 1.70 (s, 3H; CCH_3), 3.43 (dd, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4), 3.59–3.69 (m, 1H, H-5), 3.65 (s, 3H; OCH_3), 3.87–4.01 (m, 2H; H-5', H-4'), 4.70 (dd, $J_{1,2} = 2.5$ Hz, $J_{2,3} = 3.9$ Hz, 1H; H-2), 4.93 (d, $J_{1,2} = 2.0$ Hz, 1H; H-1'), 5.26 (dd, $J_{2,3} = 3.1$ Hz, 1H; H-2'), 5.42 (d, $J_{1,2} = 2.5$ Hz, 1H; H-1), 5.53 (dd, $J_{2,3} = 3.9$ Hz, H-3'), 5.63 (dd, $J_{2,3} = 3.9$ Hz, $J_{3,4} = 9.5$ Hz, 1H; H-3), 7.05–8.36 (m, 30H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25C): $\delta = 18.3$, 18.4 (C-6, C-6'), 23.5 (CCH_3), 52.6 (OCH_3), 69.2, 70.9, 71.3, 71.5, 71.8, 72.8, 78.5, 78.6 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', C-5'), 88.2 ($C(C_6H_5)_3$), 97.1, 98.5 (C-1, C-1'), 107.5 ($CH_3CCO_2CH_3$), 126.8–133.3 (C_6H_5), 144.7 (C_{quat} of C_6H_5 in $C(C_6H_5)_3$), 165.3, 165.6, 166.0 (C_6H_5CO), 169.2 (CCO_2CH_3); FABMS: $m/z = 971$ $[M+Na]^+$; $C_{56}H_{52}O_{14}$ (948.86): calcd C 70.87, H 5.52; found C 71.12, H 5.57.

3-*O*-Benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4-*O*-trityl-α-D-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-cyano)ethylidene]-β-L-rhamnopyranose (1-RR): A suspension of the trityl ether **8-RR** (2.79 g, 2.94 mmol) in a mixture of MeOH (250 mL) and CH_2Cl_2 (40 mL) was saturated with NH_3 gas at −5 °C and the solution was maintained overnight at 20 °C. TLC (PhMe/Me_2CO, 80:20) of the reaction mixture revealed the formation of a number of products. The solvents were evaporated off and the residue was dissolved in C_5H_5N (40 mL) and evaporated to dryness. The resulting residue was dissolved in C_5H_5N (40 mL),

0947-6539/97/0308-1310 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

treated with BzCl (2.1 mL, 17.64 mmol), then stirred overnight at room temperature. MeOH (2 mL) was added, the mixture was stirred for 20 min at 20 °C, and then concentrated to dryness. The residue was dissolved in CH_2Cl_2 (200 mL), washed with aqueous $NaHCO_3$ solution and H_2O, dried, and concentrated to a residue. Column chromatography (SiO_2:PhMe/EtOAc, 95:5) of the residue afforded the disaccharide monomer **1-RR** (3.79 g, 87%): $R_f = 0.33$ (PhMe/EtOAc, 95:5); m.p. 136–138 °C; $[\alpha]_D$ +38.7 ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 0.65$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6′), 1.46 (d, $J_{5,6} = 6.2$ Hz, 3H; H-6), 1.88 (s, 3H; CCH_3), 3.46 (dd, $J_{3,4} \approx J_{4,5} = 9.2$ Hz, 1H; H-4), 3.68 (dq, 1H; $J_{4,5} = 9.2$ Hz, $J_{5,6} = 6.2$ Hz, H-5′), 3.88 (dd, $J_{3,4} \approx J_{4,5} = 9.2$ Hz, 1H; H-4′), 3.99 (dq, 1H; $J_{4,5} = 9.2$ Hz, $J_{5,6} = 6.2$ Hz, H-5), 4.77 (dd, $J_{1,2} = 2.1$ Hz, $J_{2,3} = 4.2$ Hz, 1H; H-2), 4.95 (d, $J_{1,2} = 2.0$ Hz, 1H; H-1′), 5.27 (dd, $J_{1,2} = 2.0$ Hz, $J_{2,3} = 3.1$ Hz, 1H; H-2′), 5.46 (d, $J_{1,2} = 2.1$ Hz, 1H; H-1), 5.60 (dd, $J_{2,3} = 4.2$ Hz, $J_{3,4} = 9.2$ Hz, 1H; H-3), 5.64 (dd, $J_{2,3} = 3.1$ Hz, $J_{3,4} = 9.2$ Hz, 1H; H-3′), 7.05–8.36 (m, 30H, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 18.1$, 21,4 (C-6, C-6′), 26.6 (CCH_3), 69.3, 71.0, 71.1, 71.2, 71.5, 72.7, 78.3, 78.9 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 88.3 ($C(C_6H_5)_3$), 96.7, 98.5 (C-1, C-1′), 101.5 (CH_3CCN), 116.7 (CN), 125.3–133.6 (C_6H_5), 144.7 (C_{quat} of C_6H_5 in $C(C_6H_5)_3$), 165.3, 165.6, 165.8 (C_6H_5CO); FABMS: $m/z = 938$ $[M+Na]^+$; $C_{55}H_{49}NO_{12}$ (915.86): calcd C 72.12, H 5.39, N 1.53; found C 72.14, H 5.34, N 1.47.

Cyclotris[(1 → 4)-2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-L-rhamnopyranosyl] (15), Cyclotetrakis[(1 → 4)-2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-L-rhamnopyranosyl] (16), Cyclopentakis[(1 → 4)-2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-L-rhamnopyranosyl] (17), Cyclohexakis-[(1 → 4)-2,3-di-*O*-benzoyl-a-D-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-L-rhamnopyranosyl] (18), Cycloheptakis[(1 → 4)-2,3-di-*O*-benzoyl-α-D-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-L-rhamnopyranosyl] (19): A solution of the disaccharide monomer **1-RR** (1.50 g, 1.64 mmol) in C_6H_6 (12.0 mL) was divided into two equal portions, each of which was placed in one limb of tuning-fork-shaped tubes. The other arms were filled with a solution of $TrClO_4$ (563 mg, 1.64 mmol) in $MeNO_2$ (2.5 mL), the tubes were connected to a vacuum line (4×10^{-3} Torr), and the solutions were freeze-dried. C_6H_6 (3 mL) was distilled into each limb containing the monomer and the freeze-drying was repeated. CH_2Cl_2 (40 mL) was distilled into each of the reaction tubes and the solutions of the monomer and the catalyst were mixed and left for 40 h at 20 °C in the dark. The contents of all tubes were combined, washed with H_2O, and concentrated. Trityl-containing noncarbohydrate products were separated by column chromatography (SiO_2:hexane/EtOAc, 80:20) of the residue, followed by a series of impure fractions containing cyclic oligosaccharides, which were eluted with EtOAc. Further purification of the first two fractions was achieved by reverse-phase HPLC (C-18 column, MeCN) to give **15** (146 mg, 14%), **16** (181 mg, 17%), **17** (158 mg, 15%), **18** (105mg, 10%), and **19** (80 mg, 7.5%) as pure compounds.

Cyclic Hexasaccharide Derivative 15: $[\alpha]_D$ −66.1 ($c = 1.08$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.24$, 1.29 (2 × d, $J_{5,6} = 6$ Hz, 18H; H-6 L-Rha, H-6 D-Rha), 2.00 (s, 9H; CH_3CO_2), 3.70–3.81 (m, 6H; H-5 L-Rha, H-5 D-Rha), 4.15–4.28 (m, 6H; H-4 L-Rha, H-4 D-Rha), 4.96 (brs, 3H; H-1 L-Rha), 5.13 (brs, 3H; H-1 D-Rha), 5.23 (brs, 3 H; H-2 L-Rha), 5.41 (brs, 3H; H-2 D-Rha), 5.61 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9$ Hz, 3H; H-3 L-Rha), 5.70 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9$ Hz, 3H; H-3 D-Rha), 7.30–7.61 and 7.90–8.05 (m, 45H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C); $\delta = 18.3$, 18.4 (C-6 L-Rha, C-6 D-Rha), 21.0 (CH_3CO_2), 67.6, 70.6, 71.1, 71.1, 71.5, 71.6, 81.3, 81.4 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 98.5, 98.6 (C-1 L-Rha, C-1 D-Rha), 128.2–133.4 (C_6H_5), 165.4, 165.5, 165.8 (C_6H_5CO), 170.3 (CH_3CO_2); HRMS (LSIMS, NaOAc added): calcd for $C_{103}{}^{13}C_2H_{102}O_{36}Na$ $[M+Na]^+$ 1963.6116, observed 1963.6167.

Cyclic Octasaccharide Derivative 16: $[\alpha]_D$ −95.4 ($c = 0.76$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.93$, 0.94 (2 × d, $J_{5,6} = 6$ Hz, 24H; H-6 L-Rha, H-6 D-Rha), 2.05 (s, 12H; CH_3CO_2), 3.68–3.79 (m, 8H; H-5 L-Rha, H-5 D-Rha), 3.90–3.98 (m, 8H; H-4 L-Rha, H-4 D-Rha), 4.83 (brs, 4H; H-1 L-Rha), 4.96 (brs, 4H; H-1 D-Rha), 5.11 (brs, 4H; H-2 L-Rha), 5.30 (brs, 4H; H-2 D-Rha), 5.58 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9$ Hz, 4H; H-3 L-Rha), 5.67 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9$ Hz, 4H; H-3 D-Rha), 7.31–7.61 and 7.95–8.09 (m, 60H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.6$, 17.7 (C-6 L-Rha, C-6 D-Rha), 20.9 (CH_3CO_2), 68.2, 68.3, 69.9, 70.1, 70.8, 71.4, 80.8, 81.1 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 99.2, 99.3 (C-1 L-Rha, C-1 D-Rha), 128.4–134.0 (C_6H_5), 165.2, 165.2, 165.7 (C_6H_5CO); 170.1 (CH_3CO_2); HRMS (LSIMS, NaOAc added): calcd for $C_{138}{}^{13}C_2H_{136}O_{48}Na$ $[M+Na]^+$ 2609.8166, observed 2609.8159.

Cyclic Decasaccharide Derivative 17: $[\alpha]_D$ −106.9 ($c = 1.06$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.94$ (brd, $J_{5,6} = 6$ Hz, 30H; H-6 L-Rha, H-6 D-Rha), 2.07 (s, 15H; CH_3CO_2), 3.70–3.89 (m, 20H; H-4 L-Rha, H-4 D-Rha, H-5 L-Rha, H-5 D-Rha), 4.78 (brs, 5H; H-1 L-Rha), 4.89 (brs, 5H; H-1 D-Rha), 5.04 (brs, 5H; H-2 L-Rha), 5.19 (brs, 5H; H-2 D-Rha), 5.46 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9.2$ Hz, 5H; H-3 L-Rha), 5.67 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9.1$ Hz, 5H; H-3 D-Rha), 7.35–7.60 and 7.98–8.09 (m, 75H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.8$, 17.8 (C-6 L-Rha, C-6 D-Rha), 20.9 (CH_3CO_2), 68.4, 68.5, 69.7, 70.9, 70.9, 71.5, 79.2, 79.2 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 98.7, 98.7 (C-1 L-Rha, C-1 D-Rha), 128.6–133.5 (C_6H_5), 165.1, 165.1, 165.5 (C_6H_5CO); 170.0 (CH_3CO_2); HRMS (LSIMS, NaOAc added): calcd for $C_{173}{}^{13}C_2H_{170}O_{60}Na$ $[M+Na]^+$ 3256.0216, observed 3256.0276.

Cyclic Dodecasaccharide Derivative 18: $[\alpha]_D$ −105.1 ($c = 1.19$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.02$ (brd, $J_{5,6} = 5$ Hz, 36H; H-6 L-Rha, H-6 D-Rha), 2.07 (s, 18H; CH_3CO_2), 3.71–3.85 (m, 24H; H-4 L-Rha, H-4 D-Rha, H-5 L-Rha, H-5 D-Rha), 4.81 (brs, 6H; H-1 L-Rha), 4.91 (brs, 6H; H-1 D-Rha), 5.07 (brs, 6H; H-2 L-Rha), 5.22 (brs, 6H; H-2 D-Rha), 5.38–5.45 (m, 12H; H-3 L-Rha, H-3 D-Rha), 7.36–7.64 and 7.94–8.10 (m, 90H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.9$, 17.9 (C-6 L-Rha, C-6 D-Rha), 20.9 (CH_3CO_2), 67.1, 68.4, 69.6, 69.7, 70.9, 71.5, 78.2, 78.3 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 98.2, 98.4 (C-1 L-Rha, C-1 D-Rha), 128.6–133.3 (C_6H_5), 165.0, 165.0, 165.5 (C_6H_5CO); 170.0 (CH_3CO_2); HRMS (LSIMS, NaOAc added): calcd for $C_{208}{}^{13}C_2H_{204}O_{72}Na$ $[M+Na]^+$ 3902.2266, observed 3902.2433.

Cyclic Tetradecasaccharide Derivative 19: $[\alpha]_D$ −65.6 ($c = 1.09$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.04$ (brs, 42H; H-6 L-Rha, H-6 D-Rha), 2.08 (s, 21H; CH_3CO_2), 3.72–3.90 (m, 28H; H-4 L-Rha, H-4 D-Rha, H-5 L-Rha, H-5 D-Rha), 4.81 (brs, 7H; H-1 L-Rha), 4.91 (brs, 7H; H-1 D-Rha), 5.05 (brs, 7H; H-2 L-Rha), 5.23 (brs, 7H; H-2 D-Rha), 5.34–5.47 (m, 14H; H-3 L-Rha, H-3 D-Rha), 7.34–7.62 and 7.88–8.05 (m, 105H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.8$, 17.8 (C-6 L-Rha, C-6 D-Rha), 20.9 (CH_3CO_2), 68.5, 68.5, 69.7, 70.9, 70.9, 71.5, 77.7, 77.8 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 98.0, 98.2 (C-1 L-Rha, C-1 D-Rha), 128.6–133.5 (C_6H_5), 165.1, 165.1, 165.5 (C_6H_5CO); 170.0 (CH_3CO_2); HRMS (LSIMS, NaOAc added): calcd for $C_{243}{}^{13}C_2H_{238}O_{84}Na$ $[M+Na]^+$ 4548.4317, observed 4548.4296.

Cyclotris[(1 → 4)-2,3-di-*O*-acetyl-α-D-rhamnopyranosyl-(1 → 4)-2,3-di-*O*-acetyl-α-D-rhamnopyranosyl] (25): NaOMe/MeOH (1 M, 1 mL) was added to a solution of the cyclic hexasaccharide derivative **15** (23 mg, 0.012 mmol) in CH_2Cl_2 (5 mL) and MeOH (10 mL), and the reaction mixture stirred for 5 h at ambient temperature. The solvents were evaporated off and the residue was dissolved in H_2O (10 mL) and stirred overnight. The solution was then neutralized with 1 M HCl, the residue was dissolved in C_5H_5N (10 mL), and Ac_2O was added. The reaction mixture was again stirred overnight. MeOH (5 mL) was added, and the mixture was stirred for an additional 10 min. The solution was then diluted with CH_2Cl_2 (50 mL), washed with H_2O (2 × 50 mL), 1 M HCl (50 mL), and H_2O (2 × 50 mL), then concentrated to dryness. The residue was suspended in MeCN (1 mL), filtered, and then washed with another portion of MeCN (1 mL). The resulting white solid was characterized as the peracetate **25** (2 mg, 0.0014 mmol, 12%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.35$ (d, $J_{5,6} = 6$ Hz, 18H, H-6), 2.02 (s, 18H, CH_3CO), 2.13 (s, 18H, CH_3CO), 3.54 (dd, $J_{3,4} = J_{4,5} = 9.4$ Hz, 6H, H-4), 3.96 (dt, $J_{4,5} = 9.4$ Hz, $J_{5,6} = 6$ Hz, 6H, H-5), 4.86 (d, $J_{1,2} = 2$ Hz, 6H, H-1), 5.04 (dd, $J_{1,2} = 2$ Hz, $J_{2,3} = 4$ Hz, 6H, H-2), 5.24 (dd, $J_{2,3} = 4$ Hz, $J_{3,4} = 9.4$ Hz, 6H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$, 31 °C): $\delta = 18.3$ (C-6), 21.0, 21.0 (CH_3CO), 67.3, 70.4, 70.7, 80.5 (C-2, C-3, C-4, C-5), 98.4 (C-1), 170.0, 170.3 (CH_3CO); HRMS (LSIMS): calcd for $C_{60}H_{84}O_{36}Na$ $[M+Na]^+$ 1403.4606, observed 1403.4640.

Cyclotetrakis[(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyrano-syl] (21): NaOMe/MeOH (1 M, 1 mL) was added to a solution of the cyclic octasaccharide derivative **16** (104 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) and MeOH (10 mL) and the reaction mixture was stirred for 5 h at ambient temperature. The solvents were evaporated off, the residue dissolved in H_2O (20 mL), and neutralized with Amberlite (H^+). The aqueous solution was washed with CH_2Cl_2 (2 × 15 mL), concentrated, and subjected to HPLC (C-18 reverse

phase column, H_2O/MeCN 95:5) to afford the cyclic octasaccharide **21** (42 mg, 0.036 mmol, 73%); ^1H NMR (400 MHz, D_2O, 31 °C): $\delta = 1.22$ (d, $J_{5,6} = 6$ Hz, 24H, H-6), 3.39 (dd, $J_{3,4} = J_{4,5} = 9.4$ Hz, 8H, H-4), 3.74 (dd, $J_{2,3} = 4$ Hz, $J_{3,4} = 9.4$ Hz, 8H, H-3), 3.94 (dd, $J_{1,2} = 2$ Hz, $J_{2,3} = 4$ Hz, 8H, H-2), 4.02 (dt, $J_{4,5} = 9.4$ Hz, $J_{5,6} = 6$ Hz, 8H, H-5), 4.79 (d, $J_{1,2} = 2$ Hz, 8H, H-1); ^{13}C NMR (75.5 MHz, D_2O, 25 °C): $\delta = 19.0$ (C-6), 70.6 (C-5), 71.8 (C-3), 73.4 (C-2), 85.2 (C-4), 104.4 (C-1); MALDI-TOFMS: $m/z = 1192$ $[M+Na]^+$. Single crystals suitable for X-ray crystallography were grown by vapor diffusion of Me_2CO into an aqueous solution of **21**. $C_{48}H_{80}O_{32}\cdot Me_2CO\cdot 13H_2O$, $M = 1461.4$, monoclinic, $a = 34.432(5)$, $b = 7.986(2)$, $c = 31.910(3)$ Å, $\beta = 116.98(1)°$, $V = 7820(2)$ Å^3, space group $C2/c$, $Z = 4$ (molecule has crystallographic C_2 symmetry), $\rho_c = 1.24$ g cm^{-3}, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, μ ($Cu_{K\alpha}$) = 9.5 cm^{-1}, $F(000) = 3144$. Data for a crystal of dimensions $0.33 \times 0.07 \times 0.07$ mm were measured on a Siemens P4/RA diffractometer with $Cu_{K\alpha}$ radiation, graphite monochromator, and ω scans at 203 K. Of the 3987 independent reflections measured ($2\theta \leq 100°$), 2671 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods. The Me_2CO solvent molecule is disordered over two half-occupied positions, the H_2O molecules over 14 positions. Hydrogen atoms were determined from ΔF maps and subsequently optimized. The H atoms were assigned isotropic thermal parameter, $U_{eq}(H) = 1.2\ U_{eq}(C,O)$, and allowed to ride on their parent atom. Anisotropic refinement of all non-hydrogen atoms, using full-matrix least squares on F^2 gave $R_1 = 0.093$ and $wR_2 = 0.234$ for the 504 parameters. The maximum and minimum residual electron densities in the final ΔF map were +0.67 and −0.46 e Å^{-3}. All computations were carried out using the SHELXTL program system (Version 5.03).[29]

Cyclopentakis[(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl] (22): The cyclic decasaccharide derivative **17** (80 mg, 0.025 mmol) was deacylated by the same procedure as that described for compound **16**, and purified by HPLC (C-18 reverse phase column, H_2O/MeCN 90:10) to afford the cyclic decasaccharide **22** (29 mg, 0.020 mmol, 80%); ^1H NMR (400 MHz, D_2O, 31 °C): $\delta = 1.20$ (d, $J_{5,6} = 6$ Hz, 30H, H-6), 3.41 (dd, $J_{3,4} = J_{4,5} = 9.4$ Hz, 10H, H-4), 3.69 (dd, $J_{2,3} = 4$ Hz, $J_{3,4} = 9.4$ Hz, 10H, H-3), 3.94 (dd, $J_{1,2} = 2$ Hz, $J_{2,3} = 4$ Hz, 10H, H-2), 4.03 (dt, $J_{4,5} = 9.4$ Hz, $J_{5,6} = 6$ Hz, 10H, H-5), 4.76 (d, $J_{1,2} = 2$ Hz, 10H, H-1); ^{13}C NMR (75.5 MHz, D_2O, 25 °C): $\delta = 19.0$ (C-6), 71.0 (C-5), 71.6 (C-3), 73.4 (C-2), 83.6 (C-4), 104.3 (C-1); MALDI-TOFMS: $m/z = 1485$ $[M+Na]^+$.

Cyclohexakis[(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl] (23): The cyclic dodecasaccharide derivative **18** (43 mg, 0.011 mmol) was deacylated with the same procedure as that described for compound **16**, and purified by HPLC (C-18 reverse phase column, H_2O/MeCN 95:5) to afford the cyclic dodecasaccharide **23** (17 mg, 0.009 mmol, 86%); ^1H NMR (400 MHz, D_2O, 31 °C): $\delta = 1.22$ (d, $J_{5,6} = 6$ Hz, 36H; H-6), 3.47 (dd, $J_{3,4} = J_{4,5} = 9.4$ Hz, 12H; H-4), 3.73 (dd, $J_{2,3} = 4$ Hz, $J_{3,4} = 9.4$ Hz, 12H; H-3), 3.94 (dd, $J_{1,2} = 2$ Hz, $J_{2,3} = 4$ Hz, 12H; H-2), 4.00 (dt, $J_{4,5} = 9.4$ Hz, $J_{5,6} = 6$ Hz, 12H; H-5), 4.81 (d, $J_{1,2} = 2$ Hz, 12H; H-1); ^{13}C NMR (75.5 MHz, D_2O, 25C): $\delta = 19.4$ (C-6), 71.2 (C-5), 71.7 (C-3), 73.5 (C-2), 82.8 (C-4), 103.9 (C-1); MALDI-TOFMS: $m/z = 1777$ $[M+Na]^+$.

Cycloheptakis[(1 → 4)-α-D-rhamnopyranosyl-(1 → 4)-α-L-rhamnopyranosyl] (24): The cyclic tetradecasaccharide derivative **19** (40 mg, 0.0085 mmol) was deacylated by the same procedure as that described for compound **16**, and purified by HPLC (C-18 reverse phase column, H_2O/MeCN 95:15) to afford the cyclic tetradecasaccharide **23** (5 mg, 0.003 mmol, 29%); ^1H NMR (400 MHz, D_2O, 31 °C): $\delta = 1.22$ (d, $J_{5,6} = 6$ Hz, 42H; H-6), 3.42 (dd, $J_{3,4} = J_{4,5} = 9.4$ Hz, 14H; H-4), 3.77 (dd, $J_{2,3} = 4$ Hz, $J_{3,4} = 9.4$ Hz, 14H; H-3), 3.91–3.98 (m, 28H; H-2, H-5), 4.84 (d, $J_{1,2} = 2$ Hz, 14H; H-1); ^{13}C NMR (75.5 MHz, D_2O, 25 °C): $\delta = 19.4$ (C-6), 70.6 (C-5), 71.6 (C-3), 73.2 (C-2), 84.4 (C-4), 103.5 (C-1); MALDI-TOFMS: $m/z = 2070$ $[M+Na]^+$.

1,2,3,6-Tetra-*O*-benzoyl-α-L-mannopyranoside (26): L-Mannose (6.0 g, 33.4 mmol) was dissolved in dry C_5H_5N (50 mL), and BzCl (15.5 mL, 133.2 mmol) was added with cooling (−40 °C). The reaction mixture was stirred overnight at ambient temperature. MeOH (15 mL) was added and the mixture was diluted with CH_2Cl_2 (200 mL). The resulting solution was washed with H_2O (100 mL), 1 M HCl (2 × 100 mL), and H_2O (2 × 100 mL), dried, and concentrated to dryness. The product was isolated by column chromatography (SiO_2:PhMe/EtOAc, 90:10 to 95:5) to give the tetrabenzoate **26** (7.06 g, 11.9 mmol, 35%); $R_f = 0.26$ (PhMe/EtOAc, 90:10); m.p. 173–175 °C (lit.[12] 183–184 °C for the D-enantiomer); $[\alpha]_D$ −44.7 ($c = 1.14$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 3.24$ (brs, 1H, OH), 4.21–4.28 (m, $J_{4,5} = 10.0$ Hz, 1H; H-5), 4.32–4.42 (m, 1H, H-4), 4.53 (dd, $J_{5,6a} = 2$ Hz, $J_{6a,6b} = 12.2$ Hz, 1H; H-6a), 5.02 (dd, $J_{5,6b} = 2.3$ Hz, $J_{6a,6b} = 12.2$ Hz, 1H; H-6b), 5.78–5.84 (m, 2H; H-2, H-3), 6.55 (d, $J_{1,2} = 1.5$ Hz, 1H; H-1), 7.23–7.72 and 7.89–8.22 (m, 20H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 62.9$ (C-6), 65.4, 69.2, 72.0, 73.8 (C-2, C-3, C-4, C-5), 91.4 (C-1), 128.4–133.3 (C_6H_5), 165.0–166.2 (C_6H_5CO); FABMS: $m/z = 619$ $[M+Na]^+$; $C_{34}H_{28}O_{10}$ (596): calcd C 68.45, H 4.73, found C 68.44, H 4.78.

1,2,3,6-Tetra-*O*-benzoyl-4-*O*-chloroacetyl-α-L-mannopyranoside (27): The tetrabenzoate **26** (6.73 g, 11.3 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and C_5H_5N (1.37 mL, 17 mmol), and chloroacetyl chloride (1.35 mL, 17 mmol) was added with cooling (−20 °C). The reaction mixture was stirred for 4 h at ambient temperature. MeOH (2 mL) was added and the mixture diluted with CH_2Cl_2 (200 mL). The resulting solution was washed with H_2O (100 mL), aqueous $NaHCO_3$ solution (2 × 100 mL), and H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated to dryness. The product was isolated by column chromatography (SiO_2:PhMe/EtOAc, 100:0 to 90:10) to give the chloroacetate **27** (7.32 g, 10.9 mmol, 96%); $R_f = 0.52$ (PhMe/EtOAc, 90:10); m.p. 140–145 °C; $[\alpha]_D$ −4.8 ($c = 1.17$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 3.96$, 4.01 (AB system, $J_{A,B} = 14.6$ Hz, 2H; $ClCH_2CO$), 4.46 (m, $J_{4,5} = 10.0$ Hz, 1H; H-5), 4.56 (dd, $J_{5,6a} = 2.5$ Hz, $J_{6a,6b} = 12.8$ Hz, 1H; H-6a), 4.63 (dd, $J_{5,6b} = 3$ Hz, $J_{6a,6b} = 12.8$ Hz, 1H; H-6b), 4.96 (dd, $J_{1,2} = 2$ Hz, $J_{2,3} = 3$ Hz, 1H; H-2), 5.91 (dd, $J_{2,3} = 3$ Hz, $J_{3,4} = 10$ Hz, 1H; H-3), 6.06 (dd, $J_{3,4} \approx J_{2,3} = 10$ Hz, 1H; H-4), 6.58 (d, $J_{1,2} = 2$ Hz, 1H; H-1), 7.30–7.41 and 7.87–8.20 (m, 20H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 40.4$ ($ClCH_2$), 61.8 (C-6), 67.2, 69.3, 69.9, 70.8 (C-2, C-3, C-4, C-5), 91.2 (C-1), 128.6–134.2 (C_6H_5), 165.0–169.8 (C_6H_5CO); FABMS: $m/z = 695$ $[M+Na]^+$; $C_{36}H_{29}ClO_{11}$ (672.45): calcd C 64.24, H 4.34, found C 64.16, H 4.29.

2,3,6-Tri-*O*-benzoyl-4-*O*-chloroacetyl-α-L-mannopyranosyl bromide (5-M): A solution of the chloroacetate **27** (7.3 g, 10.85 mmol) and AcBr (6.7 mL, 128 mmol) in CH_2Cl_2 (80 mL) was treated while cooling (0 °C) with H_2O (1.5 mL, 83 mmol) in AcOH (10 mL). The solution was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with H_2O (100 mL) and aqueous $NaHCO_3$ solution (3 × 100 mL), dried ($MgSO_4$), and concentrated to dryness. The product, which was identified as the bromide **5-M** (6.76 g, 10.85 mmol, quant.), was used immediately for the glycosylation reaction without further purification; $R_f = 0.48$ (PhMe/EtOAc, 90:10); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 3.99$, 4.07 (AB system, $J_{A,B} = 14.7$ Hz, 2H; $ClCH_2CO$), 4.54–4.63 (m, 2H; H-5, H-6a), 4.67–4.74 (m, 1H; H-6b), 4.96 (dd, $J_{1,2} = 1.5$ Hz, $J_{2,3} = 3.3$ Hz, 1H; H-2), 6.04 (dd, $J_{3,4} \approx J_{2,3} = 10$ Hz, 1H; H-4), 6.14 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 10$ Hz, 1H; H-3), 6.58 (d, $J_{1,2} = 1.5$ Hz, 1H; H-1), 7.30–8.15 (m, 15H; C_6H_5); CIMS: $m/z = 543$ $[M - Br]^+$.

4-*O*-(4-*O*-Chloroacetyl-2,3,6-tri-*O*-benzoyl-α-L-mannopyranosyl)-3,6-di-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (6-MM): A solution of the glycosyl acceptor **4-M**[7] (2.78 g, 5.86 mmol), the glycosyl donor **5-M** (5.48 g, 8.79 mmol) and collidine (0.93 mL, 7.03 mmol) in dry CH_2Cl_2 (15 mL) were added under argon to a cooled (−40 °C) suspension of AgOTf (2.41 g, 9.37 mmol) in CH_2Cl_2 (50 mL). The mixture was allowed to warm up to room temperature. C_5H_5N (1 mL) was added and the suspension was diluted with CH_2Cl_2 (100 mL). The suspension was filtered through a layer of Celite and washed with CH_2Cl_2 (100 mL). The filtrates were mixed and washed successively with H_2O (100 mL), aqueous $Na_2S_2O_3$ solution (2 × 100 mL), and H_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated. The product was isolated by column chromatography (SiO_2:PhMe/EtOAc, 100:0 to 93:7) to give the title compound **6-MM** (4.02 g, 3.93 mmol, 67%); $R_f = 0.37$ (PhMe/EtOAc, 85:15); m.p. 93–95 °C; $[\alpha]_D$ +30.6 ($c = 2.09$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.68$ (s, 3H; CCH_3), 3.72 (s, 3H; OCH_3), 3.78 (s, 2H; $COCH_2Cl$), 3.87–4.00 (m, 2H, H-5, H-5'), 4.07–4.17 (m, 2H, H-4, H-6a'), 4.53–4.61 (m, 2H, H-6a, H-6b'), 4.75 (dd, $J_{1,2} = 1.5$ Hz, $J_{2,3} = 2.3$ Hz, 1H; H-2), 4.97 (dd, $J_{5,6} = 2.5$ Hz, $J_{6a,6b} = 12.2$ Hz, 1H; H-6b), 5.33 (d, $J_{1,2} = 1.5$ Hz, 1H; H-1'), 5.54–5.61 (m, 3H, H-1, H-2', H-3'), 5.68 (dd, $J_{2,3} = 3.5$ Hz, $J_{3,4} = 9.5$ Hz, 1H; H-3), 5.82 (dd, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4'), 7.12–7.58 and 7.79–8.18 (m, 25H;

0947-6539/97/0308-1312 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 8

C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.0 (CCH_3), 40.1 ($ClCH_2$), 52.5 (OCH_3), 61.3, 62.6 (C-6, C-6′), 66.9, 69.0, 69.2, 70.3, 71.1, 72.9, 73.0, 78.0 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 97.3, 98.0 (C-1, C-1′), 107.5 ($CH_3CCO_2CH_3$), 128.1–133.6 (C_6H_5), 165.0–169.6 (C_6H_5CO, $ClCH_2CO$, CCO_2CH_3); FABMS: m/z = 1045 $[M+Na]^+$; $C_{52}H_{47}ClO_{17}$ (1022.4) calcd C 61.75, H 4.68; found C 61.85, H 4.41.

3,6-Di-*O*-benzoyl-4-*O*-(2,3,6-tri-*O*-benzoyl-α-L-mannopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (7-MM): A solution of **6-MM** (3.56 g, 3.48 mmol) and $(NH_2)_2CS$ (0.68 g, 8.7 mmol) in a mixture of MeCN/H_2O (110 mL, 10:1) was allowed to stand for 48 h at ambient temperature, the reaction mixture was concentrated, and the residue dissolved in CH_2Cl_2 (150 mL) and washed with H_2O (2 × 200 ml). The resulting solid was purified by column chromatography (SiO_2:PhMe/EtOAc, 90:10 to 80:20) to give the title compound **7-MM** (2.87 g, 3.02 mmol, 87%); R_f = 0.28 (PhMe:EtOAc, 80:20); m.p. 99–101 °C; $[\alpha]_D$ +25.6 (c = 1.08 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.68 (s, 3H; CCH_3), 3.71 (s, 3H; OCH_3), 3.87–3.67 (m, 3H, H-5, H-5′, H-6a′), 4.14 (dd, $J_{3,4} \approx J_{4,5}$ = 9.4 Hz, 1H, H-4), 4.42 (dd, $J_{5,6}$ = 2 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6b′), 4.51–4.65 (m, 2H, H-6a, H-4′), 4.75 (dd, $J_{1,2}$ = 2.5 Hz, $J_{2,3}$ = 3 Hz, 1H; H-2), 4.92 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6b), 5.29 (d, $J_{1,2}$ = 1 Hz, 1H; H-1′), 5.47–5.53 (m, 2H, H-2′, H-3′), 5.59 (d, $J_{1,2}$ = 2.5 Hz, 1H; H-1), 5.65 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.4 Hz, 1H; H-3), 7.14–7.59 and 7.75–8.19 (m, 25H; C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.2 (CCH_3), 52.7 (OCH_3), 62.4, 62.9 (C-6, C-6′), 65.4, 70.8, 71.4, 71.6, 72.3, 73.3, 73.3, 78.2 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 97.5, 98.6 (C-1, C-1′), 107.6 ($CH_3CCO_2CH_3$), 128.4–133.7 (C_6H_5), 165.1–169.2 (C_6H_5CO, CCO_2CH_3); FABMS: m/z = 970 $[M+Na]^+$; $C_{51}H_{46}O_{18}$ (946.92): calcd C 64.69, H 4.90; found C 64.70, H 5.08.

3,6-Di-*O*-benzoyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-trityl-α-L-mannopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (8-MM): $TrClO_4$ (1.33 g, 3.88 mmol) was added in portions during ca. 2 h to a stirred solution of the alcohol **7-MM** (3.06 g, 3.23 mmol) in CH_2Cl_2 (50 mL) containing collidine (1.03 mL, 7.76 mmol) and the reaction mixture was allowed to stand for another 2 h. The mixture was then diluted with CH_2Cl_2 (200 mL), washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and concentrated to a residue. Successive column chromatography (SiO_2:*n*-hexane/EtOAc, 80:20 to 60:40) of the residue afforded the trityl ether **8-MM** (3.22 g, 2.71 mmol, 84%); R_f = 0.45 (*n*-hexane/EtOAc, 60:40); m.p. 134–136 °C; $[\alpha]_D$ −34.2 (c = 1.02 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.63 (s, 3H; CCH_3), 3.71 (s, 3H; OCH_3), 3.78 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6a′), 3.91–3.99 (m, 2H, H-5, H-5′), 4.06–4.18 (m, 2H, H-4, H-6b′), 4.54 (dd, $J_{3,4} \approx J_{4,5}$ = 9.4 Hz, 1H, H-4′), 4.62 (dd, $J_{5,6}$ = 3 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6a), 4.77 (dd, $J_{1,2}$ = 2.5 Hz, $J_{2,3}$ = 3.5 Hz, 1H; H-2), 4.94 (dd, $J_{5,6}$ = 2 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6b), 5.28 (d, $J_{1,2}$ = 2 Hz, 1H; H-1′), 5.35–5.40 (brm, 1H, H-2′), 5.59 (d, $J_{1,2}$ = 2.5 Hz, 1H; H-1), 5.71–5.78 (m, 2H; H-3, H-3′), 6.79–7.51, 7.56–7.74 and 7.98–8.18 (m, 40H; C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.2 (CCH_3), 52.7 (OCH_3), 56.1, 56.2 (C-6, C-6′), 71.0, 71.2, 71.4, 71.5, 71.6, 73.0, 73.4 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 88.3 ($C(C_6H_5)_3$), 97.4, 98.1 (C-1, C-1′), 107.6 ($CH_3CCO_2CH_3$), 127.6–133.5 (C_6H_5), 165.0–169.0 (C_6H_5CO, CCO_2CH_3); FABMS: m/z = 1211 $[M+Na]^+$; $C_{51}H_{46}O_{18}$ (1189.28): calcd C 70.70, H 5.09; found C 70.96, H 5.08.

3,6-Di-*O*-benzoyl-4-*O*-(2,3,6-tri-*O*-benzoyl-4-*O*-trityl-α-L-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-cyano)ethylidene]-β-D-mannopyranose (1-MM): A suspension of the trityl ether **8-MM** (3.20 g, 2.69 mmol) in a mixture of MeOH (200 mL) and CH_2Cl_2 (40 mL) was saturated with NH_3 gas at −5 °C and the solution was maintained overnight at 20 °C. The solvents were evaporated off, the residue was dissolved in C_5H_5N (50 mL), evaporated to dryness, dissolved in C_5H_5N (60 mL), treated with BzCl (3.72 mL, 32.2 mmol), and stirred overnight at room temperature. MeOH (2 mL) was added and the mixture was stirred for 10 min at 20 °C, then concentrated to dryness. The residue was dissolved in CH_2Cl_2 (200 mL), washed with H_2O (200 mL), aqueous $NaHCO_3$ solution (2 × 200 mL), and H_2O (2 × 200 mL); the resulting solution was dried and concentrated to a residue. Column chromatography (SiO_2:PhMe/EtOAc, 100:0 to 95:5) of the residue afforded the disaccharide monomer **1-MM** (2.31 g, 1.99 mmol, 74%); R_f = 0.47 (PhMe/EtOAc, 90:10); m.p. 97–99 °C; $[\alpha]_D$ −22.2 (c = 0.77 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.61 (s, 3H; CCH_3), 3.85 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6a′), 3.93–4.00 (m, 2H, H-5, H-5′), 4.08–4.20 (m, 2H, H-4, H-6b′), 4.47 (dd, $J_{3,4} \approx J_{4,5}$ = 9.2 Hz, 1H, H-4′), 4.57 (dd, $J_{5,6}$ = 3.5 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6a), 4.74 (dd, $J_{1,2}$ = 2.5 Hz, $J_{2,3}$ = 3.5 Hz, 1H; H-2), 4.96 (dd, $J_{5,6}$ = 2.5 Hz, $J_{6a,6b}$ = 12 Hz, 1H; H-6b), 5.28 (d, $J_{1,2}$ = 2.5 Hz, 1H; H-1′), 5.35–5.40 (brm, 1H, H-2′), 5.59 (d, $J_{1,2}$ = 2.5 Hz, 1H; H-1), 5.73–5.82 (m, 2H; H-3, H-3′), 6.82–7.52, 7.57–7.76 and 7.98–8.18 (m, 40H; C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 26.4 (CCH_3), 62.2, 62.3 (C-6, C-6′), 70.7, 71.02, 71.4, 71.4, 73.0, 73.1, 78.7, 78.8 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 88.1 ($C(C_6H_5)_3$), 97.0, 98.2 (C-1, C-1′), 101.5 (CCN), 116.7 (CN), 127.0–133.8 (C_6H_5), 144.7 (C_{quat} of C_6H_5 in $C(C_6H_5)_3$), 165.1–166.1 (C_6H_5CO); FABMS: m/z = 1178 $[M+Na]^+$; $C_{51}H_{46}O_{18}$ (1156.22): calcd C 71.68, H 4.97, N 1.21; found C 71.88, H 4.99, N 1.31.

Cyclotris[(1 → 4)-2,3-di-*O*-benzoyl-α-L-mannopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzoyl-α-D-mannopyranosyl] (28): A solution of the disaccharide monomer **1-MM** (1.50 g, 1.30 mmol) in C_6H_6 (10 mL) was divided into two equal portions, each of which was placed into one limb of tuning-fork-shaped tubes. The other arms were filled with a solution of $TrClO_4$ (445 mg, 1.30 mmol) in $MeNO_2$ (2.5 mL), the tubes were connected to a vacuum line (4 × 10^{-3} Torr) and the solutions were freeze-dried. C_6H_6 (3 mL) was distilled into each limb containing the monomer and the freeze-drying was repeated. CH_2Cl_2 (40 mL) was distilled into each of the reaction tubes and the solutions of the monomer and the catalyst were mixed and left for 40 h at 20 °C in the dark. The contents of all tubes were combined, washed with H_2O, and concentrated to a residue. The trityl-containing noncarbohydrate products were separated by column chromatography (SiO_2:PhMe/EtOAc, 95:5 to 75:25) of the residue. Further purification of the mixture was achieved by using reverse-phase HPLC (C-18 column, MeCN) to give the hexasaccharide derivative **28** (93 mg, 0.034 mmol, 8%) as a pure compound; $[\alpha]_D$ +50.4 (c = 1.01 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (s, 9H; CH_3CO_2), 4.26–4.47 (m, 18H, H-4 L-Man, H-4 D-Man, H-5 L-Man, H-5 D-Man, H-6a L-Man, H-6a D-Man), 4.95–5.20 (m, 6H, H-6b L-Man, H-6b D-Man), 5.18 (brs, 3H; H-1 D-Man), 5.32 (brs, 3H; H-1 L-Man), 5.45 (brs, 3H; H-2 D-Man), 5.66 (brs, 3H; H-2 L-Man), 5.85 (dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9 Hz, 3H; H-3 D-Man), 5.91 (dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9 Hz, 3H; H-3 L-Man), 7.02–8.12 (m, 60H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 20.6 (CH_3CO_2), 62.0, 62.1 (C-6 L-Man, C-6 D-Man), 70.1, 70.6, 70.7, 71.1, 71.3, 75.2 (C-2, C-3, C-4, C-5 L-Rha, C-2, C-3, C-4, C-5 D-Rha), 98.6, 98.9 (C-1 L-Man, C-1 D-Man), 127.9–134.3 (C_6H_5), 165.1, 165.6, 165.7, 165.8 (C_6H_5CO), 169.6 (CH_3CO_2); HRMS (LSIMS): calcd for $C_{147}H_{126}O_{48}Na$ $[M+Na]^+$ 2681.7215, observed 2681.7316.

Cyclotris[(1 → 4)-α-L-mannopyranosyl-(1 → 4)-α-D-mannopyranosyl] (29): The hexasaccharide derivative **28** (90 mg, 0.033 mmol) was deacylated using the same procedure as that described for **16**, and purified by HPLC (C-18 reverse phase column, H_2O/MeCN 95:5), to afford **29** (30 mg, 0.030 mmol, 93%); ^1H NMR (400 MHz, D_2O, 31 °C): δ = 3.60–3.82 (m, 24H; H-4, H-5, H-6a,b), 3.84 (dd, $J_{2,3}$ = 4 Hz, $J_{3,4}$ = 9.4 Hz, 6H, H-3), 3.89 (dd, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 3.5 Hz, 6H, H-2), 4.90 (d, $J_{1,2}$ = 2.2 Hz, 6H, H-1); ^{13}C NMR (100 MHz, D_2O, 31 °C): δ = 63.3 (C-6), 72.2, 72.6, 74.3, 81.1 (C-2, C-3, C-4, C-5), 103.7 (C-1); MALDI-TOFMS: m/z = 955 $[M+Na]^+$. Single crystals suitable for X-ray crystallography were obtained by cooling a D_2O solution of **29**. $C_{36}H_{42}D_{18}O_{30}\cdot 9D_2O$, M = 1171.3, monoclinic, space group $C2/c$, a = 28.005(2), b = 9.807(2), c = 20.853(2) Å, β = 117.09(1)°, V = 5098.8(9) Å^3, Z = 4 (molecule has crystallographic C_i symmetry), ρ_c = 1.53 g cm^{-3}, $Cu_{K\alpha}$ radiation, λ = 1.54178 Å, $\mu(Cu_{K\alpha})$ = 11.9 cm^{-1}, $F(000)$ = 2424. Clear platelike needle, dimensions 0.07 × 0.20 × 0.97 mm. Data were measured on a Siemens P4/RA diffractometer with $Cu_{K\alpha}$ radiation, graphite monochromator, and ω-scans at 293 K. Of the 4115 independent reflections measured ($2\theta \leq 126°$), 3270 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors, but not for absorption. The structure was solved by direct methods and all non-hydrogen atoms refined anisotropically. The positions of all hydrogen atoms were determined from a ΔF map and subsequently optimized. The H atoms were assigned isotropic thermal parameters, $U(H) = U_{eq}(C,O)$ and allowed to ride on their parent atoms. Refinement was by full-matrix least-squares based on F^2 to give R_1 = 0.053, wR_2 = 0.134 for the 373 parameters. The maximum and minimum residual electron densities in the final ΔF map were +0.35 and −0.47 e Å^{-3}. Computations were carried out using the SHELXTL program system (*version 5.03*).[29]

Acknowledgments: This research was supported in the UK by the Biotechnology and Biological Sciences Research Council and the Engineering and Physical Sciences Research Council, as well as by the University of Birmingham (UK) and the University of Messina (Italy).

Received: January 28, 1997 [F588]

[1] a) W. Saenger, in *Inclusion Compounds, Vol. 2* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol), Academic Press, London, **1984**, pp. 231–259; b) *Cyclodextrins and Their Industrial Uses* (Ed.: D. Duchêne), Editions de Santé, Paris, **1987**; c) J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, **1988**; d) J. F. Stoddart, *Carbohydr. Res.* **1989**, *192*, xii–xv; e) J. F. Stoddart, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 846–848; f) S. Li, W. C. Purdy, *Chem. Rev.* **1992**, *92*, 1457–1470; g) G. Wenz, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803–822; h) K. Takahashi, K. Hattori, *J. Incl. Phenom. Mol. Rec.* **1994**, *17*, 1–24; i) S. D. Eastburn, B. Y. Tao, *Biotech. Adv.* **1994**, *12*, 325–339; j) D. Armspach, G. Gattuso, R. Königer, J. F. Stoddart, in *Bioorganic Chemistry: Carbohydrates* (Ed.: S. M. Hecht), Oxford University Press, New York, in press; k) *Comprehensive Supramolecular Chemistry, Vol. 3: Cyclodextrins* (Eds.: J. Szejtli, T. Osa), Elsevier, Oxford, **1996**.

[2] M. Sawada, T. Tanaka, Y. Takai, T. Hanafusa, T. Taniguchi, M. Kawamura *Carbohydr. Res.* **1991**, *217*, 7–17.

[3] a) A. Amemura, M. Hisamatsu, M. Mitani, T. Harada, *Carbohydr. Res.* **1983**, *114*, 277–285; b) G. Williamson, K. Damani, P. Devenney, C. B. Faulds, V. J. Morris, B. J. H. Stevens, *J. Bacteriol.* **1992**, *174*, 7941–7947.

[4] a) T. Ogawa, Y. Takahashi, *Carbohydr. Res.* **1985**, *138*, C5–C9; b) Y. Takahashi, T. Ogawa, *ibid.* **1987**, *164*, 277–296.

[5] N. Sakairi, H. Kuzuhara, *J. Chem. Soc. Chem. Commun.* **1993**, 187–188.

[6] a) G. Excoffier, M. Paillet, M. Vignon, *Carbohydr. Res.* **1985**, *135*, C10–C11; b) P. M. Collins, A. Manro, E. C. Opara-Mottah, M. H. Ali, *J. Chem. Soc. Chem. Commun.* **1988**, 272–274; c) L. V. Backinowsky, S. A. Nepogodiev, N. K. Kochetkov, *Bioorgan. Khim.* **1988**, *14*, 1122–1124; d) L. V. Backinowsky, S. A. Nepogodiev, N. K. Kochetkov, *Carbohydr. Res.* **1989**, *185*, C1–C3; e) G. Bonas, G. Excoffier, M. Paillet, M. Vignon, *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 259–261; f) N. K. Kochetkov, S. A. Nepogodiev, L. V. Backinowsky, *Tetrahedron* **1990**, *46*, 139–150; g) P. M. Collins, M. H. Ali, *Tetrahedron Lett.* **1990**, *31*, 4517–4520; h) G. Bonas, M. Vignon, S. Pérez, *Carbohydr. Res.* **1991**, *211*, 191–205; i) S. Houdier, P. J. A. Vottéro, *ibid.* **1993**, *248*, 377–384; j) H. Driguez, J.-P. Utille, *Carbohydr. Lett.* **1994**, *1*, 125–128; k) S. Houdier, P. J. . A. Vottéro, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 354–356; l) S. Houdier, P. J. . A. Vottéro, *Carbohydr. Lett.* **1994**, *1*, 13–18.

[7] a) P. R. Ashton, C. L. Brown, S. Menzer, S. A. Nepogodiev, J. F. Stoddart, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 580–591; b) S. A. Nepogodiev, G. Gattuso, J. F. Stoddart, in *Proceedings of the 8th International Symposium on Cyclodextrins* (Eds.: J. Szejtli, L. Szente), Kluwer, Dordrecht, **1996**, pp. 89–94.

[8] a) T. Mukaiyama, Y. Murai, S. Shoda, *Chem. Lett.* **1981**, 431–434; b) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531, and references cited therein.

[9] R. J. Ferrier, R. W. Hay, N. Vethaviyasar, *Carbohydr. Res.* **1973**, *27*, 55–61.

[10] a) B. Fraser-Reid, U. E. Udodong, Z. Wu, H. Ottoson, J. R. Merritt, C. S. Rao, C. Roberts, R. Madsen, *Synlett* **1992**, 927–942; b) A. Arasappan, B. Fraser-Reid, *J. Org. Chem.* **1996**, *61*, 927–942.

[11] For a discussion of the CED method of glycosylation, see: N. K. Kochetkov, *Tetrahedron* **1987**, *43*, 2389–2436 and references cited therein.

[12] a) M. Mori, Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1989**, *30*, 1273–1276; b) M. Mori, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1989**, *192*, 131–146; c) M. Mori, Y. Ito, J. Uzawa, T. Ogawa, *Tetrahedron Lett.* **1990**, *31*, 3191–3194; d) H. Kuyama, T. Nukada, Y. Nakahara, T. Ogawa, *ibid.* **1993**, *34*, 2171–2174.

[13] a) M. Nishizawa, H. Imagawa, Y. Kan, H. Yamada, *Tetrahedron Lett.* **1991**, *32*, 5551–5554; b) M. Nishizawa, *Stud. Nat. Prod. Chem.* **1991**, *8*, 359–371; c) M. Nishizawa, H. Imagawa, K. Kubo, Y. Kan, H. Yamada, *Synlett* **1992**, 447–448; d) M. Nishizawa, H. Imagawa, E. Morikuni, S. Hatakeyama, H. Yamada, *Chem. Pharm. Bull.* **1994**, *42*, 1365–1366.

[14] a) V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, N. K. Kochetkov, *Carbohyr. Res.* **1979**, *68*, C11–C13; b) V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, N. K. Kochetkov, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1979**, *12*, 2751–1125.

[15] a) M. V. Ovchinnikov, N. E. Byramova, L. V. Backinowsky, N. K. Kochetkov, *Bioorg. Khim.* **1983**, *9*, 391–400; b) N. E. Byramova, L. V. Backinowsky, N. K. Kochetkov, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1987**, *5*, 1120–1125; c) N. E. Byramova, L. V. Backinowsky, N. K. Kochetkov, *ibid.* **1987**, *5*, 1126–1131.

[16] It has been observed that the CED decomposes under the conditions used for tritylation of secondary OH groups with $TrClO_4$/collidine. See: a) N. K. Kochetkov, N. E. Byramova, Y. E. Tsvetkov, L. V. Backinowsky, *Tetrahedron* **1985**, *41*, 3363–3375; b) N. K. Kochetkov, N. E. Nifant'ev, L. V. Backinowsky, *ibid.* **1987**, *43*, 3109–3121; c) Y. E. Tsvetkov, L. V. Backinowsky, N. K. Kochetkov, *Carbohydr. Res.* **1989**, *193*, 75–90.

[17] a) M. E. Evans, F. W Parrish, *Carbohydr. Res.* **1977**, *54*, 105–114; b) H. B. Mereyala, G. V. Reddy, *Tetrahedron* **1991**, *47*, 6435–6448.

[18] a) N. N. Malysheva, N. K. Kochetkov, *Carbohydr. Res.* **1982**, *105*, 173–179; b) N. K. Kochetkov, E. M. Klimov, N. N. Malysheva, A. S. Shashkov, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1986**, *4*, 1883–1887.

[19] B. Stahl, M. Steup, M. Karas, F. Hillenkamp, *Anal. Chem.* **1991**, *63*, 1463–1466.

[20] Attempts to employ normal-phase preparative HPLC for separation of cyclic oligosaccharides larger than the octamer were unsuccessful.

[21] A. V. Nikolaev, T. J. Rutherford, M. A. J. Ferguson, J. S. Brimacombe, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 785–788.

[22] Some differences in the reactivity of 3,6-di-*O*-benzoyl-4-*O*-trityl-1,2-*O*-(1-cyano)ethylidene-β-D-mannose and 3-*O*-benzoyl-4-*O*-trityl-1,2-*O*-(1-cyano)-ethylidene-β-L-rhamnose were also observed in their $TrClO_4$-catalyzed polycondensation leading to acylated (1 → 4)-α-D-mannan and α-L-rhamnan respectively. See ref. [18].

[23] Each of the achiral molecules **20**–**24** and **28** incorporates $5n$ chiral centres, where n is the number of monosaccharide constituents.

[24] a) M. R. Ghadiri, K. Kobayashi, J. R. Granja, R. K. Chadha, D. E. McRee, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 93–95; b) M. R. Ghadiri, *Adv. Mater.* **1995**, *7*, 675–677; c) M. Engels, D. Bushford, M. R. Ghadiri, *J. Am. Chem. Soc.* **1995**, *117*, 9151–9158; d) J. D. Hartgernik, J. R. Granja, R. A. Milligan, M. R. Ghadiri, *ibid.* **1996**, *118*, 43–50.

[25] The use of a number of mass spectrometric techniques for the characterization of CD inclusion complexes has been reported over the years. See: L. Szente, in *Comprehensive Supramolecular Chemistry, Vol. 3* (Eds.: J. Szejtli, T. Osa), Elsevier, Oxford, **1996**, pp. 253–278, and references cited therein.

[26] F. Djedaïni, B. Perly, in *New Trends in Cyclodextrin Derivatives* (Ed.: D. Duchêne), Editions de Santé, Paris, **1991**, pp. 215–246.

[27] H. J. Dauben, Jr., L. R. Honnen, K. M. Harmon, *J. Org. Chem.* **1960**, *25*, 1442–1445.

[28] D. D. Perrin, W. F. L. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pergamon, Oxford, **1989**.

[29] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100129. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code +(1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).

0947-6539/97/0308-1314 $ 17.50+.50/0