Synthetic Cyclic Oligosaccharides—Syntheses and Structural Properties of a Cyclo[(1 → 4)-α-L-rhamnopyranosyl-(1 → 4)-α-D-mannopyranosyl]trioside and -tetraoside**

Peter R. Ashton, Christopher L. Brown, Stephan Menzer, Sergey A. Nepogodiev, J. Fraser Stoddart,* and David J. Williams

Abstract: An efficient polycondensation–cyclization approach to the synthesis of cyclodextrin analogues is demonstrated by the preparation of cyclohexaoside **1** and cyclooctaoside **2**. The key intermediate, disaccharide **3**, bearing the cyanoethylidene group as a glycosyl donor function and the trityloxy group as a glycosyl acceptor function was prepared in 15 steps starting from L-rhamnose and D-mannose. The crucial cyclooligomerization of the disaccharide monomer **3** was carried out in the presence of $TrClO_4$ as a promoter with the use of ultra-dry conditions at normal concentrations. This reaction led to formation of the cyclic oligosaccharides **28** and **29** (in 34 and 31% yield, respectively), which were deprotected to afford **1** and **2**, respectively. The X-ray crystal structural analysis of the cyclooctaoside **2** reveals a cylindrical shape for the cyclic oligosaccharide with C_4 symmetry. Individual molecules of **2** are arranged perfectly in stacks that form nanotubes in the solid state.

Keywords
carbohydrates · cyclodextrin analogues · cyclooligomerizations · glycosylations · nanotubes

Introduction

Despite the fact that oligosaccharides are ubiquitous in nature, their cyclic forms are rather rare.[1] Where cyclic oligosaccharides do occur, they usually result from the action of bacterial enzymes on other sources of carbohydrates. Undoubtedly, the main category of cyclic oligosaccharides in nature are the cyclomaltooligosaccharides—the so-called cyclodextrins (CDs)[2]—which are already produced industrially on a multiton scale.[3] On account of their unique ability to form inclusion complexes[4] with a wide range of substrates, they have found numerous practical applications[5] in addition to their use as building blocks for the construction of supramolecular species.[6] Moreover, a number of other types of cyclooligosaccharides are formed as a result of bacterial action on polysaccharides: examples include cyclo(1 → 2)-β-D-glucooligosaccharides[7] (cyclosophoroses) and cyclo-β-D-fructohexaosides[8] (cycloinulohexaoses). Also, recently reported are the biosyntheses of cyclo(1 → 6)-β-D-glucooligosaccharides[9] (cycloisomaltooligosaccharides) and alternating cyclo-(1 → 3),(1 → 6)-β-D-glucooligosaccharides,[10] as well as the cyclic tetrasaccharide cyclo-(1 → 3),(1 → 6)-α-D-glucotetraoside.[11] Whereas there is some evidence that cyclosophoroses are able to complex with water-insoluble drugs,[12] cycloinulohexaose possesses a macrocyclic ring reminiscent of the crown ether constitution and therefore, not surprisingly perhaps, exhibits cation-binding properties.[13]

A large number of chemical modifications have been carried out on the native CDs[14] with the intention, for example, of 1) enhancing either their solubilities in water or in organic solvents,[15] 2) altering their binding characteristics toward substrates,[16] and 3) constructing enzyme mimics.[17] As a consequence of the different reactivities of the three hydroxyl groups at positions 2, 3, and 6 on the D-glucopyranosyl rings of the CDs, chemical modifications can be carried out regioselectively, according to the general pattern that the primary hydroxyl groups at C-6 are usually the most reactive, followed by the secondary hydroxyl groups—firstly on C-2 and then finally on C-3. Regioselectively substituted CDs can also be prepared by a chemoenzymatic approach.[18] This kind of derivatization, however, does not alter the constitution or the configuration of the repeating α-D-glucopyranosyl units in the CDs (six in α, seven in β, and eight in γ), leaving the gross molecular shape as dictated by the conformation of the D-glucopyranosyl units essentially the same. A more profound change of shape, associated with dramatic alterations in the nature of their internal cavities, results from the formation of the per-3,6-anhydrocyclodextrins[19] and per-2,3-anhydrocyclodextrins.[20] The potential of these chemically modified cyclodextrins remains to be exploited.[21]

Aside from chemical modification, another entry into cyclic oligosaccharides is by total chemical synthesis.[22] This approach has been pioneered in recent years by Ogawa in the area of CDs and their analogues. Following on from their total syntheses[23] of α- and γ-cyclodextrins, he and his group have re-

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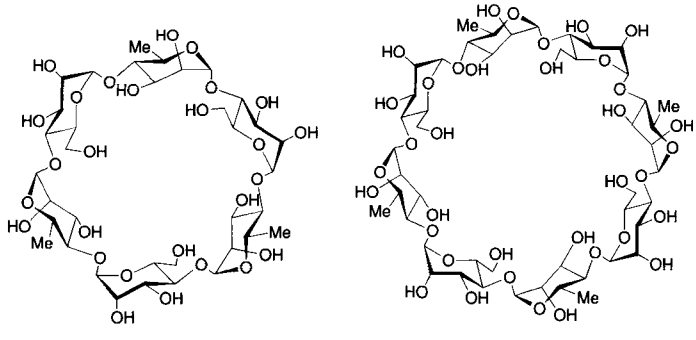
ported the syntheses of the *manno* isomers[24] of α-, β-, and γ-cyclodextrins, as well as of some cyclolactooligosaccharides.[25] Employing a similar synthetic strategy, Nakagawa and co-workers[26] have managed to synthesize a new member of the CD family—namely, cyclo(1 → 4)-α-D-glucopentaoside—while Nishizawa et al.[27] and Collins et al.[28] have reported, respectively, the syntheses of cyclo(1 → 4)-α-L-rhamnohexaoside and cyclo-(1 → 3)-β-D-glucohexaoside. At the same time, Kuzuhara and co-workers[29] have developed a methodology for the introduction of a single different monosaccharide unit into both the α- and β-cyclodextrin structure by fission of the CD ring, coupling with a heterogeneous monosaccharide residue, and recyclization by activation of a thioglycoside. The cycloglycosylation of the primary hydroxyl group on the glucopyranose unit has led[30] to the first reported synthesis of some cyclic oligosaccharides, the cyclo(1 → 6)-β-D-glucooligosaccharides. Recently, other research groups in France have reported synthetic routes to cyclo(1 → 6)-α-D-glucooligosaccharides[31] and the alternating cyclo(1 → 4)-α-D-gluco-(1 → 6)-β-D-glucooligosaccharides containing three, four, and five disaccharide repeating units.[32] Alongside these pyranosyl derivatives, it is worthy of note that a range of cyclogalactofuranooligosaccharides with β-(1 → 3), β-(1 → 5), and β-(1 → 6) linkages have been synthesized by the Kochetkov group.[33]

Cyclooligosaccharides possess a wide range of features that render them attractive as potential receptors for substrates. They contain many chiral centers and numerous functional groups. In principle, their cavities can be either hydrophobic or hydrophilic. The construction of receptors capable of binding substrates in aqueous media is an important contemporary objective[34] in chemistry. It has stimulated the synthetic work—reported in this paper for the first time—directed toward the development of a new strategy for constructing CD analogues. Here, we describe a novel cyclooligomerization process, which has led, in high yield, to the formation of the homologous compounds (Fig. 1), cyclo[(1 → 4)-α-L-rhamnopyranosyl-(1 → 4)-α-D-mannopyranosyl]trioside (**1**) and -tetraoside (**2**).[35] Additionally, we report the solid-state structure of **2** and use it to predict, by means of molecular modeling, the most stable structure for **1**. The picture that emerges is one of fascinating structural properties for these new cyclic oligosaccharides.

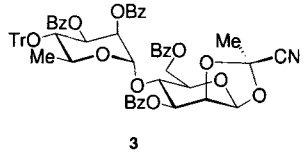


1 **2**

Fig. 1. The structural formulas of the two target cyclic oligosaccharides **1** and **2**.

Results and Discussion

Synthetic Strategy: The chemical synthesis of cyclic oligosaccharides implies the intramolecular glycosidation of a linear oligosaccharide precursor incorporating both a glycosyl donor and a glycosyl acceptor. Depending on the way in which the linear precursor is obtained, two alternative approaches to the synthesis of cyclic oligosaccharides can be identified: 1) the stepwise preparation of a long-chain linear oligosaccharide or 2) the polycondensation of an appropriately derivatized repeating unit of the cyclic oligosaccharide. The first approach, which has been the most commonly employed one to date for the construction of cyclic oligosaccharides,[23–29] lacks efficiency because of the large number of sequential steps required prior to cyclization. The second approach, cyclooligomerization, has been applied so far only to the formation of (1 → 6)-glucosidic bonds[30–32] and glycofuranosidic bonds.[33] In order to develop this second approach further, we decided to try to synthesize the CD analogues **1** and **2** since their preparation requires the formation of (1 → 4) interglycosidic linkages—a much more challenging problem altogether. Obviously, the ideal monomer must contain a glycosyl donor and a glycosyl acceptor, within a structure where the other potentially reactive functional groups are suitably protected; also, both the glycosyl donor and the glycosyl acceptor must be reactive toward each other yet stable before the promotion of the glycosylation. Amongst the very few potential monomers that fulfill all the above criteria, we have chosen triphenylmethyl (trityl) ethers of 1,2-*O*-(1-cyano)ethylidene derivatives (CEDs) of saccharides, which are known to be excellent monomers in the preparation of synthetic polysaccharides.[36] In particular, 3,4-di-*O*-acetyl-1,2-*O*-(1-cyano)ethylidene-α-L-rhamnose[37] and 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyano)ethylidene-β-D-mannose[38] undergo $TrClO_4$-catalyzed polycondensations leading to stereoregular, yet polydisperse, (1 → 4)-α-L-rhamnans and (1 → 4)-β-D-mannans, respectively. It follows that, by applying high-dilution conditions during the polycondensation, the disaccharide **3** should be a convenient monomer (Fig. 2) for the formation of protected cyclic oligosaccharides that could furnish **1** and **2** upon deacylation.

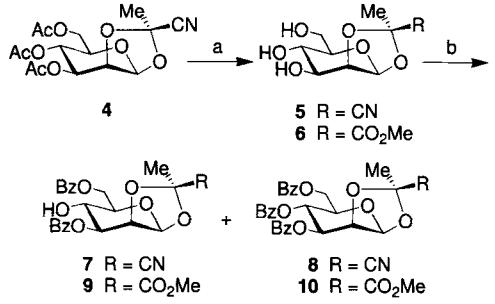


3

Fig. 2. The structural formula of the disaccharide **3** used as the monomer in the cyclooligomerization.

Syntheses of Cyclic Oligosaccharides 1 and 2: In order to construct the disaccharide monomer **3**—for subsequent cyclooligomerization—it was necessary, first of all, to address the synthesis of mannopyranosyl acceptors and rhamnopyranosyl donors.

Syntheses of the Mannopyranosyl Acceptors 7 and 9: Deacetylation of the 1,2-*O*-(1-cyano)ethylidene triacetate **4**[39] under mild conditions (Et_3N in $CHCl_3$/MeOH) afforded the known[40] triol **5** in 53% yield (Scheme 1). By contrast, saponification of **4** under stronger conditions (0.02 M NaOMe in MeOH), followed



4 **5** R = CN, **6** R = CO_2Me

7 R = CN, **9** R = CO_2Me **8** R = CN, **10** R = CO_2Me

Scheme 1. Syntheses of mannopyranosyl acceptors **7** and **9**. Reagents and conditions: a) for **5**, Et_3N/MeOH, 20 °C, 18 h, 53%; for **6**, 0.02 M NaOMe/MeOH, 20 °C, 6 h; followed by 1 M HCl, 84%; b) BzCl/C_5H_5N, −30 °C, 2.5 h; from **5**, 71% (**7**), 20% (**8**); from **6**, 65% (**9**), 12% (**10**).

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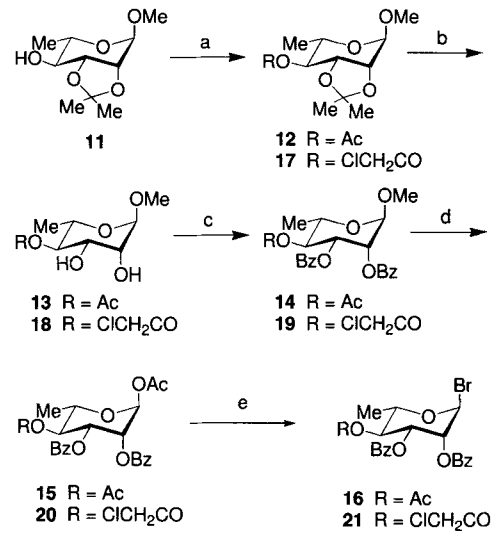
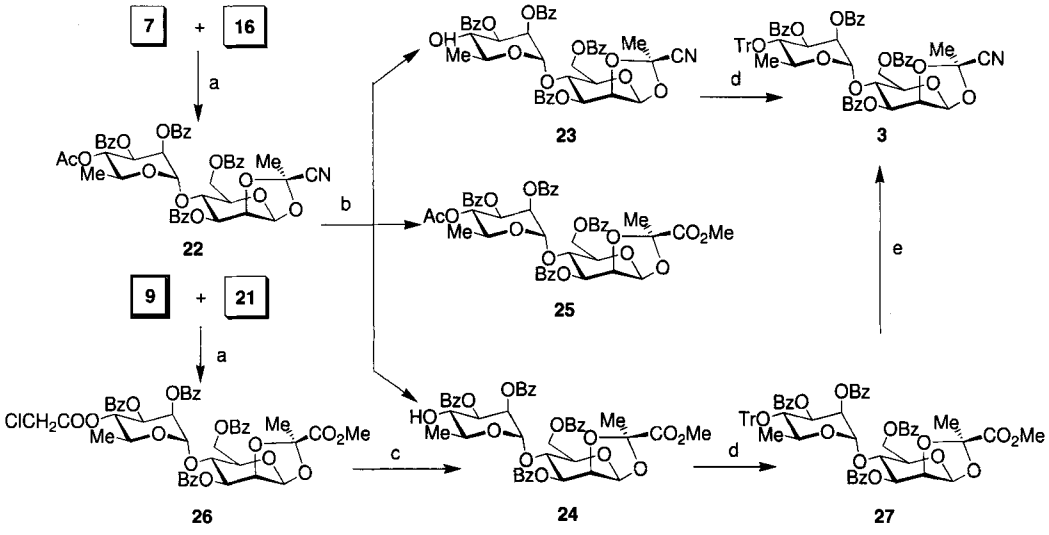
by acidification (AcOH), gave (84%) the 1,2-*O*-(1-methoxycarbonyl)ethylidene derivative **6**. The formation of **6** in this reaction was established unambiguously by the presence of the characteristic signals for the ester methyl group protons in both the ^1H ($\delta = 3.73$) and ^{13}C ($\delta = 52.6$) NMR spectra recorded in D_2O and CD_3COCD_3, respectively. Selective benzoylation ($BzCl/C_5H_5N$) of **5**, according to a slightly modified procedure[38] at low temperature ($-30\,^\circ C$), afforded the desired mannosyl acceptor **7** in 71% yield along with a 20% yield of the tribenzoate **8**. Employing exactly the same reaction conditions on **6** led predominantly to the formation of dibenzoate **9** (65% yield), together with 12% of the tribenzoate **10**.

*Syntheses of the Rhamnopyranosyl Donors **16** and **21***: The rhamnopyranosyl donors were obtained starting from methyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside **11**.[41] In the first instance, the acetyl group was chosen for the temporary protection of O-4 as it can be removed selectively by acidic methanolysis[42] in the presence of benzoyl groups—a manipulation that has been demonstrated[43] during the syntheses of several complex oligosaccharide monomers. By means of standard acetylation (Ac_2O/C_5H_5N), deacetonation (Amberlite (H^+)/MeOH), and benzoylation ($BzCl/C_5H_5N$), **11** was converted via **12** (93%), and **13** (98%) to **14** (78%) (Scheme 2). Acetolysis (Ac_2O/H_2SO_4) of the methyl glycoside **14** gave a product which was mainly the α-acetate **15**. Without further purification, this product was converted ($HBr/AcOH/CH_2Cl_2$) into the bromide **16** in 71% yield. The 4-*O*-chloroacetyl analogue of **16**—bromide **21**—was obtained by chloroacetylation ($ClCH_2CO_2H/C_5H_5N/CH_2Cl_2$) of **11**, affording the chloroacetate **17** in 85% yield. Subjecting **17** to the sequence of transformations described above for **12**, involving deacetonation, benzoylation, acetolysis, and bromination, led via **18**, **19**, and **20** to **21** in yields of 66, 88, 77, and 92%, respectively.



Scheme 2. Syntheses of rhamnosyl donors **16** and **21**. Reagents and conditions: a) for **12**, Ac_2O/C_5H_5N, 20 °C, 1 h, 93%; for **17**, $ClCH_2COCl/C_5H_5N/CH_2Cl_2$, 5 °C, 15 min, 85%; b) for **13**, Amberlite (H^+)/MeOH, 20 °C, 24 h; from **12**, 98% (**13**); from **17**, 66% (**18**); c) $BzCl/C_5H_5N$, 20 °C, 4 h; from **13**, 78% (**14**); from **18**, 88% (**19**); d) Ac_2O/H_2SO_4, 20 °C, 2 h; from **14**, 95% (**15**); from **19**, 77% (**20**); e) $HBr/AcOH/CH_2Cl_2$, 20 °C, 2H; from **15**, 71% (**16**); from **20**, 90% (**21**).

CED **7**. Acidic deacetylation[42] (1 M HCl in MeOH) afforded the required alcohol **23** in only 19% yield together with the methoxycarbonyl derivatives **24** (34%) and **25** (5%). Unfortunately, even under optimized conditions, the contribution of the competitive methanolysis of the cyano group, leading to the formation of **24** and **25**, remained high. Tritylation ($TrClO_4$/collidine/CH_2Cl_2) of the alcohol **23** gave the monomer **3** in 65% yield: however, the reaction was accompanied by the formation of several by-products. By contrast, the methoxycarbonyl derivative **24** could be tritylated without any difficulties, affording **27** in 94% yield. The instability of the cyanoethylidene group during manipulations involving protecting groups in procedures for the preparation of trityl-CED monomers has been observed previously.[43–46] Since the methoxycarbonyl group is stable under all the reaction conditions used in the preparation of the tritylated monomer precursor, we decided to employ an alternative route involving the interconversion[47] of cyanoethylidene and methoxycarbonylethylidene derivatives. This route started from the dibenzoate **9** (Scheme 3), which was cou-



Scheme 3. Synthesis of the disaccharide monomer **3**. Reagents and conditions: a) AgOTf/collidine/CH_2Cl_2, $-20 \rightarrow -10\,^\circ C$, 1 h; from **7** and **16**, 86% (**22**); from **9** and **21**, 96% (**26**); b) 1 M HCl/MeOH, 20 °C, 12 h, 19% (**23**), 34% (**24**), 5% (**25**); c) $(NH_2)_2CS/MeCN/H_2O$, 20 °C, 20 h, 92%; d) $TrClO_4$/collidine/CH_2Cl_2, 20 °C, 5 h, from **23**, 66% (**3**); from **24**, 96% (**27**); e) NH_3/MeOH, 20 °C, 17 h, then $BzCl/C_5H_5N$, 20 °C, 5 h, 87%.

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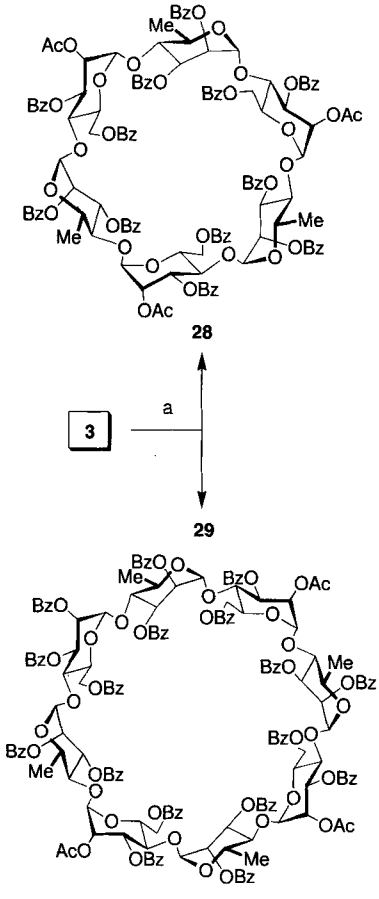
pled ($AgOTf/collidine/CH_2Cl_2$) with the bromide **21**, affording the disaccharide **26** in 96% yield. Dechloroacetylation ($(H_2N)_2CS/MeCN/H_2O$) of **26** yielded the alcohol **24** (92%), which was tritylated successfully as already described. The conversion of the methoxycarbonyl group in **27** to the cyano group in **3** was performed in a two-step procedure consisting of ammonolysis ($NH_3/MeOH$), followed by dehydration ($BzCl/C_5H_5N$) of the amide with simultaneous benzoylation of free hydroxyl groups. The yield of the disaccharide monomer **3**, prepared by this route, was 85%. The overall yield of **3** starting from **6** was 39%. The overall yield for the original route starting from **5** was 6%.

The structure of the disaccharide monomer **3** was confirmed by ^{13}C NMR spectroscopy. In particular, the presence of characteristic signals for the cyanoethylidene group (δ = 20.7, 101.5, and 116.7 for CH_3-C-CN, respectively) and the triphenylmethyl group (δ = 88.3 for the quaternary aromatic atom) were noted in the ^{13}C NMR spectrum recorded in $CDCl_3$. Also, the α configuration of the rhamnosidic bond in **3** can be inferred from the characteristic J(C,H) coupling constant[48] of 170 Hz for the anomeric carbon atom on the rhamnosyl residue.



Scheme 4. Cyclooligomerization of the disaccharide monomer **3**. Reagents and conditions: a) $TrClO_4/CH_2Cl_2$, concentration of **3** and $TrClO_4$ 0.01 M, 20 °C, 40 h, 34% (**28**) and 31% (**29**).

Cyclooligomerization of **3**: The crucial step—the cyclooligomerization of **3**—was accomplished (Scheme 4) in CH_2Cl_2 in the presence of $TrClO_4$ as a catalyst at 25 °C using a high-vacuum technique for the preparation of both the reactants and the solvents. The reaction was carried out under moderately dilute conditions (0.01 M). Although the concentration of the disaccharide monomer was not that much less than that used in earlier polycondensations (>0.1 M),[37, 38] the concentration of the catalyst was chosen such as to provide a reasonable rate of reaction. After 40 h, no tritylated carbohydrates were detected in the reaction mixture. Analytical HPLC revealed the formation of two major products and a series of slower moving components (Fig. 3) which migrate as one band on TLC. The two faster-moving major products were separated successfully as pure compounds by a combination of ordinary column chromatography and preparative HPLC on silica gel columns to give the cyclic oligosaccharides **28** and **29** in 34 and 31% yields, respectively.

The highly symmetrical structures of **28** and **29** were obvious from inspection of their NMR spectra: both the ^1H (Fig. 4) and

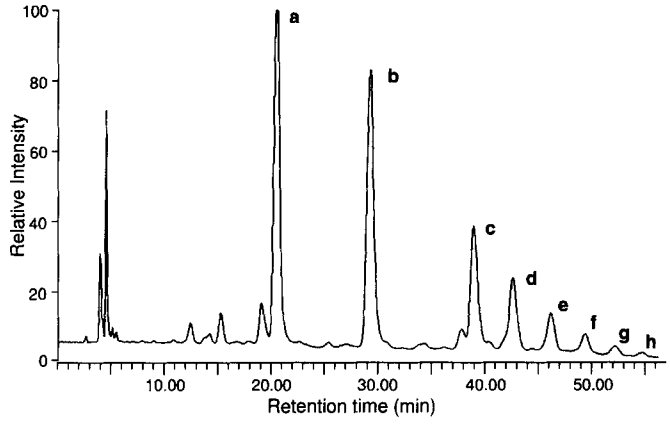


Fig. 3. The elution profile of the products from the cyclooligomerization of the disaccharide monomer **3** obtained from a Dynamax 60A HPLC column (SiO_2, 250 × 5 mm i.d.) with heptane–EtOAc (gradient elution from 40–80% of EtOAc during 80 min) as the eluant. Peaks **a** and **b** relate to compounds **28** and **29**, respectively. Peaks **c** to **h** represent a high molecular weight fraction in which **c**, **d**, and **e** have been identified by MALDI-TOF mass spectrometry (see Fig. 5) as cyclic deca-, dodeca-, and tetradecasaccharides, respectively.

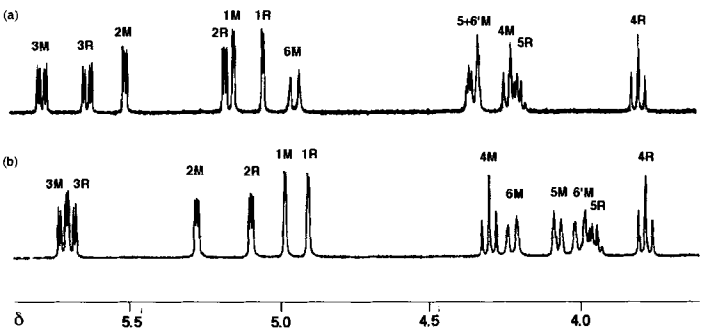


Fig. 4. The ^1H NMR spectra of the protected cyclic oligosaccharides **28** (a) and **29** (b) recorded in $CDCl_3$ at 400 MHz. In the annotation of the spectra, the numbers refer to the usual pyranose ring numbering scheme and **M** and **R** relate to the D-mannopyranosyl and L-rhamnopyranosyl residues, respectively.

^{13}C NMR spectra contain only *one* set of signals, corresponding to a disaccharide repeating unit. No minor signals which could be attributed to the presence of terminal monosaccharide residues were evident in these spectra. In the anomeric region of the ^{13}C NMR spectrum, there are only *two* signals that can be assigned to the anomeric carbon atoms of the rhamnose and mannose residues, and they are both associated with the α-glycosidic bonds since the J(C,H) values are around 170 Hz. All of this evidence indicates that compounds **28** and **29** are cyclic oligosaccharides with repeating and alternating L-rhamnopyranosyl and D-mannopyranosyl residues linked exclusively α-1,4.

The precise determination of the ring sizes of the two cyclic oligosaccharides was accomplished by LSIMS and MALDI-TOFMS (Table 1). These two mass spectrometric techniques reveal that **28** and **29** are built up from three and four disaccharide repeating units, respectively. During the LSIMS, unusual peaks corresponding to $[M+133]^+$ ions were observed and attributed to the presence of cesium ions: the peaks were completely suppressed by the addition of sodium ions. Although the same peculiarity did not characterize the original MALDI-TOFMS, in the presence of a 1:1 mixture of sodium and cesium salts, peaks corresponding to $[M+Cs]^+$ ions predominate in the mass spectra.

Even employing preparative-scale HPLC, we were unable to separate further pure compounds from the third fraction, fol-

Table 1. Mass spectrometric data for the cyclic oligosaccharides **1**, **2**, **28**, and **29**.

	Predicted M^+ [a]	Observed m/z LSIMS	MALDI
1	924.3		947 $[M+Na]^+$ 963 $[M+K]^+$
2	1232.4		1255 $[M+Na]^+$ 1271 $[M+K]^+$
28	2299.7	2431 $[M+Cs]^+$ 2322 $[M+Na]^+$ [b]	2321 $[M+Na]^+$ 2337 $[M+K]^+$
29	3065.9	3199 $[M+Cs]^+$ 3090 $[M+Na]^+$ [b]	3087 $[M+Na]^+$ 3103 $[M+K]^+$

[a] The mass of the most abundant peak in the calculated isotope distribution. [b] An excess of NaOAc was added to the probe for this run.

lowing the isolation of **28** and **29** from the cyclic oligomerization. However, when MALDI-TOFMS was applied (Fig. 5) to the analysis of this third fraction, it was found to contain three products which could be assigned to the cyclic deca-, dodeca-, and tetradecasaccharides on the basis of peaks, respectively, at m/z = 3852, 4619, and 5386 for their $[M+Na]^+$ ions.

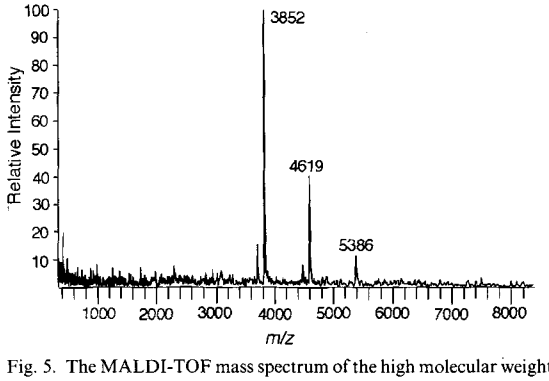


Fig. 5. The MALDI-TOF mass spectrum of the high molecular weight fraction that contains peaks **c** to **h** from the HPLC (see Fig. 3) following cyclooligomerization of the disaccharide monomer **3**. Peaks **c**, **d**, and **e** in Fig. 3 appear to give rise to $[M+Na]^+$ ions at 3852, 4619, and 5386, corresponding to cyclic deca-, dodeca-, and tetradecasaccharides, respectively.

*Deprotection of the Acylated Cyclic Oligosaccharides **28** and **29***: Deprotection of **28** and **29** was achieved by saponification with NaOMe in $MeOH/CH_2Cl_2$, followed by treatment with NaOH in aqueous MeOH. The "free" cyclic oligosaccharides **1** and **2** were purified by gel-permeation chromatography, eluting somewhat faster than α- and β-cyclodextrins, respectively. On concentration of an aqueous solution of **1**, the cyclic hexasaccharide exhibits very low solubility in water; by contrast, the cyclic octasaccharide **2** retains its aqueous solubility on concentration. The structures of the cyclic oligosaccharides **1** and **2** were confirmed by NMR spectroscopy. The ^1H NMR spectra of **1** and **2** could be assigned completely by using the COSY technique in conjunction with NOE experiments. The assignment of the carbon resonances in the ^{13}C NMR spectrum of **2** was made on the basis of a C–H correlation experiment. The MALDI-TOFMS data for **1** and **2** (Table 1) are in complete agreement with the number of repeating units already established for their fully protected precursors, namely, **28** and **29**, respectively. The cyclic octasaccharide **2** was observed to crystallize from aqueous solution, affording colorless needles—which decompose rather quickly on being taken out of water—suitable for X-ray crystallography.

X-Ray Crystal Structure of 2: The X-ray structural analysis of **2** (Fig. 6) reveals the presence of a highly symmetrical structure with two crystallographically independent C_4 symmetric molecules in the asymmetric unit. The alternating 1,4-linked α-L-rhamnopyranosyl and α-D-mannopyranosyl units in each molecule adopt normal $^1C_4$ and $^4C_1$ chair conformations, respectively. There are only very small differences between these two molecules (Fig. 7) in the conformations of the two unique disaccharide units in the cyclic oligosaccharide, namely,

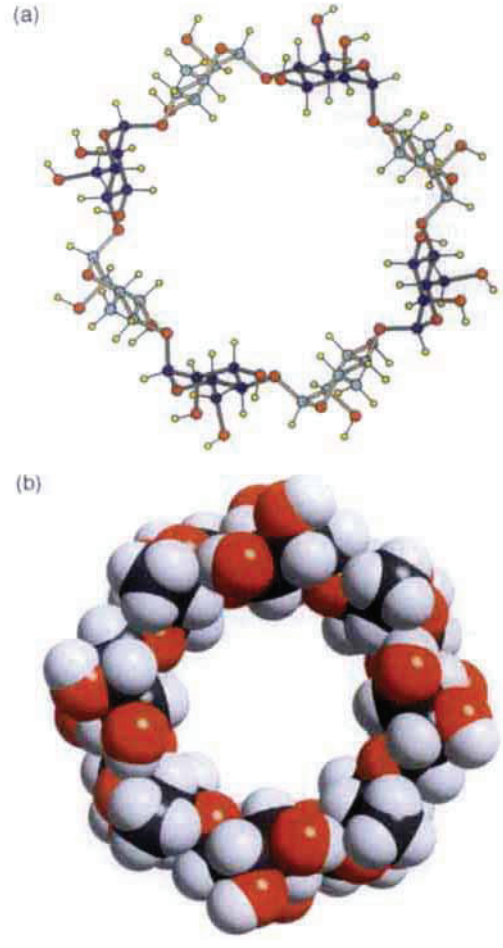


Fig. 6. a) Ball-and-stick and b) space-filling representations of the solid-state structure of the cyclooctaoside **2** (molecule 1) in plan view. In (a) the L-rhamnopyranosyl and D-mannopyranosyl residues are picked out in light and dark blue, respectively. The coloring of the atoms in (b) is conventional.

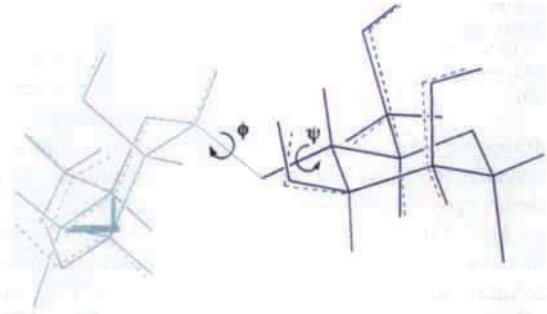


Fig. 7. The superimposition of the disaccharide repeating unit of molecule 1 (solid lines) and molecule 2 (dashed lines) in the solid-state structure of **2**. The L-rhamnopyranosyl and D-mannopyranosyl residues are traced out in light and dark blue, respectively.

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-α-L-Rha*p*-(1 → 4)-D-Man*p*- and -α-D-Man*p*-(1 → 4)-L-Rha*p*- (Fig. 8). Whereas in the first of these disaccharide repeating units (Fig. 8a) there are small differences in the ϕ and ψ torsional angles (+41 and −6°, respectively, in molecule 1, cf. +36 and 0°, respectively, in molecule 2) associated with the glycosidic bond, in the other disaccharide repeating unit (Fig. 8b) the

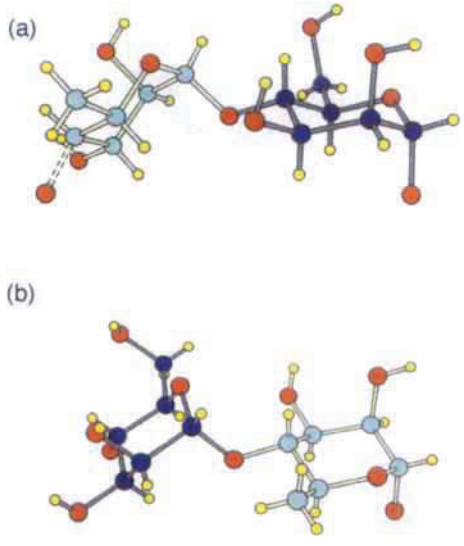

Fig. 8. The conformations of the two disaccharide fragments of **2** (molecule 1) in the solid state: a) -α-L-Rha*p*-(1 → 4)-D-Man*p*- and b) -α-D-Man*p*-(1 → 4)-L-Rha*p*-, with the L-rhamnopyranosyl and D-mannopyranosyl residues highlighted in light and dark blue, respectively.

ϕ and ψ torsional angles are, within the margin of error, the same at −36 and 0°, respectively. In terms of the overall conformation of **2**, these geometries lead to almost orthogonal dispositions of the rhamnopyranose and mannopyranose rings toward the plane of the cyclic oligosaccharide. The highly symmetrical conformation observed for **2** is in sharp contrast to the very much more distorted geometry observed for the closely related hydrated γ-cyclodextrin.[49, 50]

The symmetrical shape of **2** produces a cavity with transannular dimensions that are summarized in Table 2 with reference to 1) the two different pairs of diametrically disposed glycosidic oxygen atoms and 2) opposite pairs of inwardly directed axial

Table 2. Some selected intraannular distances (Å) in the solid-state structure of the cyclooctaoside **2**.

[Atom ··· Atom] [a]	Molecule 1	Molecule 2
[O-1A (Rha) ··· O-1C (Rha)]	11.28	11.26
[O-1A (Man) ··· O-1C (Man)]	11.15	11.22
[O-3A (Rha) ··· H-3C (Rha)]	9.37	9.31
[H-5A (Rha) ··· H-5C (Rha)]	10.48	10.77
[H-3A (Man) ··· H-3C (Man)]	9.20	9.32
[H-5A (Man) ··· H-5C (Man)]	10.62	10.54

[a] Following a well-known nomenclature system in cyclodextrin chemistry, the repeating disaccharide units are labeled clockwise A, B, C, and D.

H-3 and H-5 hydrogen atoms on the L-rhamnopyranose and D-mannopyranose rings. A very important feature of the solid-state structure of **2** is the absence of any intramolecular [O–H ··· O] hydrogen bonding between adjacent monosaccharide units—a feature that is normally considered necessary for the formation of a toroidal conformation in the case of the CDs.[51]

Both crystallographically independent molecules form discrete stacks (Fig. 9, left) that extend through a lattice translation (7.92 Å repeat) in the *c* direction. The molecules within each stack are thus perfectly in register with each other and form large open channels (Fig. 9, right) within which some of the

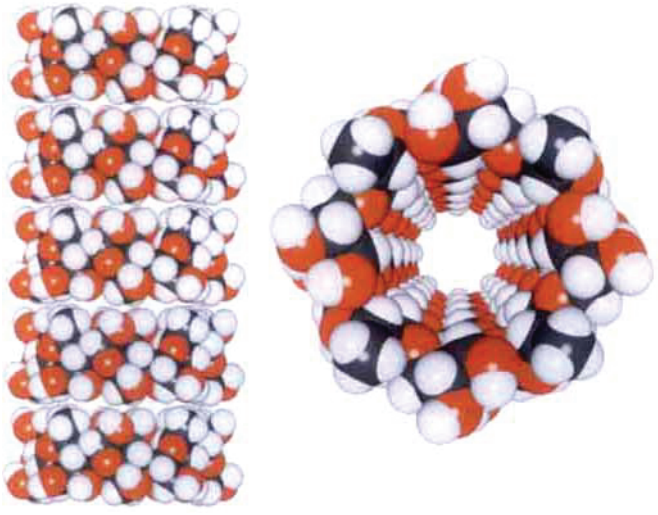

Fig. 9. The discrete stacks of **2** in the solid state, shown with a space-filling representation and conventional colorings of the atoms: a side-on view of a stack (left) and a view looking down one of the stacks (right).

included H_2O molecules are located.[52] Stacks of molecules are arranged in a cubic close-packed array (Fig. 10), with adjacent stacks that are in van der Waals contact with each other having reversed polarities[53] associated with clockwise and anticlock-

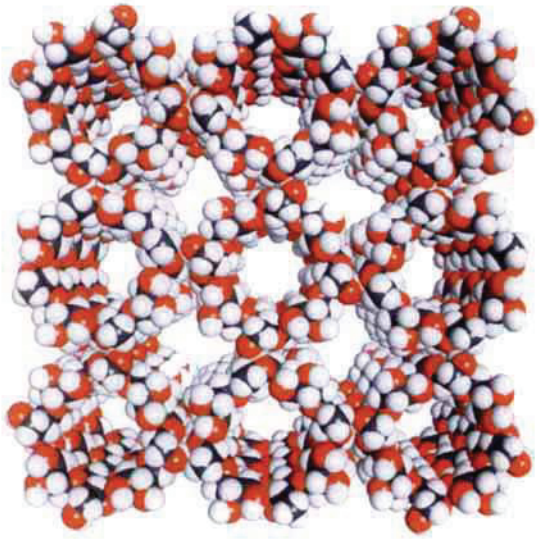

Fig. 10. The three-by-three arrangement of molecules of **2** in a cubic close-packed array, shown with a space-filling representation and conventional atom colorings. Note the interstices between the stacks of molecules as well as the open channels associated with each molecular stack.

wise sequences of the eight glycosidic bonds in **2** (Fig. 11). Immediately adjacent molecules within any one close-packed sheet are slightly stepped with respect to each other relative to the stack directions (Fig. 12). Adjacent stacks are cross-linked

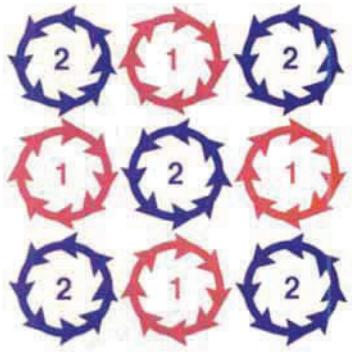

Fig. 11. A schematic representation of the two-dimensional arrangement of molecules 1 (red) and 2 (blue) in the solid-state structure of **2**. The clockwise and anticlockwise sequences of the glycosidic bonds in this three-by-three arrangement match that illustrated in Figure 10.

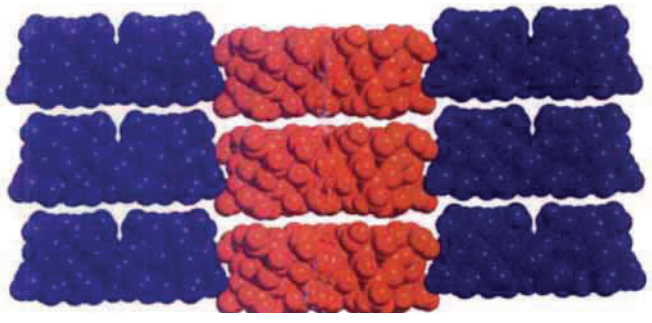

Fig. 12. A space-filling representation in elevation of the slightly stepped stacks of molecules 1 (red) and 2 (blue) of **2** in the solid state.

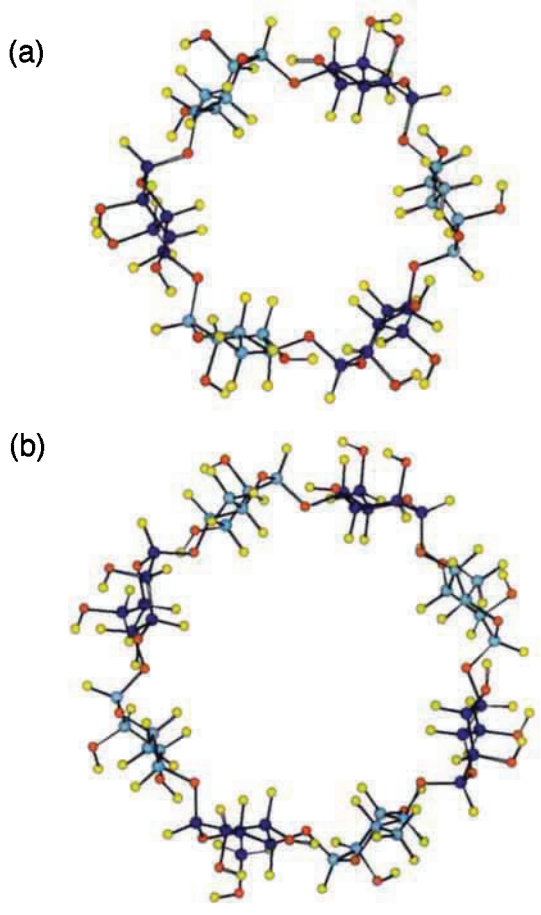

Fig. 13. The calculated structures of a) **1** and b) **2** obtained by the semiempirical method AM1.

through pairs of [O–H···O] hydrogen bonds,[54] involving in one instance an interaction between the CH_2OH group on D-mannopyranose residues in molecule 1 and the ring oxygen atoms of the D-rhamnopyranose residues in molecule 2 and between the OH groups on C-2 of the same pair of monosaccharide residues in the two molecules. Associated with the close-packed arrangement of stacked molecules is the formation of secondary interstack channels within which the remaining H_2O molecules are positioned.

Molecular Modeling of 1 and 2: Since the solid-state structural information was available for **2**, we decided to carry out some molecular simulations on **1** as well as on **2**, based on the semiempirical method AM1.[55] We argued that, if we could achieve a high degree of correlation between the calculated and experimental solid-state structure of **2**, then we could make a prediction with some certainty about the structure of **1**. The calculated structures for **1** and **2** are shown in Figure 13. Direct comparison (Fig. 14) between the calculated structure for **2** and the structure obtained for molecule 1 demonstrates a high degree of similarity: the RMS error of superimposition for the glycosidic oxygen atoms is 0.16 Å. Moreover, the relatively close match between most of the geometrical and physical data in Table 3 for the calculated structure of **2** and that based on molecule 1 in the solid-state structure is encouraging. Although there are some deviations in the torsional angles (ϕ and ψ) associated with the two different glycosidic bonds, this observation is not unexpected since semiempirical methods often predict conformations that are lower in energy than those found in the solid state.[56] Indeed, estimates of the heats of formation for the calculated and X-ray-derived conformations suggest that the calculated structure is some 115 kcal mol^{-1} more stable (in the gas phase) than the solid-state structure, which is, of course, stabilized extensively by solvation with water. Thus, we present a calculated conformation for **1** in Figure 13 with some confidence about its gross structural relationship to the actual molecule. More significantly, we have demonstrated to ourselves that we can predict the gross structural features of this new generation of cyclic oligosaccharides with a high degree of precision.

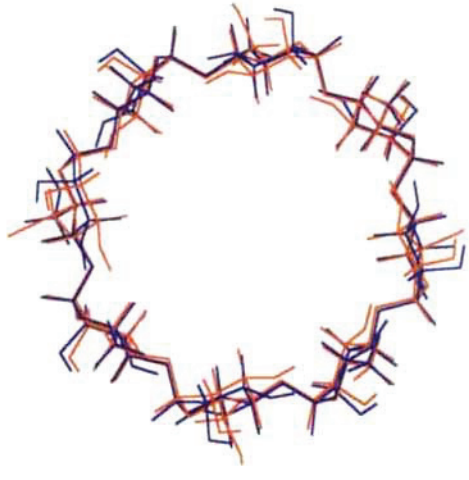

Fig. 14. A superimposition of the structures of **2** obtained from X-ray crystallographic data on molecule 1 (red lines) and from a semiempirical calculation using AM1 (blue lines).

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Table 3. Summary of calculated parameters for the cyclohexaoside **1** and the cyclooctaside **2**.

	1 [a]	**2** [a]	**2** [b]
Intraannular distances (Å) [c]			
O-1 A (Rha)···O-1 C (Rha)	–	11.45	11.28
O-1 A (Man)···O-1 C (Man)	–	11.39	11.15
O-1 A (Rha)···O-1 B (Man)	8.29	–	–
O-1 A (Man)···O-1 C (Rha)	8.33	–	–
Glycosidic torsional angles (°)			
ϕ [d]	13.0	22.5	41.0
ψ [d]	−15.4	−5.6	−6.0
ϕ [e]	−18.4	−20.3	−36.0
ψ [e]	22.0	3.8	0
Average glycosidic bond angle (°)	116.9	115.9	116.2
Final ΔH_f (kcal mol^{-1})	−1269	−1701	−1588 [f]
Calculated dipole moment (D)	1.5	4.7	4.8 [f]

[a] Structures deduced by semiempirical AM1 calculation. [b] Structure of molecule 1 of the cyclooctaside **2** obtained by X-ray crystallography. [c] Following a well-known nomenclature system in cyclodextrin chemistry, repeating disaccharide units are labeled clockwise A, B, C, and D. [d] Torsion angles associated with the glycosidic bond in α-L-Rha*p*-(1 → 4)-D-Man*p*. [e] Torsional angles associated with the glycosidic bond in α-D-Man*p*-(1 → 4)-L-Rha*p*. [f] Values obtained from a single-point AM1 calculation based on the X-ray crystal structure of **2** (molecule 1).

Conclusion

The polycondensation–cycloglycosylation approach to the synthesis of cyclic oligosaccharides resembling CDs has been applied successfully to the construction of cyclo[(1 → 4)-α-L-rhamnosyl-(1 → 4)-α-D-mannopyranosyl]trioside (**1**) and -tetraoside (**2**). The approach depends on the identification of a rationally designed precursor—the disaccharide monomer **3**—and the use of high-dilution conditions in the cyclooligomerization. The predominant formation of cyclic hexa- and octasaccharides—as well as the relative absence of high molecular weight linear products—can be accounted for by the preorganization of the growing oligosaccharide chain during the reaction: the consequence of the axial and equatorial orientations at the C-1–O and C-4–O bonds, respectively, on the two pyranosyl rings, determines the helical conformations for the linear oligosaccharides. Although their separation and characterization has still to be accomplished, cyclic oligosaccharides containing more than eight monosaccharide residues have also been identified in the product mixture following the cyclooligomerization. The polycondensation–cycloglycosylation approach seems to be an attractive one for the construction of a range of cyclic oligosaccharides, which, unlike the CDs, do not contain α-1,4-linked D-glucopyranosyl residues.

The fact that, in the solid state, the cyclic octasaccharide forms nanotubules with a diameter of approximately 1 nm is reminiscent of the solid-state structures of cyclic peptides with alternating D- and L-amino acids.[57] It is conceivable that these new cyclic oligosaccharides could become attractive candidates for research at air–water interfaces and on solid substrates. Such activities in the area of interfacial science would be particularly worthwhile if the cyclic oligosaccharides **1** and **2** behave as receptors toward appropriately structured substrates after the fashion of α- and γ-cyclodextrins—the naturally occurring cyclic octasaccharides.

Experimental Section

General Techniques: Chemicals, including monosaccharides, were purchased from Aldrich or Lancaster. $TrClO_4$ was prepared according to a literature procedure [58]. Solvents were dried as recommended in the literature [59]. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated 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 carried out using silica gel 60 F (Merck 9385, 230–400 mesh). High-performance liquid chromatography (HPLC) was carried out on Dynamax 60 columns (Anachem) with a Gilson 714 system fitted with a variable UV detector. Gel-permeation chromatography (GPC) was performed on a column (80 × 1.6 cm with $V_0 \approx 60$ mL) packed with Fractogel TSK HW-40(S) (Merck) in 0.1 M AcOH. Fractions were monitored with a differential refractometer 141 supplied by Waters. 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 with either the solvent reference or TMS 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 2,5-dihydroxybenzoic acid matrix. Microanalyses were performed by the University of Birmingham or University of Sheffield microanalytical services.

1,2-*O*-[1-(*exo*-Cyano)ethylidene]-β-D-mannopyranose [40] (**5**): The triacetate **4** [39] (3.57 g, 10 mmol) was dissolved in a mixture of $CHCl_3$/MeOH (1:6, 35 mL) at 40 °C, Et_3N (3 mL) was added, and the reaction mixture was stirred for 20 min at 40 °C before being left to stand overnight at room temperature. The solution was then concentrated and the residue subjected to chromatography (SiO_2: EtOAc/MeOH, 9:1) to give the triol **5** (1.22 g, 53% yield), R_F = 0.54 (EtOAc:MeOH, 9:1); $[\alpha]_D$ = + 20.7 (c = 1.2 in Me_2CO), ref. [40]: $[\alpha]_D$ = + 22.3 (c = 1.0 in MeOH); ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 1.85 (s, 3H; CCH_3), 3.35 (ddd, $J_{5,6a}$ = 5.8 Hz, $J_{5,6b}$ = 2.4 Hz, 1H; H-5), 3.65 (pt, $J_{3,4} = J_{4,5}$ = 9.2 Hz, 1H; H-4), 3.67 (dd, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6a), 3.80 (dd, 1H; H-6b), 3.97 (dd, $J_{2,3}$ = 4.2 Hz, 1H; H-3), 4.58 (dd, $J_{1,2}$ = 2.2 Hz, 1H; H-2), 5.40 (d, 1H; H-1); ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$, 25 °C): δ = 26.9 (CH_3C), 62.4 (C-6), 68.2, 71.9, 77.1 (C-3, C-4, C-5), 82,3 (C-2), 98.1 (C-1), 101.9 (CH_3C), 118.2 (CN), FABMS: m/z 254 $[M + Na]^+$, 205 $[M - CN]^+$.

3,6-Di-*O*-benzoyl-1,2-*O*-[1-(*exo*-cyano)ethylidene]-β-D-mannopyranose (**7**) and **3,4,6-Tri-*O*-benzoyl-1,2-*O*-[1-(*exo*-cyano)ethylidene]-β-D-mannopyranose** (**8**): A solution of BzCl (3.24 mL, 28 mmol) was added gradually to a cooled (−30 °C) and stirred solution of the triol **5** (1.70 g, 7.00 mmol) in C_5H_5N (35 mL). Stirring was continued for 2 h at −30 °C. After treatment with MeOH (2 mL), the mixture was allowed to warm up to room temperature, before it was diluted with $CHCl_3$ (100 mL), washed with aq. $NaHCO_3$ (2 × 30 mL) and H_2O (30 mL), and then concentrated. Column chromatography of the residue (SiO_2: hexane/EtOAc, 95:5 to 70:30) afforded dibenzoate **7** (2.20 g, 71%) and tribenzoate **8** (760 mg, 20%).

7: R_F = 0.47 (hexane/EtOAc, 7:3); m.p. 152–153 °C; $[\alpha]_D$ = + 30.4 (c = 1.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.86 (s, 3H; CCH_3), 3.70 (m, 1H; H-5), 4.06 (pt, $J_{3,4} = J_{4,5}$ = 9.8 Hz, 1H; H-4), 4.52 (dd, $J_{5,6a}$ = 2.6 Hz, $J_{6a,6b}$ = 12.4 Hz, 1H; H-6a), 4.72 (dd, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 4.1 Hz, 1H; H-2), 4.83 (dd, $J_{5,6b}$ = 3.6 Hz, 1H; H-6b), 5.43 (dd, 1H; H-3), 5.55 (dd, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 26.7 (CH_3C), 63.2 (C-6), 65.0 (C-4), 72.2 (C-3), 74.2 (C-5), 78.8 (C-2), 97.1 (C-1), 101.7 (CH_3C), 116,7 (CN), 166.4, 167.2 (C=O); FABMS: m/z 452 $[M + Na]^+$, 440 $[M + H]^+$, 413 $[M - CN]^+$, 371 $[M - CN - CH_2CO]^+$; $C_{23}H_{21}NO_8$ (439.43): calcd C 62.87, H 4.82, N 3.19; found C 63.20, H 4.83, N 2.92.

8: R_F = 0.65 (hexane/EtOAc, 7:3); m.p. 96 °C (softening) then 118–118.5 °C (EtOAc/hexane); $[\alpha]_D$ = −1.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.93 (s, 3H; CCH_3), 4.12 (m, 1H; H-5), 4.42 (dd, $J_{5,6a}$ = 5.0 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H; H-6a), 4.62 (dd, $J_{5,6b}$ = 3.2 Hz, 1H; H-6b), 4.85 (dd, $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 3.6 Hz, 1H; H-2), 5.65 (dd, 1H; H-1), 5.69 (dd, $J_{3,4}$ = 10.0 Hz, 1H; H-3), 5.89 (pt, $J_{4,5}$ = 10.0 Hz, 1H; H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 26.2 (CH_3C), 62.8 (C-6), 66.1 (C-4), 69.9, 72.0 (C-3, C-5), 78.2 (C-2), 97.1(C-1), 101.5 (CH_3C), 116.4 (CN), 165.1, 165.5, 165.8 (C=O); FABMS: m/z 556 $[M + Na]^+$, 544 $[M + H]^+$, 517 $[M - CN]^+$, 475 $[M - CN - CH_2CO]^+$; $C_{30}H_{25}NO_9$ (543.53): calcd C 66.29, H 4.64, N 2.58; found C 66.35, H 4.71, N 2.20.

1,2-*O*-[1-(*exo*-Methoxycarbonyl)ethylidene]-β-D-mannopyranose (**6**): The triacetate **4** (7.14 g, 20 mmol) was stirred for 6 h in 0.02 M NaOMe in MeOH (255 mL) at 25 °C. The solution was treated with 1 M HCl (ca. 10 mL) to neutralize and then kept for 0.5 h before being concentrated. The product was separated by filtration through the silica gel column with EtOAc/MeOH (9:1) as eluant to give the pure triol **6** (4.43 g, 84%), R_F = 0.46 (EtOAc/MeOH, 9:1); m.p. 72–73 °C; $[\alpha]_D$ = +18.9 °(c = 1.1 in Me_2CO); ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 1.63 (s, 3H; CCH_3), 3.35 (m, 1H; H-5), 3.65 (pt, $J_{3,4} = J_{4,5}$ = 9.6 Hz, 1H; H-4), 3.66 (dd, $J_{5,6a}$ = 6.0 Hz, $J_{6a,6b}$ = 12.7 Hz, 1H; H-6a), 3.73 (s, 3H; $COCH_3$), 3.80 (dd, $J_{5,6b}$ = 2.4 Hz, 1H; H-6b), 3.87 (dd, $J_{2,3}$ = 4.2 Hz, 1H; H-3), 4.36 (dd, $J_{1,2}$ = 2.3 Hz, 1H; H-2), 5.44 (d, 1H; H-1); ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$, 25 °C):

δ = 26.6 (CH_3C), 52.6 (OCH_3), 62.7 (C-6), 68.4, 72.6, 77.0 (C-3, C-4, C-5), 81.6 (C-2), 98.4 (C-1), 108.0 (CH_3C), 170.2 (C=O); FABMS: m/z 287 $[M+Na]^+$, 265 $[M+H]^+$, 203 $[M-COOMe]^+$, 163 $[M-COOMe-CH_2CO]^+$; $C_{10}H_{16}O_8$ (264.23): calcd C 45.46, H 6.10; found C 45.20, H 5.85.

3,6-Di-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (9) and **3,4,6-Tri-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (10)**: The triol **6** (2.82 g, 10.7 mmol) was partially benzoylated with BzCl (2.3 mL, 20 mmol) in C_5H_5N (50 mL) as described for the preparation of dibenzoate **7** and the tribenzoate **8**. The products were isolated by column chromatography (SiO_2: PhMe/EtOAc, 95:5 to 4:1) to give the dibenzoate **9** (3.29 g, 65%) and the tribenzoate **10** (740 mg, 12%).

9: R_F = 0.44 (PhMe/EtOAc, 4:1); $[\alpha]_D$ = + 25.1 (c = 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.72 (s, 3H; CCH_3), 3.70 (m, 1H; H-5), 3.72 (s, 3H; $COCH_3$), 4.13 (pt, $J_{3,4} \approx J_{4,5}$ = 9.9 Hz, 1H; H-4), 4.52 (dd, $J_{5,6a}$ = 2.6 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H; H-6a), 4.75 (dd, $J_{1,2}$ = 2.1 Hz, $J_{2,3}$ = 3.8 Hz, 1H; H-2), 4.85 (dd, $J_{5,6b}$ = 3.6 Hz, 1H; H-6b), 5.39 (dd, 1H; H-3), 5.55 (dd, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.5 (CH_3C), 52.7 (OCH_3), 63.5 (C-6), 65.0 (C-4), 73.1 (C-3), 74.1 (C-5), 78.4 (C-2), 97.5 (C-1), 107.7 (CH_3C), 166.5, 167.2, 169.2 (C=O); FABMS: m/z 485 $[M+Na]^+$, 473 $[M+H]^+$, 413 $[M-COOMe]^+$, 371 $[M-COOMe-CH_2CO]^+$; $C_{24}H_{24}O_{10}$ (472.45): C 61.02, H 5.12; found C 61.00, H 5.17.

10: R_F = 0.68 (PhMe/EtOAc, 4:1); m.p. 143–144 °C (EtOAc/hexane); $[\alpha]_D$ = −13.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.81 (s, 3H; CCH_3), 3.73 (s, 3H; $COCH_3$), 4.13 (m, 1H; H-5), 4.48 (dd, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H; H-6a), 4.64 (dd, $J_{5,6b}$ = 3.5 Hz, 1H; H-6b), 4.90 (dd, $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 3.6 Hz, 1H; H-2), 5.66 (dd, $J_{3,4}$ = 10.1 Hz, 1H; H-3), 5.68 (dd, 1H; H-1), 5.98 (pt, $J_{4,5}$ = 10.1 Hz, 1H; H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.1 (CH_3C), 52.5 (OCH_3), 63.25 (C-6), 66.4 (C-4), 70.7, 72.1 (C-3, C-5), 77.8 (C-2), 97.7 (C-1), 107.7 (CH_3C)165.1, 165.7, 166.0, 168.1 (C=O); FABMS: m/z 599 $[M+Na]^+$, 577 $[M+H]^+$, 517 $[M-COOMe]^+$, 475 $[M-COOMe-CH_2CO]^+$; $C_{31}H_{28}O_{11}$ (576.56): calcd C 64.58, H 4.90; found C 64.50, H 4.71.

Methyl 4-*O*-Acetyl-2,3-di-*O*-isopropylidene-α-L-rhamnopyranoside [60] (12): Conventional acetylation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside [41] (**11**) (12.0 g) by the action of an Ac_2O–C_5H_5N mixture (40 mL, 1:3) at 20 °C for 1 h afforded the acetate **12** (13.3 g, 93%), which crystallized on standing; R_F = 0.58 (hexane/EtOAc, 9:1); m.p. 60–62 °C; $[\alpha]_D$ = −15.8 (c = 1.0 in $CHCl_3$); ref. [60]: m.p. 61–63 °C (aq. MeOH), $[\alpha]_D$ = −14.5 (in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.15 (d, $J_{5,6}$ = 6.3 Hz, 3H; H-6), 1.32 (s, 3H; $C(CH_3)_2$), 1.54 (s, 3H; $C(CH_3)_2$), 2.08 (s, 3H; $OCOCH_3$), 3.37 (s, 3H; OCH_3), 3.68 (dq, 1H; H-5), 4.09–41.6 (m, 2H; H-2, H-3), 4.84 (dd, $J_{3,4}$ = 7.0 Hz, $J_{4,5}$ = 10.0 Hz, 1H; H-4), 4.87 (bs, $J_{1,2}$ < 1 Hz, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.9 (C-6), 21.0 ($OCOCH_3$), 26.3, 27.6 ($C(CH_3)_2$), 54.9 (OCH_3), 63.8 (C-5), 74.4, 75.8, 75.9 (C-2, C-3, C-4), 98.0 (C-1), 109.7 ($C(CH_3)_2$), 170.0 (C=O).

Methyl 4-*O*-Acetyl-α-L-rhamnopyranoside (13): The acetonide **12** was stirred with Amberlite 15 (H^+) (5 g) in MeOH (100 mL) overnight at room temperature, and then the resin was filtered off and the solvent removed by evaporation. The residue was recrystallized from an Et_2O/hexane mixture to give the diol **13** (11.0 g, 98%); R_F = 0.19 $CHCl_3$/MeOH, 9:1); m.p. 112–113.5 °C; $[\alpha]_D$ = −97.5 (c = 1.2 in $CHCl_3$); ref. [60]: m.p. 112–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.22 (d, $J_{5,6}$ = 6.2 Hz, 3H; H-6), 2.13 (s, 3H; $OCOCH_3$), 3.38 (s, 3H; OCH_3), 3.77 (dq, 1H; H-5), 3.84 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5Hz, 1H; H-3), 3.93 (dd, $J_{1,2}$ = 1.3 Hz, 1H; H-2), 4.71 (d, 1H; H-1), 4.81 (pt, $J_{4,5}$ = 9.5 Hz, 1H; H-4); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 17.4 (C-6), 21.1 ($OCOCH_3$), 55.0 (OCH_3), 65.6 (C-5), 70.1, 70.9 (C-2, C-3), 75.0 (C-4), 100.7 (C-1),171.9 (C=O).

Methyl 4-*O*-Acetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranoside [60] (14): BzCl (11.6 mL, 100 mmol) was added to a solution of the diol **13** (11.0 g, 50 mmol) in C_5H_5N, and the reaction mixture was stirred for 4 h at room temperature followed by a conventional workup procedure. Column chromatography of the resulting mixture on silica gel using light petroleum (b.p. 60–80 °C)/hexane (95:5) as eluant gave the dibenzoate **14** (16.8 g, 78%); R_F = 0.62 (hexane/EtOAc, 9:1); m.p. 60–61 °C; $[\alpha]_D$ = +116.5 (c = 1.1 in $CHCl_3$); ref. [60]: m.p. 40–60 °C (aq. MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.31 (d, $J_{5,6}$ = 6.4 Hz, 3H; H-6), 1.97 (s, 3H; $OCOCH_3$), 3.46 (s, 3H; OCH_3), 4.01 (dq, 1H; H-5), 4.85 (d, $J_{1,2}$ = 1.2 Hz, 1H; H-1), 5.39 (pt, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H; H-4), 5.59 (dd, $J_{2,3}$ = 3.6 Hz,1H; H-2), 5.62 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.6 (C-6), 20.8 ($OCOCH_3$), 55.3 (OCH_3), 66.3 (C-5), 70.1, 70.7, 71.3 (C-2, C-3, C-4), 98.5 (C-1), 165.5, 165.6 (PhCO), 170.1 (C=O).

1,4-Di-*O*-acetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranose (15): The methyl glycoside **14** (16.0 g, 37 mmol) was dissolved in Ac_2O (60 mL), and treated with conc. H_2SO_4 (0.6 mL) at 0–5 °C. The reaction mixture was allowed to stand for 2 h at room temperature. NaOAc (2 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), and the combined organic layers were washed with H_2O (100 mL) and aq. $NaHCO_3$ (3 × 100 mL), before being dried and concentrated. The residue (16.1 g, 95%) containing the α-acetate **15** as a major component, contaminated with a small amount of the β-anomer, was used in the next stage without purification. An analytically pure sample of **15** was isolated by column chromatography (SiO_2: hexane/EtOAc, 95:5); R_F = 0.46 (hexane/EtOAc, 9:1); $[\alpha]_D$ = +71.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.32 (d, $J_{5,6}$ = 6.6 Hz, 3H; H-6), 1.98 (s, 3H; $COCH_3$), 2.21 (s, 3H; $COCH_3$), 4.10 (dq, 1H; H-5), 5.44 (pt, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H; H-4), 5.60–5.67 (m, 2H; H-2, H-3), 6.23 (s, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.6 (C-6), 20.7, 20.9 ($COCH_3$), 68,7, 69.5, 69.8, 70.7 (C-2, C-3, C-4, C-5), 90.7 (C-1), 165.2, 165.5 (PhCO), 168.3, 169.8 (C=O); $C_{24}H_{29}O_9$ (461.49): calcd C 62.46, H 6.33; found C 62.65, H 6.30.

4-*O*-Acetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranosylbromide (16): A solution of the α-acetate **15** (2.4 g, 5.0 mmol) in CH_2Cl_2 (20 mL) containing AcBr (2.2 mL, 30 mmol) was cooled in ice–water, followed by treatment with MeOH (1.06 mL, 26.5 mmol) in CH_2Cl_2 (5 mL). The solution was maintained at room temperature for 2 h before being poured into a separating funnel filled with crushed ice (100 g). The crude product was separated by extraction with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with H_2O (50 mL) and aq. $NaHCO_3$ (2 × 50 mL). They were then dried and concentrated, and the residue was crystallized from a PhMe/hexane mixture to give the bromide **16** (1.70 g, 71%); R_F = 0.76 (hexane/EtOAc, 9:1); m.p. 146.5–147 °; $[\alpha]_D$ = +7.5 (c = 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.38 (d, $J_{5,6}$ = 6.4 Hz, 3H; H-6), 2.03 (s, 1H; $COCH_3$), 4.28 (dq, 1H; H-5), 5.51 (pt, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H; H-4), 5.82 (dd, $J_{1,2}$ = 1.1 Hz, $J_{2,3}$ = 3.4 Hz, 1H; H-2), 6.01 (dd, 1H; H-3), 6.50 (d, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.1 (C-6), 20.8 ($COCH_3$), 70.0, 70.5, 71.2, 73.3 (C-2, C-3, C-4, C-5), 83.8 (C-1), 165.1, 165.3 (PhCO), 169.9 (C=O); FABMS: m/z 477 $[M+H]^+$, 397 $[M-Br]^+$, 105 $[Bz]^+$.

Methyl 2,3-Di-*O*-isopropylidene-4-*O*-chloroacetyl-α-L-rhamnopyranoside (17): The alcohol **11** (6.00 g, 27.5 mmol) was acylated with $ClCH_2COCl$ (3.00 mL, 37.5 mmol) in the presence of C_5H_5N (3.0 mL, 37 mmol) in CH_2Cl_2 (25 mL) at 5 °C for 15 min. The excess of the acyl chloride was destroyed by the addition of MeOH (2 mL) in CH_2Cl_2 (25 mL), before the solution was washed with aq. $NaHCO_3$ (30 mL) and H_2O (2 × 30 mL), and then concentrated. Column chromatography of the residue on silica gel with light petroleum (b.p. 60–80 °C)/ethyl acetate (95:5) as eluant afforded compound **17** (6.9 g, 85%); R_F = 0.81 (hexane/EtOAc, 9:1); $[\alpha]_D$ = − 28.9 (c = 1.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.16 (d, $J_{5,6}$ = 6.3 Hz, 3H; H-6), 1.33 (s, 3H; $C(CH_3)_2$), 1.56 (s, 3H; $C(CH_3)_2$), 3.37 (s, 3H; OCH_3), 3.73 (dq, 1H; H-5), 4.08 (m, 2H; $COCH_2Cl$), 4.10–4.19 (m, 2H; H-2, H-3), 4.89 (dd, $J_{3,4}$ = 7.3 Hz, $J_{4,5}$ = 10.0 Hz, 1H; H-4), 4.88 (s, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 16.9 (C-6), 26.3, 27.6 ($C(CH_3)_2$), 40.8 ($COCH_2Cl$), 54.9 (OCH_3), 63.4 (C-5), 75.4, 76.0, 76.6 (C-2, C-3, C-4), 98.0 (C-1), 109.9 ($C(CH_3)_2$), 166.6 ($COCH_2Cl$); CIMS: m/z 312 $[M+NH_4]^+$, 280 $[M-MeOH+NH_4]^+$, 263 $[M-MeOH+H]^+$, 217 $[M-ClCH_2CO]^+$; $C_{12}H_{19}ClO_6$ (294.73): calcd C 48.90, H 6.50, Cl 12.03, found C 48.60, H 6.58, Cl 11.84.

Methyl 4-*O*-Chloroacetyl-α-L-rhamnopyranoside (18): The acetonide **17** (6.74 g, 22.8 mmol) was deisopropylideneated by stirring it with Amberlite 200 (H^+) ion-exchange resin (3.0 g) in MeOH (100 mL) for 24 h at room temperature. After removal of the resin and concentration of the solution, the residue was crystallized from an EtOAc/hexane mixture to give the diol **18** (4.02 g, 66%); R_F = 0.28 ($CHCl_3$/MeOH, 9:1); m.p. 111–112 °C; $[\alpha]_D$ = −78.9 (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, 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); CIMS: m/z 272 $[M+NH_4]^+$, 240 $[M-MeOH+NH_4]^+$, 223 $[M-MeOH+H]^+$; $C_9H_{15}ClO_6$ (254.67): C 42.45, H 5.94, Cl 13.92; found C 42.38, H 5.79, Cl 13.63.

Methyl 2,3-Di-*O*-benzoyl-4-*O*-chloroacetyl-α-L-rhamnopyranoside (19): A solution of the diol **18** (3.18 g, 12.5 mmol) in CH_2Cl_2 (50 mL) containing C_5H_5N (7.2 mL) was treated with BzCl (4.35 mL, 37.5 mmol) at 0–5 °C and the reaction mixture was stirred for 4 h at room temperature. The mixture was treated with H_2O (5 mL), diluted with CH_2Cl_2 (50 mL) and washed with aq. $NaHCO_3$ (4 × 30 mL) and H_2O (30 mL). The organic solvent was evaporated off and the residue was subjected to chromatography (SiO_2: PhMe/EtOAc, 98:2 to 95:5), affording the dibenzoate **15** (5.09 g, 88%); 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): δ = 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, $J_{3,4} = J_{4,5}$ = 10.0Hz, 1H; H-4), 5.61 (dd, $J_{2,3}$ = 3.4 Hz, 1H; H-2), 5.66 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 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), 165.4, 165.5, 166.8, ($COCH_2Cl$); CIMS: m/z 480 $[M+NH_4]^+$, 463 $[M+H]^+$; $C_{23}H_{23}ClO_8$ (462.88): calcd C 59.68, H 5.01, Cl 7.66; found C 59.88, H 4.89, Cl 7.47.

1-*O*-Acetyl 2,3-Di-*O*-benzoyl-4-*O*-chloroacetyl-α-L-rhamnopyranoside (20): Compound **19** (5.10 g, 11.0 mmol) was treated with Ac_2O (25 mL) in the presence of conc. H_2SO_4 (0.25 mL), as described for methyl glycoside **14**. The product was isolated following column chromatography (SiO_2: EtOAc/hexane, 9:1) to give com-

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pound **20** (4.15 g, 77%); $R_F = 0.59$ (PhMe/EtOAc, 96:4); m.p. 107–108 °C; $[\alpha]_D = +81.6$ ($c = 1.1$ in $CHCl_3$); ^1H 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, 1H; H-3), 6.26 (s, 1H; H-1); ^{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), 165.2, 165.4 (PhCO), 166.6 ($COCH_2Cl$), 168.3 (CH_3CO); CIMS: m/z 508 $[M + NH_4]^+$, 474 $[M - MeOH + NH_4]^+$, 431 $[M - AcOH + H]^+$, 397 $[M - ClCH_2CO]^+$; $C_{24}H_{23}ClO_9$ (490.90): calcd C 58.72, H 4.72, Cl 7.22, found C 58.71, H 4.44, Cl 7.29.

2,3-Di-*O*-benzoyl-4-*O*-chloroacetyl-α-L-rhamnopyranosylbromide (21): A solution of the α-acetate **20** (5.00 g, 10.2 mmol) and AcBr (4.40 mL, 60 mmol) in CH_2Cl_2 (40 mL) was treated while being cooled with MeOH (2.12 mL, 53 mmol) in CH_2Cl_2 (10 mL). The solution was maintained for 2 h at room temperature and then worked-up as described for the bromide **16**. The product was crystallized from an Et_2O–hexane mixture yielding the bromide **21** (4.71 g, 90%); $R_F = 0.75$ (PhMe/EtOAc, 96:4); m.p. 124–126.5 °C; $[\alpha]_D = +82$ ($c = 1.2$ in $CHCl_3$); ^1H 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, 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, 1H; H-3), 6.50 (d, 1H; H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.1$ (C-6), 40.5 ($COCH_2Cl$), 68.9, 70.9, 72.4, 73.3 (C-2, C-3, C-4, C-5), 83.6 (C-1), 165.0, 165.3 (PhCO), 166.7 ($COCH_2Cl$), CIMS: m/z 431 $[M - Br]^+$.

4-*O*-(4-*O*-Acetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-cyano)ethylidene]-3,6-di-*O*-benzoyl]-β-D-mannopyranose (22): A solution of the bromide **16** (1.60 g, 3.35 mmol), the alcohol **7** (1.22 g, 2.80 mmol), and 2,4,6-collidine (0.39 mL, 3.00 mmol) in CH_2Cl_2 (10 mL) was added gradually to a cooled (−20 °C) and stirred suspension of AgOTf (1.0 g, 4.0 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h at −10 °C, before the mixture was treated with some drops of C_5H_5N, diluted with CH_2Cl_2 (100 mL), and washed with 10% $Na_2S_2O_3$ solution (2 × 50 mL) and finally with H_2O (50 mL). The organic solution was concentrated and the residue was subjected to chromatography (SiO_2: PhMe/EtOAc, 9:1) to afford **22** (2.01 g, 86%); $R_F = 0.64$ (PhMe/:EtOAc, 4:1); $[\alpha]_D = +80$ ($c = 1.3$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.83$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.82 (s, 3H; CCH_3), 3.82–3.97 (m, 2H; H-5, H-5'), 4.43 (pt, $J_{3,4} \approx J_{4,5} = 9.4$ Hz, 1H; H-4), 4.57 (dd, $J_{5,6a} = 2.6$ Hz, $J_{6a,6b} = 12.2$ Hz, 1H; H-6a), 4.71 (dd, $J_{1,2} = 2.5$ Hz, $J_{2,3} = 4.1$ Hz, 1H; H-2), 4.98 (dd, $J_{5,6b} = 2.9$ Hz, 1H; H-6b), 5.23 (d, $J_{1,2} = 1.4$ Hz, 1H; H-1'), 5.26 (m, 1H; H-4'), 5.45–5.51 (m, 2H; H-2', H-3'), 5.58 (d, $J_{1,2} = 2.5$ Hz, 1H; H-1), 5.67 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.2$ (C-6'), 20.7 (CH_3CO_2), 26.5 (CH_3CCN), 62.5 (C-6), 67.6 (C-5'), 69.5 (C-3'), 70.7, 70.8 (C-2', C-4'), 71.0 (C-3), 73.1, 73.3 (C-4, C-5), 78.8 (C-2), 97.1 (C-1), 98.5 (C-1'), 101.5 (CH_3CCN), 116.7 (CN), 165.5–165.9 (PhCO), 169.9 (CH_3CO); FABMS: m/z 858 $[M + Na]^+$, 809 $[M - CN]^+$, 422 $[M - RhaO]^+$, 397 $[Rha]^+$, 275 $[Rha - BzOH]^+$, 215 $[Rha - BzOH - AcOH]^+$; $C_{45}H_{41}NO_{15}$ (835.83): calcd C 64.67, H 4.94, N 1.68; found C 64.52, H 5.06, N 1.48.

1,2-*O*-[1-(*exo*-Cyano)ethylidene]-3,6-di-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-mannopyranose (23), 3,6-Di-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)-ethylidene]-α-D-mannopyranose (24), and 4-*O*-(4-*O*-Acetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-β-D-mannopyranose (25): A solution of **22** in MeOH/HCl [ca. 35 mL, prepared by the reaction of AcCl (2.5 mL) with MeOH (35 mL) with cooling] was kept for 12 h at 20 °C and neutralized with NaOAc. The mixture was concentrated, diluted with CH_2Cl_2 (75 mL), and washed with aq. $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 50 mL). After drying, the solvents were evaporated. The residue was subjected to chromatography (SiO_2: PhMe/EtOAc, 20:1 to 4:1) to afford **23** (458 mg, 19%), **24** (854 mg, 34%), **25** (140 mg, 5.4%), and recovered **22** (58 mg, 2%).

23: $R_F = 0.36$ (PhMe:EtOAc, 4:1); $[\alpha]_D = +52.3$ °C ($c = 1.1$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.95$ (d, $J_{5,6} = 5.7$ Hz, 3H; H-6'), 1.82 (s, 3H; CCH_3), 3.70–3.80 (m, 2H, H-4', H-5'), 3.91 (ddd, $J_{4,5} = 9.4$ Hz, $J_{5,6a} = 4.7$ Hz, $J_{5,6b} = 3.7$ Hz, 1H; H-5), 4.41 (pt, $J_{3,4} \approx J_{4,5} = 9.4$ Hz, 1H; H-4), 4.56 (dd, $J_{6a,6b} = 12.5$ Hz, 1H; H-6a), 4.71 (dd, $J_{1,2} = 2.1$ Hz, $J_{2,3} = 3.9$ Hz, 1H; H-2), 4.94 (dd, 1H; H-6b), 5.19 (d, $J_{1,2} = 1.8$ Hz, 1H; H-1'), 5.39 (dd, $J_{2,3} = 3.3$ Hz, $J_{3,4} = 9.4$ Hz, 1H; H-3'), 5.45 (dd, 1H; H-2'), 5.58 (d, 1H; H-1), 5.67 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.4$ (C-6'), 26.5 (CCH_3), 62.6 (C-6), 70.0 (C-5'), 70.7 (C-3), 71.3 (C-4'), 71.5 (C-2'), 72.3 (C-3'), 73.3 (C-4, C-5), 78.7 (C-2), 97.0 (C-1), 98.8 (C-1'), 101.5 (CH_3CCN), 165.6-165.7 (PhCO); FABMS: m/z 816 $[M + Na]^+$, 767 $M - CN]^+$, 355 $[Rha]^+$, 233 $[Rha - BzOH]^+$; $C_{43}H_{39}NO_{14}$ (793.79): C 65.07, H 4.95, N 1.76; found C 64.67, H 5.13, N 1.57.

24: $R_F = 0.30$ (PhMe:EtOAc, 4:1); $[\alpha]_D = +43.7$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.94$ (d, $J_{5,6} = 5.2$ Hz, 3H; H-6'), 1.82 (s, 3H; CH_3CO_2), 3.67–3.79 (m, 2H, H-4', H-5'), 3.70 (s, 3H; OCH_3), 3.90 (m, 1H; H-5), 4.49 (pt, $J_{3,4} \approx J_{4,5} = 9.4$ Hz, 1H; H-4), 4.60 (dd, $J_{5,6a} = 3.6$ Hz, $J_{6a,6b} = 12.4$ Hz, 1H; H-6a), 4.74 (dd, $J_{1,2} = 2.5$ Hz, $J_{2,3} = 3.0$ Hz, 1H; H-2), 4.92 (dd, $J_{5,6b} = 2.6$ Hz, 1H; H-6b), 5.19 (d, $J_{1,2} = 1.6$ Hz, 1H; H-1'), 5.39 (dd, $J_{2,3} = 3.0$ Hz, $J_{3,4} = 9.3$ Hz, 1H; H-3'), 5.45 (dd, 1H; H-2'), 5.58 (d, 1H; H-1), 5.63 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.4$ (C-6'), 23.4 (CCH_3), 52.7 (OCH_3), 63.0 (C-6), 69.9 (C-5'), 71.4 (C-4'), 71.6 (C-3, C-2'), 72.3 (C-3'), 73.1 (C-5), 73.5 (C-4), 78.4 (C-2), 97.5 (C-1), 98.7 (C-1'), 107.6 ($CH_3CCO_2CH_3$), 165.5–166.6 (PhCO), 169.1 ($CH_3CCO_2CH_3$); FABMS: m/z 849 $[M + Na]^+$, 455 $[M - RhaO]^+$, 355 $[Rha]^+$, 233 $[Rha - BzOH]^+$; $C_{46}H_{42}O_{16}$ (826.82): calcd C 63.92, H 5.12; found C 63.63, H 5.20.

25: $R_F = 0.50$ (PhMe:EtOAc, 4:1); $[\alpha]_D = +65.9$ ($c = 1.2$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.83$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.69 (s, 3H; CH_3CCO_2), 1.86 (s, 3H; CH_3CO_2), 3.70 (s, 3H; OCH_3), 3.85–3.96 (m, 2H; H-5, H-5'), 4.52 (pt, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4), 4.62 (dd, $J_{5,6a} = 3.8$ Hz, $J_{6a,6b} = 12.4$ Hz, 1H; H-6a), 4.75 (dd, $J_{1,2} = 2.4$ Hz, $J_{2,3} = 3.3$ Hz, 1H; H-2), 4.97 (dd, $J_{5,6b} = 2.9$ Hz, 1H; H-6b), 5.24 (d, $J_{1,2} = 1.4$ Hz, 1H; H-1'), 5.26 (pt, $J_{3,4} = 3.0$ Hz, $J_{4,5} = 10.0$ Hz, 1H; H-4'), 5.48–5.53 (m, 2H; H-2', H-3'), 5.58 (d, 1H; H-1), 5.65 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.2$ (C-6'), 20.7 (CH_3CO_2), 23.3 ($CH_3CCO_2CH_3$), 52.7 (OCH_3), 62.9 (C-6), 67.4 (C-5'), 69.5 (C-3'), 70.9, 71.0 (C-2' and C-4'), 71.5 (C-3), 73.2, 73.3 (C-4 and C-5), 78.3 (C-2), 97.5 (C-1), 98.5 (C-1'), 107.6 ($CH_3CCO_2CH_3$), 165.4–165.9 (PhCO), 169.0 ($CH_3CCO_2CH_3$); FABMS: m/z 891 $[M + Na]^+$, 455 $[M - Rha]^+$, 397 $[Rha]^+$, 275 $[Rha - BzOH]^+$; $C_{46}H_{44}O_{17}$ (868.85): C 63.59 H 5.10; found C 63.51, H 4.81.

4-O-(4-*O*-Chloroacetyl-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-3,6-di-*O*-benzoyl-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-α-D-mannopyranose (26): The alcohol **9** (3.00 g, 6.83 mmol) was glycosylated with bromide **21** (4.50 g, 8.80 mmol) in the presence of AgOTf (3.30 g, 13.2 mmol) and collidine (0.88 mL, 6.8 mmol) in an analogous fashion to the preparation of **25**. The product was isolated by column chromatography (SiO_2: PhMe/EtOAc, 95:5) to give **26** (5.92 g, 96%); $R_F = 0.65$ (PhMe/EtOAc, 9:1); $[\alpha]_D = +63.4$ ($c = 1.3$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.85$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.69 (s, 3H; CCH_3), 3.71 (s, 3H; OCH_3), 3.82 (s, 2H; $COCH_2Cl$), 3.89–3.99 (m, 2H; H-5, H-5'), 4.51 (pt, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4), 4.61 (dd, $J_{5,6a} = 3.7$ Hz, $J_{6a,6b} = 12.3$ Hz, 1H; H-6a), 4.74 (dd, $J_{1,2} = 2.5$ Hz, $J_{2,3} = 4.2$ Hz, 1H; H-2), 4.97 (dd, $J_{5,6b} = 2.6$ Hz, 1H; H-6b), 5.25 (d, $J_{1,2} = 0.9$ Hz, 1H; H-1'), 5.30 (m, 1H; H-4'), 5.49–5.53 (m, 2H, H-2', H-3'), 5.58 (d, $J_{1,2} = 2.5$ Hz, 1H; H-1), 5.65 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 17.1$ (C-6'), 23.3 (CCH_3), 40.4 (CH_2Cl), 52.7 (OCH_3), 62.8 (C-6), 67.1 (C-5'), 69.3 (C-3'), 71.0 (C-2'), 71.4 (C-3), 72.8 (C-4'), 73.2,73.3 (C-4, C-5), 78.3 (C-2), 97.5 (C-1), 98.8 (C-1'), 107.6 ($CH_3CCO_2CH_3$), 165.4–166.6 (PhCO, $ClCH_2CO$), 169.0 ($CH_3CCO_2CH_3$); FABMS: m/z 843 $[M - CO_2Me]^+$, 431 $[Rha]^+$; $C_{46}H_{43}ClO_{17}$ (903.303) calcd C 61.17, H 4.80, Cl 3.92; found C 61.02, H 4.56, Cl 3.62.

3,6-Di-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-α-D-mannopyranose (24): A solution of **26** (5.00 g, 5.54 mmol) and $(NH_2)_2CS$ (2.5 g) in a mixture of MeCN/H_2O (110 mL, 10:1) was allowed to stand for 20 h at 20 °C, before the reaction was concentrated, and the residue purified by column chromatography (SiO_2: PhMe/EtOAc, 20:1) to give **24** (4.22 g, 92%),

3,6-Di-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4-*O*-trityl-α-L-rhamnopyranosyl)-1,2-*O*-[1-(*exo*-methoxycarbonyl)ethylidene]-α-D-mannopyranose (27): $TrClO_4$ (1.65 g, 4.82 mmol) was added in portions during ca. 2 h to a stirred solution of the alcohol **24** (3.50 g, 4.20 mmol) in CH_2Cl_2 (40 mL) containing collidine (1.1 mL, 8.4 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, and concentrated. Column chromatography (SiO_2: PhMe/EtOAc, 95:5 to 9:1) of the residue afforded the trityl ether **27** (4.32 g, 96%); $R_F = 0.40$ (PhMe/EtOAc, 9:1); $[\alpha]_D = +0.9$ ($c = 1.1$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.65$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.65 (s, 3H; CCH_3), 3.46 (pt, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4), 3.71 (s, 3H; OCH_3), 3.90–4.05 (m, 2H; H-5, H-5'), 449 (pt, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, 1H; H-4'), 4.59 (dd, $J_{5,6a} = 3.2$ Hz, $J_{6a,6b} = 12.5$ Hz, 1H; H-6a), 4.77 (dd, $J_{1,2} = 2.5$ Hz, $J_{2,3} = 3.9$ Hz, 1H; H-2), 4.95 (dd, $J_{5,6b} = 2.6$ Hz, 1H; H-6b), 5.06 (d, $J_{1,2} = 2.0$ Hz, 1H; H-1'), 5.29 (dd, $J_{2,3} = 3.1$ Hz, 1H; H-2'), 5.59 (d, 1H; H-1), 5.68 (dd, $J_{2,3} = 3.9$ Hz, H-3'), 5.71 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 18.5$ (C-6'), 23.3 (CCH_3), 52.7 (OCH_3), 62.8 (C-6), 69.6 (C-5'), 71.4 (C-2', C-3'), 71.6 (C-3), 72.9 (C-4'), 73.2, 73.3 (C-4, C-5), 78.4 (C-2), 88.3 (CPh_3), 97.6 (C-1), 98.3 (C-1'), 107.6 ($CH_3CCO_2CH_3$), 144.8 (C_{quat} of Ph in CPh_3), 165.1–166.0 (PhCO), 169.1 ($CH_3CCO_2CH_3$); FABMS: m/z 1092 $[M + Na]^+$, 455 $[M - RhaO]^+$, 243 $[Tr]^+$; $C_{63}H_{56}O_{16}$ (1069.14): calcd C 70.78, H 5.28; found C 70.78, H 5.32.

1,2-*O*-[1-(*exo*-Cyano)ethylidene]-3,6-di-*O*-benzoyl-4-*O*-(2,3-di-*O*-benzoyl-4-*O*-trityl-α-L-rhamnopyranosyl)-α-D-mannopyranose (3): **Method A**: $TrClO_4$ (250 mg, 0.73 mmol) was added in ca. 50 mg portions during 2 h to a stirred mixture of the alcohol **23** (440 mg, 0.55 mmol) and collidine (0.13 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was maintained at room temperature for 3 h. The violet solution was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 × 25 mL), before being dried and concentrated. Column chromatography (SiO_2: PhMe/EtOAc, 20:1) of the residue gave the disaccharide monomer **3** (370 mg, 65%); $R_F = 0.49$ (PhMe/EtOAc, 9:1); $[\alpha]_D = +5.1$ °C ($c = 1.6$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.71$ (d, $J_{5,6} = 6.2$ Hz, 3H; H-6'), 1.81 (s, 3H; CCH_3), 3.51 (pt, $J_{3,4} \approx J_{4,5} = 9.8$ Hz, 1H; H-4), 3.97 (m, 1H; H-5'), 4.05 (m, 1H; H-5), 4.44 (pt, $J_{3,4} \approx J_{4,5} = 8.8$ Hz, 1H; H-4'), 4.59 (dd, $J_{5,6a} = 3.5$ Hz, $J_{6a,6b} = 12.5$ Hz, 1H; H-6a), 4.77 (dd, $J_{1,2} = 2.1$ Hz, $J_{2,3} = 3.6$ Hz, 1H; H-2), 5.00

(dd, $J_{5,6b}$ = 2.6 Hz, 1H; H-6b), 5.10 (d, $J_{1,2}$ = 1.6 Hz, 1H; H-1'), 5.33 (dd, $J_{2,3}$ = 3.1 Hz, 1H; H-2'), 5.59 (d, 1H; H-1), 5.72 (dd, $J_{2,3}$ = 3.9 Hz, 1H; H-3'), 5.79 (dd, 1H; H-3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 18.5 (C-6'), 26.5 (CCH_3), 62.4 (C-6), 69.7 (C-5'), 70.8 (C-3), 71.4 (C-2', C-3'), 72.9, 73.0, 73.5 (C-4, C-4', C-5), 78.8 (C-2), 88.3 (CPh_3), 97.1 (C-1), 98.3 (C-1'), 101.5 (CH_3CN), 116.7 (CN), 144.7 (C_{qual}.of Ph in CPh_3), 165.1–165.8 (PhCO); FABMS: *m/z* 1058 $[M+Na]^+$, 442 $[M-RhaO]^+$, 243 $[Tr]^+$; $C_{62}H_{53}O_{14}$ (1036.10): calcd C 71.87, H 5.16, N 1.35; found C 72.11, H 5.00, N 1.16.

Method B: A suspension of **27** (4.49 g, 4.20 mmol) in a mixture of MeOH (80 mL) and CH_2Cl_2 (15 mL) was saturated with NH_3 gas at −5 °C and the solution was maintained overnight at 20 °C. TLC ($CHCl_3$:MeOH, 9:1) of the reaction mixture revealed the formation of a number of products. The solvents were evaporated off, and the residue was coevaporated with C_5H_5N (10 mL), dissolved in C_5H_5N (40 mL) and treated with BzCl (4.8 mL, 44 mmol) for 5 h at 20 °C. MeOH (0.5 mL) was added, and the mixture was stirred for 20 min at 20 °C before being concentrated to dryness. The residue was dissolved in CH_2Cl_2 (200 mL), washed with aq. $NaHCO_3$ and H_2O before being dried and concentrated to a residue. Column chromatography (SiO_2: PhMe/EtOAc, 20:1) of the residue afforded the disaccharide monomer **3** (3.79 g, 87%).

Cyclo[(1 → 4)-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3,6-di-*O*-benzoyl-α-D-mannopyranosyl]trioside (28) and **Cyclo[(1 → 4)-2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1 → 4)-2-*O*-acetyl-3,6-di-O-benzoyl-α-D-mannopyranosyl]-tetraoside (29)**: A solution of the disaccharide monomer **3** (2.40 g, 2.32 mmol) in C_6H_6 (12.0 mL) was divided into six equal portions and each of them was placed into one limb of tuning-fork-shaped tubes. Other arms were filled with a solution of $TrClO_4$ (100 mg, 0.36 mmol) in $MeNO_2$ (2.5 mL), the tubes were connected to a vacuum line (4×10^{-3} Torr), and the solutions were freeze-died. 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. The contents of all tubes were combined, washed with H_2O and concentrated. Trityl-containing non-carbohydrate products were separated by column chromatography (SiO_2: heptane/EtOAc, 4:1) of the residue. Three impure fractions containing cyclic oligosaccharides were then eluted with heptane/EtOAc (1:4). Further purification of the first two fractions was achieved by using HPLC (heptane/EtOAc, 4:6) to give **28** (620 mg, 34%) and **29** (550 mg, 31%) as pure compounds.

28: m.p. 174–178 °C (heptane/EtOAc); $[\alpha]_D$ = +124.5 (*c* = 1.31 in $CHCl_3$); ^{1}H NMR NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (s, $J_{5,6}$ = 6.2 Hz, 3H; H-6 Rha), 1.82 (s, 3H; CH_3CO_2), 3.79 (pt, $J_{3,4}=J_{4,5}\approx$9.2 Hz, 1H; H-4 Rha), 4.17–4.24 (m, 1H; H-5 Rha), 4.22 (pt, $J_{3,4}=J_{4,5}\approx$9 Hz, 1H; H-4 Man), 4.33–4.36 (m, 2H; H-5 Man, H-6 Man), 4.94 (brdd, $J_{6a,6b}$ = 11.3 Hz, 1H; H-6b Man), 5.05 (d, $J_{1,2}$ = 2.1 Hz, 1H; H-1 Rha), 5.15 (d, $J_{1,2}$ = 1.9 Hz, 1H; H-1 Man), 5.18 (pt, 1H; H-2 Rha), 5.52 (dd, $J_{2,3}$ = 3.3 Hz, 1H; H-2 Man), 5.64 (dd, $J_{2,3}$ = 3.3 Hz, 1H; H-3 Rha), 5.80 (dd, $J_{3,4}$ = 9.3 Hz, 1H; H-3 Man); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 18.4 (C-6 Rha), 26.7 (CH_3CO_2), 62.2 (C-6 Man), 67.6 (C-5 Rha), 70.2 (C-5 Man), 70.3 (C-2 Rha), 71.3 (C-3 Man), 71.4 (C-2 Rha and C-2 Man), 74.8 (C-4 Man), 81.8 (C-4Rha), 98.5 (C-1 Rha and C-1 Man), 165.4, 165.5, 165.7, 165.8 (PhCO), 169.9 (CH_3CO_2); LSIMS: *m/z* 2431 $[M+Cs]^+$; LSIMS (NaOAc added): *m/z* 2322 $[M+Na]^+$; MALDI-TOF MS: *m/z* 2321 $[M+Na]^+$, 2337 $[M+K]^+$; $C_{126}H_{114}O_{42}$ (2300.29): calcd C 65.79, H 5.00; found C 65.41, H 5.05.

29: $[\alpha]_D$ = +117.5 (*c* = 1.01 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, $J_{5,6}$ = 6.1 Hz, 1H; H-6 Rha), 1.92 (s, 1H; CH_3CO_2), 3.78 (pt, $J_{3,4}=J_{4,5}\approx$9.4 Hz, 1H; H-4 Rha), 3.94–3.98 (m, 1H; H-5 Rha), 3.99 (brd, $J_{6a,6b}\approx$12 Hz, 1H; H-6a Man), 4.07 (brd, $J_{5,6a}\approx J_{5,6b}\approx$3 Hz, 1H; H-5 Man), 4.22 (brd, 1H; H-6b Man), 4.30 (pt, $J_{3,4}=J_{4,5}$ = 9.6 Hz, 1H; H-4 Man), 4.91 (d, $J_{1,2}$ = 1.8 Hz, 1H; H-1 Rha), 4.98 (d, $J_{1,2}$ = 1.4 Hz, 1H; H-1 Man), 5.10 (pt, 1H; H-2 Rha), 5.28 (dd, $J_{2,3}$ = 3.2 Hz, 1H; H-2 Man), 5.70 (dd, $J_{2,3}$ = 3.2 Hz, 1H; H-3 Rha), 5.73 (dd, 1H; H-3 Man); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 17.6 (C-6 Rha), 20.6 (CH_3CO_2), 62.0 (C-6 Man), 68.4 (C-5 Rha), 69.8 (C-3 Man and C-3 Rha), 70.6 (C-2 Rha), 70.7 (C-5 Man), 71.5 (C-2 Man), 74.8 (C-4 Man), 81.0 (C-4 Rha), 99.0 (C-1 Rha), 99.3 (C-1 Man), 165.1, 165.1, 165.2, 165.5 (PhCO); 169.84 (CH_3CO_2); LSIMS: *m/z* 3199 $[M+Cs]^+$; LSIMS (NaOAc added): *m/z* 3090 $[M+Na]^+$; MALDI-TOF MS: *m/z* 3087 $[M+Na]^+$, 3103 $[M+K]^+$; $C_{168}H_{152}O_{56}$ (3067.05); calcd C 65.79, H 5.00; found C 65.39, H 4.96.

Cyclo[(1 → 4)-α-L-rhamnopyranosyl-(1 → 4)-α-D-mannopyranosyl]trioside (1): NaOMe/MeOH (1M, 1 mL) was added to a solution of compound **28** (145 mg, 0.063 mmol) in CH_2Cl_2 (2 mL) and MeOH (4 mL), and the reaction mixture was stirred for 4 h. The solvents were then evaporated and the residue was dissolved in a mixture of H_2O (4 mL) and MeOH (2 mL), stirred for 20 h, diluted with H_2O (20 mL), and neutralized with Amberlite (H^+). The aqueous solution was washed with hexane (2 × 10 mL) and concentrated and the residue was subjected to GPC, affording **1** (36 mg, 62%); ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 1.39 (d, $J_{5,6}$ = 6.2 Hz, 3H; H-6 Rha), 3.56 (pt, $J_{3,4}\approx J_{4,5}$ = 9.0 Hz, 1H; H-4 Rha), 3.79 (dd, *J* = 9.0 Hz, *J* = 9.5 Hz, 1H; H-4 Man), 3.86 (dd, $J_{5,6a}$ = 7.0 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H; H-6 Man), 3.90 (dd, $J_{5,6b}$ = 2.5 Hz, 1H; H-6b Man), 3.94 (dd, $J_{2,3}$ = 3.8 Hz, 1H; H-3 Rha), 3.94 (m, 1H; H-5 Man), 3.99 (dd, $J_{2,3}$ = 3.2 Hz, 1H; H-3 Man), 4.00 (m, 1H; H-5 Rha), 4.04 (dd, $J_{1,2}$ = 2.4 Hz, 1H; H-2 Rha), 4.07 (dd, $J_{1,2}$ = 2.2 Hz, 1H; H-2 Man), 4.98 (d, 1H; H-1 Rha), 5.07 (d, 1H; H-1 Man); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$, 25 °C): δ = 18.1 (C-6 Rha), 60.9 (C-6 Man), 67.2, 69.5, 70.1, 70.2 (×2), 72.6 (C-2, C-3, C-5 Man, C-2, C-3, C-5 Rha), 79.3 (C-4 Man), 85.0 (C-4 Rha), 101.4, 101.4 (C-1 Man and C-1 Rha); MALDI-TOF MS: *m/z* 947 $[M+Na]^+$, 963 $[M+K]^+$.

Cyclo[(1 → 4)-α-L-rhamnopyranosyl-(1 → 4)-α-D-mannopyranosyl]tetraoside (2): Compound **29** (338 mg, 0.11 mmol) was deacylated using the same procedure as that described for **28**, and purified on a gel-permeation colum to give **2** (118 mg, 87%), $[\alpha]_D$ = +10.5 (c = 0.99 in H_2O); ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 1.28 (d, $J_{5,6}$ = 6.5 Hz, 1H; H-6 Rha), 3.50 (pt, $J_{3,4}=J_{4,5}$ = 9.5 Hz, 1H; H-4 Rha), 3.75 (dd, $J_{5,6}$ = 4.0 Hz, $J_{6a,6b}$ = 12.5 Hz, 1H; H-6a Man), 3.78–3.86 (m, 3H; H-3 Rha, H-4 and H-6b Man), 3.86 (dd, $J_{2,3}$ = 3.2 Hz, 1H; H-3 Man), 3.98 (dd, $J_{1,2}$ = 2.1 Hz, 1H; H-2 Rha), 3.99–4.02 (m, 2H; H-2 and H-5 Man), 4.08 (m, 1H; H-5 Rha), 4.83 (d, 1H; H-1 Rha), 4.93 (d, $J_{1,2}$ = 2.1 Hz, 1H; H-1 Man); ^{13}C NMR (75.5 MHz, D_2O, 25 °C): δ = 19.4 (C-6 Rha), 62.9 (C-6 Man), 70.7 (C-5 Rha), 71.9 (C-3 Rha), 72.1 (C-3 Man), 73.4 (C-2 Rha and C-2 Man), 74.6 (C-5 Man), 79.3 (C-4 Man), 85.4 (C-4 Rha), 104.1, (C-1 Rha), 104.7 (C-1 Man); MALDI-TOF MS: *m/z* 1255 $[M+Na]^+$, 1271 $[M+K]^+$.

Crystallographic Measurements: for **2**: single crystals suitable for X-ray crystallography were produced by slow cooling of an aqueous solution of **2**. $2[(C_{12}H_{20}O_9)_4]\cdot 67H_2O$, *M* = 3673.3, tetragonal, *a* = *b* = 24.200(5), *c* = 7.918(3) Å, *V* = 4,637(2) Å^3, space group *P*4, *Z* = 1, D_c = 1.315 g cm^{-3}, $\mu(Cu_{K\alpha})$ = 11.0 cm^{-1}, *F*(000) = 1982, dimensions 0.17 × 0.17 × 0.50 mm were measured on a Siemens P4 rotating anode diffractometer ($2\theta < 124°$) with $Cu_{K\alpha}$ radiation (graphite monochromator) using ω scans. 3910 independent reflections were measured and of these 2931 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors; no absorption correction was applied. The structure was solved by direct methods, and the non-hydrogen atoms were refined anisotropically. The oxygen atoms of the major occupancy H_2O molecules were refined anisotropically, the minor occupancy molecules isotropically. The hydroxyl hydrogen atoms were located from ΔF maps and refined isotropically subject to an O–H distance constraint; the remaining cyclic oligosaccharide hydrogen atoms were placed in calculated positions and allowed to ride on their parent carbon atoms. The hydrogen atoms of the H_2O molecules could not be located. Refinement was by full-matrix least-squares based on F^2 to give R_1 = 0.0846 and wR_2 = 0.2327, 550 refined parameters. The maximum and minimum residual electron densities in the final ΔF map were 0.54 and −0.37 e Å^{-3}. Computations were carried out on a 486 PC with the SHELXTL-PC program system version 5.03. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1220-4. 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: teched@chemcrys.cam.ac.uk).

Molecular Modeling: The starting structures for the cyclic oligosaccharides **1** and **2** were both generated from an X-ray crystal structure of α-cyclodextrin on the Cambridge Crystallographic Data Base. Appropriate modifications to both the constitution and the configuration of α-cyclodextrin were made using the program Macromodel on a Silicon Graphics Indy Workstation. Clearly, α-D-glucopyranose residues had to be replaced in an alternate fashion by α-L-rhamnopyranose and α-D-mannopyranose residues.

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