Synthetic Cyclic Oligosaccharides

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Contents

I. Preamble

Large ring molecules[1] have provided excellent opportunities to chemists interested in the design and synthesis of molecular receptors that are able to express their recognition features toward a range of substrates, using the panoply of noncovalent bonding interactions.[2] Research on the synthesis of macrocyclic compounds has blossomed over the last three decades in the wake of the discovery by Pedersen[3] in 1967 of the so-called crown ethers.[4] As a result, a whole range of large-sized ring compounds have appeared in the literature: some of the best known include the calixarenes,[5] the spherands and cavitands,[6] and an assortment of cyclophanes[7] with a variety of different constitutions. In essence, the chemistry of large ring molecules has been very much part and parcel of the development of supramolecular chemistry.[8]

There are also numerous examples of large-sized ring compounds to be found in nature. In some instances—for example, many cyclic peptides[9] and some macrolide antibiotics[10]—they are known to be biologically important ionophores.[11] Even among naturally occurring carbohydrates, large ring molecules in the shape of cyclic oligosaccharides had been isolated and characterized well before the middle of this century.[12] In all the examples identified to date, these intriguing natural products are a result of bacterial processes. The best known members of this class of natural product are the cyclodextrins[13] (CDs) or cyclomaltooligosaccharides **1**−**3**, shown in Figure 1. More specifically, α-, β-, and γ-CDs, as they are commonly referred to, are composed of six, seven, and eight α-(1→4)-linked D-glucopyranose units, respectively. CDs are formed[14] during the degradation of the linear amylose component of starch by enzymes called cyclodextrin glucosyltransferases (CGTases), isolated from the bacterium *Bacillus macerans*, and related amylases. Indeed, it is this process that forms the basis for the industrial production[15] of CDs. A few other bacterial enzymes can also act like CGTases, catalyzing both the cleavage of polysaccharide chains and the subsequent cyclizations of their degradation products. In these cases, linear polysaccharides also usually serve as the precursors of the cyclic oligosaccharides. As a result, the range of natural or semisynthetic, enzymatically produced cyclic oligosaccharides is rather limited. Some examples will be discussed briefly later on in Section VII.

Of late, however, attention has become focused[16] on the higher homologues of the CDs with 9, 10, 11,

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Giuseppe Gattuso was born and raised in the city of Messina, Italy. He received his Laurea in Chimica in 1993 from the University of Messina where he carried out research in the laboratories of Dr. M. F. Parisi, working in the area of the synthesis and properties of fluorinated inhibitors of the serine proteases. He gained his Ph.D. in 1997 in the research laboratories of Professor J. Fraser Stoddart in the School of Chemistry at the University of Birmingham. The subject of his Ph.D. thesis was the development of novel approaches to the syntheses of unnatural cyclic oligosaccharides. His major achievement during this period was the preparation and structural characterization of the first family of achiral cyclodextrin analogues. Presently, he is conducting research in the Department of Chemistry and Biology at the University of Messina.

Dr. Sergey A. Nepogodiev was born in the Moscow region of Russia in 1960. He graduated from the Moscow State University with an M.Sc. Degree in Chemistry in 1982 and joined N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences in Moscow where he continued to pursue research for the next 10 years. He received his Ph.D. in Organic Chemistry from this Institute in 1987. His research in the field of carbohydrate chemistry was associated with oligosaccharide synthesis and the chemical synthesis of natural polysaccharides. In 1994, he joined the research group of Professor J. Fraser Stoddart at the University of Birmingham in the United Kingdom where he has played a key role in the development of new synthetic approaches to cyclic oligosaccharides and carbohydrate dendrimers. Currently, he works at the University of Birmingham as a Research Fellow sponsored by Pfizer Central Research (UK), while being closely associated with reseach group of Professor J. Fraser Stoddart at UCLA.

12, and 13 α-(1→4)-linked D-glucopyranose units, referred to as δ-, ϵ-, ζ-, η-, and θ-CDs, respectively. Indeed, the smaller cyclodextrins are not the major cyclic α-1,4-glucans produced by the initial action of CGTase on amylose. Interestingly, cyclic α-1,4-glucans with degrees of polymerization in excess of 60 have been shown[17] to be present in incubations when enzyme-catalyzed reactions are terminated at an early stage. The structural and recognition properties of these remarkable natural products promise to be intriguing to say the least.

J. Fraser Stoddart was born in Edinburgh, Scotland, in 1942. He received all of his degrees from the University of Edinburgh (B.Sc., 1964; Ph.D., 1966; D.Sc., 1980). After a seven-year spell as the Professor of Organic Chemistry at the University of Birmingham in the United Kingdom, he moved in 1997 to the Saul Winstein Chair of Organic Chemistry at UCLA. His current research interests are concerned with transporting well-established biological principles, such as self-assembly, from the life sciences into chemistry—with one aim being to produce molecules with device-like characteristics. Carbohydrates—particularly cyclic oligosaccharides—have often, during his research career which began in the 1960s, provided building blocks for the construction of molecular receptors and switches.

The fascination of many researchers for more than a century[12] now in the vast range of inclusion complexes formed by CDs, as well as in their abilities to exhibit enzyme-like reactivities, has given α-, β-, and γ-CDs a unique and special status in chemistry. The rigid cavities of these torus-shaped molecules turn out to be havens for a wide spectrum of guest species. This particular property of the CDs is well documented in the early literature[13,18−22] and has found applications not only in research laboratories,[23−25] but also in the industrial sector.[26,27] Since they are polyhydroxy compounds, CDs may be transformed into a large range of derivatives: indeed, chemical modifications[28−30] of the hydroxyl groups in CDs have been employed extensively in their derivatization. However, there is no escaping from the straitjacket that is imposed simply by always having to start the practice of chemical modification from a rather limited range of readily available natural products. And so the prospect of opening up exciting new research opportunities by pursuing the de novo synthesis of cyclic oligosaccharides has gained ground since the mid-1980s. The time is now ripe to summarize the early achievements in this relatively new area of synthetic chemistry. In writing this review, we hope to draw attention to an area where we believe synthetic chemists can make major contributions in the next few years.

During the last 20 years, many efficient glycosylation methodologies[31−42] have been developed in response to the growing demand of glycobiology for synthetic oligosaccharides and glycoconjugates. Consequently, a very large number of different oligosaccharides and related compounds have been synthesized. In this review, we shall cover *only* that research relating to the *synthesis of cyclic oligosaccharides* and, in a few instances, their structural properties. Oligosaccharides that are cyclic and result from the act of synthesis, starting from precur-

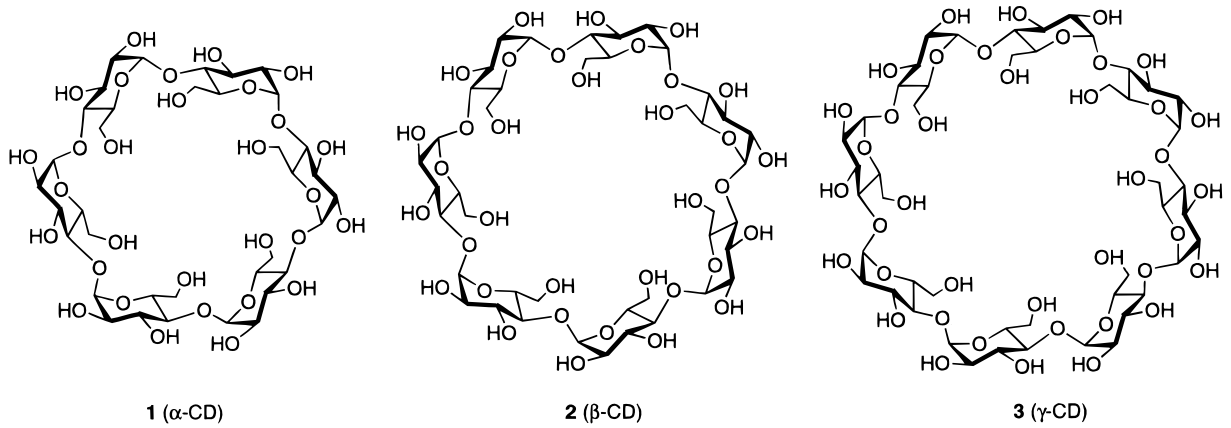

Figure 1. Structural formulas of α-CD (**1**), *β*-CD (**2**), and *γ*-CD (**3**).

sors that are *not* in themselves cyclic in constitution, will be referred to by us as *synthetic cyclic oligosaccharides*. Also, cyclic oligosaccharides, formed as a result of the actions of enzymes on linear oligo- and polysaccharides, will be featured in this review. In addition, the parent compounds relating to the cyclodextrin family will also fall under the umbrella of *synthetic cyclic oligosaccharides* if they have been prepared by *chemical* syntheses. However, the very large number of derivatives of naturally occurring cyclodextrins, resulting from chemical modifications of CDs, will not be regarded as *synthetic cyclic oligosaccharides* per se in this review. This is not to say, however, that a few of these chemically modified CDs will not be mentioned briefly in passing: they will—but for a comprehensive coverage of this area of cyclodextrin chemistry, the reader is referred to some excellent reviews[28−30] and the wider CD literature as a whole.

The review begins with a consideration (Section II) of the general structural features of known and hypothetical cyclic oligosaccharides and a discussion (Section III) of the different approaches that have been employed to date in the chemical synthesis of cyclic oligosaccharides. Achievements relating to the chemical syntheses and structural characterizations of CDs and their analogues (i.e., compounds built up partly, or solely, from α-(1→4)-linked glycopyranosidic residues), as well as of other types of cyclic oligosaccharides containing α- or *β*-(1→6)- and (1→3)-glycosidic linkages, will be discussed in Sections IV−VII. Enzymatic and chemoenzymatic syntheses of cyclic oligosaccharides, other than CDs, are described in Section VIII. This discussion is followed by a survey (Section IX) of small ring cyclic oligosaccharides, leaving the way open to draw some conclusions and offer a few reflections in the final section—namely Section X. The main purpose of this review is to try and systematize the information that is currently available on the different approaches to constructing *synthetic cyclic oligosaccharides* as well as on their structural characterization. We hope that the review will stimulate further research in this fascinating area of carbohydrate chemistry.

II. Survey and Assessment of Possible Structures

The challenge presented by the synthesis of oligosaccharides is illustrated by the enormous number

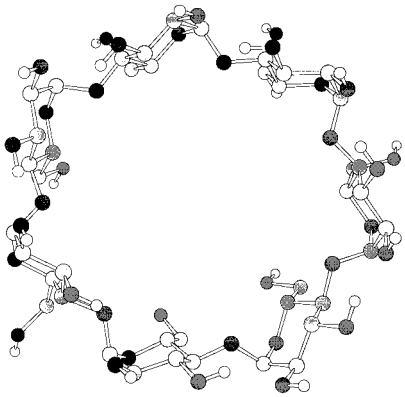

Figure 2. Solid-state structure[45] of *β*-CD showing a typical arrangement of α-(1→4)-linked glucopyranose rings forming a large macro(poly)cyclic cavity. Black = oxygen atoms; light gray = carbon atoms; open circles = hydrogen atoms. (The picture is generated using the CS Chem3D Pro software on the basis of atomic coordinates taken from EPSRC's Chemical Database Service at Daresbury, UK.)

of possibilities which arise even when coupling a limited number of monosaccharide units. For example, just coupling six hexopyranoses with identical structures (e.g. the $^4C_1$ chair conformation of D-glucopyranose) could, in principle at least, give rise to several hundred thousand cyclic hexasaccharides if it were not for the fact that a lot of these structures are simply rendered impossible by the relatively narrow range of structural geometries that can be accommodated within cyclic frameworks. In this section, we shall consider only those geometries, i.e. relative conformations associated with the glycosidic linkages, that can possibly lead to stable cyclic oligosaccharides. Furthermore, we shall restrict our analysis to compounds (with C_n symmetry) that are composed of the same monosaccharide repeating units.

A. Cyclic (1→4)-Linked Oligopyranosides

The structural characteristics of the three major members of the CD family (α-, *β*-, and *γ*-CD) are well-established on the basis of X-ray crystallographic investigations[44] carried out in the solid state. The crystal structure[45] of *β*-CD is shown in Figure 2. The CDs are comprised of six or more α-D-glucopyranose residues that exist as $^4C_1$ chair conformations and are joined to each other by glycosidic linkages involv-

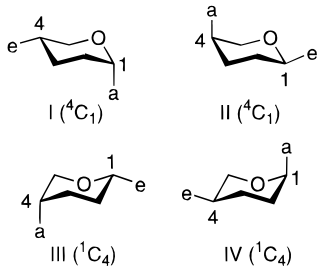

Figure 3. The four possible relative configurations for axially and equatorially oriented C−O bonds at positions 1 and 4 on the $^4C_1$ and $^1C_4$ chair configurations[47] of the pyranose rings.

Table 1. Classification of Cyclic (1→4)-Linked Oligopyranosides according to the Configurations and Conformations of the Pyranose Residues

configurations of monosaccharide residues by type[a]			
I ($^4C_1$)	II ($^4C_1$)	III ($^1C_4$)	IV ($^1C_4$)
α-D-*xylo*	β-D-*galacto*	α-D-*arabino*	β-D-*ido*
α-D-*ribo*	β-D-*gulo*	α-D-*ribo*	
α-D-*lyxo*	β-D-*talo*	α-D-*lyxo*	
α-D-*gluco*[b]	α-D-*ido*	α-D-*altro*	
α-D-*allo*			
α-D-*manno*			
α-D-*altro*			

[a] See Figure 3. [b] Cyclodextrin family.

ing axial C-1−O and equatorial C-4−O bonds. The existence[16,17] of higher homologues with more than nine α-D-glucopyranose residues has already been the subject of comment in Section I. The homologue containing only five residues has been obtained by chemical synthesis (see Section IV). Recently, the possibility of the existence of smaller CD homologues with four, and even three, α-D-glucopyranose residues has been proposed by Lichtenthaler et al.[46] on the basis of molecular modeling studies.

To a first approximation, it seems not unreasonable to expect any (1→4)-linked aldopyranose (pentose or hexose) residue carrying one axial and one equatorial bond, respectively, at either C-1 and C-4, or C-4 and C-1, to be capable of incorporation into a cyclic oligosaccharide. This expectation assumes that the nature of the functional groups at C-2, C-3, C-6, and—where appropriate—C-5, as well as their particular configurations, are not so consequential. It follows that by (i) considering only the stable pyranose chair conformations[47] ($^4C_1$ or $^1C_4$) and (ii) requiring the axial/equatorial combination of orientations at C-1/C-4, the aldopentoses and aldohexoses, which meet the above constraints, fall into one or more of the four categories shown in Figure 3. The classification, according to the configurations of the monosaccharide residues, is given in Table 1. If the free energies of the $^4C_1$ and $^1C_4$ conformations of a particular pyranosidic residue are very similar, then it may be anticipated that the corresponding cyclic oligosaccharide could incorporate residues with different chair conformations, either entirely or in part, as indicated in Figure 3 and Table 1. Indeed, cycloheptakis[(1→4)-α-D-altropyranosyl], which has been prepared[48,49] by chemical modification of β-CD, shows, in its ^1H NMR spectrum, coupling constants commensurate with either a dynamic equilibration taking place between $^4C_1$ and $^1C_4$ chair conformations or a twist-boat conformation for the α-D-altropyranose residues. Likewise, α-CD has been converted[50] into cyclohexakis[(1→4)-α-D-altropyranosyl] (**4**)—also referred to trivially as α-cycloaltrin—and been shown conclusively by X-ray crystallography to be a cyclooligosaccharide with alternating $^4C_1/^1C_4$ pyranoid chair conformations in the solid state. In aqueous solution, it appears that α-cycloaltrin adopts a variety of conformations within a pseudorotational "turntable" that is coordinated in a relative sense with respect to its overall movements.

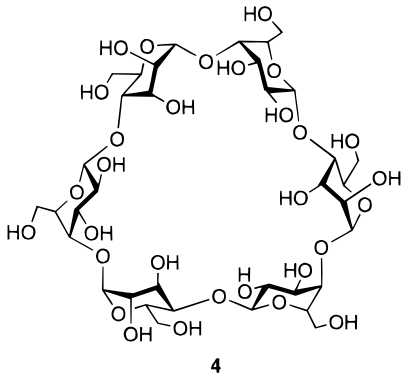

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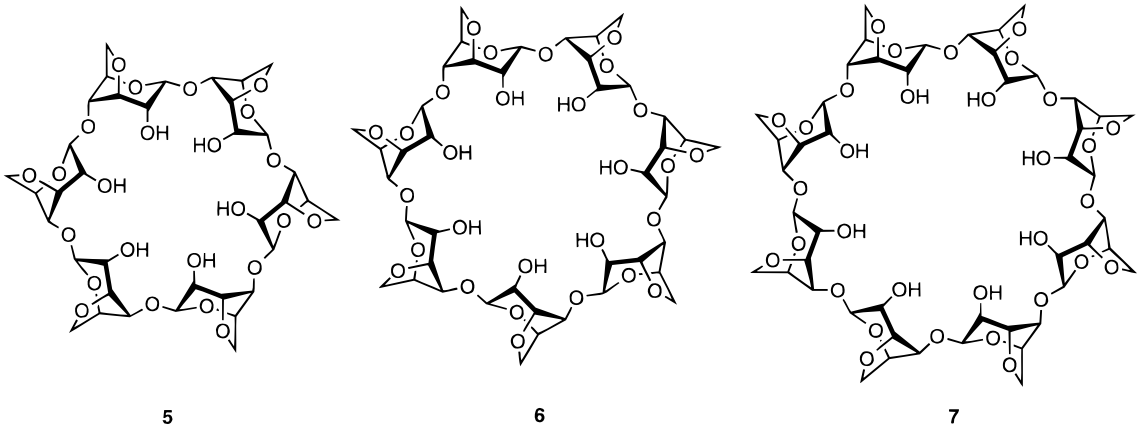
Figure 4. Cyclohexakis[(1→4)-α-D-altropyranosyl] (**4**), shown as a conformation with an alternating sequence of $^4C_1$ and $^1C_4$ altropyranoid chair forms as found in the solid state.[50] Similar structures with different substituents at the C-3 positions of the D-altropyranose residues can be envisaged as a result of the nucleophilic ring opening of per-2,3-manno-epoxide of α-CD.

The 3,6-anhydrocyclodextrins **5**−**7** (Figure 5) provide[51] yet another example of cyclic oligosaccharides in which all the 3,6-anhydro-D-glucopyranose residues are obliged to adopt the $^1C_4$ chair conformation.

It is generally accepted that the relative hydrophobicities of the CDs' internal cavities are the driving force in their formation of inclusion complexes. However, the situation for analogues of the CDs is far from clear and will only be revealed by a combination of computer molecular modeling and the appropriate binding studies. For example, in the case of a cyclogalactin, composed of six β(1→4)-linked D-galactopyranose residues, molecular modeling[52] supports an α-CD-like geometry, but with a distinctly different lipophilicity distribution from that calculated for α-CD itself.

B. Cyclic (1→3)-Linked Oligopyranosides

Medium- and large-sized cyclic oligosaccharides can be constructed from D-glucopyranose residues—and other pyranoses with diequatorial orientations about their C-1−O and C-3−O bonds—by the formation of β-(1→3)-glycosidic bonds. The "primary faces", bearing the C-4 and C-6 hydroxyl groups, of these molecules are wide open and their overall shapes are flat when compared with the torus shapes of the CDs. As a consequence, their cavities are not nearly as deep and pronounced as in the case of the CDs. By contrast, α-(1→3)-glucopyranooligosaccharides—and related oligosaccharides with an axial orientation of the glycosidic oxygen atom at C-1 and an equatorial one at C-3—have essentially linear shapes and do not



5 **6** **7**

Figure 5. Structural formulas of per-3,6-anhydro-α-, *β*-, and *γ*-cyclodextrins (**5**, **6**, and **7**, respectively).

lend themselves to cyclization. The situation is similar when the pyranose ring contains C-1−O and C-3−O bonds that are, respectively, equatorial and axial as in *β*-(1→3)-altropyranan, i.e., the oligosaccharide chain prefers to adopt a linear conformation. Finally, inspection of space-filling molecular models reveals that cyclic oligosaccharides can be formed by glycopyranose residues in which both the C-1−O and C-3−O bonds are axial.

C. Cyclic (1→2)-Linked Oligopyranosides

Since the backbones of (1→2)-linked oligosaccharides are composed of O-1−C-2−O sequences of bonds, they may be considered formally as substituted poly(ethylene glycol) derivatives. However, the efficiencies of the closures of the macrocyclic rings, leading to the formation of crown ether-like compounds (Figure 6), are rather low on account of the steric interactions between the aldopyranose residues. (1→2)-Linked oligosaccharides, composed of pyranose residues connected by one equatorial and one axial bond—e.g., (1→2)-α-D-glucan and (1→2)-*β*-D-mannan—adopt linear rigid conformations and cannot cyclize. Oligosaccharides, where both the C-1−O and O−C-2 bonds are equatorial—e.g., (1→2)-*β*-D-glucan—are more flexible and can adopt helical conformations which can eventually cyclize, but only when the oligosaccharide chains are sufficiently long. Indeed, the natural cyclic (1→2)-*β*-glucans (see Section III.C) contain 17 or more glucopyranose residues. Ring closure to give cyclic oligosaccharides is also geometrically possible when both the C-1−O and O−C-2 bonds are axial, as in (1→2)-α-D-mannan, for example. However, in this case, the glycosidic oxygen atoms—which correspond to the polyether oxygen atoms in crown ethers—are obliged to adopt anti conformations with respect to each other, rather than the desired gauche conformations preferred by the $-OCH_2CH_2O-$ in macrocyclic polyethers.

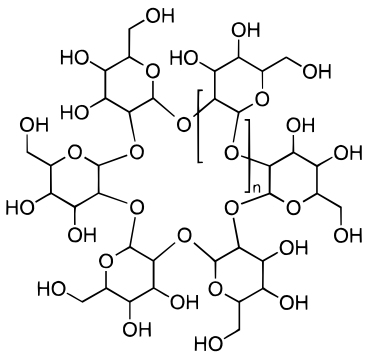
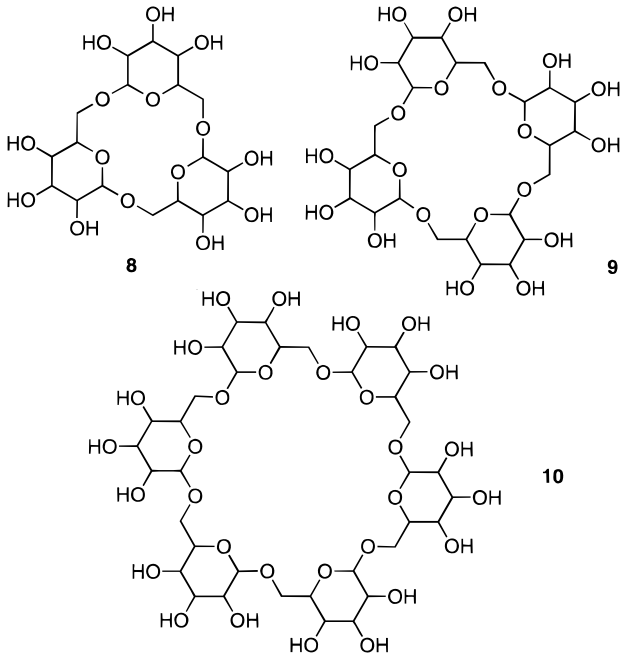


Figure 6. Schematic representation of the skeleton of (1→2)-linked cyclic oligosaccharides.

D. Cyclic (1→6)-Linked Oligopyranosides

The constitutions of some cyclic oligosaccharides (**8**−**10**), built up from hexapyranosyl residues linked by (1→6)-glycosidic bonds, are shown in Figure 7. The macrocyclic components of these constitutions reveal one and two carbon atoms alternating between oxygen atoms conferring both acetal and ether-like functionalities upon the macrocycles. The remaining portions of the hexopyranose rings occupy the outer surfaces of these cyclic oligosaccharides. It is, therefore, reasonable to assume that, neither the configurations at C-1 and C-5, nor the configurations of the remaining stereogenic centers on the hexopyranose



8 **9** **10**

Figure 7. Structures of cyclic (1→6)-hexopyranotrioside (**8**), -tetraoside (**9**), and -hexaoside (**10**) without specifying the stereochemistry of the pyranose residues.

rings, are crucial in relation to the formation of cyclic oligosaccharides. Although the gross conformations of the cyclo[(1→6)-hexopyrano]oligosaccharides will depend on the nature of the monosaccharide residues, the increased flexibility of the (1→6)-glycosidic linkages provides enough conformational freedom for the incorporation of a wide variety of monosaccharide residues. It should be mentioned here that molecular modeling has been performed on the fully acetylated cyclotris[(1→6)-β-D-glucopyranosyl][53] and that some predictions as to the most stable conformations of the parent oligosaccharide have also been advanced.[54]

III. Synthetic Strategies

The formation of cyclic oligosaccharides must proceed through a final macrocyclization step or, more specifically, through a cycloglycosylation event. Although this event presents quite different challenges when compared with those that characterize more traditional oligosaccharide synthesis, it is familiar to chemists acquainted with the preparation of macrocyclic compounds. However, there are not many examples of ring closures which involve such a complex mechanism as that associated with cycloglycosylation. A precursor for the preparation of a cyclic oligosaccharide requires that one key structural feature is present: that is, both ends of a linear oligosaccharide precursor should be suitably functionalized for the intramolecular coupling reaction, i.e., the precursor should bear, at one and the same time, both a glycosyl acceptor function (normally a hydroxyl group) and a glycosyl donor function (a leaving group that activates the anomeric center). The problem associated with the presence simultaneously of both these functions in the same molecule lies in the rather fine balance between the appropriate stability and the required reactivity of such a system. Theoretically, many of the extensively employed glycosylating agents,[35] such as thioglycosides, glycosyl fluorides, *n*-pentenyl glycosides, glycals, 1-*O*-acyl sugars, ortho esters, and indeed other less frequently used reagents, have sufficient stabilities to permit postactivation modifications on the linear oligosaccharide precursors to be carried out. These modifications are directed usually toward the discrimination of a particular glycosyl acceptor center by deblocking one particular hydroxyl group and, in some cases, the subsequent transformation of this hydroxyl group into either trityl or silyl ethers, which can then act as glycosyl acceptors in certain glycosylations. Another possibility for the construction of a linear precursor involves the generation of a glycosyl donor function (e.g., glycosyl bromide) which bears already one "free" hydroxyl group in a protected oligosaccharide. However, this approach is less convenient than the former one.

Two main approaches to the chemical synthesis of cyclic oligosaccharides may be outlined. They are as follows:

(1) Cycloglycosylation of a long-chain linear oligosaccharide derivative bearing both glycosyl donor and acceptor functions—the latter, obviously, located at the nonreducing end of the molecule (Figure 8). In this approach, ideally, only the ring closure should take place. However, the preparation of cyclic oligosaccharides by this method is usually achieved following multistep reaction sequences employed in the construction of the linear precursor.

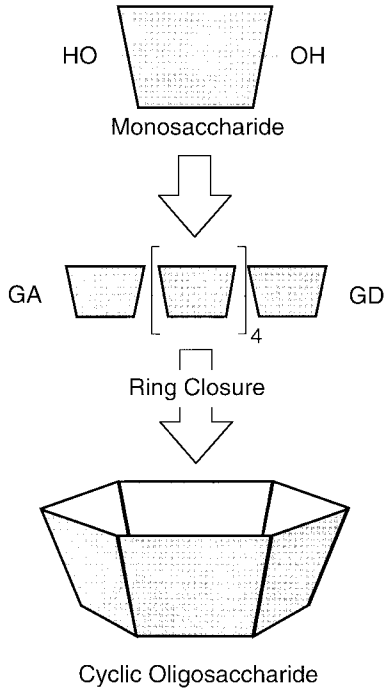


Figure 8. Cartoon representation of the synthetic strategy leading to cyclic oligosaccharides via *cycloglycosidation of a linear precursor*. GD = glycosyl donor function (leaving group at the anomeric center). GA = glycosyl acceptor function.

A unique opportunity of using a preformed oligosaccharide for the construction of a linear precursor is offered by the ring fission of CDs. The controlled cleavage of a single glucosidic bond in a CD, followed by the addition of a different saccharide unit, and then recyclization, produces a new macrocycle incorporating a heterogeneous residue (Figure 9). Considering the difficulties associated with the monofunctionalization of the parent CDs, this synthetic strategy can sometimes be extremely useful in this regard.

(2) Polycondensation−cyclization or cyclooligomerization of an appropriately functionalized saccharide derivative, corresponding to the smallest repeating unit of a particular target cyclic oligosaccharide (Figure 10). The preparation of the so-called "saccharide monomer" (it may even be a monosaccharide derivative) is usually much less laborious than the synthesis of a long-chain oligosaccharide. The glycosylation procedure employed for the cyclooligomerization should attain a very high efficiency and stereoselectivity during the coupling process, which is then repeated sequentially during the assembly of the cyclic oligomer. If the "saccharide monomer" possesses sufficient reactivity, cyclic products can be produced in acceptable yields. It must be stressed that a range of cyclic oligomers of different sizes is generally obtained, since the macrocyclization, in this case, is not controllable. However, this feature can be regarded as an advantage of this strategy over others, since it provides easy access to a series of

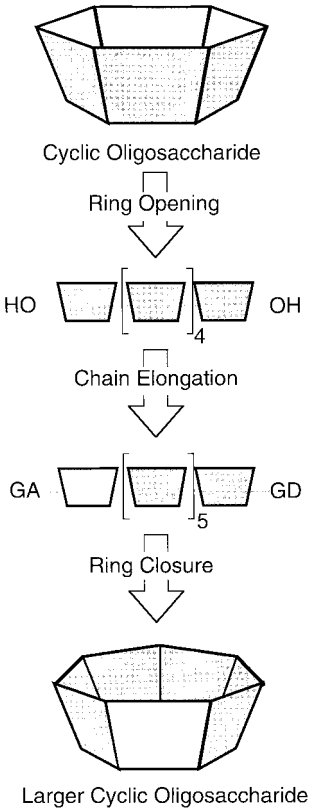


Figure 9. Cartoon representation of the *cycloglycosidation of a modified linear precursor* strategy. The long-chain oligosaccharide precursor for cycloglycosidation is prepared from readily available CDs by opening of their macro(poly)-cyclic ring.

homologous compounds from one-pot reactions, provided that the separation of the oligomers is not too daunting a task. An obvious limitation of this approach is that only cyclic oligosaccharides, composed of a number of residues that are a multiple of the number of monosaccharides in the monomer, can be prepared.

The use of enzymes[55] for the preparation of complex oligosaccharides is a method of considerable promise, when its many advantages are compared with the disadvantages associated with the more classical approaches to oligosaccharide synthesis. Cyclic oligosaccharides can be prepared quite efficiently by the action of several types of hydrolases of bacterial origin upon polysaccharides—as in the case of the well-known CGTases on starch. Some particular enzymes can also utilize small polysaccharide fragments, or their chemically modified forms, as substrates. Enzymatic and chemoenzymatic approaches are very attractive as a consequence of their accessibility, but they have not been widely applied to date on account of the fact that the number of known glycosidases able to catalyze the cyclization of oligosaccharides is still rather limited.

When facing the task of constructing large ring molecules, we can now employ several approaches and principles, such as high dilution techniques,[56] the rigid group principle,[57] structure-directed protocols,[58] and template-directed methods.[59] In the chemical syntheses of the cyclic oligosaccharides described in this review, the high dilution technique is generally applied. It is particularly successful when an open-chain precursor is flexible enough to adopt a coiled conformation, which is a prerequisite for an efficient cycloglycosylation. Another driving force, which assists the formation of cyclic oligosaccharides, is the structure-directed one. As a result of the restricted conformational space occupied by the maltooligosaccharides, they are reasonably well preorganized[6] for ring closure when the number of D-glucopyranose units is six, seven, or eight. This preorganization explains the efficiency of the enzymatic production of CDs and provides the basis for the chemical syntheses of them and their analogues.

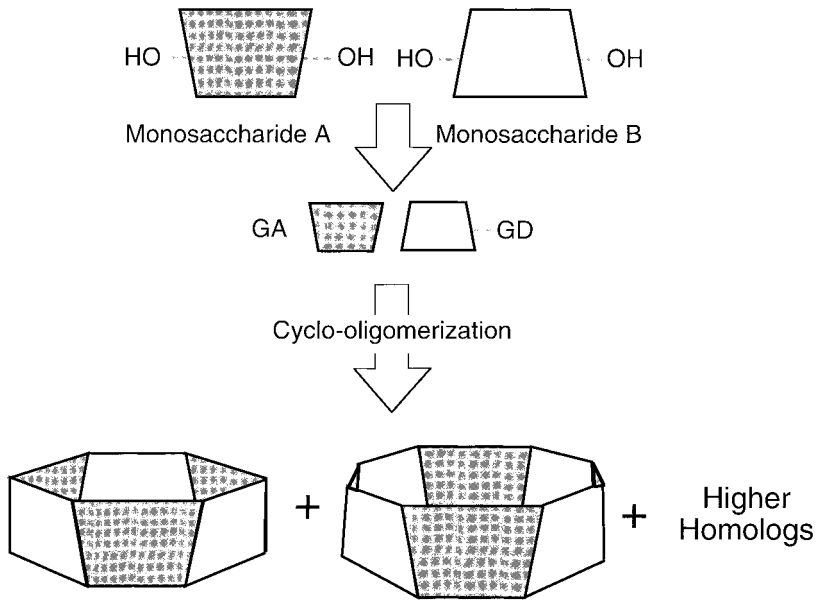


Figure 10. *Polycondensation−cyclization* or *cyclooligomerization* strategy employed in the synthesis of cyclic oligosaccharides illustrated by the use of cartoons. The "disaccharide monomer" is shown as an example of the application of this strategy.

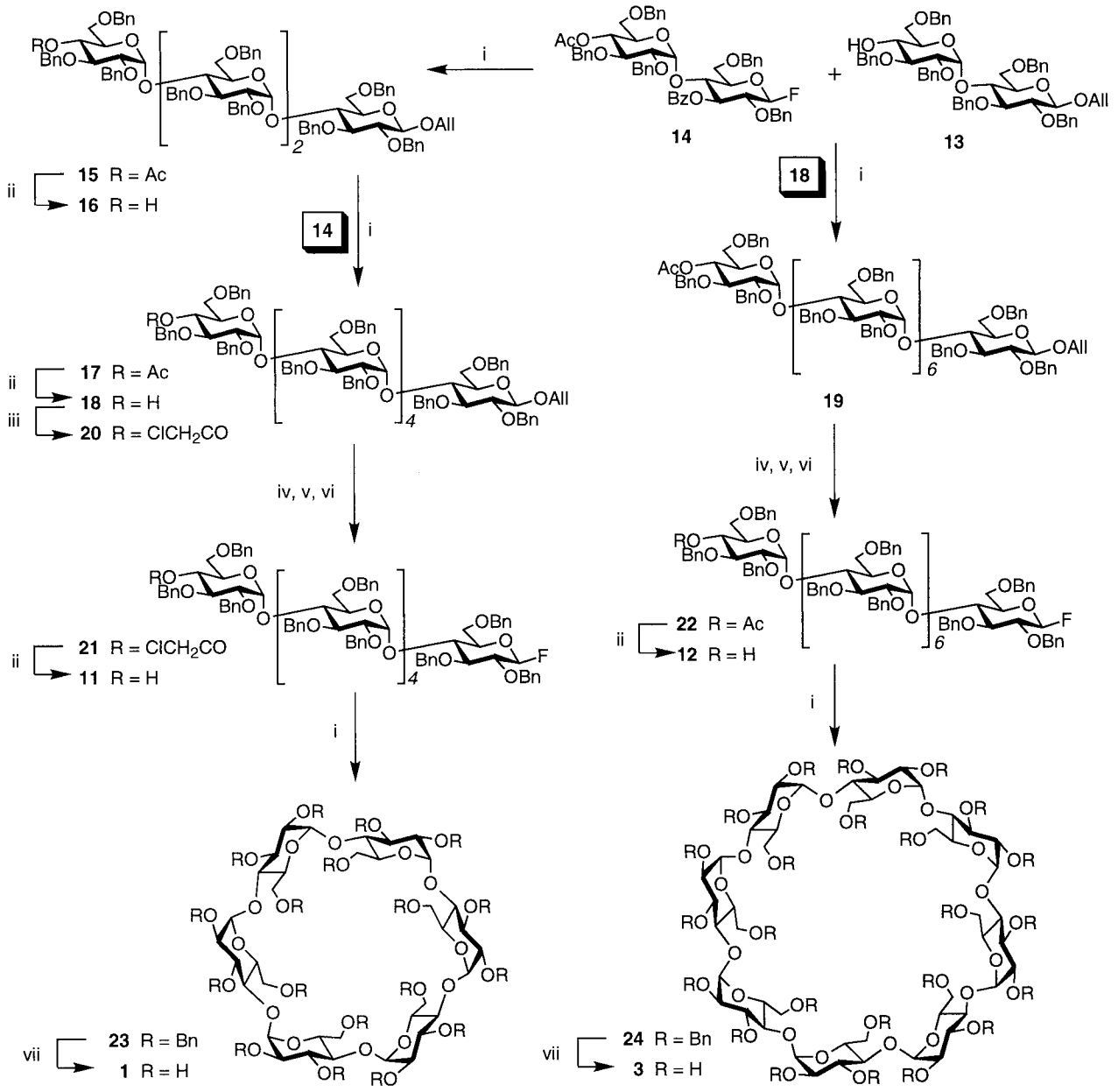


Figure 11. Synthesis of α-CD (**1**) and γ-CD (**3**). Reagents: (i) $SnCl_2$/AgOTf; (ii) NaOMe/MeOH/THF; (iii) $(ClCH_2CO)_2O$/DCE/C_5H_5N; (iv) $PdCl_2$/AcOH; (v) SO_2Cl_2/DMF; (vi) AgF/MeCN; (vii) H_2/Pd/C/THF−MeOH/H_2O.

IV. Synthesis of Cyclic α-(1→4)-Linked Oligopyranosides

The total chemical synthesis of α-(1→4)-linked cyclic oligosaccharides is of particular interest, because it is directed toward the creation of large ring molecules which are expected to have well-defined internal cavities and, consequently, to exibit binding of appropriate substrates. The syntheses, however, are quite demanding, since they are associated with the construction of α-(1→4)-glycosidic bonds, which are difficult to access because of the relatively low reactivities of 4-OH groups. In the case of the cyclodextrins, there is the additional challenge of having to effect the stereoselective formation of a 1,2-*cis*-glycosidic bond.

A. Total Syntheses of Cyclodextrins

The first reported chemical syntheses of cyclic oligosaccharides were the total syntheses of α-CD (**1**) and γ-CD (**3**) performed by Ogawa and co-workers.[60−67] These syntheses represent pioneering investigations. They opened up the way to the preparation of a whole new range of cyclic oligosaccharides. The synthetic pathways (Figure 11) to both α-CD and γ-CD involved 21 steps in each case, starting from maltose. The cycloglycosylation of the glucohexaosyl fluoride **11**—or the glucooctaosyl fluoride **12**—was the key reaction, while the construction of the maltooligosaccharide dervatives **11** and **12** were performed by repetitive addition of a maltosyl residue, employing Mukaiyama's glycosylation method[63]—using glycosyl fluorides.

The building blocks **13** and **14**—derived from maltose—were coupled in the presence of $SnCl_2$/$AgClO_4$ to afford (40%) the tetrasaccharide **15**. Deacetylation of **15** gave the alcohol **16**, which was then glycosylated again with the maltosyl fluoride **14**, to yield (43%) the hexasaccharide **17**. Further elon-

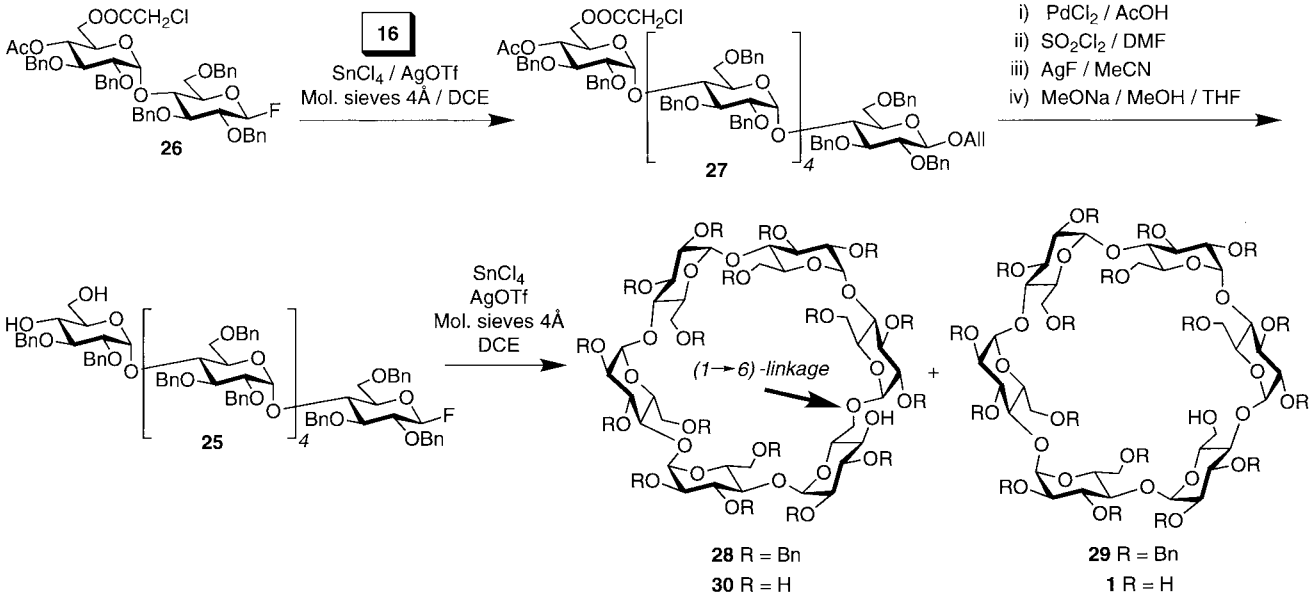


Figure 12. Synthesis of cyclo{6)-[α-D-Glc*p*-(1→4)]$_5$-α-D-Glc*p*-(1→} (**30**).

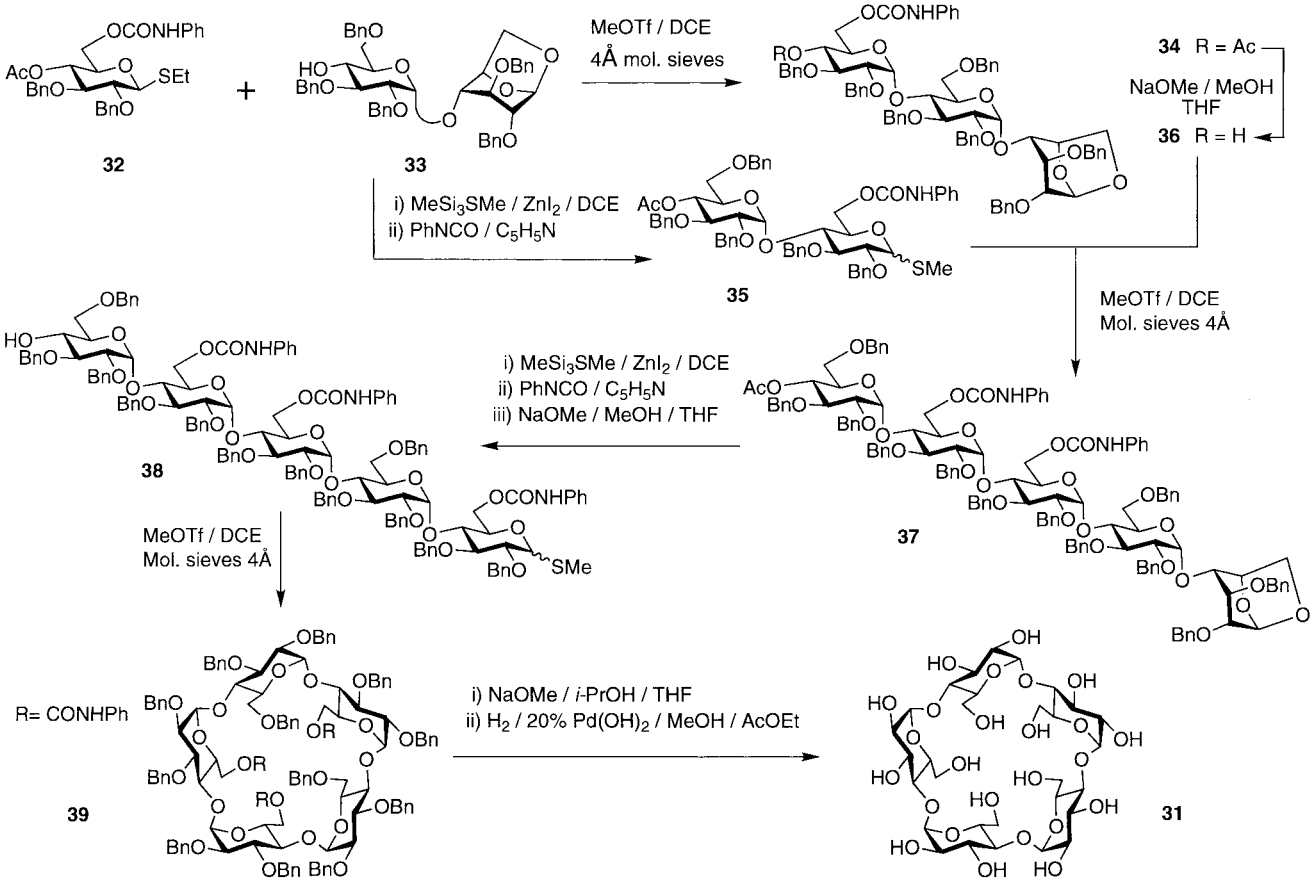


Figure 13. Synthesis of cyclo[4)-α-D-Glc*p*-(1→]$_5$ (**31**).

gation of the maltooligosaccharide chain was achieved in the same fashion: the terminal 4-OH group in **17** was deprotected by deacetylation, to give compound **18**, which, after condensation with **14**, afforded (21%) the octasaccharide **19**. Conversion of the allyl glycosides **17** and **19** into glycosyl fluorides was performed in three steps involving (iv) Pd-catalyzed deallylation, (v) generation of the glycosyl chloride from the hemiacetal by the action of SO_2Cl_2-DMF, and (vi) substitution of the chlorine atom with a fluorine atom by treatment with AgF. In the case of the allyl hexaoside **17**, prior to these transformations, an acetyl group was replaced with a more labile chloroacetyl group, giving compound **20**. This modification was carried out to prevent the basic hydrolysis of the C−F bond that could have taken place during the following deacetylation.[60,61] However, these precautions were unnecessary because the removal of both the chloroacetyl group from the fluoride **21**, prepared from **20**, and of the acetyl group

from the fluoride **22**, prepared from **19**, proceeded equally smoothly in each case under the Zemplén deacylation conditions, to afford the alcohols **11** and **12**, respectively. These derivatives were subjected to cycloglycosylation under the same catalytic conditions as were applied to the previous glycosylations, but under high dilution conditions—the final concentration of precursors was about 2×10^{-3} M. The reactions afforded α-CD and γ-CD as the perbenzylated derivatives **23** and **24** in 21% and 8.4% yields, respectively, and these compounds were debenzylated finally to give α-CD (**1**) and γ-CD (**3**). The major problem associated with these total syntheses seems to reside in the efficiency of the creation of the α-(1→4)-glycopyranosidic linkages. In all the glycosylation steps, the production of the desired compound was accompanied by the formation of substantial amounts of side products—glycals, 1,6-anhydro derivatives, and hemiacetals as products of hydrolysis—originating from the glycosyl donors. Additionally, the synthesis of the linear oligosaccharides **15**, **17**, and **19** proceeded with low stereoselectivities. As a result, the overall yields of the target compounds—α-CD (**1**) and γ-CD (**3**)—were rather low—namely, 0.3% and 0.02%, respectively.

With the objective of synthesizing an unsymmetrical CD analogue incorporating one α-(1→6)-glucosidic linkage, Ogawa and co-workers[61,64] designed the hexasaccharide precursor **25** (Figure 12), which bears two unprotected hydroxyl groups in positions 4 and 6 of the "nonreducing" end of the oligosaccharide. This precursor was prepared by employing a similar sequence (Figure 11) of reactions to those that led to the production of **11**, the only difference being that the maltose building block **26**—containing temporary 4′,6′-diacyl protecting groups—was used in the place of the glycosyl donor **14**, for the maltosylation of the tetrasaccharide **16**, leading to the hexasaccharide **27**. As anticipated, the main product of the cycloglycosylation of **25**, which was prepared in four steps (47%) from **27**, was compound **28**, which was produced as a result of the ring-closure involving α-(1→6) bond formation, whereas the protected α-CD **29** was formed in a 19% yield. Although the lower reactivity of the 4-OH group in **25** is quite obvious from this experiment, the yield of the corresponding product, namely the α-CD derivative **29**, was practically the same as the yield of the α-CD derivative **23** obtained from the precursor **11**, which bears only one deprotected hydroxyl group. Therefore, two isomeric cyclic oligosaccharides, namely compound **30** and α-CD (**1**), were obtained by employing the diol **25**, which is easier to prepare than the precursor alcohol **11**.

For a long time, on the basis of some early computational work,[65] the existence of cyclopentakis-[(1→4)-α-D-glucopyranosyl] **31** was considered not to be possible. It was not until the work of Nakagawa et al.[66] at the beginning of the 1990s that the synthesis of the unnatural CD homologue, composed of five α-D-glucopyranose residues, was attempted and achieved. The synthesis (Figure 13) of a pentasaccharide precursor of **31** was achieved, starting

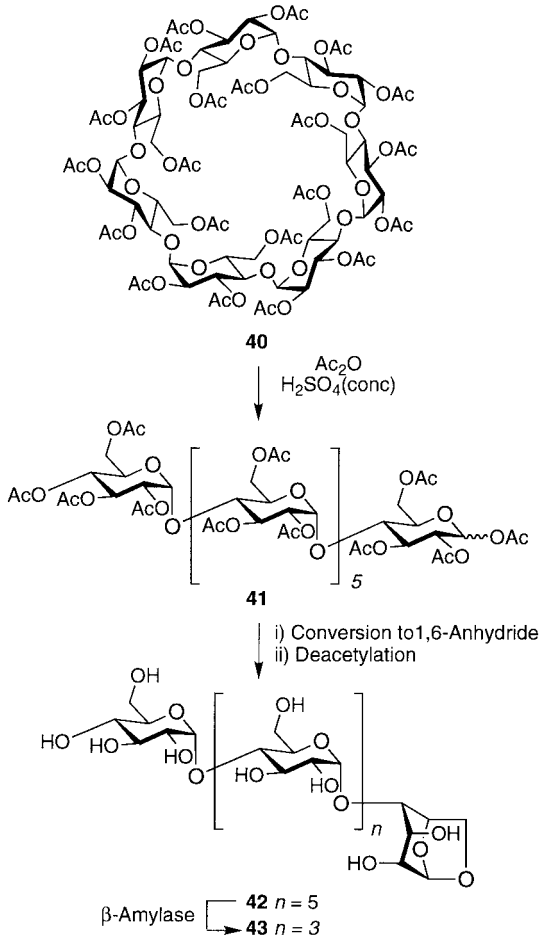


Figure 14. Synthesis of the maltopentaose precursor of **42** from acetylated β-CD.

from the protected thioglucoside **32** and the disaccharide acceptor **33**, derived from 1,6-anhydro-β-maltose. The condensation of **32** and **33** in the presence of MeOTf afforded the glucotriose derivative **34** in a 75% yield, along with 18% of the β-anomer. Thiolysis of the anhydro ring in **33**, followed by phenylcarbamoylation, led to the thioglycoside **35**, which was used as the glycosyl donor in a coupling with the alcohol **36**, which, in turn, was obtained by deacetylation of **34**. This coupling reaction was carried out under the same conditions as those employed for the glycosylation of **33** with **32**, and proceeded with the same stereoselectivity, affording the desired pentasaccharide derivative **37**, in 49% yield, and its β-anomer, in 12% yield. The 1,6-anhydro derivative **37** was then transformed into the oligosaccharide precursor **38**, again by thiolysis/carbamoylation, followed subsequently by deacetylation. The thioglycoside **38** was finally subjected to macrocyclization, via intramolecular glycosylation under high-dilution conditions, which was promoted once again by MeOTf, to give the expected pentasaccharide **39** in 27% yield, along with 40% of the glycal derivative, and 10% of another compound, tentatively assigned to an isomer of **39** in which one β-glucosidic linkage was formed instead of the desired α-linkage. Deprotection of **39** afforded the target cycloglucopentaoside **31**.

Although the efficiency of the cycloglycosylation of **38** leading to **31** is quite good, the preparation of the

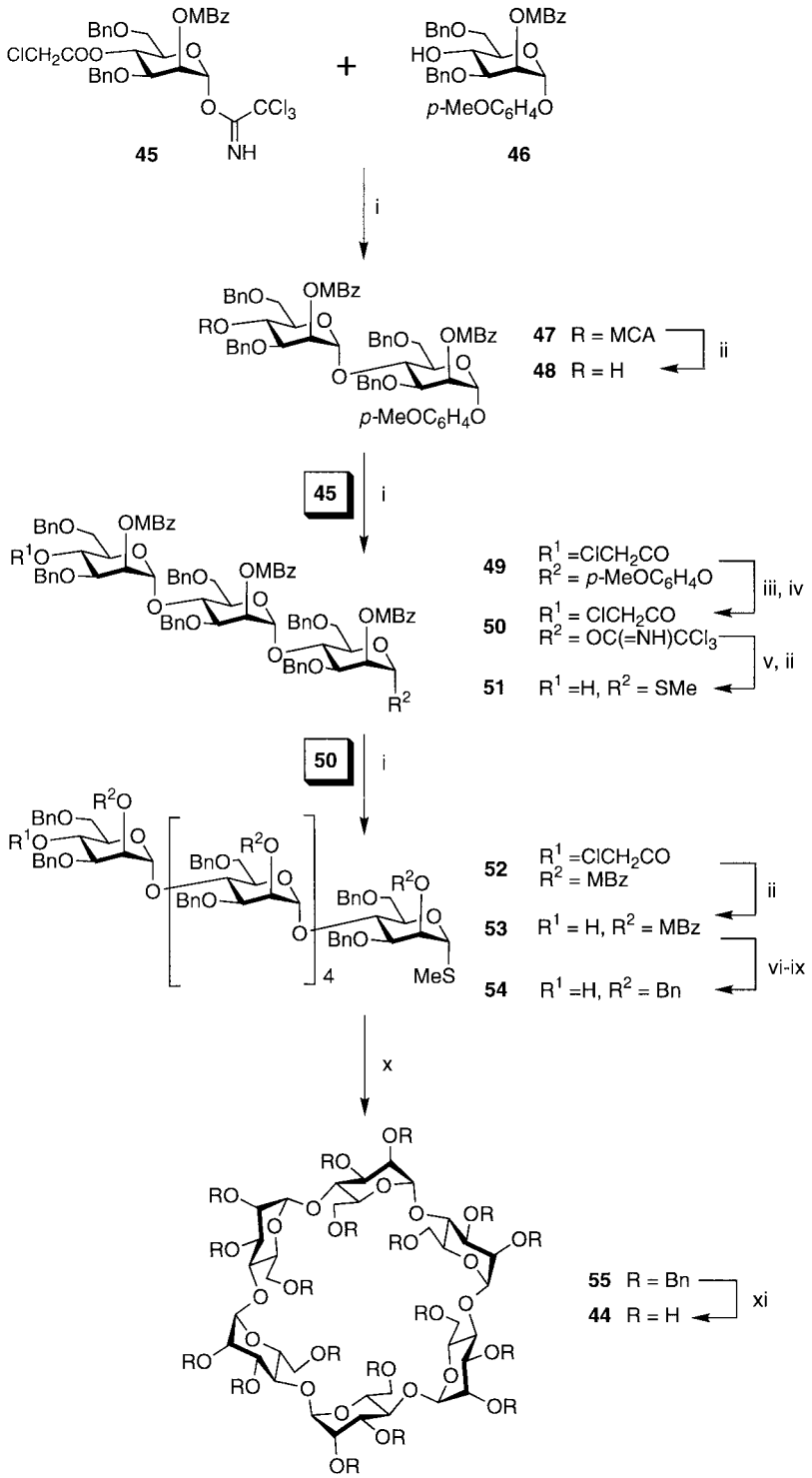


Figure 15. Synthesis of cyclo[4)-α-D-Man*p*-(1→]$_6$ (**44**). Reagents: (i) TMSOTf/mol. sieves 4 Å/DCE; (ii) $(NH_2)_2CS$/EtOH; (iii) $(NH_4)_2Ce(NO_3)_6$/MeCN/H_2O; (iv) CCl_3CN/DBU/DCE; (v) Bu_3SnSMe/BF_3OEt_2/DCE; (vi) $EtOCH{=}CH_2$/PPTS/DCE; (vii) NaOMe/MeOH; (viii) BnBr/NaH/DMF; (ix) Amberlyst 15 resin/$CHCl_3$/MeOH; (x) PhSeOTf/DCE, −20 °C; (xi) H_2/Pd/C/MeOH. MBz = *p*-methylbenzoyl.

precursor **38** requires a long sequence of reactions. It follows that an improvement in the synthesis of **31** requires a more efficient route for the preparation of a linear precursor. One possibility relies on the use[67] of the commercially available, but expensive, maltopentaose as the starting material. It can, however, be replaced by β-CD, which is inexpensive and, in a few steps,[68] can be converted into a glucopentaose derivative. Thus, acetolytic fission of peracetylated β-CD **40** affords (Figure 14) the glucoheptaose **41**, which was transformed into the 1,6-anhydro derivative **42**. The "nonreducing" maltosyl residue of **42** was removed selectively by β-amylase, giving a key intermediate—the 1,6-anhydromaltopentaose **43**, cf., derivative **37**. This compound was converted into the precursor of the cyclic glucopentaoside with a structure analogous to that of compound **37**.

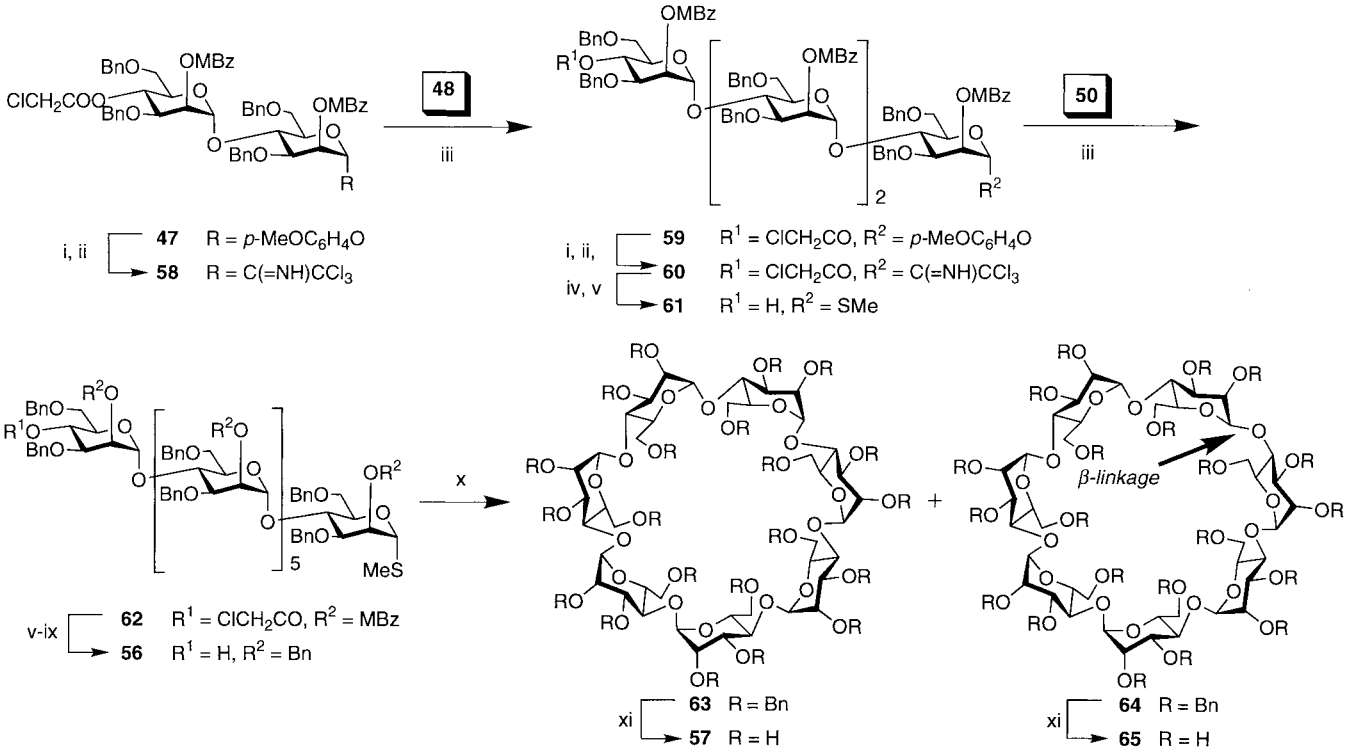


Figure 16. Synthesis of cyclo[4)-α-D-Man*p*-(1→]$_7$ (**57**). Reagents: (i) $(NH_4)_2Ce(NO_3)_6$/MeCN/H_2O; (ii) CCl_3CN/DBU/DCE; (iii) TMSOTf/mol. sieves 4 Å/DCE; (iv) Bu_3SnSMe/BF_3OEt_2/DCE; (v) $(NH_2)_2CS$/EtOH; (vi) $EtOCH{=}CH_2$/PPTS/DCE; (vii) NaOMe/MeOH; (viii) BnBr/NaH/DMF; (ix) Amberlyst 15 resin/$CHCl_3$/MeOH; (x) PhSeOTf/DCE, −20 °C; (xi) H_2/Pd/C/MeOH.

B. The Manno-Isomers of Cyclodextrins

Although the transformation of CDs into their manno-isomers by chemical means is an extremely difficult modification to effect, cyclic mannooligosaccharides can be prepared by total chemical synthesis. After their successful synthesis of α-CD and γ-CD, Ogawa and co-workers[69−71] applied the same strategy—which relies upon the cyclization of a linear oligosaccharide precursor—to the preparation of the cyclomannohexaoside **44** (Figure 15).

In this case, however, a methyl sulfide group was chosen as the glycosyl donor function for the key cyclization step, whereas, for the assembly of the linear hexasaccharide precursor, the trichloroacetimidate glycosylation method[26,27] was preferred. Thus, the trichloroacetimidate **45** was coupled with the mannoside acceptor **46** to give the mannobioside **47** in 87% yield. It is worth noting that all the mannose units were designed to carry *p*-methoxybenzoyl groups at the O-2 positions as a stereocontrolling auxiliary for the subsequent α-mannosylations. The temporary protecting group at the 4′-position was removed, and the resulting glycosyl acceptor **48** was coupled with another molecule of **45**. The product—the trisaccharide **49**—which was obtained in 84% yield, was then used for transformation into both the mannotriosyl donor **50** and the mannotriosyl acceptor **51**. These two compounds were coupled under the same conditions as those used in the synthesis of α-CD to give (87%) the mannohexaose derivative as its methyl α-thioglycoside **52**, which was then dechloroacetylated to afford the alcohol **53**. In this hexasaccharide, although the functional groups seem to be arranged appropriately in order to allow the cycloglycosylation reaction, surprisingly, the reaction does not proceed under the action of a number of promoters (PhSeOTf, $CuBr_2$−Bu_4NBr, or AgOTf) which are known to be efficient for disaccharide synthesis with the participation of thioglucosides carrying 2-*O*-*p*-methoxybenzoyl groups. Since the cycloglycosylation was successful in the case of CD syntheses (see Section IV.A) using 2-*O*-benzyl groups, the *p*-methoxybenzoyl groups in **53** were replaced with benzyl groups—which involved a sequence of manipulations involving different protecting groups and, in particular, a temporary protection of the 4-OH functions with 1-ethoxyethyl groups. The resulting derivative **54** was subjected to macrocylization in the presence of PhSeOTf, to afford, in a remarkable 92% yield, the perbenzylated derivative **55**, which was then deprotected to give the target cyclomannohexaoside **44**.

The methodology developed for the synthesis of the manno-isomer of α-CD **44** was extended to the syntheses of the manno-isomers of β-CD and γ-CD. The linear precursors employed were analogous to the hexamannoside **54**—the precursor of the cyclic hexamannoside **44**. Thus, the linear heptamer **56**, designed for the preparation (Figure 16) of the cyclomannoheptaoside **57**, was prepared[71] using the building blocks **47**, **48**, and **50**. First, the glycoside **47** was converted into the trichloroacetimidate **58**, which acts as the glycosyl donor in the condensation with **48**, affording the tetraoside **59** in 85% yield. The *p*-methoxyphenyl protecting group at the anomeric center of **59** was replaced with a trichloroacetamido group, giving compound **60**, which was then converted into the thioglycoside **61**, as described for the

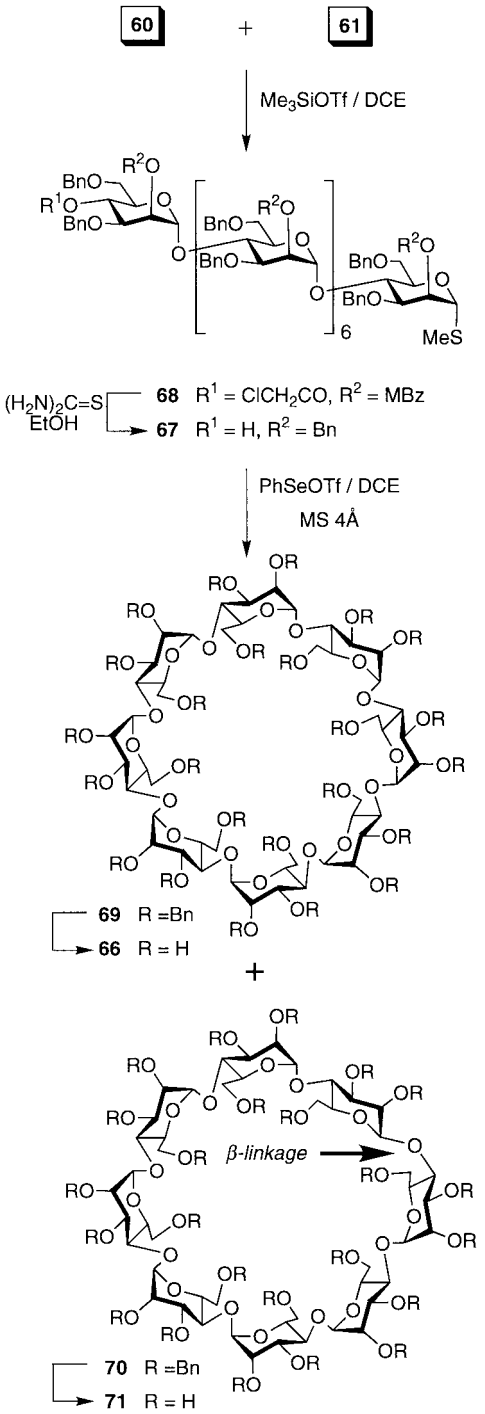


Figure 17. Synthesis of cyclo[4)-α-D-Man*p*-(1→]$_8$ (**66**).

transformation **50** → **51**. The resulting alcohol **61** was coupled with the mannotriosyl donor **50** to give the heptasaccharide **62** (66%), which was then subjected first to a protecting group interconversion—*p*-methoxybenzoyl to benzyl—as it was necessary for an efficient cycloglycosylation (cf., the synthesis of **54**), and then second to the deprotection of the 4-OH group at the "nonreducing" end to afford the precursor **56**. The macrocyclization, promoted once again by PhSeOTf, gave two different cyclic products—namely, the expected perbenzylated cyclo[4)-α-D-Man*p*-(1→]$_7$ (**63**) (46%) and its isomer **64** (33%), in which the newly formed glycosidic bond has a β-configuration. These derivatives were subjected to hydrogenolysis over $Pd(OH)_2$/C to give **57** and **65**, respectively, in quantitative yields.

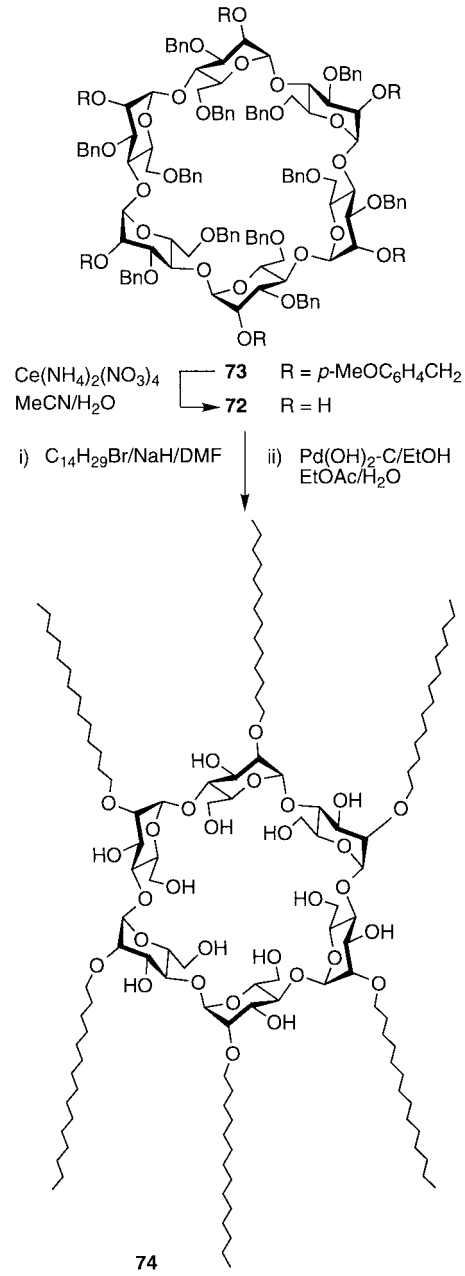


Figure 18. Synthesis of per-2-*O*-tetradecyl cyclomannohexaoside (**74**).

The synthesis (Figure 17) of the cyclomannooctaoside **66**—an isomer of γ-CD—has been achieved[71,72] by cycloglycosylation of the octasaccharide precursor **67**, employing the mannotetraose derivatives **60** and **61** for its preparation. Condensation of the alcohol **60** with the trichloroacetoimidate **61** led, in 62% yield, to the mannooctaoside derivative **68**, which was then transformed in one step into the derivative **67**. The macrocyclization—carried out under the same conditions as used before (PhSeOTf)—afforded, once again, two main products, **69** and **70**, in 53% and 25% yields, respectively. These products, after deprotection, were characterized as the desired symmetrical compound **66**, and as the isomeric cyclic octasaccharide **71**, in which a β-glycosidic linkage has been formed instead of an α-linkage.

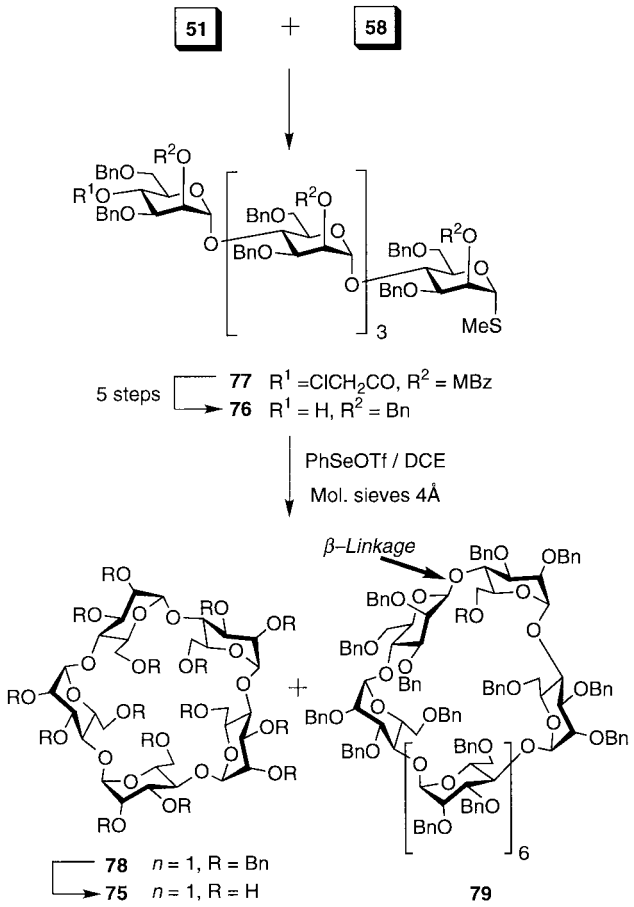


Figure 19. Synthesis of cyclo[4)-α-D-Man*p*-(1→]$_5$ (**75**). The five steps between **77** and **76** involve the same reactions as used for the conversion **62**→**56** and correspond to reactions v−ix outlined in Figure 16.

The high yields of cyclic products obtained from the mannooligosaccharide precursors **54**, **56**, and **67** are in sharp contrast to the moderate to low yields of the CD derivatives **23** and **24**, produced by macrocyclization of the glucooligosaccharide precursors **11** and **12**. It is worth mentioning that in the gluco series, no formation of the undesired β-glycosidic linkage was observed, whereas in the manno series, the stereoselectivity of cycloglycosylation was highly dependent upon the chain length of the precursor employed in the reaction. The ratios between α- and β-products in the manno series were as follows: only α in the case of the cyclic mannohexaoside, 1.4:1 for α:β in the case of the cyclic mannoheptaoside, and 2.1:1 for α:β in the case of the cyclic mannooctaoside. The formation of the β-isomers in the last two cases may be explained by the lack of an appropriate O-2 stereocontrolling auxiliary like, for instance, an acyl group. Although the unsymmetrical cyclic oligosaccharides **65** and **71** have emerged as byproducts in the synthesis of the manno-CD analogues of the CDs, they are interesting in themselves since they demonstrate the possibility of incorporating a heteroresidue into cyclic systems, while mantaining the CD framework in the remainder of the molecule.

Aside from the possibility of creating new cyclic oligosaccharides, their chemical synthesis provides the opportunity for further regioselective introduction of functional groups.[73] Thus, the cyclic hexaoside **72**,

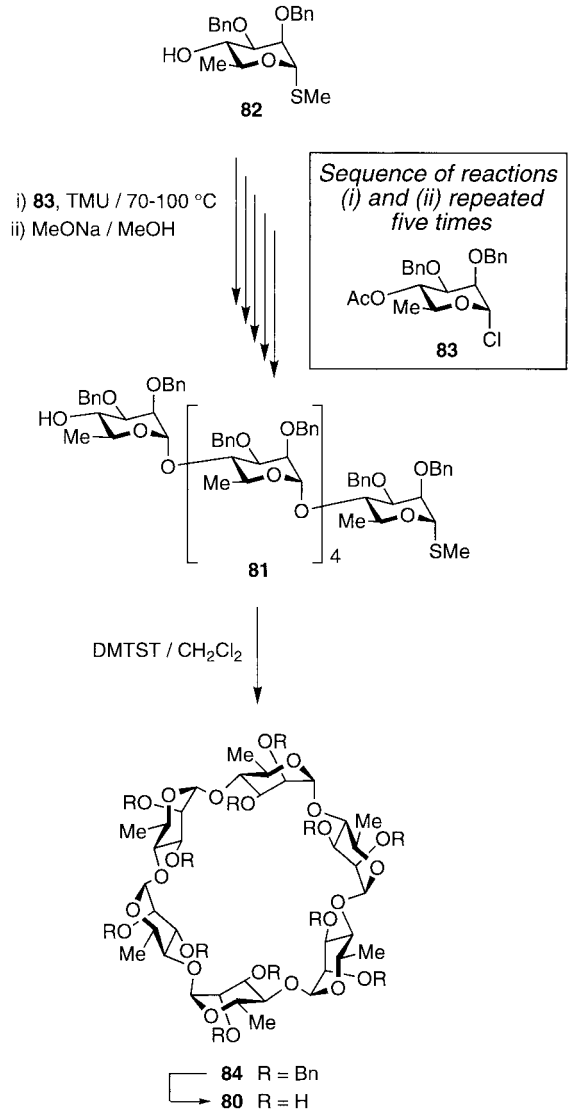


Figure 20. Synthesis of cyclo[4)-α-L-Rha*p*-(1→]$_6$ (**80**).

which may be easily converted into a variety of per-2-*O*-substituted cyclic mannohexaosides, has been prepared (Figure 18) by deblocking of the 2-*O*-methoxybenzylated derivative **73**, which, in turn, has been synthesized in an analogous manner to its 2-*O*-benzylated analogue **55**. The synthesis of the per-2-*O*-tetradecyl cyclic mannohexaosides derivative **74** is a good example of the kind of novel synthetic cyclic oligosaccharide that is easily within the reach of the synthetic chemist.

The series of cyclic mannooligosaccharides was completed in Ogawa's group by the preparation[72] of the cyclomannopentaoside **75**. The pentasaccharide precursor **76** was constructed (Figure 19) by coupling of the previously synthesized building blocks **51** and **58**, which led to the derivative **77** in 87% yield. In five steps, compound **77** was transformed into the precursor **76**, which, in turn, was cyclized under the conditions described for the cyclization of **54** to give, in 8.4% yield, the protected cyclic pentasaccharide **78**, which was subsequently debenzylated, affording **75**. Another compound, which was isolated in 4.3% yield from the cyclization, was characterized as the decasaccharide **79** containing one β-mannosidic

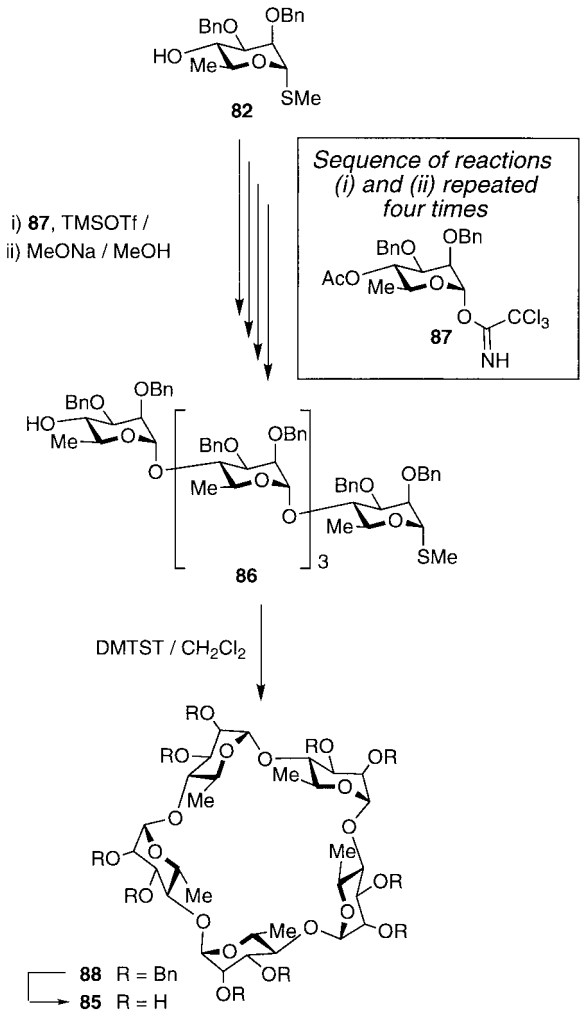


Figure 21. Synthesis of cyclo[4)-α-L-Rha*p*-(1→]$_5$ (**85**).

bond: however, foolproof evidence for the presence of this bond in the structure of **79** was not presented.

C. Cyclic α-L-(1→4)-Rhamnooligosaccharides

The first synthesis of a cyclodextrin analogue composed of L-sugars—cyclo[(1→4)-α-L-rhamno]hexaoside (**80**)—was reported by Nishizawa et al.[74−76] It was achieved (Figure 20) by cycloglycosylation of compound **81** which, like Ogawa's precursors for cyclomannins, bore a methyl sulfide as the glycosyl donor function. The linear hexasaccharide **81** was constructed by reiterative addition of a rhamnosyl residue to the "nonreducing" end of the elongated chain by the alternation of glycosylations and 4-OH group deprotections. The alcohol **82** and the rhamnosyl chloride **83**—which bears an acetyl group as a temporary protecting group—were used as the glycosyl acceptor and glycosyl donor, respectively. The reaction scheme involved five subsequent coupling reactions, performed under identical glycosylation conditions—70−100 °C in the presence of TMU, the so-called thermal glycosylation procedure elaborated in previous work by the same authors. The key macrocyclization of the linear hexasaccharide **81**, promoted by DMTST, afforded, in 56% yield, the perbenzylated rhamnohexaoside **84**, which was then deprotected to give **80** employing the usual conditions.

The synthetic strategy described for the preparation of **80** can be applied to the preparation of the homologous cyclic L-rhamnooligosaccharides. Nishizawa and co-workers[77] have reported (Figure 21) the total synthesis of cyclorhamnopentaoside **85** as a result of cyclizing the pentameric precursor **86** analogous to the hexasaccharide **81**. The only difference

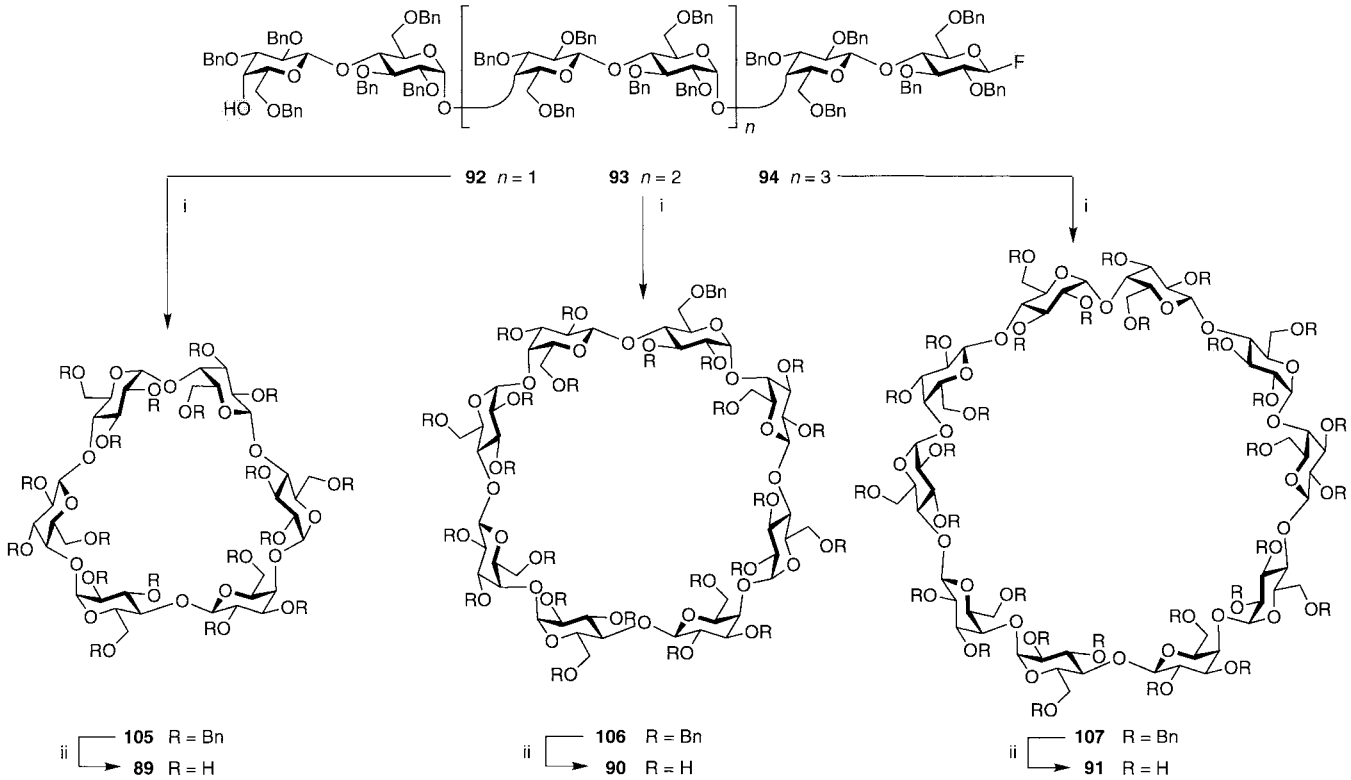


Figure 22. Synthesis of cyclic (1→4)-α-lactooligosaccharides **89**−**91** by intramolecular glycosylation of linear precursors **92**−**94**. Reagents: (i) $Cp_2Zr(ClO_4)_2/Et_2O$; (ii) $H_2/Pd(OH)_2$/MeOH/EtOAc/H_2O.

between the assembly of the precursors **81** and **86** was that, in the construction of the latter, the trichloroacetimidate glycosylation method[32] was preferred over the "thermal glycosylation" employed in the former case, i.e., the trichloroacetoimidate **87** was employed as a glycosyl donor. Once again, DMTST-promoted cycloglycosylation of **86** afforded, in 20% yield, the protected cyclorhamnopentaoside **88**, which, after debenzoylation, gave the target compound **85**.

D. Cyclic α-(1→4)-Lactooligosaccharides

After reporting the total syntheses of cyclodextrins and their manno-isomers, Ogawa and co-workers[78,79] went on to create a new family of (1→4)-linked cyclic oligosaccharides composed of heterogeneous saccharide units. The novelty of their first target structure, which was the cyclolactohexaoside **89**,[78] resides (Figure 22) in the marked difference it exhibits compared with the CD framework. In the cyclic oligosaccharide **89**, each pyranose unit has one axial and one equatorial bond involved in the formation of the glycosidic linkages just as in the CDs: however, the sequence of these bonds in the cyclic lactotrioside is substantially different. In the macrocyclic compound **89**, glycosidic linkages composed of equatorial−equatorial C−O bonds alternate with linkages formed by axial−axial bonds, whereas, in CDs, and their analogues, all the glycosidic linkages have the same configuration and are formed by one axial and one equatorial C−O bond.

The syntheses (Figure 22) of the cyclic lactotrioside **89**,[78] as well as its higher homologues **90** and **91**,[79] were achieved—as in the cases of CDs and their analogues described in Sections IV.A−IV.C—via cycloglycosylation of linear precursors. These precursors, the oligolactosyl fluorides **92**−**94**, have been constructed according to the scheme shown in Figure 23.

The convergent nature of the reaction scheme, which relies upon lactosyl building blocks, was provided by the use of two orthogonal protecting groups—*p*-methoxyphenyl for the anomeric hydroxyl group and levulinoyl for the 4-OH group at the "nonreducing" end of the oligosaccharides—as well as employing a set of only four reactions throughout all the reaction sequence. These reactions involved (i) glycosylation using glycosyl fluorides as glycosyl donors in the presence of $Cp_2Zr(ClO_4)_2$, (ii) the two-step conversion of *p*-methoxyphenyl glycosides into glycosyl fluorides, involving treatment with $Ce(NH_4)_2(NO_3)_6$ in aqueous MeCN followed by the reaction with Et_2NSF_3, and (iii) removal of the levulinoyl group from the terminal 4-OH position, by the action of NH_2NH_2·HOAc, to generate the glycosyl acceptor function. The preparation of the oligolactosyl precursors **92**−**94** for the cyclic oligosaccharides **89**−**91** are shown in Figures 24−26.

The two starting building blocks, both prepared from the lactoside **95**, were the alcohol **96** and glycosyl fluoride **97**. Coupling of these derivatives produced (Figure 24) the tetrasaccharide **98** in 64% yield. This compound gave rise to a new pair of building blocks—the glycosyl acceptor **99** and the glycosyl donor **100**. Condensation of **99** with another

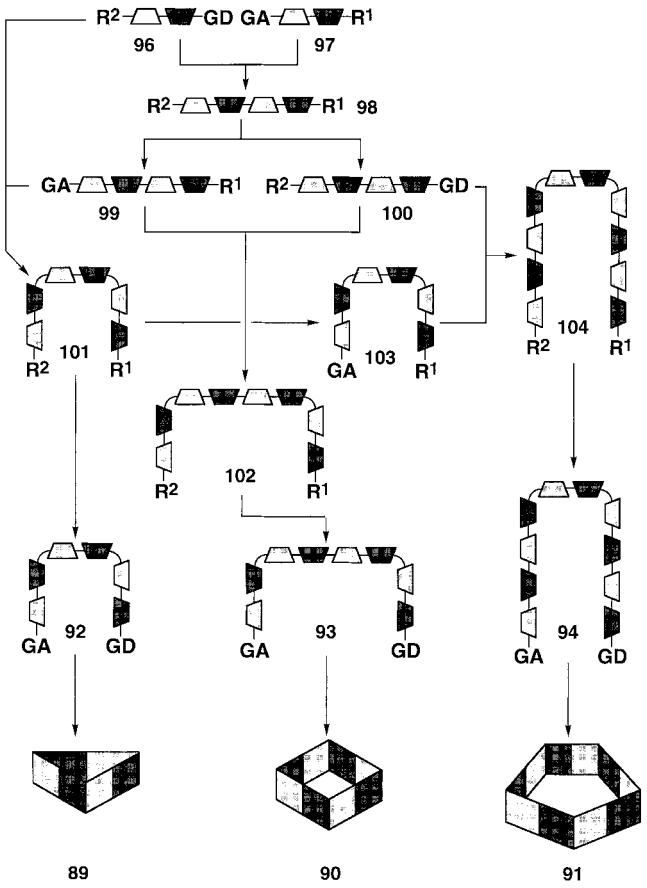


Figure 23. Cartoon representation of the reaction sequence used in assembling the precursors of the cyclolactooligosaccharides **89**−**91**. R^1 and R^2 denote temporary protecting groups; GD, leaving group; and GA, glycosyl acceptor function (OH group) at the glycosyl donor part of the oligosaccharide derivative. Dark polygons = D-glucopyranose residues, and gray polygons = D-galactopyranose residues.

molecule of the fluoride **97** afforded (53%) the desired lactotrioside **101**, which was then transfomed into the key intermediate **92** via the preparation of the glycosyl fluoride and removal of the levulinoyl group.

The octasaccharide precursor **93** was prepared (Figure 25) in a manner similar to **92**, with the only difference being that alcohol **99** was coupled with the glycosyl fluoride **100**. This glycosylation produced the octasaccharide **102** in 54% yield. It was then converted into the fluoride and deacylated to give the desired derivative **93**.

For the assembly (Figure 26) of the decasaccharide precursor **94**, the alcohol **103** derived from hexasaccharide **101** was glycosylated with the lactotetraosyl fluoride **100**, to yield (32%) the decasaccharide **104**, along with its isomer (26%) containing a newly formed glycosidic bond with the β-configuration. Replacement of the anomeric *p*-methoxyphenyl group of **104** with the fluorine, followed by dechloroacetylation, afforded the target precursor **94**.

Cycloglycosylation of the precursors **92**−**94** was carried out in the presence of $Cp_2Zr(ClO_4)_2$, affording the cyclic lactosides **105**−**107** (Figure 22) in good yields (74, 85, and 51%, respectively). The stereoselectivity of this reaction was quite high in the case of compounds **105** and **106**, where no formation of

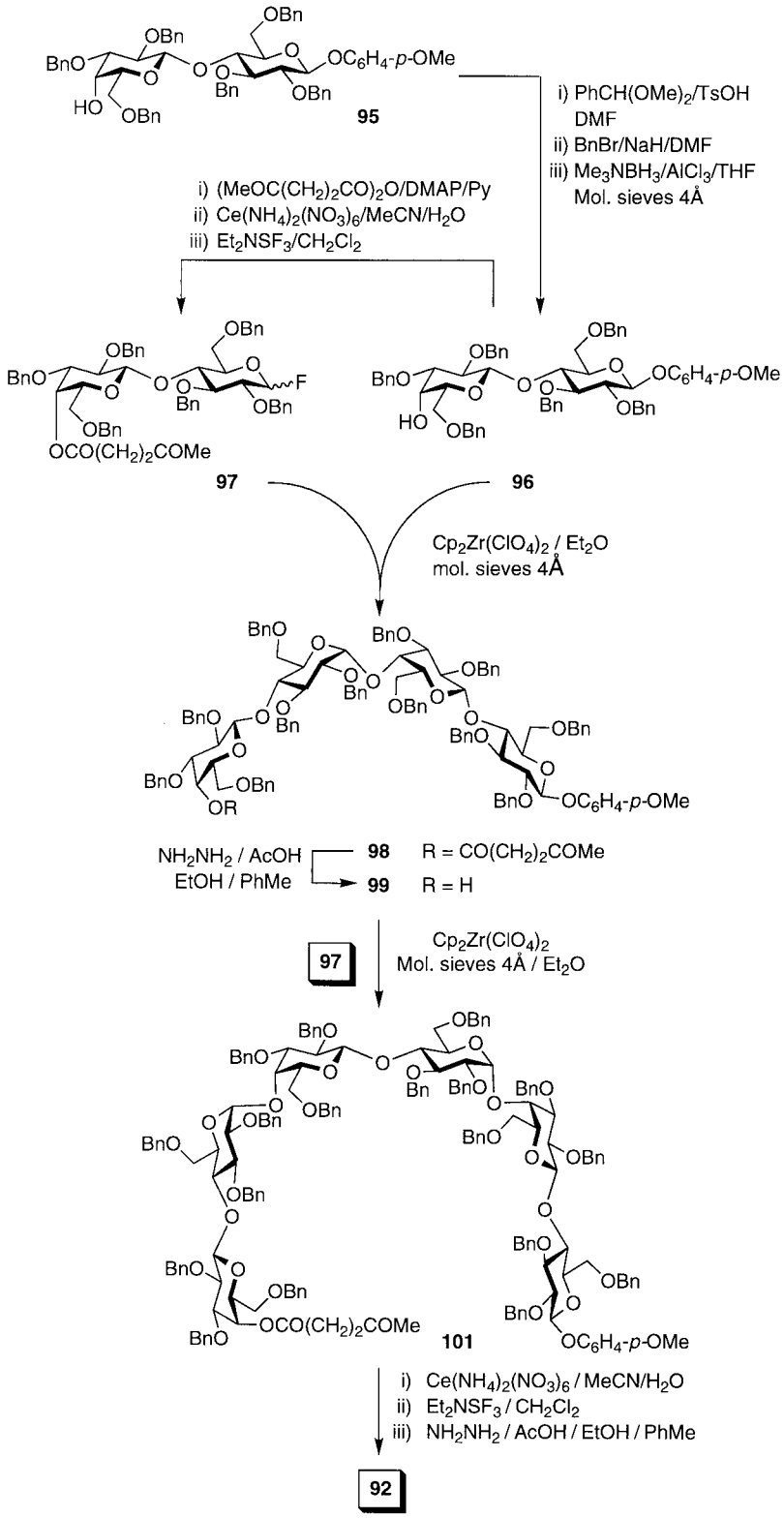


Figure 24. Synthesis of the precursor **92** of the cyclolactohexaoside **89**.

the β-isomers was observed. This situation could be a consequence of the fact that the β-isomers of **105** and **106**—which incorporate one β-glucosidic linkage—are geometrically unfavorable. Indeed, the attempt (Figure 27) at the cyclization of the hexasaccharide **108**, which is isomeric with the precursor **92**, was totally unsuccessful. On the other hand, the macrocyclization of the decasaccharide **94** gave two cyclic products, the target compound **107** (51%), and its unsymmetrical isomer **109** (14%), incorporating one (1→4)-β-glucosidic linkage. Compound **109** was also obtained (Figure 28) in 34% yield from the macrocyclization of the glycosyl fluoride **110**—isomeric with the decasaccharide precursor **94**: compound **110** contains one β-glucosidic bond instead of an α-bond as in **94**. Therefore stereocontrol in the cycloglycosylation, as in the case of the synthesis of cyclomannooligosaccharides (Section IV.B), was provided by

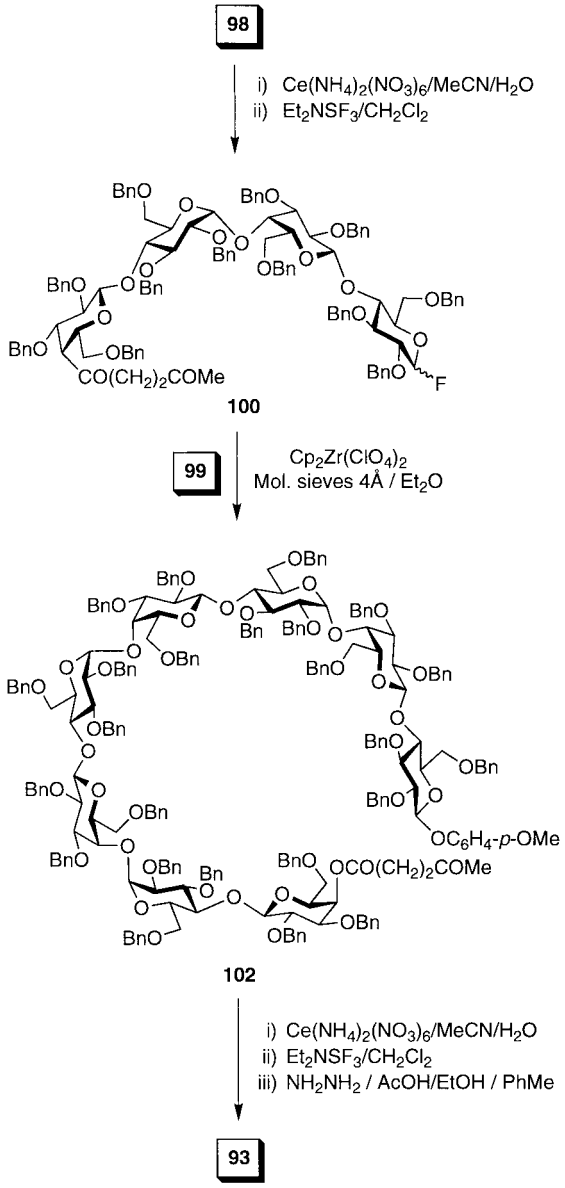


Figure 25. Synthesis of the precursor **93** of the cyclolactooctaoside **90**.

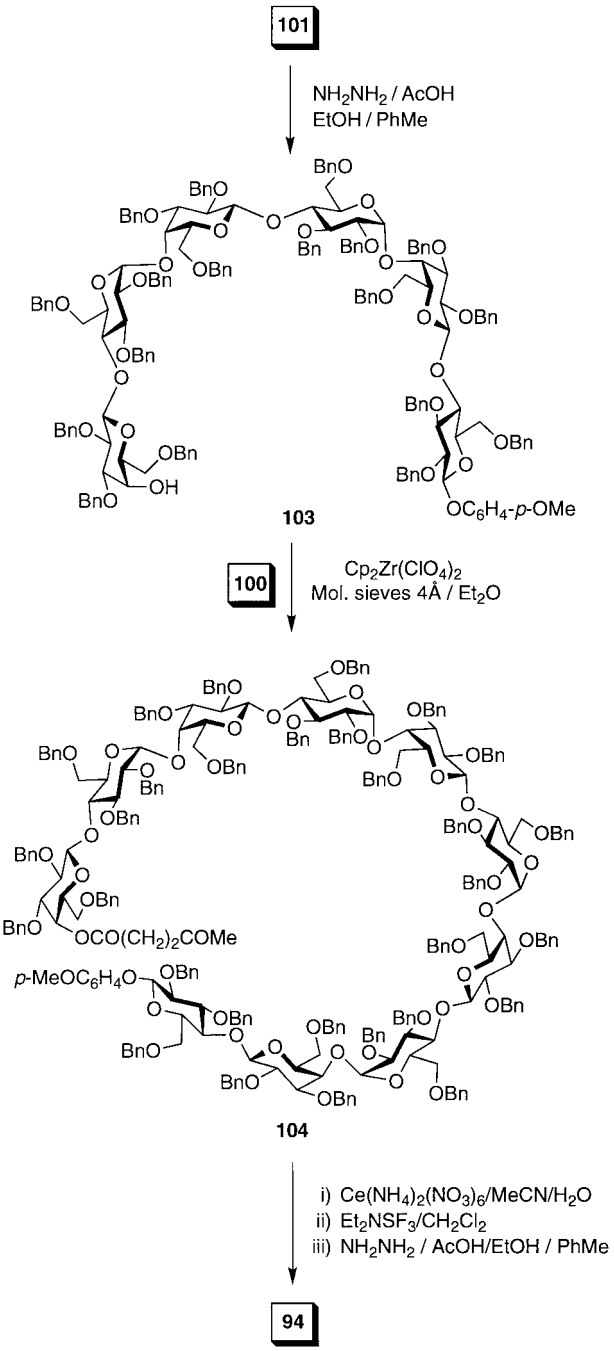


Figure 26. Synthesis of the precursor **94** of the cyclolactodecaoside **91**.

the length of a linear oligosaccharide precursor. It is also worth mentioning that all the coupling reactions which were carried out for the construction of the precursors **92**−**94** were not stereoselective: in addition to the desired products **98**, **100**, **102**, and **103** shown in Figures 24−26, the formation of β-isomers was also observed (Table 2) in substantial proportions.

The benzylated cyclic oligosaccharides **105** and **106** (Figure 22) and **109** (Figure 28) were deprotected to give the target C_n symmetrical cyclic lactooligosaccharides **89**−**91** and the unsymmetrical isomer **111**.

E. α-(1→4)-Linked Cyclic Oligosaccharides Composed of Alternating D- and L- Pyranoses

The successful synthesis of cyclic D-manno- and L-rhamnooligosaccharides performed by Ogawa and co-workers[69−73,78,79] and Nishizawa and co-workers[74−77] encouraged us to attempt the synthesis[80,81] of a new type of CD analogue incorporating both D- and L-sugars. The alternation of such D- and L-residues, having the same relative configurations in a macrocyclic structure, gives rise to compounds with S_n-type symmetry—where n is equal to the number of monosaccharide residues. On the other hand, if the D- and L-monosaccharides do not possess the same relative configuration, C_n-symmetric cyclic oligosaccharides are produced, where, in this case, n is equal to the number of disaccharide repeating units. Another objective of this research program was to make available alternative synthetic strategies for the production of cyclic oligosaccharides. We have seen (Sections IV.A−IV.C) that α-(1→4)-linked cyclic oligosaccharides can be prepared in relatively high yields by the cycloglycosylation of linear precursors which are apparently appropriately preorganized[6] for

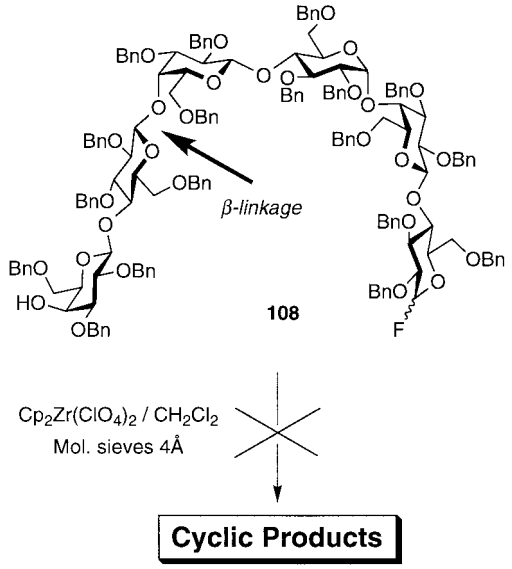


Figure 27. An attempt at preparing cyclic oligosaccharides from the hexasaccharide precursor **108**.

macrocyclization. Presumably they adopt helical conformations—just as in the case of the unprotected maltooligomers: of course, in making this statement, we assume that bulky protecting groups do not affect the conformational situation dramatically. Also, one feels that it should be possible to achieve improvements in the synthesis of α-(1→4)-linked cyclic oligosaccharides by decreasing the number of reactions required for the preparation of the linear precursors. Indeed, the development of better routes toward these long-chain precursors was the major concern in the multistep approach outlined in Sections IV.A–IV.D. In contrast with this approach, we have relied upon a cyclooligomerization methodology (Figure 10) which employs disaccharide derivatives as precursors for alternating D/L cyclic oligosaccharides. For the cyclooligomerization, we appealed to the tritylcyanoethylidene glycosylation method, which has been investigated extensively by Kochetkov and co-workers[82] and is known to be an efficient process for the construction of linear polysaccharides. Thus, "disaccharide monomers" (Figure 29), incorporating both the 1,2-*O*-cyanoethylidene and the 4′-*O*-trityl group, were designed as precursors of D/L alternating cyclic oligosacchride composed of L(D) rhamnose and/or D-(L) mannose residues. As a consequence of the structural similarities between these monomers, they can be prepared by following a common synthetic pathway which involves six steps, starting from a cyanoethylidene derivative and a glycosyl bromide with a temporary protecting group (chloroacetyl) at O-4—the preparation of which, obviously, requires some additional effort.

The first disaccharide monomer obtained (Figure 30), according to the general scheme shown in Figure 29 was compound **112**, composed of D-mannose and L-rhamnose residues.[80] This disaccharide derivative bears a trityloxy group as the glycosyl acceptor function in the L-rhamnose residue, and the 1,2-*O*-cyanoethylidene group as the glycosyl donor function in the D-mannose residue. The cyanoethylidene group was kept in a latent state, throughout all the

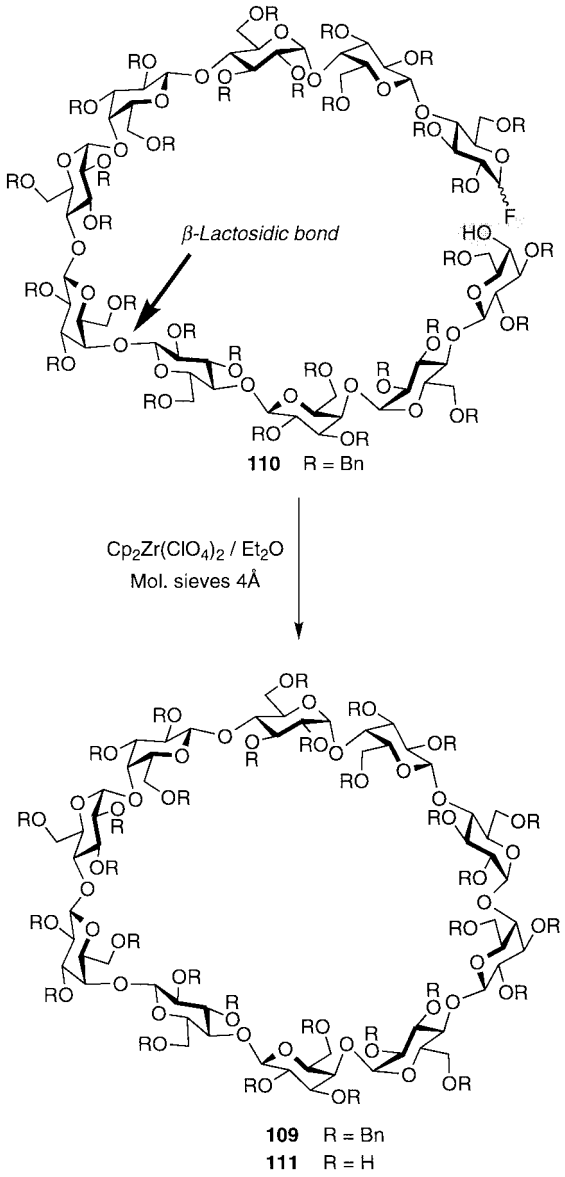


Figure 28. Cyclization of the decaosyl fluoride **110** leading to the unsymmetrical cyclodecaoside **109**.

Table 2. Yields of the Linear Protected Lactooligosaccharides

	coupling reaction			
	96+97	**96+99**	**99+100**	**100+103**
major product of the glycosylation (α-isomer)	**98**	**101**	**102**	**104**
yield (%) of the α-isomer	64	53	54	32
yield (%) of the second product of the glycosylation (β-isomer)	22	18	23	26
α/β ratio	2.9:1	2.9:1	2.3:1	1.2:1

"monomer" synthesis, in the form of a 1,2-*O*-methoxycarbonylethylidene group, before being converted back into a cyanoethylidene group in the reaction prior to the cyclooligomerization.

Compound **113** was obtained in three steps from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide. It was then used as the glycosyl acceptor in a coupling reaction with the rhamnosyl bromide **114**. This bromide—with a temporary protecting group at 4-OH—can be prepared from L-rhamnose utilizing

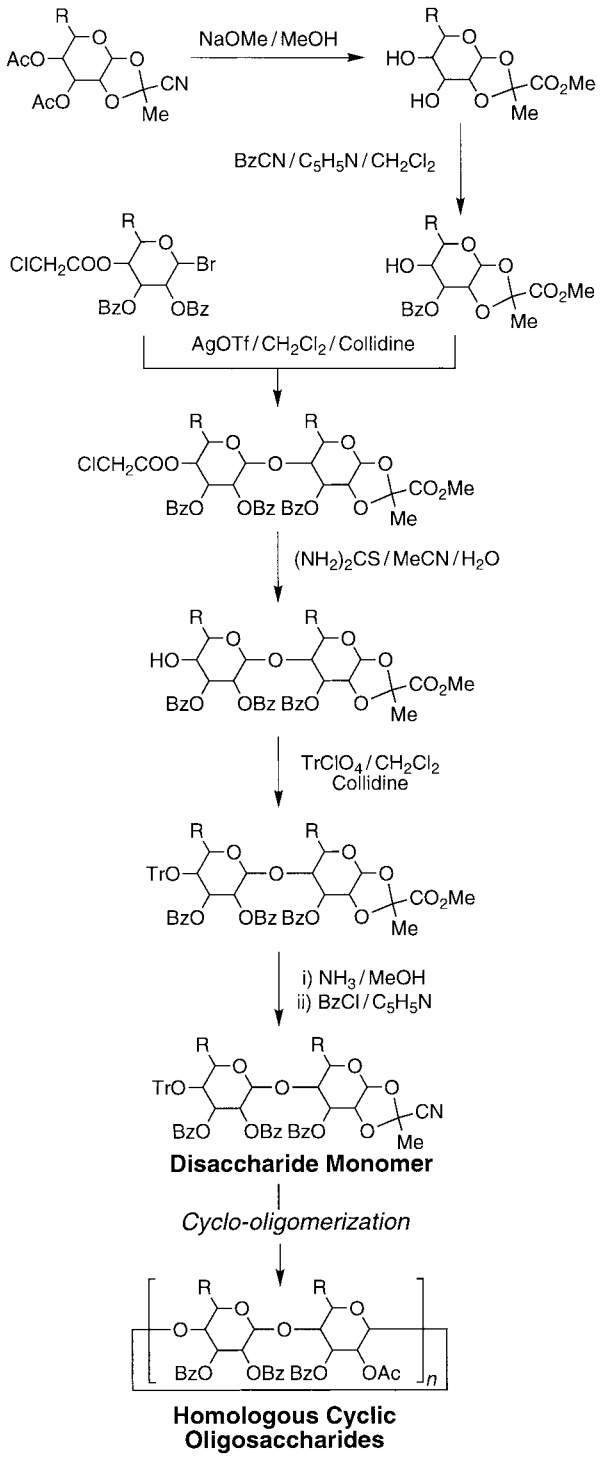


Figure 29. General reaction scheme for the synthesis of disaccharide precursors for alternating D/L cyclic oligosaccharides.

methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside as the starting material. Condensation of the bromide **114** with the alcohol **113** was successful in the presence of silver triflate, affording 90% of the disaccharide **115**, which was subsequently dechloroacetylated (**115** and **116**) and tritylated at the 4′-position to give the trityl ether **117**. The two-step transformation of the methoxycarbonyl group of the D-mannose moiety into the nitrile led to the desired "monomer" **112**. This compound undergoes polycondensation when it is treated with a cyanophilic reagent such as $TrClO_4$, which acts, in this case, as a catalyst. As in any polymerization, three different processes are possible—namely, linear growth, chain breaking, and cyclization. In light of the efficiency of the tritylcyanoethylidene condensation, it is possible to ignore the chain-breaking process. Therefore, the two processes that could take place are the linear growth and the macrocyclization. It transpired that carrying out the polycondensation of **112** in dilute solution favored cyclization over the linear growth. Remarkably, rather moderate dilution (0.01 M of the monomer **112**) led almost exclusively to cyclic products with an overall yield of 75%. Obviously, control of the ring size is not possible, and a series of homologous compounds **118**−**121** was obtained, among which the hexa- and octasaccharides **118** (34%) and **119** (31%) were the predominant ones. The number of repeating units in **118**−**121** was determined by mass spectrometry (FAB and MALDI-TOF-MS are both applicable but the second technique is especially advantageous for the analysis of mixtures of products). The structure of the cyclic oligosaccharides **118**−**121** was clarified by the inspection of their NMR spectra. On the NMR time scale, the cyclic oligosaccharides appear as single sets of signals—corresponding to a disaccharide moiety—demonstrating the high symmetry of these compounds. Derivatives **118**−**121** were deprotected to afford the "free" cyclic oligosaccharides **122**−**125**, analogous to α-, γ-, ϵ-, and η-CD, respectively.

The same synthetic strategy, described for the synthesis of the disaccharide precursor **112** was employed[81] for the preparation (Figure 31) of compound **126**, which has been used as the monomer for the construction of cyclodextrin analogues composed of alternating D- and L-rhamnose residues. D-Rhamnosyl bromide **127** was obtained by starting from methyl α-D-mannoside, via the selective reduction of the CH_2OH group, followed by applying the same synthetic steps as those employed for the preparation of the L-analogue **114**. Coupling of the bromide **127** with the alcohol **128**, prepared by monobenzoylation ($BzCN/C_5H_5N$) of the 1,2-*O*-methoxycarbonylethylidene-L-rhamnose, gave the rhamnobiose derivative **129**. This protected disaccharide was then transformed into the monomer **126** in four steps, namely dechloroacetylation (**130**), tritylation (**131**), and ammonolysis, followed by dehydration. The cyclooligomerization of **126** was carried out under the same conditions as those employed in the case of L-rhamnosyl-D-mannose monomer **112**. The reaction afforded a series of homologous cyclic oligosaccharides **132**−**136** ranging from hexa- to tetradecasaccharides—obviously, composed only of even numbers of sugar residues. Deacylation of the derivatives **133**−**136** afforded the free D/L-rhamno-oligosaccharides **137**−**140**.

The third tritylcyanoethylidene disaccharide monomer, which was subjected to $TrClO_4$-catalyzed cyclooligomerization,[81] was compound **141** (Figure 32), bearing D- and L-mannose residues. The construction of this monomer was accomplished according to the general strategy already described in Figure 29 and starts from the preparation of the disaccharide **142**

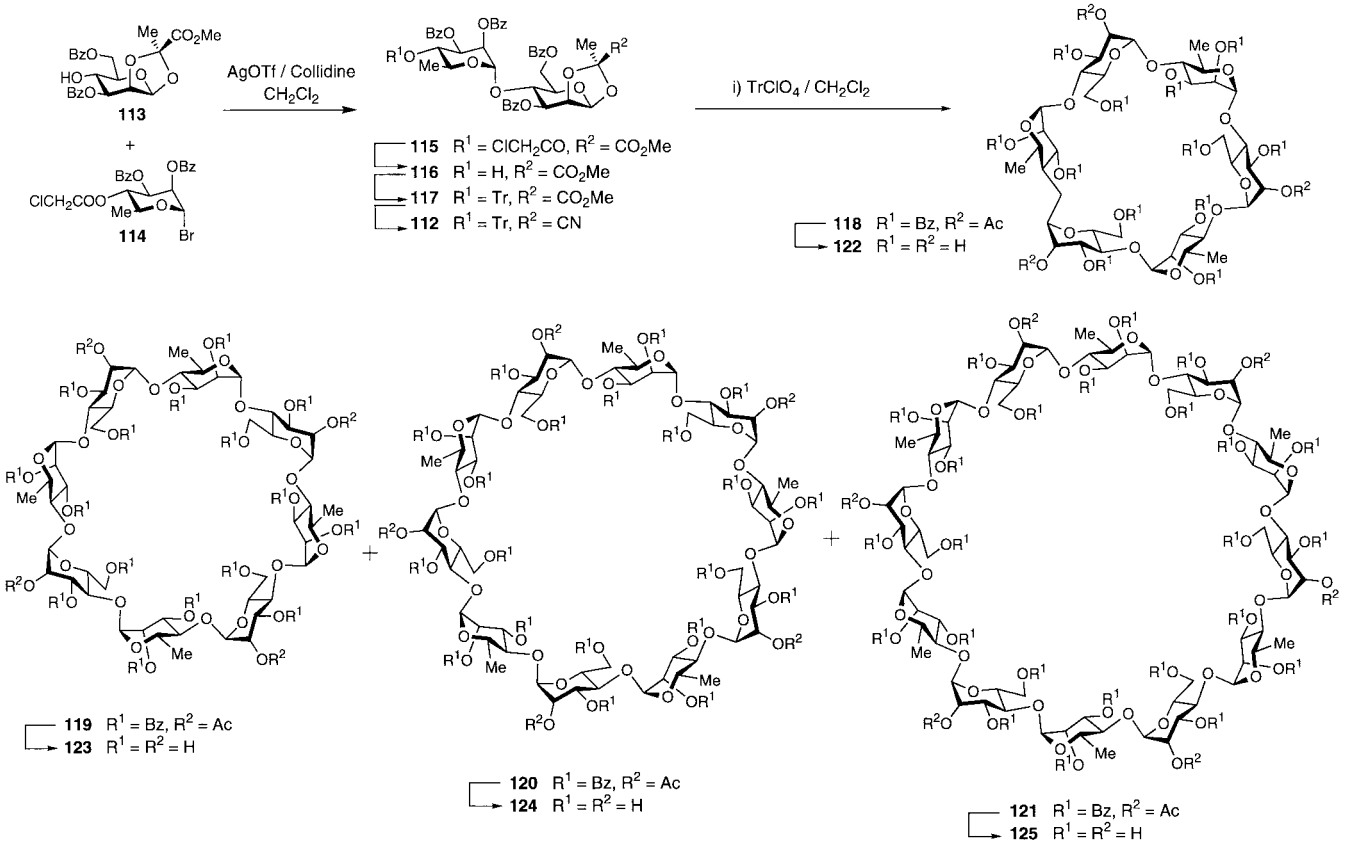


Figure 30. Synthesis of cyclo[4)-α-L-Rha*p*-(1→4)-α-D-Man*p*-(1→]$_n$, where n = 3, 4, 5, and 6.

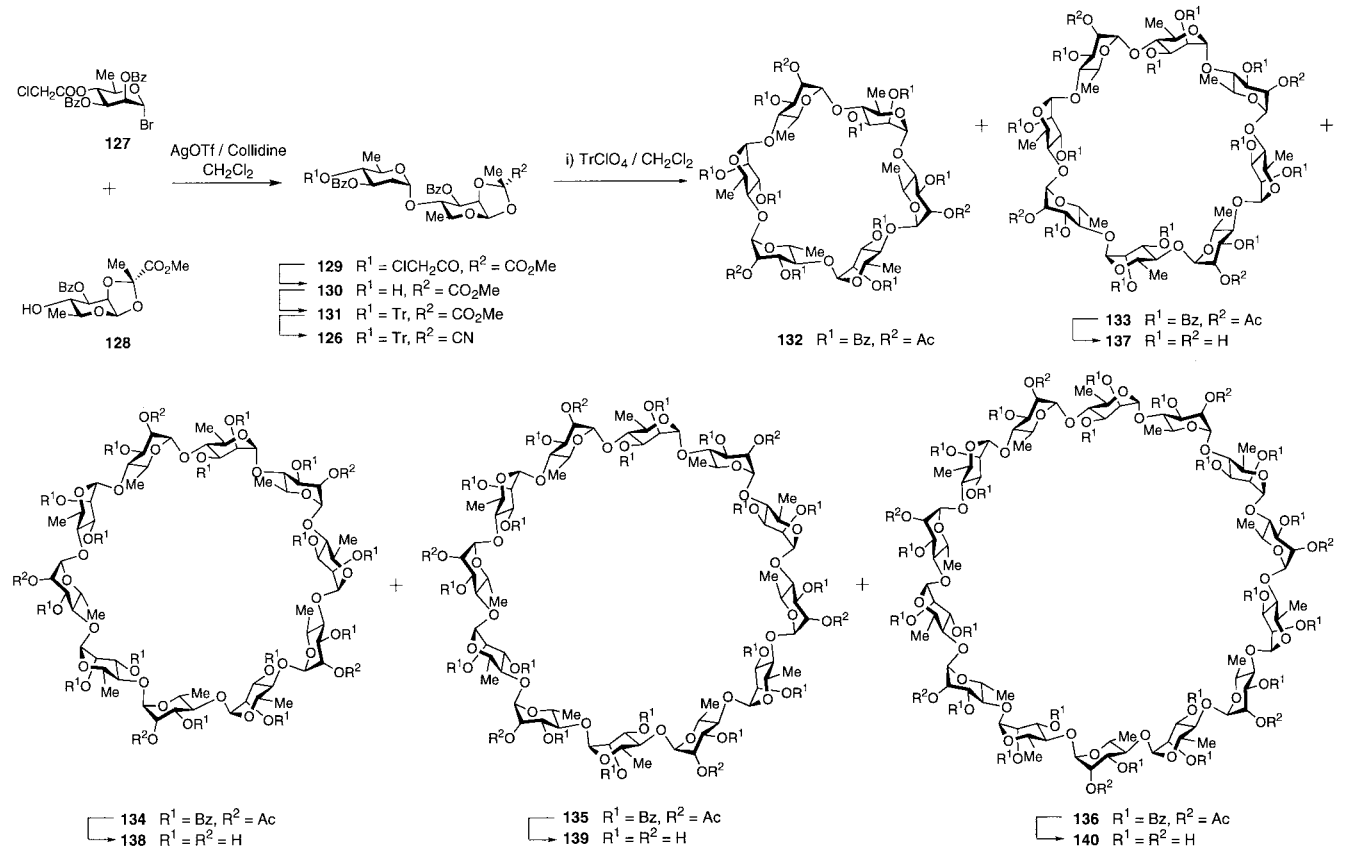


Figure 31. Synthesis of cyclo[4)-α-D-Rha*p*-(1→4)-α-L-Rha*p*-(1→]$_n$, where n = 3−7.

by glycosylation of the methoxycarbonyl derivative **113** with the L-mannosyl bromide **143**. The disaccharide **142** was dechloroacetylated to yield **144**, tritylated to give **145** and then subjected to subsequent treatment with ammonia and BzCl to perform the conversion of the methoxycarbonyl group into a

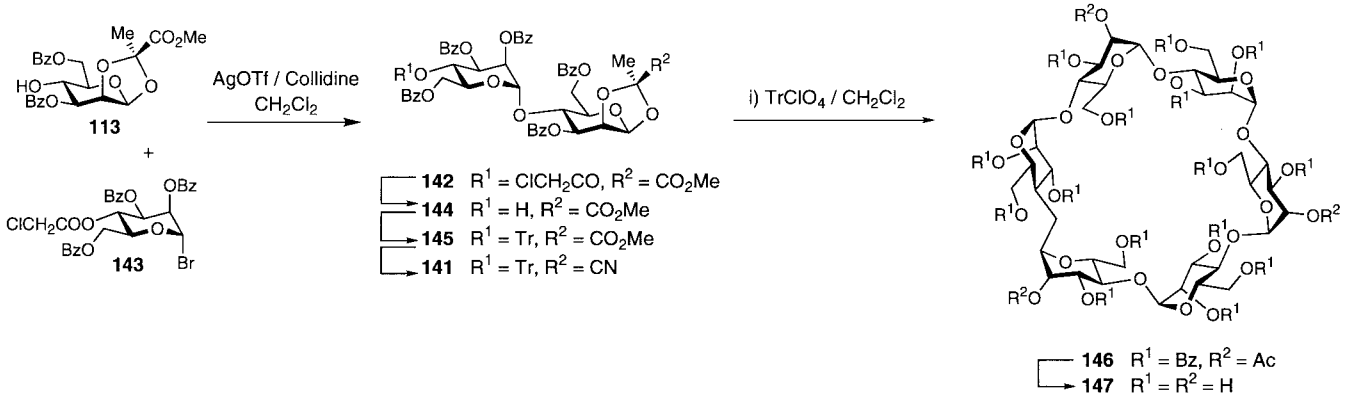
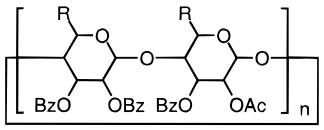


Figure 32. Synthesis of cyclo[4)-α-L-Man*p*-(1→4)-α-D-Man*p*-(1→]$_3$ (**147**).

Table 3. Yields of Cyclic Oligosaccharides in Polycondensation−Cycloglycosylation Reactions of the Disaccharide Monomers 112, 126, and 141



disaccharide monomer	no. of disaccharide repeating units (*n*) in a cyclic oligosaccharide				
	3	4	5	6	7
126	**118** (34%)	**119** (31%)			
112	**132** (14%)	**133** (17%)	**134** (15%)	**135** (10%)	**136** (7.5%)
141	**146** (9%)				

cyano group, leading to the target precursor **141**. The crucial macrocyclization—carried out under the same conditions described for the two previous cases—afforded a number of products from which only one, namely, the cyclic hexasaccharide **146** (9%), was identified as a cyclic oligosaccharide, and gave, after the deprotection, the free cyclic product **147**.

The three similar disaccharide monomers **112**, **126**, and **141**, which have been investigated as precursors of cyclic D/L-alternating oligosaccharides, while showing absolute stereoselectivity in the formation of glycosidic linkages, presented different reactivities during the formation of macrocyclic systems. The D/L-mannose-based monomer **141** exhibited the lowest ability to form cyclic oligosaccharides, whereas the disaccharide monomers **112** and **126**, bearing rhamnose residues at the "nonreducing" end, produced (Table 3) mixtures of cyclic oligosaccharides very efficiently.

The distinctive feature of the cyclic oligosaccharides described in this section is the absence of the so-called primary and secondary faces as they are defined in the case of the CDs. The secondary hydroxyl groups in the D/L alternating cyclic oligosaccharides are located at both rims of cylindrically shaped molecules. Furthermore, these rims have an enantiotopic relationship in cyclic D/L-rhamno- and D/L-manno-oligosaccharides, whereas the molecules themselves are achiral. For a number of these synthetic D/L cyclic oligosaccharides, single crystals suitable for X-ray analysis were produced and the solid-state structures of compounds **123**,[80] **137**,[81] **138**,[81] and **147**[83] were solved. In all cases, the crystallographic analyses revealed the presence of doughnut-shaped structures (Figure 33) formed by the symmetrically arranged disaccharide repeating units. The crystallographic symmetry of the octasaccharide **123** is C_4, i.e., the same as its molecular symmetry. In contrast, molecules of **137**, **138**, and **147** are slightly deformed in the solid state, leading to a departure from ideal S_n symmetry. As a result, compound **137** exhibits C_2 crystallographic symmetry instead of the ideal S_6 symmetry, and compounds **138** and **147** show C_i crystallographic symmetry instead of the higher S_{10} and S_6 symmetries, respectively. Although crystals of **123** and **147** contain two crystallographically independent molecules, the conformational differences are very small.

The monosaccharide residues of cyclic oligosaccharides **123**, **137**, **138**, and **147** adopt normal chair conformations ($^1C_4$ for D-residues and $^4C_1$ for L-residues) and their deviations from orthogonal positions with respect to the mean planes of the macrocycles are relatively small. As a result, all these cyclic oligosaccharides have cylindrical shapes and well-defined internal cavities with intraannular diameters equal to 11 Å (**123**), 8 Å (**137**), 10 Å (**138**), and 13 Å (**147**), respectively. Inspection of the packing of these cylindrical molecules in the crystal lattice shows that the smallest member of the family—compound **147**—is arranged in a parquet-like superstructure (Figure 34), whereas the cyclic octasaccharides **123** and **137** and cyclic decasaccharide **147** form infinite stacks, creating nanotube-like arrangements. The molecules of cyclic octasaccharides **123** and **137** within each stack are perfectly in register with each other (Figure 35), thus forming large open channels within which some water molecules are located. Adjacent stacks of **123** and **137** are arranged (Figure 36) in closed packed square and hexagonal arrays, respectively.

In the case of the cyclic decasaccharide **138**, the slightly sheared nanotubes (Figure 37) are formed by the two alternating crystallographically independent molecules which have different sequences of glycosidic bonds in a cyclic sense. The packing of the stacks (Figure 38) is hexagonal as in the case of **137**.

F. $2^I,2^{II}$-Dideoxy-$2^I,2^{II}$-diiodo-α-cyclodextrin

Sakairi and Kuzuhara[84] have introduced another example of the application of the cyclooligomerization approach to the synthesis of the cyclic oligosaccha-

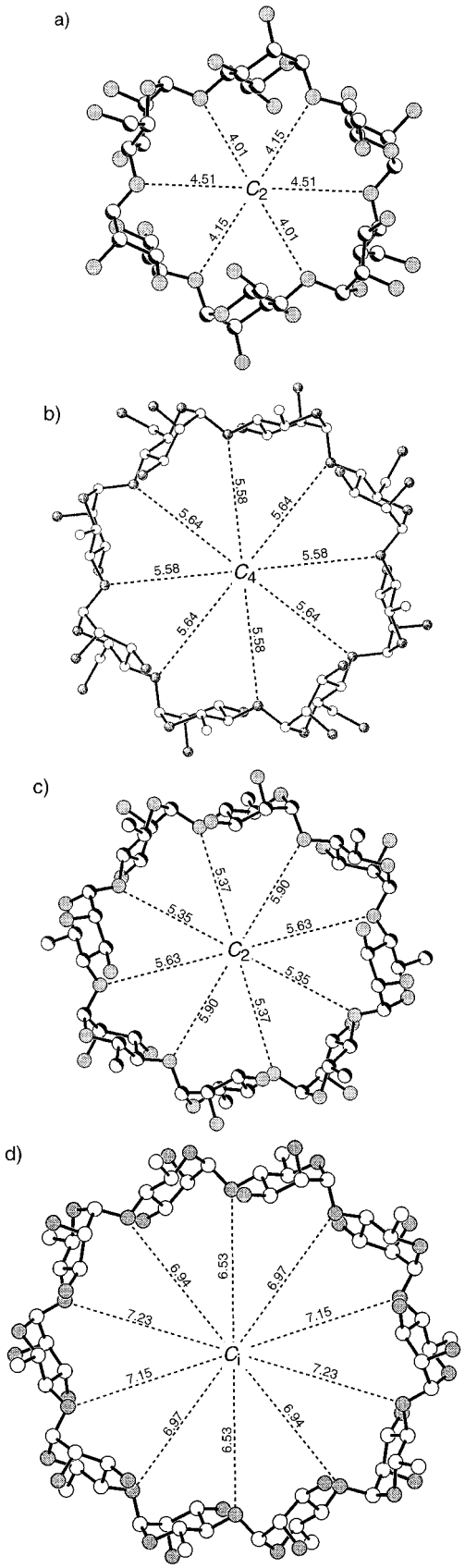


Figure 33. Ball-and-stick representation of the solid-state structures of the cyclohexaoside **147** (a), the cyclooctaoside **123** (b), the cyclooctaoside **137** (c), and the cyclodecaoside **138** (d) with indications of some structural parameters (in Å). For compounds **123** and **147**, two crystallographically independent molecules were identified in the unit cells in each case but the differences in the structures are very small.

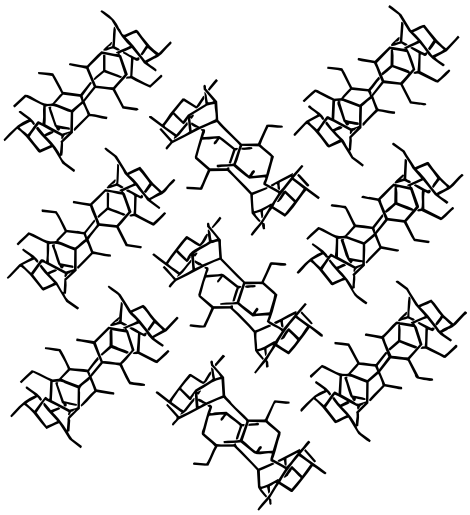


Figure 34. Packing of molecules of **147** in the solid state.

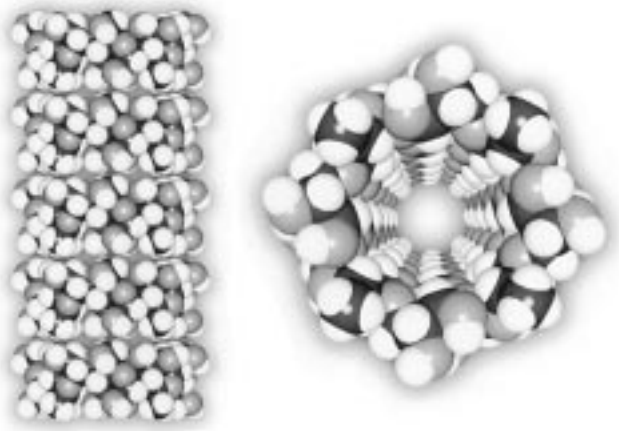


Figure 35. The discrete stacks of **123** in the solid state, shown with a space-filling representation: a side-on view of a stack (left) and a view looking down one of the stacks (right). Molecules of **138** form very similar stacks so that the view from the side of the rim bearing C-6 of rhamnose is identical to the view shown on the right of the figure.

rides. They synthesized (Figure 39) an epimer of a methylated α-cyclodextrin—compound **148**—bearing two 2-deoxy-2-iodo-α-D-mannopyranose residues situated at opposite positions, by dimerization/cycloglycosylation of the 1,2-unsaturated maltotriosyl glycal derivative **149**, which was, in turn, prepared from the known peracetylated phenylthiomaltotrioside **150**. After deacetylation, compound **150** was 4″,6″-*O*-benzylidenated and the remaining hydroxyl groups were methylated to give **151**. Reductive opening of the benzylidene ring afforded a derivative with a free hydroxyl group in the 6″-position, which was methylated to give compound **152**. Transformation of **152** into the glycal **149** occurs under the action of lithium naphthalenide which induces both the elimination of thiophenol and *O*-debenzylation. The final cycloglycosylation was catalyzed by iodonium di-*sym*-collidine perchlorate (IDCP), yielding 33% of the permethylated cyclohexasaccharide **148**.

G. Insertion of One Heterogeneous Saccharide Residue into the Cyclodextrin Framework

Modifications of single glucopyranose residues in the parent CDs are quite a common, but not trivial,

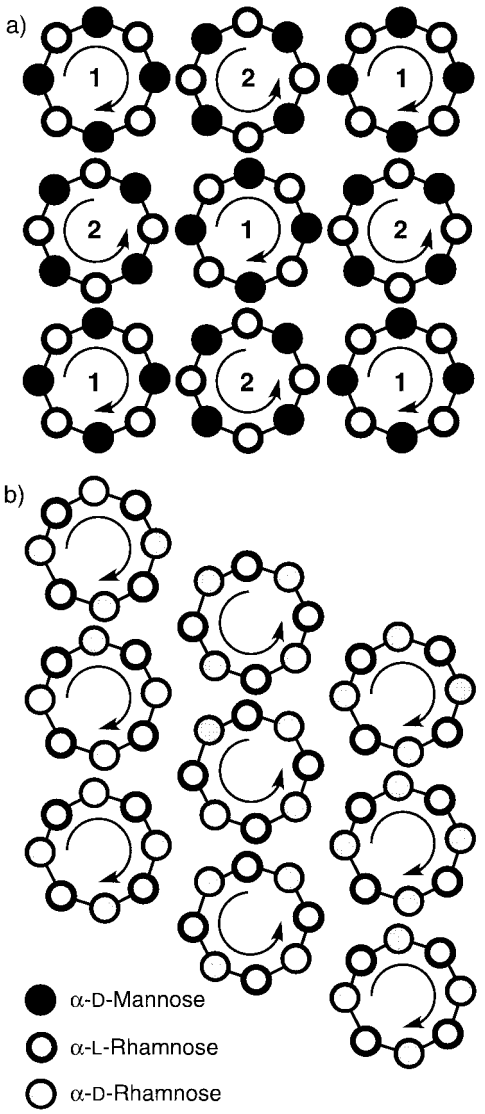


Figure 36. Schematic representation of the two-dimensional arrangement of molecules of **123** (a) and **137** (b) in the solid state. Monosaccharide residues are shown as disks with the arrows indicating the directionality of the glycosidic (C-1−O−C-4) bonds. The rings with clockwise and anticlockwise sequence of glycosidic bonds (a) correspond to the two crystallographically independent molecules 1 and 2 of **123**.

task in CD chemistry.[22,29] Cases in which modifications affect the configuration of the monosaccharide incorporated into the CD macrocycle are rather limited. For example, a series of mono-altro-α-CDs containing different substituents at C-3 can be prepared via the nucleophilic opening of the epoxy ring in the so-called 2,3-anhydro-α-CD.[85] An alternative synthetic methodology (Figure 9), which involves the fission of the cyclodextrin ring, elongation of the resulting linear oligosaccharide and then cyclization of this extended derivative to afford a new cyclic oligosaccharide, was developed by Kuzuhara et al.[86−88] This approach has been employed for the synthesis of cyclodextrin analogues containing one different monosaccharide residue, such as compound **153**, which contains an α-D-glucosamine residue along with six α-D-glucopyranose residues. It was prepared[86] from the per-*O*-acetyl-α-CD **154** (Figure 40). Under acetolysis conditions (Ac_2O/H_2SO_4), one glu-

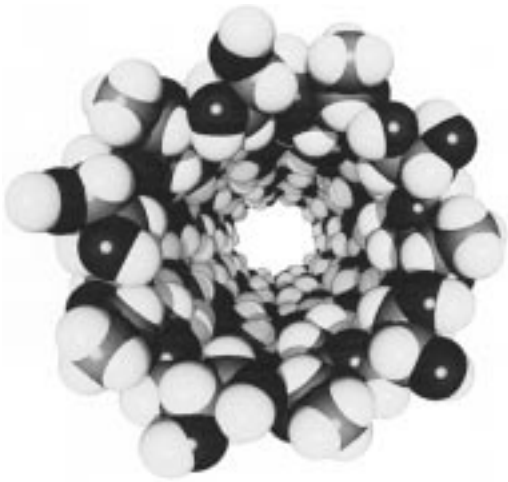


Figure 37. An infinite channel formed by stacked molecules of cyclic decasaccharide **138** in the solid state.

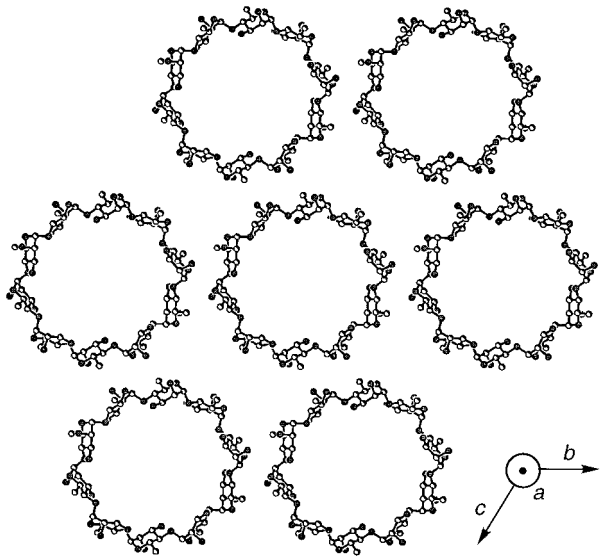


Figure 38. The two-dimensional arrangement of molecules of **138** in the solid-state structure.

cosidic bond of **154** can be cleaved with high selectivity to produce the linear peracetylated maltohexaose derivative **155**, which can then be transformed in three steps into the thioglycoside **156**. Removal of the acetyl groups was followed by *O*-benzylidenation and exhaustive benzylation. Reductive opening of the benzylidene acetal ring gave the alcohol **157**, which was coupled with the trichloroacetimidate **158**, affording the heptasaccharide **159**. After the removal of the *p*-methoxybenzyl group, the resulting compound was subjected to MeOTf-promoted cycloglycosylation to afford a protected product in 41% yield. Removal of the protecting groups gave the cyclic oligosaccharide, cyclo{4)-[α-D-Glc*p*-(1→4)]$_6$-α-D-Glc*p*-NH_2-(1→} (**153**) in a quantitative yield.

The same methodology, that was used for the insertion of an additional residue into the CD skeleton, can also be employed in the monofunctionalization of cyclodextrins, without modifying their ring size. This goal can be achieved through the opening/recyclization of a CD ring, a process which is accompanied by the alteration of a single functionality. According to this strategy, the monoiodinated cyclic

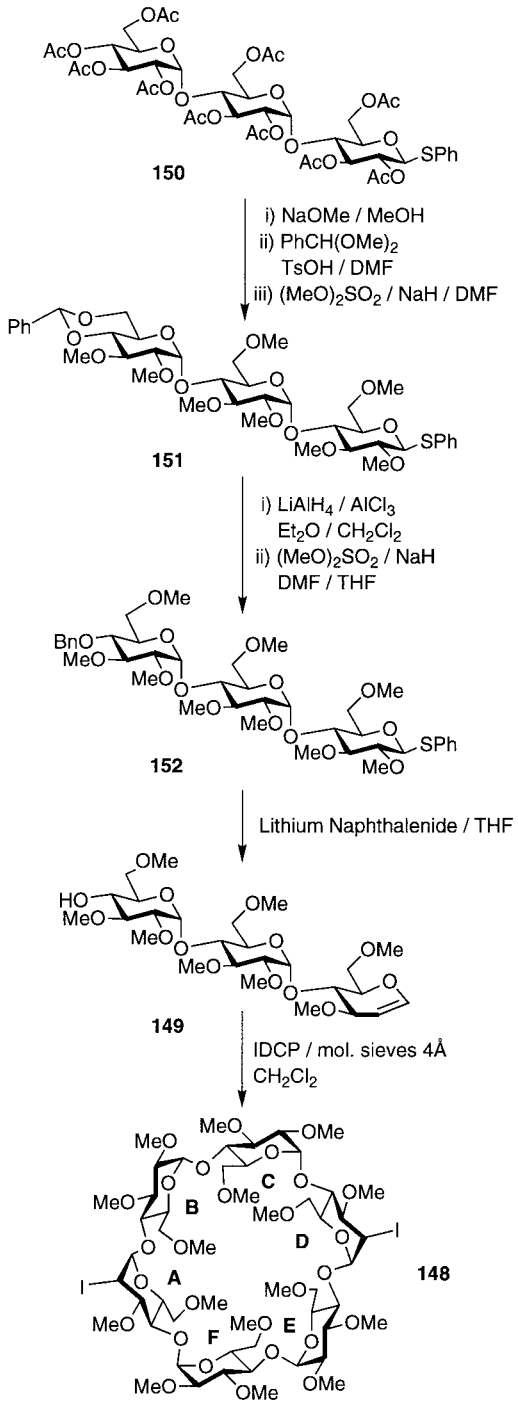


Figure 39. Preparation of the methylated cyclo{4)-[α-D-Glc*p*-(1→4)]$_2$-2-deoxy-2-iodo-α-D-Man*p*-(1→}$_2$ derivative **148**.

oligosaccharides **160** and **161** (Figure 41) were synthesized[87] starting, respectively, from the perbenzylated thioglucohexaoside[86] **157**, and its heptaoside analogue **162**, prepared in a similar manner from the *β*-CD peracetate. The thioglycosides **157** and **162** were converted initially into the glycals **163** and **164**, respectively, by the same procedure as that described for the synthesis of the maltotriose glycal **149** (see Figure 39). The cycloglycosylation of glycals **163** and **164** was initiated by iodonium ion addition, leading to compounds **160** and **161** in 48% and 25% yield, respectively. The overall yields of **160** and **161** from α-CD and *β*-CD were relatively low on account of the multistep reaction sequences, but it seems that there is no alternative method for the preparation of CD derivatives. Removal of the benzyl groups from **160** and **161** by catalytic hydrogenolysis was accompanied by reduction, affording the mono(2-deoxy)-α-CD **165** and the mono(2-deoxy)-*β*-CD **166**, respectively.

The syntheses (Figure 42) of compounds **167** and **168**, the methylated analogues of the monoiodo compounds **160** and **161**, as well as the higher homologue **169** have also been reported.[88] Again, oligosaccharide glycals were employed as the linear precursors in the cycloglycosylation processes. However, in these syntheses, the authors described a different method for the fission of the CD rings, involving thiolysis of the methylated CDs **170**−**172** with the Me_3SiSPh/ZnI_2 reagent system. This treatment led to the protected phenyl thioglycosides with silylated terminal 4-OH groups which, for purification purposes, were replaced with benzoyl groups. Treatment of the resulting phenyl thioglycosides **173**−**175** with lithium naphthalenide induced glycal formation, along with concomitant debenzoylation, to give **176**−**178**. The cycloglycosylation of the derivatives **176**−**178** in the presence of a range of iodonium ion generators (NIS, IDCP, $BnMe_3NCl_2I$) afforded the permethylated compounds **167**−**169** containing one 2-deoxy-2-iodo-α-D-mannopyranose inserted into the skeletons of the permethylated CDs. The yields obtained in the cyclizations and the promoters employed in the reactions are summarized in Table 4.

Although the methodology presented in this section is quite efficient, its application has so far been limited to the syntheses of CD derivatives bearing one different monosaccharide residue only. It would not be unreasonable to speculate that the insertion of heterogeneous di- or trisaccharide units into the CD rings might also be possible. Although no oligomerization was observed during cyclization, it would be interesting to test this strategy against the preparation of higher members of the CD family. This goal could be achieved simply through the dimerization of an oligosaccharide like **157**, followed by cycloglycosylation.

V. β-(1→3)-Linked Cycloglucopyranooligosaccharides

In 1990, Collins et al.[89] reported the synthesis (Figure 43) of the cyclic hexasaccharide **179**, composed of *β*-(1→3)-linked 4,6-*O*-ethylidene-D-glucopyranose residues. The synthetic strategy employed involves the preparation and then cycloglycosylation of the glucohexaosyl bromide **180**.

For the final cycloglycosylation, as well as for the construction of the linear oligosaccharide precursor **180**, glycosyl bromides were used as glycosylating agents. This choice was motivated by the possibility of applying a smooth and efficient method[90] for glycosyl bromide generation, involving the photolytic brominolysis of 1,2-*O*-benzylidene glycoses with $BrCCl_3$. Notably, the presence of unprotected hydroxyl groups does not interfere with the formation of the bromide. The growth of the oligosaccharide chain was carried out, in this case, at its "reducing" end. The initial discrimination of the 3-OH group was achieved by double acetylation of glucose, af-

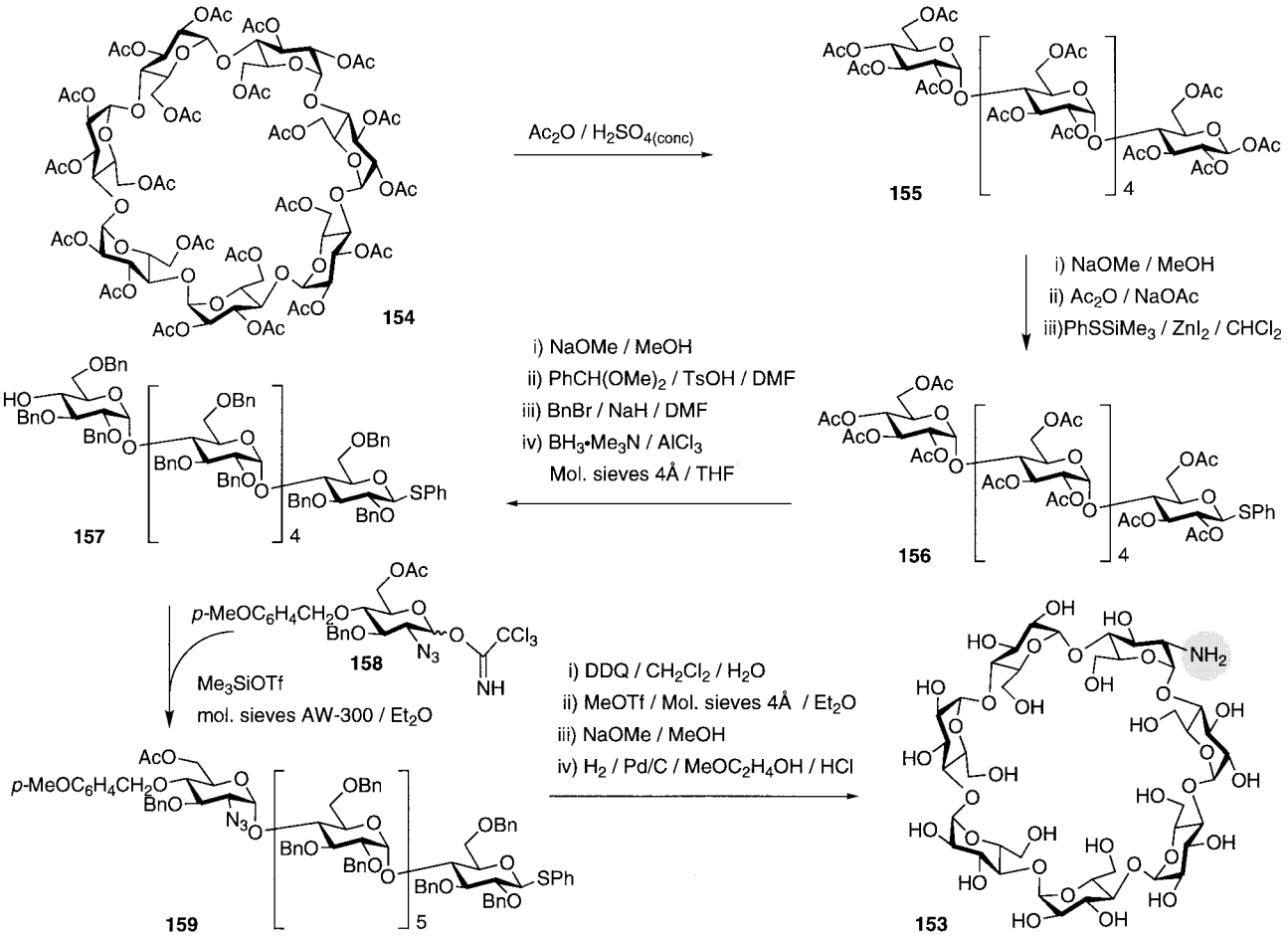


Figure 40. Synthesis of the β-CD derivative **153** incorporating an α-D-glucosamine residue.

fording compound **181**. The 3-chloroacetate derived from **181** was transformed into the glycosyl donor **182** via a photobromination procedure and coupled with the alcohol **181** in the presence of AgOTf to give the disaccharide **183** in 84% yield. From this disaccharide, both the glycosyl bromide **184**—by photobromination—and the glycosyl acceptor **185**—by dechloroacetylation—were derived. The AgOTf-promoted condensation of **184** and **185** afforded a tetrasaccharide derivative which, after photobromination, gave the tetraglucosyl bromide **186** in 62% overall yield. Further elongation of the oligoglucosyl chain was achieved by the condensation of this bromide with the glycosyl acceptor **185**. The resulting hexasaccharide was obtained in 88% yield and converted into the precursor **180** in two steps, involving dechloroacetylation followed by photobromination. The crucial intramolecular glycosylation—performed in the presence of AgOTf—afforded the fully protected cyclic oligosaccharide **187** in 30% yield. Removal of the benzoates led to the target compound **179**.

An easier route to the cyclic hexasaccharide **179** would be through the cyclooligomerization of more readily available tri-, di-, or monosaccharide fragments of **179** bearing the same functionalities as the precursor **180**. Collins and Ali[91] have tested the feasibility of this approach (Figure 44) by carrying out the dimerization/macrocyclization of the hydroxy bromo trisaccharide **188** and they found that it is as successful as the cyclization of the hexasaccharide precursor **180**. However, when the tetrasaccharide analogue of **180**, namely compound **189**, was treated using the same cyclization conditions, no cyclic octasaccharide was detected. Instead, the cyclic tetrasaccharide **190** and the cyclic dodecasaccharide **191** were formed.

VI. Cyclic Oligosaccharides Constructed via the Formation of (1→6)-Glycopyranosidic Linkages

A. Cyclogentiobioside, -trioside, and -tetraoside Peracetates

An early example of small cyclic oligosaccharides synthesized from a disaccharide precursor was reported in 1976 by Gagnaire and Vignon.[92−94] These authors detected the formation of cyclic products in an experiment directed toward the preparation (Figure 45) of β-(1→6)-glucopyranan using the $Hg(CN)_2$/$HgBr_2$-promoted polycondensation of the glycosyl bromide **192**. Along with the target linear oligomer **193**, they isolated the cyclic disaccharide **194** (12%) and the cyclic tetrasaccharide **195** (6%), produced from the intramolecular glycosylation of **193** and its dimer, respectively.

To improve the efficiency of the synthesis of the cyclotetraoside **195**, an alternative strategy (Figure 46), which relies upon a linear tetrasaccharide precursor, was employed.[95,96] First, the peracetylated tetrasaccharide **196**, which bears a temporary trichloroacetyl protecting group at the 6-position of the "nonreducing" residue, was assembled. Activation of

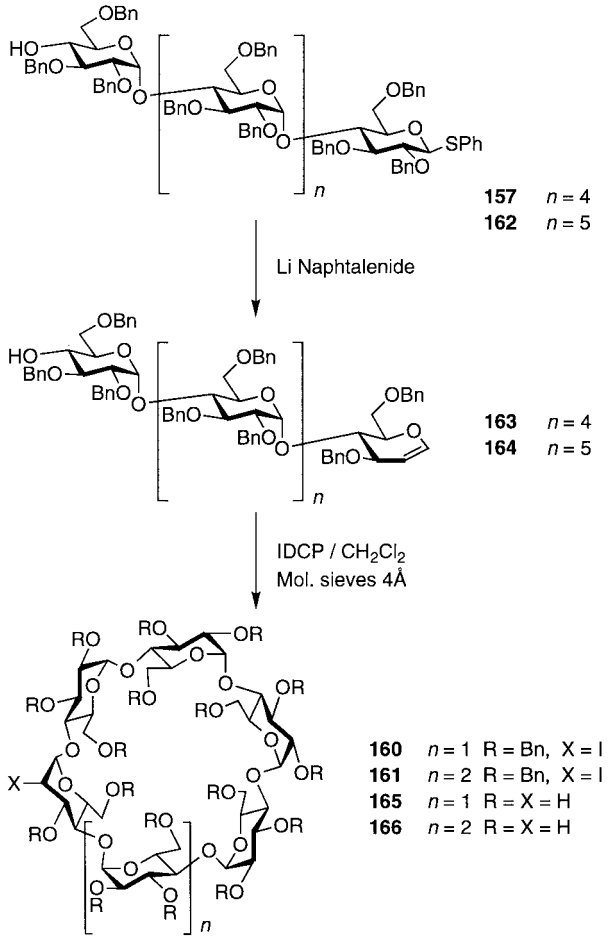


Figure 41. Synthesis of modified cyclodextrins **160** and **161** incorporating one different residue following ring opening/recyclization of the parent CDs.

the anomeric center in this compound was achieved by the action of $Cl_2CHOMe/BF_3{\cdot}OEt_2$, followed by deprotection of the glycosyl acceptor function by ammonolysis of the trichloroacetyl group to afford the tetraosyl chloride **197**. The macrocyclization of **197**, performed in the presence of $HgBr_2$ and 4 Å MS, led to the formation of **195** in 25% overall yield, starting from **196**.

The same methodology[95,96] as that used for the synthesis of **195** was employed (Figure 46) for the preparation of its smaller homologue—cyclogentiotrioside **198**. This cyclic oligosaccharide was obtained in 22% overall yield from the trisaccharide **199** via intramolecular glycosylation of the intermediate gentiotriosyl chloride **200**, which was prepared from **199** in two steps. The higher homologues of **195** and **198**, which could be expected as a result of the cyclooligomerization of the linear precursors **197** and **200**, were not reported. Compounds **194**, **195**, and **198** were not deprotected, but detailed data about the structure of **194** were obtained on the basis of X-ray crystallographic analysis[97] and molecular modeling.[98] It was shown that, in the solid state, the cyclic disaccharide **194** exists (Figure 47) in two crystallographically independent forms incorporating two pyranose rings either as boat or twist-boat conformations. Such deviations from the typical $^1C_4$ chair conformation for the glucopyranose rings is not surprising and results from the conformational con-

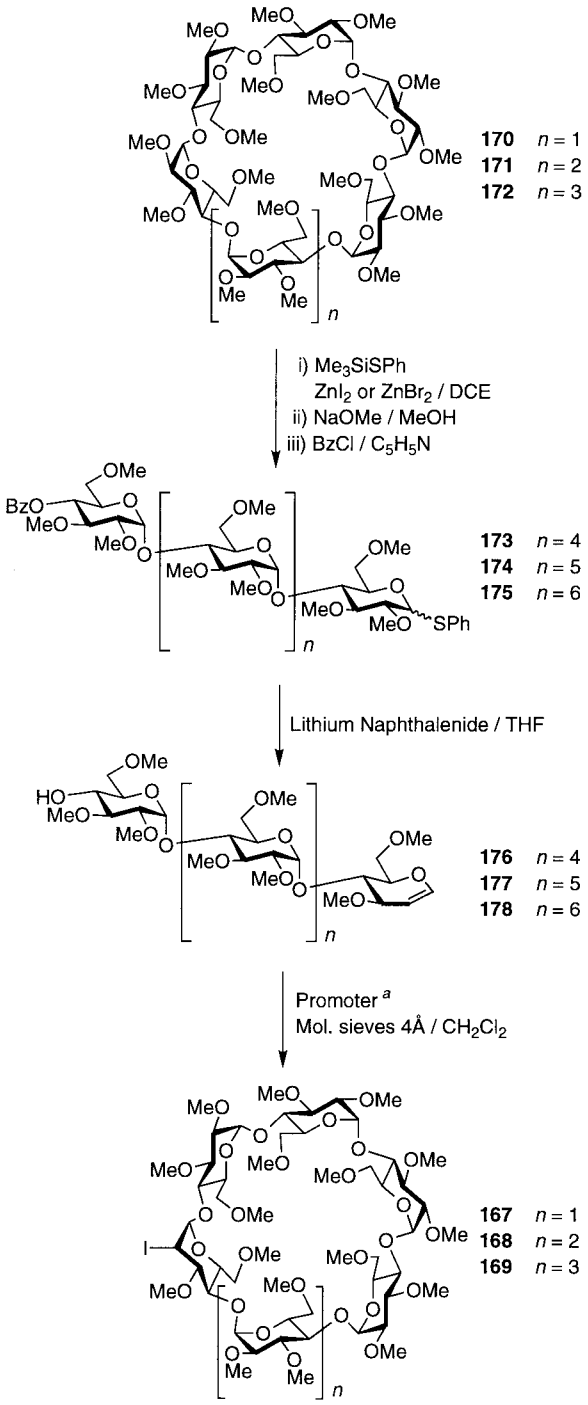


Figure 42. Synthesis of 2^I-deoxy-2^I-iodo-α-, β-, and γ-CD analogues **167**−**169**. [a] The promoters employed in the cyclization reactions are shown in Table 4.

strains arising from the formation of a 10-membered ring.

Conversely, ^1H NMR spectroscopic studies[53] on the cyclic trisaccharide **198** showed that all the glucopyranose residues adopt $^1C_4$ conformations. More detailed conformational studies[53] of **198** were performed by means of comparisons between calculated NOEs in its ^1H NMR spectrum and the observed values. It was revealed that, in solution, the cyclic trisaccharide **198** exists as an equimolar mixture of two low-energy conformations, both exhibiting 3-fold symmetry. In terms of the geometry of the (1→6)-glycosidic linkage, these conformations are described (Figure 48) as the

Table 4. Promoters Employed and Yields Obtained for the Cyclizations Leading to Compounds 160, 161, and 167−169

glycal	promoter	yield (%)
160	IDCP	48
161	IDCP	25
167	NIS[a]	13
167	IDCP[b]	39
167	$BnMe_3NCl_2I$	52
168	IDCP	25
168	$BnMe_3NCl_2I$	28
169	IDCP	11
169	$BnMe_3NCl_2I$	13

[a] NIS = *N*-iodo succinimide. [b] IDCP = iodonium di-*sym*-collidine perchlorate.

gg and *gt* models.

Compound **195** was shown to possess binding properties toward metal cations. The binding studies were performed using fast atom bombardment mass spectrometry[99] and ^{1}H NMR spectroscopy.[100]

B. Alternating Cyclic α-(1→4)-β-(1→6)-Glucooligosaccharides

As the formation of a β-(1→6)-glucosidic linkage is relatively easy, it may be anticipated that this property might be used in the intramolecular glycosylation of linear oligosaccharides comprised of different—not strictly (1→6)—glycosidic linkages. An example is the synthesis of the CD isomer **30**.[62] Another example was reported by Driguez and Utille,[101] who described the preparation (Figure 49) of a series of cyclic compounds **201**−**203** composed of β-(1→6)-linked maltose repeating units. The synthesis was performed by employing the cyclooligomerization approach, starting from a 5:7 mixture of the disaccharide precursors **204** and **205**, which differ only in the presence of a TrO group on the 6-position in **205**, as opposed to the hydroxyl group present in **204**. The reason for this combination is not clear, but treatment of the mixture of **204** and **205** with $SnCl_4$, afforded the cyclic hexa- (**201**), octa- (**202**), and deca- (**203**) saccharides in 30%, 40%, and 20% yields, respectively. When the same reaction was carried out on the trityl ether **205** alone, linear oligomers were formed predominantly, along with cyclic oligosacharides (20−30%). Recently, Driguez et al.[102] reported the application of the same cyclization methodology (Figure 49) to the preparation of 4′-thio analogues of compounds **201** and **202**—the cyclic hexa- and octasaccharides **206** and **207**. They were obtained as a result of the cyclooligomerization of compounds **208** and **209** in 23% and 7% yields, respectively.

C. Cycloisomalto-trioside, -tetraoside, and -hexaoside

Almost two decades elapsed between the first communication[92] on the formation of cyclic β-(1→6)-glucooligosaccharides and the announcement of the preparation of their analogues with α-(1→6) glucosidic bonds, by Houdier and Vottéro[103] in 1993. The cyclic tetrasaccharide **210** was formed (Figure 50) in 40% yield, as the result of a reaction employing the

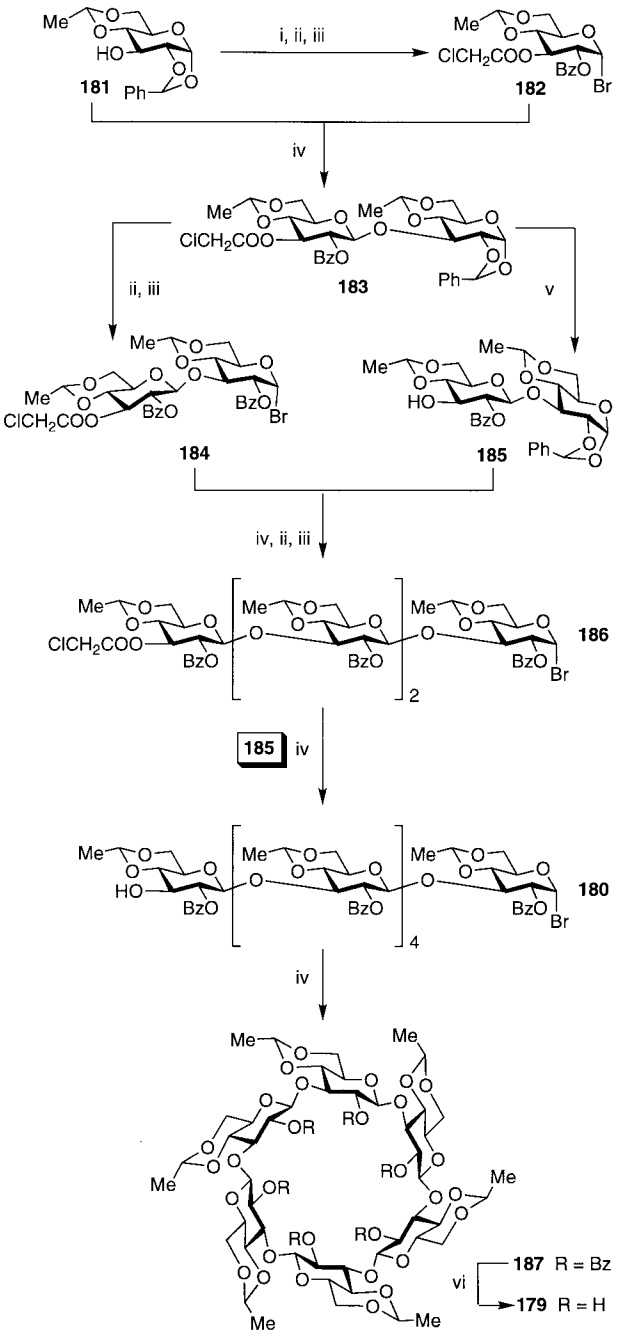


Figure 43. Synthesis of per-4,6-*O*-ethylidene-cyclo{3)-β-D-Glc*p*-(1→}$_6$ (**179**). Reactions or reagents: (i) chloroacetylation, (ii) *hν*/$BrCCl_3$/CCl_4, (iii) Bu_4NBr/CCl_4, (iv) AgOTf/CH_2Cl_2, (v) dechloroacetylation, (vi) Zemplen deacylation.

disaccharide derivative **211** as precursor and a modified Mukaiyama's[104] glycosylation procedure (1-acetates as glycosyl donor in the presence of Lewis acids, whereas the usual Me_3Si group was replaced with a Tr group as the glycosyl acceptor function) for the cyclization step.

When the benzylated triglucoside **212**,[105] bearing an *n*-pentenyl aglycon as the leaving group, was subjected to cyclization using Fraser-Reid's glycosylation conditions,[33,106] the cyclic trisaccharide **213** was produced (Figure 51) in 47% yield. However, the stereoselectivity of the cycloglycosylation was not high and an isomer of **213** incorporating one undesired β-glucosidic linkage—namely the trisaccharide **214**—was isolated from the reaction mixture in 24%

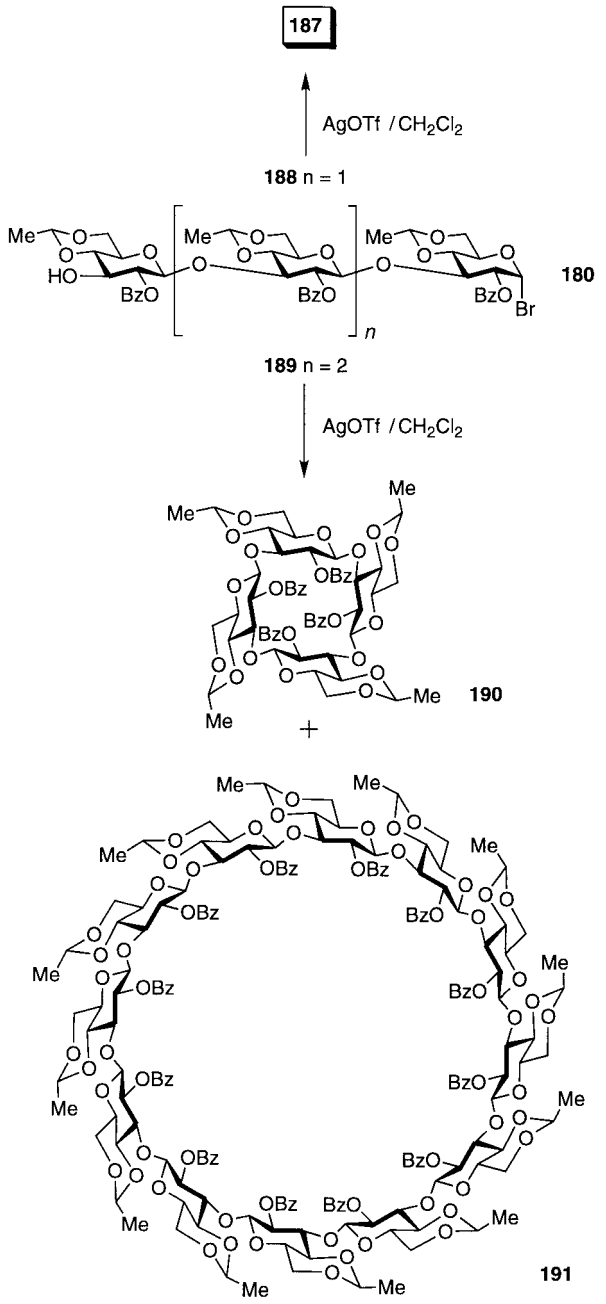


Figure 44. Cyclization of the trisaccharide **180** and tetrasaccharide **181** leading to a series of protected cyclo-{3)-β-D-Glc*p*-(1→}$_n$, derivatives **187** (n = 6), **190** (n = 4), and **191** (n = 12).

yield. The product of the dimerization−cyclization—the cyclic hexasaccharide **215**—was also formed but only in a modest yield of 10%. This result, as well as the absence of cyclic hexasaccharides in the reaction mixture derived from **211**, showed that the relatively small isomaltooligosaccharide precursors are prone to intramolecular cyclization. Therefore, attempts at preparing larger homologues should start from the synthesis of longer linear precursors that, like **211** and **212**, appear to be accessible targets.

The protecting groups were not removed from the cyclic oligosaccharides **210** and **213**−**215**, which were characterized as their benzylated derivatives. For the tetrasaccharide **210**, low-temperature NMR spectroscopic studies revealed[107] the existence of two equally populated symmetrical conformations emerging as a result of different values for the dihedral angles ω, ϕ, and φ around C-1−O-6−C-6 linkages.

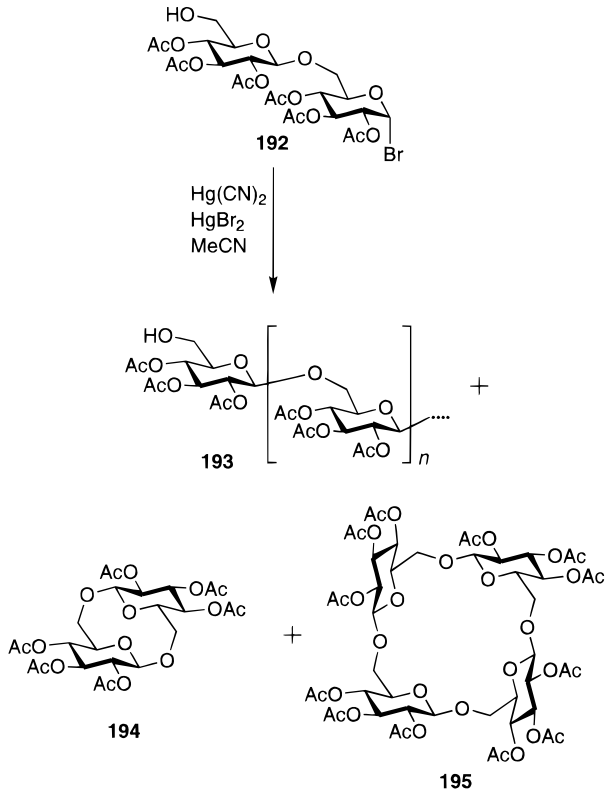


Figure 45. Preparation of the β-(1→6)-linked cyclic disaccharide **194** and cyclic tetrasaccharide **195**.

VII. Cyclic β-D-Galactofuranooligosaccharides

The first observation of the formation of cyclic oligosaccharides composed of glycofuranose residues was made by Kochetkov and co-workers[108] during investigations on the polycondensation of tritylcyanoethylidene derivatives **216** and **217** of galactofuranose. For many years, the tritylcyanoethylidene condensation had been recognized as an efficient method for the creation of synthetic polysaccharides,[82] but no traces of cyclic compounds were detected before the experiments with the furanoid monomers. It turns out that all three isomeric trityl ethers of the 1,2-*O*-(1-cyano)ethylidene derivatives of α-D-galactofuranose—namely compounds **216**,[108] **217**,[108] and **218**[109]—on treatment (Figures 52−54) with a cyanophilic initiator ($TrClO_4$ or AgOTf), can be transformed—depending on the extent of the dilution of the reaction mixture—either into linear galactofuranans (**219**, **220**, and **221**, respectively), or into mixtures of cyclic oligosaccharides. Thus, the monomer **216** was converted into a series of cyclic β-(1→6)-D-galactofuranooligosaccharides **222**−**225**, ranging from the dimer to the pentamer. Isomers of **216**, containing the glycosyl acceptor function at positions 3 and 5—compounds **217** and **218**, respectively—afforded only two cyclic oligosaccharides each. In the first case, these were the cyclic tetramer **226** and pentamer **227**, and in the second, the cyclic trimer **228** and tetramer **229**.

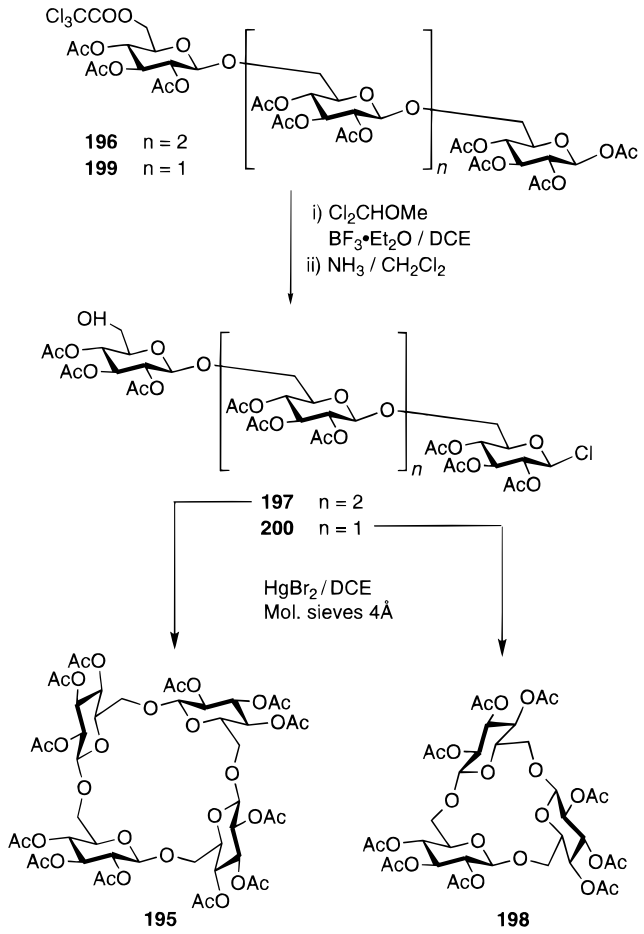


Figure 46. Preparation of the cyclic tetrasaccharide **195** and cyclic trisaccharide **198** by cyclization of the linear tetra- and trisaccharides **197** and **199**, respectively.

More detailed studies were carried out[110] on the (1→6)-linked systems. To achieve easier separation of products, as well as obtain larger cyclic compounds, the disaccharide derivative **230** (Figure 55) and the trisaccharide derivative **231** (Figure 56) were employed as "monomers" in the cyclooligomerization process. In the first case, from compound **230**, four products were formed which, after deprotection, were identified as the cyclic disaccharide **222** (21%), tetrasaccharide **224** (20.5%), hexasaccharide **232** (15.5%), and octasaccharide **233** (12%).

The trisaccharide **231** was successfully employed (Figure 56) for the production of another set of analogous cyclic oligosaccharides composed of three (**223**, 24%), six (**232**, 24%; this compound was identical to the hexasaccharide obtained from the disaccharide monomer **230**), and nine (**235**, 17%) galactofuranosyl residues. The higher reactivity of glycofuranosyl derivatives, in comparison with the analogous glycopyranosyl derivatives, in glycosylation reactions, is well-known.[111] This observation, together with the flexibility of the C-4−C-5−C-6 fragment in hexofuranoses, could explain the remarkable tendency of galactofuranose derivatives to form macrocyclic compounds as a result of intramolecular glycosylation under conditions of high dilution.

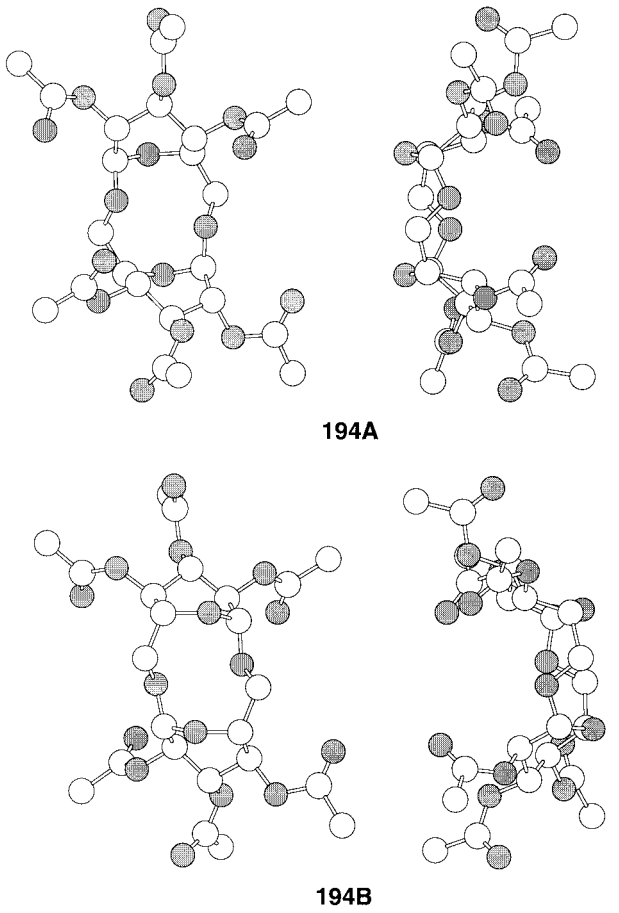


Figure 47. Solid-state X-ray crystal structure of cyclo{6)-β-D-Glc*p*-(1→}$_2$ (**194**): **194A** and **194B** represent the two independent crystallographic forms.

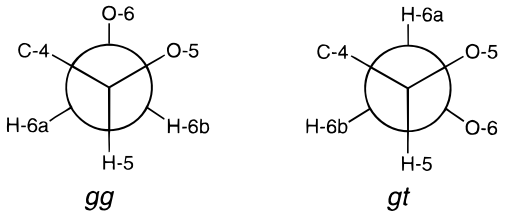


Figure 48. Newman projection of the most stable *gg* and *gt* conformers formed as a result of the rotation of the CH_2O group around the C-5−C-6 bond.

VIII. Chemoenzymatic and Enzymatic Synthesis of Cyclic Oligosaccharides

The industrial production of cyclodextrins is based on the enzymatic conversion of prehydrolyzed starch into a mixture of cyclic and acyclic oligomers. Indeed, a large number of publications[15,112] have been devoted to the investigation of this process. In recent years, the use of enzymes[55,108] has become one of the major activities in carbohydrate chemistry and, particularly, for the development of oligosaccharide synthesis. Not surprisingly, perhaps, some researchers have tried to approach the synthesis of cyclic oligosaccharides by employing enzymes. The limitation is, obviously, in the availability of enzymes capable of performing cycloglycosylations. The most suitable candidates for this role are the glycosidases—natural catalysts for the reversible cleavage of glycosidic

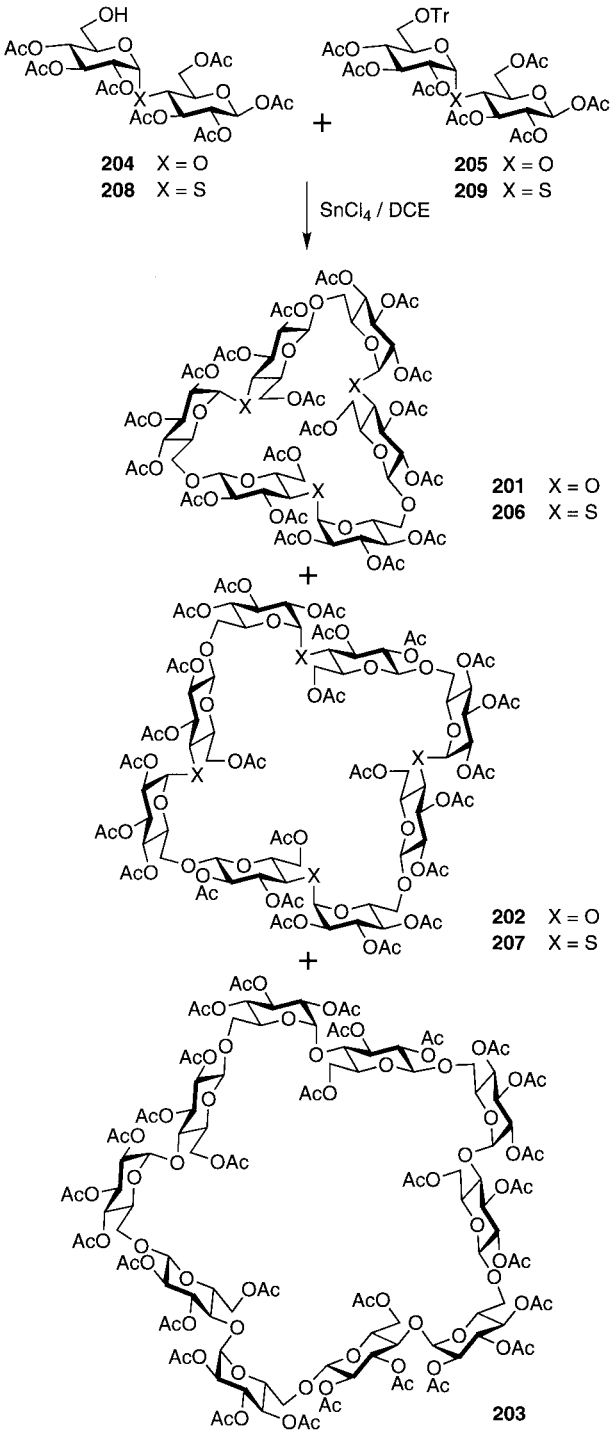


Figure 49. Synthesis of cyclo{6)-α-D-Glc*p*-(1→4)-*β*-D-Glc*p*-(1→}$_n$, **201** (n = 3), **202** (n = 4), and **203** (n = 5) and cyclo-{6)-α-D-Glc*p*-(1→4)-*β*-D-Glc*p*-S-(1→}$_n$, **206** (n = 3) and **207** (n = 4).

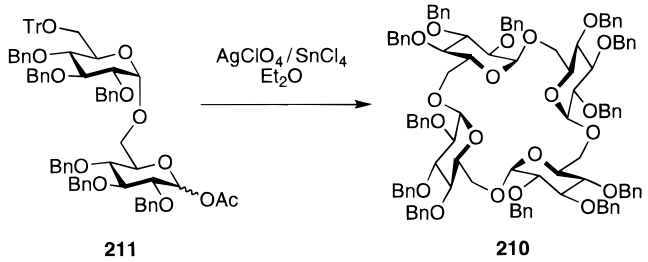


Figure 50. Formation of a cyclic glucotetraoside **210** from the cyclodimerization of the disaccharide derivative **211**.

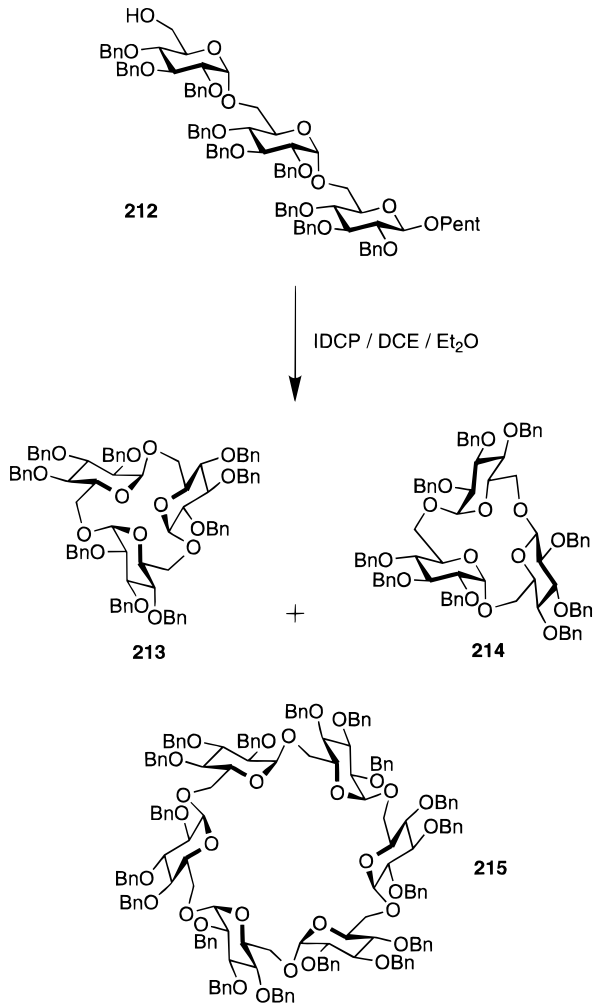


Figure 51. Cyclization products from the reaction of the trisaccharide **212**.

bonds—and the most appropriate substrates seem to be polysaccharides. In the case of the preparation of cyclodextrins,[114] the enzymatic function is performed by CGTases, which react with starch and other α-(1→4)-glucans. As many types of CGTases are readily accessible, the variation of the structure of possible substrates is one route to novel cyclic oligosaccharides, or, more precisely, modified cyclodextrins. Another approach to the enzymatic production of cyclic oligosaccharides involves a search for glycosidases which may act on particular polysaccharides, just as CGTases act on starch. The in vitro syntheses of cyclic oligosaccharides using glycosyl transferases—enzymes responsible for the biosynthesis of natural polysaccharides—is also possible, but so far only the preparation of a few types of cyclic glucans has been described (see Section VIII.C).

A. Applications of CGTases for the Preparation of Modified Cyclodextrins

An enzymatic entry to regioselectively substituted cyclodextrins was described[115] back in 1983 when α-maltosyl fluoride was demonstrated to be a suitable precursor for α-CD, *β*-CD, and *γ*-CD in reactions

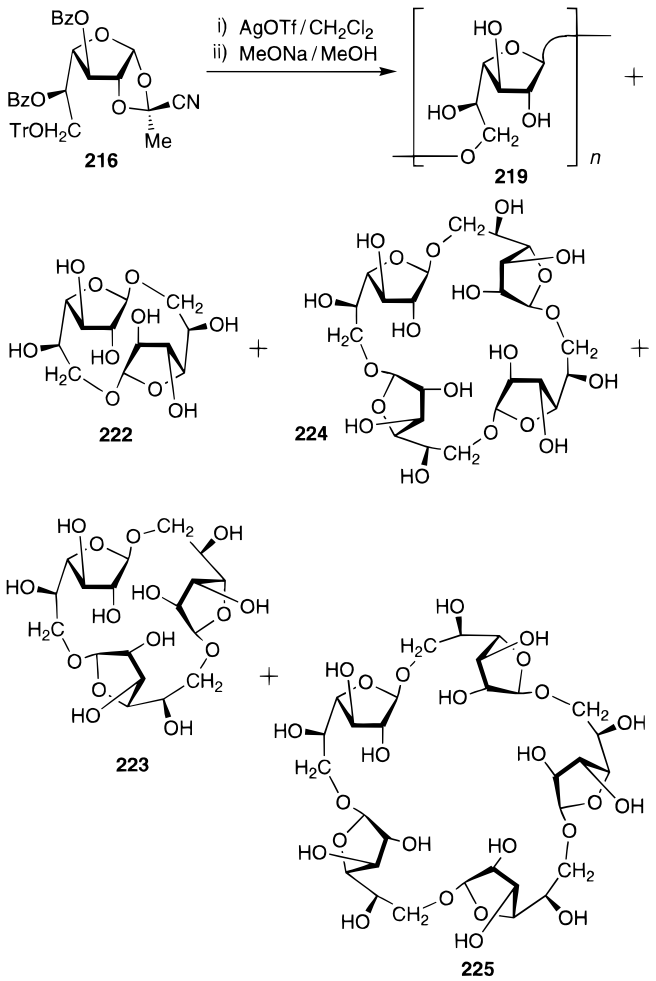


Figure 52. Synthesis of linear and cyclic (1→6)-β-D-galactofuranooligosaccharides.

catalyzed by CGTases. To investigate the possibility of employing this approach for the preparation of chemically modified cyclodextrins, Driguez and coworkers[116,117] tested a range of α-maltosyl fluoride derivatives bearing different substituents at the 6- or 6′-position. They found that 6-*O*-methylmaltosyl fluoride **235**, when incubated with CGTase, affords (Figure 57) $6^{I},6^{III},6^{V}$-tri-*O*-methyl-α-CD (**236**, 42%) and $6^{I},6^{III},6^{V},6^{VII}$-tetra-*O*-methyl-$\gamma$-CD (**237**,16%), which are the products of cyclotrimerization and cyclotetramerization, respectively. Furthermore, the formation of the $6^{I},6^{III},6^{V}$-tri-*O*-methyl-β-CD (**238**) was also observed, which implies that some disproportionations are taking place along with the condensations.

The synthetic utility of the chemoenzymatic methodology was also demonstrated by employing (Figure 58) the maltotriosyl fluoride **239**—which possesses a 6-deoxy-6-iodo group at the "nonreducing" end of the molecule—as a substrate for CGTase.[118] Under the same conditions exploited for the preparation of **236**—**238**, this substrate was converted into the C_2 symmetrical $6^{I},6^{IV}$-dideoxy-$6^{I},6^{II}$-diiodo-α-CD (**240**), which was isolated and characterized as its peracetate (**241**) in an overall yield of 38%. This compound contains two reactive iodo functions and could be used in further chemical modifications.

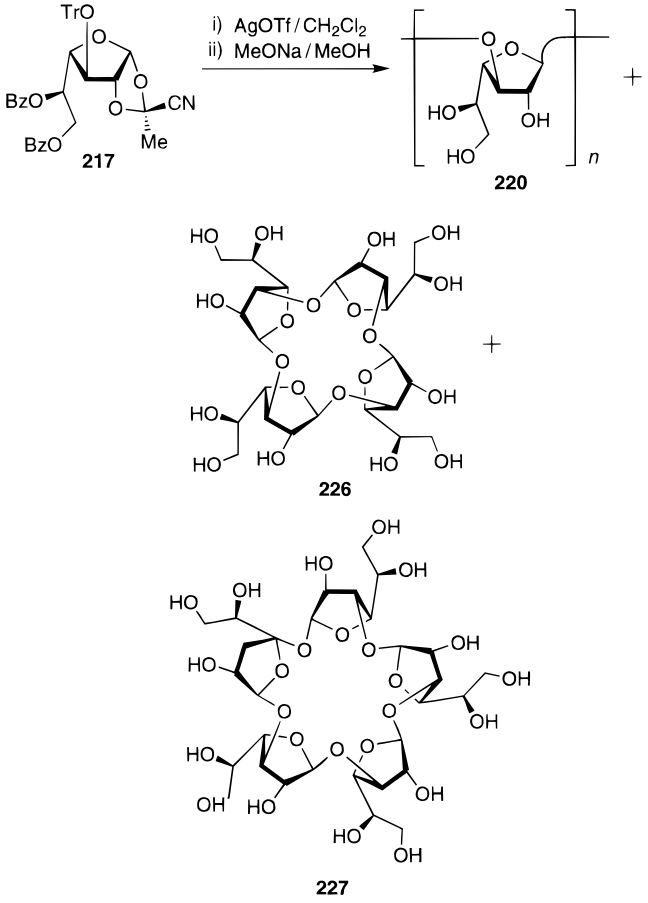


Figure 53. Synthesis of linear and cyclic (1→3)-β-D-galactofuranooligosaccharides.

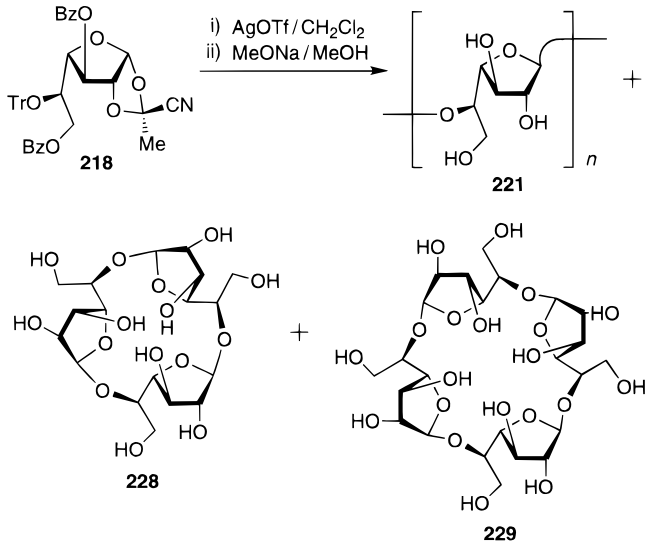


Figure 54. Synthesis of linear and cyclic (1→5)-β-D-galactofuranooligosaccharides.

Cyclodextrin analogues, in which some glycosidic oxygen atoms are replaced by sulfur atoms, have also been synthesized[119] by enzymatic methods. Treatment (Figure 59) of the 4-thiomaltosyl fluoride **242** with a CGTase, followed by hydrolysis of the linear products of the reaction with β-amylase, led, in 37% overall yield, to a series of cyclooligomerization products **243**—**245** composed of 8, 10, and 12 glucose residues. Notably, the ring size of unmodified cyclo-

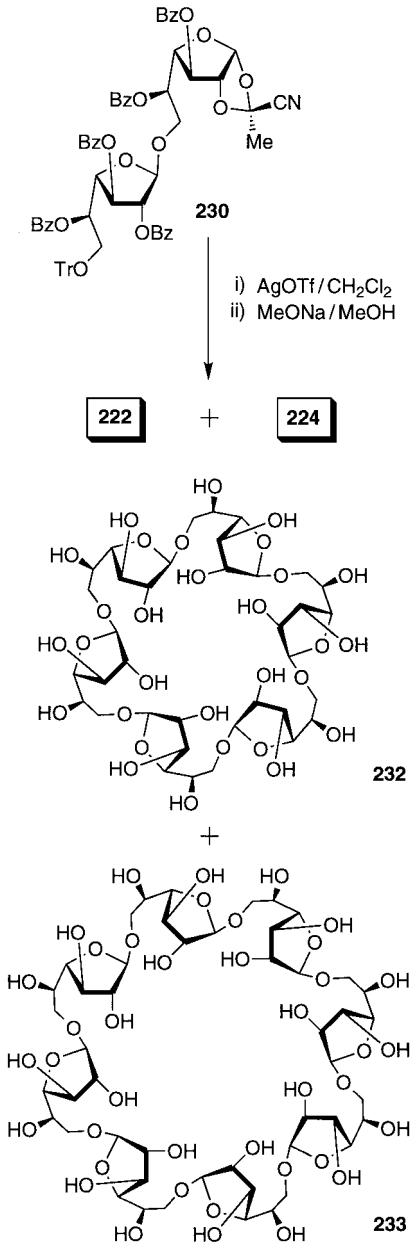


Figure 55. Cyclooligomerization of the galactofuranobiose derivative **230**.

dextrins, formed under the same conditions from maltosyl fluoride, is smaller: only α-, *β*-, and *γ*-CD are formed.

B. Cyclic Oligosaccharides Produced by the Action of Bacterial Glycosidases on Polysaccharides

Apart from CGTases, only a few enzymes are known to exert a similar action on polysaccharides when degradation is accompanied by the formation of cyclic oligosaccharides. Thus, one of the types of bacterial fructotransferases, isolated from *Bacillus circulans*, catalyzes the conversion of inulin (*β*-(1→2)-fructofuranan, **246**) into cyclic fructins.[120] The major product in this transformation was identified (Figure 60) as compound **247**, composed of six *β*-(1→2)-linked D-fructofuranose residues. In addition, small amounts

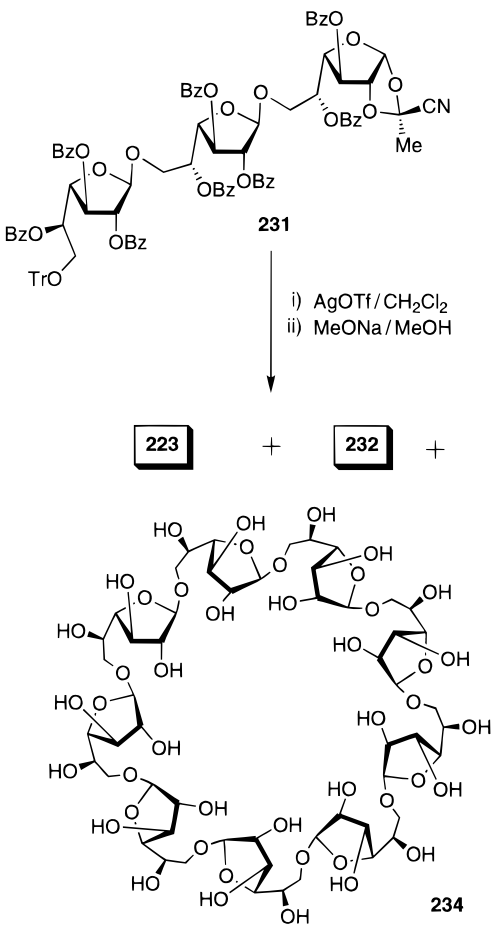


Figure 56. Cyclooligomerization of the galactofuranotriose derivative **231**.

of the larger cyclic hepta- and octafructosides **248** and **249** were also isolated.[121]

In the solid state,[122,123] the cycloinulohexaoside **247** possesses (Figure 61) a C_3 symmetric structure, with the fructose units—arranged in a spiro fashion around the 18-crown-6 skeleton of the molecule—pointing alternatively in opposite directions with respect to the plane of the cyclic hexasaccharide. The geometry and lipophilic potential profiles of **247** were also deduced[124] by molecular modeling.

As analogues of crown ethers, the cycloinulooligosaccharides **247**−**249** are capable of complexing with metal cations.[125] The binding abilities of their permethylated derivatives **250** and **251** (Figure 60) have been investigated[126,127] by FAB mass spectrometry and NMR spectroscopy. It was revealed that, in organic solvents, from a range of metal cations, the cyclic hexamer **250** binds Ba^{2+} ions preferentially, whereas the cyclic heptamer **251** exhibits its strongest complexation toward Cs^+ ions. Furthermore, single crystals of the complex of the permethylated cycloinulohexaose **250** and a Ba^{2+} ion were obtained[127] and an X-ray crystallographic analysis has been carried out on them. In the solid state, the cycloinulohexaoside adopts (Figure 62) a folded C_2-symmetric conformation, with the barium cation nestling above the cavity of the 18-crown-6-type macrocycle at the nearest location to the 3-OMe oxygen atoms.

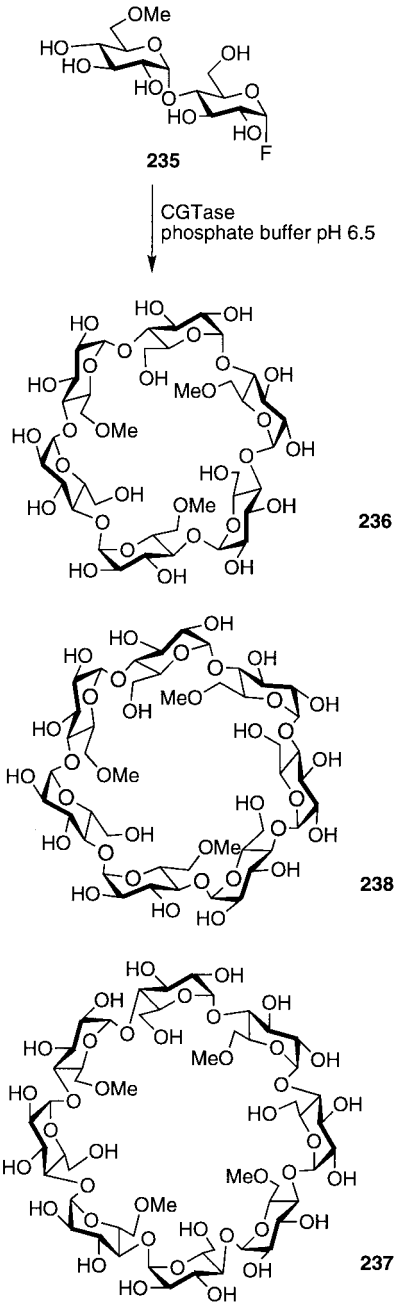


Figure 57. Enzymatic synthesis of the cyclodextrin derivatives **236**−**238** from the maltosyl fluoride **235**.

Three kinds of cyclic oligosaccharides were produced[128] from dextran by cultivation with *Bacillus* sp. T-3040. They were identified (Figure 63) as the cyclic hexa-, octa-, and nonaisomaltooligosaccharides **252**, **253**, and **254**, which are composed of α-(1→6)-linked glucopyranose residues.

Another example of the enzymatic transformation of polysaccharide into cyclic oligosaccharides was reported recently by Côté et al.[129] When alternan, a polysaccharide composed of alternating α-(1→3)-α-(1→6)-linked D-glucopyranose residues, was incubated with the enzyme alternanase—a new variety of D-glucanase—the main compound isolated from a complex mixture of products was cyclo{6)-α-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→}$_2$ (**255**) and is shown in Figure 64. An interesting feature of this research is that

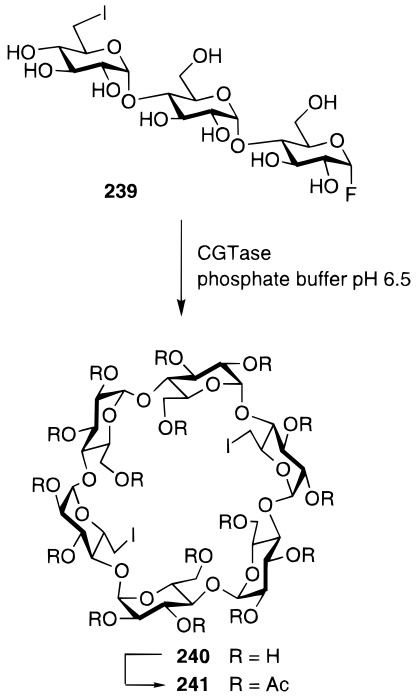


Figure 58. Enzymatic synthesis of the $6^{I},6^{II}$-dideoxy-$6^{I},6^{II}$-diiodo-per-*O*-methyl-α-CD (**240**).

the cyclic tetrasaccharide **255** represents the first semisynthetic small ring cyclic oligosaccharide.

C. Bacterial Cyclic Oligosaccharides

Bacteria of the genera *Agrobacterium* and *Rhizobium* are known to produce[130] in vivo cyclic β-(1→2)-glucopyranooligosaccharides (Figure 65) commonly referred to as cyclic β-(1→2)-glucans or cyclosophorans. These compounds are usually composed of from 17 (**256**) to 25 glucose residues[131] but in some bacterial species this number reaches 40. The biosynthesis of β-(1→2)-glucopyranooligosaccharides has been studied extensively and in vitro preparations[128] have been performed. Isolation of the individual compounds is only possible by HPLC.[132] However, the fact that the cyclic β-(1→2)-glucans possess[133] some biological activity has stimulated investigations on their structures, mostly by NMR spectroscopy[134] and by molecular modeling.[135]

Cyclic glucans are also secreted by bacterial species of *Bradyrhizobium japonicum* (strain USDA 110) which belongs to the *Rhizobiaceae* family. In these cases,[136,137] the cyclic oligosaccharides are comprised of β-(1→3)-β-(1→6)-interglucopyranosidic linkages and have a degree of polymerization higher than 10. However, the detailed structures of these compounds have not yet been elucidated.

Very recently,[138] a new cyclic glucan **257** was isolated from a recombinant strain of a *Rhizobium meliloti* TY7. It was discovered that this cyclic oligosaccharide possesses a ring which is composed of 10 β-(1→3)-linked D-glucopyranose residues (Figure 66) and one β-nigerose residue is present as a branching unit attached to the 6-position of a glucose residue.

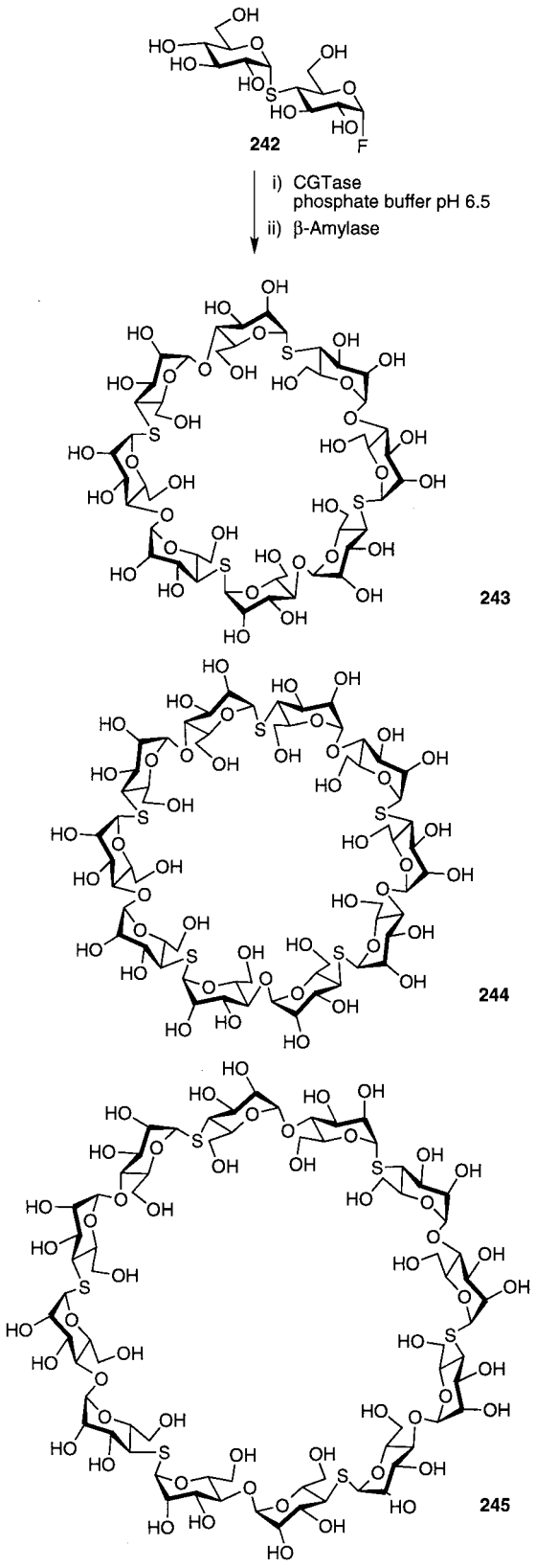


Figure 59. Enzymatic synthesis of thiocyclodextrins **243**−**245**.

IX. Cyclic Disaccharides

Cyclic disaccharides, which are also called saccharide dianhydrides, have been known for a long time. One of the most representative examples[139−143] are the D-fructose dianhydrides **258**−**263** portrayed in Figure 67. They are formed by the treatment of inulin or D-fructose with strong acids and are composed of different combinations of D-fructofuranose and D-fructopyranose residues linked by α- or *β*-(1→2)-glycosidic bonds, i.e., they possess dispiro structures. The only exception within this series is compound **262**,[142] which incorporates both *β*-(1→2) and *β*-(2→3)-linkages. Likewise, treatment of L-sorbose with concentrated HCl[144] or anhydrous HF[145,146] afforded (Figure 68) the disaccharides **264** and **265**, composed of (1→2)-linked α- or *β*-L-sorbopyranose residues. The details of the solid-state structure of **259** and **260** have also been reported.[147,148]

It has also been noted[149] that some of these ketose 2′,1:2,1′-dianhydrides form complexes with metal cations provided the two anomeric carbon atoms have the same configuration. Complex formation involves O-1, O-1′, O-3, and O-3′ atoms as confirmed by an X-ray crystal structure analysis of the strontium complex of **261**. The α,*β*-anomers and the dianhydrides containing only furanose rings, do not form such complexes.

Aside from the diketose dianhydrides **258**−**267**, there are several examples of cyclic disaccharides based on aldoses. These include di-*β*-D-ribofuranose-1,5′:1′,5-dianhydride (cyclobis[(1→5)-*β*-D-ribofuranosyl]),[150,151] compounds **194** and **222** (see Sections VI.A and VII), formed as a result of intramolecular glycosylation, and cyclo[(1→2)-α-D-Glc*p*]$_2$, which was recently reported by Pozsgay et al.[152]

X. Conclusions and Reflections

The synthesis of cyclic oligosaccharides was undoubtedly given a fillip by Ogawa's total synthesis of α-cyclodextrin[60] in 1985. More than a decade on from the publication of this seminal paper, we have acquired the knowledge and skill to manipulate oligosaccharides to produce cyclic analogues with good regio- and stereocontrol. In Figure 69, we illustrate schematically the four conceptually different approaches to cyclic oligosaccharide synthesis which have been developed during the last 10 years: they are (i) the stepwise preparation of a linear precursor that is subjected to cycloglycosylaton; (ii) the one-pot polycondensation/cycloglycosylation of a small "oligosaccharide monomer"—typically, a di- or trisaccharide—that can yield a range of macrocycles of different sizes; (iii) the enzyme-assisted synthesis of natural or unnatural cyclic oligosaccharides; and (iv) the ring opening of cyclodextrins followed by oligosaccharide chain elongation and cycloglycosylation. It has to be said, however, that the synthesis of these types of molecules is still not an easy task. Chemists interested in synthesizing cyclic oligosaccharides have to contend with a number of associated problems: they include long synthetic procedures, with low overall yields, and a crucial need of regio- and stereoselectivity, especially in the final cyclization steps.

In Sections IV−X, we discussed the syntheses of compounds which are built up solely of glycosidically

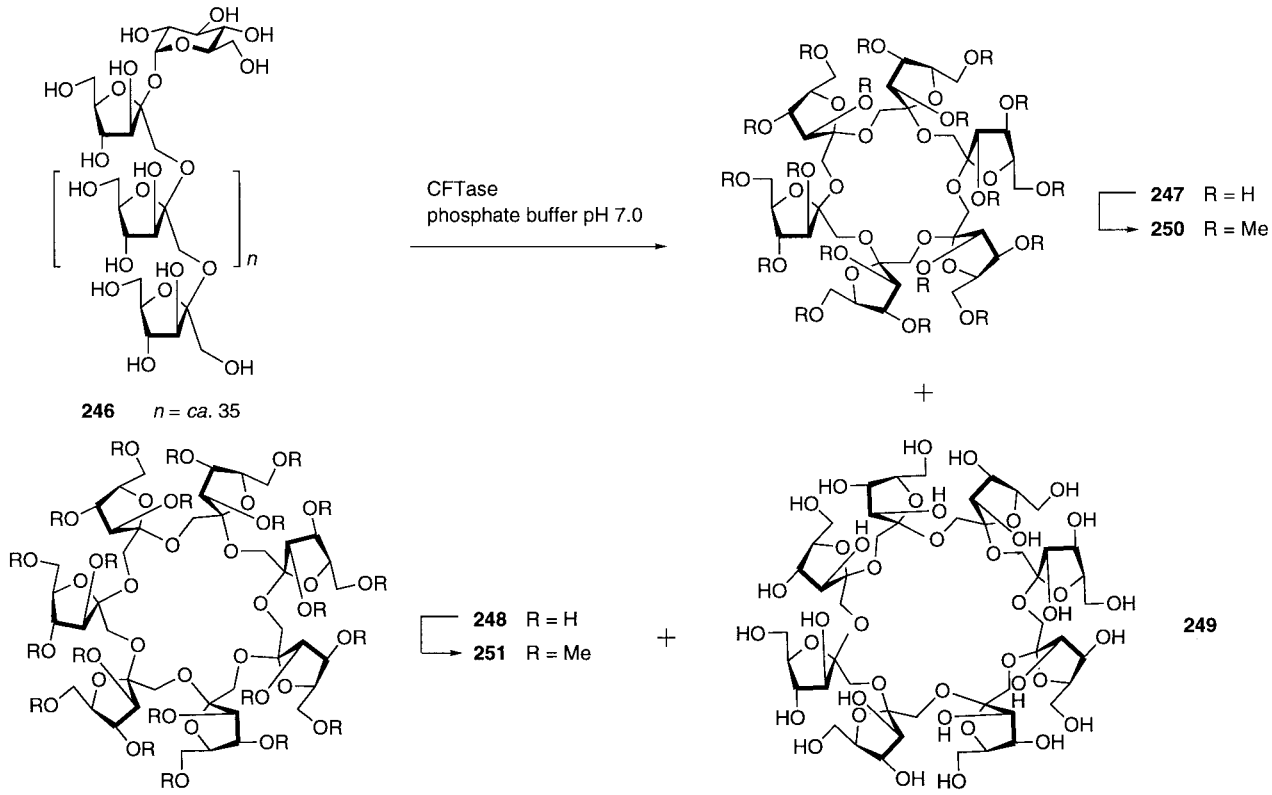


Figure 60. Enzymatic preparation of cycloinulooligosaccharides.

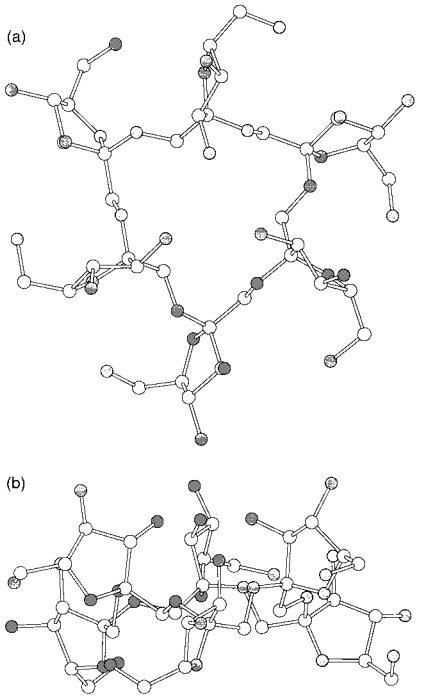


Figure 61. (a) Top view and (b) side-on view of the X-ray crystal structure of the cycloinulohexaoside **247**.

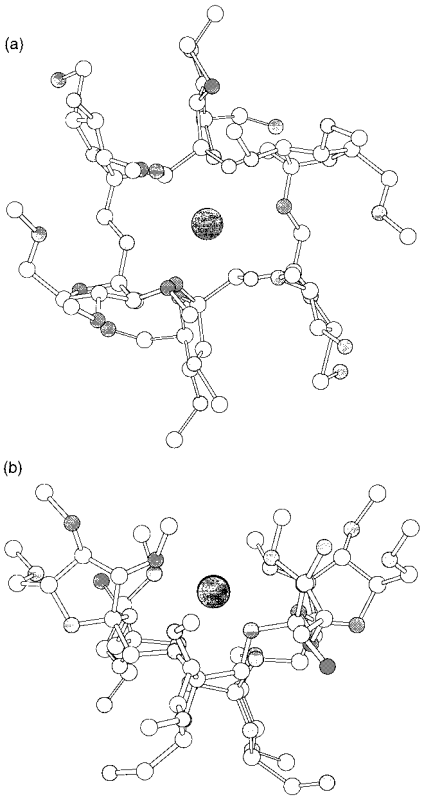


Figure 62. (a) Top view and (b) side-on view of the X-ray crystal structure of the complex between the permethylated cycloinulohexaoside **247** and a Ba^{2+} cation.

linked saccharide residues. Certainly, there are many other possibilities to incorporate monosaccharides into macrocyclic systems, and, indeed, several types of cyclic pseudooligosaccharides have been described.[153−161] The design of these compounds has the ultimate goal to create novel water-soluble chiral molecular receptors possessing specific complexation properties.

Although, in the case of many of the examples discussed in this review, the preparation of novel and appealing cyclic oligosaccharides was undertaken mainly as an exercise in synthetic chemistry, there

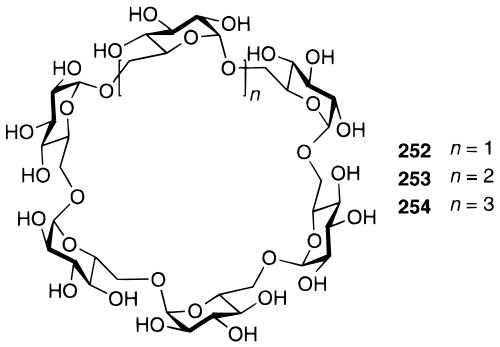


Figure 63. Structures of the isomaltooligosaccharides **252**−**254**.

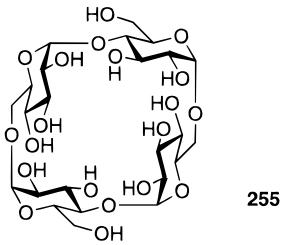


Figure 64. Structure of the cyclo{6)-α-D-Glc*p*-(1→3)-α-D-Glc*p*-(1→}$_2$ (**255**).

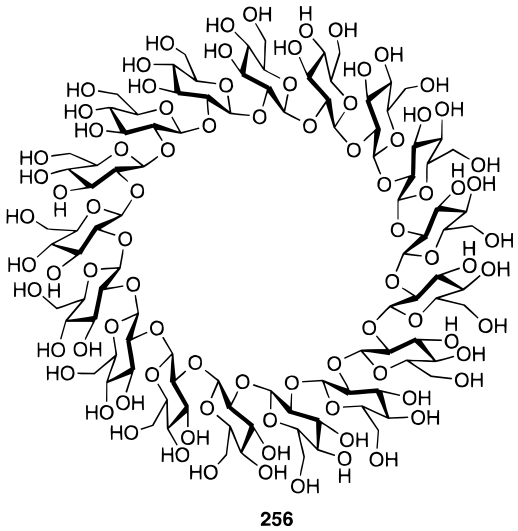


Figure 65. Structure of the cyclic (1→2)-*β*-D-glucoheptadecaoside **256**—a member of the cyclic (1→2)-*β*-D-glucan family.

is now some reason to believe that the one-step polycondensation/cycloglycosylation procedure[80−83] for synthesizing these compounds could be sufficiently efficient to make it an attractive entry into a novel range of cylindrically shaped receptors and building blocks for use in synthetic supramolecular chemistry.[162] Any development of their potential as enzyme mimics[163] would, on one hand, be aided and abetted by the enormous knowledge base[18−30] surrounding CDs and their analogues, but yet, on the other hand, be sufficiently different and unique to be able to compete with the "off the shelf" availability[164] of the three most popular CDs—namely α-CD, *β*-CD, and *γ*-CD—and their best known derivatives, e.g., dimethyl-*β*-cyclodextrin (DM-*β*-CD). It is possible that synthetic cyclic oligosaccharides could be derivatized

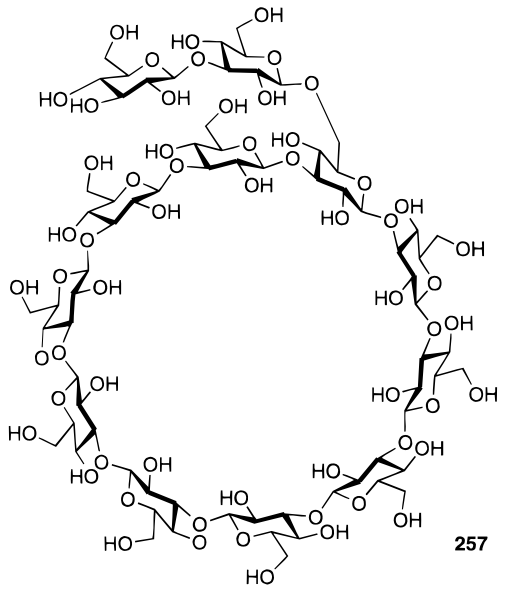


Figure 66. Structure of the branched cyclic glucan **248** produced by the recombinant strain of a *Rhizobium meliloti* TY7.

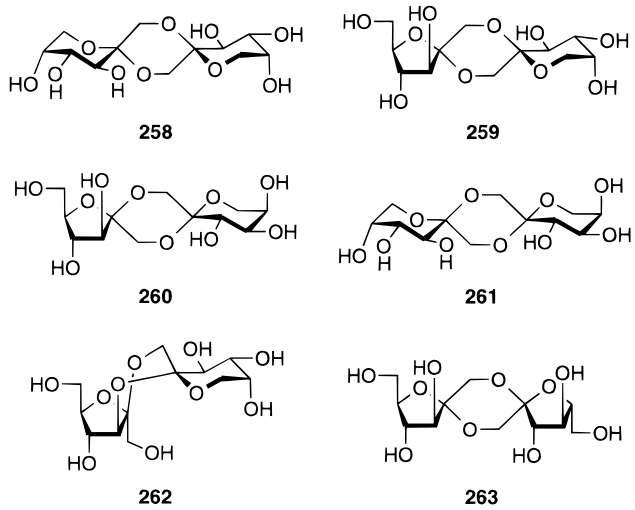


Figure 67. The structures of the cyclic di-D-fructose anhydrides formed by acidic degradation of inulin.

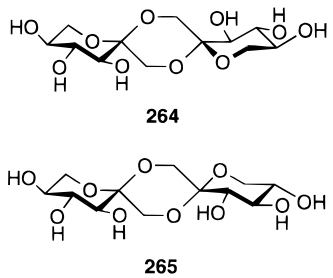


Figure 68. The structures of the cyclic di-L-sorbose anhydrides formed by acidic treatment of L-sorbose.

(Figure 70) in a highly controlled and even selective manner at the di- and trisaccharide monomer stage in the one-step polycondensation/cycloglycosylation approach to their synthesis.

One thing is certain. The opportunities to find applications in both biomedical and materials science for synthetic cyclic oligosaccharides has been much enhanced by the progress that has been made in a

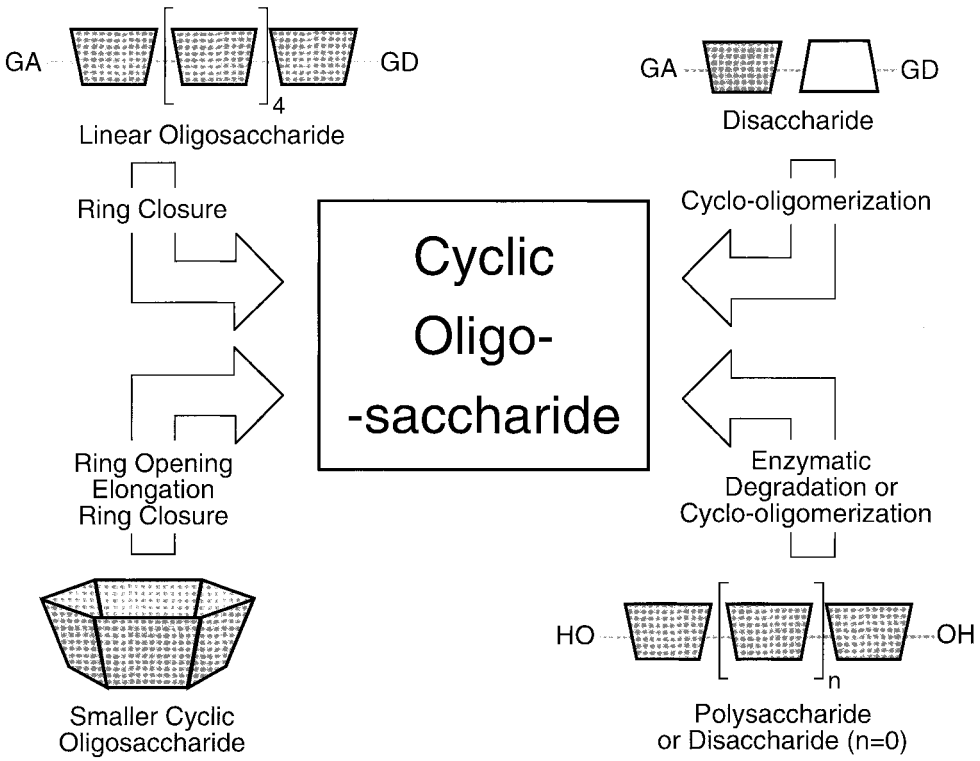


Figure 69. The four approaches to the synthesis of cyclic oligosaccharides.

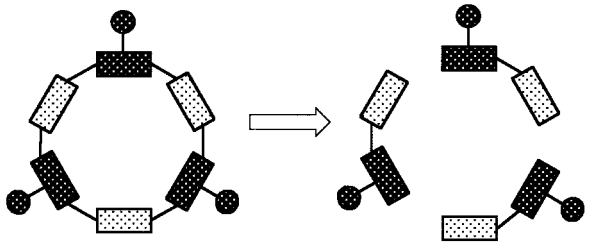


Figure 70. Retrosynthetic analysis of an alternately substituted cyclohexaoside.

few research laboratories around the world during the past decade in devising new and efficient ways of synthesizing cyclic oligosaccharides.

XI. Acknowledgments

Those sections of this review which refer to our own research have been supported generously during the 1990s by the University of Birmingham, the University of Messina, the British Council, the Royal Society, the Nuffield Foundation, the Wolfson Foundation, and the Research Councils (formerly SERC and latterly BBSRC and EPSRC) in the UK. We are also indebted to Professor David Williams of the Chemical Crystallography Laboratory in the Department of Chemistry at Imperial College, London, UK, for unraveling the X-ray crystal structures of quite a number of synthetic cyclic oligosaccharides in recent years: the solutions to most of these structures were really quite demanding to say the least! Our own recent research in the field of synthetic cyclic oligosaccharides was made possible by the earlier experiences one of us—Dr. S. A. Nepogodiev—enjoyed under the supervision of Professors N. K. Kochetkov and L. V. Backinowsky at the Zelinsky Institute of Organic Chemistry within the now Russian Academy of Sciences in Moscow. We thank Professor Backinowsky for reading through the manuscript very carefully in full, for his helpful comments, and for numerous useful discussions during its preparation.

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