Chemical Synthesis of Linear and Cyclic Unnatural Oligosaccharides by Iterative Glycosidation of Ketoses

Alessandro Dondoni,*[a] Alberto Marra,*[a] Marie-Christine Scherrmann,[b] and Valerio Bertolasi[c]

Dedicated to Professor Fernando Montanari

Abstract: The development of an efficient method for the stereoselective synthesis of α-D-$(2\rightarrow1)$-linked ketoside oligomers is described. The method is based on an iterative protocol composed of two key steps: a) the coupling of a thiazolylketosyl phosphite donor with an hydroxymethylketoside acceptor; and b) the introduction of the hydroxymethyl group at the anomeric carbon atom of the resulting oligomer. To highlight its efficiency, the protocol was used in the assembly of D-*galacto*-2-heptulopyranose-containing oligoketosides through α-$(2\rightarrow1)$ linkages up to the pentameric stage. The yield of the isolated oligomers ranged from 48% in the first cycle to 29% in the fourth cycle. Having employed a pentenyl-substituted hydroxymethylketoside acceptor in the first cycle, all the derived oligomers contained the pentenyl group at their reducing end. This group was exploited to transform the linear oligomers into cyclic products through intramolecular glycosidation. The major product derived from the linear trisaccharide was confirmed by X-ray crystallography to be the cyclotris-$(2\rightarrow1)$-(α-D-*galacto*-2-heptulopyranosyl). The structure of this compound was essentially that of a [9]crown-3 ether bearing three galactopyranose rings spiroanellated in a propellerlike fashion. This arrangement of carbohydrate units linked to the crown ether created a densely alkoxylated cavity suitable for the encapsulation of alkali-metal cations (Li, Na, K, Ca, Mg).

Keywords: crown compounds · glycosylations · noncovalent interactions · oligosaccharides · thiazoles

Introduction

The development of new chemical or enzymatic methods and technologies for oligosaccharide[1] and glycoconjugate[2] synthesis is one of the most intensively investigated research topics in modern carbohydrate chemistry. The widespread interest in this area of research arises mainly from the increasing awareness that carbohydrates play a vital role in molecular recognition processes of biomolecules such as glycoproteins and glycolipids that are found on the outer surface of cells.[3] These processes are responsible for important events in living organisms, including inflammation, immunological response, cancer metastasis, and fertilization.[4] Oligosaccharides and glycoconjugates are difficult to isolate in a homogeneous form from natural sources, and even when possible, their purification and characterization are quite laborious. Consequently, the pressing need for the access to usable quantities of these materials and their unnatural analogues for research and therapeutic purposes opens up a major opportunity for the development of new synthetic methods.

Remarkable progress has been made in the glycosidation of aldoses,[1] and the assembly of oligosaccharide chains containing aldosyl units by means of iterative chemical methods both in solution and in the solid phase has been reported in recent years.[5] Considerable attention has also focused on the chemical and enzymatic synthesis of cyclic oligosaccharides of aldoses.[6] On the other hand, few syntheses of ketodisaccharides have been reported, very likely because of the low reactivity and stereoselectivity of the glycosidation reactions of ketoses. Recent examples include the glycosidation of a fructofuranose phosphite,[7] some fructofuranose thioglyco-

[a] Prof. Dr. A. Dondoni, Prof. Dr. A. Marra
Dipartimento di Chimica, Laboratorio di Chimica Organica
Università di Ferrara
Via L. Borsari 46, 44100 Ferrara (Italy)
Fax: (+39) 0532-291-167
E-mail: adn@dns.unife.it

[b] Dr. M.-C. Scherrmann
Visiting scientist on leave from Université Paris XI,
Laboratoire de Chimie Organique Multifonctionelle,
BT 420, 91405 Orsay Cedex (France)

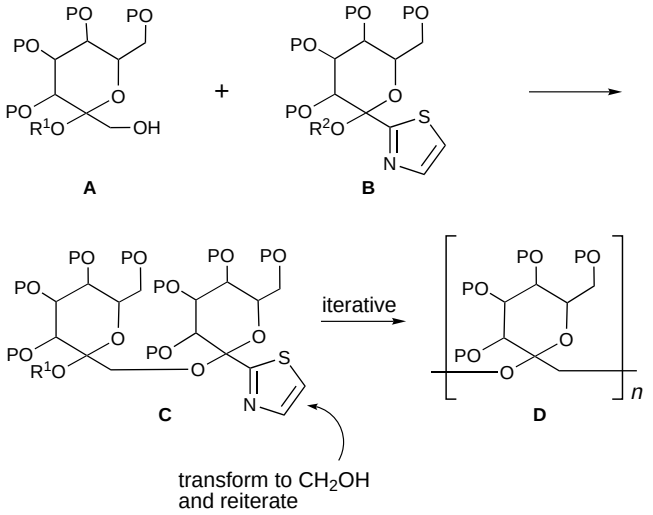
[c] Prof. Dr. V. Bertolasi
Centro di Strutturistica Diffrattometrica, Dipartimento di Chimica,
Università di Ferrara, 44100 Ferrara (Italy)

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

  0947-6539/01/0707-1371 $ 17.50+.50/0

sides,[8] and various activated ketopyranoses.[9] Natural ulosonic acids were prepared by Danishefsky and co-workers some years ago[10] by employing furylketoses as glycosyl donors. This method relied on the electron-donating furan ring that served both as an activator of the glycosidation reaction and as a precursor of the carboxylate group. Hence, the chemical synthesis of oligosaccharides containing ketosyl units either by linear or by convergent iterative glycosidation of ketoses has, to the best of our knowledge, not been reported. Cyclic oligomers of fructofuranose, called cyclofructins[11] to emphasize their analogy to cyclodextrins, have been obtained by the enzymatic degradation of inulin, the natural polymer of D-fructose.[12]

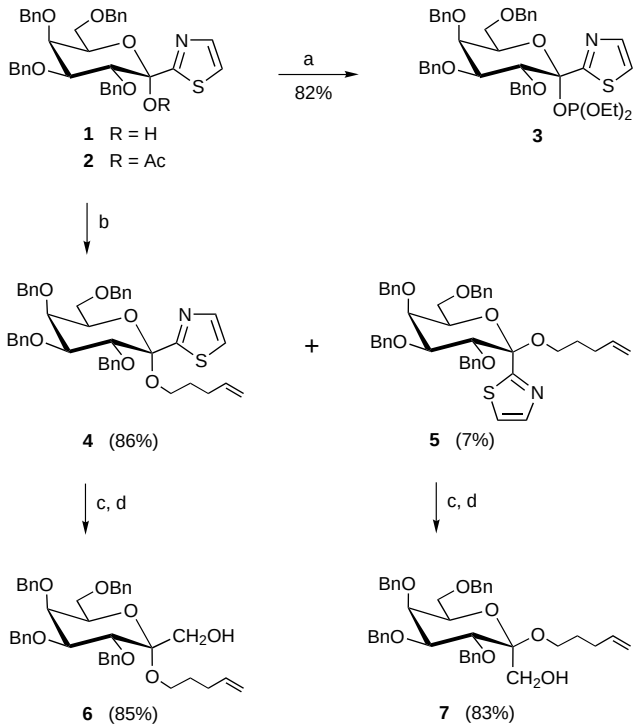
We now report a protocol for the chemical synthesis of $(2\rightarrow1)$-linked oligoketosaccharides **D** (Scheme 1) by means of an iterative glycosidation employing an activated thiazolylketose **B** as ketosyl donor. This building block and the initial ketosyl acceptor **A** were designed to bear different activating groups R^1 and R^2 so that the alcohol derived from the dimer **C** as well as from further elongated derivatives can undergo either inter- or intramolecular glycosidation to give linear or cyclic oligomers, respectively. The method is illustrated by the synthesis of linear oligomers up to the pentameric stage and cyclic dimers and trimers of α-D-*galacto*-2-heptulopyranose. The complexation properties of a cyclic ketotrisaccharide towards metal cations will be also described.



Scheme 1. Protocol for the synthesis of $(2\rightarrow1)$-linked oligosaccharides **D**.

Results and Discussion

Synthesis of ketoside building blocks 3 and 6: In recent reports from our laboratory we described the preparation of thiazolylketoses,[13, 14] for example, galactopyranose derivative **1** and activated *O*-acetate **2** (Scheme 2). These compounds proved to be efficient ketosyl donors in trimethylsilyl triflate(TMSOTf)-promoted coupling reactions with various carbon and heteroatom acceptors, including alcohols of



Scheme 2. a) $i\mathrm{Pr_2EtN}$ (2 equiv), $\mathrm{ClP(OEt)_2}$ (1.3 equiv), $\mathrm{CH_2Cl_2}$, room temperature, 20 min; b) 4-penten-1-ol (3 equiv), TMSOTf (1 equiv), 4 Å molecular sieves, $\mathrm{CH_2Cl_2}$, 0 °C to room temperature, 75 min; c) MeOTf (1.3 equiv), 4 Å molecular sieves, $\mathrm{CH_3CN}$, room temperature, 15 min; $\mathrm{NaBH_4}$ (2 equiv), $\mathrm{Et_2O/MeOH}$, room temperature, 5 min; $\mathrm{AgNO_3}$ (1.5 equiv), $\mathrm{CH_3CN/H_2O}$, room temperature, 20 min; d) $\mathrm{NaBH_4}$ (2 equiv), $\mathrm{Et_2O/MeOH}$, room temperature, 15 min.

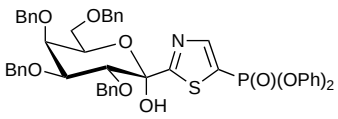
aldoses[15] and calix[4]arenes,[16] trimethylsilyl azide,[17] triethylphosphite,[18] and carbon nucleophiles.[14, 19] The advantages associated with the use of the thiazole ring in this type of chemistry are evident when considering that this heterocycle is stable under glycosidation reaction conditions, while it is readily transformed into the formyl group by means of a simple and efficient reaction sequence.[20] In fact the thiazolylketosides obtained from the above glycosidation reactions were transformed into various ketosyl and ulosonyl derivatives, some of which were barely accessible by different routes. Hence the challenge lied in demonstrating the use of thiazolylketoses in synthetic endeavours to more elaborate glycosides.

In order to assemble various D-*galacto*-2-heptulopyranose units through a 2,1-glycoside linkage in either a linear or cyclic fashion as schematically shown in Scheme 1, we designed the thiazolylketosyl phosphite **3** and the pentenyl hydroxymethylketoside **6** (Scheme 2) as the ketosyl donor and acceptor partners. The successful implementation of the above strategy relied on the easy access to these required starting materials. The coupling of the acetate **2** with 4-penten-1-ol in the presence of TMSOTf gave, after column chromatography, the α-D-ketoside **4** and the β-D-anomer **5** in 86 and 7% yield, respectively. The anomeric configuration of these compounds was established by NMR analysis. Irradiation of the two protons adjacent to the oxygen atom in the pentenyl group of **4** induced a significant enhancement of the signal for H-5 of

0947-6539/01/0707-1372 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 7

the pyranose ring; the same experiment carried out with **5** affected the signal for H-2. Since both compounds adopt the $^4C_1$ conformation (see Experimental Section), it can be deduced that the pentenyl group is axial in **4**, but equatorial in **5**. The assigned stereochemistry was confirmed by the downfield chemical shift of the H-3 proton of the α-D-anomer **4** ($\delta = 4.18$) with respect to β-D-anomer **5** ($\delta = 4.02$) as a consequence of the 1,3-diaxial interaction with the anomeric C–O bond.[13, 21] The individual thiazolylketosides **4** and **5** were transformed into the corresponding alcohols **6** and **7** (ca. 77% yield) by means of the thiazole-to-formyl deblocking protocol[22] (*N*-methylation, reduction, metal assisted-hydrolysis) followed by the reduction of the aldehydes with $NaBH_4$. Optimized conditions were established by replacing $CuCl_2$/CuO with $AgNO_3$ in the last step of the unmasking protocol.[23] By this method, the multigram preparation of compound **6** was carried out several times with an average yield of 85% from **4**. This improvement in the thiazole-to-aldehyde transformation proved to be essential in subsequent cycles. In order to confirm that the configuration at the anomeric center in compounds **4** and **5** remained unaffected throughout the above reaction sequence, the hydroxymethylketosides **6** and **7** were subjected to careful ^{1}HNMR spectroscopic analysis. Irradiation of the two protons adjacent to the oxygen atom in the pentenyl aglycone of **6** (in C_6D_6) gave rise to an NOE interaction with the axial H-6 proton (heptulose numbering). On the other hand, irradiation of H-3 of **7** (in $CDCl_3$) induced an enhancement of the signals for the same protons in the pentenyl group. Furthermore, in $CDCl_3$ the H-4 signal of **6** resonated further downfield ($\delta = 4.09$) than H-4 of **7** ($\delta = 3.72$). The synthesis of **6** demonstrated the tolerance of the *O*-pentenyl group towards the transformation of the thiazole ring into the hydroxymethyl group, a key step in the planned iterative homologation sequence. However, the glycosylation reaction of **6** with the thiazolylketose acetate **2** gave the corresponding ketoside in low yield (ca. 20%). Hence, we considered the use of the thiazolylketose phosphite **3**, a potentially more reactive ketosyl donor. The choice of a diethyl ester was based on the easier and more economical synthesis than the corresponding dibenzyl and dimethyl analogues whose preparation requires the expensive dialkyl *N*,*N*-diethylphosphoramidites.[24] The high-yielding preparation of phosphite **3** was carried out on a multigram scale by treatment of ketol **1** with diethyl chlorophosphite in the presence of ethyldiisopropylamine (Hünig's base). Flash-column chromatography with eluents containing triethylamine (3%) afforded compound **3** in 82% yield. This phosphite can be stored for several weeks at $-20\,^\circ$C without appreciable decomposition.

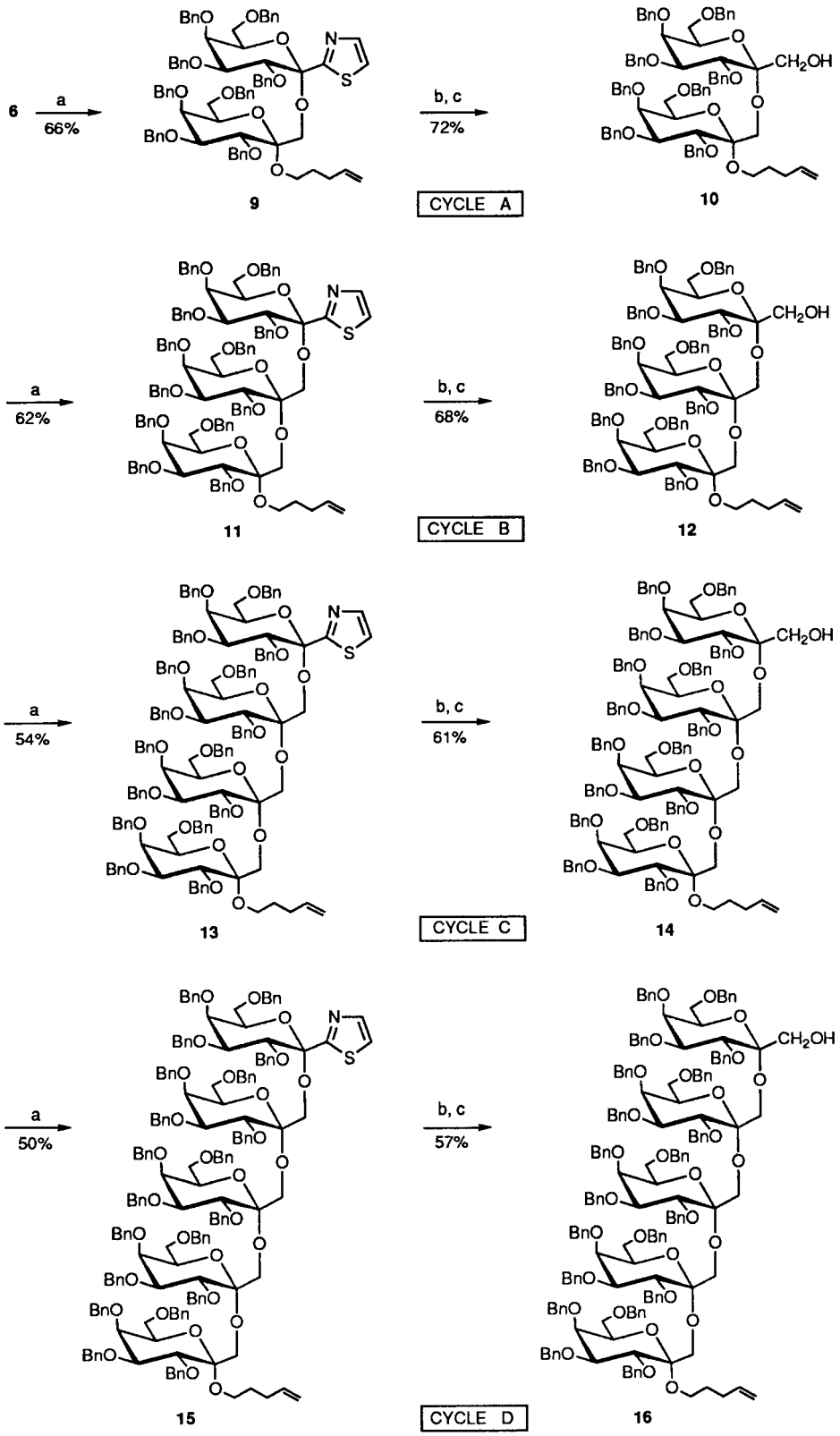
It should be mentioned that some attempts at preparing ketosyl donors bearing other powerful activating groups were unsuccessful. For example, we failed to prepare the *O*-trichloroacetimidate and the *O*-phosphate derivatives of **1** upon treatment with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and diphenyl chlorophosphate and BuLi,[25] respectively. Unreacted **1** was recovered in both reactions, while the thiazolyl phosphonate **8** was isolated in 40% yield in the latter reaction.[26]



8

Iterative glycosidation: At the outset, we carried out the coupling between the glycosyl donor **3** and the acceptor **6** under conditions similar to those employed in our ketodisaccharide synthesis.[15] Thus, treatment of an equimolar solution of **3** and **6** in CH_2Cl_2 with a stoichiometric amount of the promoter TMSOTf or TfOH at $0\,^\circ$C afforded exclusively the α-D-ketodisaccharide **9** in approximately 45% yield (Scheme 3). The stereochemistry at the anomeric center of **9** was deduced from the NMR spectroscopic analysis of the methyl ulosonate **18** which was obtained via the aldehyde **17** (Scheme 4). The ^{13}CNMR (75 MHz, C_6D_6) spectrum of **18**, recorded with selective decoupling of the methyl ester protons at $\delta = 3.14$, showed the C=O signal (C-1′, $\delta = 168.3$) as a broad singlet since ^3J(C-1′,H-3′) was approximately 1 Hz. This can be expected for an α-D-ulosonate in a $^5C_2$ conformation (equatorial CO_2Me group) having a dihedral angle C-1–C-2–C-3–H-3 (ulosonic acid numbering) of nearly 60°.[15, 27] The above yield of **9** could not be improved by using the so-called "inverse procedure"[28] already exploited in our earlier work,[15] that is, slow addition of the donor **3** to the solution of the acceptor **6** and the Lewis acid, because **6** decomposed under these conditions. A higher conversion of **6** into **9** (66%) was obtained by the addition of two equivalents of **3** and $BF_3 \cdot Et_2O$ in two portions with a 20-min interval at $0\,^\circ$C (Scheme 3).[29] Fortunately, in both the $BF_3 \cdot Et_2O$- and TMSOTf-promoted reactions, the unreacted alcohol **6** was recovered unaltered or as the *O*-trimethylsilyl derivative, respectively. On the other hand, the excess phosphite **3** rearranged almost quantitatively into the known[18] isomeric phosphonate **22** (Scheme 5). It has been reported that glycosylation reactions with acetylated glycosyl phosphites led to orthoester-type phosphonate by-products, which upon acid catalysis at higher temperatures, were transformed into the desired glycosides.[30] Accordingly, we suggest that the acid-stable glycoside **22** is formed by *P*-glycosylation of the sugar oxycarbenium ion intermediate **19** by trimethylsilyl phosphite **20** or by the borophosphite complex **21**. In support of this mechanistic proposal, treatment of **3** with an equimolar amount of TMSOTf or $BF_3 \cdot Et_2O$ (CH_2Cl_2, $0\,^\circ$C, 15 min) afforded the sugar phosphonate **22** in 90 and 87% yields, respectively.

As the *O*-pentenyl group was unaffected by the thiazole-to-formyl unmasking protocol and $NaBH_4$ reduction (see Scheme 2), the same reaction sequence was successfully applied to convert **9** into the hydroxymethyl ketodisaccharide **10** in a consistently good overall yield. This operation completed the first cycle A. The same homologative cycle, made up of a sequential glycosidation and an hydroxymethylation, was repeated three times using the $BF_3 \cdot Et_2O$-promoted reaction conditions. Cycle B gave the thiazolyl glycoside **11** and the trisaccharide **12**; cycle C gave the thiazolyl glycoside

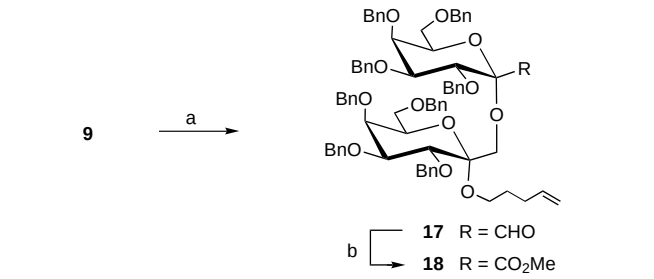


Scheme 3. a) **3** (2 equiv), $BF_3 \cdot Et_2O$ (2 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 40 min; b) MeOTf (1.3 equiv), 4 Å molecular sieves, CH_3CN, room temperature, 15 min; $NaBH_4$ (2 equiv), Et_2O/MeOH, room temperature, 5 min; $AgNO_3$ (1.5 equiv), CH_3CN/H_2O, room temperature, 20 min; c) $NaBH_4$ (2 equiv), Et_2O/MeOH, room temperature, 15 min.

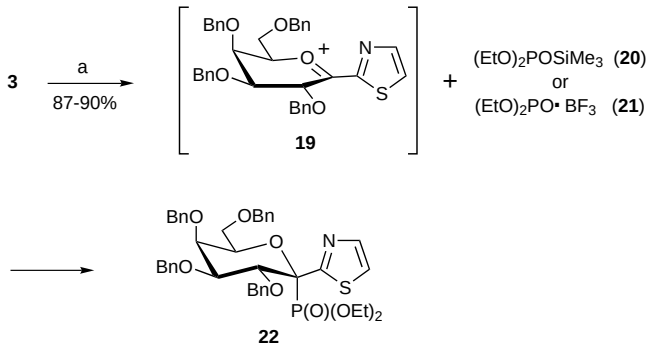
13 and the tetrasaccharide **14**; cycle D gave the thiazolyl glycoside **15** and the pentasaccharide **16**. The glycosidation reaction in each cycle was highly stereoselective as it only afforded a single oligosaccharide stereoisomer. The α-D-stereoselectivity was confirmed for the trimer **12** by X-ray crystallography (see below), whereas the same stereochemistry was assumed for the tetramer **14** and pentamer **16** based on the close similarity of the chemical shift of the anomeric carbons at the non-reducing end. In fact, the chemical shifts of these carbon atoms of the α-D-hydroxymethylketosides **6**, **10**, **12**, **14**, and **16** were in the range of $\delta = 99.1 - 99.6$, while the chemical shift of the anomeric carbon atom of the β-D-anomer **7** was $\delta = 101.1$. It is worth noting that only a slight decrease in the yields (5–9%) was observed from cycle A to D. Hence, it appears that we did not reach the limit of application of the above iterative homologation and therefore the assembly of a longer oligoketosaccharidic chain is, in principle, feasible. Furthermore, the ketosides **9**, **11**, **13**, and **15** may serve as glycosyl donors by means of the Fraser–Reid pentenyl glycoside method[31] for achieving complex carbohydrate or non-carbohydrate linkages.

Synthesis of cyclic oligomers: We first considered the pentenyl-based intramolecular glycosidation of the most readily accessible oligomers **10** and **12** to cyclic di- and triketosaccharides. Hence, a diluted solution of **10** (ca. 10^{-2} M) in dichloromethane was treated at 0 °C with *N*-iodosuccinimide (NIS) and TMSOTf. This reaction afforded the spirodisaccharides **23** (62%) and **24** (20%) in fairly good overall yields (Scheme 6). The ^1H and ^{13}CNMR spectra of the major product **23** showed two sets of signals which indicated α- and β-D-(2 → 1)-glycosidic linkages of the pyranose residues. On the other hand, the NMR spectra of **24** revealed the presence of a single type of monosaccharide unit whose α-D-(2 → 1)-glycosidic linkage was assigned by NOE experiments. In fact,

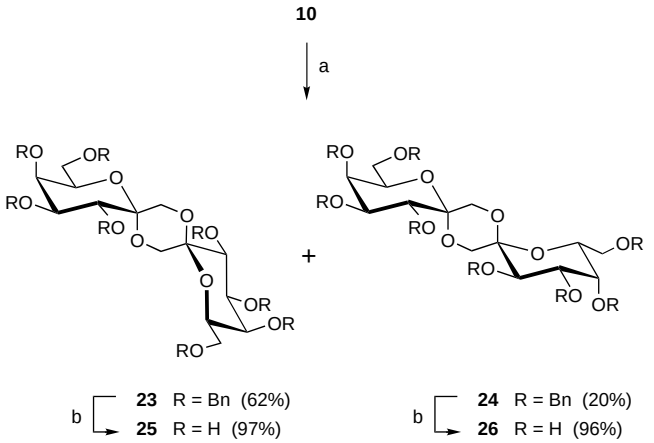
0947-6539/01/0707-1374 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 7



Scheme 4. a) MeOTf (1.3 equiv), 4 Å molecular sieves, CH_3CN, room temperature, 15 min; $NaBH_4$ (2 equiv), Et_2O/MeOH, room temperature, 5 min; $AgNO_3$ (1.5 equiv), CH_3CN/H_2O, room temperature, 20 min; b) I_2, KOH, Et_2O/MeOH, room temperature, 74 % (two steps).

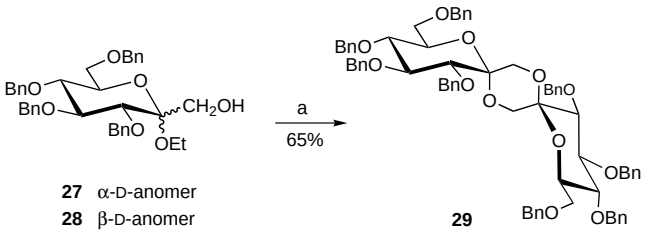


Scheme 5. a) TMSOTf (1 equiv) or $BF_3 \cdot Et_2O$ (1 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 15 min.



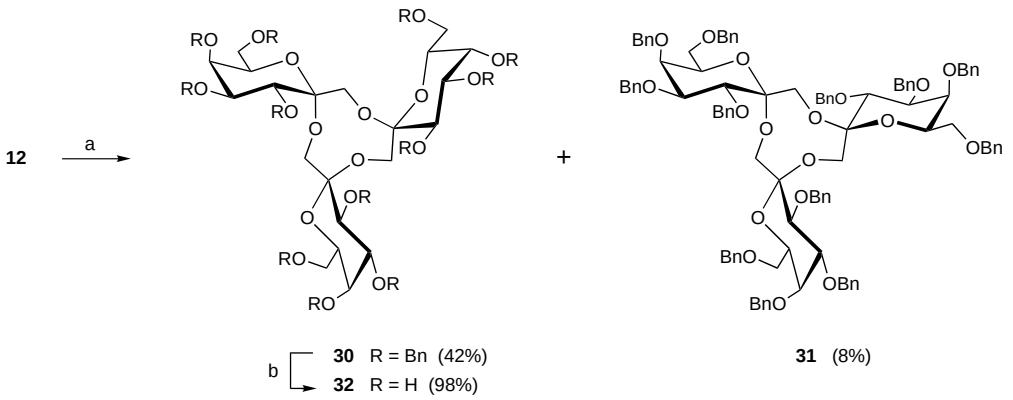
Scheme 6. a) NIS (2 equiv), TMSOTf (1 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 1 h; b) H_2, $Pd(OH)_2$, AcOEt/MeOH, room temperature, 3 h.

irradiation of H-1 at $\delta = 3.75$ ($CDCl_3$) gave rise to an NOE interaction with the axial H-3, thus indicating the *cis*-relationship between these protons.[32] Inspection of molecular models showed a higher congestion in the ring-closing reaction by α-glycosidic than by β-glycosidic bond formation. Therefore the formation of the major isomer **23** should be mainly determined by steric factors. The same stereochemical control appeared to be operative in the TMSOTf-promoted self-condensation of the pentenyl hydroxymethylgalactoside **6** which, in fact, afforded the (α,β)-isomer **23** in 64 % yield. This finding is inconsistent with the existence of two α-D-(2 → 1)-linkages in the self-condensation product of 3,4,5,7-tetra-*O*-benzyl-α-D-*gluco*-2-heptulopyranose.[33] In our hands the cyclic dimer **29** obtained in 65 % yield by self-condensation of either ethyl α-(**27**) or β-(**28**) D-*gluco*-2-heptulopyranoside showed NMR spectra fully consistent with the presence of two pyranose units with α- and β-D-(2 → 1)-glycosidic bonds (Scheme 7). Hence the earlier stereochemical assignment of van Boom and co-workers[33] appears to be incorrect.



Scheme 7. a) TMSOTf (1.5 equiv), 4 Å molecular sieves, CCl_3CN, room temperature, 30 min.

While there are several examples of cyclic (2 → 1)-disaccharides, called ketose dianhydrides, made up of D-fructofuranose,[34] D-fructopyranose,[35] L-ribulose,[36] L-fucose,[37] and D-*manno*-octulose residues,[38] no examples are known of higher oligomers prepared by chemical synthesis. The only products of this class of compounds are the above-mentioned cyclofructins, the cyclic oligomers of D-fructofuranose produced by enzymatic degradation of inulin.[12] Therefore it was quite rewarding to observe that the intramolecular glycosylation of **12** under the conditions employed for **10** occurred in a stereoselective manner to give the cyclic (α,α,α)-D-trisaccharide **30** and its (α,α,β)-D-anomer **31** in 42 and 8% yields, respectively (Scheme 8). Evidently, in this case the steric factors did not adversely affect the formation of the α(axial)-linkage which was expected on the basis of a nonparticipating neighboring group and solvent.[1] The yields and stereoselectivity of the glycosidation did not improve at higher dilutions of up to 10^{-3} M or by the presence of metal cations such as lithium, sodium, potassium, or calcium, which were efficiently captured by **30** (see below). The highly symmetrical ^1H and ^{13}CNMR spectra of **30** indicated that the three monosaccharide units exhibited identical (2 → 1)-glycoside bonds. The α-D-configuration of these bonds was firmly established by X-ray crystallography (Figure 1). On the other hand, the structure assignment for the syrupy isomer **31** was less straightforward because the ^1HNMR spectra in $CDCl_3$ and [D_6]DMSO at room temperature displayed some broadened signals together with sharp ones. The coalescence of the signals in [D_6]DMSO at 100 °C revealed the dynamic nature of the observed phenomenon, that is, some conformational changes of the molecule on a time scale that approached the NMR time scale at room temperature. Since the high-temperature NMR spectrum indicated a nonsymmetrical structure, compound **31** was characterized as being made up of two galactopyranose units with α-D-(2 → 1)-glycoside linkages and of one unit with a β-D-(2 → 1)-glycoside linkage. Finally, dimers **23** and **24** and trimer **30** were debenzylated by catalytic hydrogenolysis to give the hydroxy-free products **25**, **26**, and **32**, respectively, in nearly quantitative yields.



Scheme 8. a) NIS (2 equiv), TMSOTf (1 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 1 h; b) H_2, $Pd(OH)_2$, AcOEt/MeOH, room temperature, 3 h.

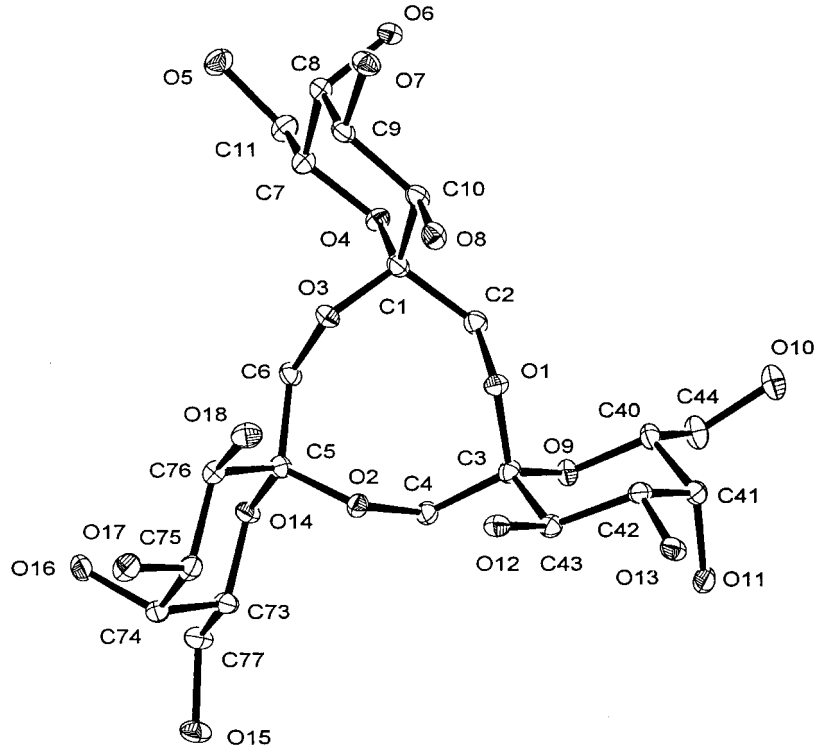


Figure 1. ORTEP view of the cyclic trisaccharide **30** showing the thermal ellipsoids at the 40% probability level (the benzyl groups and the hydrogen atoms are omitted for clarity).

Several attempts were made to prepare cyclic tetra- and pentasaccharide oligomers by means of intramolecular glycosidation of the corresponding linear alcohols **14** and **16**. In both cases, the NIS-TMSOTf reactions afforded complex mixtures of products as determined by MS analysis. However, the cyclic trimers **30** and **31** (ca. 20%) and the dimer **23** (traces) were isolated by column chromatography. A very small sample of a cyclic tetramer was also obtained. Unfortunately, attempts to purify this compound failed, thus preventing its characterization by NMR spectroscopy. It is suggested that the cleavage of the oligosaccharide chain of **14** and **16** occurs either by intramolecular glycosidation or by hydrolysis followed by ring closure. The latter hypothesis seems unlikely since cleavage reactions were not observed in the intermolecular glycosylation of di-, tri-, and tetrasaccharide alcohols with phosphite **3**, in the presence of TMSOTf.

Structure and binding properties of the cyclic trimer 30: The most investigated carbohydrate-based macrocycles are the natural and unnatural cyclic oligoaldosides called cyclodextrins.[6] Carbohydrate-containing crown ethers in which the sugar moieties are part or an appendage of the macrocyclic ring were also prepared.[39] Inspection of the structure of the cyclic trisaccharide **30** determined by X-ray crystallography at 100 K (Figure 1) revealed a [9]crown-3 ether core bearing the galactopyranose rings spiroanellated in a propellerlike fashion. The oxygen atoms of the crown ether are nearly coplanar and face the oxygen atoms linked to C-3 of the D-*galacto*-2-heptulopyranose units. This conformation of the macrocycle was expected on the basis of the *exo*-anomeric effect,[32] that is, the O1–C2 bond is antiperiplanar to the C3–C43 bond, O2–C4 to C5–C76, and O3–C6 to C1–C10 (see Figure 1). Owing to this spatial arrangement of the pyranose rings, the three oxygen atoms linked to C-3 and the three linked to C-4 lie in two planes above the crown ether macrocyclic core. The distance between these oxygen atoms indicate that the relevant holes are larger than that delimited by the crown ether below.[40] We envisaged the complexation ability of the polyalkoxylated cavity created by the oxygen atoms of the sugar moieties in the proximity of the crown ether toward guests which are sterically far beyond the binding properties of the very small macrocycle ring. Thus, the recognition ability of the trimer **30** was tested using various neutral and charged molecules as potential guests. While several organic molecules and some metal cations gave a negative response,[41] alkali metal cations revealed significant complexations. Ac-

0947-6539/01/0707-1376 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 7

cording to a recent method,[42] the tests were carried out by ^{1}HNMR spectroscopic analysis of **30** treated with a presaturated solution of salt in $CHCl_3/CH_3CN$ (see Experimental Section). The salts employed were $LiClO_4$, $NaClO_4$, KI,[43] $Ca(ClO_4)_2$, and $Mg(ClO_4)_2$. The spectra of the samples prepared with the lithium, sodium, potassium, and calcium salts showed only the presence of the corresponding complexes. These spectra were different for each complex (see Supporting Information). On the other hand, the spectrum obtained from the magnesium sample exhibited two sets of host signals, one corresponding to free **30** (ca. 85%) and the other to the metal cation complex (ca. 15%). However, the addition of finely powdered $Mg(ClO_4)_2$ into the NMR tube, followed by sonication and heating (50 °C) for a few seconds resulted in the quantitative formation of a new complex of **30**. All the complexes were totally dissociated by the addition of small amounts of water. Unfortunately, the same complexation experiments could not be carried out with the cyclic trisaccharide **31** because of the severe signal broadening in its ^{1}HNMR spectrum at room temperature. On the other hand, repetition of the above recognition tests[42] using the cyclic α,β-dimer **23** and the α,α-anomer **24** did not show binding properties.

Conclusion

Following earlier work on thiazolylketose chemistry, a new and efficient method has been developed that allows the assembly of $(2\rightarrow1)$-linked ketoside units with high α-stereoselectivity by means of an iterative glycosidation–hydroxymethylation. The method has been illustrated by the synthesis of oligomers of D-*galacto*-2-heptulopyranose up to the pentameric stage. Further chain lengthening appears to be feasible. The strategy is highlighted by the transformation of linear di- and trisaccharide oligomers into cyclic products. The use of the latter compound as a potent although unselective receptor for alkali metal cations was demonstrated. The extension of this strategy to the synthesis of both linear and cyclic ketoside oligomers of pyranoses and furanoses will be investigated in the future. The successful implementation of this method for the synthesis of cyclic higher oligomers, such as those containing four and five carbohydrate units spiroanellated in [12]crown-4 and [15]crown-5 ether cores presents another challenge. The use of this new class of chiral crown ether derivatives can be foreseen in molecular recognition processes of important biomolecules such as lectins and selectins and for the study of chiral recognition in various enzymatic reactions.[39]

Experimental Section

General: All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Anhydrous solvents were dried over standard drying agents[44] and were freshly distilled prior to use. Commercially available powdered molecular sieves (4 Å, 5 μm average particle size) were used without further activation. Commercially available *N*-iodosuccinimide (white crystals, ≈97% pure) was not recrystallised but only powdered prior to use. Reactions were monitored by TLC on silica gel 60 F_{254}, detection by charring with sulfuric acid. Flash-column chromatography[45] was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{31}P (121 MHz) NMR spectra were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were acquired using α-cyano-4-hydroxycinnamic acid or 2,5-dihydroxybenzoic acid as the matrix.

2,3,4,6-Tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α-D-galactopyranosyl diethyl phosphite (3): Freshly distilled *i*Pr_2EtN (1.74 mL, 10.00 mmol) and freshly distilled $ClP(OEt)_2$ (0.94 mL, 6.50 mmol) were added successively to a stirred solution of **1** (3.12 g, 5.00 mmol) in anhydrous CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 20 min, then concentrated (bath temperature not exceeding 30 °C). The residue was eluted from a short column (4 × 10 cm, d × h) of silica gel with cyclohexane/AcOEt (10:1, containing 3% of Et_3N). The first product to be isolated was **3** (3.05 g, 82%) as a syrup, slightly contaminated with uncharacterised by-products. ^{1}H NMR: $\delta = 7.81$ (d, $J = 3.2$ Hz, 1H; Th), 7.39–7.21 (m, 21H; 4 Ph, Th), 5.01 and 4.69 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 4.76 (s, 2H; PhCH_2), 4.70 and 4.47 (2 d, $J = 10.7$ Hz, 2H; PhCH_2), 4.52 and 4.47 (2 d, $J = 12.0$ Hz, 2H; PhCH_2), 4.40 (ddd, $J_{4,5} = 0.7$, $J_{5,6a} = 7.8$, $J_{5,6b} = 5.5$ Hz, 1H; H-5), 4.33 (dd, $J_{2,3} = 9.5$, $J_{2,P} = 1.7$ Hz, 1H; H-2), 4.14 (dd, $J_{3,4} = 2.7$ Hz, 1H; H-4), 4.13 (dd, 1H; H-3), 4.01–3.81 (m, 4H; 2CH_2CH$_3$), 3.77 (dd, $J_{6a,6b} = 9.3$ Hz, 1H; H-6a), 3.64 (dd, 1H; H-6b), 1.21 and 1.20 (2t, $J = 7.0$ Hz, 6H; 2CH_2CH_3); ^{31}P NMR: $\delta = 136.1$. Further elution with cyclohexane/AcOEt (3:1) afforded **1** (0.19 g, 6%).

4-Pentenyl 2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α- and **-β-D-galactopyranoside (4 and 5)**: A mixture of **2** (6.66 g, 10.00 mmol), 4-penten-1-ol (3.10 mL, 30.00 mmol), activated powdered molecular sieves (4 Å, 5.00 g), and anhydrous CH_2Cl_2 (50 mL) was stirred at room temperature for 10 min. The suspension was then cooled to 0 °C and treated with TMSOTf (1.81 mL, 10.00 mmol). The mixture was stirred at 0 °C for 15 min, warmed to room temperature, stirred for an additional 60 min, diluted with Et_3N (2.0 mL) and CH_2Cl_2 (150 mL), and then filtered through a pad of Celite. The solution was washed with H_2O (30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 5:1 to 3:1). The first product to be eluted was **5** (0.48 g, 7%) as a white solid. M.p. 62–63 °C (from MeOH); $[\alpha]_D = +57.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR: $\delta = 7.78$ (d, $J = 3.2$ Hz, 1H; Th), 7.35–7.23 (m, 21H; Ph, Th), 5.78 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; CH=CH$_2$), 4.99 and 4.63 (2 d, $J = 11.6$ Hz, 2H; PhCH_2), 4.98 and 4.81 (2 d, $J = 11.4$ Hz, 2H; PhCH_2), 4.98 (dddd, $J = 1.7$, 1.7, 2.0, 17.0 Hz, 1H; CH=CH_2), 4.91 (dddd, $J = 1.3$, 1.3, 2.0, 10.2 Hz, 1H; CH=CH_2), 4.74 and 4.67 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 4.53 (ddd, $J_{4,5} = 1.0$, $J_{5,6a} = J_{5,6b} = 6.8$ Hz, 1H; H-5), 4.51 and 4.44 (2 d, $J = 11.6$ Hz, 2H; PhCH_2), 4.38 (d, $J_{2,3} = 10.3$ Hz, 1H; H-2), 4.04 (dd, $J_{3,4} = 2.7$ Hz, 1H; H-4), 4.03 (dd, 1H; H-3), 3.76–3.64 (m, 3H; 2 H-6, OCH_2CH$_2$), 3.52–3.44 (m, 1H; OCH_2CH$_2$), 2.18–2.03 and 1.70–1.59 (2 m, 4H; OCH$_2$CH_2CH_2); ^{13}C NMR: $\delta = 167.8$, 141.5, and 120.6 (Th), 139.0, 138.7, 138.5, 138.1, and 128.3–127.3 (Ph), 138.2 and 114.6 (CH=CH$_2$), 101.5 (C-1), 80.2, 79.1, 75.2, 74.5 (2C), 73.3, 73.0, 72.7, 68.4, 61.7, 30.3, 29.1; elemental analysis for $C_{42}H_{45}NO_6S$ (691.89): calcd: C 72.91, H 6.56, N 2.02; found: C 72.83, H 6.61, N 2.11. Further elution afforded **4** (5.95 g, 86%). $[\alpha]_D = +11.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR: $\delta = 7.82$ (d, $J = 3.2$ Hz, 1H; Th), 7.37–7.20 (m, 21H; 4 Ph, Th), 5.79 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; CH=CH$_2$), 4.98 (dddd, $J = 1.7$, 1.7, 2.0, 17.0 Hz, 1H; CH=CH_2), 4.98 and 4.64 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.92 (dddd, $J = 1.3$, 1.3, 2.0, 10.2 Hz, 1H; CH=CH_2), 4.78 and 4.72 (2 d, $J = 11.5$ Hz, 2H; PhCH_2), 4.60 and 4.30 (2 d, $J = 10.9$ Hz, 2H; PhCH_2), 4.53 and 4.47 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 4.18 (dd, $J_{2,3} = 10.1$, $J_{3,4} = 2.6$ Hz, 1H; H-3), 4.08 (d, 1H; H-2), 4.07 (dd, $J_{4,5} = 1.2$ Hz, 1H; H-4), 4.00 (ddd, $J_{5,6a} = 7.1$, $J_{5,6b} = 6.0$ Hz, 1H; H-5), 3.76 (dd, $J_{6a,6b} = 9.3$ Hz, 1H; H-6a), 3.69 (dd, 1H; H-6b), 3.51–3.39 (m, 2H; OCH_2CH$_2$), 2.13–2.04 and 1.81–1.71 (2 m, 4H; OCH$_2$CH_2CH_2); ^{13}C NMR: $\delta = 167.9$, 142.6, and 120.6 (Th), 138.9, 138.6, 138.1, 138.0, and 128.5–127.3 (Ph), 138.2 and 114.7 (CH=CH$_2$), 100.9 (C-1), 80.2, 79.9, 75.3, 74.8, 74.4, 73.5, 73.0, 71.5, 68.8, 62.4, 30.4, 28.7; elemental analysis for $C_{42}H_{45}NO_6S$ (691.89): calcd: C 72.91, H 6.56, N 2.02; found: C 73.16, H 6.69, N 2.20.

4-Pentenyl 3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranoside (6): A mixture of **4** (5.53 g, 8.00 mmol), activated powdered molecular sieves (4 Å, 4.00 g), and anhydrous CH_3CN (40 mL) was stirred at room temperature

for 10 min. Methyl triflate (1.18 mL, 10.40 mmol) was then added. The suspension was stirred at room temperature for 15 min, and then concentrated to dryness without filtering off the molecular sieves. $NaBH_4$ (0.60 g, 16.00 mmol) was added to a stirred suspension of the crude *N*-methylthiazolium salt in Et_2O/MeOH (1:1, 40 mL). The mixture was stirred at room temperature for an additional 5 min, diluted with acetone (4 mL), filtered through a pad of Celite, and concentrated. H_2O (7.0 mL) and then $AgNO_3$ (2.04 g, 12.00 mmol) were slowly added to a vigorously stirred solution of the crude diastereomeric mixture of thiazolidines in CH_3CN (73 mL). The mixture was stirred at room temperature for 10 min, then treated with phosphate buffer at pH 7 (1M, 8.0 mL, 8.00 mmol), stirred for an additional 10 min, diluted with more phosphate buffer (ca. 50 mL), and concentrated to remove acetonitrile (bath temperature not exceeding 40 °C). The mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic phases were dried (Na_2SO_4), and concentrated. The residue was suspended in Et_2O (50 mL), filtered through a pad of Celite to remove most of the silver salts, and concentrated to afford the aldehyde. Selected ^{1}HNMR data: $\delta = 9.34$ (s, 1H; H-1). $NaBH_4$ (0.60 g, 16.00 mmol) was added to a stirred solution of the crude aldehyde in Et_2O/MeOH (1:1, 40 mL). The mixture was stirred at room temperature for an additional 15 min, diluted with acetone (4 mL), and concentrated. The brown residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 5:1 to 3:1) to give **6** (4.34 g, 85%) as a syrup. $[\alpha]_D = +26.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR: $\delta = 7.41 - 7.25$ (m, 20H; 4Ph), 5.81 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 5.01 (dddd, $J = 1.7$, 1.7, 2.0, 17.0 Hz, 1H; CH=CH_2), 4.98 and 4.77 (2 d, $J = 11.3$ Hz, 2H; PhCH_2), 4.96 and 4.59 (2 d, $J = 11.4$ Hz, 2H; PhCH_2), 4.94 (dddd, $J = 1.3$, 1.3, 2.0, 10.2 Hz, 1H; CH=CH_2), 4.78 and 4.74 (2 d, $J = 11.6$ Hz, 2H; PhCH_2), 4.50 and 4.44 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.19 (d, $J_{3,4} = 10.1$ Hz, 1H; H-3), 4.09 (dd, $J_{4,5} = 2.7$ Hz, 1H; H-4), 4.01 (dd, $J_{5,6} = 1.3$ Hz, 1H; H-5), 3.88 (ddd, $J_{6,7a} = J_{6,7b} = 6.5$ Hz, 1H; H-6), 3.64 (d, 2H; 2 H-7), 3.58 (dd, $J_{1a,OH} = 6.7$, $J_{1a,1b} = 9.3$ Hz, 1H; H-1a), 3.58 – 3.43 (m, 2H; OCH_2CH$_2$), 3.53 (dd, $J_{1b,OH} = 6.2$ Hz, 1H; H-1b), 2.28 (dd, 1H; OH), 2.15 – 2.06 and 1.76 – 1.66 (2 m, 4H; OCH$_2$CH_2CH_2); ^{1}H NMR (C_6D_6): $\delta = 7.40 - 7.00$ (m, 20H; 4 Ph), 5.75 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 5.05 and 4.60 (2 d, $J = 11.4$ Hz, 2H; PhCH_2), 5.02 and 4.72 (2 d, $J = 11.1$ Hz, 2H; PhCH_2), 5.02 (dddd, $J = 1.7$, 1.7, 2.0, 17.0 Hz, 1H; CH=CH_2), 4.95 (dddd, $J = 1.3$, 1.3, 2.0, 10.2 Hz, 1H; CH=CH_2), 4.49 (d, $J_{3,4} = 10.1$ Hz, 1H; H-3), 4.49 and 4.45 (2 d, $J = 11.3$ Hz, 2H; PhCH_2), 4.36 and 4.30 (2 d, $J = 12.0$ Hz, 2H; PhCH_2), 4.17 (dd, $J_{4,5} = 2.8$ Hz, 1H; H-4), 4.04 (ddd, $J_{5,6} = 1.3$, $J_{6,7a} = 6.8$, $J_{6,7b} = 6.2$ Hz, 1H; H-6), 3.95 (dd, 1H; H-5), 3.90 (dd, $J_{1a,OH} = 9.5$, $J_{1a,1b} = 11.5$ Hz, 1H; H-1a), 3.78 (dd, $J_{1b,OH} = 1.6$ Hz, 1H; H-1b), 3.74 (dd, $J_{7a,7b} = 9.1$ Hz, 1H; H-7a), 3.68 (dd, 1H; H-7b), 3.54 (dd, $J = 6.5$, 6.5 Hz, 2H; OCH_2CH$_2$), 2.44 (dd, 1H; OH), 2.12 – 2.04 and 1.66 – 1.55 (2m, 4H; OCH$_2$CH_2CH_2); ^{13}C NMR: $\delta = 138.6$, 138.4, 138.0, 137.9, and 128.5 – 127.4 (Ph), 138.1 and 114.7 (CH=CH$_2$), 99.5 (C-2), 80.3, 77.9, 75.2, 74.5 (2 C), 73.4, 72.5, 70.6, 68.8, 63.9, 60.6, 30.3, 29.0; elemental analysis for $C_{40}H_{46}O_7$ (638.81): calcd: C 75.21, H 7.26; found: C 75.34, H 7.38.

4-Pentenyl 3,4,5,7-tetra-*O*-benzyl-*β*-D-*galacto*-heptulopyranoside (7): The thiazolylketoside **5** (0.69 g, 1.00 mmol) was treated as described for the preparation of **6** to afford the corresponding aldehyde. Selected ^{1}HNMR data: $\delta = 9.72$ (d, $J_{1,3} = 1.2$ Hz, 1H; H-1). The aldehyde was then reduced to give, after column chromatography on silica gel (3:1 cyclohexane/AcOEt), compound **7** (0.53 g, 83%) as a syrup. $[\alpha]_D = +20.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR: $\delta = 7.40 - 7.28$ (m, 20H; 4Ph), 5.85 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 5.03 (dddd, $J = 1.7$, 1.7, 2.0, 17.0 Hz, 1H; CH=CH_2), 5.00 and 4.64 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 4.97 (dddd, $J = 1.3$, 1.3, 2.0, 10.2 Hz, 1H; CH=CH_2), 4.88 and 4.78 (2 d, $J = 11.0$ Hz, 2H; PhCH_2), 4.51 and 4.46 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.24 (d, $J_{3,4} = 10.0$ Hz, 1H; H-3), 3.97 (dd, $J_{4,5} = 3.8$, $J_{5,6} = 0.7$ Hz, 1H; H-5), 3.95 (dd, $J_{1a,OH} = 4.9$, $J_{1a,1b} = 12.3$ Hz, 1H; H-1a), 3.83 (dd, $J_{1b,OH} = 7.1$ Hz, 1H; H-1b), 3.77 (dd, $J_{6,7a} = 7.2$, $J_{7a,7b} = 9.3$ Hz, 1H; H-7a), 3.76 (ddd, $J_{6,7b} = 6.6$ Hz, 1H; H-6), 3.72 (dd, 1H; H-4), 3.64 – 3.60 (m, 2H; OCH_2CH$_2$), 3.58 (dd, 1H; H-7b), 2.38 (dd, 1H; OH), 2.19 – 2.10 (m, 2H; OCH$_2$CH$_2$CH_2), 1.79 – 1.65 (m, 2H; OCH$_2$CH_2CH$_2$); ^{13}C NMR: $\delta = 138.8$, 138.4, 138.3, 137.8, and 128.3 – 127.3 (Ph), 138.3 and 114.6 (CH=CH$_2$), 101.1 (C-2), 81.3, 78.4, 75.2, 74.3, 73.7, 73.4, 72.8, 72.2, 68.8, 61.9, 60.9, 30.3, 29.3; elemental analysis for $C_{40}H_{46}O_7$ (638.81): calcd: C 75.21, H 7.26; found: C 75.44, H 7.29.

2,3,4,6-Tetra-*O*-benzyl-1-*C*-[2-(5-diphenoxyphosphorylthiazolyl)]-*α*-D-galactopyranose (8): *n*-Butyllithium (0.69 mL, 1.10 mmol, 1.6M solution in hexanes) was slowly added to a cooled (0 °C), stirred solution of **1** (0.62 g, 1.00 mmol) in anhydrous THF (5.0 mL). After 10 min, a solution of $ClP(O)(OPh)_2$ (0.25 mL, 1.20 mmol) in anhydrous THF (2.0 mL) was added to the stirred solution. The mixture was stirred at −60 °C for 30 min, then diluted with phosphate buffer at pH 7 (1M, 20 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 3:1 to 1:1) to give **1** (0.28 g, 45%). Further elution afforded **8** (0.34 g, 40%). M.p. 95 – 97 °C (from cyclohexane); $[\alpha]_D = -12.2$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR: $\delta = 8.26$ (d, $J_{H,P} = 4.2$ Hz, 1H; Th), 7.38 – 7.12 and 7.01 – 6.97 (2 m, 30H; 6 Ph), 5.00 and 4.69 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 4.76 and 4.70 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.66 and 4.24 (2 d, $J = 10.8$ Hz, 2H; PhCH_2), 4.54 (s, 1H; OH), 4.48 (d, $J_{2,3} = 9.6$ Hz, 1H; H-2), 4.48 and 4.42 (2 d, $J = 12.0$ Hz, 2H; PhCH_2), 4.28 (ddd, $J_{4,5} = 0.6$, $J_{5,6a} = 7.6$, $J_{5,6b} = 5.8$ Hz, 1H; H-5), 4.10 (dd, $J_{3,4} = 2.6$ Hz, 1H; H-4), 3.98 (dd, 1H; H-3), 3.66 (dd, $J_{6a,6b} = 9.1$ Hz, 1H; H-6a), 3.59 (dd, 1H; H-6b); ^{31}P NMR: $\delta = 2.4$; MALDI-TOF MS: 879.1 [*M*+Na], 895.3 [*M*+K]; elemental analysis for $C_{49}H_{46}NO_9PS$ (855.95): calcd: C 68.76, H 5.42, N 1.64; found: C 68.88, H 5.51, N 1.76.

CYCLE A

4-Pentenyl 3,4,5,7-tetra-*O*-benzyl-1-*O*-[2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-*α*-D-galactopyranosyl]-*α*-D-*galacto*-heptulopyranoside (9): A mixture of phosphite **3** (2.97 g, 4.00 mmol), alcohol **6** (2.55 g, 4.00 mmol), activated powdered molecular sieves (4 Å, 4.00 g), and anhydrous CH_2Cl_2 (40 mL) was stirred at room temperature for 10 min, and then cooled to 0 °C. Freshly distilled $BF_3 \cdot Et_2O$ (0.61 mL, 4.00 mmol) was added dropwise to the mixture. After 15 min, a solution of **3** (2.97 g, 4.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added over a 10-min period, followed by $BF_3 \cdot Et_2O$ (0.61 mL, 4.00 mmol). The mixture was stirred at 0 °C for an additional 15 min, diluted with Et_3N (1.7 mL, 12.0 mmol), warmed to room temperature, diluted with CH_2Cl_2, filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 7:1 to 1:1) to afford **9** (3.28 g, 66%) as a syrup. $[\alpha]_D = +37.2$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.78$ (d, $J = 3.2$ Hz, 1H; Th), 7.42 – 6.83 (m, 41H; 8 Ph, Th), 5.72 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 5.05 and 4.59 (2 d, $J = 11.6$ Hz, 2H; PhCH_2), 5.03 and 4.75 (2 d, $J = 11.0$ Hz, 2H; PhCH_2), 4.97 – 4.86 (m, 2H; CH=CH_2), 4.90 and 4.63 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.81 and 4.75 (2 d, $J = 11.6$ Hz, 2H; PhCH_2), 4.67 and 4.10 (2 d, $J = 11.0$ Hz, 2H; PhCH_2), 4.58 and 4.49 (2 d, $J = 11.7$ Hz, 2H; PhCH_2), 4.36 and 4.28 (2 d, $J = 11.8$ Hz, 2H; PhCH_2), 3.47 – 3.38 and 3.25 – 3.18 (2 m, 2H; OCH_2CH$_2$), 2.03 – 1.94 and 1.62 – 1.56 (2 m, 4H; OCH$_2$CH_2CH_2); ^{13}C NMR: $\delta = 166.6$, 142.1, and 120.8 (Th), 139.6, 139.3, 139.1, 138.9, 138.3, 138.1, 138.0 (2 C), and 128.6 – 126.6 (Ph), 138.4 and 114.7 (CH=CH$_2$), 101.2 (C-2), 100.5 (C-1′), 80.0 (2 C), 76.0 (2 C), 75.4, 74.9, 74.7, 74.3, 74.2, 73.4, 73.1, 72.8, 71.7, 70.6, 70.5, 68.9, 68.5, 63.2, 60.2, 30.1, 28.9; elemental analysis for $C_{77}H_{81}NO_{12}S$ (1244.57): calcd: C 74.31, H 6.56, N 1.12; found: C 74.12, H 6.66, N 1.20. Further elution led to the recovery of unreacted alcohol **7** (0.54 g, 21%). Eluted third was phosphonate **22** (3.27 g, 55%).

4-Pentenyl 3,4,5,7-tetra-*O*-benzyl-1-*O*-[3,4,5,7-tetra-*O*-benzyl-*α*-D-*galacto*-heptulopyranosyl]-*α*-D-*galacto*-heptulopyranoside (10): A mixture of **9** (4.98 g, 4.00 mmol), activated powdered molecular sieves (4 Å, 4.00 g), and anhydrous CH_3CN (80 mL) was stirred at room temperature for 10 min. Methyl triflate (0.59 mL, 5.20 mmol) was then added. The suspension was stirred at room temperature for 15 min and then concentrated to dryness without filtering off the molecular sieves. $NaBH_4$ (0.30 g, 8.00 mmol) was added to a stirred suspension of the crude *N*-methylthiazolium salt in Et_2O/MeOH (1:1, 80 mL). The mixture was stirred at room temperature for an additional 5 min, diluted with acetone (4 mL), filtered through a pad of Celite, and concentrated. H_2O (3.0 mL) and then $AgNO_3$ (1.02 g, 6.00 mmol) were slowly added to a vigorously stirred solution of the residue in CH_3CN (77 mL). The mixture was stirred at room temperature for 10 min, then treated with phosphate buffer at pH 7 (1M, 4.0 mL, 4.00 mmol), stirred for an additional 10 min, diluted with more phosphate buffer (ca. 50 mL), and concentrated to remove acetonitrile (bath temperature not exceeding 40 °C). The mixture was extracted with CH_2Cl_2 (2 · 100 mL), and the combined organic phases were dried (Na_2SO_4), and concentrated. The residue was suspended in Et_2O (50 mL), filtered through a pad of Celite to remove most of the silver salts, and concentrated to give **17**. Selected ^{1}H NMR data: $\delta = 9.38$ (s, 1H; H-1′). $NaBH_4$ (0.30 g, 8.00 mmol) was added to a stirred solution of the crude aldehyde in Et_2O/MeOH (1:1, 80 mL). The mixture was stirred at room temperature for

0947-6539/01/0707-1378 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 7

an additional 15 min, diluted with acetone (4 mL), and concentrated. The brown residue was eluted from a column of silica gel with cyclohexane/AcOEt (5:1) to give **10** (3.43 g, 72%) as a syrup. $[\alpha]_D = +48.5$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.43-6.92$ (m, 40H; 8 Ph), 5.78 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 3.54–3.47 and 3.42–3.35 (2 m, 2H; OC*H*$_2$CH$_2$), 2.53 (dd, $J_{1',OH} = 3.4$, $J_{1'b,OH} = 8.4$ Hz, 1H; OH), 2.13–1.99 and 1.71–1.62 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); ^{13}C NMR: $\delta = 139.7$, 139.1, 139.0, 138.9, 138.2 (2 C), 138.1, 138.0, and 128.2–127.0 (Ph), 138.1 and 114.7 (CH=CH$_2$), 101.3 (C-2), 99.1 (C-2′), 80.0 (2 C), 79.0, 76.1 (2 C), 75.4, 75.1, 74.7, 74.5, 74.0, 73.4, 73.2, 72.9, 71.1, 70.6, 69.8, 69.0, 68.6, 64.9, 62.0, 60.3, 30.3, 29.0; elemental analysis for $C_{75}H_{82}O_{13}$ (1191.48): calcd: C 75.61, H 6.94; found: C 75.77, H 6.89.

CYCLE B

Thiazolyltrisaccharide 11: Alcohol **10** (2.38 g, 2.00 mmol) was glycosylated with **3** (2.97 g, 4.00 mmol) as described for the preparation of **9** to give, after column chromatography on silica gel with cyclohexane/AcOEt (from 7:1 to 1:1) **11** (2.23 g, 62%) as a syrup. $[\alpha]_D = +38.5$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.78$ (d, $J = 3.2$ Hz, 1H; Th), 7.40–6.90 (m, 61H; 12 Ph, Th), 5.78 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 3.30–3.22 (m, 1H; OC*H*$_2$CH$_2$), 2.10–1.98 and 1.67–1.58 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); Selected ^{13}C NMR data: $\delta = 166.5$, 142.1, and 121.0 (Th), 114.7 (CH=*C*H$_2$), 101.3 (C-2, C-2′), 100.6 (C-1″); MALDI-TOF MS: 1820.6 [*M*+Na], 1835.8 [*M*+K]; elemental analysis for $C_{112}H_{117}NO_{18}S$ (1797.24): calcd: C 74.85, H 6.56, N 0.78; found: C 75.11, H 6.65, N 0.91. Further elution led to the recovery of unreacted **10** (0.71 g, 30%). Eluted third was phosphonate **22** (1.61 g, 54%).

Trisaccharide 12: Thiazolyltrisaccharide **11** (3.59 g, 2.00 mmol) was treated as described for the preparation of **10** to give, after column chromatography on silica gel with cyclohexane/AcOEt (5:1), compound **12** (2.37 g, 68%) as a syrup; $[\alpha]_D = +44.6$ ($c = 0.9$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.40-6.81$ (m, 60H; 12 Ph), 5.80 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 3.53–3.46 and 3.37–3.30 (2 m, 2H; OC*H*$_2$CH$_2$), 2.47 (dd, 1H; $J = 3.8$, 8.2 Hz, OH), 2.13–1.98 and 1.70–1.60 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); selected ^{13}C NMR data: $\delta = 114.7$ (CH=*C*H$_2$), 101.3 (C-2, C-2′), 99.3 (C-2″); MALDI-TOF MS: 1767.6 [*M*+Na], 1784.0 [*M*+K]; elemental analysis for $C_{110}H_{118}O_{19}$ (1744.15): calcd: C 75.75, H 6.82; found: C 75.58, H 6.92.

CYCLE C

Thiazolyltetrasaccharide 13: Alcohol **12** (1.74 g, 1.00 mmol) was glycosylated with **3** (1.49 g, 2.00 mmol) as described for the preparation of **9** to give, after column chromatography on silica gel with cyclohexane/AcOEt (from 6:1 to 1:1), compound **13** (1.27 g, 54%) as a syrup. $[\alpha]_D = +32.3$ ($c = 0.8$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.80$ (d, $J = 3.2$ Hz, 1H; Th), 7.42–6.70 (m, 81H; 16 Ph, Th), 5.82 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 2.12–2.04 and 1.71–1.62 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); Selected ^{13}C NMR data: $\delta = 166.4$, 142.0, and 121.2 (Th), 114.6 (CH=*C*H$_2$), 101.5 and 101.4 (C-2, C-2′, C-2″), 100.7 (C-1‴); MALDI-TOF MS: 2373.3 [*M*+Na], 2389.8 [*M*+K]; elemental analysis for $C_{147}H_{153}NO_{24}S$ (2349.91): calcd: C 75.14, H 6.56, N 0.60; found: C 75.38, H 6.69, N 0.83. Further elution led to the recovery of unreacted **12** (0.70 g, 40%). Eluted third was phosphonate **22** (0.91 g, 61%).

Tetrasaccharide 14: Thiazolyltetrasaccharide **13** (1.17 g, 0.50 mmol) was treated as described for the preparation of **10** to give, after column chromatography on silica gel with cyclohexane/AcOEt (5:1), compound **14** (0.70 g, 61%) as a syrup. $[\alpha]_D = +37.5$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.40-6.79$ (m, 80H; 16 Ph), 5.78 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H* ~ CH$_2$), 3.48–3.40 and 3.32–3.24 (2 m, 2H; OC*H*$_2$CH$_2$), 2.46 (dd, $J = 5.2$, 7.0 Hz, 1H; OH), 2.09–1.95 and 1.66–1.55 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); selected ^{13}C NMR data: $\delta = 114.6$ (CH=*C*H$_2$), 101.6 and 101.4 (C-2, C-2′, C-2″), 99.4 (C-2‴); MALDI-TOF MS: 2320.3 [*M*+Na], 2336.8 [*M*+K]; elemental analysis for $C_{145}H_{154}O_{25}$ (2296.83): calcd: C 75.83, H 6.76; found: C 75.71, H 6.86.

CYCLE D

Thiazolylpentasaccharide 15: Alcohol **14** (0.46 g, 0.20 mmol) was glycosylated with **3** (0.30 g, 0.40 mmol) as described for the preparation of **9** to give, after column chromatography on silica gel with cyclohexane/AcOEt (from 7:1 to 1:1), compound **15** (0.29 g, 50%) as a syrup. $[\alpha]_D = +26.1$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR data: $\delta = 7.78$ (d, $J = 3.2$ Hz, 1H; Th), 7.43–6.64 (m, 101H; 20 Ph, Th), 5.84 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 2.14–2.04 and 1.75–1.63 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); selected ^{13}C NMR data: $\delta = 166.2$, 142.1, and 121.4 (Th), 114.6 (CH=*C*H$_2$), 101.8, 101.7, 101.6, and 101.5 (C-2, C-2′, C-2″, C-2‴), 100.7 (C-1‴′); MALDI-TOF MS: 2925.9 [*M*+Na], 2942.7 [*M*+K]; elemental analysis for $C_{182}H_{189}NO_{30}S$ (2902.59): calcd: C 75.31, H 6.56, N 0.48; found: C 75.50, H 6.63, N 0.65. Further elution led to the recovery of unreacted **14** (0.24 g, 53%). Eluted third was phosphonate **22** (0.18 g, 60%).

Pentasaccharide 16: Thiazolylpentasaccharide **15** (0.29 g, 0.10 mmol) was treated as described for the preparation of **10** to give, after column chromatography on silica gel with cyclohexane/AcOEt (7:1), **16** (0.16 g, 57%) as a syrup. $[\alpha]_D = +32.1$ ($c = 0.7$, $CHCl_3$); selected ^{1}H NMR data: $\delta = 7.41-6.75$ (m, 100H; 20 Ph), 5.77 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 3.17–3.09 (m, 1H; OC*H*$_2$CH$_2$), 2.47 (dd, $J = 4.8$, 7.0 Hz, 1H; OH), 2.07–1.92 and 1.62–1.52 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); selected ^{13}C NMR data: $\delta = 114.6$ (CH=*C*H$_2$), 101.8 (2 C), 101.6, and 101.5 (C-2, C-2′, C-2″, C-2‴), 99.6 (C-2‴′); MALDI-TOF MS: 2870.9 [M+Na], 2886.7 [M+K]; elemental analysis for $C_{180}H_{190}O_{31}$ (2849.50): calcd: C 75.87, H 6.72; found: C 75.70, H 6.85.

4-Pentenyl 3,4,5,7-tetra-*O*-benzyl-1-*O*-[methyl 3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranosylonate]-α-D-*galacto*-heptulopyranoside (18): Thiazolylketoside **9** (249 mg, 0.20 mmol) was treated as described for the preparation of **10** to afford the corresponding aldehyde **17**. A solution of KOH in MeOH (1M) and a solution of I_2 in MeOH (0.5M) were added dropwise and simultaneously to a vigorously stirred solution of the crude aldehyde **17** in Et$_2$O/MeOH (1:1, 4.0 mL), until the intermediate methyl hemiacetals, which formed in situ, had disappeared (TLC analysis). The mixture was then neutralised with AcOH and concentrated. The residue was diluted with CH_2Cl_2 (50 mL), washed with aqueous $Na_2S_2O_3 \cdot 5H_2O$ (10%, 10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (7:1) to give **18** (180 mg, 74%) as a syrup. $[\alpha]_D = +43.3$ ($c = 1.0$, $CHCl_3$); Selected ^{1}H NMR (C_6D_6) data: $\delta = 7.61-6.85$ (m, 40H; 8 Ph), 5.69 (dddd, $J = 6.5$, 6.5, 10.2, 17.0 Hz, 1H; C*H*=CH$_2$), 3.57–3.49 and 3.30–3.22 (2 m, 2H; OC*H*$_2$CH$_2$), 3.14 (s, 3H; CH$_3$), 2.04–1.95 and 1.57–1.47 (2 m, 4H; OCH$_2$C*H*$_2$C*H*$_2$); ^{13}C NMR (C_6D_6): $\delta = 168.3$ (C-1′), 140.2, 139.7, 138.9, 138.4, and 128.9–127.2 (Ph), 139.1 and 114.9 (CH=CH$_2$), 101.9 and 100.3 (C-2, C-2′), 80.4, 80.3, 79.0, 77.0, 76.7, 75.9, 75.5, 75.3 (2 C), 75.1, 73.5, 73.4, 73.2, 72.2, 71.4 (2 C), 69.8, 69.1, 64.7, 60.2, 51.7; elemental analysis for $C_{76}H_{82}O_{14}$ (1219.49): calcd: C 74.85, H 6.78; found: C 74.99, H 6.70.

Diethyl (2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α-D-galactopyranosyl)-phosphonate (22): A mixture of phosphite **3** (223 mg, 0.30 mmol), activated powdered molecular sieves (4 Å, 0.30 g), and anhydrous CH_2Cl_2 (3.0 mL) was stirred at room temperature for 10 min, then cooled to 0 °C. The mixture was treated with freshly distilled $BF_3 \cdot Et_2O$ (38 μL, 0.30 mmol), stirred at 0 °C for an additional 15 min, diluted with Et_3N (0.1 mL) and CH_2Cl_2, filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (2:1) to give **22** (194 mg, 87%) identical in all respects to the product prepared by a different route.[18] When the same reaction was performed using TMSOTf instead of $BF_3 \cdot Et_2O$ as the Lewis acid, the phosphonate **22** was isolated in 90% yield.

3,4,5,7-Tetra-*O*-benzyl-α-D-*galacto*-heptulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-β-D-*galacto*-heptulopyranose 1,2′:1′,2-dianhydride (23) and 3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranose 1,2′:1′,2-dianhydride (24): *Route A*: A mixture of **10** (238 mg, 0.20 mmol), activated powdered molecular sieves (4 Å, 1.00 g), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 min, then cooled to 0 °C. Powdered *N*-iodosuccinimide (90 mg, 0.40 mmol) was added to the mixture. After 5 min, a solution of TMSOTf in anhydrous CH_2Cl_2 (0.2M, 250 μL, 0.05 mmol) was added. Three portions of the same TMSOTf solution (250 μL each) were added to the reaction mixture after 15, 30, and 45 min. Stirring was continued at 0 °C for an additional 15 min. The reddish mixture was then diluted with Et_3N (0.5 mL), filtered through a pad of Celite, and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), washed with aqueous $Na_2S_2O_3 \cdot 5H_2O$ (10%, 2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (from 8:1 to 4:1) to give **24** (44 mg, 20%) as a syrup. $[\alpha]_D = +64.4$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR: $\delta = 7.44-7.24$ and 7.18–7.13 (2 m, 40H; 8 Ph), 4.96 and 4.61 (2 d, $J = 11.5$ Hz, 4H; 2 PhC*H*$_2$), 4.93 and 4.77 (2 d, $J = 11.4$ Hz, 4H; 2 PhC*H*$_2$), 4.78 and 4.74 (2 d, $J = 11.5$ Hz, 4H; 2 PhC*H*$_2$), 4.45 and 4.38 (2 d, $J = 11.8$ Hz, 4H; 2 PhC*H*$_2$), 4.08 (dd, $J_{3,4} = 9.9$, $J_{4,5} = 2.8$ Hz, 2H; 2 H-4), 4.01 (dd, $J_{5,6} = 1.2$ Hz, 2H; 2 H-5), 3.98 (ddd, $J_{6,7a} = 7.7$, $J_{6,7b} = 5.5$ Hz, 2H; 2 H-6),

3.92 (d, 2H; 2 H-3), 3.75 and 3.55 (2 d, $J_{1a,1b}=12.2$ Hz, 4H; 4 H-1), 3.58 (dd, $J_{7a,7b}=9.3$ Hz, 2H; 2 H-7a), 3.50 (dd, 2H; 2 H-7b); ^{13}C NMR: $\delta=138.9$, 138.8, 138.6, 138.0, and 128.4–127.1 (Ph), 97.3 (C-2), 79.7 (C-4), 79.5 (C-3), 74.9 (C-5), 74.7, 74.2, 73.4, and 72.9 (Ph*C*H$_2$), 70.6 (C-6), 68.6 (C-7), 63.9 (C-1); MALDI-TOF MS: 1128.7 [*M*+Na], 1144.7 [*M*+K]; elemental analysis for $C_{70}H_{72}O_{12}$ (1105.35): calcd: C 76.06, H 6.57; found: C 76.32, H 6.73. Further elution afforded **23** (137 mg, 62%) as a syrup. M.p. 127–128°C (from MeOH); $[\alpha]_D=+38.7$ ($c=0.5$, $CHCl_3$); ^{1}H NMR: $\delta=7.39-7.22$ (m, 40H; 8 Ph), 4.98 and 4.72 (2 d, $J=11.2$ Hz, 2H; PhC*H*$_2$), 4.93 and 4.67 (2 d, $J=11.5$ Hz, 2H; PhC*H*$_2$), 4.93 and 4.59 (2 d, $J=11.4$ Hz, 2H; PhC*H*$_2$), 4.91 and 4.56 (2 d, $J=10.9$ Hz, 2H; PhC*H*$_2$), 4.75 and 4.69 (2 d, $J=11.6$ Hz, 2H; PhC*H*$_2$), 4.72 and 4.66 (2 d, $J=12.0$ Hz, 2H; PhC*H*$_2$), 4.47 and 3.44 (2 d, $J_{1a,1b}=11.3$ Hz, 2H; 2 H-1), 4.38 and 4.34 (2 d, $J=11.5$ Hz, 2H; PhC*H*$_2$), 4.35 and 4.29 (2 d, $J=11.5$ Hz, 2H; PhC*H*$_2$), 4.24 and 3.76 (2 d, $J_{1a,1b}=12.5$ Hz, 2H; 2 H-1), 4.10 (dd, $J_{4,5}=2.7$, $J_{5,6}=0.8$ Hz, 1H; H-5α), 4.05 (dd, $J_{3,4}=9.8$ Hz, 1H; H-4α), 4.04 (dd, $J_{4,5}=2.8$, $J_{5,6}=0.5$ Hz, 1H; H-5β), 3.95 (d, $J_{3,4}=10.6$ Hz, 1H; H-3β), 3.86 (ddd, $J_{6,7a}=9.1$, $J_{6,7b}=4.8$ Hz, 1H; H-6α), 3.81 (dd, $J_{6,7a}=9.1$, $J_{7a,7b}=7.3$ Hz, 1H; H-7aβ), 3.74 (ddd, $J_{6,7b}=3.5$ Hz, 1H; H-6β), 3.73 (d, 1H; H-3α), 3.72 (dd, $J_{7a,7b}=8.2$ Hz, 1H; H-7aα), 3.61 (dd, 1H; H-7bβ), 3.46 (dd, 1H; H-4β), 3.43 (dd, 1H; H-7bα); ^{13}C NMR: $\delta=$ 138.9, 138.7, 138.6, 138.5, 138.4, 138.0, 137.8, 137.7, and 128.5–127.4 (Ph), 97.0 (C-2β), 95.8 (C-2α), 80.9 (C-3β), 80.5 (C-4α), 80.2 (C-4β), 76.3 (C-3α), 75.8, 74.9, 74.7 (2 C), 73.6, 73.3, 73.1, and 72.6 (Ph*C*H$_2$), 73.9 (C-5α), 73.5 (C-5β), 71.6 (C-6β), 69.4 (C-6α), 68.1 (C-7α), 67.9 (C-7β), 62.4 and 55.3 (2 C-1); MALDI-TOF MS: 1128.8 [*M*+Na], 1144.7 [*M*+K]; elemental analysis for $C_{70}H_{72}O_{12}$ (1105.35): calcd: C 76.06, H 6.57; found: C 76.20, H 6.68.

Route B: TMSOTf (54 µL, 0.30 mmol) was added to a stirred mixture of **6** (128 mg, 0.20 mmol), activated powdered molecular sieves (4 Å, 0.20 g), and CCl_3CN (2.0 mL). The mixture was stirred at room temperature for 30 min, then diluted with Et_3N (0.2 mL) and CH_2Cl_2 (50 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (6:1) to give **23** (71 mg, 64%) as a syrup.

α-D-*Galacto*-heptulopyranose β-D-*galacto*-heptulopyranose 1,2′:1′,2-dianhydride (25): A vigorously stirred mixture of **23** (110 mg, 0.10 mmol), palladium hydroxide on carbon (20%, 55 mg), and MeOH/AcOEt (2:1, 5.0 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 3 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated to give **25** (37 mg, 97%) as a syrup. $[\alpha]_D=+63.1$ ($c=0.5$, H_2O); ^{1}H NMR (D_2O): $\delta=4.26$ and 3.36 (2 d, $J_{1a,1b}=11.9$ Hz, 2H; 2 H-1), 3.93 and 3.77 (2 d, $J_{1a,1b}=13.0$ Hz, 2H; 2 H-1), 3.82–3.52 (m, 9H), 3.49 (s, 2H), 3.32 (d, $J_{3,4}=9.8$ Hz, 1H; H-3); ^{13}C NMR (D_2O): $\delta=96.7$ (C-2β), 95.3 (C-2α), 74.0, 72.5, 71.9, 70.5, 70.0, 69.4, 69.0, 68.8, 62.5, 61.5 (2 C), 54.2; MALDI-TOF MS: 407.9 [*M*+Na], 423.9 [*M*+K]; elemental analysis for $C_{14}H_{24}O_{12}\cdot H_2O$ (402.36): C 41.79, H 6.51; found: C 41.70, H 6.55.

α-D-*Galacto*-heptulopyranose α-D-*galacto*-heptulopyranose 1,2′:1′,2-dianhydride (26): The cyclic disaccharide **24** (55 mg, 0.05 mmol) was hydrogenated as described for the preparation of **25** to give **26** (18 mg, 94%) as a syrup. $[\alpha]_D=+198.3$ ($c=0.4$, H_2O); ^{1}H NMR (D_2O): $\delta=3.89$ (ddd, $J_{5,6}=1.1$, $J_{6,7a}=7.2$, $J_{6,7b}=6.8$ Hz, 2H; 2 H-6), 3.85 (dd, $J_{4,5}=3.3$ Hz, 2H; 2 H-5), 3.83 and 3.64 (2 d, $J_{1a,1b}=12.6$ Hz, 4H; 4 H-1), 3.78 (dd, $J_{3,4}=10.1$ Hz, 2H; 2 H-4), 3.64 (dd, $J_{7a,7b}=11.7$ Hz, 2H; 2 H-7a), 3.60 (dd, 2H; 2 H-7b), 3.58 (d, 2H; 2 H-3); ^{13}C NMR (D_2O): $\delta=96.9$ (C-2), 72.8 (C-3, C-6), 70.3 (C-4), 69.5 (C-5), 63.7 (C-1), 61.5 (C-7); MALDI-TOF MS: 391.7 [*M*+Li]; elemental analysis for $C_{14}H_{24}O_{12}\cdot 2H_2O$ (420.38): calcd: C 40.00, H 6.71; found: C 40.05, H 6.79.

Ethyl 3,4,5,7-tetra-*O*-benzyl-α- and β-D-*gluco*-heptulopyranoside (27 and **28)**: A mixture of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-1-*C*-(2-thiazolyl)-α-D-glucopyranose[13] (1.33 g, 2.00 mmol), anhydrous ethanol (0.34 mL, 6.00 mmol), activated powdered molecular sieves (4 Å, 1.00 g), and anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature for 10 min, then cooled to 0°C and treated with TMSOTf (0.36 mL, 2.00 mmol). The mixture was stirred at 0°C for 15 min, warmed to room temperature, stirred for an additional 60 min, diluted with Et_3N (0.5 mL) and CH_2Cl_2 (100 mL), and filtered through a pad of Celite. The solution was washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane/AcOEt (4:1) to give a mixture of ethyl α- and β-D-thiazolylketosides (1:1, 1.12 g, 86%). This mixture was treated as described for the preparation of **6** to give, after column chromatography on silica gel with cyclohexane/AcOEt (3:1), compound **28** (0.42 g, 82%) as a syrup. $[\alpha]_D=+32.2$ ($c=1.1$, $CHCl_3$); ^{1}H NMR: $\delta=$ 7.40–7.17 (m, 20H; 4 Ph), 4.88 and 4.80 (2 d, $J=11.2$ Hz, 2H; PhC*H*$_2$), 4.86 and 4.71 (2 d, $J=10.9$ Hz, 2H; PhC*H*$_2$), 4.83 and 4.60 (2 d, $J=10.8$ Hz, 2H; PhC*H*$_2$), 4.62 and 4.56 (2 d, $J=12.4$ Hz, 2H; PhC*H*$_2$), 3.96 (dd, $J_{1a,OH}=$ 5.1, $J_{1a,1b}=12.6$ Hz, 1H; H-1a), 3.85 (dd, $J_{1b,OH}=7.3$ Hz, 1H; H-1b), 3.81–3.66 (m, 8H), 2.28 (dd, 1H; OH), 1.24 (t, 3H; $J=7.0$ Hz, CH_3); elemental analysis for $C_{37}H_{42}O_7$ (598.74): calcd: C 74.22, H 7.07; found: C 74.45, H 7.15. Further elution afforded **27** (0.40 g, 78%). M.p. 109–110°C (from cyclohexane); $[\alpha]_D=+25.9$ ($c=1.0$, $CHCl_3$); ^{1}H NMR: $\delta=7.39-7.26$ and 7.22–7.15 (2 m, 20H; 4 Ph), 4.96 and 4.92 (2 d, $J=11.2$ Hz, 2H; PhC*H*$_2$), 4.94 and 4.76 (2 d, $J=11.1$ Hz, 2H; PhC*H*$_2$), 4.85 and 4.55 (2 d, $J=10.8$ Hz, 2H; PhC*H*$_2$), 4.59 and 4.51 (2 d, $J=12.0$ Hz, 2H; PhC*H*$_2$), 4.53 (dd, $J_{3,4}=$ 9.7, $J_{4,5}=8.8$ Hz, 1H; H-4), 3.77–3.57 (m, 9H), 2.17 (dd, $J_{1a,OH}=4.8$, $J_{1b,OH}=8.1$ Hz, 1H; OH), 1.22 (t, $J=7.0$ Hz, 3H; CH_3); elemental analysis for $C_{37}H_{42}O_7$ (598.74): calcd: C 74.22, H 7.07; found: C 74.31, H 7.13.

3,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-heptulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-β-D-*gluco*-heptulopyranose 1,2′:1′,2-dianhydride (29): Alcohol **27** (120 mg, 0.20 mmol) was treated as described for the preparation of **23** in route B to give, after column chromatography on silica gel with cyclohexane/AcOEt (6:1), compound **29** (72 mg, 65%) as a syrup. Similar results were obtained when the β-D-anomer **28** was used as starting material. M.p. 144–146°C (from MeOH); $[\alpha]_D=+48.1$ ($c=0.4$, $CHCl_3$); lit.[33] M.p. 143°C; $[\alpha]_D=+34.2$ ($c=1$, $CHCl_3$); ^{1}H NMR: $\delta=7.40-7.11$ (m, 40H; 8 Ph), 5.02 and 4.69 (2 d, $J=11.7$ Hz, 2H; PhC*H*$_2$), 4.91 (s, 2H; PhC*H*$_2$), 4.88 and 4.58 (2 d, $J=11.5$ Hz, 2H; PhC*H*$_2$), 4.87 and 4.74 (2 d, $J=11.2$ Hz, 2H; PhC*H*$_2$), 4.83 and 4.56 (2 d, $J=10.8$ Hz, 2H; PhC*H*$_2$), 4.81 and 4.56 (2 d, $J=$ 10.7 Hz, 2H; PhC*H*$_2$), 4.69 and 4.50 (2 d, $J=12.0$ Hz, 2H; PhC*H*$_2$), 4.59 and 4.38 (2 d, $J=12.2$ Hz, 2H; PhC*H*$_2$), 4.42 and 3.41 (2 d, $J_{1a,1b}=11.2$ Hz, 2H; 2 H-1), 4.18 (d, $J_{1a,1b}=12.3$ Hz, H-1), 4.11 (dd, 1H; $J_{3,4}=9.2$, $J_{4,5}=9.0$ Hz, 1H; H-4α), 3.90–3.51 (m, 11H), 3.31 (d, 1H; H-3α); ^{13}C NMR: $\delta=138.5$ (2 C), 138.4, 138.2, 138.1 (2 C), 138.0, 137.6, and 128.3–127.1 (Ph), 96.3 (C-2β), 95.3 (C-2α), 83.6, 83.0 (C-4α), 82.6, 79.6 (C-3α), 78.1, 77.4, 75.6 (2 C), 75.4, 75.0, 74.9, 74.1, 73.7, 73.5, 73.3, 71.2, 68.8, 68.3, 62.3 (C-1), 55.6 (C-1); MALDI-TOF MS: 1128.5 [*M*+Na], 1144.4 [*M*+K]; elemental analysis for $C_{70}H_{72}O_{12}$ (1105.35): calcd: C 76.06, H 6.57; found: C 76.11, H 6.71.

Cyclotris-(2→1)-(3,4,5,7-tetra-*O*-benzyl-α-D-*galacto*-heptulopyranosyl) (30) and cyclic α,α,β-trisaccharide 31: Alcohol **12** (174 mg, 0.10 mmol) was treated as described for the preparation of **24** in route A. The crude reaction mixture was eluted from a column of silica gel with cyclohexane/AcOEt (9:1 then 6:1) to give compound **30** (70 mg, 40%). M.p. 127–129°C (from MeOH or cyclohexane); $[\alpha]_D=+118.1$ ($c=0.5$, $CHCl_3$); ^{1}H NMR: $\delta=7.58$ (dd, $J=1.2$, 7.7 Hz, 6H; 6 H_{ortho}), 7.34–7.16 and 7.01–6.97 (m, 45H; 9 Ph), 6.94 (tt, $J=1.2$, 7.7 Hz, 3H; 3 H_{para}), 6.56 (t, $J=7.7$ Hz, 6H; 6 H_{meta}), 5.16 and 4.55 (2 d, $J=9.5$ Hz, 6H; 3 PhC*H*$_2$), 5.00 and 4.59 (2 d, $J=11.6$ Hz, 6H; 3 PhC*H*$_2$), 4.44 and 4.38 (2 d, $J=12.4$ Hz, 6H; 3 PhC*H*$_2$), 4.42 and 4.22 (2 d, $J=11.8$ Hz, 6H; 3 PhC*H*$_2$), 4.03 and 3.46 (2 d, $J_{1a,1b}=14.5$ Hz, 6H; 6 H-1), 4.02 (d, $J_{3,4}=9.9$ Hz, 3H; 3 H-3), 3.86 (dd, $J_{4,5}=2.8$, $J_{5,6}=0.9$ Hz, 3H; 3 H-5), 3.78 (dd, 3H; 3 H-4), 3.73 (ddd, $J_{6,7a}=7.8$, $J_{6,7b}=5.6$ Hz, 3H; 3 H-6), 3.55 (dd, $J_{7a,7b}=9.0$ Hz, 3H; 3 H-7a), 3.44 (dd, 3H; 3 H-7b); ^{13}C NMR: $\delta=$ 139.2, 138.9, 138.6, 137.8, and 129.4–127.0 (Ph), 100.2 (C-2), 82.9 (C-3), 79.6 (C-4), 76.3, 74.7, and 73.7 (Ph*C*H$_2$), 75.2 (C-5), 71.0 (C-6), 68.5 (C-7), 62.4 (C-1); MALDI-TOF MS: 1681.1 [*M*+Na], 1696.5 [*M*+K]; elemental analysis for $C_{105}H_{108}O_{18}$ (1658.02): calcd: C 76.06, H 6.57; found: C 75.91, H 6.72. Compound **31** was eluted next (13 mg, 8%), slightly contaminated with uncharacterised by-products. An analytical sample was obtained by elution from a column of silica gel with $CHCl_3$. $[\alpha]_D=+38.6$ ($c=0.4$, $CHCl_3$); Selected ^{1}H NMR ([D]$_6$DMSO, 100°C) data: $\delta=7.40-7.03$ (m, 60H; 12 Ph), 5.02 and 4.55 (2 d, $J_{1a,1b}=12.0$ Hz, 2H; 2 H-1), 4.88 and 3.14 (2 d, $J_{1a,1b}=12.9$ Hz, 2H; 2 H-1), 4.17 and 3.91 (2 d, $J_{1a,1b}=13.0$ Hz, 2H; 2 H-1); MALDI-TOF MS: 1680.9 [*M*+Na], 1696.8 [*M*+K]; elemental analysis for $C_{105}H_{108}O_{18}$ (1658.02): calcd: C 76.06, H 6.57; found: C 76.33, H 6.63.

Cyclotris-(2→1)-(α-D-*galacto*-heptulopyranosyl) (32): Cyclic trisaccharide **30** (83 mg, 0.05 mmol) was hydrogenated as described for the preparation of **25** to give **32** (28 mg, 97%) as a syrup. $[\alpha]_D=+192.5$ ($c=$ 0.3, H_2O); ^{1}H NMR (D_2O): $\delta=4.07$ and 3.44 (2 d, $J_{1a,1b}=13.6$ Hz, 6H; 6 H-1), 3.82–3.71 (m, 12H), 3.62–3.53 (m, 6H); ^{13}C NMR (D_2O): $\delta=99.3$ (C-2), 73.1, 72.9, 70.4, 68.9, 62.4, 61.4; MALDI-TOF MS: 583.6 [*M*+Li], 599.5 [*M*+Na], 615.5 [*M*+K]; elemental analysis for $C_{21}H_{36}O_{18}\cdot H_2O$ (594.53): calcd: C 42.42, H 6.44; found: C 42.31, H 6.53.

0947-6539/01/0707-1380 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 7

Complexation experiments: A solution of the host (4 μmol) in a $CHCl_3$/CH_3CN mixture (1:1, 1.0 mL, commercially available HPLC-grade solvents), pre-saturated with $LiCLO_4$, $NaClO_4$, KI, $Ca(ClO_4)_2$, or $Mg(ClO_4)_2$ (dried for 2 h at 120 °C/0.1 mbar), was kept at room temperature for 1 h, then concentrated under high vacuum. The residue was diluted with $CDCl_3$ (0.8 mL), filtered into a NMR tube through a plug of cotton (previously washed with H_2O, MeOH, and $CHCl_3$ and dried in the oven), and analysed by ^{1}H NMR (300 MHz) spectroscopy. After the NMR spectroscopic analysis, the host was quantitatively recovered in the free form by washing the organic phase with H_2O. The ^{1}H NMR spectra of compound **30** complexed with the alkali metal cations are shown in the Supporting information.

Crystallographic measurements at $T = 100$ K: Single crystals of compound **30** suitable for X-ray crystallography were obtained by recrystallisation from cyclohexane. Crystal data: $C_{105}H_{108}O_{18} \cdot C_6H_{12}$, $M_r = 1742.08$, orthorhombic, space group $P2_12_12_1$, $a = 16.9676(2)$, $b = 20.0321(2)$, $c = 27.4653(3)$ Å, $V = 9335.4(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.240$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.83$ cm^{-1}, $F(000) = 3720$, crystal dimensions: $0.60 \times 0.31 \times 0.15$ mm. Data Collection and Processing: Nonius Kappa-CCD diffractometer, graphite-monochromated $Mo_{K\alpha}$ radiation, $T = 100$ K, 11 446 unique reflections measured, $\theta \leq 27.5°$, giving 9846 observed reflections with $I \geq 2\sigma(I)$. The data were corrected for Lorentz and polarisation effects, no absorption correction was applied. The structure was solved by direct methods using the SIR2000 system of programs.[46] The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were placed in calculated positions and allowed to ride on their parent atom carbons. Refinement by full matrix least-squares using SHELXL-97,[47] on F^2, with R (observed reflections) = 0.0367 and wR (all reflections) = 0.0849, 1162 parameters, $S = 1.04$. ORTEP[48] views of the molecule are shown in Figure 1 and in the Supporting Information.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-145423. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Mr. P. Formaglio (University of Ferrara) for the NMR measurements and Dr. G. Cascarano and Prof. C. Giacovazzo (University of Bari, Italy) for their valuable assistance in the crystal-structure determination of **30** by direct methods using the new release SIR2000 of the SIR program.

[1] a) H. Paulsen, *Angew. Chem.* **1982**, *94*, 184–253; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155–224; b) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213–236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212–235; c) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531; d) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482–1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380–1419; e) G.-J. Boons, *Tetrahedron* **1996**, *52*, 1095–1121; f) G.-J. Boons, *Contemp. Org. Synt.* **1996**, *3*, 173–200; g) P. H. Seeberger, S. J. Danishefsky, *Acc. Chem. Res.* **1998**, *31*, 685–695; h) H. M. I. Osborn, T. H. Khan, *Tetrahedron* **1999**, *55*, 1807–1850.

[2] a) H. Kunz, *Angew. Chem.* **1987**, *99*, 297–311; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 294–308; b) H. Paulsen, *Angew. Chem.* **1990**, *102*, 851–867; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 823–839; c) H. Kunz, *Pure Appl. Chem.* **1993**, *65*, 1223–1232; d) M. Meldal, K. Bock, *Glycoconjugate J.* **1994**, *11*, 59–63; e) G. Arsequell, G. Valencia, *Tetrahedron Asymmetry* **1997**, *8*, 2839–2876; f) A. Hasegawa, M. Kiso in *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), M. Dekker, New York, **1997**, pp. 357–379; g) R. Roy in *Carbohydrate Chemistry* (Ed.: G.-J. Boons), Blackie Academic & Professional, London, **1998**, pp. 243–321.

[3] a) A. Varki, *Glycobiology* **1993**, *3*, 97–130; b) A. Kobata, *Acc. Chem. Res.* **1993**, *26*, 319–324; c) Y. C. Lee, R. T. Lee, *Acc. Chem. Res.* **1995**, *28*, 321–327; d) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683–720; e) R. U. Lemieux, *Acc. Chem. Res.* **1996**, *29*, 373–380; f) *Essentials of Glycobiology* (Eds.: A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart, J. Marth), Cold Spring Harbor Laboratory Press, New York, **1999**.

[4] a) K.-A. Karlsson, *Molecular Mechanism of Microbial Adhesion*, Springer, New York, **1988**; b) Z. J. Witczack, *Curr. Med. Chem.* **1995**, *1*, 392–405; c) E. F. Hounsell in *Carbohydrate Chemistry* (Ed.: G.-J. Boons), Blackie Academic & Professional, London, **1998**, pp. 430–447; d) P. Sears, C.-H. Wong, *Chem. Commun.* **1998**, 1161–1170; e) H. Lis, N. Sharon, *Chem. Rev.* **1998**, *98*, 637–674.

[5] Selected papers: a) K. K.-C. Liu, S. J. Danishefsky, *J. Org. Chem.* **1994**, *59*, 1895–1897; b) J. R. Merritt, E. Naisang, B. Fraser-Reid, *J. Org. Chem.* **1994**, *59*, 4443–4449; c) J. Rademann, R. R. Schmidt, *J. Org. Chem.* **1997**, *62*, 3650–3653; d) C. Zheng, P. H. Seeberger, S. J. Danishefsky, *J. Org. Chem.* **1998**, *63*, 1126–1130; e) K. C. Nicolaou, N. Watanabe, J. Li, J. Pastor, N. Winssinger, *Angew. Chem.* **1998**, *110*, 1636–1638; *Angew. Chem. Int. Ed.* **1998**, *37*, 1559–1561; f) V. Pozsgay, *Tetrahedron Asymmetry* **2000**, *11*, 151–172.

[6] a) G. Gattuso, S. A. Nepogodiev, J. F. Stoddart, *Chem. Rev.* **1998**, *98*, 1919–1958; b) S. A. Nepogodiev, J. F. Stoddart in *Carbohydrate Chemistry* (Ed.: G.-J. Boons), Blackie Academic & Professional, London, **1998**, pp. 322–383.

[7] T. Müller, R. Schneider, R. R. Schmidt, *Tetrahedron Lett.* **1994**, *35*, 4763–4766.

[8] C. Krog-Jensen, S. Oscarson, *J. Org. Chem.* **1996**, *61*, 1234–1238.

[9] a) B. M. Heskamp, D. Noort, G. A. van der Marel, J. H. van Boom, *Synlett* **1992**, 713–715; b) B. M. Heskamp, G. H. Veeneman, G. A. van der Marel, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron* **1995**, *51*, 5657–5670; c) A. Borbás, G. Szabovik, Z. Antal, P. Herczegh, A. Agócs, A. Lipták, *Tetrahedron Lett.* **1999**, *40*, 3639–3642.

[10] S. J. Danishefsky, M. P. DeNinno, S.-H. Chen, *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.

[11] S. Immel, F. W. Lichtenthaler, *Liebigs Ann.* **1996**, 39–44.

[12] a) M. Kawamura, T. Uchiyama, T. Kuramoto, Y. Tamura, K. Mizutani, *Carbohydr. Res.* **1989**, *192*, 83–90; b) M. Sawada, T. Tanaka, Y. Takai, T. Hanafusa, T. Taniguchi, M. Kawamura, T. Uchiyama, *Carbohydr. Res.* **1991**, *217*, 7–17. Chemically modified cyclofructins: c) Y. Takai, Y. Okumura, S. Takahashi, M. Sawada, M. Kawamura, T. Uchiyama, *J. Chem. Soc. Chem. Commun.* **1993**, 53–54; d) M. Atsumi, M. Mizuochi, K. Ohta, K. Fujita, *Tetrahedron Lett.* **1994**, *35*, 5661–5664; e) Y. Takai, Y. Okumura, T. Tanaka, M. Sawada, S. Takahashi, M. Shiro, M. Kawamura, T. Uchiyama, *J. Org. Chem.* **1994**, *59*, 2967–2975; f) T. Kida, Y. Inoue, W. Zhang, Y. Nakatsuji, I. Ikeda, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1201–1205.

[13] A. Dondoni, M.-C. Scherrmann, *J. Org. Chem.* **1994**, *59*, 6404–6412.

[14] For a review on thiazolylketoses, see: A. Dondoni, A. Marra, *Chem. Commun.* **1999**, 2133–2145.

[15] A. Dondoni, A. Marra, I. Rojo, M.-C. Scherrmann, *Tetrahedron* **1996**, *52*, 3057–3074.

[16] A. Marra, A. Dondoni, F. Sansone, *J. Org. Chem.* **1996**, *61*, 5155–5158.

[17] A. Dondoni, M.-C. Scherrmann, A. Marra, J.-L. Delépine, *J. Org. Chem.* **1994**, *59*, 7517–7520.

[18] A. Dondoni, S. Daninos, A. Marra, P. Formaglio, *Tetrahedron* **1998**, *54*, 9859–9874.

[19] A. Dondoni, C. Ferrari, A. Marra, *X European Carbohydrate Symposium*, (Galway, Ireland), **1999**, p. 260.

[20] For a review on the thiazole aldehyde synthesis, see: A. Dondoni, *Synthesis* **1998**, 1681–1706.

[21] H. Paulsen, T. Holger, *Carbohydr. Res.* **1984**, *125*, 47–64.

[22] A. Dondoni, A. Marra, D. Perrone, *J. Org. Chem.* **1993**, *58*, 275–277.

[23] Silver nitrate has been employed for the conversion of substituted benzothiazoles into aldehydes or ketones (E. J. Corey, D. L. Boger, *Tetrahedron Lett.* **1978**, *19*, 5–8, 9–12, and 13–16; H. Chikashita, M. Ishibaba, K. Ori, K. Itoh, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3637—3648). It is worth noting that the cost of 99+% pure $AgNO_3$ (ca. 0.4 USD mmol^{-1}) is in the range of other common chemicals currently used in carbohydrate synthesis (price in USD mmol^{-1}: DBU = 0.2; MeOTf = 0.5; TMSOTf = 0.5; 4-penten-1-ol = 0.6; $ClP(OEt)_2$ = 1.0; NIS = 1.8).

[24] Anomeric diethyl phosphites were introduced as glycosyl donors by Schmidt and co-workers (see reference [7] and T. J. Martin, R. R. Schmidt, *Tetrahedron Lett.* **1992**, *33*, 6123—6126), while Wong exploited dibenzyl derivatives (H. Kondo, Y. Ichikawa, C.-H. Wong,

J. Am. Chem. Soc. **1992**, *114*, 8748 – 8750; M. M. Sim, H. Kondo, C.-H. Wong, *J. Am. Chem. Soc.* **1993**, *115*, 2260 – 2267; S. Aoki, H. Kondo, C.-H. Wong, *Methods in Enzymology* **1994**, *247*, 193—211) and Watanabe used dimethyl derivatives (Y. Watanabe, C. Nakamoto, S. Ozaki, *Synlett* **1993**, 115 – 116; Y. Watanabe, C. Nakamoto, T. Yamamoto, S. Ozaki, *Tetrahedron* **1994**, *50*, 6523 – 6536).

[25] S. Hashimoto, T. Honda, S. Ikegami, *J. Chem. Soc. Chem. Commun.* **1989**, 685 – 687.

[26] For a discussion on the relative acidity of the thiazole hydrogens, see: A. Dondoni, P. Merino in *Comprehensive Heterocyclic Chemistry II, Vol. 3* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, pp. 373 – 474.

[27] a) J. Haverkamp, T. Spoormaker, L. Dorland, J. F. G. Vliegenthart, R. Schauer, *J. Am. Chem. Soc.* **1979**, *101*, 4851 – 4853; b) H. Hori, T. Nakajima, Y. Nishida, H. Ohrui, H. Meguro, *Tetrahedron Lett.* **1988**, *29*, 6317 – 6320; c) S. Prytulla, J. Lauterwein, M. Klessinger, J. Thiem, *Carbohydr. Res.* **1991**, *215*, 345 – 349.

[28] R. R. Schmidt, A. Toepfer, *Tetrahedron Lett.* **1991**, *32*, 3353 – 3356.

[29] Although $BF_3 \cdot Et_2O$ was considered as the promoter of choice for high-yielding and stereoselective *O*-glycosidation of aldopyranosyl diethyl phosphites (S. Hashimoto, K. Umeo, A. Sano, N. Watanabe, M. Nakajima, S. Ikegami, *Tetrahedron Lett.* **1995**, *36*, 2251—2254), the same authors found that TMSOTf gave better results when 2-deoxy-aldopyranosyl diethyl phosphites were employed as the glycosyl donors (S. Hashimoto, A. Sano, H. Sakamoto, M. Nakajima, Y. Yanagiya, S. Ikegami, *Synlett* **1995**, 1271 – 1273).

[30] The glycosylation with glycosyl phosphites has been the subject of various mechanistic studies showing that different mechanisms can operate, depending on how the substrates and the promoter are mixed, see: H. Kondo, S. Aoki, Y. Ichikawa, R. L. Halcomb, H. Ritzen, C.-H. Wong, *J. Org. Chem.* **1994**, *59*, 864 – 877.

[31] a) R. Madsen, B. Fraser-Reid in *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic Publishers, Amsterdam, **1996**, pp. 155 – 170; b) B. Fraser-Reid, R. Madsen in *Preparative Carbohydrate Chemistry*, (Ed.: S. Hanessian) M. Dekker, New York, **1997**, pp. 339 – 356.

[32] The small difference in chemical shifts between the two H-1 protons ($\Delta\delta = 0.2$ ppm) suggested that the 1,4-dioxane ring of **24** adopts a *skew-boat* conformation, as favoured by the concomitant *exo*-anomeric effect with both the pyranoside rings. For a discussion on the *exo*-anomeric effect, see: S. David, *The Molecular and Supramolecular Chemistry of Carbohydrates. A Chemical Introduction to the Glycosciences*, Oxford University Press, Oxford, **1997**, pp. 145 – 148.

[33] D. Noort, G. A. van der Marel, G. J. Mulder, J. H. van Boom, *Synlett* **1992**, 224 – 226.

[34] a) J. Defaye, A. Gadelle, C. Pedersen, *Carbohydr. Res.* **1988**, *174*, 323 – 329; b) M. Manley-Harris, G. N. Richards, *Carbohydr. Res.* **1996**, *287*, 183 – 202.

[35] J. M. García Fernández, R.-R. Schnelle, J. Defaye, *Tetrahedron Asymmetry* **1995**, *6*, 307 – 312.

[36] J. M. García Fernández, R.-R. Schnelle, J. Defaye, *Aust. J. Chem.* **1996**, *49*, 319 – 325.

[37] M. Ludewig, D. Lazarevic, J. Kopf, J. Thiem, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1751 – 1752.

[38] S. Horito, M. Tada, H. Hashimoto, *Chem. Lett.* **1991**, 117 – 120.

[39] a) M. Alonso-Lopez, J. Jimenez-Barbero, M. Martin-Lomas, S. Penades, *Tetrahedron* **1988**, *44*, 1535 – 1543; b) D. A. H. van Maarschalkerwaart, N. P. Willard, U. K. Pandit, *Tetrahedron* **1992**, *48*, 8825 – 8840; c) P. P. Kanakamma, N. S. Mani, U. Maitra, V. Nair, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2339 – 2344; d) M. Nazhaoui, J.-P. A. Joly, B. J. Jean-Claude, V. Del Duca, A. Aubry, M. Boubouh, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2919 – 2926; e) Y. E. Tsvetkov, R. R. Schmidt, *Carbohydr. Lett.* **1996**, *2*, 149 – 156; f) R. Miethchen, V. Fehring, *Liebigs Ann./ Recueil* **1997**, 553 – 561; g) R. Miethchen, V. Fehring, *Synthesis* **1997**, 94 – 98; h) B. Dumont-Hornebeck, J.-P. Joly, J. Coulon, Y. Chapleur, *Carbohydr. Res.* **1999**, *320*, 147 – 160.

[40] The distance between O1, O2, and O3 is approximately 2.8 Å, that between O8, O12, and O18 is approximately 4.4 Å, and that between O7, O13, and O17 is approximately 8.6 Å (the oxygens are numbered according to the ORTEP view of **30** in Figure 1).

[41] The following compounds were examined: *N*-phthaloyl-glycine, *N*-acetyl-D- and L-phenylglycine, L-phenylalanine ethyl ester hydrochloride, (*R*)- and (*S*)-Mosher's acid, tetrabutylammonium iodide, (*R*)- and (*S*)-trimethyl(1-phenylethyl)ammonium iodide, (*R*)- and (*S*)-1-phenylethanol, succinimide, cesium fluoride, cesium acetate, silver nitrate.

[42] S. B. Lee, S. Hwang, D. S. Chung, J.-I. Hong, *Tetrahedron Lett.* **1997**, *38*, 8713 – 8716.

[43] Potassium perchlorate could not be used because of its poor solubility in $CHCl_3/CH_3CN$ (1:1). The salts employed in this complexation study were insoluble in $CDCl_3$ in the absence of the host.

[44] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals,* 4th ed., Butterworth-Heinemann, Oxford, **1996**.

[45] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923 – 2925.

[46] M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, *Acta Crystallogr. Sect. A*, **2000**, *56*, 451 – 457.

[47] G. M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.

[48] C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

Received: July 18, 2000 [F2608]

  0947-6539/01/0707-1382 $ 17.50+.50/0