Saccharides of Biological Importance: Challenges and Opportunities for Organic Synthesis

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In 1923, Avery and Heidelberger demonstrated that the immunoactive, antigenic part of the outer cell wall of the *Streptococcus pneumoniae* bacteria was a polysaccharide and not a protein as previously assumed.[1] The discovery that carbohydrate surfaces are biologically active ushered in a new era of carbohydrate chemistry and was fundamental in leading into the area now known as glycobiology. Twenty-five years later, Morgan demonstrated the importance of carbohydrate structures in blood group substances.[2] It thus became clear that carbohydrates, usually in the form of conjugates such as glycolipids and glycoproteins, are of major importance in cell interaction processes. Carbohydrates were traditionally viewed as energy-storage materials, structural materials, and primary metabolites that were produced in photosynthesis and were destined for further conversions in Nature. It thus became clear that they played a far wider and much more subtle role in natural processes than earlier believed.

With the emergence of information on the role of carbohydrate structures in biological processes arose the challenge to organic chemistry of structural determination, conformational analysis, molecular dynamics analysis, and synthesis. The present Account will relate some of the author's experiences in the fascinating field of carbohydrate synthesis.[3]

The concept of protecting group strategies is one of the cornerstones of carbohydrate chemistry because of the extremely high degree of functionality in carbohydrate molecules. In many synthetic sequences it becomes necessary to protect all hydroxyl groups except one in an unambiguous manner. For this purpose we have found regioselective opening of benzylidene and 2-propenylidene acetals to be useful in obtaining short routes to intermediates for oligosaccharide synthesis. This topic will form the first part of this Account. The remainder will relate some experiences in glycosidation reactions and oligosaccharide synthesis.

Although considerable progress has been made in the synthesis of glycosides with 1,2-*cis*-α-D (1,2-*cis*-β-L) and 1,2-*trans*-α(or β)-D (1,2-*trans*-β(or α)-L) configurations at carbons 1 and 2, problems remain with other steric situations (Figure 1). A particular problem is the synthesis of β-D-mannopyranosides. These have the 1,2-*cis*-β-D configuration, and despite considerable efforts, their synthesis remains difficult. This will form the second topic.

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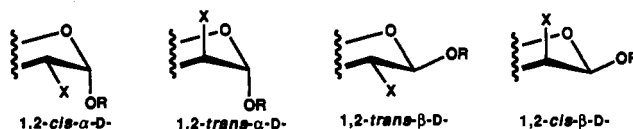
Figure 1. Configurations at C-1/C-2 in glycosides; X = OH, NH$_2$, or NHAc.

The use of thioglycosides in oligosaccharide synthesis will be discussed as the third topic. The final topic will be the use of the above methodology in the synthesis of oligosaccharides destined for various biological investigations.

Reductive Ring Opening of Acetals

Lipták, Nánási, and co-workers demonstrated that reductive cleavage of 4,6-*O*-benzylidene acetals with lithium aluminum hydride and aluminum chloride generally gives reductive opening of the dioxane ring so that the predominant product is the 4-*O*-benzyl compound with the 6-OH free.[4,5] The corresponding reaction with dioxolane rings, e.g. 2,3-*O*-benzylidene acetals of hexopyranosides, also proceeded with high regioselectivity; the position of the resulting *O*-benzyl group depended upon the configuration (*R* or *S*) at the benzylidene acetalic carbon. This phenomenon is not observed in the 4,6-*O*-benzylidene acetals because these invariably have the phenyl group in the equatorial orientation.

A paper by Horne and Jordan on the treatment of the phenylethylidene acetal of ethylene glycol with sodium cyanoborohydride and hydrogen chloride[6] prompted us to investigate this reaction on pyranosidic acetals. We were fortunate in finding that when tetrahydrofuran was used as solvent, the regioselectivity for dioxane rings was opposite to that produced by the above-mentioned LiAlH$_4$/AlCl$_3$ reagent. In other words, 4,6-*O*-benzylidene acetals now produced a benzyl group in the 6-position and a free 4-OH group, and they did so independently of the anomeric configuration at C-1 and of the stereochemistry at C-2, C-3, and C-4. The reaction is compatible with the presence of acyl groups (e.g. benzoyl) and acetamido groups in the molecule. On the other hand, the reductive opening of the corresponding dioxolane rings (e.g. 2,3-*O*-benzylidene

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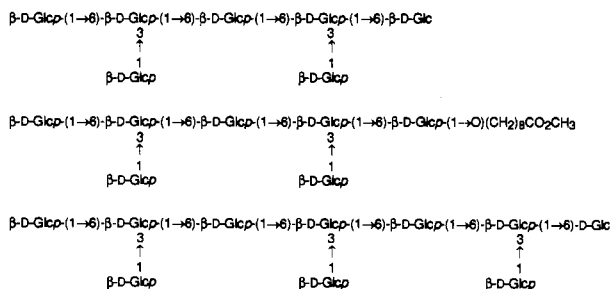(6) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978,** 1357–1358.

Figure 2. Reductive opening of cyclic acetals.

Figure 3. β-D-Mannopyranosides via C-2 inversion.

→2)- β–D-Man*p*-(1→2)-α-D-Man*p*-(1→2)-α-D-Man*p*-(1→2)-β-D-Man*p*-(1→2)-β-D-Glc*p*NAc-(1-
3
↑   R = H or α-D-Glc*p*
1
R

Figure 4. *Salmonella thompson* penta- and hexasaccharide repeating unit.

acetals of hexopyranosides) intriguingly gave the same regioselectivity as did the original LiAlH₄/AlCl₃ reagent.[7,8]

Later, we found that for 4,6-*O*-benzylidene acetals we could reverse the regioselectivity using Na(CN)-BH₃/HCl in toluene or in dichloromethane, thus obtaining 4-*O*-benzyl ethers with free 6-OH. In variations on this theme, we also found that the same regioselectivities and solvent dependence were obtained using trimethylaminoborane–aluminum chloride.[9]

Allyl groups are versatile O-protection groups in carbohydrate synthesis. The above findings thus led us to investigate the regioselectivity of treating 4,6-*O*-(2′-propenylidene) acetals with the Na(CN)BH₃/HCl/ THF reagent (Figure 2). These acrolein acetals behaved in the same manner as did the benzylidene ones, giving predominantly 6-*O*-(2′-propenyl) ethers with free

Figure 5. Hans Lönn's concept for oligosaccharide synthesis.

4-OH.[10] Solvent dependence has not yet been investigated for these reactions.

Ester (e.g. *O*-benzoyl group), amide groups (e.g. *N*-acetyl groups), and aromatic nitro groups (e.g. in *p*-nitrophenyl glycosides) are stable in the above reductive ring opening reactions.[7-10]

β-D-Mannopyranosides

In the synthesis of glycosides with the 1,2-*cis*-α-D (1,2-*cis*-β-L) configuration, such as α-D-glucopyranosides and -galactopyranosides, the anomeric effect may be

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β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc
3 3
↑ ↑
1 1
β-D-Glc*p* β-D-Glc*p*

β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→O)(CH₂)₈CO₂CH₃
3 3
↑ ↑
1 1
β-D-Glc*p* β-D-Glc*p*

β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-D-Glc
3 3 3
↑ ↑ ↑
1 1 1
β-D-Glc*p* β-D-Glc*p* β-D-Glc*p*

Figure 6. Phytoelicitor-active oligosaccharides.

used to persuade glycosyl halides and thioglycosides with a nonparticipating substituent in the 2-position to yield glycosides with the desired configuration. Conversely the use of a glycosyl halide or thioglycoside with a participating substituent such as an acetoxy or benzyloxy group in the 2-position will give β-D-1,2-*trans*-(α-L-1,2-*trans*) glycosides. This is because of formation of 1,2-dioxolenium ions as intermediates in the latter reactions.

However, neither the anomeric effect nor neighboring group participation is of any use in β-D-mannopyranoside synthesis. Stereospecific synthesis of the corresponding β-D-glucopyranoside, followed by inversion of configuration in the 2-position by oxidation–reduction, was thought to be potentially useful. As a start, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl halide (bromide or chloride) is condensed with a hydroxylic compound in the presence of a suitable silver salt promoter, e.g. silver triflate, to yield the expected β-D-glucoside. Removal of the 2-*O*-acetyl group and then oxidation, followed by stereoselective reduction, inverts the configuration at C-2 to give the corresponding β-D-mannoside (Figure 3).[11-13] Although this sequence is rather lengthy, it remains one of the few reasonably reliable β-D-mannopyranoside syntheses—a long-standing problem in glycoside chemistry.

We have recently had occasion to return to this method in a synthesis of a penta- and a hexasaccharide corresponding to the repeating unit(s) of the *Salmonella thompson* O-antigenic lipopolysaccharides (Figure 4).[14] In more direct synthesis of β-D-mannopyranoside from α-D-mannopyranosyl halides, with a nonparticipating benzyloxy group at C-2, insoluble promoters have been found moderately useful in promoting glycosidation with inversion of configuration at the anomeric position. These promoters, which include silver silicate[15] and silver zeolite,[16] give less stereoselectivity, however. A preliminary account has presented yet another indirect route which appears to give β-D-mannopyranosides with high stereoselectivity; the method has not yet been optimized.[17]

Thioglycosides in Oligosaccharide Synthesis

One advantage of the convergent block synthesis approach to oligosaccharides over a stepwise addition of one monomer sugar residue at a time is that in block synthesis the necessary protecting group manipulations are performed on smaller fragments than in the stepwise approach. The block synthesis, however, requires that oligosaccharide blocks can be activated into glycosyl donors. The classical glycosyl donors for creating a glycosidic bond are glycosyl bromides and chlorides. Conversion of an oligosaccharide block into a glycosyl bromide or chloride may result in low yields and concomitant loss of material far into the synthetic sequence.[18] Several solutions to this problem have emerged in the last few years. These include the use of glycosyl trichloroimidates[19] and 4-pentenyl glycosides.[20]

The renaissance of thioglycosides as glycosyl donors was heralded by a paper by Ferrier and co-workers[21] who in 1973 reported that mercury(II) sulfate activated phenyl thioglycosides into glycosyl donors. Subsequent reports on the activation of thioglycosides included the use of mercury(II) chloride,[22,23] phenylmercury triflate,[24] mercury(II) benzoate,[25] mercury(II) nitrate,[26] copper-(II) triflate,[27] lead(II) perchlorate,[28,29] and N-bromosuccinimide.[26,30] However, these did not give the consistent high yields required for standardized synthesis. One way of activating thioglycosides is to convert them into glycosyl halides and use these either after isolation[30-38] in situ.[39]

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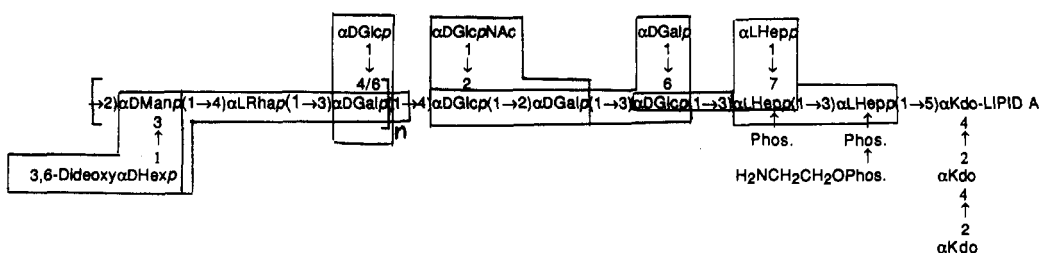(38) Kreuzer, M.; Thiem, J. *Carbohydr. Res.* 1986, 149, 347–361.

Figure 7. *Salmonella* serogroups A, B, and D_1. Enclosed fragments correspond to structures synthesized in the author's laboratory.
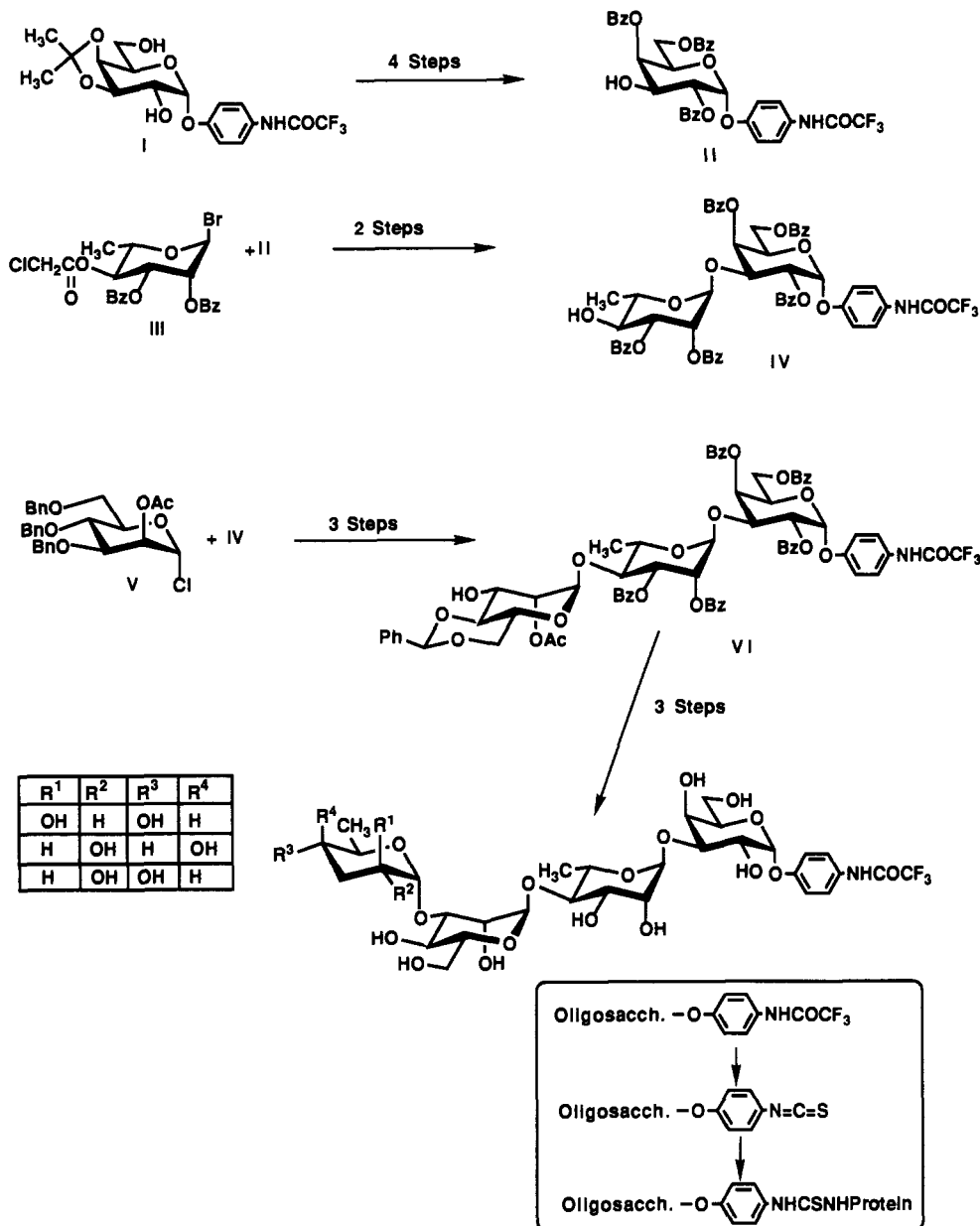

Figure 8. Syntheses of the *Salmonella* serogroups A, B, and D_1 tetrasaccharides.

In our laboratories, intense interest in using thioglycosides as glycosyl donors by way of direct activation arose from Lönn's observation[40] that methyl triflate is an efficient activator for thioglycosides and that this promoter is most useful for making both α- and β-linked glycosidic bonds in block synthesis of oligosaccharides (Figure 5). Conviction of the usefulness of this approach grew as a number of oligosaccharides were made. In

these syntheses conventional glycoside chemistry, e.g. silver triflate,[41,42] was used for making 1,2-trans glycosidic bonds and halide assistance or silver triflate in the presence of a nonparticipating 2-substituent[43,44] was used for making 1,2-cis glycosidic bonds in oligosac-

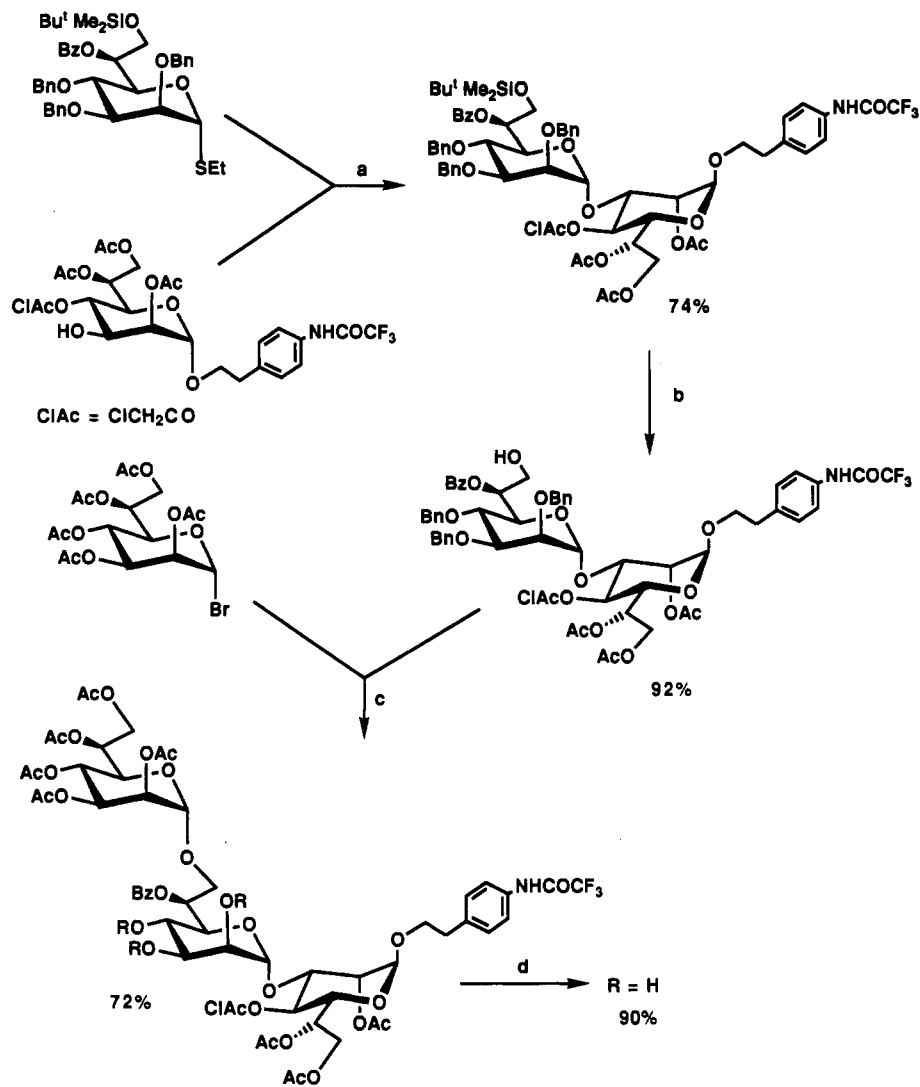(39) Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986,** *155,* c6–c10.

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Bu^t Me$_2$SiO
BzO
BnO
BnO
OBn
-O
SEt

a →

Bu^t Me$_2$SiO
BzO
BnO
BnO
OBn
-O
ClAcO
AcO'''
AcO
OAc
NHCOCF$_3$
O
74%

AcO
AcO
ClAcO
HO
OAc
-O
NHCOCF$_3$

ClAc = ClCH$_2$CO

b ↓

HO
BzO
BnO
BnO
OBn
-O
ClAcO
AcO'''
AcO
OAc
NHCOCF$_3$
O
92%

AcO
AcO
AcO
AcO
OAc
-O
Br

c

AcO
AcO
AcO
AcO
OAc
-O
O
BzO
RO
RO
OR
-O
ClAcO
AcO'''
AcO
OAc
NHCOCF$_3$
O
72%

d → R = H
90%

Reagents: a: DMTST, diethyl ether, 4Å molecular sieves; b: 70% aq. acetic acid; c: Silver triflate, toluene-dichloromethane, 4Å molecular sieves; d: H$_2$, Pd-C, ethyl acetate.

Figure 9. Synthesis of the *Salmonella* heptose core trisaccharide.

charide blocks with a thioalkyl or thioaryl group at C-1. Methyl triflate promotion was then used to join the thioglycoside block to an acceptor with a free OH group.[40,45] Syntheses of some phytoelicitor-active oligosaccharides were particularly gratifying examples of this strategy for oligosaccharide synthesis (Figure 6).[46,47]

Methyl triflate promotion, however, has some disadvantages. The promoter is highly toxic and must be handled with extreme care. Also, it is an *O*-alkylating agent. In reactions of an alcohol with a slow-reacting thioglycoside donor, methyl ethers have been observed as byproducts. To overcome this, use of the uniquely thiophilic dimethyl(methylthio)sulfonium triflate (DMTST)[48] was introduced, and subsequently methylsulfenium bromide and methylsulfenium triflate was used.[49] Recently developed promoters include iodo-

nium dicollidine perchlorate[50] and *N*-halosuccinimides–triflic acid.[51]

Numerous variations on the theme of thioglycosides, including selenoglycosides,[52] and various other activation systems have by now been reported. The concept is still undergoing intensive development.

Some Examples of Oligosaccharide Synthesis

Synthesis of oligosaccharides destined for various biological/medical research purposes has proven to be an excellent testing ground for various methods and strategies developed over the years. Two examples have already been described: the synthesis of the *Salmonella thompson* penta- and hexasaccharides and the phytoelicitor-active oligosaccharides. Another set of examples from our laboratory is given by the syntheses of a number of oligosaccharides corresponding to the immunogenic lipopolysaccharide of the *Salmonella*

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serogroups A, B, and D₁, *O*-antigens (Figure 7). Starting from the outer repeating unit, we have synthesized fragments through to the KDO (3-deoxy-D-*manno*-octulosonic acid) part of the molecules.

These approaches are exemplified by an early synthesis of the tetrasaccharide repeating units[53] (Figure 8) and also by a recent synthesis of a trisaccharide containing L-*glycero*-D-mannoheptose units[54] (Figure 9). These were all made in the form of oligosaccharides joined with the appropriate glycosidic linkage to a spacer. In this manner they may be attached to amino groups in proteins to make artificial antigens. These various oligosaccharides have been used in collaboration with Professor Alf A. Lindberg and his co-workers at the Karolinska Institute in Stockholm, for research directed toward improved diagnostic methods and for the selection and typing of monoclonal antibodies.

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Great strides have been made in oligosaccharide synthesis over the past couple of decades. It is now possible to synthesize oligosaccharides of up to and sometimes beyond 10 monosaccharide units. However, chemical oligosaccharide synthesis remains an art. Each new synthesis presents a new set of problems. There are no standard strategies available, such as those used in peptide and oligonucleotide synthesis. Synthetic oligosaccharides will, therefore, in the foreseeable future remain expensive. Emerging enzymatic methods[55–60] may eventually make a number of structures more cheaply and easily available. Chemical synthesis will, however, retain the advantage of making available analogues, (e.g. deoxy and fluoro analogues), "unnatural" part structures, and unusual structures not obtainable through the use of enzymes. Continued development of chemical synthesis therefore remains important. Looking toward the future, a greater emphasis on mechanistic studies using physical–chemical methods could prove useful in this context, especially in the bewildering area of glycoside synthesis.