Abbreviations

Ac	acetyl
All	allyl
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	unspecified Aryl substituent
Asn	asparagine
ATP	adenosine 5′-triphosphate disodium salt
BDA	butane diacetal
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BSA	bovine serum albumin
Bu	butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
c	concentration
C.I.	chemical ionisation
CAN	ceric ammonium nitrate
cat.	catalytic
CDA	cyclohexane-1,2-diacetal
CDP	cytidine diphosphate
ClAc	chloroacetyl
CMP	cytidine 5′-monophosphate
conc.	concentrated
COSY	correlation spectroscopy
CSA	(+/−)-10-camphorsulfonic acid
d	doublet
δ	chemical shift
DAST	diethylamino sulfurtrifluoride
DBU	1,5-diazabicyclo[4.3.0]non-5-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
dispoke	dispiroketal
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide

DMPM	3,4-dimethoxybenzyl
DMSO	dimethylsulfoxide
DMTST	dimethyl(methythio)sulfonium triflate
DTBMP	2,6-di-t-butyl-4-methylpyridine
Dts	dithiasuccinoyl
EEDQ	2-ethyoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
equiv.	stoichiometric equivalents
Et	ethyl
FAB	fast atom bombardment
Fmoc	9-fluorenylmethyloxycarbonyl
Fuc	fucose
Gal	galactose
GalNAc	galactosamine
GDP	guanidine diphosphate
Glc	glucose
GlcNAc	glucosamine
h	hours
Hz	Hertz
IDCP	iodonium di-*sym*-collidine perchlorate
^{i}Pr	*iso*-propyl
IR	infra red
J	coupling constant
KDN	3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid
LDMAN	lithium 1-(dimethylamino) naphthalenide
Lev	levulinate
lit.	literature value
LN	lithium naphthalenide
m	multiplet
m	*meta*
M	molar conentration
MCPBA	*meta*-chloroperbenzoic acid
m.p.	melting point
m/z	mass to charge ratio
Me	methyl
Man	mannose
min	minutes
mol	mole
MS	molecular sieves
Ms	mesyl
NBA	*N*-bromoacetamide
NBB	*N*-bromobenzamide
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
Neu	neuraminic acid

Neu5Ac	*N*-acetyl derivative of neuraminic acid
Neu5Gc	*N*-glycolyl derivative of neuraminic acid
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NPG	*n*-pentenyl glycoside
NTP	nucleotide triphosphate
o	*ortho*
p	*para*
Pfp	pentafluorophenyl
Ph	phenyl
phth	phthaloyl
Piv	pivaloyl
PMB	*p*-Methoxybenzyl
PNP	*para*-nitrophenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Py	pyridine
R_f	retention factor
Rha	rhamnose
rt	room temperature
Ser	serine
sLe^x	sialyl Lewis^x
S.M.	starting material
sTn	sialyl Tn
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetra butyl ammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBPA	tris(4-bromophenyl)ammoniumyl hexachloroantimonate
Teoc	2,2,2-trichloroethoxycarbonyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFAc	*N*-trifluoroacetyl
TfOH	triflic acid
THF	tetrahydrofuran
THP	tetrahydropyran
Thr	threonine
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPS	triphenylsilyl

Tr	trityl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluene sulfonyl
U	units
UDP	uridine triphosphate
ν_{max}	frequency maximum
Xyl	xylose

Contributors to this Volume

HIROMUNE ANDO

Department of Applied Bioorganic Chemistry, Faculty of Agriculture and Life Sciences, Gifu University, Gifu 501-1193, Japan

DAVID CHAMBERS

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

IAN CUMPSTEY

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

BENJAMIN G. DAVIS

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

SETH C. ENNIS

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

PHILIP G. EVANS

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

ANTONY J. FAIRBANKS

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

ROBERT A. FIELD

Centre for Carbohydrate Chemistry, School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

ROBERT FRANCE

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

DAVID GAMBLIN

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

NATASHA GEMMELL

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AZ, UK

SUSAN M. HANCOCK

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

HIDEHARU ISHIDA

Department of Applied Bioorganic Chemistry, Faculty of Agriculture and Life Sciences, Gifu University, Gifu 501-1193, Japan

K.P. RAVINDRANATHAN KARTHA

Centre for Carbohydrate Chemistry, School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

MAKOTO KISO

Department of Applied Bioorganic Chemistry, Faculty of Agriculture and Life Sciences, Gifu University, Gifu 501-1193, Japan

PAUL MEO

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

HELEN OSBORN

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

JÖRG PIETRUSZKA

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

JEREMY ROBERTSON

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

CHRISTOPHER M.P. SEWARD

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

PETRA M. STAFFORD

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

Acknowledgements

The successful preparation of this book has been largely due to the cooperation of the contributing authors. I am very grateful to them for working so efficiently, to submit excellent material to me, and meeting some tight deadlines. I am also grateful to my family for their patience and support whilst I have been working on this book–the project wouldn't have been completed without them.

– 1 –

An Introduction to Carbohydrate Synthesis

Helen Osborn

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

1.1 BIOLOGICAL ROLES OF CARBOHYDRATES

In the past, carbohydrates were considered to be solely of use for energy storage, and as skeletal components. However, this naïve view was challenged in 1963 when a protein was isolated from *Canavalia ensiformis* that demonstrated ability to bind to carbohydrates on erythrocytes. In 1982 the first animal carbohydrate binding protein was identified, and this sparked interest into the wider roles of carbohydrates and carbohydrate binding proteins within biological systems. These carbohydrate binding proteins are termed lectins and it is now known that they are found in varying densities on all cell-surface membranes [1]. They interact specifically with oligosaccharides and glycoconjugates (such as glycolipids and glycoproteins) on the surrounding cells via hydrogen bonding, metal coordination, van der Waals forces, and hydrophobic interactions. It is believed that favourable interactions occur between the hydroxyl groups of the carbohydrates and the amino acid functionalities of the proteins, to aid molecular recognition processes. These interactions are relatively weak, but they are so numerous that specific interactions occur. Selectivity is believed to be further increased through additional binding of the carbohydrate to the lectin's subsites.

The study of carbohydrates within biological systems has illustrated that they are involved in a number of fundamental biological functions such as cell–cell recognition and cell-external agent interactions [2]. These interactions can initiate beneficial biological events [2], such as fertilization, cell growth and differentiation (for example during embryogenesis) [3] and immune responses, as well as detrimental disease processes [2], such as inflammation, viral and bacterial

infections, and cancer metastasis (*vide infra*). Carbohydrates of even short sequences are used for carrying biological information, for example, the human blood groups are differentiated by relatively simple changes in oligosaccharide structure (Figure 1.1).

Therefore the view that carbohydrates are of limited importance within biological systems has been challenged and renewed interest into the science of 'Glycobiology' has emerged.

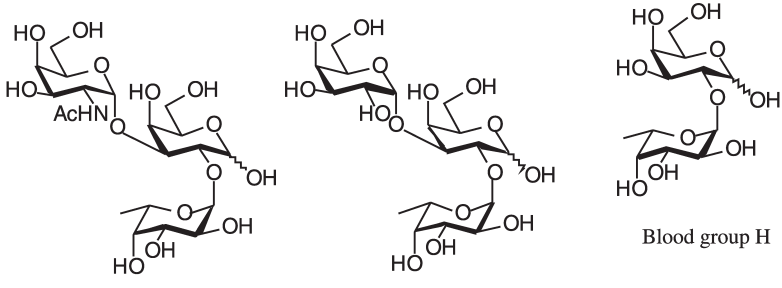
In order for the roles of carbohydrates to be thoroughly analysed and assessed, glycobiologists require access to defined target carbohydrates in useful quantities. Thus carbohydrates and glycoconjugates are now recognized as important targets for total synthesis programmes. If access to biologically important carbohydrates can be achieved, then material will be available for a number of means:

(1) Some bacterial surface proteins demonstrate specific binding for carbohydrates expressed on human cells, and such interactions form an essential part of the infection pathway. It has been demonstrated that administration of synthetic or natural carbohydrate derivatives can disrupt this infective pathway, so long as the administered derivatives have a high affinity for the bacterial lectins [4]. In such cases, the bacteria are no longer able to interact with the host, and therefore pass through the body without initiating infection. Such therapeutic agents have been termed anti-infective agents. A number of anti-infective agents occur naturally, for example, human breast milk contains numerous soluble oligosaccharides that provide newborn babies with a mechanism for aborting infection processes (Figure 1.2) [5].

An alternative approach for treating bacterial infections has seen the development of carbohydrate based antibiotics to target carbohydrate receptors and carbohydrate modifying enzymes [6].

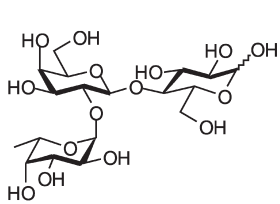
(2) The synthesis of disease associated carbohydrates may hold the key for the development of vaccination strategies for the respective diseases [7]. For example, the use of tumour associated carbohydrate antigens for raising antibodies for the treatment of cancer is currently being developed (Figure 1.3) [8].

(3) The synthesis of carbohydrate analogues is also being pursued in an attempt to inhibit the interactions between the carbohydrates and selectins that are essential for

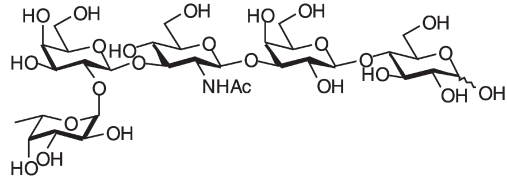


Blood group A Blood group B Blood group H

Figure 1.1



Represents one-third to one-half of the total milk oligosaccharides.

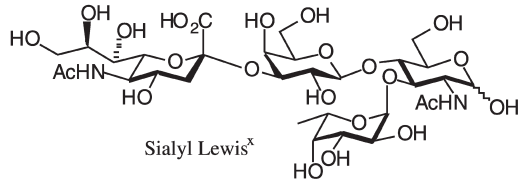


Major human milk oligosaccharide constituent.

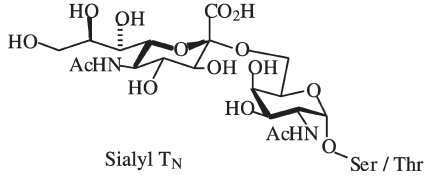
Figure 1.2

disease progression [9]. This has received particular attention for inhibiting tumour growth and metastasis. The natural role of the selectins is to assist the 'rolling' of leukocytes on the surface of activated endothelial cells in the blood vessels. However, the unusual carbohydrates on cancer cells also provide tumour cells with a mechanism for moving along the endothelial cells, in a process known as metastasis [10]. Therefore novel cancer treatments are investigating the possibility of utilizing soluble carbohydrates to block the selectin sites on the epithelial cells in the blood vessels to inhibit metastasis.

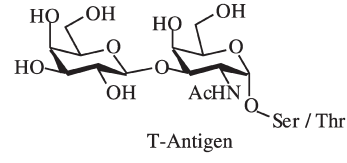
An alternative approach has concentrated on aborting the synthesis of disease associated carbohydrates, and this again requires access to carbohydrate



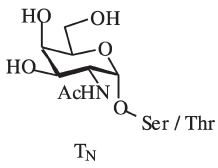
Sialyl Lewis^x



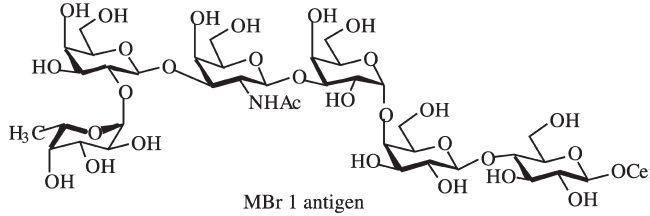
Sialyl T_N



T-Antigen



T_N



MBr 1 antigen

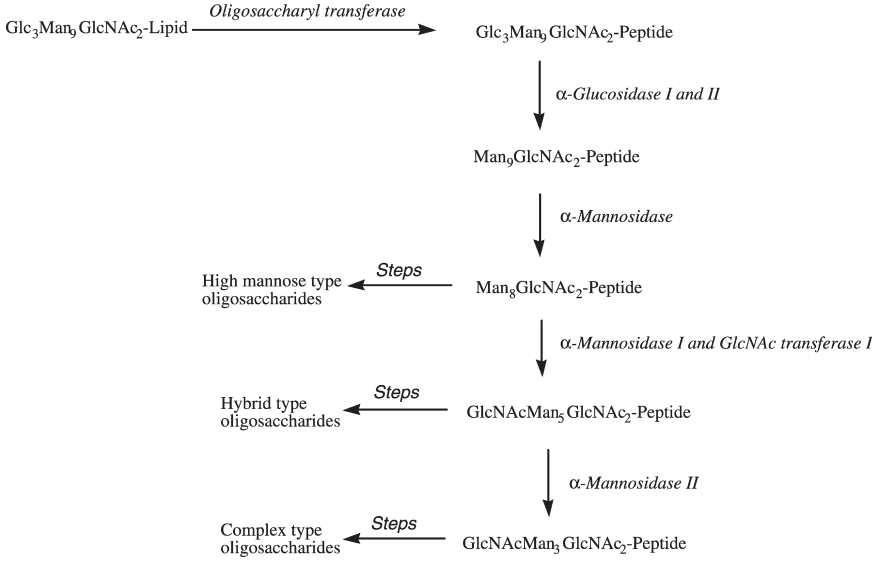
Figure 1.3

analogues [11]. The assembly of carbohydrates within biological systems occurs in the endoplasmic reticulum of the golgi apparatus and involves a number of enzyme mediated steps [12]. Biosynthesis commences with the formation of a $Glc_3Man_9GlcNAc_2$ oligosaccharide which is covalently bound to a lipid. This is transferred from the lipid to a peptide via a further enzyme and a series of glycosyl hydrolase and glycosyl transferase enzymes then process the oligosaccharide further to afford a wide range of structurally diverse oligosaccharides (Scheme 1.1).

It has been demonstrated that carbohydrate analogues are capable of inhibiting specific enzymes involved in the carbohydrate biosynthesis, offering the potential to engineer the synthesis of different carbohydrates. This has proved of use for aborting the synthesis of disease associated carbohydrates that are central to the infection pathway [13].

(4) Carbohydrate derivatives have also proved of use for targeting drugs or genes to hepatocytes [14]. An asialoglycoprotein receptor is found on mammalian hepatocytes that has high specificity for ligands displaying terminal Gal or GalNAc residues. Thus liver specific carriers, such as liposomes and polymers that display these residues have been created for the selective delivery of drugs and genes to hepatocytes. In theory this approach could be extended to allow more general carbohydrate-directed therapies [15].

In order to fully explore the biological roles of carbohydrates and exploit the therapeutic opportunities divulged above, it is essential to develop efficient regio- and stereoselective methods for the synthesis of carbohydrates. Whilst carbohydrates can sometimes be isolated from natural sources, synthetic strategies



Scheme 1.1

often offer the advantage of allowing access to larger quantities of material as well as entry to analogues of the natural carbohydrates.

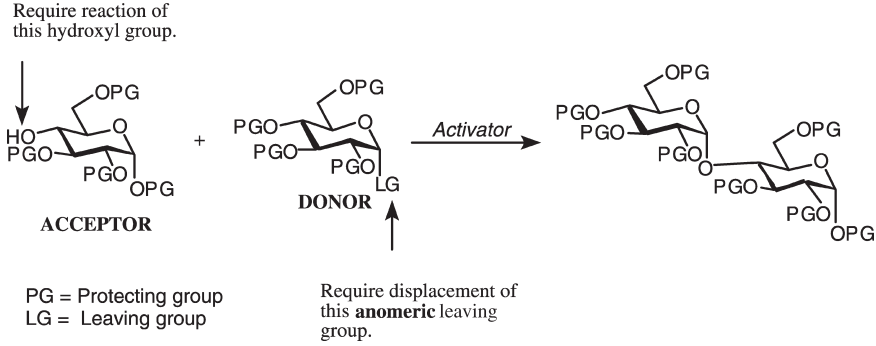
1.2 SYNTHESIS OF CARBOHYDRATES

Factors governing the synthesis of saccharides can be appreciated by considering the synthesis of a disaccharide. This generally involves the reaction of a glycosyl acceptor with a glycosyl donor, with an activator being utilized to activate the donor for glycoside bond formation (Scheme 1.2).

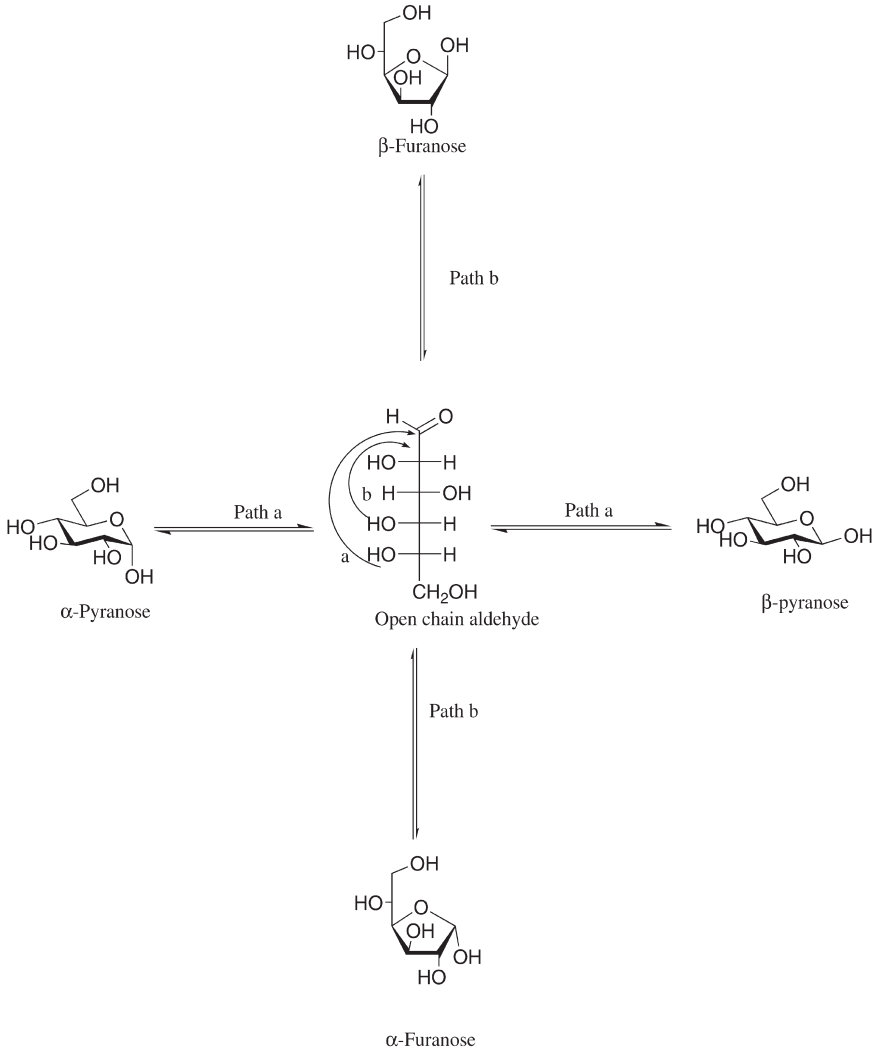
There are a number of factors that make carbohydrates particularly difficult to synthesise and analyse:

1. Carbohydrate building blocks are capable of existing in more than one form (pyranose and furanose forms), and so it is important to control which form is available for reaction (Scheme 1.3).
2. Carbohydrates characteristically have a number of hydroxyl groups which are often of similar reactivity. If no protecting groups are incoporated within the building blocks then mixtures of products will result from chemical synthetic strategies. Hence protecting group strategies are often required to ensure that only the hydroxyl group required for reaction is left in a reactive form. It is essential that the protecting groups are introduced and removed with excellent yield, whilst leaving other parts of the molecule in-tact. This important aspect of carbohydrate synthesis is discussed in Chapter 2.
3. The creation of a new bond between two carbohydrate units offers the potential to form two epimeric (anomeric) isomers (Figure 1.4).

In order to access only the required stereoisomer, it is essential that the geometries of the glycosidic bonds are controlled. Some linkages are particularly difficult to form, for example β-mannosidic linkages, even though they are abundant within



Scheme 1.2



Scheme 1.3

natural systems. This specific problem, and some solutions for efficient assembly of the β-mannosidic linkage, are presented in Chapter 8.

There are, however, advantages associated with the synthesis of carbohydrates: a large number of building blocks (both monosaccharide and higher oligomers) are commercially available in large quantities, at economic prices, for incorporation within synthetic strategies. D-Monosaccharides are usually incorporated within natural oligosaccharides rather than the enantiomeric L-series. Also, there are a number of chemical methods that can be utilized to influence

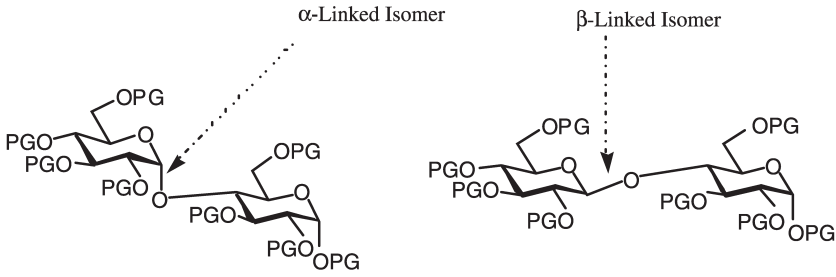


Figure 1.4

which regio- and stereoisomer will result. Although methods for the solid phase synthesis of carbohydrate targets have developed at a slower rate than for peptide and oligonucelotide targets, significant progress has been made recently and it is likely that exciting results will be presented in this area in the near future [16].

Each chapter in this book will detail a particular theme associated with carbohydrate synthesis. A brief review of the subject area is provided, but the emphasis in all cases is on describing efficient practical methods to effect the transformations described. Indeed, a number of best synthetic methods are provided within each Chapter. Thus methods will be provided for the synthesis of acceptors, using protecting group chemistry (Chapter 2), as well as entry to, and activation of, a range of popular donors (Chapters 3–5). Modern chemical (Chapters 6 and 7) and enzymatic strategies (Chapter 12) for the assembly of the carbohydrates will also be described. Some specific targets that are either particularly difficult to prepare, or have exceptionally important roles within biological systems, also receive detailed attention. Thus chapters detailing entry to β-linked mannosides (Chapter 8), sialic acid containing carbohydrates (Chapter 9), glycosyl amino acids, of use for accessing glycopeptides, (Chapter 10) and *C*-linked glycosides (Chapter 11) are presented.

REFERENCES

1. For useful reviews see (a) PR Crocker and T Feizi, *Curr. Opin. Struct. Biol.*, 1996, **6**, 679; (b) E Herbert, *Biosci. Rep.*, 2000, **20**, 213.
2. For useful reviews see (a) H Lis and N Sharon, *Chem. Rev.*, 1998, **98**, 637; (b) S Houlton, *Chem. Br.*, 2002, **38**, 46; (c) KM Koeeler and C-H Wong, *Nat. Biotech.*, 2000, **18**, 835; (d) T Maeder, *Sci. Am.*, 2002, **287**, 40; (e) *Chem. Rev.*, 2000, 100; all of part 12; (f) *Chem Rev.*, 2002, 102; all of part 2; (g) J Rojo, JC Morales and S Penades, *Top. Curr. Chem.*, 2002, **218**, 45; (h) CR Bertozzi and LL Kiessling, *Science*, 2001, **291**, 2357; (i) M Fukuda, *Bio. Org. Med. Chem.*, 1995, **3**, 207.
3. DD Carson, *Front. Biosci.*, 2002, **7**, D1535.
4. (a) D Zopf and S Roth, *Lancet*, 1996, **347**, 1017–1021; (b) G Mulvey, PI Kitov, P Marcato, DR Bundle and GD Armstrong, *Biochimie*, 2001, **83**, 841–847.
5. M Mouricout, JM Petit, JR Carias and R Julien, *Infect. Immun.*, 1990, **58**, 98–106.

6. TK Ritter and C-H Wong, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3508.
7. (a) V Pozsgay, *Adv. Carbohydr. Chem. Biochem.*, 2001, **56**, 153; (b) B Monzavi-Karbassi and T Kieber-Emmons, *Biotechniques*, 2001, **30**, 170; (c) B Kuberan and RJ Lindhart, *Curr. Org. Chem.*, 2000, **4**, 653.
8. SJ Danishefsky and JR Allen, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 836.
9. (a) SAW Gruner, E Locardi, E Lohof and H Kessler, *Chem. Rev.*, 2002; (b) FM Unger, *Adv. Carbohydr. Chem. Biochem.*, 2001, **57**, 210; (c) EE Simanek, GJ McGarvey, JA Jablonowski and C-H Wong, *Chem. Rev.*, 1998, **98**, 833.
10. (a) E Gorelik, U Galili and A Raz, *Cancer Metastasis Rev.*, 2001, **20**, 245; (b) JW Dennis, M Granovsky and CE Warren, *Biochim. Biophys. Acta*, 1999, **1473**, 21.
11. (a) VH Lillelund, HH Jensen, X Liang and M Bols, *Chem. Rev.*, 2002, **102**, 515; (b) PE Goss, MA Baker, JP Carver and JW Dennis, *Clin. Cancer Res.*, 1995, **1**, 935; (c) PE Goss, CL Reid, D Bailey and JW Dennis, *Clin. Cancer Res.*, 1997, **3**, 1077; (d) B Winchester and GWJ Fleet, *J. Carbohydr. Chem.*, 2000, **19**, 471.
12. TW Rademacher, B Parekh and RA Dwek, *Ann. Rev. Biochem.*, 1988, **57**, 785.
13. E Saxon and CR Bertozzi, *Ann. Rev. Cell Devel. Bio.*, 2001, **17**, 1.
14. J Wu, MH Natz and MA Zern, *Front. Biosci.*, 2002, **7**, D717.
15. EC Lavelle, *Crit. Rev. Ther. Drug*, 2001, **18**, 341.
16. PH Seeberger, W-C Haase *Chem. Rev.*, 2000, **100**, 4349.

– 2 –

Selective Hydroxyl Protection and Deprotection

Jeremy Robertson and Petra M. Stafford

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

2.1 INTRODUCTION

In an ideal world it would be possible to effect any desired glycosylation between two free sugars with total control of regio- and stereochemistry to produce a single oligosaccharide. Although enzymes can be sufficiently selective to catalyse such transformations, a general *chemical* solution to this problem is yet to be found. Aside from the problem of controlling the stereochemistry at the newly formed glycosidic linkage, it is simply not possible to select unambiguously, and at will, which hydroxyl group participates in glycosylation and complex mixtures often result.

As in other areas of organic synthesis, ensuring that a particular functional group undergoes reaction without interference from others can be achieved by blocking those others with protecting groups. The general principles of protecting group chemistry and the multitude of methods for their introduction and removal have been summarised in a number of excellent books [1] and review articles [2] but carbohydrates present particular problems as they possess a number of nucleophilic and mildly acidic hydroxyl groups arranged on relatively short carbon chains, and the density of functionality is accordingly high [3]. In general, the various hydroxyl groups cannot be considered in isolation; their reactivity influences, and is influenced by, neighbouring functionality and any modifications made to one of them often leads to changes in the relative reactivity of the others. Because of these subtleties, carbohydrate chemistry may appear to have a large associated 'lore' which can seem unnecessarily arcane to the uninitiated; this has led, in the past, to a separation of carbohydrate chemistry from what was regarded as mainstream organic synthesis. Fortunately, the importance of the problems that can be addressed with carbohydrate synthesis, coupled with an extensive and thorough review

literature, has led to a steady integration of the field which now occupies a central position within organic synthesis.

Because of this integration, control of carbohydrate reactivity is increasingly required, not only in the traditional areas of monosaccharide and oligosaccharide synthesis, but also for the preparation of carbohydrate mimics such as *C*-glycosides and imino sugars, and in the synthesis of glycosylated natural products and intermediates for non-carbohydrate compounds.

Capping one or more of the hydroxyl groups reduces the ambiguity in site selectivity during subsequent reactions and judicious choice of protecting group can impart favourable steric and electronic characteristics that may influence reactivity and stereoselectivity. Obviously a protecting group regime needs to be carefully chosen, and this requires many factors to be balanced; of utmost importance are (a) whether a given hydroxyl group can be protected selectively; (b) whether a potential protecting group will survive the conditions of the intended reactions; and (c) whether selective deprotection can be achieved, if required, at the end of the sequence.

2.2 HYDROXYL GROUP REACTIVITY

The issue of the relative reactivity of carbohydrate hydroxyl groups has been the subject of intense investigation for many decades. Comparatively recent developments in chromatographic methods and NMR spectroscopy have allowed reliable product distributions to be assigned from reactions run to low conversion and these results indicate the intrinsic reactivity of particular carbohydrate hydroxyl groups under specified conditions. This information eases the development of protecting group regimes that allow selective masking and unmasking of the various hydroxyl groups as required. Most of the key trends had been identified by the end of the 1970s and this information has been reviewed comprehensively [4].

Under acidic conditions, activation of the anomeric (1-) position (Figure 2.1) is straightforward and selective modifications to this centre are easily achieved; as such, protection of the anomeric position will not be specifically discussed in this chapter. Under basic conditions, and in the broadest terms, hexopyranose reactivity follows reasonably consistent lines: the (primary) 6-OH group, being the least hindered, reacts first followed by the (anomeric) 1-OH; of the remaining (secondary) hydroxyls the 2-OH is often the more reactive followed by the 3- and 4-hydroxyls, respectively. Differences in this order reflect the axial/equatorial orientation of

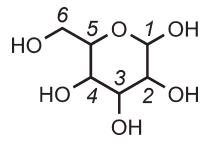


Figure 2.1 Hexopyranose numbering.

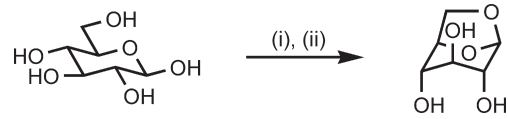


Figure 2.2 (i) TsCl, pyridine; (ii) aq. NaOH.

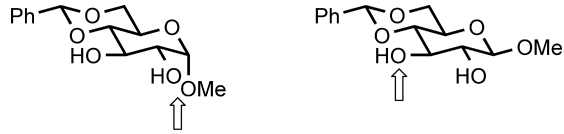


Figure 2.3 Preferred sites for benzylation with BnBr, BaO, DMF.

the hydroxyl groups: axial hydroxyls tend to react more slowly than those in equatorial positions. By forming the 1,6-anhydrosugar, the relative reactivity of the various hydroxyls can be altered because the orientation at each ring position is inverted; Figure 2.2 shows how, in glucose, the three equatorial 2°-hydroxyls become axially disposed in the anhydro sugar [5].

Such generalisations can, however, be misleading as the various hexopyranoses exhibit slightly different reactivity patterns and the anomeric configuration can be critical in determining the site selectivity. In particular, when a (protected) anomeric hydroxyl is *cis* to the 2-OH it is often found that the 2-OH shows enhanced reactivity towards etherification and esterification as exemplified by benzylation of methyl 4,6-*O*-benzylidene α-D-glucopyranoside under basic conditions (Figure 2.3) [6].

More important are the choice of protecting group and the exact conditions under which it is introduced as these dictate which of the hydroxyl groups reacts. Although the variety of hydroxyl protecting groups [7] can appear bewildering, in practice, the vast majority of carbohydrate syntheses are built around just a handful of tried and tested groups. These are conveniently separated into ethers, esters, silyl ethers, and cyclic acetals (for diol protection).

2.3 ETHERS

Simple alkyl groups offer the most reliable form of protection; for example, methyl ethers are stable under aqueous conditions over a wide pH range, are essentially inert to bases, nucleophiles, organometallic reagents, oxidizing and reducing agents, and alkylating agents. In fact, this stability can be problematic in terms of temporary protection as, eventually, the protecting group has to be removed. In the case of methyl ethers the only widely applicable deprotection solution is to employ a combination of Lewis acid and nucleophile, and the conditions may be sufficiently

vigorous to induce unwanted chemistry at other sites in the molecule; in this respect the anomeric centre is especially vulnerable.

For this reason, in complex carbohydrate synthesis, simple ethers are not preferred and, instead, the ethers that have found favour incorporate functionality that can lead to cleavage under rather specific conditions: useful alkyl protecting groups possess good stability under a wide variety of conditions but they have an Achilles' heel that can be targeted when deprotection is needed. Of the ethers the most important are the benzyl (Bn) and allyl (All) groups and their derivatives, the methods for their introduction being roughly equivalent for the two and falling into four classes [8]:

(a) Basic conditions using the appropriate alkyl halide in a polar solvent (or in a relatively non-polar solvent such as THF with an added tetraalkylammonium halide catalyst).

(i) RBr, NaH, DMF or DMSO; (Method 1)
(ii) RBr, NaH, THF, cat. Bu_4NI; (Method 2)
(iii) RCl, KOH;
(iv) RCl or RBr, aqueous NaOH, cat. Bu_4NHSO_4;
(v) RBr, BaO, DMF;
(vi) RBr, NaH, $CuCl_2$, Bu_4NI; (Method 3)

(b) Essentially neutral conditions using silver(I) oxide, or via stannyl ethers and stannylene acetals.

(i) RBr, Ag_2O, DMF; (Method 4)
(ii) $(Bu_3Sn)_2O$; then RBr, *N*-methylimidazole;
(iii) Bu_2SnO; then RBr, DMF (or RBr, $PhCH_3$, cat. Bu_4NX); (Method 5)

(c) Acidic conditions using the appropriate *O*-alkyltrichloroacetimidate.

(i) $ROC(=NH)CCl_3$, CF_3SO_3H; (Method 6)

(d) Methods specific to either allyl or benzyl ethers, see below.

The choice of conditions for alkylation (or any protection method) is dictated by the existing functionality within the carbohydrate. Where there are alternatives within a category, the specific choice is usually made on the basis of previous experience or if the method offers a desired level of selectivity for protection of a particular site. For example, the alkylation conditions within category (a) above [with the exception of (vi)] and that under (c) lead to more or less equivalent levels of selectivity (summarised in section **2.2**, Hydroxyl group reactivity) and will not be discussed further. However alkylations and acylations proceeding via *O*-stannyl intermediates (b) and via copper chelates [(a)(vi)] follow set patterns that may differ from these general trends. These alternatives are discussed within sections **2.3.1**, Benzyl ethers and **2.3.2**, Allyl ethers.

2.3.1 Benzyl ethers

Benzyl ethers are commonly introduced by the conditions in category (a), section **2.3**, Ethers, particularly when perbenzylation is required. The choice of conditions does not affect selectivity greatly (Figure 2.4) [9] except when the copper chelate method is employed. In the latter method dialkoxides (produced from diols with NaH) are deactivated by regioselective complexation of a copper salt so that the free alkoxide reacts preferentially; Figure 2.5 illustrates a typical case [10] which should be compared with the variants in Figure 2.4.

The use of stannylene acetals and stannyl ethers is widely used for achieving selective benzylation, the selectivity paralleling that observed for allylation (see section **2.3.2**, Allyl ethers).

Divergent selectivity in obtaining benzyl-protected sugars can be achieved by Lewis acid mediated reduction of benzylidene acetals (Methods 7 and 8). Figure 2.6 illustrates selective release of the 6-OH using the combination $LiAlH_4/AlCl_3$ in which the comparitively bulky Lewis acid initiates oxonium ion formation by complexing to the sterically more available 1°-benzylidene acetal oxygen [11]. Conversely (Figure 2.7) use of protic acid in combination with $NaBH_3CN$ leads to ring-opening in the opposite sense via protonation of the slightly more basic 2°-acetal oxygen [12]. Interestingly, the regiochemistry in the cleavage of benzylidene derivatives of 1,2-diols (see section **2.6**, Acetals) is dependent on the stereochemistry at the benzylic carbon (Figure 2.8); the enhanced basicity of dioxolane oxygens compared to dioxane oxygens is apparent in this example [13].

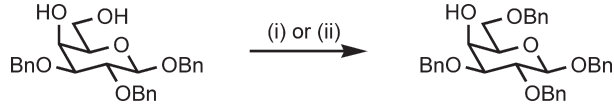


Figure 2.4 (i) BnCl, NaH, DMF; (ii) BnBr, 5% aq. NaOH, cat. Bu_4NHSO_4.

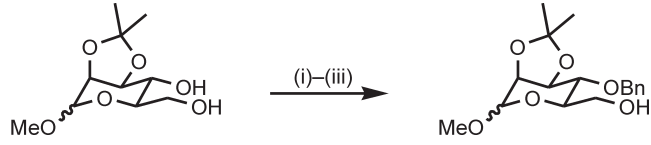


Figure 2.5 (i) NaH (2.0 equiv.); (ii) $CuCl_2$; (iii) BnI.

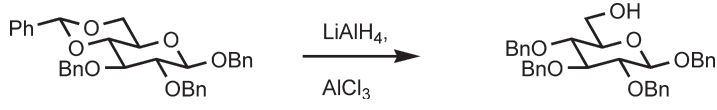


Figure 2.6