# The Chemistry of Natural Products

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Edited by

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# Preface

The rapid growth of the study of natural products in recent years has been accompanied by the publication of numerous specialist monographs on alkaloids, carbohydrates, coumarins, acetylenes, terpenes, etc., and there are several on biosynthesis. In contrast general texts covering the whole field no longer exist, and a comprehensive work would be enormous. This volume aims to partly fill the gap in a modest way by describing what has been happening in the main areas of natural products research during approximately the last ten years. The emphasis is entirely on the structure, chemistry, and synthesis of natural products with only passing reference to biosynthesis.

R.H. Thomson

# Abbreviations

| | |
|---|---|
| ABIBN | azobisisobutyronitrile |
| Ac | acetyl |
| BDMS | *n*-butyldimethylsilyl |
| BOP-Cl | *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride |
| Bz | benzoyl |
| Bzl | benzyl |
| $Cb_3$ | benzyloxycarbonyl |
| DBN | 1,5-diazabicyclo[4,3,0]non-5-ene |
| DBU | 1,8-diazabicyclo[5,4,0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DHP | dihydropyran |
| DIBAL | diisobutylaluminium hydride |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMS | dimethyl sulphide |
| DMSO | dimethyl sulphoxide |
| Fuc | fucose |
| Gal | galactose |
| Glc | glucose |
| GlcNAc | 2-acetamido-2-deoxyglucose |
| HMDS | hexamethyldisilazane |
| HMPA = HMPT | |
| HMPT | hexamethylphosphoric triamide |
| LAH | lithium aluminium hydride |
| LDA | lithium diisopropylamide |
| Man | mannose |
| MCPBA | *m*-chloroperbenzoic acid |
| MEM | methoxyethoxymethyl |
| MOM | methoxymethyl |

| | |
|---|---|
| Ms | methanesulphonyl |
| MSA | mesitylenesulphonic acid |
| MTHP | 4-methoxytetrahydropyranyl |
| NBS | *N*-bromosuccinimide |
| PCC | pyridinium chlorochromate |
| Piv | pivaloyl |
| py | pyridine |
| Rha | rhamnose |
| TBDMS | *t*-butyldimethylsilyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| Tm | mesitylenesulphonyl |
| TMS | trimethylsilyl |
| TPS-Cl | 2,4,6-tri-isopropylbenzenesulphonyl chloride |
| Ts | toluene-*p*-sulphonyl |
| Tr | trityl |

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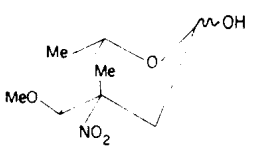
# 1 Carbohydrates

J.S. BRIMACOMBE

During the past decade there has been unprecedented growth in syntheses that involve carbohydrates. This upsurge of activity can be attributed to a number of factors. First, the discovery of sugars of unusual structures, for example, L-evernitrose[1] (1) and D-aldgarose[2] (2), as components of antibiotic substances has presented the carbohydrate chemist with unusually difficult synthetic targets. Second, there has been exceptional activity in the total synthesis of other classes of natural product (for example pheromones and macrolide antibiotics) using 'chiral templates' derived from carbohydrates.[3] Third, the oligosaccharide chains of glycoconjugates, which include glycolipids and glycoproteins, are now known[4] to have important roles in cellular biology, including, among others, intercellular recognition, the transportation of proteins between cells, the specificity of the immune reaction, and as receptors for enzymes, hormones, proteins, and viruses. Since biogenic material is often difficult to obtain, considerable efforts[5,6] are now being directed towards the synthesis of part or whole of the oligosaccharide chains of glycoconjugates in order that their biological functions can be studied in depth. One of the aims of this chapter is to give a broad impression of what has been achieved in these areas.

Carbohydrates possess a higher density of functional groups than any other class of compound, so that protection of one or more of these groups (usually hydroxyl groups) is of fundamental importance to any synthetic strategy. Temporary protecting groups developed for use with other hydroxylic compounds are used increasingly in carbohydrate chemistry,[7] but, as will be seen later, others (for example, allyl and related ethers[8]) have been developed specifically to endow an added flexibility to syntheses involving carbohydrates.

The protection of carbohydrates as cyclic acetals is of long-standing and

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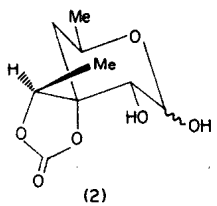


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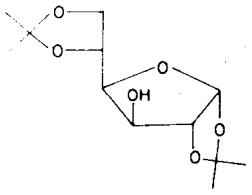


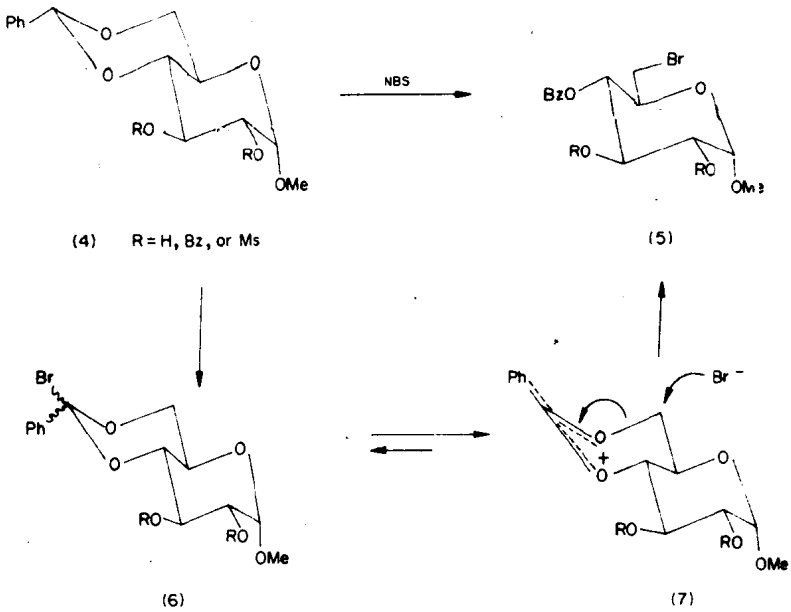

(3)

enduring importance in carbohydrate chemistry.[9] It is easy to see why, for example, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**), which is readily prepared by acid-catalysed acetonation of D-glucose,[9] has been such a popular starting material for the synthesis of many other sugars.[3,10] The isolated hydroxyl group on C-3 of **3** can be protected or modified prior to exposure of the hydroxyl groups on C-5 and C-6 by selective hydrolysis of the 5,6-*O*-isopropylidene group with acid. Differences between the reactivities of the primary hydroxyl group on C-6 and the secondary hydroxyl group on C-5 can then be exploited in effecting further modifications at these positions. More vigorous acidic hydrolysis removes the 1,2-*O*-isopropylidene group, thereby exposing the hydroxyl group on C-2 and, if the molecule reverts to a pyranose ring, the hydroxyl group on C-4. Such procedures, in which cyclic acetals have fulfilled the fundamental role of a protecting group, are commonplace in syntheses involving carbohydrates. During the past few years, procedures for the regioselective (even regiospecific) cleavage of cyclic acetals in a synthetically useful way have been introduced into carbohydrate chemistry, so that these groups assume a much more active role in the route to the target molecule—in this context, cyclic acetals may be regarded as functional groups.[11] Some aspects of the chemistry of cyclic acetals, which have had a decisive influence on the structural modification of carbohydrates, and other useful reactions and protecting groups are discussed in the following sections.

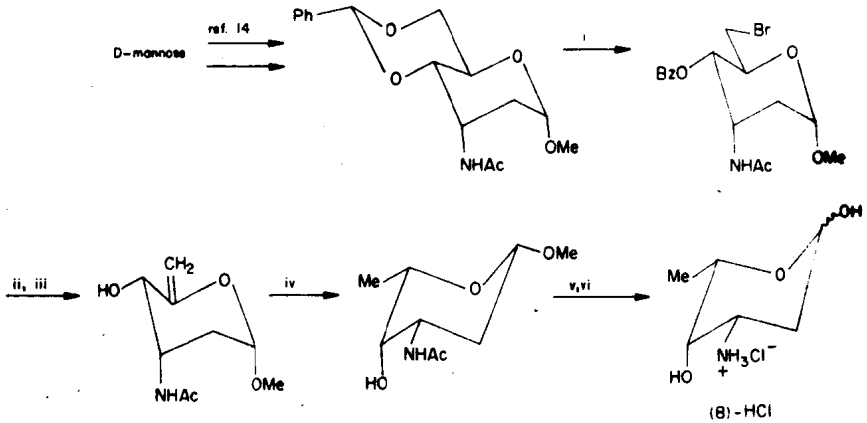
## 1.1 Cyclic acetals as functional groups

### 1.1.1 *Halogenation*

An important method for the structural modification of carbohydrates is founded on the cleavage of *O*-benzylidene acetals by *N*-bromosuccinimide.[12,13] Thus, treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, R = H) and its derivatives **4** (R = Bz or Ms) with *N*-bromosuccinimide in refluxing carbon tetrachloride, in the presence of barium carbonate, gave the corresponding methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (**5**) regiospecifically and in good yield. This reaction can be conducted in the presence of a wide range of other groups (*O*-mesyl, -tosyl,




**Scheme 1**

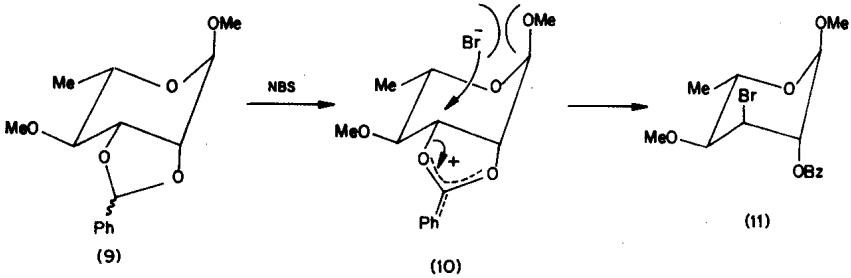



**Scheme 2**

**Reagents**: i, NBS; ii, AgF; iii, NaOMe; iv, $H_2$-Pd; v, $Ba(OH)_2$; vi, $H_3O^+$

-acetyl, -benzoyl, *N*-acetyl, and α-epoxides), and is often followed by reductive cleavage of the 6-bromo group to give the corresponding 6-deoxy sugar. The first step of the reaction appears to involve attack by *N*-bromosuccinimide (or bromine) on the acetal carbon atom, probably by a free-radical process (a free-radical initiator is sometimes included[13]), to give the *gem*-bromoacetal **6** (Scheme 1). This is followed by rearrangement of **6** to the benzoxonium ion **7**, which is then attacked by bromide ion to give the 4-*O*-benzoyl-6-bromo derivative **5**. The reaction provided the means for generating the required L-*lyxo* stereochemistry in an efficient synthesis of L-daunosamine (**8**), the carbohydrate constituent of the antitumour antibiotics adriamycin and daunorubicin, from D-mannose (Scheme 2).[14]

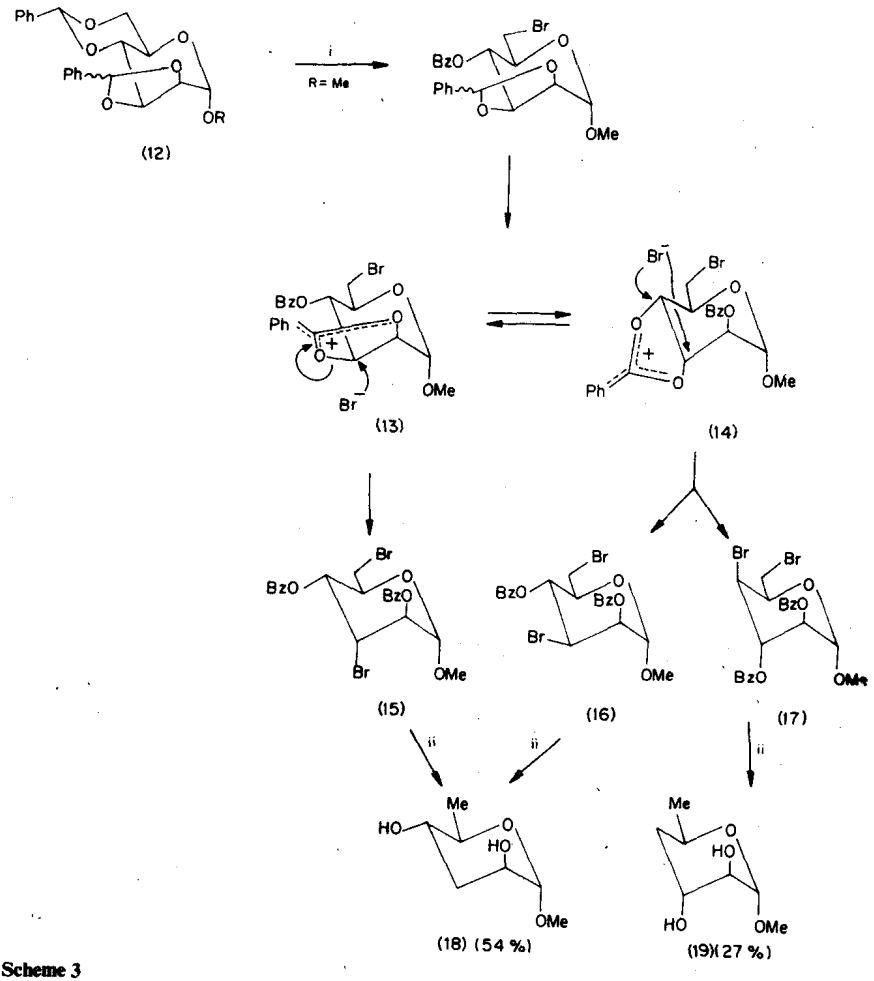
*N*-Bromosuccinimide reacted with the L-rhamnoside 2,3-*O*-benzylidene acetal **9** to yield[15] the 3-bromo derivative **11**, despite the strong *syn*-axial interaction that develops during the attack of bromide ion at C-3 of the 2,3-benzoxonium ion **10**. Conformational factors or the reluctance of pyranoside derivatives to undergo nucleophilic attack at C-2 have been invoked to explain the regiospecificity of this and related reactions.[16]




(9) (10) (11)

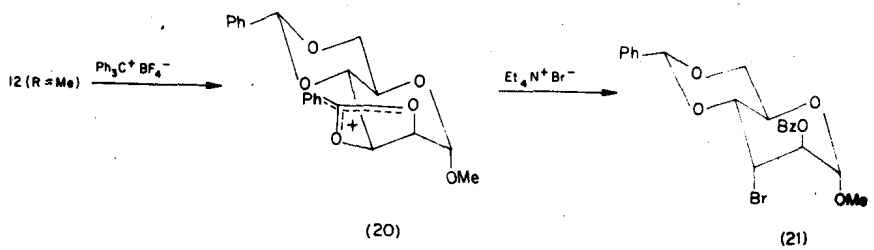
On the basis of these results, the diacetal **12** (R = Me) might be expected to react with *N*-bromosuccinimide to give the 3,6-dibromo derivative **15**, via the 2,3-benzoxonium ion **13**. In fact, the isomeric dibromo derivatives **16** and **17** were also formed,[17] in all likelihood by ring-opening of the 3,4-benzoxonium ion **14** resulting from rearrangement of **13** (Scheme 3). The dibromo derivatives **15**–**17** can be reduced collectively to a separable mixture of the dideoxy sugars **18** (methyl α-tyveloside) and **19**,[15] so that an effective procedure for the deoxygenation of methyl α-D-mannopyranoside at positions 3 and 6 is available.

Regiospecificity was observed in the reaction of the diacetal **12** (R = Me) with triphenylmethyl fluoroborate (a strong hydride-acceptor), the only ion formed being **20**.[18] On the addition of tetraethylammonium bromide, **20** underwent regiospecific ring-opening to give the 3-bromo compound **21** in 50% yield. Other examples of the formation of halogenated carbohydrates from 1,3-dioxolanylium ions have been comprehensively reviewed.[11]




**Scheme 3**

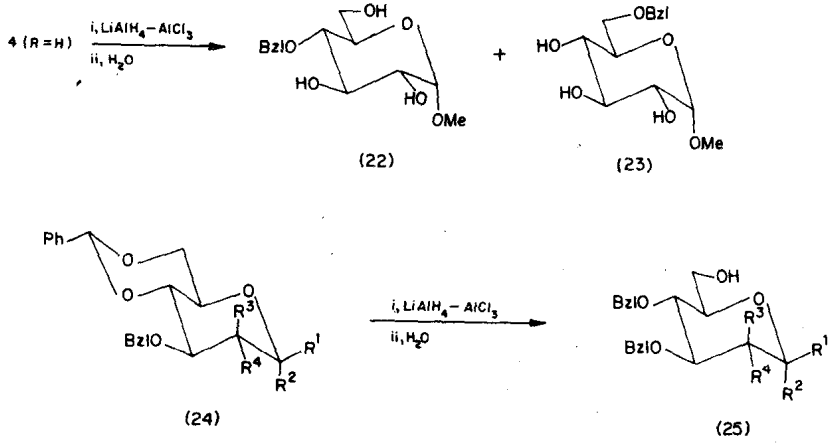
**Reagents**: i, NBS; ii, $LiAlH_4$



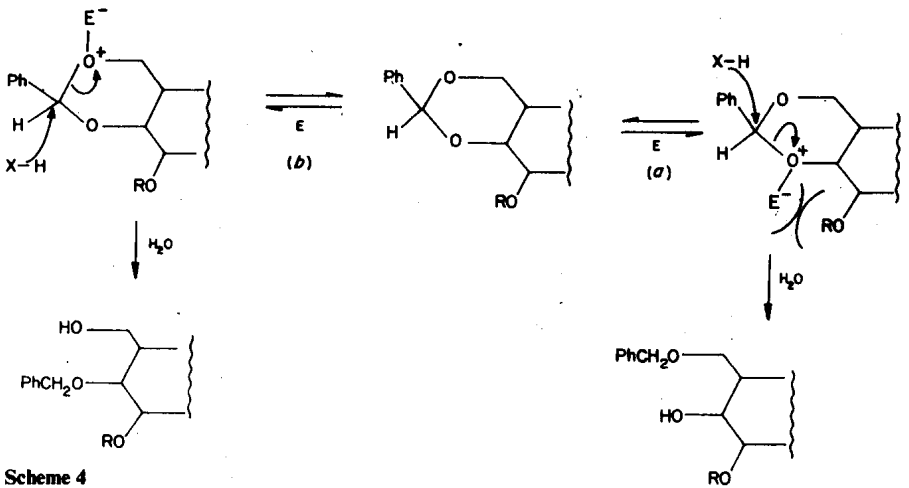
### 1.1.2 *Hydrogenolysis*

1,3-Dioxolanes and 1,3-dioxanes are stable to the action of lithium aluminium hydride and sodium borohydride,[19] but they can be cleaved[20] with a so-called 'mixed hydride', usually a mixture of $LiAlH_4$ and $AlCl_3$. The identity of the 'mixed hydride' depends on the proportions of Lewis acid and hydride used; when $LiAlH_4$ and $AlCl_3$ are used in a ratio of 1:1, for example, the reactive species is probably $AlH_2Cl$.[21] The polar effects that influence the direction of cleavage of 1,3-dioxolanes and 1,3-dioxanes with 'mixed hydrides' have been extensively examined,[20,21] but, as the following examples will show, steric factors may also be involved.

The direction of hydrogenolysis of the 4,6-*O*-benzylidene group of hexopyranosides is determined primarily by the nature of the substituent on O-3, but is not dependent on the anomeric configuration or the nature of the substituents at O-1 and -2.[22] Hydrogenolysis of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **4** (R = H), for example, with a one-molar equivalent of $LiAlH_4$-$AlCl_3$ (1:1 ratio) in an inert solvent gave[23] a mixture of the 4- and 6-*O*-benzyl compounds **22** and **23**, respectively, in a ratio of 3:2, whereas the 3-*O*-benzyl- and 2,3-di-*O*-benzyl-D-gluco- and -D-manno-pyranoside deri-

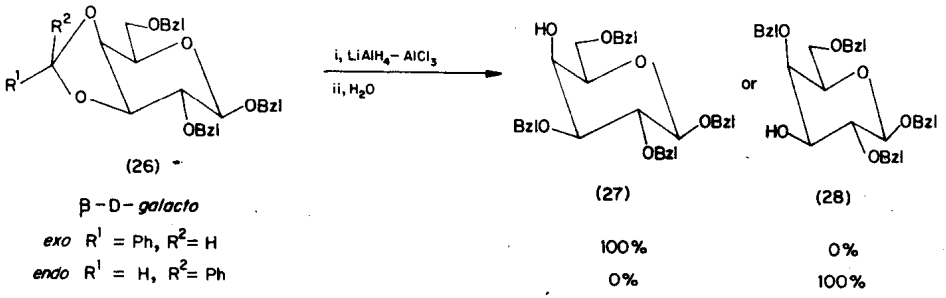



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| β-D-*gluco* | OBzl | H | H | OBzl |
| α-D-*gluco* | H | OPh | H | OBzl |
| | H | OMe | H | OBzl |
| | H | OMe | H | OH |
| α-D-*manno* | H | OBzl | OBzl | H |



**Scheme 4**

E is $AlH_2Cl$ or a related species



(26)

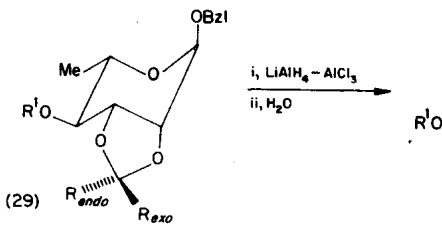
β-D-*galacto*

*exo* $R^1$ = Ph, $R^2$ = H

*endo* $R^1$ = H, $R^2$ = Ph

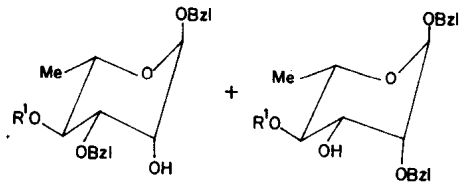
(27) 100% 0%

(28) 0% 100%



(29)

α-L-*rhamno*



(30) (31)

| $R_{exo}$ | $R_{endo}$ | $R^1$ | % | % |
|---|---|---|---|---|
| Ph | H | H | 98 | 2 |
| Ph | H | Bzl | 94 | 6 |
| Ph | H | $CH_2CH=CH_2$ | 85 | 15 |
| H | Ph | H | 2 | 98 |
| H | Ph | Bzl | 18.5 | 81.5 |