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187 Topics in Current Chemistry

Glycoscience

Synthesis of Substrate Analogs and Mimetics

Springer

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With contributions by
J. M. Beau, P. Boullanger, A. de Raadt,
H. Driguez, M. Ebner, C. W. Ekhart,
T. Gallagher, I. Lundt, F. Nicotra, R. Roy,
R. V. Stick, A. E. Stütz, H. P. Wessel

Springer

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Volume Editors

Dr. Hugues Driguez
Centre de Recherches sur les
Macromolécules Végétales (CERMAV)
601, Rue de la Chimie, B. P. 53
F-38041 Grenoble Cedex 9, France
E-mail: HDriguez@cermav.grenet.fr

Prof. Dr. Joachim Thiem
Institut für Organische Chemie
Universität Hamburg
Martin-Luther-King-Platz 6
D-20146 Hamburg, FRG
E-mail: thiem@chemie.uni-hamburg.de

Editorial Board

Preface

Within recent years and after a first coverage of carbohydrate chemistry in the series Topics in Current Chemistry (Vol. 154 in 1990) this field has undergone something like a "quantum jump" with regard to interest for a wider community of scientists. Apparently, for most areas of the natural sciences in general and in particular for those bordering natural products chemistry, progress in the saccharide field has attracted considerable attention and, in fact, many bridging collaborations have resulted. Glycoscience is becoming a term to cover all sorts of activities within or at the edge of carbohydrate research.

It was within the course of a sabbatical collaboration that the editors – both "born" carbohydrate chemists – felt it highly appropriate and desirable to compile a number of contemporary reviews focussing on developments in this field. A number of colleagues actively pursueing outstanding research in the saccharide field agreed to discuss topical issues to which they with their groups have contributed significantly. The result is a fresh and contemporary coverage of selected topics including future outlooks in glycoscience.

In this current volume, particular emphasis has been placed on the demanding synthetic approaches to and on the biological implications of carbohydrate-derived modulators or inhibitors. The sophisticated and now already highly developed synthetic approaches to complex C-glycosides is highlighted by *J.-M. Beau* and *T. Gallagher* and the synthesis of the more biological revelant C-glycosides by *F. Nicotra. H. Driguez* focusses on the synthesis and application of thiooligosaccharides for inhibitory studies. The previously nicely developed sugar lactone chemistry allows its synthetic wealth to flow into very attractive syntheses of functionalized heterocycles as described by *I. Lundt*. Further glycosidase inhibitors have been elaborated as outlined by *A. de Raadt, C.W. Ekhart, M. Ebner* and *A.E. Stütz*. Approaches to inhibitors for other glycanohydrolyses are reported by *R.V. Stick*, and the synthetic development of heparinoid mimetics is elaborated by *H.P. Wessel*. The increasing interest and recent development of multivalent glycoconjugates is covered by *R. Roy*, and in his contribution on amphiphilic sugar derivatives *P. Boullanger* allows us to imagine the supramolecular features embedded in carbohydrate structures.

The authors, the editors and the publisher hope that, by reading this volume, many scientists in the life sciences area will have been able to acquire a taste for

the subject and that they will join the growing glycoscience community and actively contribute to this most fascinating research.

Grenoble and Hamburg
December 1996

Hugues Driguez
Joachim Thiem

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Glycoscience
Synthesis of Glycoconjugates and Oligosaccharides

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Nucleophilic C-Glycosyl Donors for C-Glycoside Synthesis

Jean-Marie Beau[1] and Timothy Gallagher[2]

[1] Institut de Chimie Moléculaire, Université de Paris-Sud, F-91405 Orsay, France
[2] School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom

This chapter reviews the methods available for the synthesis of C-glycosides that involve the use of carbohydrate units expressing nucleophilic reactivity at C(1) (the anomeric site). A wide variety of "anionic" (organometallic derivatives) and neutral (free radical) C(1) nucleophiles are known and examples of all structural types are presented. Coverage includes methods for generating effective C(1)-nucleophiles, their reactivity and utility in C-glycoside synthesis and, where appropriate, any associated limitations.

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Symbols and abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AIBN	1,1-azobisisobutyronitrile
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
Dibal-H	diisobutyl aluminium hydride
DIPS	diisopropylsulfide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
HMPA	hexamethylphosphoramide
LCIPA	lithium cyclohexylisopropylamide
LDA	lithium diisopropylamide
LDBB	lithium di-*tert*-butylbiphenylide
LN	lithium naphthalenide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
mCPBA	meta chloroperoxybenzoic acid
MOM	methoxymethyl
NIS	*N*-iodosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
py	pyridine
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethane sulfonyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TPS	triisopropylsilyl

1 Introduction

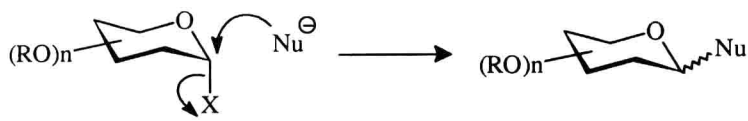
The synthesis of C-glycosides has experienced a rapid and widespread evolution over the last two decades [1–4]. While a variety of methods exist for establishing C-glycosyl linkages, conventional carbohydrate reactivity, that is the addition of an external nucleophile to an electrophilic C(1) (anomeric) center (Scheme 1), is most widely employed. Access to this reactivity is governed by the presence of the ring-oxygen atom, but this residue will also support the establishment of nucleophilic reactivity at C(1). Such nucleophilicity, though not readily exploited in *O*-glycosylation, does provide a versatile and complementary approach to the synthesis of C-glycosides (Scheme 2).

Defining the boundaries associated with nucleophilic reactivity is, however, less clear cut. With this in mind (and to allow the reader to make an informed assessment of the chemistry that is now available), we have avoided making our classifications too rigid.

In the following we have broadly divided the available C(1) nucleophiles according to structure and reactivity. C(1)-Nucleophiles based on metallation at an sp^3-center are categorized in terms of the presence and, as appropriate, the nature of a hetero atom (O or N) substituent at C(2). C(1)-Lithiated glycals correspond to nucleophilic sp^2-centers, and variations on this theme (concerning the nature of the metal component) are covered in depth.

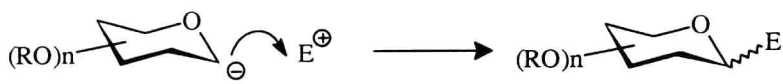
Enolates represent a special class of sp^2-hybridized C(1) nucleophiles. This is an important and developing aspect of carbohydrate reactivity and the carbonyl function can either be located at C(2), or be external to the sugar ring (as in sialic acid derivatives). Although the latter are not strictly C(1) nucleophiles, both their value in C-glycoside synthesis and relationship to other topics covered in this chapter merit inclusion of these systems.

Carbon-based radicals stabilized by oxygen, though electronically neutral, can exhibit nucleophilic reactivity. C-Glycoside synthesis based on anomeric



Electrophilic *C*-Glycosyl Donor

Scheme 1



Nucleophilic *C*-Glycosyl Donor

Scheme 2

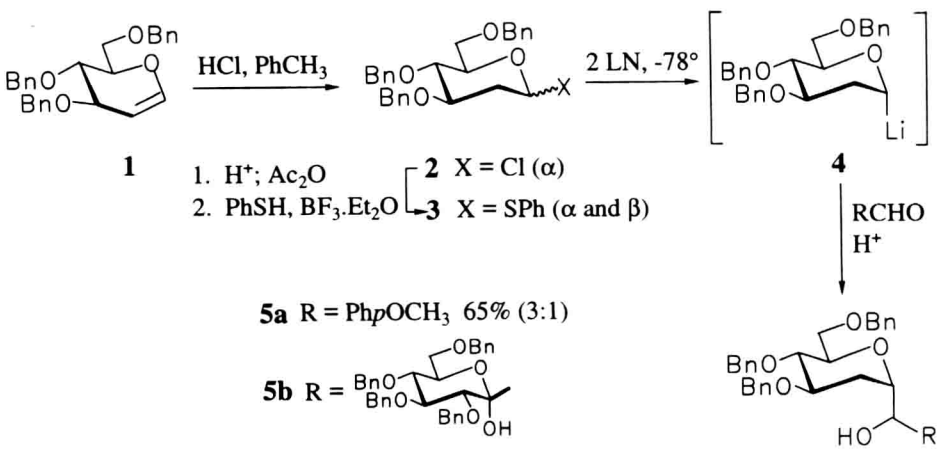
radicals is very important, but the space available here precludes a comprehensive coverage of the topic. Key features, which accentuate the nucleophilic aspects of anomeric radicals will, however, be addressed.

2
Nucleophilic sp^3-Anomeric Centers

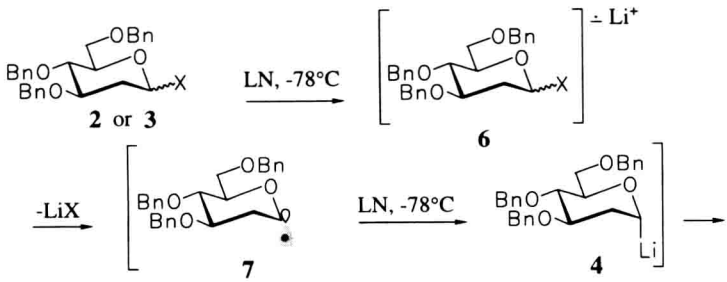
2.1
C(1)-Metallated 2-Deoxypyranosyl Compounds

2.1.1
Reductive Metallation Processes

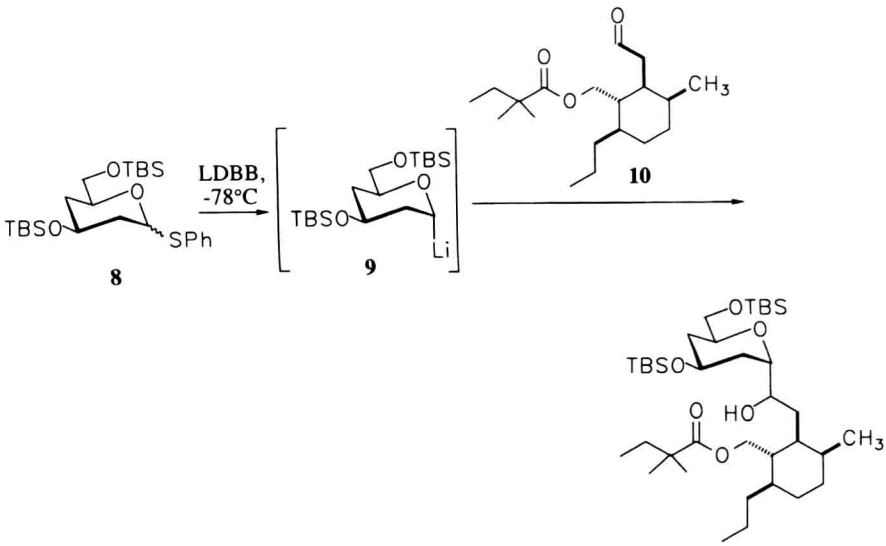
The first example of the non-stabilized C(1)-organolithium nucleophile was provided by reductive lithiation of 2-deoxy-D-glucopyranosyl chloride **2** or phenylsulfides **3** [5] with lithium naphthalenide (LN), a process discovered by Cohen and Matz [6] on cyclic α-alkoxysulfides, to give the C(1)-lithiated 2-deoxypyranoside **4**. Lithio reagent **4** reacts with electrophiles in moderate yields to provide selectively the corresponding α-D-C-glycosides **5** (Scheme 3). The stereoselectivity results from a two-step single-electron transfer mechanism. In the first step, transfer of one electron occurs from LN to the LUMO of X (X = Cl, SPh) to provide anion radical **6** which cleaves to generate axial radical **7** (stabilized by the anomeric effect) (Scheme 4). A second electron transfer to **7** then leads, under kinetic control, to the organolithium **4**, which is configurationally stable at −78 °C and reacts with electrophiles with retention of configuration. This method has been used as a key step in a synthesis of **11**, a monocyclic analogue of compactin, by reductive lithiation of thioglycoside **8** with lithium di-*tert*-butylbiphenylide (LDBB) at low tem-



Scheme 3



Scheme 4

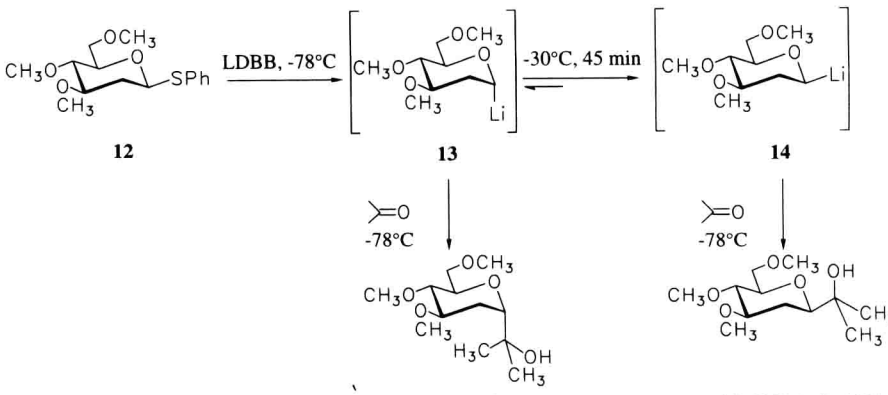


Scheme 5

perature followed by addition of the α-lithio reagent **9** to aldehyde **10** [7] (Scheme 5).

All attempts to transform the α-lithio reagent **4** to the more stable β-anomer by warming to −20 °C, a process that is successful with less functionalized substrates [8], failed, though C(1) isomerization was achieved when the hydroxyl groups of the sugar are protected as methyl ethers [9]. Thus, reductive lithiation (LDBB) of sulfide **12** gives the α-lithio reagent **13** at −78 °C which reacts with acetone to furnish the α-C-glycoside **15** (Scheme 6). When the lithiated reagent **13** is warmed to −20 °C for 45 min, essentially complete isomerization takes places leading to the β-lithio reagent **14** which was trapped by acetone to give β-C-glycoside **16**. The lower yield observed with **16** (vs. **15**) is attributed to competing protonation during isomerisation but this study also provided a detailed analysis of the stereoselectivity of this type of process.

When electrophiles other than carbonyl compounds or alkyl halides are employed, the basic α-lithio reagents need to be converted to other organo-



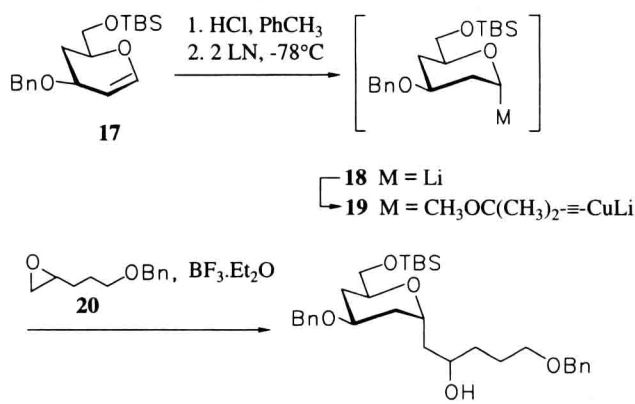
12 **13** **14**

15 81% (α:β, 98:2) **16** 59% (α:β, 1:99)

Scheme 6

metallic nucleophiles. Access to cuprate reagents is possible, which occurs with retention of configuration, and an example is shown in Scheme 7. Reductive lithiation of the α-chloride (obtained by hydrochlorination of glycal **17**) provides the α-lithio reagent **18** which was converted into the mixed cuprate reagent **19** [10]. Reaction of **19** with racemic epoxide **20** requires the presence of an excess of $BF_3.Et_2O$, and leads to the α-C-glycosides **21** (as a mixture of diastereomers) (Scheme 7). This transformation has been used as a key step in the stereochemical assignment of the C(1)-C(10) fragment of nystatin A1 [10].

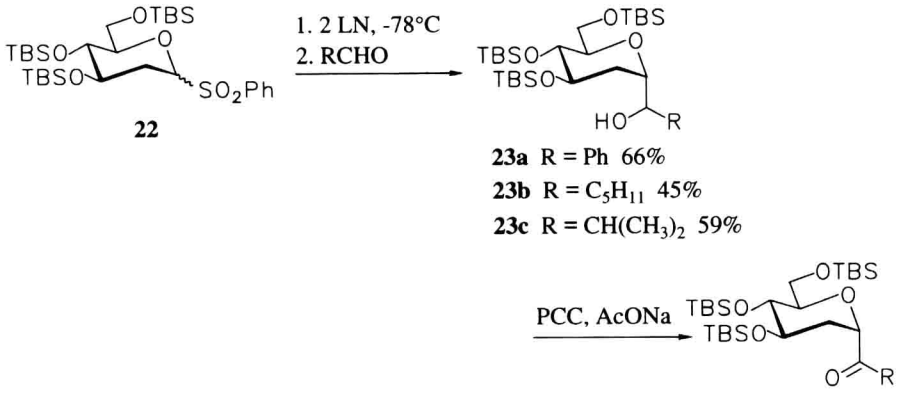
The reductive lithiation of α-alkoxy phenylsulfides is a slow process (typically 0.5–1 h at −78 °C) and lowering the LUMO of the electron acceptor by using, for example, an anomeric sulfone, leads to a much faster electron transfer [11]. Reductive lithiation of sulfone **22** is fast (less than 1 min) and leads to similar α-lithio reagents to those described above and Scheme 8 shows examples of simple α-C-2-deoxyglycosides **23** and **24** prepared by this protocol. The most interesting feature of anomeric sulfones is that alkylation *prior to* the reductive desulfonylation event is achievable. In this way, a one-pot four-step sequence



17 **20**

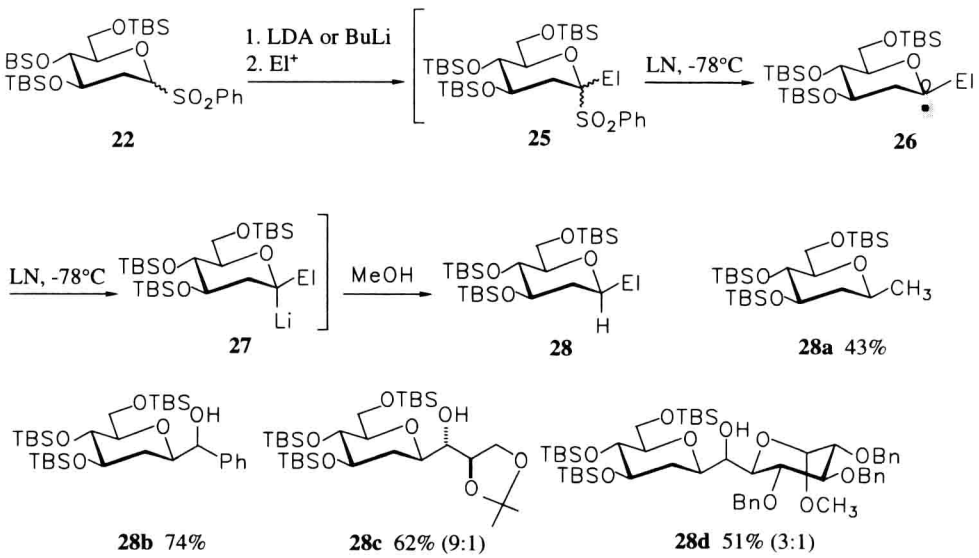
21 (36% from **17**)

Scheme 7



Scheme 8

involving sequential sulfone deprotonation-electrophile (El^+) addition-reductive lithiation-protonation provides a stereoselective entry to β-C–2-deoxyglycosides **28** from sulfone **22** [12] (Scheme 9). Again, homolytic C–S bond cleavage of the initial alkylated intermediate **25** provides an axial radical **26** that, after a second electron transfer, generates the configurationally stable lithium reagent **27** which is protonated, using methanol, to give **28** with retention of configuration.



Scheme 9

If dimethyl carbonate or phenyl esters (e.g. phenyl 1,2-*O*-isopropylidene-D-glycerate **29**) are used as electrophiles towards **22**, then α-C-2-deoxyglycosides are obtained selectively [13] (Scheme 10). In this case, the intermediate acylated