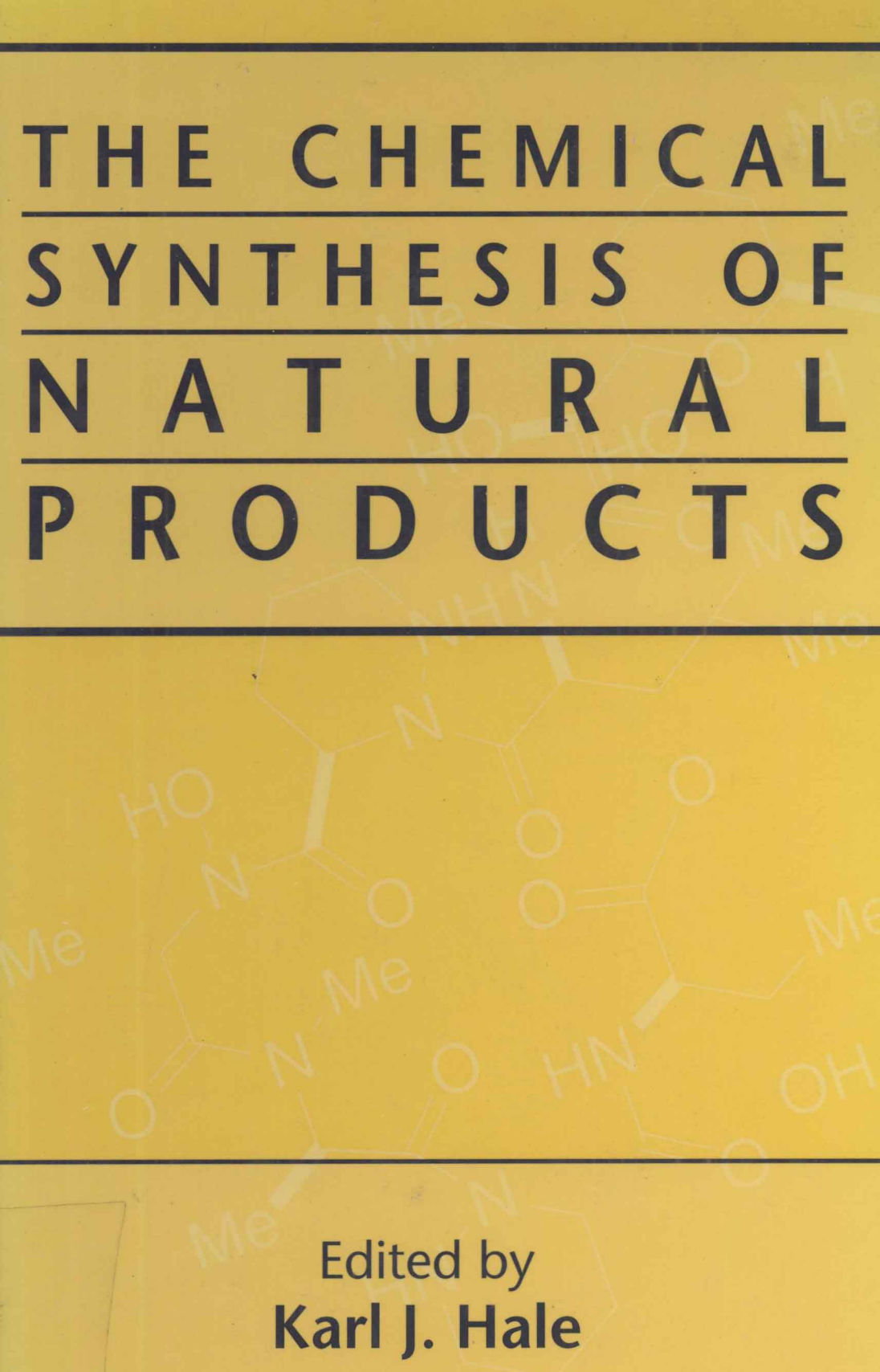
THE CHEMICAL SYNTHESIS OF NATURAL PRODUCTS



Edited by
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The Chemical Synthesis of Natural Products

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The Chemical Synthesis of Natural Products

Dedicated to the memory of
a very fine organic chemist
Dr Clive Bird
of King's College London

Preface

The synthesis of complex natural products continues to occupy a central position in organic chemistry research, not only because nature keeps providing us with some of the most awe-inspiring and synthetically challenging molecules that we can ever aspire to synthesise, but also because research in this area frequently drives many important breakthroughs in methodology. Given the tremendous contribution that complex natural product synthesis makes to chemistry as a whole, it is essential that up-to-date reference volumes appear regularly on this massive subject area, to assist organic chemists engaged in this activity. Such volumes should summarise concisely the most important technological advances and research achievements that have occurred in the sub-disciplines of natural product synthesis over stated periods of time, and they should not attempt to be comprehensive.

I am happy to say that this book goes a considerable way to fulfilling this role, with all the authors having effectively highlighted most of the key advances that have occurred within their specialist sub-areas in the past decade. I believe that it will be of considerable value to all synthetic organic chemists.

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1 Strategies for the chemical synthesis of complex carbohydrates

J.M. Gardiner

1.1 Introduction

The 1990s have seen particularly vigorous activity in the arena of oligosaccharide synthesis, and, in the broadest sense, the synthesis of oligosaccharide analogues. This chemical interest has in large part been driven by the emerging understanding of the biological roles of oligosaccharide moieties, together with the need for material for biological investigations, and the exciting opportunities for creating new therapeutic agents. There have been major advances in a variety of areas of complex carbohydrate chemistry since the late 1980s. These have encompassed new chemical glycosylation methodologies and improved strategies for using these methods in oligosaccharide assembly. Applications of enzymes in oligosaccharide synthesis have also seen major developments. The synthesis of carbohydrates on solid supports and the synthesis of saccharide libraries (solid-supported and in solution) and of multivalent saccharide assemblies have been progressing, and numerous complex oligosaccharides and related glycoconjugates have now been synthesised as a result of this array of methodological developments. And last, but not least, recent years have seen a rapidly growing interest in carbohydrate structural mimetics, where not just intersugar atoms are altered, but where structural motifs are replaced by nonsugars. In this chapter, we will briefly outline the successes of some new chemical glycosylations and also of enzymatic protocols since the late 1980s, directing readers to various more comprehensive reviews. The synthesis of carbohydrates on solid-supports, and libraries on support or in solution will be highlighted, and the growing areas of carbohydrate mimetics and multivalent carbohydrates will be reviewed.

1.2 Chemical glycosylations

The synthetic challenges presented by oligosaccharide assembly reside in the requirement for regioselective glycosylation of acceptor sugars, and in the requirement for the stereoselective introduction of one anomeric stereochemistry in the coupled product. The first issue has traditionally been dealt with by selective protection strategies. The control of anomeric

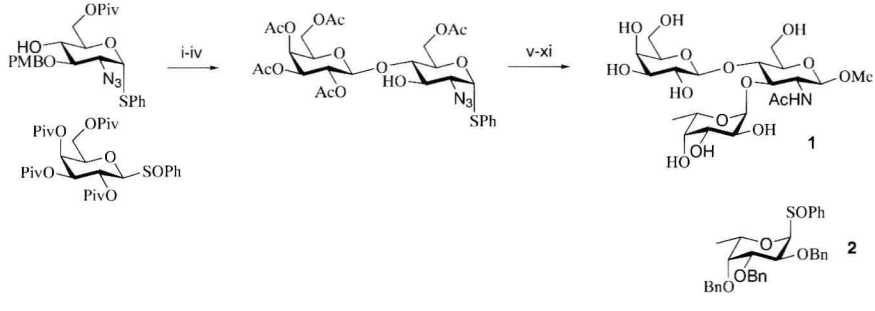
stereochemistry has been tackled in a number of ways through novel chemical methodologies.

A central issue in complex oligosaccharide assembly is control of anomeric reactivity; in particular, chemoselectivity in the reactivity of different anomeric functional groups. Recent years have seen a tremendous simplification of the range of operations needed to implement each glycosidic coupling step, and an overall reduction in the number of different glycosyl donors needed to implement a given oligosaccharide synthesis. Several strategies have been devised which rely on replacement or modification of one anomeric functionality which does not serve as a donor, with another which does. (This is in addition to the phenomenon of O(2) functionality being used to modulate anomeric reactivity, by 'arming' or 'disarming' the donor).[1] These combined approaches have led to oligosaccharide syntheses being developed that have exploited a common anomeric donor group. They have also made possible the reiterative assembly of oligosaccharides, wherein identical sugar building blocks are repeatedly used as acceptor and then as donor. Good acceptor/donor intermediates for reiterative approaches include glycals and glycal epoxides (Section 1.2.4),[1] thiophenyl glycosides,[1] phenyl sulfoxides,[2] *n*-pentenyl glycosides and *n*-pentenyl dibromides,[1] *p*-*N*-acetylphenyl sulfides,[3] and *O*-allyl and vinyl glycosides.[4,5] In addition, Nicolaou and coworkers have employed thiophenyl and fluoro glycosides in the same way, converting thiophenyl glycosides to fluoro glycosides before using these as donors, and relying on the fact that the fluoroglycoside can couple to acceptor thioglycosides.[6] An extrapolation of this latter approach is the so-called orthogonal use of thiosulfides and fluorides, which can each act as glycosyl donors using different conditions under which the other functionality is inert. This obviates the need to modify or substitute the anomeric functionality as is required in those methods listed above. Thus, phenylthioglycosides couple to glycosylfluoride acceptors under NIS-TfOH (or AgOTf) promotion, and the product glycosyl-fluorides can then be further extended by coupling to a phenylthioglycoside acceptor using Cp_2HfCl_2-$AgClO_4$ promotion.[7] A heptasaccharide repeating β-(1 → 4) linked oligo-GlcNAc was prepared using this strategy,[7] and other systems such as an extended blood group B determinant tetrasaccharide have also been prepared.[8] The alternative of employing a spectrum of anomeric reactivities has been adapted into a one-pot sequential synthesis of a number of trisaccharides, using a combination of bromides, fluorides or trichloroacetimidates, with phenyl sulfides and methyl glycosides.[9] Additionally, phenylselenoglycosides have extended such series (section 1.2.2). For more comprehensive reviews of chemical glycosylation in general, including an explanation of the latent–active and armed–disarmed reactivity concepts, readers are directed to other sources.[1,10]

1.2.1 Glycosyl sulfoxides

Glycosyl sulfoxides, first developed by Kahne's group,[11] have proven efficient and valuable glycosyl donors. They can be selectively activated in the presence of thiophenylglycosides (from which the sulfoxides are derived), and thus can be used as donors in glycosylation reactions where the thioglycoside acts as an acceptor. Thus, all building blocks can originate from thioglycosides. The thioglycoside can then be used subsequently to extend further the saccharide structure without the need for changing anomeric functionality.

Kahne and co-workers have demonstrated the utility of this type of donor, in an attractive synthetic route to Le^a, Le^b and Le^X, all syntheses simply relying on iterative use of the same sulfoxide coupling conditions [for the synthesis of Le^X (**1**), see Scheme 1.1].[12] The reactivity of sulfoxides over thioglycosides has also been exploited by others. For example, Martin-Lomas's group has used this to good effect in an efficient synthesis of tetragalactoside **5** (Scheme 1.2), which retains the thioglycosidic functionality originating from starting monosaccharide **4** (the other 3 galactosides being derived from sulfoxide **3**).[13]

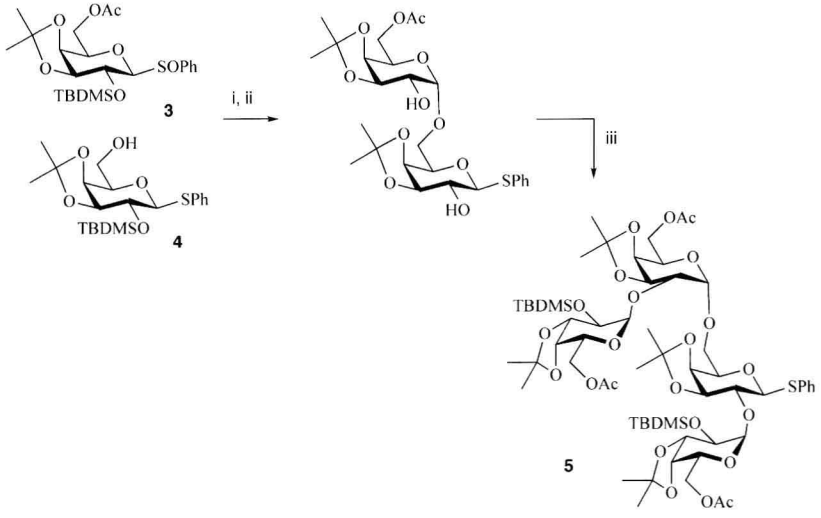


Scheme 1.1 (i) Tf_2O, DTBMP; (ii) LiOH, MeOH; (iii) Ac_2O, Pyr.; (iv) 10% TFA, CH_2Cl_2; (v) Tf_2O, DTBMP, **2**; (vi) $HgTFA_2$, wet CH_2Cl_2; (vii) NaH, MeI; (viii) Lindlar reduction; (ix) Pd/C. H_2; (x) Ac_2O, Pyr., DMAP; (xi) NaOMe, MeOH.

1.2.2 Selenoglycosides and telluroglycosides

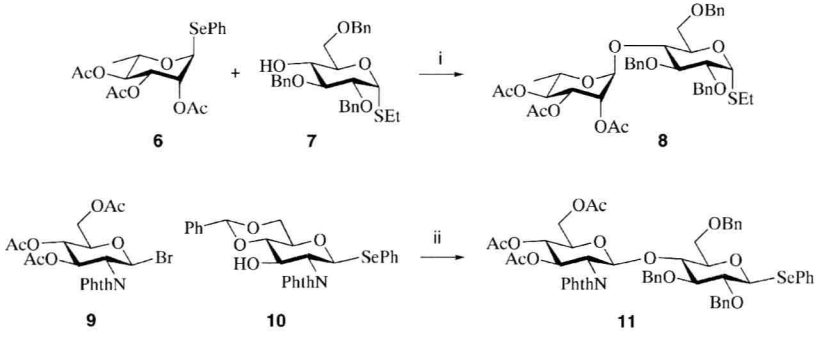
Throughout the 1990s, the utility of selenoglycosides has been evidenced in a number of valuable ways. Such glycosides have conveniently extended the anomeric reactivity spectrum. They provide a valuable strategic alternative to the iterative interchange of anomeric functionality or the use of truly orthogonal reactivity.

Pinto's group were the first to demonstrate that (armed or disarmed) selenoglycosides could be activated over thioglycosides (armed or



Scheme 1.2 (i) Tf_2O, di-*t*-Bu-4-Me-pyridine; (ii) TBAF; (iii) **3**, Tf_2O, di-*t*-Bu-4-Me-pyridine.

disarmed, respectively), using silver triflate as promoter.[14] Selenoglycosides can thus be selectively employed with thioglycoside acceptors to afford thioglycosidic disaccharide donors directly. Even *disarmed* selenoglycosides [those bearing O(2) acyl groups] such as the selenophenyl rhamnoside **6** can be activated over *armed* [bearing O(2) benzylic]thioglycosides such as **7** to afford specific disaccharides (e.g. **8**) (see Scheme 1.3).[15] Additionally, organic bases (collidine or 1,1,3,3-tetramethylurea) and silver triflate provide a catalyst system which allows glycosyl bromides (e.g. **9**) to be used as donors with selenoglycosidic acceptors (e.g. **10**). Furthermore, trichloroacetimidates can be activated over selenoglycosides using TMSOTf as catalyst. Similar selectivities



Scheme 1.3 (i) AgOTf, K_2CO_3; (ii) AgOTf, collidine or 1,1,3,3-tetramethylurea.