301

Topics in Current Chemistry

Topics in Current Chemistry

Recently Published and Forthcoming Volumes

Reactivity Tuning in Oligosaccharide Assembly
Volume Editors: Bert Fraser-Reid,
J. Cristóbal López
Vol. 301, 2011

Luminescence Applied in Sensor Science
Volume Editors: Luca Prodi, Marco Montalti,
Nelsi Zaccheroni
Vol. 300, 2011

Chemistry of Opioids
Volume Editor: Hiroshi Nagase
Vol. 299, 2011

Electronic and Magnetic Properties of Chiral Molecules and Supramolecular Architectures
Volume Editors: Ron Naaman,
David N. Beratan, David H. Waldeck
Vol. 298, 2011

Natural Products via Enzymatic Reactions
Volume Editor: Jörn Piel
Vol. 297, 2010

Nucleic Acid Transfection
Volume Editors: Wolfgang Bielke,
Christoph Erbacher
Vol. 296, 2010

Carbohydrates in Sustainable Development II
Volume Editors: Amélia P. Rauter,
Pierre Vogel, Yves Queneau
Vol. 295, 2010

Carbohydrates in Sustainable Development I
Volume Editors: Amélia P. Rauter,
Pierre Vogel, Yves Queneau
Vol. 294, 2010

Functional Metal-Organic Frameworks: Gas Storage, Separation and Catalysis
Volume Editor: Martin Schröder
Vol. 293, 2010

C-H Activation
Volume Editors: Jin-Quan Yu, Zhangjie Shi
Vol. 292, 2010

Asymmetric Organocatalysis
Volume Editor: Benjamin List
Vol. 291, 2010

Ionic Liquids
Volume Editor: Barbara Kirchner
Vol. 290, 2010

Orbitals in Chemistry
Volume Editor: Satoshi Inagaki
Vol. 289, 2009

Glycoscience and Microbial Adhesion
Volume Editors: Thisbe K. Lindhorst,
Stefan Oscarson
Vol. 288, 2009

Templates in Chemistry III
Volume Editors: Broekmann, P., Dötz, K.-H.,
Schalley, C.A.
Vol. 287, 2009

Tubulin-Binding Agents: Synthetic, Structural and Mechanistic Insights
Volume Editor: Carlomagno, T.
Vol. 286, 2009

STM and AFM Studies on (Bio)molecular Systems: Unravelling the Nanoworld
Volume Editor: Samorì, P.
Vol. 285, 2008

Amplification of Chirality
Volume Editor: Soai, K.
Vol. 284, 2008

Anthracycline Chemistry and Biology II
Mode of Action, Clinical Aspects and New Drugs
Volume Editor: Krohn, K.
Vol. 283, 2008

Reactivity Tuning in Oligosaccharide Assembly

Volume Editors: Bert Fraser-Reid · José Cristóbal López

With Contributions by

S. Aubry · A.E. Christina · J.D.C. Codée · D. Crich · J.C. López · A.V. Demchenko · B. Fraser-Reid · A.M. Gómez · K.S. Kim · G.A. van der Marel · H.S. Overkleeft · H.D. Premathilake · R. Roy · K. Sasaki · I. Sharma · T.C. Shiao · D.-H. Suk · M.T.C. Walvoort · C.-H. Wong · C.-Y. Wu

Springer

Editors
Prof. Dr. Bert Fraser-Reid
595F Weathersfield Road
Fearrington 595F
Pittsboro
North Carolina 27312
USA
Dglucose@aol.com

Prof. Dr. José Cristóbal López
Instituto de Quimica Orgánica
General CSIC
Juan de la Cierva 3
28006 Madrid
Spain
jc.lopez@csic.es

ISSN 0340-1022 e-ISSN 1436-5049
ISBN 978-3-642-20913-0 e-ISBN 978-3-642-20914-7
DOI 10.1007/978-3-642-20914-7
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011928912

Cover design: WMXDesign GmbH, Heidelberg, Germany

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Volume Editors

Prof. Dr. Bert Fraser-Reid

595F Weathersfield Road
Fearrington 595F
Pittsboro
North Carolina 27312
USA
Dglucose@aol.com

Prof. Dr. José Cristóbal López

Instituto de Quimica Orgánica
General CSIC
Juan de la Cierva 3
28006 Madrid
Spain
jc.lopez@csic.es

Editorial Board

Topics in Current Chemistry Also Available Electronically

Topics in Current Chemistry is included in Springer's eBook package *Chemistry and Materials Science*. If a library does not opt for the whole package the book series may be bought on a subscription basis. Also, all back volumes are available electronically.

For all customers with a print standing order we offer free access to the electronic volumes of the series published in the current year.

If you do not have access, you can still view the table of contents of each volume and the abstract of each article by going to the SpringerLink homepage, clicking on "Chemistry and Materials Science," under Subject Collection, then "Book Series," under Content Type and finally by selecting *Topics in Current Chemistry*.

You will find information about the

– Editorial Board
– Aims and Scope
– Instructions for Authors
– Sample Contribution

at springer.com using the search function by typing in *Topics in Current Chemistry*.

Color figures are published in full color in the electronic version on SpringerLink.

Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal.

Impact Factor 2009: 4.291; Section "Chemistry, Multidisciplinary": Rank 20 of 138

Foreword

Carbohydrates play a crucial role in our daily lives whether as renewable energy stores or as molecular scaffolds in trees and plants. They act as the very backbones of life in various biopolymers such as DNA and are responsible for mediating a whole host of biological events such as the antigenic determinants of blood groups to cell adhesion and surface moderation during metastasis of primary tumours or during viral and bacterial recognition. Accordingly, methods to effect their chemical synthesis and to attach these oligosaccharide arrays to appropriate proteins as glycoconjugates have become an important area of science.

This very timely new volume addresses some of the more important questions concerning the assembly of complex oligosaccharides, particularly the construction of multi-antennae arrays using powerful glycosylation reaction tuning techniques. The chapters nicely illustrate the concepts and strategies for oligosaccharide synthesis through knowledge of reactivity, orthogonal functionalisation and protecting group manipulation. Especially attractive is the elegant use and acquired knowledge of how to arm and disarm appropriate glycosyl building blocks to control the product outcomes with exquisite selectivity, leading eventually to a computer programmable approach to one-pot glycosylation.

I am sure this text will stimulate further research in this increasingly important area of molecular science and provide an informed background to the complexity of the problems faced during the chemical assembly of functionally active oligosaccharides.

Department of Chemistry
University of Cambridge, UK
November 2010

Steven V. Ley

Preface

Issue Number 8 of the 1975 *Journal Accounts of Chemical Research* included an article captioned "Some Progeny of 2,3-Unsaturated Sugars – They Little Resemble Grandfather Glucose," in which the early work of our research group (Fraser-Reid's Rowdies as they called themselves) was reviewed. In the introduction, I noted that "the mainstream of organic chemistry—[was]—innocent of these non-'natural products'," and that "[a] Nobel Laureate known to the author declared that—[stabilization at the anomeric center]—constitutes half of sugar chemistry" (see also David Crich's chapter). Nevertheless, there was "a growing willingness for 'organic chemists' to come into contact with sugars voluntarily." By way of recommendation, I expressed the hope that although "the names are a pain in the abstracts—and the wretched things just will not crystallize—working with syrups is a state of mind very much like eating green eggs and ham."

Carbohydrate chemistry was at that time foreign territory except to the few who encountered it during the fateful 2 weeks of stereochemistry in the sophomore organic course. Admittedly, carbohydrates are ideal for demonstrating the differences between enantiomers and diastereomers, *R* and *S*, D and L, d and l, (+) and (−), etc.; but with such arid fare, it is not surprising that sophomores have been known to say that "studying organic chemistry is like beating your head against the wall, because it feels so good when you stop."

One wonders whether that sentiment may have been different if text books expressly noted that Emil Fischer's synthesis of glucose provided the first experimental validation for van't Hoff's then spurned concept of tetrahedral carbon. Fischer therefore confirmed the three-dimensional parameters, decades before the advent of sp^3 hybridization that is on the high school curriculum. Indeed, the clumsy attempts at drawing tetrahedral carbon skeleta undoubtedly inspired the 1875 development of the Fischer projection, so despised by sophomores.

The connection between chirality and glucose, begun by Fischer, resurfaced in the 1970s, when a frisson of "chiral syntheses" rippled through organic chemistry. The prostaglandins were then of major scientific interest, and so Gilbert Stork's report of rapid enantiopure syntheses of three members of the family, PGA_2 from erythrose (1976), PGE_1 from glyceraldehyde (1977), and $PGF_{2\alpha}$ from glucose

(1978), was seminal, because an eminent organic chemist had ventured into the minefield of "sugar" chemistry. To some, this achievement may have seemed an apostasy, especially for those who did not know of Stork's early attempts to synthesize sucrose.

By breaking the ice, Stork facilitated the fledging efforts of enthusiasts, including me and a brilliant group of undergraduate collaborators at Canada's University of Waterloo, who accomplished enantiodivergent syntheses of (+) and (−) chrysanthemic acid, (+) and (−) frontalin, and also established, by synthesis, the chirality of avenaciolide and, hence, its congeners.

A decade later, *Accounts of Chemical Research* carried a 10 years later update of our "Grandfather Glucose" experiments, accompanied by my editorial, entitled "The Malaise Reaction." The editorial extolled the merits of serendipity in organic synthesis noting that "I am green with envy (although those who know me will find this hard to visualize)," of those who have the creativity to transform a fortuitous encounter into an advantage. I did not anticipate that within 5 years, Fraser-Reid Rowdies would also be visited by "the three Princes of Serendip."

In light of the above-mentioned "chiral synthesis" ripple, our sugar chemistry inspired us to undertake enantiopure syntheses of "natural products." However, Chap. 1 of this book shows that this exploration had the reverse effect, in which our enantiopure syntheses inspired us to undertake sugar syntheses – or more precisely to embark on oligosaccharide syntheses.

Thus, in synthesizing a molecule with nine contiguous chiral centers from D-glucose (see Chap. 1), David Mootoo, then one of the Rowdies, made a tangential observation. A seemingly well-planned reaction had given him an excellent yield – alas of the wrong product. He nevertheless took the time to do a structure determination. Insight into how this "wrong" product had been formed led to the development of *n*-pentenyl glycosides (NPGs).

Aggressive prosecution continued, and Mootoo made a further serendipitous observation. Benzylated NPGs had undergone oxidative hydrolysis in 6 h, and the same was expected for acetylated NPGs. However, for the sake of completeness, I asked another graduate student to verify that which "was expected." After 6 h, the student reported that the acetylated NPG was not responding to oxidative hydrolysis.

I discussed the potential of this interesting anomaly with Mootoo, but "to make assurances doubly sure," he volunteered to verify the results. In short, he found that the reaction of the acetylated NPG's required 36 h – not 6 h. And within days of uncovering this disparity, the electronic armed/disarmed strategy for oligosaccharide assembly had been promulgated.

That acyl-protecting groups deactivate glycosyl donors in comparison to other counterparts had been known. Why the disparity had not been earlier exploited for synthetic advantage is open to speculation. However, experiments in our laboratory suggest that if the "disarmed" partner is too reactive, chemoselectivity will be poor – a condition that would apply to glycosyl bromides, the major donors then in use.

It is truly gratifying for Fraser-Reid's Rowdies and the writer to witness the remarkable advances that are now possible in oligosaccharide synthesis. Our furtive efforts at chemoselectivity 25 years ago did not anticipate that regio- and

stereo-selectivities would join chemoselectivity in being protecting group-dependent phenomena.

The very terms "armed and disarmed" drew rebuke for sounding too warlike. Why not active and inactive? My answer at that time was contrived – for I could not have foreseen that the latter terms would find their way into the lexicon as in "active-latent or disarmed-latent donors," invoking a totally different meaning from "armed." So would super-armed, super-disarmed, and semi-disarmed.

All of these, and more, are featured in this book's chapters, confirming that "protecting groups do more than protect." Indeed they are shown to be implements for saccharide tuning whereby chemo-, regio-, and stereo-selectivity can be specifically designed. What about Trost's fourth, and remaining, factor, enantioselectivity? This question may not be as irrelevant as the writer once thought. Boon's intriguing double-stereo differentiation strategy for anomeric stereocontrol is an elegant example of the synergy between regio- and stereo-selectivities. Whether these effects can be "tuned" by protecting groups remains to be seen.

I cannot conclude this Preface without recalling the 1988 event that really launched NPG investigations. An international group of Fraser-Reid's Rowdies comprised of C. Webster Andrews (USA), Peter Konradsson (Sweden), Jose Manuel Llera (Spain), David Mootoo (Trinidad and Tobago), Andrew Ratcliffe (England), Uko Udodong (Nigeria), Zufan Wu (China), and I (Jamaica) traveled by station wagon from Durham, North Carolina to Pittsburgh, Pennsylvania to attend a conference. Throughout the 16 h going and 16 h returning, these colleagues engaged in an endless stream of ideas about how NPGs could be used to address synthetic, mechanistic, and theoretical issues. All that remained was for me to secure the funding to enable them to pursue their enthusiasms, and in this regard we are specifically indebted to the then independent Burroughs Wellcome and Glaxo, whose early funding enabled us to establish that NPGs were not merely "a new version of the Koenig's Knorr reaction" as one reviewer had proclaimed. The National Science Foundation gave support from the earliest days and continues to the present. For our major programs not reviewed in this book, we are indebted to the National Institutes of Health and the Mitzutani Foundation for generous support.

I must also express my gratitude to two other Rowdies, J. Cristobal Lopez and Ana Gomez, who are not only exploring new frontiers to NPG chemistry, but also relentlessly trying to keep me alert about what is happening "out there" – and even helping to edit this book.

Finally, I must thank my wife Lillian for constant support and patience for all 47 years of our marriage, and my two children, Andrea and Terry. All three of them make me realize that how very fortunate and blessed I am, to have experienced the true meaning of family.

Pittsboro, NC
USA
April 2011

Bertram Fraser-Reid

Contents

Top Curr Chem (2011) 301: 1–29
DOI: 10.1007/128_2010_105

Published online: 1 December 2010

Armed–Disarmed Effects in Carbohydrate Chemistry: History, Synthetic and Mechanistic Studies

Bert Fraser-Reid and J. Cristóbal López

Abstract This chapter begins with an account of the serendipitous events that led to the development of *n*-pentenyl glycosides (NPGs) as glycosyl donors, followed by the chance events that laid the foundation for the armed–disarmed strategy for oligosaccharide assembly. A key mechanistic issue for this strategy was that, although both armed and disarmed entities could function independently as glycosyl donors, when one was forced to compete with the other for one equivalent of a halonium ion, the disarmed partner was found to function as a glycosyl acceptor. The phenomenon was undoubtedly based on reactivity, but further insight came unexpectedly. Curiosity prompted an examination of how ω-alkenyl glycosides, other than *n*-pentenyl, would behave. Upon treatment with wet *N*-bromosuccinimide, allyl, butenyl, and hexenyl glucosides gave bromohydrins, whereas the pentenyl analog underwent oxidative hydrolysis to a hemiacetal. Although the answer was definitive, an in depth comparison of *n*-pentenyl and *n*-hexenyl glucosides was carried out which provided evidence in support of the transfer of cyclic bromonium ion between alkenes in a steady-state phenomenon. It was found that for two ω-alkenyl glycosides having a relative reactivity ratio of only 2.6:1, nondegenerate bromonium transfer enabled the faster reacting entity to be converted completely to product, while the slower reacting counterpart was recovered completely. This nuance suggests that in the armed/disarmed coupling, such a

B. Fraser-Reid (✉)
Natural Products and Glycotechnology Research Institute Inc. (NPG), 595F Weathersfield Road, Pittsboro 27312, NC, USA
e-mail: Dglucose@aol.com

J.C. López
Natural Products and Glycotechnology Research Institute Inc. (NPG), 595F Weathersfield Road, Pittsboro 27312, NC, USA
and
Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, Madrid 28006, Spain

nondegenerate steady-state transfer is ultimately responsible for determining how the reactants are relegated to donor or acceptor roles.

Development of chemoselective armed/disarmed coupling led to another phase in the sequence of serendipities. During experiments to glycosylate an acceptor diol, it was found that armed and disarmed donor's glycosylated different hydroxyl groups. This observation caused us to embark on studies of regioselective glycosylation. One of these studies showed that it is possible to activate selectively *n*-pentenyl orthoesters (NPOEs) over other *n*-pentenyl donors, and that this chemoselective process enables regioselective glycosylation. As a result, reaction partners can be so tuned that glycosylation of an acceptor with nine free hydroxyl groups by an *n*-pentenyl orthoester donor carrying two free hydroxyl groups is able to furnish a single product in 42% yield. Experiments such as the latter suggest that the donor favors a particular hydroxyl group, and/or that a particular hydroxyl favors the donor. Either option implies that the principle of reciprocal donor acceptor selectivity (RDAS) is in operation.

Such examples of regioselective glycosylation provide an alternative to the traditional practice of multiple protection/deprotection events to ensure that the only free hydroxyl group among glycosyl partners is the one to be presented to the donor. By avoiding such protection/deprotections, there can be substantial savings of time and material – as well as nervous anxiety.

Keywords Armed–disarmed effect, Chemoselective, Glycosylation, *n*-Pentenyl glycosides, *n*-Pentenyl orthoesters, Regioselectivity, Sidetracking

Contents

Abbreviations

Ac	Acetyl
Bn	Benzyl (CH_2Ph)
Boc	*tert*-Butoxycarbonyl
Cbz	Benzyloxycarbonyl
HPLC	High pressure liquid chromatography
IDCP	Iodonium dicollidine perchlorate
MM2	Molecular mechanics
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NPG	*n*-Pentenyl glycoside
NPOE	*n*-Pentenyl orthoester
Phth	Phthalimido
RDAS	Reciprocal donor acceptor selectivity
S_N2	Bimolecular nucleophilic substitution
STAZ	*S*-Thiazolyl
TBAF	Tetra-*n*-butyl ammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TESOTf	Triethylsilyltrifluoromethanesulfonate

1 Introduction

In 1983, Trost postulated that stereo-, regio-, chemo-, and enantioselectivities are four factors that confront organic synthesis [1]. With respect to oligosaccharides that are derived from natural sources, enantioselectivity is usually irrelevant since the constituent sugars are usually optically active. Stereoselectivity had been substantially solved by Isbell's seminal discovery [2] of what has come to be known as neighboring group participation [3]. Thus, one could use an acyl group at O2 of a glycosyl donor to ensure 1,2-*trans* relationship in the major coupling product, whereas the O2 alkyl counterpart would be less stereoselective.

The availability of sugar derivatives with anomeric leaving groups that could be activated under different conditions saw the advent of Ogawa's orthogonal glycosylation strategy [4], but *chemo*selective discriminations between two sugars having the same leaving group remained conceptual.

Regioselectivity was even more conceptual. Thus for years it has been customary to design elaborate protection schemes to ensure that the only free hydroxyl group among all reactants was the one to be presented to the donor. However, protection/deprotection episodes consume time, labor, and material. The alternative of regioselective glycosylation of a polyol acceptor should therefore be encouraged. Indeed, a recent paper noted that "the elegance of regioselective glycosylation is

underexploited and exploring its utility here allowed access to the desired ... product in reasonable yield (59%) with excellent regio- and stereoselectivity" [5].

In this chapter we describe some of the observations in our laboratory that now enable chemo- and regioselective glycosylations.

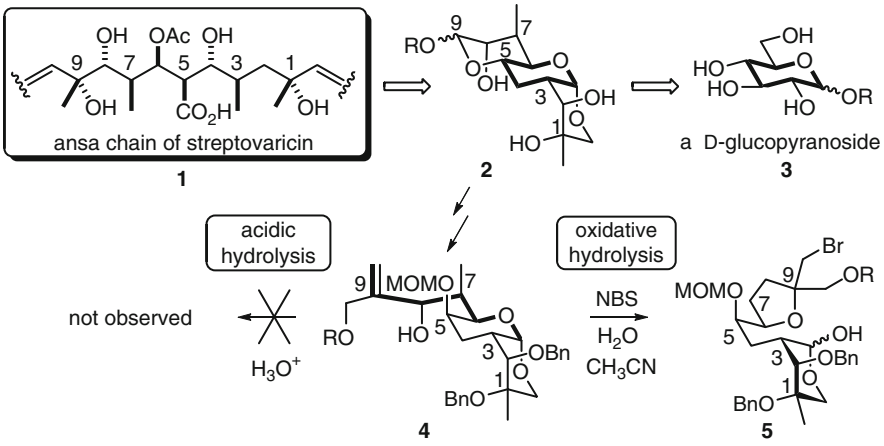
2 The Armed/Disarmed Principle

2.1 Discovery

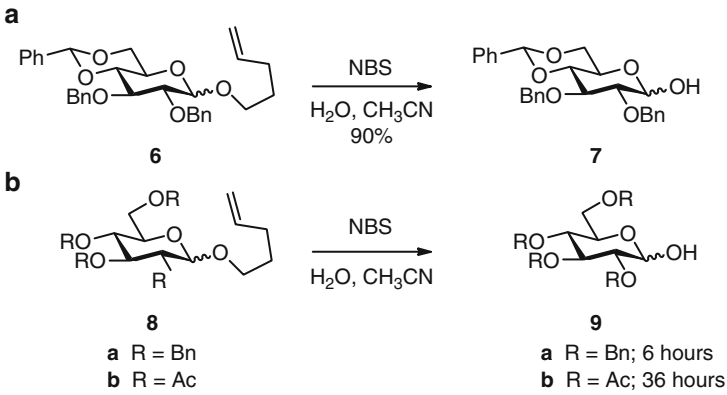
Our work on chemo- and regioselectivity emanated from a cascade of fortuitous events [6]. The linear component from the ansa chain of streptovaricin A [7], **1**, presents a concatenation of nine contiguous chiral centers, which add up to more than twice as many as are available from normal sugar templates [8]. One alternative was to construct the array by combining chiral fragments derived from common sugars. However, this strategy was rejected because the perils of double asymmetric synthesis [9] (i.e., double stereodifferentiation [10]) would result in complex mixtures that would erode all advantages of working with chiral subunits (Scheme 1).

The concept of *pyranosidic homologation* [11], in which pyranose rings are crafted at the "front" and "back" of a central pyranose template, was introduced as a strategy for controlling the creation of each chiral center of array **1**. Thus beginning with a D-glucopyranoside **3**, retrosynthesis led to tripyranoside **2** which could accommodate eight of the nine contiguous chiral centers of **1**. Tripyranoside **2** was indeed prepared [12], and a number of transformations afforded the bipyranoside **4** [13, 14].

Attempts to cleave the internal acetal of **4** by means of acid catalyzed hydrolysis were spectacularly unsuccessful. Attention was therefore shifted to the double-bond of **4** which had been incorporated as the synthon for the tertiary hydroxyl at position



Scheme 1 The inspiration for *n*-pentenyl glycosides (NPGs)



Scheme 2 Effect of protecting groups on oxidative hydrolysis of NPGs

9 of array **1**, and to this end compound **4** was treated with wet *N*-bromosuccinimide (NBS) in the hope of preparing the corresponding bromohydrin as an appropriate intermediate [15]. However, instead of a bromohydrin, the bromomethyl tetrahydrofuran **5** was obtained quantitatively and rapidly [16–18]. Thus, although the acetal residue of **4** had resisted acid catalyzed hydrolysis, oxidative hydrolysis had been readily achieved.

This serendipitous observation implied that a strategically placed double bond could be used to trigger cleavage of an acetal. Accordingly, a series of pent-4-enyl glycosides (aka *n*-pentenyl glycosides: NPGs) was synthesized in which the array, highlighted in **4**, was approximated at the anomeric center of glucosides **6** and **8** (Scheme 2). Tests were devised to learn how widely-used protecting groups would respond to NBS/H_2O treatment [19]. The benzylidinated derivative **6** underwent hydrolysis in 90% yield, without any evidence of Hanessian–Hullar [20–22] brominolysis of the benzylidene ring, nor any vulnerability of the benzyl groups.

Further tests, undertaken for the sake of completeness, resulted in a second serendipitous observation. The tetra-*O*-benzyl derivative **8a** required 6 h for oxidative hydrolysis to **9a**, while the corresponding tetraacetate **8b**, needed 36 h for complete conversion to **9b** (Scheme 2b) [19].

We were aware of Paulsen's encyclopedic 1982 review [23] which included the information that "*benzyl compounds are always more reactive than the acetylated or benzoylated derivatives*." This implied that the difference in behavior of **8a** and **8b** was to be expected.

2.2 Acyl Versus Alkyl Driven Chemoselectivity

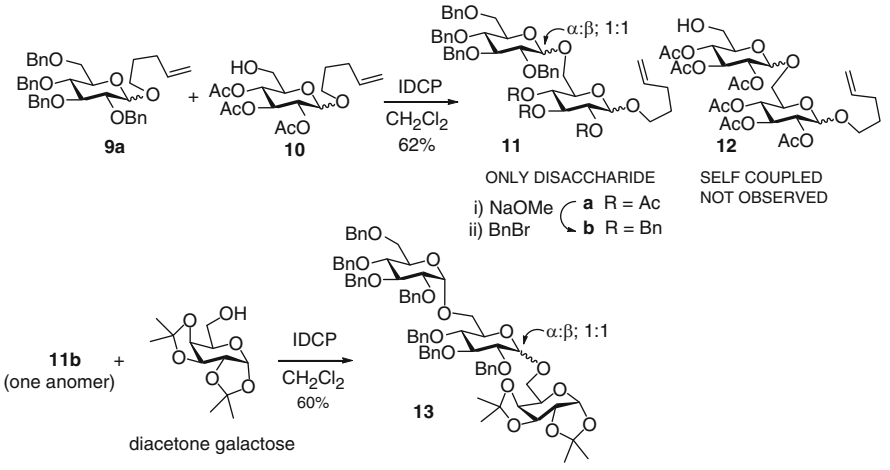
However, Paulsen's statement in the 1982 article [23] had been made in relation to glycosyl halides, the principal donors at that time, and we realized that our new *n*-pentenyl glycoside (NPG) donors had totally different properties. We reasoned

that the (apparent) sixfold reactivity difference between **8a** and **8b** was due primarily to the inductive effect of the respective O2 substituent. Accordingly, it was conceivable that if the slower-reacting entity was equipped with a free hydroxyl group, as in **10**, slower cleavage would force it to function as an acceptor with respect to its more reactive competitor, **9a** (Scheme 3). Furthermore, the expected product, **11a**, would be inhibited from functioning as a disaccharide donor because of the acetates.

In the event, the NPGs **9a** and **10** reacted smoothly to give disaccharide **11a** only, with no evidence of the alternate possibility, **12**, resulting from self coupling of **10**. The inert nature of the reducing end of **11a** could be overcome by replacing the disarming acetate(s) with arming benzyl groups in **11b**. Indeed, the latter functioned as a donor for diacetone galactose, resulting in ready formation of trisaccharide **13** [24].

The experiments in Scheme 3 did not *discover* reactivity differences between acetylated and benzylated sugars, these having been noted in Paulsen's article [23]. However, they did discover that such reactivity differences could be exploited synthetically. We are not aware of any attempts to carry out chemoselective couplings of differently protected glycosyl halides. However, we believe that the prospects for such coupling are poor, for reasons that will be discussed in Sect. 2.4.

The armed/disarmed chemoselectivity, although useful and serviceable, required further investigation to determine the limits of its effectiveness. From the earliest stages it had been evident that a disarmed donor was not inert, because it could be activated, probably under different conditions. Thus the disarmed partner, **10**, on its own could serve as a glycosyl donor as will be exemplified in Scheme 6 [25]. However, this role was subjugated when it was forced to compete with the armed counterpart **9a** in Scheme 3.



Scheme 3 The first example of armed/disarmed saccharide assembly

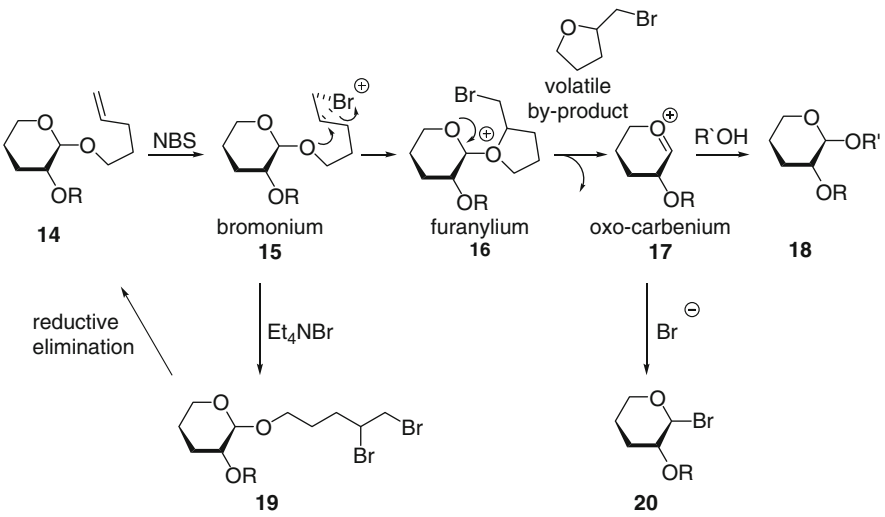
2.3 Sidetracking

The serendipitous event that inspired the development of NPGs (see Sect. 2.1) was the attempt to prepare a bromohydrin from alkene **4** (Scheme 1) [6, 19]. With the benefit of hindsight, we now realize that this objective was predestined to fail, because the first-formed cyclic bromonium ion, e.g., **15** (Scheme 4), would undergo facile RO5 interaction [26] to give a furanylium ion, **16**, and thence the oxocarbenium ion **17**. The latter would be scavenged by water to give **18** (R′=H), the product of oxidative hydrolysis.

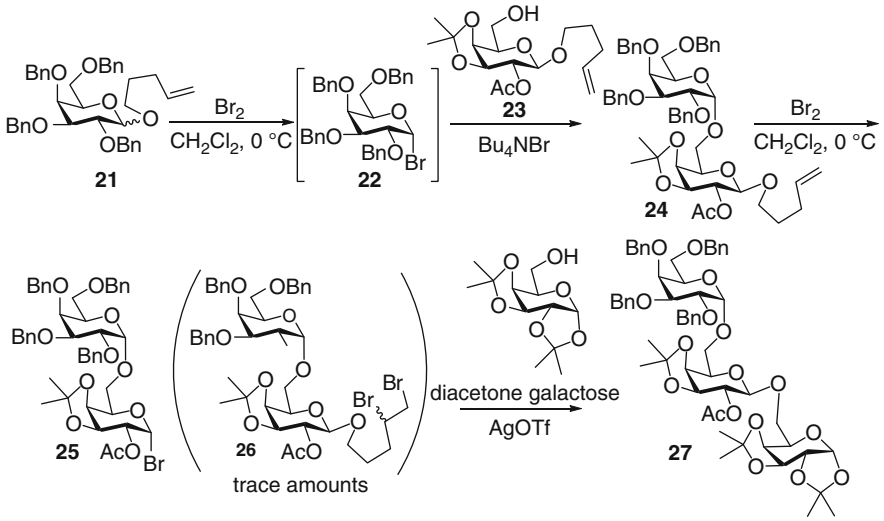
In light of this analysis, it seemed reasonable that use of molecular bromine, instead of NBS, should generate a similar cascade of intermediates, but that the oxocarbenium ion **17** would be captured by the bromide counter ion, culminating in formation of a glycosyl bromide, e.g., **20** [27].

This concept was reduced to practice as shown in Scheme 5. Thus, one equivalent of molecular bromine in methylene chloride was added drop-wise, in the dark, to a solution of NPG **21** at 0°C [27]. When completion was signaled by persistence of a light brown color, the solvents were removed under vacuum at room temperature. To the residue, **22**, was added a solution containing acceptor **23** and Bu_4NBr to effect halide-catalyzed glycosylation [28] affording the disarmed saccharide **24** in 70% yield [27].

Similar brominolysis of the disarmed disaccharide donor **24** gave glycosyl bromide **25** which, after isolation as described above, was glycosylated with diacetone galactose under the agency of silver triflate [29] to give trisaccharide **27** [27].



Scheme 4 Some potential options for NPGs



Scheme 5 NPGs facilitate orthogonal saccharide assembly

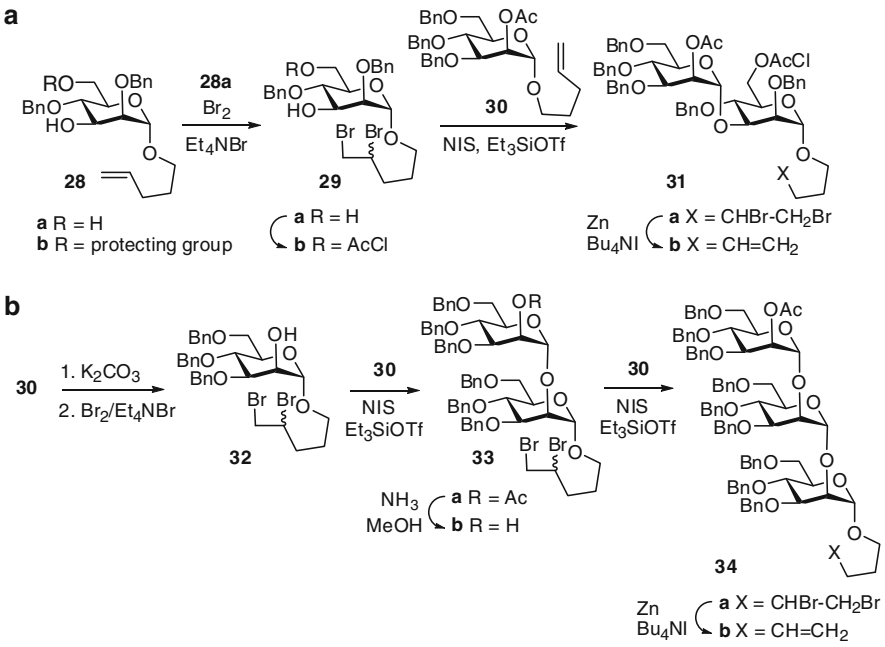
Fig. 1 Options for the armed and disarmed partners

The glycosyl bromide **25** was frequently accompanied by small amounts of vicinal bromination product, **26**. This observation raised the possibility that cyclic bromonium ions (such as **15**, Scheme 4) could be induced to produce larger amounts of a vicinal dibromide, e.g., **19**. NPG activity could therefore be "*sidetracked*" until needed, when the double bond would be restored by reductive elimination, e.g., **19** → **14** (Scheme 4) [30, 31].

The merit of such *sidetracking* can be envisaged in Scheme 6a where the desired product, **31b,** could *theoretically* be obtained by glycosylating **28b** with donor **30**. However, such coupling would be contrary to the typical armed/disarmed protocol, summarized in option A (Fig. 1), where the disarmed partner functions as the acceptor. In contrast, the objective in Scheme 6a is to reverse this protocol, as in option B, where a disarmed donor, **30** (although more recent studies from Demchenko and coworkers [32] have demonstrated that **30** is indeed a "super-armed" donor, the validity of the approach remains unchanged), was required to glycosylate an armed acceptor, **28b**.

Sidetracking of **28a** would enable option B, and this was pursued in Scheme 6.

Vicinal bromination requires bimolecular cleavage of the cyclic bromonium ion **15** by a bromide anion (Scheme 4), a process that would have to overcome the



Scheme 6 Sidetracking creates a latent donor

favored unimolecular RO5 alternative leading to oxocarbenium ion **16**, and thence glycosyl bromide **20**. This outcome could be facilitated by increasing the concentration of bromide ion, so as to enhance the rate of bimolecular reaction needed to foster the conversion of **15** to **19**.

Accordingly, two equivalents of Et_4NBr were added to a solution of NPG **28** at 0°C, and a solution of molecular bromine was added drop-wise until a slight brown color persisted. The product proved to be dibromide **29a**, selective acylation of which gave the desired acceptor **29b** [33].

Simultaneous with the exploratory studies described above were searches for other sources of halonium ion activators. Iodonium dicollidine perchlorate (IDCP) had served our group well [34], and van Boom and coworkers introduced the corresponding triflate [35]. But since these salts had to be prepared ahead of time, more convenient sources of iodonium ion were sought by our group [36, 37] and van Boom's [38]. Notable among these was the acid catalyzed decomposition of *N*-iodosuccinimide (NIS), long used for electrophilic iodination of aromatic systems [39]. In our hands, Lewis acids, e.g., Et_3SiOTf, had produced a source of iodonium ion that would activate disarmed donors [36]. With this system, acceptor **29b** was glycosylated smoothly by disarmed donor **30** (see [32]) to give product **31a**. The double bond could now be restored by reductive elimination [30, 31] when needed, allowing *n*-pentenyl disaccharide **31b** to serve as a donor.

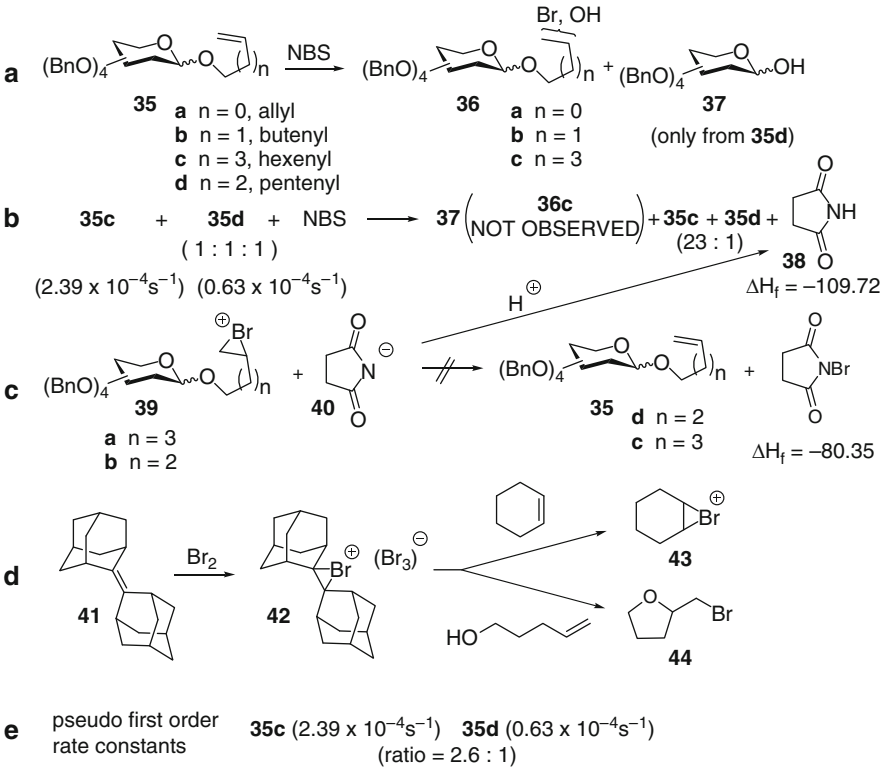
An additional value of sidetracking is seen in Scheme 6b where disarmed donor **30** was able to serve as both donor and acceptor. Thus routine processing of **30** gave

the sidetracked acceptor **32**, ready for glycosidation by its progenitor **30**, by use of the potent iodonium ion source [37]. Product **33a**, after deacetylation to **33b**, was again glycosylated by **30** to give **34a** from which the trisaccharide donor **34b** was obtained.

The mannans **31** and **34** in Scheme 6 were used for a convergent synthesis of a nonamannan oligosaccharide related to high-mannose glycoproteins [33, 40].

2.4 Cyclic Bromonium Ion Transfer Between Alkenes

The success with NPGs prompted us to test whether a similar cascade of ionic intermediates would be generated by other ω-alkenyl glycosides. Allyl, butenyl, and hexenyl glycosides, **35a–c**, respectively, along with the pentenyl analog **35d**, were prepared, and each was treated with a slight excess of *N*-bromosuccinimide under similar conditions [41]. Analogs **35a–c** gave bromohydrins **36a–c** in near quantitative yield, whereas the pentenyl analog, **35d**, uniquely underwent cleavage to the hemiacetal **37** (Scheme 7a).



Scheme 7 Bromination of alkenes revisited

The hexenyl and pentenyl analogs, **35c**,**d**, were then chosen for in-depth study. When both were allowed to compete for only ONE equivalent of NBS, as shown in Scheme 7b, the only reaction product observed was **37** from oxidative hydrolysis of **35d**, while the ratio of *recovered* starting materials **35c**/**35d** was 23:1 as judged by HPLC [42].

It could be argued that the absence of bromohydrin **36c** could be attributed to a reversible reaction, a circumstance that would affect the slower-reacting intermediate **39a** more than its competitor **39b** (Scheme 7c). Reversibility would require that the succinimide anion **40** extract bromonium to regenerate NBS, rather than add a proton to give succinimide **38**. However the relative heats of formation shown in Scheme 7 [43, 44] argue against this possibility.

We were aware that Wynberg [45] had isolated an adduct when adamantylideneadamantane, **41** (Scheme 7d), had been treated with bromine. Brown and coworkers [46], with the help of X-ray crystallography, showed that the adduct was the cyclic bromonium ion **42**.

Brown and coworkers showed further that nondegenerate translocation of Br^+ to cyclohexene and pent-4-enol could be effected to give **43** and **44** respectively by what was deemed to be a diffusion controlled phenomenon [47].

It was of interest to see whether analogous transfer of Br^+ was occurring, e.g., from the hexenyl cyclic bromonium ion **39a** to pentenyl residue of **35d** (Scheme 7). The process can be envisaged as in Fig. 2, where we begin in panel **A** with an equal mixture of the two alkenes, reactivities of each being fast (F) or slow (S). Assuming that NBS reacts equally well with each alkene, we postulate that a mixture will be produced with a distribution of alkenes and bromonium ions as shown in panel **B**. The fate of the two bromonium ions now comes into play, with RO5 attack [26], ushering in the cascade of ionic intermediates exemplified in Scheme 4. The "fast" substrate reacts faster and its departure leads to the vacancy shown in panel **C**. There is then halonium ion transfer, depicted in panel **D**, which generates a steady-state process that favors the faster reactant. Thus, the latter proceeds to product at the expense of the slower counterpart ending in panel **E** [41].

The steady-state transfer depicted in panel **D** would account for the preponderance of the **36c** shown in Scheme 7b. Notably, such a process should be concentration dependent, and for this to be tested, the *pseudo*first order rate constant of each

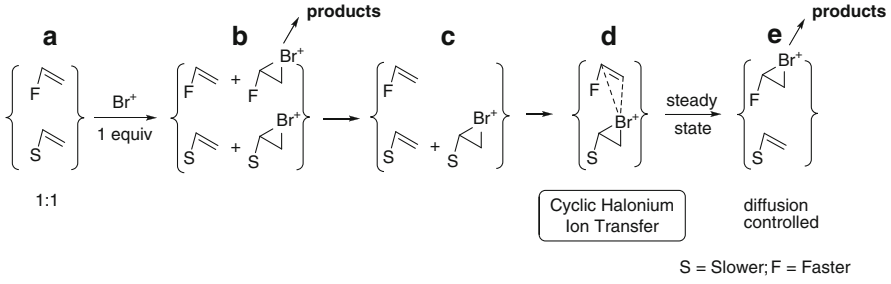


Fig. 2 A sketch of nondegenerate bromonium ion transfer between alkenes

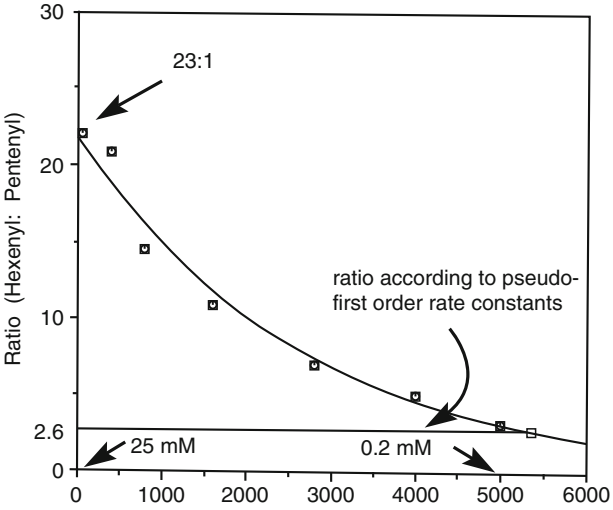


Fig. 3 Cyclic bromonium transfer is concentration dependent

reaction had to be determined. The values shown in Scheme 7e [41] are seen to be very close, the ratio of **35c**/**35d** being 2.6:1.

This ratio of the rates is very different from the HPLC ratio of recovered **35c**/**35d** which was 23:1 (Scheme 7b). In light of these data, the experiment in Scheme 7b was repeated, but under increasingly dilute conditions. The HPLC ratio of recovered **35c**/**35d**, shown in Fig. 3, decreased from 23:1 (at 25 mM) towards 3.1:1 (at 0.2 mM), the latter value being well within experimental error of the 2.6:1 ratio of the *pseudo*first order rate constants [42].

We drew the conclusion that, at 0.2 mM, the concentration is too dilute for the Br^+ transfer depicted in panel **D** to occur. Each alkene was therefore reacting independently, and without the intrusion of nondegenerate Br^+ transfer, the reactions occurring according to their rate constants [41, 42]. As noted above, Brown [46, 48] had previously observed cyclic bromonium ion transfer with highly hindered alkenes, notably adamantylideneadamantane[s]. But Fig. 3 makes it evident that unhindered alkenes are also candidates, and thus bromonium ion transfer appears to be a hitherto unrecognized phenomenon in the bromination of alkenes [47, 49].

2.5 Revisiting the Rationalization for the Armed/Disarmed Phenomenon

The initial rationalization of the armed/disarmed effect was that the electron-withdrawing group at O2, for example **15** (R=Ac), depleted electron density of the glycosidic oxygen, thereby suppressing RO5 attack upon the cyclic bromonium ion

[19] (Scheme 4). However, the experiments in Scheme 7 and Fig. 3 compel us to consider whether the phenomenon could be due to the fact that the NPG substrates in Scheme 3, being olefins, were subject to nondegenerate Br^+ transfer.

The data in Fig. 3 are consistent with results in Scheme 7b which shows that a difference in reactivity as small as 2.6:1 can be leveraged into complete reaction of the "faster" alkene, and complete recovery of the "slower" competitor. The result may account for the fact that in some armed/disarmed couplings, as exemplified in Scheme 3, there were no products, such as **12**, resulting from self-coupling of the disarmed partner.

However, the result in Scheme 7b provoked further thought.

An obvious limitation imposed by the above rationalization is that the slower reacting intermediate in panel **C** must be sufficiently unreactive to permit the steady state exchange in panel **D** to develop. *On this basis, armed/disarmed coupling requires that the disarmed partner should not be too reactive!* Interestingly, although thioglycoside and STAZ [50–52] donors display armed/disarmed effects, trichloroacetimidates do not, according to our tests [53].

In Sect. 2.2 we noted that we were unaware of any early attempts at chemoselective coupling of glycosyl bromides. The likelihood of armed/disarmed phenomena being observed under Koenigs–Knorr conditions is low because the solubility product of silver bromide would override the steady-state requirement in panel **D** of Fig. 2.

3 Torsional Armed/Disarmed Coupling

The techniques which were developed for the mechanistic studies in Fig. 3 taught us how to compare the reactivity pairs of NPGs. Thus α/β pairs of armed and disarmed analogs were allowed to compete for an insufficient amount of NBS [54]. The unreacted substrates were recovered, the ratio measured by HPLC, and the values used to compute relative reactivity rates. Some results are shown in Fig. 4 [54]. Strategies for measuring relative reactivity rates of donors by NMR and HPLC were independently developed by the groups of Ley [55] and Wong [56], respectively.

For the perbenzylated anomeric mixture **8a**, the β/α rate-ratio was 1.70 while, for the corresponding peracetates **8b**, the β/α rate-ratio had risen to 5.19. Similarly, for the 4,6-*O*-benzylidene derivatives, the β/α ratio was 1.45 for the dibenzylated substrates **45a**, and slightly higher for the corresponding acetates **45b**.

These data are consistent with the well-known faster hydrolysis of β-glucosides [57], but it is clear that, by choosing appropriate "protecting groups," the disparity in β/α rates can be tuned up or down. This was demonstrated by examining the ratio of the *n*-pentenyl glucosides **8a**(β) and **45a**(β), which turned out to be 1.59. By contrast, with the peracetylated (disarmed) analogs, in Fig. 4c, the rate-ratio for **8b**(β)/**45b**(β) was greater than 10.4:1.

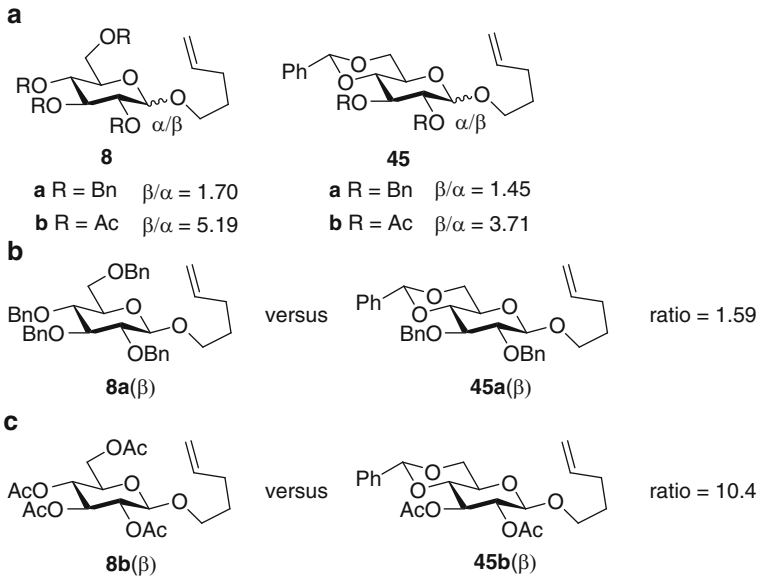
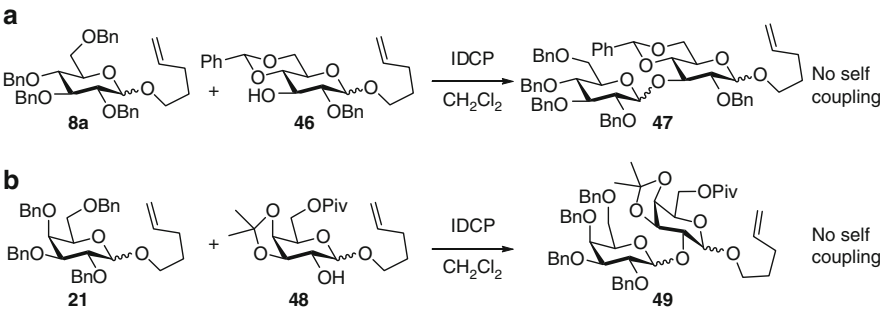


Fig. 4 Relative rates of oxidative hydrolysis of pairs of NPGs



Scheme 8 Torsional armed/disarmed coupling

The 10.4:1 disparity imposed by the benzylidene ring (Fig. 4c) caused us to recall that oxidative hydrolysis of the benzylidinated substrate **6** (Scheme 2) had also been sluggish. This observation was not probed because our concern, at that time, was the survival of protecting groups under the reaction conditions. However, since the reactivity disparity had been leveraged into the "electronic" armed/disarmed strategy, we decided to test for the complementary "torsional" phenomenon.

Thus the faster reacting entity **8a** was chosen as the donor, while the slower reacting entity was conceived as acceptor **46** (Scheme 8a). Under the agency of IDCP [34], disaccharide **47** was obtained, there being no evidence of self-coupled products of the acceptor **46** [58].

A similar result was obtained even with the conformationally flexible *galacto* donor **21**, which coupled to the galactoside **48** to form disaccharide **49** (Scheme 8b).

The torsional armed/disarmed protocol is therefore a complement to the electronic armed/disarmed phenomenon.

3.1 Conformational Tuning and Effects at the Anomeric Center

The effect benzylidene rings on oxidative hydrolyses of NPGs opened an opportunity for us to participate in the dispute over the conformational requirements for hydrolysis of α and β glycosides [59]. The theory of stereoelectronic control [59] had postulated that β glucosides had to change conformation from chair to boat so that a lone pair of electrons on the ring oxygen could become antiperiplanar to the leaving group.

This issue is clearly of great significance to enzymatic mechanisms, and the subject has attracted broad interest from bio-organic scientists [60]. Early model experiments on alkyl glycosides employed protic or Lewis acids, which proscribed the use of test substrates bearing acid sensitive protecting groups. As an alternative, substrates with hypersensitive-leaving groups that could depart "spontaneously" under neutral conditions (e.g., *p*-nitrophenyl) were used [61], and carbocyclic, conformational surrogates were studied [60].

With the advent of NPGs, it was now possible to escape from the acid-lability restrictions and impose conformational restraints by strategic placing of cyclic acetals. Unrestrained, **8a**, and restrained substrates **50** and **51** (Fig. 5) were

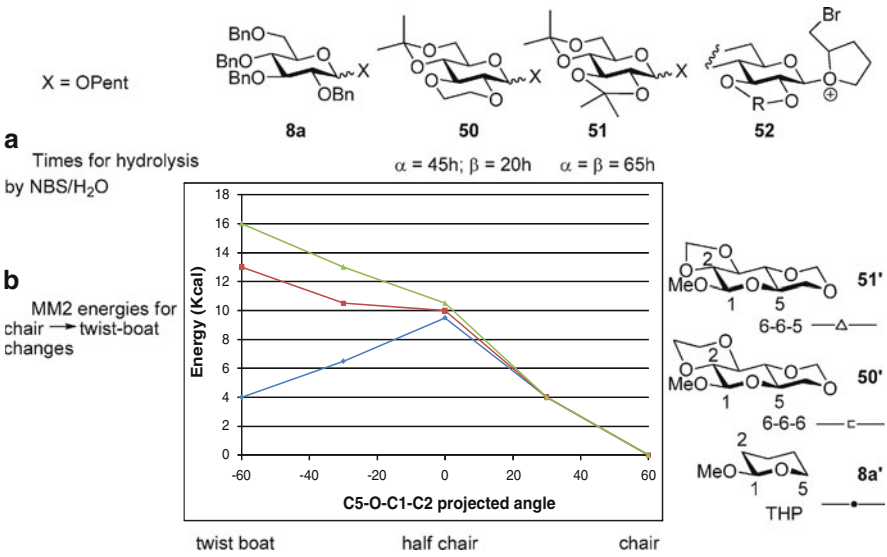


Fig. 5 Conformational structures on oxidative hydrolysis

synthesized. As a prelude to experimental study, we carried out MM2 energy calculations for twisting the sugar ring of the corresponding stripped-down analogs (β anomers only) of **51′**, **50′**, and **8a′** through chair → half-chair → twist-boat conformations. *It is seen that energy investment is* (*nearly*) *the same as each structure goes from chair → half-chair* (60° → 0°). Further twisting of the unrestrained system, **8a′**, is highly favored, with the twist boat lying ~5 kcal/mol *below* the half-chair – in excellent agreement with precedents [62]. By contrast, further twisting of the restrained structure **50′** requires an investment of 2.5 kcal above the half-chair, and **51′** requires ~6 kcal.

The oxidative hydrolyses were then carried out on the **50**α and **50**β anomers, and required 45 and 20 h respectively, whereas for **51**α and **51** the time was 65 h for each (Fig. 5a). These results were not consistent with the postulated chair → boat change for β glucosides [61, 63].

To obtain insight into the attendant conformational changes, we carried out MM2 analysis of protonated alkyloxy(methoxy)methane, which was used as surrogate for the furanylium ion **52** shown in Fig. 5. Assuming sp^3 hybridization of oxygen [64, 65], the C5–O–C1–OMe domain of **8a′**, **50′**, or **51′** can be represented by the 180° *gauche* Newman projection in Fig. 6. As the rotation is made from *gauche* to *syn*periplanar, there is a decrease in potential energy, and further rotation causes the system to plunge into the minimum, the structure of which corresponds to the oxocarbenium ion shown in Fig. 6. Thus the *syn*periplanar alignment of the nσ* system meets the condition for *syn* elimination [66]. Figure 6 further indicates that energy would have to be *invested* for further rotation to the *anti*periplanar arrangement, a prohibitive prospect.

Therefore, the conclusion from these studies was that β glucosides hydrolyze by a *syn* elimination mechanism [67] which is supported by the conclusion reached by Perrin and Nunez in their study of amidine hydrolysis [68]. This conclusion also conforms to Sinnott's principle of least nuclear motion theory [69].

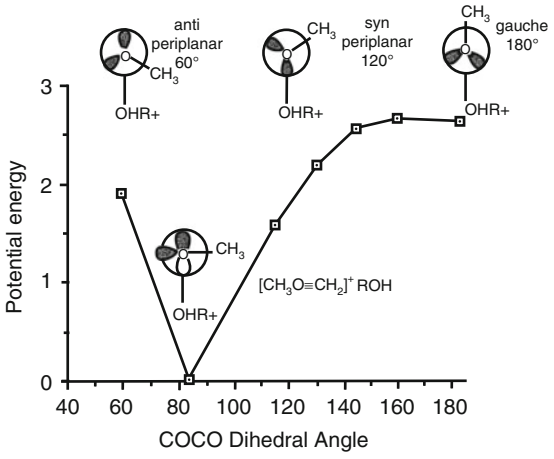


Fig. 6 MM2 analysis for rotating protonated dimethoxymethane

3.2 *Stereoselective Synthesis of α or β Glucopeptides*

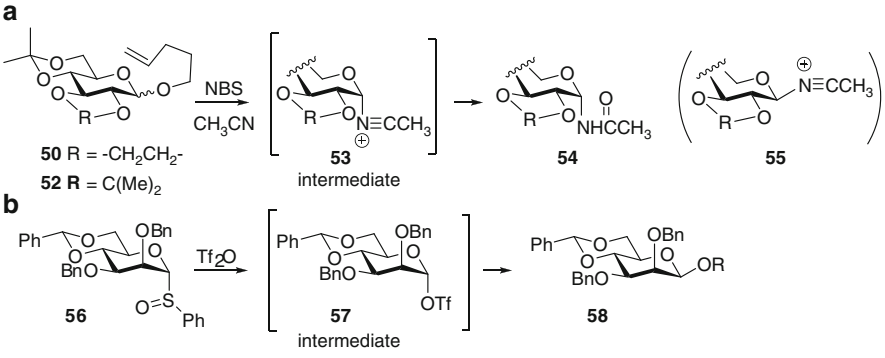
Although the conformational studies in Figs. 5 and 6 relate to mechanistic issues, the *product* of the hydrolyses also drew our attention. Thus, the α-acetamide **54** ($n = 1$ or 2) was the major product from hydrolyses of the restrained precursors **50** (α/β) and **51** (α/β) shown in Fig. 5, and reproduced in Scheme 9a [70]. Such compounds result from a Ritter reaction [71, 72] to give a nitrilium intermediate, e.g., **53**, which rapidly scavenges water.

The subsequent seminal studies of Crich and Sun [73] relating to the synthesis of β-mannosides are summarized in Scheme 9b. Their work showed that the 4,6-*O*-benzylidene ring is a compulsory requirement for β-glycosylation, and extensive mechanistic scrutiny has revealed that the α mannosyl triflate, **57**, is a key intermediate, isolable with caution, which is displaced by acceptor, ROH, in a S_N2-like process [74].

The dramatic requirement for the specifically placed benzylidene has been subjected to elegant analysis by Bols [75], who noted that the stereoselective synthesis "employs, as its key element, donors that have been disarmed by locking their conformation . . . ." The purpose of the "lock," Bols contends, is to provide an antiperiplanar relationship between the O6–C6 and C5–O5 bonds, an arrangement that facilitates electron withdrawal that stabilizes the oxocarbenium ion intermediate.

However, in spite of these observations, the α-orientation of the reactive intermediates **53** and **57** (Scheme 9) was purely fortuitous [76], and so torsional restraint was not essential for the observed α-acetamide formation.

Indeed, Pougny and Sinaÿ had shown that Ritter products could be captured by an in situ carboxylic acid [77]. In keeping with this precedent (Scheme 10a) the glucoside **59** was treated with NBS in very dry acetonitrile, and the Ritter intermediate **60** was captured by the in situ aspartic acid **61** [78], leading to the rearranged α-imide **62a**. In view of the three acyl residues, it took several experiments before finding that smooth *N*-deacylation could be effected by piperidine to give **62b** [79].

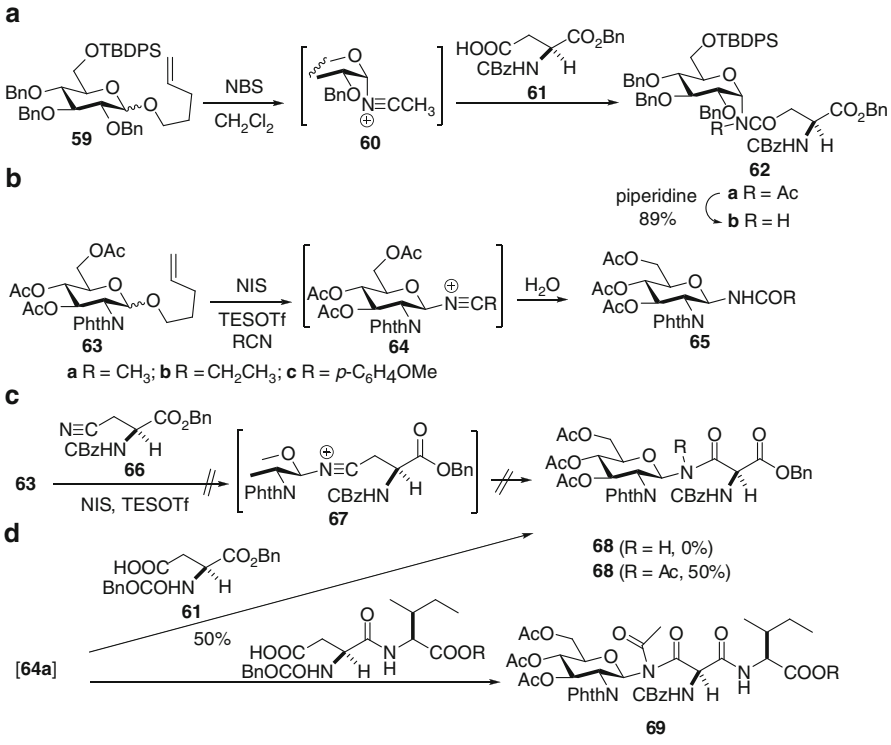


Scheme 9 Conformational restrictions and anomeric replacement

The result in Scheme 10a was key to a synthesis of an α-nephritogenic glycopeptide [79], which like our acetamide **54**, had been assigned (abnormal) α-D-orientation [80]. The α orientation of **54** or **62** was of interest, because β orientation of the glycosyl amino group (1) is favored by the anomeric effect [81] and (2) would originate from the β nitrilium intermediate, e.g., **64** (Scheme 10b), which is also favored (over **60**) by the reverse anomeric effect [82].

The 2-acetamido-2-deoxy-β-D-glucopyranosyl moiety is a common link between oligosaccharide and polypeptide components [83], and to pursue this link, the phthalimido protected NPG **63** was tested as a starting material. Acetonitrile, propionitrile, and *p*-methoxybenzonitrile gave good yields of β-glycopeptides **65a,b** and **c**, respectively, consistent with the intermediacy of the corresponding nitrilium ions **64a,b** and **c** (Scheme 10b).

The latter information compelled us to investigate the Ritter reaction of a more elaborate nitrile. Accordingly, the protected cyanoalanine **66** was tested for a direct route to glycopeptide **68** (R=H). This was unsuccessful and implied that the required Ritter reaction intermediate **67** was apparently not formed [71] (Scheme 10c).



Scheme 10 In situ syntheses of α- or β-glucosyl peptides

However, the indirect route involving the acetonitrilium ion adduct **64a** was successful. Thus the aspartic acid derivative **61** captured nitrilium intermediate **64a** (Scheme 10d) to give glycopeptide **68** (R=Ac) in ~50% yield [84].

Similarly, a dipeptide was captured to give the glycosyldipeptide **69** (R=Ac) (Scheme 10d) [84].

4 Chemoselective Glycosyl Activation: Discriminating Between NPGs and NPOEs

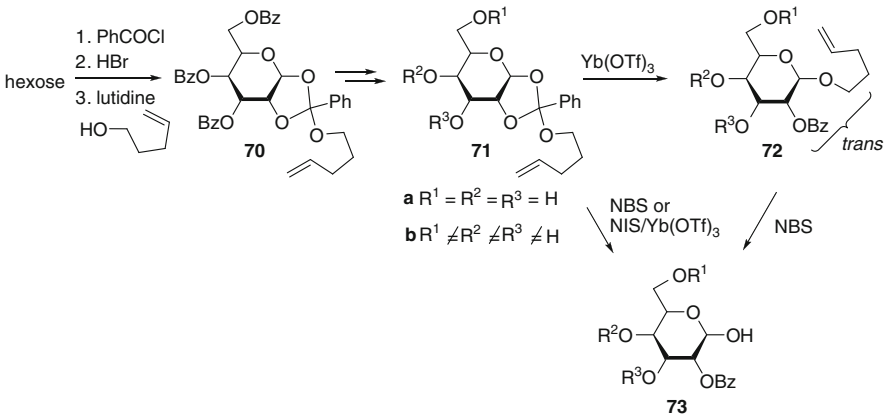
Trost coined the term chemoselective to describe the process where one of two similar functional groups is made to react, while the other is not affected or affected to a lesser extent [1]. This discrimination usually results from nuanced changes to a reagent's behavior, e.g., by addition of a salt. A typical example is the modification of sodium borohydride reduction by addition of cerium chloride in the Luche process, whereby the double bond of an α-enone is not saturated during the reaction [85]. Similarly, a new approach to chemoselective reaction of *n*-pentenyl donors was soon to emerge.

The original armed/disarmed protocol, as exemplified in Scheme 3, required tinkering with protecting groups to convert disarmed disaccharide donor **11a** to its armed counterpart **11b**. Obviously a procedure that allows chemoselective discrimination without having to tinker with protecting groups of the reactants would be advantageous. An opening to this possibility was provided, again, by a fortuitous observation.

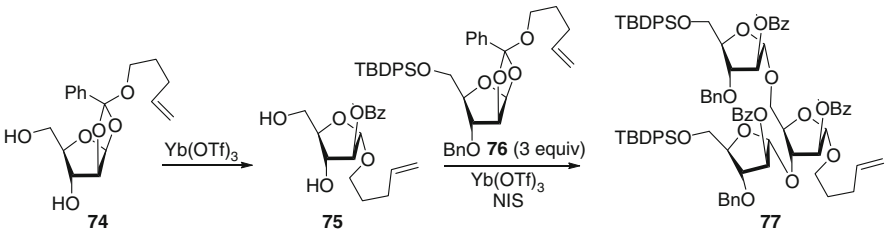
n-Pentenyl orthoesters (NPOEs), e.g., **70**, had been prepared and used in our laboratory [24, 86] soon after the discovery of NPGs; but the ready and economical rearrangement **71** → **72** (Scheme 11) soon became our preferred procedure for preparing NPGs. Thus, three simple steps were required to go from the starting hexose to orthoester **70**, which could undergo differential protection at O3, O4, and O6 to give **71** [87]. This differentiation could then be exported to the corresponding NPG, e.g., **72**.

The rearrangement **71** → **72** requires use of an acid and, as noted above, an acid is also used to generate iodonium ion from *N*-iodosuccinimide (NIS) [86]. However, the need to preserve acid-sensitive protecting groups caused us to look at lanthanide triflates. We found that ytterbium triflate/*N*-iodosuccinimide ($Yb(OTf)_3$/NIS) combination could be used to trigger NPOEs, but not NPGs [88, 89]. The advantage of this development can be seen in Scheme 11. NBS induced oxidative hydrolysis can be applied to either NPOE **71** or NPG **72** to obtain glycose **73**. However, chemoselective hydrolysis of NPOE **71** is possible by specific use of Yb $(OTf)_3$/NIS [88].

This selectivity can also be applied synthetically as seen in Scheme 12. First, the NPOE diol **74** was smoothly rearranged with ytterbium triflate, $Yb(OTf)_3$, and the resulting NPG diol **75** was doubly glycosylated with NPOE **76** to give trisaccharide **77** [90].



Scheme 11 *n*-Pentenyl orthoesters (NPOEs) and *n*-pentenyl glycosides (NPGs)



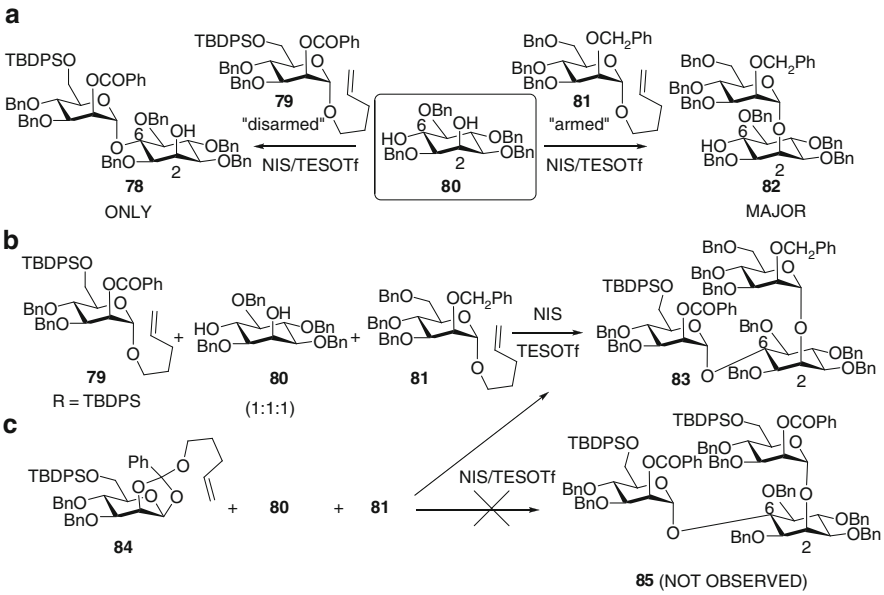
Scheme 12 Chemoselectivity between NPOEs and NPGs

The result is reminiscent of the original armed/disarmed experiment (Scheme 3) in that each reactant (**75** or **76**) can serve*, separately*, as a donor, but when they are forced to compete, one becomes the acceptor and the other the donor, thereby satisfying the condition for chemoselectivity.

The foregoing results show that it is possible to effect tuning by tinkering with reagent combinations rather than with the substrates' protecting groups, as was the practice in Scheme 3.

5 Regioselectivity in Glycosyl Couplings

Our interest in the issue of regioselectivity, the remaining one of Trost's four factors [1] that had not been examined for glycosidation, had been triggered by the fortuitous observation in Scheme 13a.



Scheme 13 Regioselective glycosylation does not depend on donor reactivities (I)

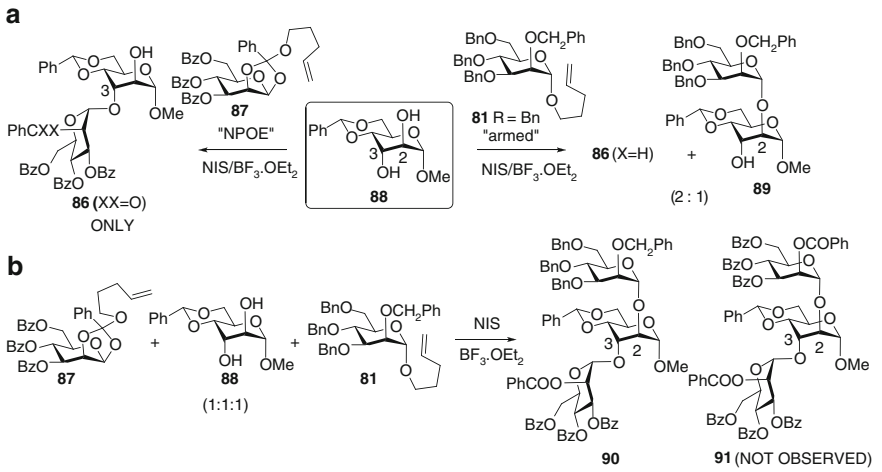
5.1 Secondary Versus Secondary Hydroxyl Groups in Diols

The history of this observation has been recounted elsewhere [91] but, in summary, the disarmed donor **79** was found to glycosylate the diol **80** at O6 to give disaccharide **78** as the only product, even when used in excess. In contrast, the armed counterpart **81** was promiscuous, although going to O2 mainly to give **82** as the major product (Scheme 13a).

When acceptor diol **80** was presented simultaneously to both donors **79** and **81**, the product **83** was the only trisaccharide obtained (Scheme 13b), each donor having gone to its preferred-OH as previously revealed in Scheme 13a [92].

This result could not be rationalized on the basis of the relative reactivity of the two donors because, on that basis, the armed donor **81** would have glycosylated BOTH O6 and O2. *The reactivity rationalization was further discredited with the experiment shown in Scheme 13c. NPOE* **84** *is infinitely more reactive than the armed donor* **81***, and therefore it should have glycosylated both hydroxyls. However, the product was again* **83**, *no trisaccharide* **85** *having been observed.*

On the other hand, it was reasonable to ask whether equatorial vs axial preference played any part in the selectivities in Scheme 13. In that context, we decided to evaluate axial vs axial preference with the glycosylation of diol **88** [93]. As glycosyl donors we selected NPOE **87** and armed donor **81** (Scheme 14). The results obtained with **87** were similar to those observed with diol **80** in Scheme 13. NPOE **87** was again found to be the more selective donor and glycosylated **88** at O3 exclusively to give disaccharide **86** (XX=O), whereas armed donor **81** reacted



Scheme 14 Regioselective glycosylation does not depend on donor reactivities (II)

at O2 and O3 to give disaccharides **86** (X=H) and **89**, respectively, in a 2:1 ratio (Scheme 14a). Reaction of diol **88** with equal amounts of donors **87** and **81** (Scheme 14b) resulted in the exclusive formation of trisaccharide **90** where there was no trisaccharide **91** resulting from the reaction of the more reactive NPOE **87** at O6 and O2 [94].

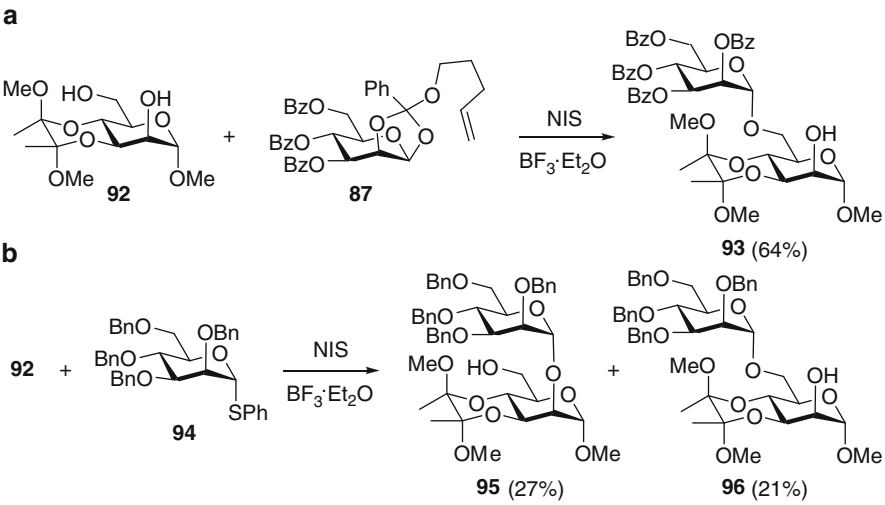
Attempts to elicit equatorial vs equatorial selectivity were only partially successful (with vicinal diols) when an NPOE was used as glycosyl donor, whereas armed donors were less discriminating [93, 95].

5.2 Primary Versus Secondary Hydroxyl Groups in Diols

Along this line, we decided to explore the question of primary vs secondary hydroxyl groups [96] with simultaneous examination of the applicability of thioglycoside donors which are known to also undergo armed/disarmed coupling [38]. The "dispoke" [97–99] mannoside **92** underwent glycosylation with NPOE **87** regioselectively at the primary position to give **93** only (Scheme 15a). In contrast, reaction of **92** with the armed thioglycoside **94** was promiscuous, occurring at both hydroxyls to give **95** and **96** in nearly equal amounts (Scheme 15b).

6 Reciprocal Donor Acceptor Selectivity

The results in Schemes 13–15 suggest that, in all cases, one of the donors is choosing one of the two available hydroxyl groups, while simultaneously rejecting the other – and vice versa. Thus the choice is being reciprocated by each partner,



Scheme 15 Regioselective glycosylation does not depend on donor reactivities (III)

suggesting that there may be an underlying principle of *reciprocal donor acceptor selectivity* (RDAS) [100–102].

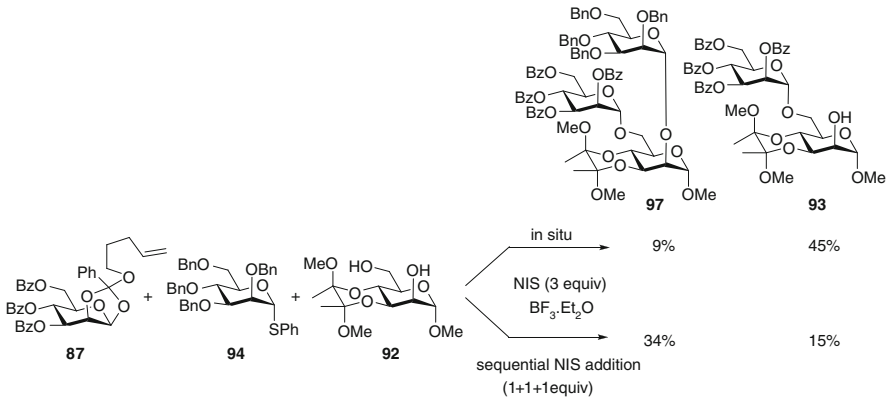
At the time of this writing the "reason" behind RDAS remains elusive, but undoubtedly a rationalization will emerge, in the same way that the "reason" for the stereoselectivity of the Koenigs–Knorr reaction [103] was eventually promulgated by Isbell [104] – albeit 40 years after the initial report.

Nevertheless, the experimental evidence is accumulating as may be judged from the recent study summarized in Schemes 14–16. In view of the 1 + 1 glycosidations in Scheme 13a,b, a 1 + 1 + 1 mixture of donors **87** and **94** was presented to diol **92**, along with three equivalents of NIS (Scheme 16). When the NIS was all added at the outset, trisaccharide **97**, expected on the basis of RDAS, was indeed obtained – but in the disappointing yield of 9%. The disaccharide **93** (Scheme 15a), which was isolated in 45% yield, had clearly failed to couple with the armed donor **94** to any great extent.

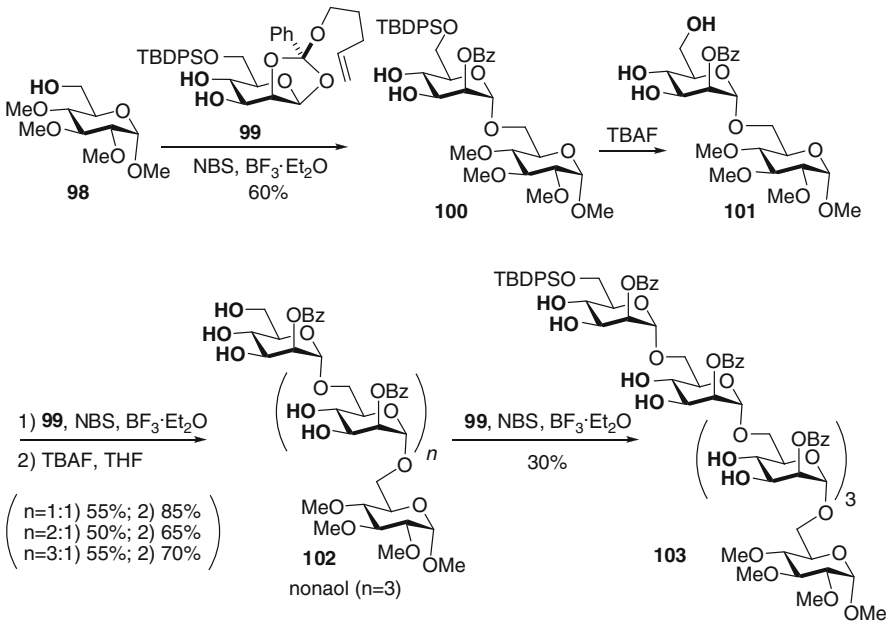
In a different approach, the reaction was repeated with the exception that the three equivalents of NIS were added gradually rather than all-at-once (in situ). The salutary effect on the RDAS outcome is evident, since the yield of trisaccharide **97** increased to 34% (from 9%), with the concomitant decrease of **93** from 45% to 15% (Scheme 16).

6.1 RDAS-Based Iterative Glycosylation Strategies

Encouraged by the results in Schemes 14–16, we decided to explore how far regioselectivity could be pushed in glycosyl couplings. So far the focus had been

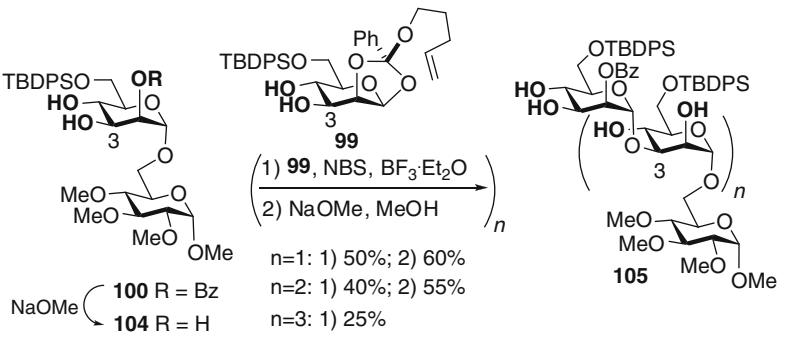


Scheme 16 Influence of the mode of NIS addition in *RDAS*-driven two-donors-plus-one-diol-acceptor glycosylations



Scheme 17 Influence of the mode on NIS addition in *RDAS*-driven two-donors-one-diol-acceptor glycosylations

on acceptor diols. In contrast, examples in which the glycosyl donor itself has one or more free hydroxyl groups are rarely seen [105–107]. We therefore set out to explore the couplings of NPOE diol **99** with polyol acceptors (Scheme 17) [102]. Reaction with methyl glucoside **98** furnished a single compound **100**, *thus showing that self-coupling of* **99** *was not a competing reaction*.



Scheme 18 Iterative glycosylation of secondary triols with NPOE diol **99**

The product was treated with TBAF, and the resulting triol, **101**, was glycosylated with the NPOE donor diol **99**, followed directly by TBAF deprotection, whereupon only one compound, **102** ($n = 1$), was obtained.

Sequential threefold iteration of the glycosylation/desilylation process permitted the synthesis of pentasaccharide **102** ($n = 3$) with nine free-OH groups, resulting from the glycosylation of a heptaol acceptor with NPOE diol **99**. Glycosidation of **102** with **99** then gave hexasaccharide **103** with ten free-OH groups [102].

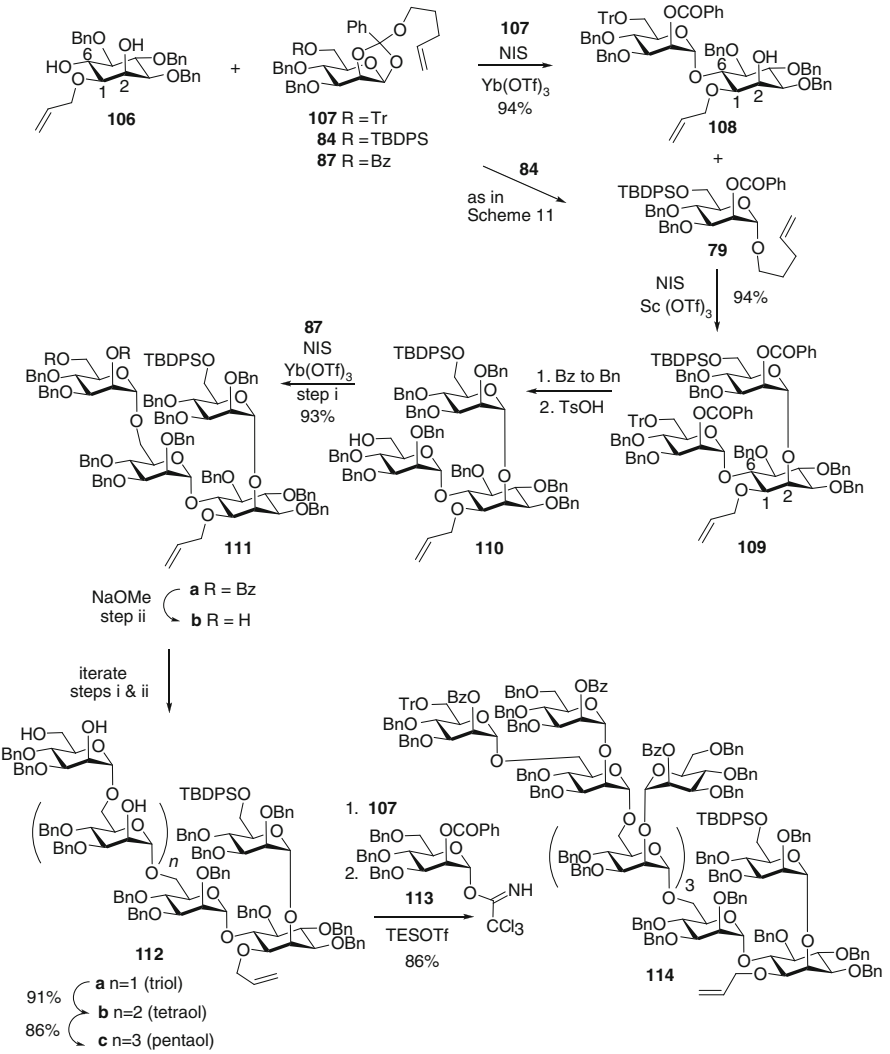
In none of the above cases were significant amounts of products from self condensation of **99** seen.

The synthesis of a hexasaccharide by successful differentiation between one primary OH group and up to ten secondary OH groups (eight in the acceptor plus two in the donor) might have seemed straightforward based on the "higher reactivity of primary hydroxyl groups" [23]. However the strategy may have been successful only because of the choice of the NPOE glycosyl donor. In fact, inspection of the results displayed in Scheme 15a,b show that an armed thioglycosyl donor had not been able to discriminate between primary and secondary hydroxyl groups in diol acceptors.

Based on these results, we were tempted to explore the feasibility of oligosaccharide synthesis through secondary vs secondary hydroxyl group selectivity (Scheme 18). Accordingly, triol **104**, obtained by debenzylation of **100**, upon glycosylation with NPOE **99,** resulted in the formation of a single trisaccharide **105** ($n = 1$) in 50% yield by selective glycosylation at O3, thus showing that discrimination was also possible between three secondary OH groups (Scheme 18). Iteration of the protocol twice more permitted the preparation of octaol pentasaccharide **105** ($n = 3$) [102].

6.2 *RDAS-Based Iterative Glycosylation Strategies Towards an Oligomannan Fragment of* Mycobacterium tuberculosis

A straightforward approach to the oligomannan fragment from *Mycobacterium tuberculosis* is summarized in Scheme 19 [108].



Scheme 19 Iterative regioselectivities facilitate dodecasaccharide synthesis

The approach relies heavily on the knowledge gained in our studies with pentenyl-based glycosyl donors, and serves to illustrate the usefulness of RDAS-based strategies in the synthesis of oligosaccharides.

The observations depicted in Scheme 13a taught us the best *n*-pentenyl donors for assembling the *pseudo*trisaccharide **109**. And since NPOEs and disarmed NPGs display similar regio-preferences, we could now apply the NPOE/Yb(OTf)$_3$ synergy (see Scheme 12) to enhance and improve upon the options in Scheme 13.

Accordingly, as shown in Scheme 19, treatment of **106** with an excess of the tritylated NPOE **107** could be carried out, confident that mannosylation would only

occur at O6, and that O2 would remain free in product **108**. According to the RDAS tendencies shown in Scheme 13, the donor for O2 should be an armed NPG, and with this in mind, the silylated NPOE **84** was rearranged (as in Scheme 11) and routinely processed to give **79**. Reaction of the latter with **108** now gave pseudotrisaccharide **109**, and detritylation readied **110** for building up the mannan array.

First, we wished to build the α1,6–"backbone" of target **114** through a regioselective iterative glycosylation process. The NPOE **87** has two benzoyl groups, one actual (O6), the other latent (O2), and so its use led to the diester **111a** in step (1). Step (2) involved saponification, which afforded the corresponding diol **111b**. By iterative processes involving steps (1) and (2), the *pseudo*tetrasaccharide diol **111b** was sequentially homologated to *pseudo*pentasaccharide triol **112a**, and then to the *pseudo*hexasaccharide tetraol **112b** and *pseudo*heptasaccharide pentaol **112c**, yields being maintained in the 86–90% range [108].

Several preliminary experiments taught us that simultaneous mannosylation of all five hydroxyls of **112c** was best accomplished by a trichloroacetimidate, and so donor **103** was prepared from the appropriate NPOE precursor by hydrolysis and reaction of the ensuing hemiacetal with Cl_3CCN [109]. Glycosidation of the pentaol **112c** with **103** in the presence of TESOTf produced the pseudododecasaccharide **114** in the satisfying yield of 86%.

References

1. Trost BM (1983) Science 219:245
2. Frush HL, Isbell HS (1941) J Res Nat Bureau Stand 27:413
3. Capon B, McManus SP (1976) Neighboring group participation. Plenum, New York
4. Kanie O, Ito Y, Ogawa T (1944) J Am Chem Soc 116:12073
5. Allman SA, Jensen HH, Vijayakrishnan B, Garnett JA, Leon E, Liu Y, Anthony DC, Sibson NR, Feizi T, Matthews S, Davis BG (2009) ChemBioChem 10:2522
6. Fraser-Reid B, Udodong UE, Wu Z, Ottosson H, Merritt R, Rao CS, Roberts C, Madsen R (1992) Synlett 217
7. Reinhart KL (1976) Fortschritt Chem Org Naturt 33:231
8. Hanessian S (1983) Total synthesis of natural products: the chiron approach. Pergamon, Oxford
9. Masamune S, Choy W, Petersen JS, Sita LR (1985) Angew Chem Int Ed Engl 24:1
10. Spijker NM, van Boeckel CAA (1991) Angew Chem Int Ed Engl 30:180
11. Fraser-Reid B, Magdzinski L, Molino B (1984) J Am Chem Soc 106:731
12. Fraser-Reid B, Molino BF, Magdzinski L, Mootoo DR (1987) J Org Chem 52:4505
13. Fraser-Reid B, Magdzinski L, Molino BF, Mootoo DR (1987) J Org Chem 52:4495
14. Molino BF, Fraser-Reid B (1987) Can J Chem 65:2834
15. Mootoo DR, Fraser-Reid B (1987) J Org Chem 52:4511
16. Mootoo DR, Fraser-Reid B (1988) Carbohydr Res 174:99
17. Mootoo DR, Fraser-Reid B (1990) Tetrahedron 46:185
18. Mootoo DR, Fraser-Reid B (1990) J Chem Soc Perkin I 739
19. Mootoo DR, Date V, Fraser-Reid B (1988) J Am Chem Soc 110:2662
20. Hanessian S (1966) Carbohydr Res 2:86
21. Failla DL, Hullar TL, Siskin SB (1966) J Chem Soc Chem Commun 716
22. Crich D, Yao Q, Bowers AA (2006) Carbohydr Res 341:1748

23. Paulsen H (1982) Angew Chem Int Ed Engl 21:155
24. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B (1988) J Am Chem Soc 110:5583
25. Konradsson P, Mootoo DR, McDevitt RE, Fraser-Reid B (1990) J Chem Soc Chem Commun 270
26. Alslani-Shotorbani G, Buchanan JG, Edgar AR, Shanks GT, Williams GC (1981) J Chem Soc Perkin I 2267
27. Konradsson P, Fraser-Reid B (1989) J Chem Soc Chem Commun 1124
28. Lemieux RU, Hendriks KB, Stick RV, James K (1975) J Am Chem Soc 97:4056
29. Hanessian S, Banoub J (1977) Carbohydr Res 53:C13
30. Fraser-Reid B, Wu Z, Udodong UE, Ottosson H (1990) J Org Chem 55:6068
31. Merritt JR, Debenham JS, Fraser-Reid B (1996) J Carbohydr Chem 15:65
32. Premathilake HD, Mydock LK, Demchenko AV (2010) J Org Chem 75:1095
33. Merritt JR, Naisang E, Fraser-Reid B (1994) J Org Chem 59:4443
34. Fraser-Reid B, Iley DE (1979) Can J Chem 57:645
35. Veeneman GH, Van Leeuwen SH, Zurmond H, van Boom JH (1990) J Carbohydr Chem 9:783
36. Mootoo DR, Konradsson P, Fraser-Reid B (1989) J Am Chem Soc 111:8540
37. Konradsson P, Udodong UE, Fraser-Reid B (1990) Tetrahedron Lett 31:4313
38. Veeneman GH, van Leeuwen SH, van Boom JH (1990) Tetrahedron Lett 31:1331
39. Arotsky J, Darby AC, Hamilton JBA (1973) J Chem Soc Perkin Trans 2:595
40. Merritt JR, Fraser-Reid B (1992) J Am Chem Soc 114:8334
41. Rodebaugh R, Fraser-Reid B (1994) J Am Chem Soc 116:3155
42. Rodebaugh R, Fraser-Reid B (1996) Tetrahedron 52:7663
43. Coleman DG, Skinner HA (1966) Trans Faraday Soc 62:2057
44. Howard PB, Skinner HA (1966) J Chem Soc 1536
45. Strating J, Wieringa JH, Wynberg H (1969) Chem Commun 907
46. Slebocka-Tilk H, Ball RG, Brown RS (1985) J Am Chem Soc 107:4504
47. Bennet AJ, Brown RS, McClung RED, Klobukowski M, Aarts GHM, Santarsiero BD, Bellucci G, Bianchini R (1991) J Am Chem Soc 113:8532
48. Brown RS, Slebocka-Tilk H, Bennet AJ, Bellucci G, Blanchini R, Ambrosetti R (1990) J Am Chem Soc 112:6310
49. Bellucci G, Bianchini R, Chiappe C, Ambrosetti R, Catalano D, Bennet AJ, Slebocka-Tilk H, Aarts GHM, Brown RS (1993) J Org Chem 58:3401
50. De Meo C, Kamat MN, Demchenko AV (2005) Eur J Org Chem 706
51. Demchenko AV, Pornsuriyasak P, De Meo C, Malysheva NN (2004) Angew Chem Int Ed 43:3069
52. Smoot JT, Pornsuriyasak P, Demchenko AV (2005) Angew Chem Int Ed 44:7123
53. López JC, Gómez AM, Uriel C, Fraser-Reid B (2003) Tetrahedron Lett 44:1417
54. Wilson BG, Fraser-Reid B (1995) J Org Chem 60:317
55. Douglas NL, Ley SV, Lucking U, Warriner SL (1998) J Chem Soc Perkin Trans I 51
56. Zhang ZY, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) J Am Chem Soc 121:734
57. Feather MS, Harris JF (1965) J Org Chem 30:153
58. Fraser-Reid B, Wu Z, Andrews CW, Skowronski E, Bowen JP (1991) J Am Chem Soc 113:1434
59. Jencks WP (1975) Adv Enzymol 43:219
60. Sinnott ML (2007) Carbohydrate chemistry and biochemistry. RSC, Cambridge
61. Briggs AJ, Evans CM, Glenn R, Kirby AJ (1983) J Chem Soc Perkin II 1637
62. Eliel EL, Willen SH (1994) Stereochemistry of organic compounds. Wiley-Interscience, New York
63. Deslongchamps P (1983) Stereoelectronic effects in organic chemistry. Pergamon, Oxford
64. Andrews CW, Bowen JP, Fraser-Reid B (1989) J Chem Soc Chem Commun 1913
65. Andrews CW, Rodebaugh R, Fraser-Reid B (1996) J Org Chem 61:5280

66. Sicher J (1972) Angew Chem Int Ed Engl 11:200
67. Ratcliffe AJ, Mootoo DR, Andrews CW, Fraser-Reid B (1989) J Am Chem Soc 111:7661
68. Perrin CL, Nunez O (1986) J Am Chem Soc 108:5997
69. Sinott ML (1988) Adv Phys Org Chem 24:113
70. Ratcliffe AJ, Konradsson P, Fraser-Reid B (1990) J Am Chem Soc 112:5665
71. Ritter JJ, Minieri PP (1948) J Am Chem Soc 70:4045
72. Ritter JJ, Kalish J (1948) J Am Chem Soc 70:4048
73. Crich D, Sun S (1996) J Org Chem 61:4506
74. Crich D, Sun S (1997) J Am Chem Soc 119:11217
75. Pedersen CM, Nordstrøm LU, Bols M (2007) J Am Chem Soc 129:9222
76. Crich D, Banerjee A (2006) J Am Chem Soc 128:8078
77. Pougny JR, Sinaÿ P (1976) Tetrahedron Lett 4073
78. Bryant PM, Moore RH, Pimlott PJ, Young GT (1959) J Chem Soc 3868
79. Ratcliffe AJ, Fraser-Reid B (1990) J Chem Soc Perkin Trans I 747
80. Sawaki M, Takeda T, Ogiharay T, Shibata S (1985) Chem Pharm Bull 33:5134
81. Kirby AJ (1983) The anomeric effect and related stereoelectronic effects at oxygen. Springer, Berlin
82. Lemieux RL, Morgan AR (1965) Can J Chem 43:2205
83. Kunz H (1987) Angew Chem Int Ed Engl 26:294
84. Handlon AL, Fraser-Reid B (1993) J Am Chem Soc 115:3796
85. Luche J-L, Rodriguez-Hahn L, Crabbé P (1978) Chem Commun 601
86. Allen JG, Fraser-Reid B (1999) J Am Chem Soc 121:468
87. Mach M, Schlueter U, Mathew F, Fraser-Reid B (2002) Tetrahedron 58:7345
88. Jayaprakash KN, Radhakrishnan KV, Fraser-Reid B (2002) Tetrahedron Lett 43:6953
89. Jayaprakash KN, Fraser-Reid B (2004) Synlett 301
90. Lu J, Fraser-Reid B (2004) Org Lett 6:3051
91. Anilkumar G, Jia ZJ, Kraehmer R, Fraser-Reid B (1999) J Chem Soc Perkin Trans I 3591
92. Anilkumar G, Nair LG, Fraser-Reid B (2000) Org Lett 2:2587
93. Fraser-Reid B, López JC, Radhakrishnan KV, Mach M, Schluetter U, Gómez AM, Uriel C (2002) J Am Chem Soc 124:3198
94. Fraser-Reid B, López JC, Radhakrishnan KV, Nandakumar MV, Gómez AM, Uriel C (2002) Chem Commun 2104
95. Fraser-Reid B, Anilkumar G, Nair LG, Radhakrishnan KV, López JC, Gómez AM, Uriel C (2002) Aust J Chem 55:123
96. Uriel C, Agocs A, Gómez AM, López JC, Fraser-Reid B (2005) Org Lett 7:4899
97. Ley SV, Priepke HWM, Warriner SL (1994) Angew Chem Int Ed Engl 33:2290
98. Ley SV, Priepke HWM (1994) Angew Chem Int Ed Engl 33:2292
99. Montchamp J-L, Tian F, Hart ME, Frost JW (1996) J Org Chem 61:3897
100. Fraser-Reid B, López JC, Gómez AM, Uriel C (2004) Eur J Org Chem 1387
101. Uriel C, Gómez AM, López JC, Fraser-Reid B (2003) Synlett 2203
102. López JC, Agocs A, Uriel C, Gómez AM, Fraser-Reid B (2005) Chem Commun 5088
103. Koenigs W, Knorr E (1901) Chemistry (Berl) 34:957
104. Isbell HS (1940) Annu Rev Biochem 7:65
105. Boons G-J, Zhu T (1997) Synlett 809
106. Hanessian S, Lou B (2000) Chem Rev 100:4443
107. Plante OJ, Palmacci ER, Andrade RB, Seeberger PH (2001) J Am Chem Soc 123:9545
108. Jayaprakash KN, Lu J, Fraser-Reid B (2005) Angew Chem Int Ed 44:5894
109. Schmidt RR, Michel J (1980) Angew Chem Int Ed Engl 19:731

Top Curr Chem (2011) 301: 31–68
DOI: 10.1007/128_2010_112

Published online: 13 January 2011

A Survey of Ley's Reactivity Tuning in Oligosaccharide Synthesis

Ana M. Gómez

Abstract This chapter summarizes the concepts and chemistry developed by Ley's group in relation to the relevance of reactivity tuning in oligosaccharide coupling reactions. The recognition that protecting groups affect the reactivity of glycosyl donors allowed Ley's group to make imaginative use of their 1,2-diacetal protecting groups. The combination of 1,2-diacetals with the presence of different anomeric leaving groups provides up to four different levels of reactivity. The exploitation of these reactivity levels in chemoselective glycosylation processes (reactivity tuning) has allowed the development of highly simplified routes to several complex oligosaccharides in step-wise or one-pot procedures.

Keywords 1,2-Diacetals, Glycoproteins, Glycosylation, Protecting groups

Contents

A.M. Gómez
Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain
e-mail: anagomez@iqog.csic.es

Abbreviations

Aloc	Allyloxycarbonyl
BDA	Butane-2,3-diacetals
bis-DHP	3.3′,4.4′-Tetrahydro-6,6′-bis-2*H*-pyran
Bn	Benzyl (CH_2Ph)
Boc	*tert*-Butoxycarbonyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CDA	Cyclohexane-1,2-diacetals
CSA	Camphorsulfonic acid
DF	Deactivation factor
Dispoke	Dispiroketal
FBn	*p*-Fluorobenzyl
gp	Glycoprotein
GPI	Glycosylphosphatidylinositol
HIV	Human immunodeficiency virus
HPLC	High pressure liquid chromatography
IDCP	Iodonium dicollidine perchlorate
NIS	*N*-Iodosuccinimide
RRV	Relative reactivity values
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetra-*n*-butyl ammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TESOTf	Triethylsilyltrifluoromethanesulfonate
TFA	Trifluoromethanesulfonic acid
TfOH	Triflic acid
TMB	2,2,3,3-Tetramethoxybutane
TMC	1,1,2,2-Tetramethoxycyclohexane

1 Introduction

An enduring area of research in both chemistry and biology is that of carbohydrates. In recent years, advances in analytical methods have shown that, as well as being renewable stores of energy and skeletal components [1, 2], carbohydrates play an

extensive role in biochemical processes [3]. The structural diversity of sugar oligomers leads to their involvement in many key inter- and intra-molecular events [4]. The glycans of glycoconjugates are essential for biological recognition, whilst cells, bacteria, viruses, and toxins all use cell-surface carbohydrates as points of attachment [5–16]. Such important discoveries have reinvigorated research interest in oligosaccharides, focusing on both their synthesis and function.

The concise preparation of complex oligosaccharides remains a significant challenge for synthetic organic chemists. Many factors can influence the outcome of a glycosylation event. These include the leaving group at the glycosyl donor, the activating system, the reaction conditions, and the nature of the protective groups on both coupling partners (donor and acceptor).

Protecting groups have traditionally played crucial roles in the synthesis of carbohydrate derivatives, and will continue to do so however many problems related to them still exist. For example, syntheses tend to be lengthened owing to the multiple steps that are often necessary to deliver appropriately protected coupling partners. Additionally, there is a general lack of appreciation for the effect of protecting groups on glycosidic bond formation, both in terms of the rate and anomeric control, as well as for the relevance of the final global deprotection steps, which often lead to low yields or contaminated products.

For efficient chemical synthesis of complex oligosaccharides, the use of protective agents in the smaller saccharide units must be very precisely planned. To this end, a key element is the need for selective protection of the carbohydrate building blocks to facilitate further processing [17–20]. Therefore, carbohydrate chemists have developed a significant amount of knowledge related to protective group planning, and have established a toolbox of methods that can be applied to particular problems. In the search for new avenues in the protection of *trans*-1,2-diequatorial diols, Ley's laboratory at Cambridge introduced the use of 1,2-diacetals (for a detailed discussion of the application of 1,2-diacetals to complex natural product synthesis, see [21–23]). Fortunately, the application of 1,2-diacetals proved not to be limited to the selective protection of *trans*-1,2-diols. The fusion of a diacetal to a diol group of a sugar derivative imparts considerable rigidity to the system and provides a tunable element that might induce reactivity control during the oligosaccharide coupling process.

In this chapter we will summarize the efforts to achieve these goals, and how methods derived from the use of 1,2-diacetals can considerably shorten some of the more convoluted, multistep processes common to classical oligosaccharide assembly.

2 Selective Protection of 1,2-Diols: Synthesis of the Saccharide Building Blocks

Of the protecting groups which are favored in oligosaccharide synthesis, cyclic acetals have significance because they open the possibility of blocking, simultaneously and selectively, two hydroxyl functions of a monosaccharide. In this

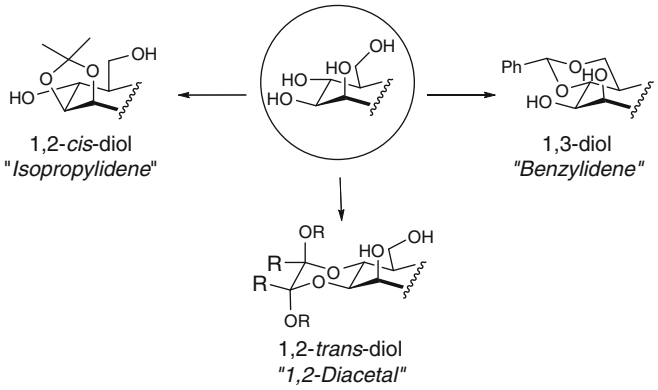
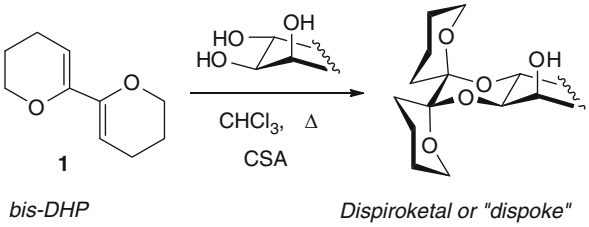


Fig. 1 Selective protection of diol systems in monosaccharides as cyclic acetals



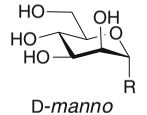
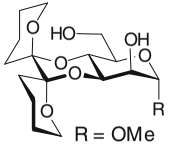
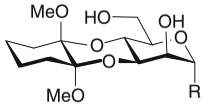
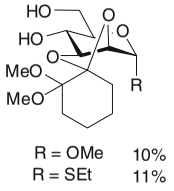
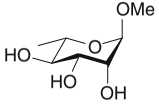
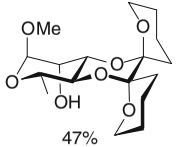
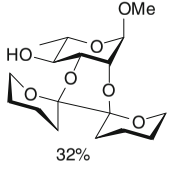
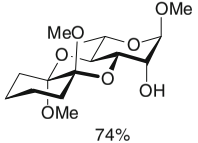
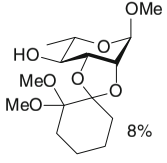
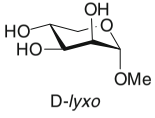
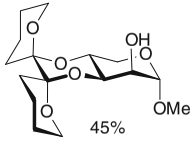
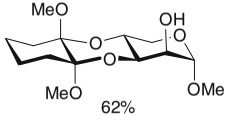
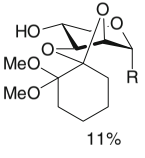
Scheme 1 Dispiroketal or "dispoke" protection of *trans*-1,2-diols

context, benzylidene acetals are preferentially formed as six-membered dioxane-type acetals (i.e., hexopyranosides form 4,6-*O*-benzylidene derivatives), whereas isopropylidene acetals are more stable as five-membered dioxolane acetals formed on vicinal *cis*-diols.

In contrast, selective protection of 1,2-diequatorial diols in sugars, in the presence of other hydroxyl group combinations, had proved to be an especially difficult task. Until a few years ago, the protection could only be achieved using disiloxanylidene acetals [24]. However, this type of protecting group is frequently not sufficiently stable as to withstand normal glycosylation conditions. The final solution to the protection of *trans*-1,2-diols [25] was provided in the 1990s by Ley and co-workers with the development of 1,2-diacetals (Fig. 1).

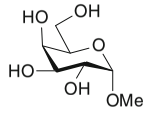
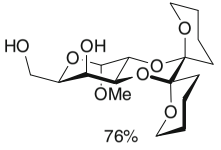
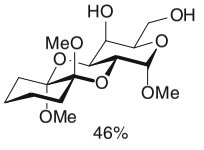
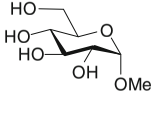
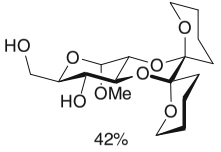
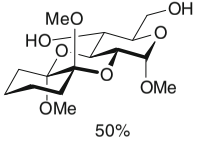
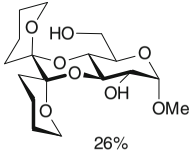
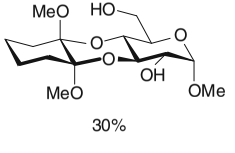
In 1992, Ley and co-workers demonstrated the inherent selectivity of 3.3′,4.4′-tetrahydro-6,6′-bis-2*H*-pyran (bis-DHP) **1** for *trans* diequatorial vicinal diols in polyol systems in carbohydrate derivatives (Scheme 1) [26]. In a typical experiment, the carbohydrate polyol was reacted with an excess of bis-DHP **1** in refluxing chloroform and in the presence of a catalytic amount of camphorsulfonic acid to afford the corresponding dispiroketal. For representative examples see Table 1. The protection process proceeds in moderate to good yields and gives diequatorial diol protection as the major outcome in all cases. In a few cases some *cis*-diol protection was noticed as a minor process when steric interactions were of lesser magnitude.

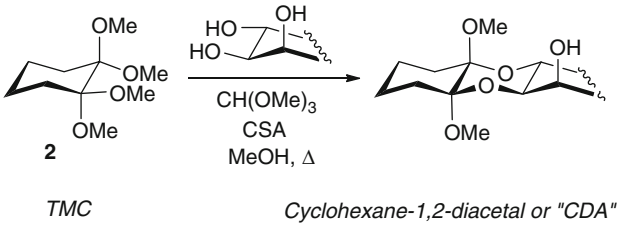
Table 1 Synthesis of CDA- and dispoke-protected pyranosides

Sugar	"Dispoke"		CDA	
	1,2-*trans*-Diol-protected	1,2-*cis*-Diol-protected	1,2-*trans*-Diol-protected	1,2-*cis*-Diol-protected
 D-*manno*	 R = OMe 0% R = SEt 36%	–	 R = OMe 48% R = SEt 53%	 R = OMe 10% R = SEt 11%
 L-*rhamno*	 47%	 32%	 74%	 8%
 D-*lyxo*	 45%	–	 62%	 11%

(*continued*)

Table 1 (continued)

Sugar	"Dispoke"		CDA	
	1,2-*trans*-Diol-protected	1,2-*cis*-Diol-protected	1,2-*trans*-Diol-protected	1,2-*cis*-Diol-protected
 D-*galacto*	 76%	–	 46%	
 D-*gluco*	 42% +		 50% +	
	 26%	–	 30%	–



Scheme 2 Cyclohexane-1,2-diacetal or "CDA" protection

It was also shown that the presence of lipophilic groups in a carbohydrate derivative results in higher yields of dispiroketal products, thus reflecting the greater solubility of the compounds in $CHCl_3$ [27].

It was found, however, that this dispiroketal chemistry was not satisfactory in all cases. Although the exclusive formation of only one isomer was often observed, the result with important *manno*- and *rhamno*-type sugars was less satisfactory (Table 1). The low yields and the lack of regioselectivity observed were attributed to the scarce solubility of these compounds in chloroform and to the instability of bis-DHP **1** when heated over prolonged time periods.

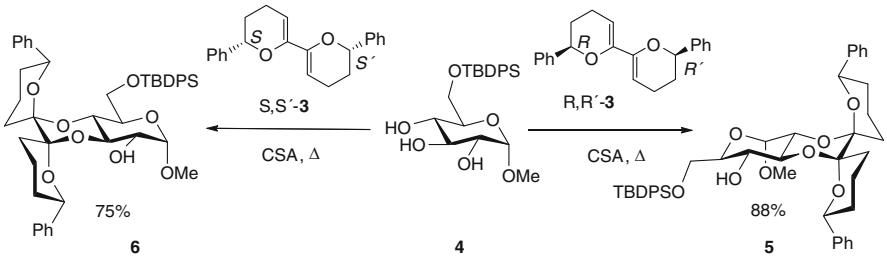
To overcome these problems, 1,1,2,2-tetramethoxycyclohexane (TMC) **2** was developed as an alternative to bis-DHP for carbohydrate protection (Scheme 2) [28]. Initially, TMC **2** was easily prepared from inexpensive cyclohexane-1,2-dione although it is currently commercially available. TMC **2** allows the use of more polar solvents, such as methanol, and cyclohexane-1,2-diacetals (CDA) are obtained in higher yields than the corresponding dispiroketals.

In a typical experiment, the carbohydrate derivative was reacted with TMC **2** in boiling methanol containing some trimethylorthoformate and a catalytic amount of camphorsulfonic acid. In all cases the corresponding CDA, often highly crystalline, were formed as the major product. Table 1 summarizes selected examples of CDA formation in comparison with the related dispoke protection.

Interestingly, each protecting group appears to favor certain monosaccharide configurations over others, and therefore both methods are complementary. For example, CDA protection is superior in the *manno*-configurated pyranosides, whereas dispoke protection is the method of choice for sugars having the *galacto*-configuration.

The high regio- and diastereo-selectivity demonstrated in the protection of *trans*-1,2-diols as 1,2-diacetals (dispoke or CDA) can be attributed to a combination of two factors. First, the formation of the less sterically demanding *trans*-ring junction and, second the stabilization by anomeric effects [29, 30] leading to the most stable 1,4-dioxane derivative that has two oxygen atoms located in the axial positions of the 1,4-dioxane ring. Similar protection for *cis*-1,2-diols would lead to derivatives that would suffer steric hindrance and a flattening of the central dioxane ring, reducing the magnitude of anomeric stabilization of both spirocenters and thereby augmenting the unfavorable steric effects.

The efficiency of the CDA or dispoke strategies was, however, hampered by the lack of regioselection in D-*gluco* derivatives, owing to the presence of two 1,2-*trans*



Scheme 3 Chiral recognition in the regioselective protection of D-glucopyranose derivatives

diequatorial diol arrangements. To overcome this regiochemical challenge an original solution, based on the chiral recognition of enantiomeric pairs of *trans*-diols by a phenyl-substituted chiral bis-DHP **3**, was developed. Thus, chiral bis-dihydropyrans were successfully used to discriminate between the enantiomeric pairs of *trans*-1,2-diols present in D-*gluco* substrates [31, 32].

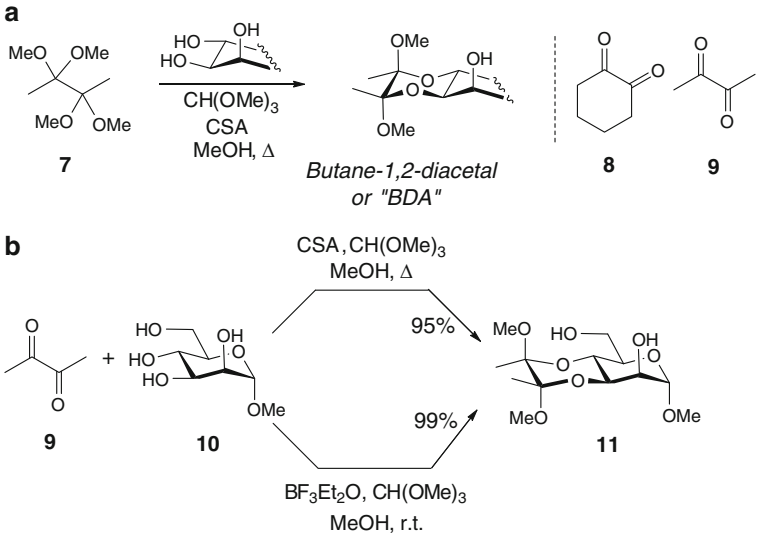
Thus, when methyl 6-*O*-*tert*-butyldiphenylsilyl-α-methyl glucoside **4** (Scheme 3) was reacted with the R,R′-isomer of diphenyl-substituted dihydropyran *R,R′*-**3**, only one product was isolated, the corresponding 2,3-protected dispiroketal **5**. Conversely, the use of the enantiomer *S,S′*-**3** resulted in the formation the 3,4-protected dispiroketal **6**. This process, once again, benefits from the preference of (phenyl) substituents to adopt an equatorial disposition while maintaining maximum anomeric stabilization at the spiro centers. The most thermodynamically stable products are formed. No mixed products were detected since these would involve serious steric clashes, owing to the loss of anomeric effects and placement of phenyl group side chains in axial position. The phenyl substituents in these dihydropyrans not only control the spirocyclization event, they also facilitate the hydrogenolytic removal of the ensuing tricyclic system.

Later, it was shown that 2,2,3,3-tetramethoxybutane (TMB) **7** [33] is also an efficient selective protecting group for diequatorial 1,2-diols, providing butane-2,3 diacetals (BDA) in good to excellent yields (Scheme 4a). Soon after, TMC **2** and TMB **7** were replaced by their corresponding synthetic precursors cyclohexene-1,2-dione **8** and butane-2,3-dione **9** [34, 35].

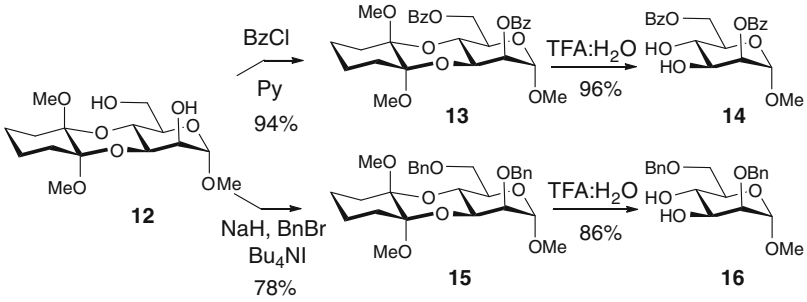
The use of 1,2-diketones avoids the need for the preparation of the tetramethoxydiacetal reagent and represents an overall simplification of the process. Reaction conditions using Lewis acids at room temperature have also been investigated [35]. For example, it was found that reaction of butane-2,3-dione with methyl α-D-mannopyranoside **10** occurred at room temperature in the presence of $BF_3{\cdot}Et_2O$, providing better yields (near quantitative) than the standard protic conditions (Scheme 4b).

The stability of these 1,2-diacetal protected monosaccharides to standard reactions, such as silylation, benzylation or benzoylation, was investigated. Cleavage of the 1,2-diacetal protective groups is readily achieved under acidic conditions (aqueous trifluoroacetic) that do not tamper with glycosidic linkages (Scheme 5) [36].

According to these studies, 1,2-diacetals provide new opportunities for rapid selective protection of monosaccharides. This strategy can be applied to a wide



Scheme 4 BDA protection and direct preparation of diacetals from 1,2-diketones



Scheme 5 Tolerance and cleavage of 1,2-diacetals

variety of monosaccharide precursors, and is compatible with usually performed synthetic manipulations. On the other hand, the selective protection of vicinal diequatorial diol relationships complements the classical chemistry of cyclic acetals and as such greatly improves the scope of monosaccharide manipulations.

All this chemistry sets the basis for the concise assembly of versatile building blocks in oligosaccharide synthesis.

But, more importantly, the synthetic applications of 1,2-diacetals proved not to be limited to the selective protection of *trans*-diequatorial-1,2-diols alone. In the following sections we will illustrate how these protective groups have an effect on the next level of carbohydrate architecture: 1,2-acetals of sugar derivatives can have a dramatic effect on controlling the rates of coupling reactions in oligosaccharide synthesis.

3 Reactivity Tuning in Oligosaccharide Synthesis

3.1 Influence of Protecting Group on Donor Reactivity: Electronic Effects

The idea that protecting groups may affect the reactivity of glycosides in coupling reactions is well established. Paulsen noted a significant influence of the protecting groups situated on a glycosyl halide on the rate of hydrolysis of the anomeric position [37, 38]. However, these ideas had not been synthetically exploited until 1988, when Fraser-Reid and co-workers observed similar effects in the glycosidation of *n*-pentenyl glycosides [39], and were able to develop a new strategy for oligosaccharide synthesis based on them [40]. The key observation in this protocol was that when two glycosyl donors of different reactivity were treated with just one equivalent of promoter, only the most reactive glycosyl donor in the system was activated and could glycosylate the less reactive unit. Such a reaction profile arose because activation of the glycosyl donor, by reaction with the promoter, is reversible and rapid compared with the subsequent steps leading to glycoside formation. (Reaction with the promoter may in fact not be reversible. Transfer of the promoting agent may instead occur directly between activated and unactivated donor systems in a bimolecular reaction. The effect is however the same as if the promotion reaction were reversible.) The inherent reactivity of the glycosyl donor is thus revealed in the final product distribution. If the acceptor functionality is located on the less reactive component, selective glycosylation can occur, leading to a specific disaccharide. Further glycosylation of the ensuing disaccharide could then be accomplished by the use of a more powerful anomeric activator, or via functional group interconversion (Fig. 2).

According to Fraser-Reid et al., the reactivity of a glycosyl donor can be regulated by the flanking protecting group at C-2, owing to stereoelectronic effects (e.g., ether = armed, ester = disarmed). The origin of this effect lies in the destabilizing effect of the exocyclic ring oxygen on the development of a positive charge

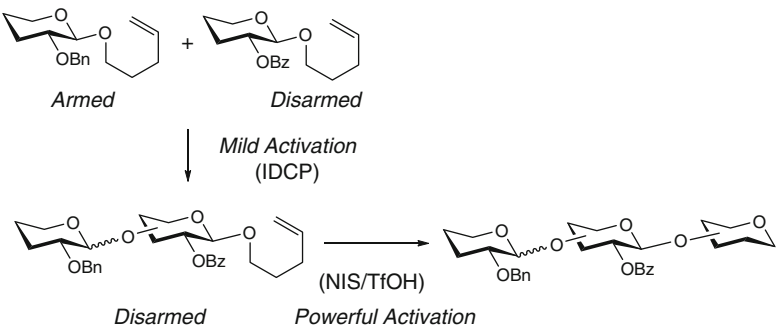


Fig. 2 Fraser-Reid's armed–disarmed strategy

at the endocyclic oxygen. An ester protecting group, owing to its electron-withdrawing nature, increases the electronegativity of the oxygen bearing it thereby increasing the deactivating effect of that oxygen. The deactivation effect translates to increased resistance to incipient oxonium-ion formation, i.e., the leaving group is stabilized. In contrast, a benzyl group does not disturb the oxygen in the same manner (not being electron-withdrawing) and thus the fugacity of the leaving group is untempered.

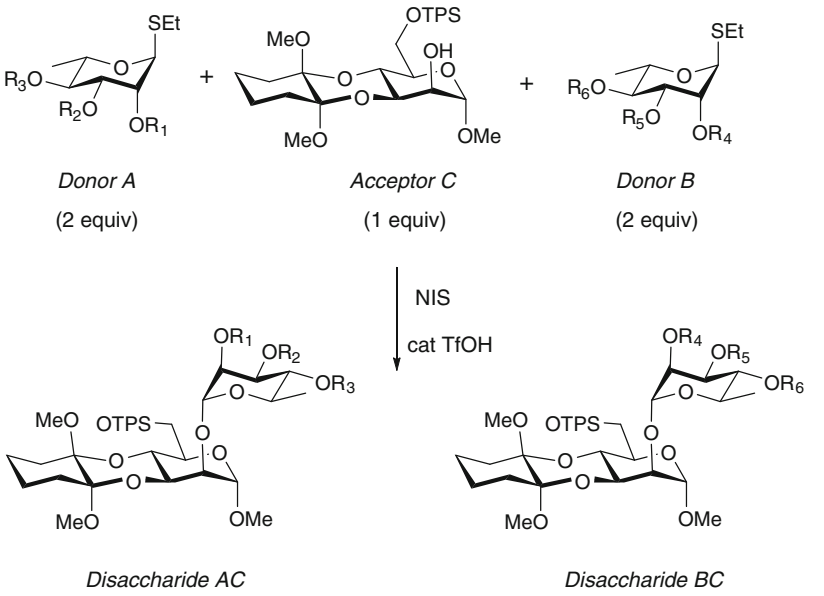
Although initially developed for *n*-pentenyl glycosides, this concept has proven to be of a general nature and it has been exploited in chemoselective glycosidations of ethyl thioglycosides [41], glycals [42], glycosyl fluorides [43], selenoglycosides [44], phosphoroamidates [45], substituted thioformimidates [46], and *S*-benzoxazolyl and *S*-thiazolinyl glycosides [47, 48]. More recently, Demchenko and coworkers have expanded the armed–disarmed concept by reporting that mixed protecting group patterns can also affect the glycosyl donor reactivity [49–51], while Bols and coworkers reported conformationally armed glycosyl donors (or so-called super-armed) [52, 53].

3.2 Relative Reactivities of Glycosyl Donors

This approach to selective oligosaccharide assembly by use of designed, chemoselective glycosidation sequences requires a change in the perception of the reactivity of glycosyl donors as a continuum rather than the systems being divided simply into reactive or unreactive groups. In fact, many factors affect the reactivity of a given system: the protecting groups, the anomeric leaving group, and the nature and stereochemistry of the monosaccharide skeleton. Therefore, attempts to classify, and even predict, the outcome of a glycosylation reaction (or a sequence) have led to the development of approaches to quantify the reactivity of building blocks.

Along this line, Ley and co-workers investigated this effect for the first time by quantifying the individual contributions that a variety of protecting groups at different hydroxyl positions of thioglycosyl donors derived from rhamnose and mannose, caused in their reactivity [54, 55].

Accordingly, two differently protected glycosyl donors were made to compete for a standard glycosyl acceptor (Scheme 6). The carbohydrate acceptor was specifically chosen to simulate actual glycosylation conditions, because the steric profile of the alcohol can influence reaction kinetics through variations in its nucleophilicity. Each donor is present in excess so that as the reaction progresses the availability of each remains high. The reaction is complete when all the acceptor has reacted and the product ratio reflects the inherent reactivity of the two glycosyl donors. The choice of rhamnose as the model system greatly simplifies the initial trial study since the glycosylations are highly alpha-selective and hence only two products are formed in the competition reaction. Furthermore, since rhamnose has only three hydroxyl groups, only eight combinations of benzyl and benzoyl protected systems needed to be prepared.



Scheme 6 Competition experiments for thiorhamnosides

Table 2 Selected results from competition experiments

Donor A	Donor B	Quotient AC/BC
Tri-*O*-Bn	3-*O*-Bz	3.1
Tri-*O*-Bn	4-*O*-Bz	8.9
Tri-*O*-Bn	2-*O*-Bz	26.6
2,4-Di-*O*-Bz	Tri-*O*-Bz	2.5
2,3-Di-*O*-Bz	Tri-*O*-Bz	13.0
3,4-Di-*O*-Bz	Tri-*O*-Bz	24.2

Thus, combinations of benzyl and benzoyl protecting group patterns were prepared and the ratio of disaccharides AC and BC was determined by ^{1}H NMR, thereby providing a quantitative reactivity analysis of the various protecting group patterns (Table 2). It was observed that the amount of electronic deactivation arising from a benzoyl protecting group varied with its proximity to the ring oxygen/reacting center, the order of importance being C2 > C4 > C3.

In order to convert the data from these competition reactions into a more usable form, a "deactivation factor" (DF) was defined for a given protecting group as the reduction of the glycosylation rate by the presence of that group with respect to the fully benzylated compound. As a simplifying approximation, the individual contribution from each protecting group was treated as being independent of any other protecting groups in the system. This approximation does enable semi-quantitative prediction of donor reactivities by multiplication of the quotients or DFs for each position. For example, the 2,4-di-*O*-benzoyl-2-*O*-benzyl glycosyl donor is predicted to have a total deactivation of $26.6 \times 8.9 = 236.7$ whilst a 2,3,4-tri-*O*-benzoyl

donor is predicted to have a total deactivation of 26.6 × 3.1 × 8.9 = 733.9. The competition experiment between them should therefore give a quotient of 733.9/236.7 = 3.1 which is close to the observed value of 2.5 (Table 2). The concordance of the predicted result with the observed value is indicative of the usefulness of this approximation.

A similar set of competition experiments was performed for thiomannoside donors. Compared to rhamnose, the relative importance of the various positions remained unchanged, but C6 emerged as the most influential after C2. Further tuning could be achieved by varying the electronic nature of the benzoyl group by making it more electron rich (*p*-methoxy benzoyl) or more electron deficient (*p*-nitro benzoyl).

Wong and co-workers also developed a similar competition strategy to characterize and quantify the influence in the reactivity of *p*-methylphenyl thioglycoside donors of different protecting groups and structural effects [56, 57]. During this study a vast database of relative reactivity values (RRVs) was assembled, and the collected data were compiled into a predictive computer program called Optimer. The determination of RRVs was performed under standard reaction conditions using methanol as the acceptor alcohol, and *p*-tolyl thioglycoside donors in the presence of NIS/TfOH as the promoter system. It was noted that optimal chemoselective couplings generally occurred when there was a large difference in the RRVs. Wong et al. also demonstrated that the deactivating power of the different electron-withdrawing groups investigated followed the order $-N_3$ > –OAcCl > –NPhth > –OBz > –NHTroc > –OBn.

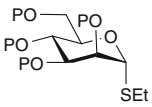
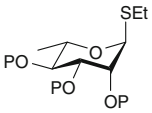
More recently, other studies aiming to quantify relative reactivities of other glycosyl donors have appeared [58–60].

3.3 *Influence of Protecting Group on Donor Reactivity: Torsional Effects*

In 1991, Fraser-Reid and co-workers reported that anomeric deactivation could also be achieved when a cyclic acetal group was attached to the pyranose ring. They suggested that the *trans* fusion induced by the acetal restricts the ring flexibility of the molecule, thereby making it increasingly difficult to achieve the requisite planar geometry (about the C-2–C-1–O-5–C-5 atoms) in the half-chair transition state [61, 62]. This modulation of reactivity by the benzylidene acetal group was termed "torsional disarmament". In further mechanistic probing, Bols and co-workers proposed that the origin of the deactivation of an acetal group is not exclusively "torsional" but is also due to a stereoelectronic effect associated with locking the hydroxymethyl group in the *tg* conformation (charge–dipole interactions) [63].

The concept of torsional deactivation was expanded further by Ley and co-workers in their exploration of 1,2-diacetal systems. The acetal and ketal groups, when fused to carbohydrate coupling donors, impart rigidity into the structure, making more difficult the conformational changes required for glycosylation, hence the reactivity of the sugar is diminished.

Table 3 Standardized DFs for non-Bn protecting groups on thiomannosides and thiorhamnosides

Sugar	Position of non-Bn group	Deactivation factor (DF)
	3-Bz	1.1
	4-Bz	5.0
	3,4-CDA	13.9
	3,4-Dispoke	14.9
	3,4-BDA	16.5
	2,Bz	33.6
	3-Bz	2,3
	4-Bz	9.0
	3,4-CDA	27.0
	2-Bz	36.5

With the aim of calculating the DF for the 1,2-diacetal protecting groups, a set of competition experiments related to those shown in Scheme 6 was performed [54, 55].

It was found that the reactivity of glycosyl donors protected with dispoke, CDA, or BDA groups had a range in reactivity between the fully benzylated and fully benzoylated system, which implies that 1,2-diacetal protected thioglycosides might be regarded as semidisarmed substrates.

Furthermore, in mannose and rhamnose systems, the protection of the C3 and C4 positions with a CDA group produced a greater deactivation effect than when these two positions were protected with benzoyl groups. The reactivity of CDA was also compared with dispoke and BDA systems, and it was found that the reactivity differences between these systems were small. However indications are that deactivating effects are in the order BDA > dispoke > CDA (see Table 3). The influence of protecting groups on the reactivity does however change between monosaccharide types. This probably reflects changes in the character of the transition state leading to glycosylation.

4 Reactivity Tuning of Thioethyl Glycosides

The perception that 1,2-diacetal protected sugars exhibit an intermediate reactivity in glycosylation reactions allowed Ley and co-workers to deliver a new range of reactivity partners for oligosaccharide synthesis (Fig. 3). Based on this concept, they anticipated that the fusion of a diacetal to a sugar derivative would provide a tunable element to control reactivity during the oligosaccharide coupling process.

Owing to the torsional strain imparted by the presence of a 1,2-diacetal fused to the carbohydrate ring, one could expect these donors to be less reactive than the more flexible per-benzylated derivatives during a glycosylation process. If, in addition, the acceptor functionality is located in the 1,2-diacetal containing building block, selective glycosylation could take place, leading to a specific disaccharide. Glycosylation of the ensuing disaccharide could then be accomplished by further activation and coupling with the third acceptor to give a trisaccharide derivative.

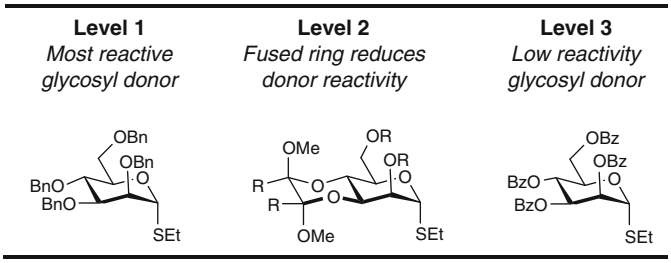


Fig. 3 Three levels of anomeric reactivity in thioethyl glycosides

4.1 Dispoke-Mediated Reactivity Tuning

According to this concept, in 1993, Ley and co-workers reported the use of the three levels of anomeric reactivity in thioglycosides for the preparation of the protected pseudopentasaccharide unit common to the variant surface glycoprotein of *Trypanosoma brucei* (Scheme 7) [64].

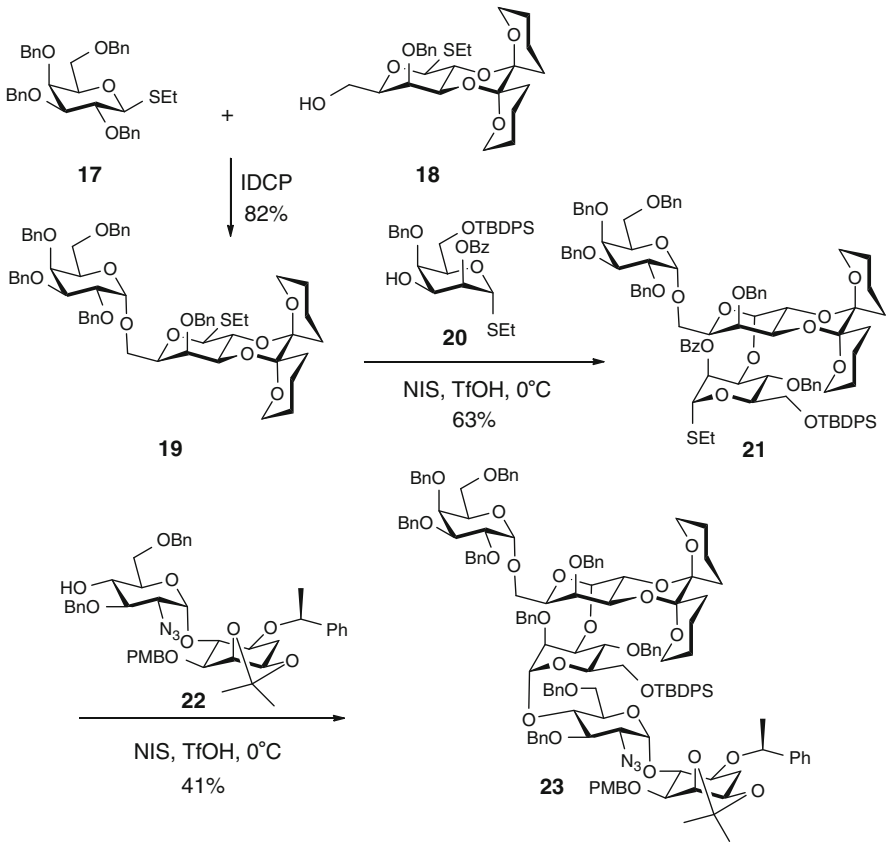
Thus, iodonium dicollidine perchlorate (IDCP)-mediated chemoselective glycosylation of the benzylated thioglycosyl donor **17** with detuned dispiroketal-protected acceptor **18** produced the disaccharide **19** in excellent yield (82%, $\alpha/\beta = 5{:}2$). This disaccharide could then chemoselectively glycosylate an electronically deactivated manno-acceptor **20** (benzoyl substitution at C-2) with the use of the more powerful activator NIS/TfOH. Although the ensuing trisaccharide **21** is deactivated by ester substitution it was still capable of glycosylating an inositol containing glucosyl acceptor **22** to provide pentasaccharide **23**, which after deprotection is a component of the glycosylphosphatidylinositol (GPI) anchor from *T. brucei* (see below).

4.2 CDA-Mediated Reactivity Tuning

This work served to demonstrate how the product resulting from a glycosylation reaction could be used directly in the next coupling reaction without any functional group interconversion (e.g., **19** → **21** or **21** → **23**). This property opened the way for omitting the isolation steps and performing reactivity-tuning based one-pot strategies.

The term one-pot glycosylation [65] refers to a process in which several glycosyl donors are allowed to react sequentially in the same flask, resulting in a single main oligosaccharide product. Thus, in this approach, the most reactive donor (armed) could be condensed with the less reactive donor (semidisarmed) to provide a new saccharide, which could subsequently glycosylate the least reactive donor (disarmed).

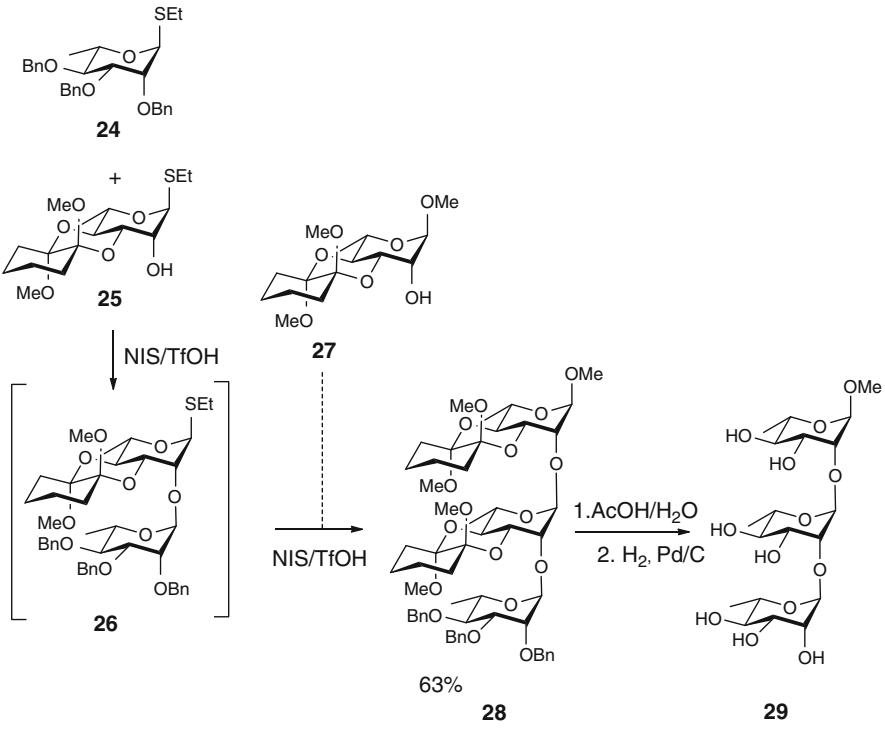
Following this strategy and using CDA-protected rhamnosides as precursors, Ley and co-workers reported, in 1994, the synthesis of the trisaccharide unit found



Scheme 7 Dispoke-mediated synthesis of a pseudopentasaccharide unit of GPI

in the common polysaccharide antigen Group B *Streptococci* (Scheme 8) [66]. Thus, a perbenzylated thioethyl glycoside **24** was selectively activated with *N*-iodosuccinimide (NIS) and catalytic triflic acid in the presence of a CDA-detuned acceptor **25**. The in situ obtained disaccharide **26** was then coupled, without isolation, with the final methyl glycoside acceptor **27**, thus assembling the desired trisaccharide **28** in one reaction vessel and in 63% isolated yield. No homocoupling product from the thioethyl acceptor was observed. Finally, simple deprotection furnished the target trirhamnoside **29** in excellent overall yield. It should be noted that no cleavage of the trisaccharide occurs during the final hydrolytic removal of the CDA by $AcOH/H_2O$ treatment. This is an important feature of the reaction, especially for the preparation of more complex systems.

This one-pot chemoselective coupling sequence complements other methods in the literature, e.g., those using orthogonal leaving groups, but provides the added bonus of being able to be combined with these alternative methods to prepare much larger oligosaccharide arrays in a single reaction pot (see below).



Scheme 8 One-pot synthesis of the trisaccharide unit of antigen group B *Streptococci*

5 Reactivity Tuning of Thioethyl and Selenophenyl Glycosides

Having established principles for one-pot coupling reactions using torsional effects, these ideas were extended by Ley's group by merging this approach with the use of different leaving groups at the anomeric position.

The concept was based upon the ability to control the reactivity of thioethyl and selenophenyl glycosyl donors by careful choice of anomeric substituent and hydroxyl protecting groups. Selenoglycosides are more reactive than their sulfur analogs and therefore four different levels of reactivity can be attained using only one promoter system (NIS/TfOH) (Fig. 4). As iodonium transfer to the sulfur or selenium atom is rapid and reversible under the conditions of the reaction, only the most reactive glycosyl donor in the mixture is activated when one equivalent of NIS is used. Sequential addition of NIS and acceptor units thus allows the rapid, controlled synthesis of complex carbohydrate structures.

An example is illustrated in Scheme 9 by the preparation of the model tetrasaccharide **36** [67]. The design of the synthesis was such that the protecting groups and the anomeric substituent of the building blocks would induce a decrease in reactivity of the donor functionality from the non-reducing to the reducing end of

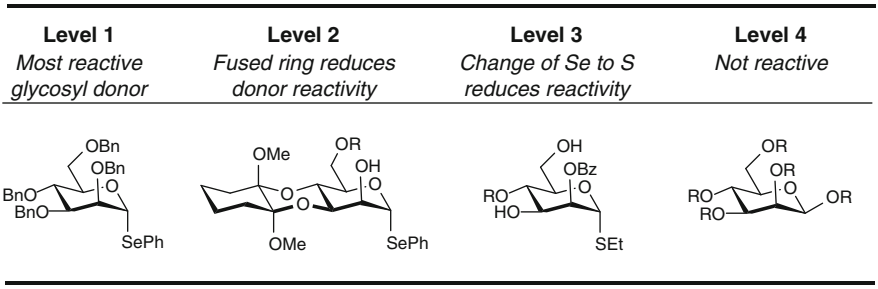
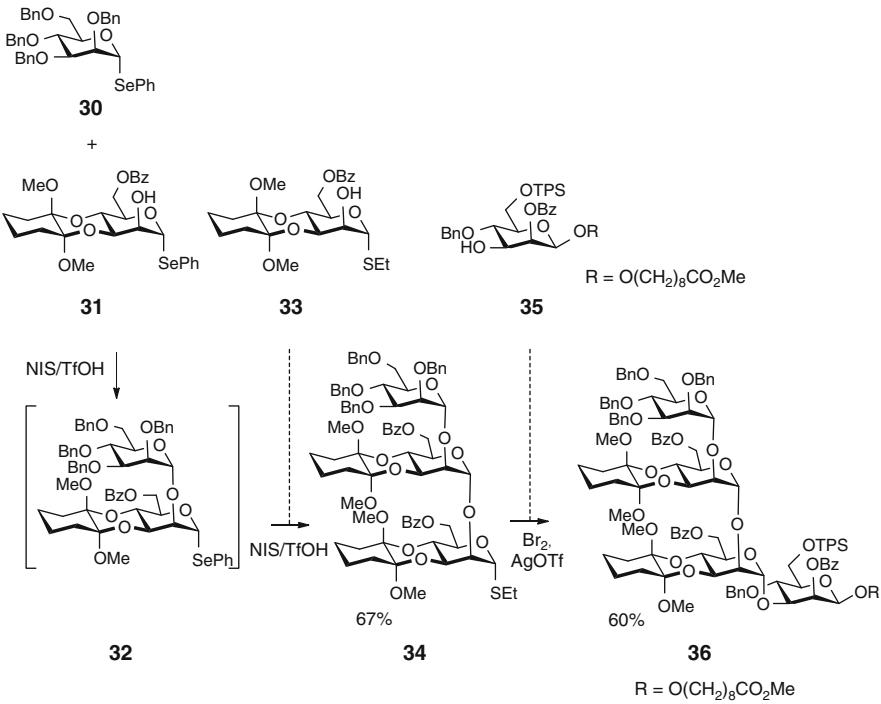


Fig. 4 Four levels of anomeric reactivity by using thioethyl and selenophenyl glycosides



Scheme 9 One-pot preparation of a tetrasaccharide **36** by reactivity tuning of thioethyl and selenophenyl glycosides

the tetrasaccharide. The key to the strategy is fragment **31**, which contains both donor and acceptor functionalities. In the first reaction selenoglycosides **30** and **31** are mixed and one equivalent of NIS added. In this process, detuned phenyl seleno donor **31** is the less reactive glycosyl donor, and hence armed **30** is activated and trapped with the free hydroxyl of **31** to give the disaccharide **32**. In the second reaction, the disaccharide **32** is mixed with thioglycoside **33** and a further

equivalent of NIS added. In this case the phenyl seleno donor functionality of **32** is more reactive and so the disaccharide is selectively activated and trapped with the hydroxyl of **33** to give the trisaccharide **34**. Although the ensuing thioethyl trisaccharide **34** is now very deactivated by both the CDA and the C-6 benzoyl substituent, it can be persuaded to react with Br_2 in the presence of silver triflate. The presumed bromide intermediate can then be coupled with a fourth monomeric building block **35** to give the tetrasaccharide **36**.

5.1 Synthesis of the Nonamannan Residue of gp-120

The reactivity tuning one-pot synthesis of this tetrasaccharide set the stage for Ley and co-workers to tackle more challenging situations. That was the case for high-mannose-type oligosaccharides, which are ubiquitous in nature [68–70]. They are a member of the N-linked family of carbohydrates which are conjugated to glycoproteins via an *N*-acetyl-glucosamine unit to the amide group of an asparagine residue on the polypeptide backbone. In particular 29 different N-linked oligosaccharides are present on the envelope glycoprotein gp120 of the human immunodeficiency virus (HIV), which is known to bind with high affinity to human T4 lymphocytes causing AIDS (Fig. 5) [71]. The glycans on the viral envelope of this protein are possible targets for immunotherapy and for vaccine-development [72–79].

Earlier studies had indicated that the two *N*-acetylglucosamine residues of gp-120 were not essential for specific binding of the mannan moiety to target

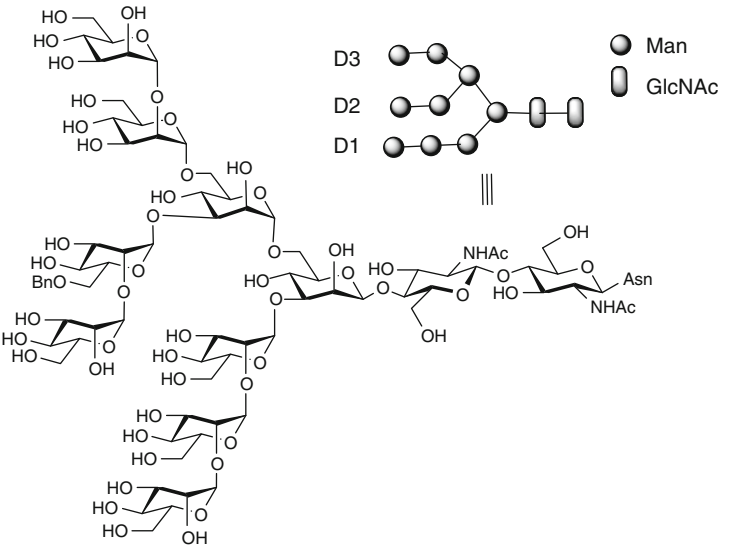


Fig. 5 Nonamannan residue of glycoprotein of HIV gp-120

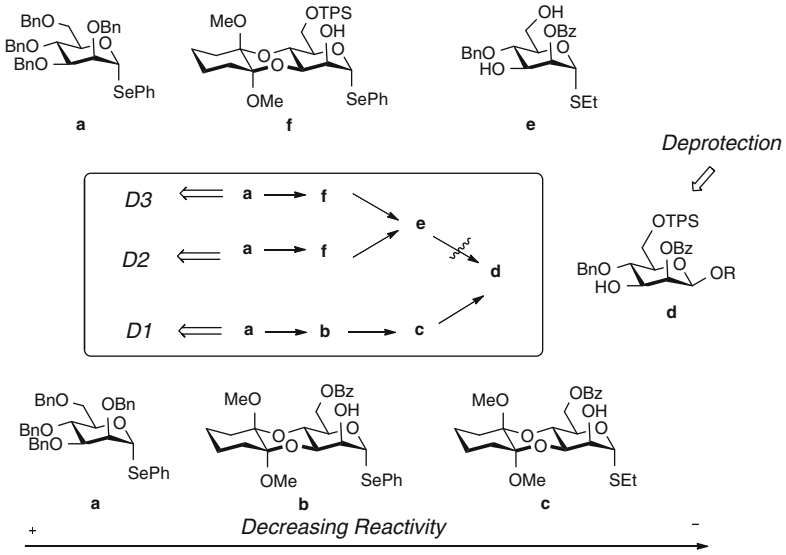
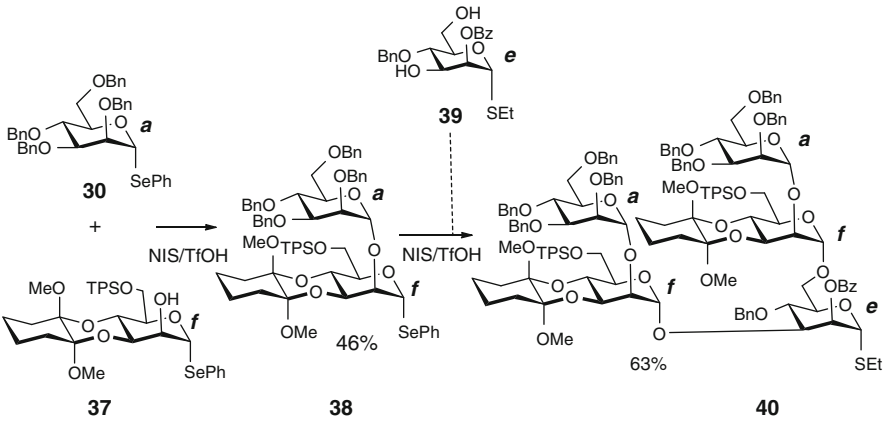


Fig. 6 Building blocks for the synthesis of the nonamannan residue of gp-120

systems, and that they might be replaced with other groups which present the opportunity for linking the glycan to a protein or solid support to give a number of desirable biological tools. Consequently, routes to this high-mannose residue are particularly important.

The strategy designed by Ley's group [80] for the assembly of the target nonasaccharide is outlined in Fig. 6. Four levels of reactivity and six building blocks **a**–**f** were sufficient to assemble the complete nonasaccharide framework and without the need for repeated protecting group manipulation. In fact only one deprotection step, the cleavage of the silyl ether at the primary hydroxyl group in **d** unit, was necessary during the whole assembly of the oligosaccharide. The final coupling was designed to be the glycosylation between a tetrasaccharide acceptor, which represents the so-called D1 arm, with branched pentasaccharide donor, which embodies both the D2 and D3 arms (in Fig. 6 pentasaccharide involving **afeaf** units).

The synthesis of the branched pentasaccharide was found to require a subtle control of the reactivity of the glycosyl donors, and illustrated the need to consider even remote protecting groups in the design of selective glycosylation sequences (Fig. 6). In fact, although the strategy was originally designed to combine five building blocks (**a**–**e**) to prepare the tetrasaccharide **abcd** and the branched pentasaccharide **abeab**, attempts to couple disaccharide **ab** with diol acceptor **e** failed to yield any of the desired product, as **ab** was not sufficiently reactive to give selectivity in the coupling. Clearly a more reactive disaccharide donor was required for the synthesis of this unit and an additional building block **f** had to be considered. Use of the alternative, C6 silyl-protected, monosaccharide building



Scheme 10 Assembly of the pentasaccharide containing D2 and D3 arms

block **f** instead of C6 benzoylated unit **b**, allowed the pentasaccharide to be synthesized with ease, in keeping with the highly deactivating nature of a C6 benzoate.

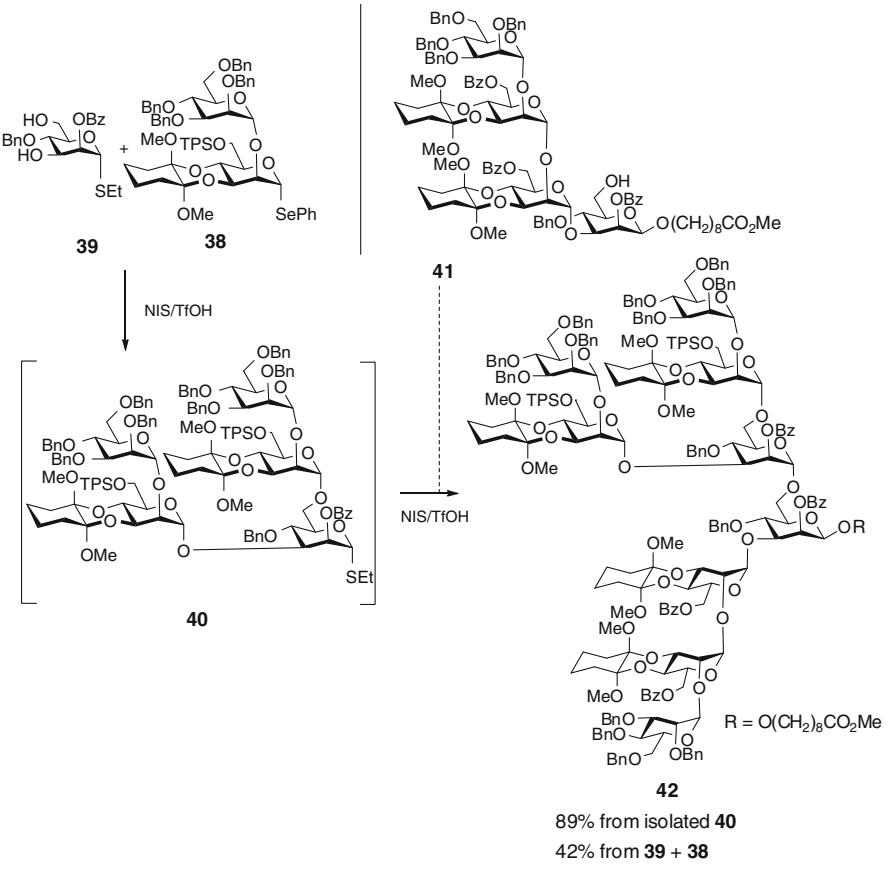
Thus the selective coupling of armed selenophenyl block **30** with acceptor **37** produced the disaccharide **38** in moderate yield (Scheme 10). The branching at the C3 and C6 positions in the pentasaccharide was then achieved by reacting two equivalents of the phenylseleno disaccharide **38** with the thio ethyl deactivated diol **39** to afford the pentasaccharide **40** ready for the final coupling.

Coupling of the pentasaccharide **40** containing the D2 and D3 arms with the tetrasaccharide **41**, whose synthesis was carried out by desilylation of **36** (see Scheme 9), was pleasingly high-yielding giving the target nonasaccharide in 89% yield (Scheme 11). Even more appealing was the fact that, starting from disaccharide **38** and acceptor **39**, the pentasaccharide was formed and, without isolation, directly treated in a one-pot operation with the tetrasaccharidic acceptor **41**, to yield the desired nonasaccharide in an unoptimized 42% yield [81]. This remarkable procedure cut the number of reaction vessels down to five for the assembly of the fully protected nonasaccharide from the monosaccharide building blocks.

Other research groups have also reported total synthesis of GP-120 glycans along with the synthesis of various partial structures (see for example [82–96]).

5.2 *Synthesis of the Glycosylphosphatidylinositol Anchor of* Trypanosoma brucei

Another even more challenging demonstration of the use of 1,2-diacetals in the synthesis of complex carbohydrates was illustrated with the synthesis of the GPI



Scheme 11 One-pot assembly of the nonasaccharide residue of glycoprotein of HIV gp-120

anchor from *T. brucei* [97, 98], the African parasite responsible for human sleeping sickness [99].

GPI anchors not only exist in *T. brucei* but are ubiquitous in eukaryotic cells [100]. Their principal function is to attach proteins to the plasma membrane. Various proteins have been found to be GPI anchored and their role in biological recognition processes has attracted a great deal of attention [101]. GPI anchors attach proteins to membranes via a phosphoethanolamine unit linked to a trimannose–glucosamine–inositol backbone and a hydrophobic lipid that anchors the system to the membrane [102, 103]. The carbohydrate backbone is conserved in all GPI anchors described to date. Nevertheless, various species specific carbohydrate side chains are observed alongside additional phosphoethanolamine units and variations in the lipid unit.

A highly convergent strategy was chosen for Ley and co-workers to minimize the number of manipulations on the growing oligosaccharide (Fig. 7). In their plan

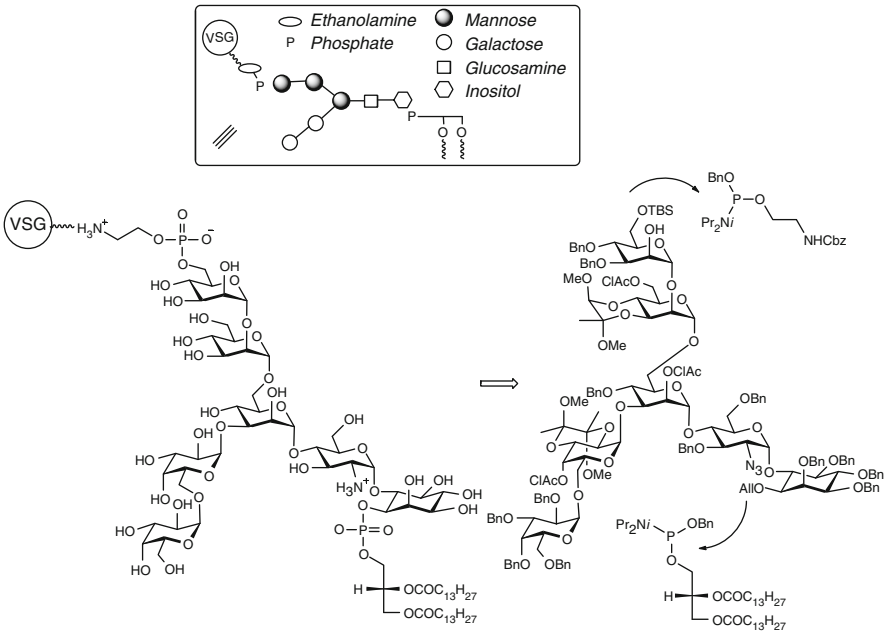


Fig. 7 Structure and retrosynthesis of the GPI anchor of *Trypanosoma brucei*

for making the GPI anchor, the coupling of three major components was envisaged. First, an appropriately protected carbohydrate core had to be constructed which would then be coupled with a phosphorylated ethanolamine derivative and finally assembled by additional coupling with a phosphorylated glycerol unit, containing the two fatty acid side chains. In this chapter we will not comment upon the preparation of the enantiopure glycerol side chain and the inositol fragment using dispiroketal and BDA methodologies, and readers are referred to the full paper [98].

The reactivity-tuning principles discussed earlier using 1,2-diacetals were efficiently exploited to synthesize the GPI carbohydrate core (Fig. 8). It was anticipated that the use of the butane diacetal groups and appropriate anomeric leaving groups would give four levels of descending reactivity and would allow the assembly of the carbohydrate core to take place in just six steps from six building blocks and including only one protecting group manipulation. Thus, mannose phenylselenide **g** and galactose selenide **e** units were expected to be the most reactive glycosyl donors, while the two butane diacetal protected derivatives, **f** and **d**, should be less reactive owing to torsional constraints, and these selenides in turn should both be less reactive than the ethylthio mannose building block **c**. The **ab** unit would be the remaining glucosamine inositol disaccharide fragment functioning as the final glycosyl acceptor.

Accordingly, fully benzylated selenogalactoside **43** was selectively activated with NIS/TMSOTf in the presence of detuned phenylseleno glycoside acceptor **44**

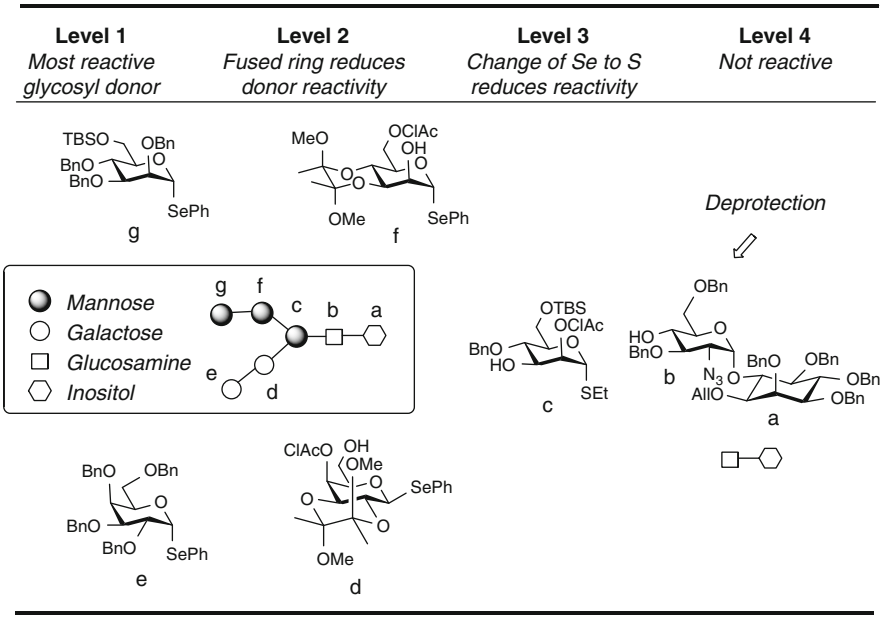


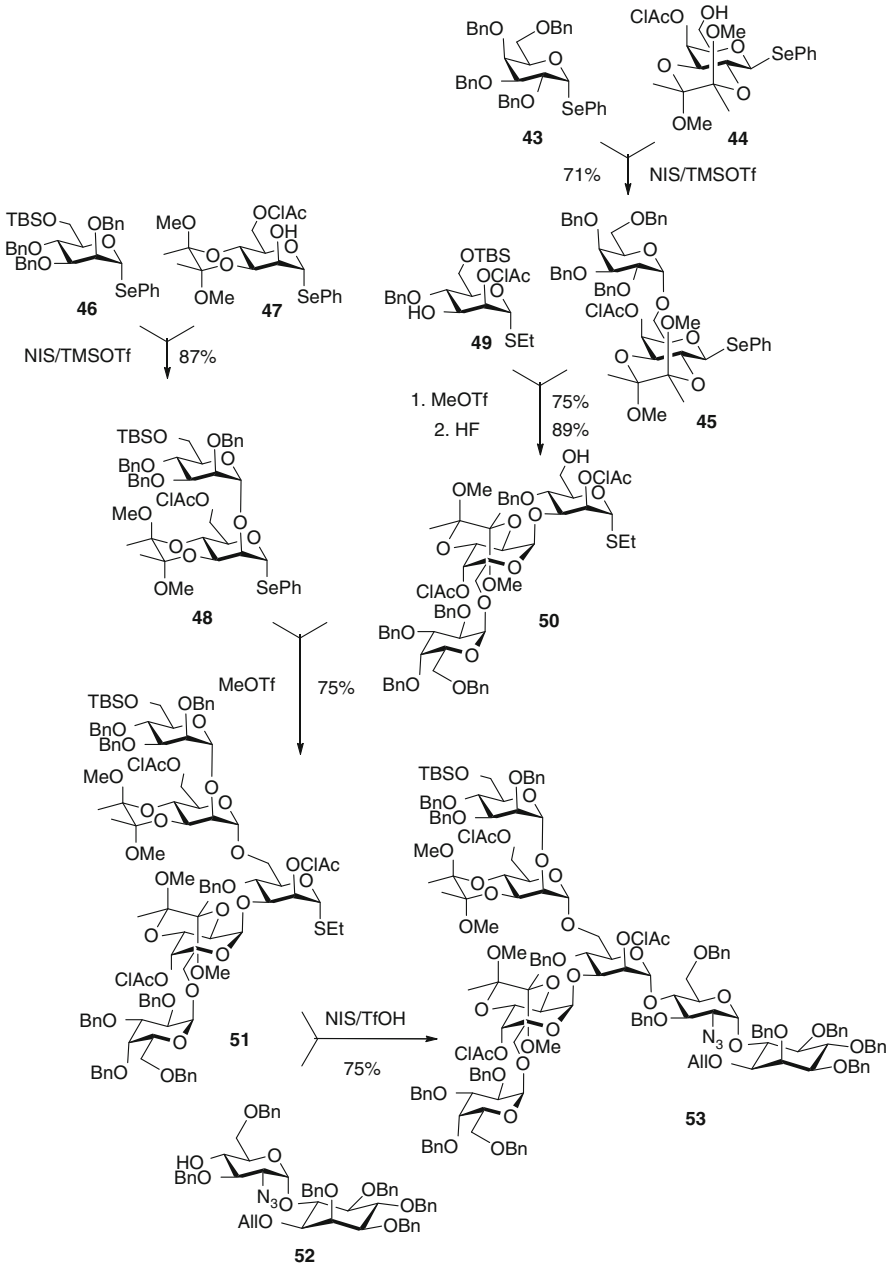
Fig. 8 Building blocks for the synthesis of the carbohydrate core of GPI

to furnish α-linked digalactoside **45** in 71% yield accompanied by the separable β-linked isomer (15%) (Scheme 12). Prior investigations had shown that the combined deactivating effects of the BDA and the chloroacetate group in **44** were required to prevent any homocoupling. Similarly, dimannoside **48** was obtained as one diastereoisomer in 87% yield from armed donor **46** and detuned acceptor **47** under NIS/TMSOTf activation. The central mannoside **49** was then 3-*O*-glycosylated with digalactoside **45** in the presence of MeOTf, and subsequently desilylated with HF, to afford trisaccharide **50** in 67% yield over two steps. It should be noted that, although MeOTf could in principle have also activated the SEt group, it was found in this instance too weak as promoter to activate the considerably electronically disarmed SEt group in compound **49**, and also in trisaccharide **50**. The latter was then 6-*O*-glycosylated with disaccharide donor **48** in the presence of MeOTf to provide pentasaccharide **51** in 75% yield.

Finally, the branched pentasaccharide donor **51** was used to glycosylate disaccharide acceptor **52** in the presence of NIS/TfOH, and produced the corresponding heptasaccharide **53** in 50% yield. The TfOH concentration, and the amount and type of molecular sieves used in this final coupling turned out to be crucial.

It is important to note that the BDA protecting groups are able to survive all the reaction conditions throughout the synthesis.

The remaining steps in the synthesis required selective deprotection and coupling, first of the ethanolamine phosphate side chain and last the acylglyceride



Scheme 12 Synthesis of the glycosyl inositol anchor of *Trypanosoma brucei*

phosphate fragment followed by removal of the protecting groups. All these steps proceeded uneventfully to give the fully unprotected GPI anchor.

This synthesis is a testimony to the usefulness of 1,2-diacetals in oligosaccharide assembly and, obviously, could be adapted to the preparation of many other analogs of GPI anchors.

In this context, studies towards the synthesis of a yeast (*Saccharomyces cerevisiae*) GPI anchor will be discussed later in this chapter. Other total synthesis of GPI anchors have been reported by other research groups [104–116].

6 Reactivity-Tuning of Thioethyl, Selenophenyl, and Fluoro Leaving Groups

As shown earlier in this chapter, seleno- and thio-glycosides have proven to be versatile building blocks for the stereoselective construction of complex oligosaccharides. Owing to their inherent higher reactivity, selenoglycosyl donors are selectively activated in the presence of thioglycosyl donors when one equivalent of promoter (NIS/TfOH) is used.

To introduce even greater flexibility, this pair of glycosyl donors (which are activated with the same promoter system) were combined with glycosyl fluorides, which in turn can be activated over the SePh/SEt pair in the presence of hafnocene dichloride/silver triflate [117]. An example applying such selective-activation strategy is the synthesis of the biantennary heptasaccharide of gp63, the major surface glycoprotein from *Leishmania mexicana amazonensis* (Fig. 9) [118].

Ley and co-workers targeted a heptasaccharide containing a β-linked methoxycarbonyl octyl chain, instead of the di-*N*-acetylchitobiose (GlcNAc(β1-4) GlcNAc) moiety of the natural occurring *N*-glycans. This group would allow

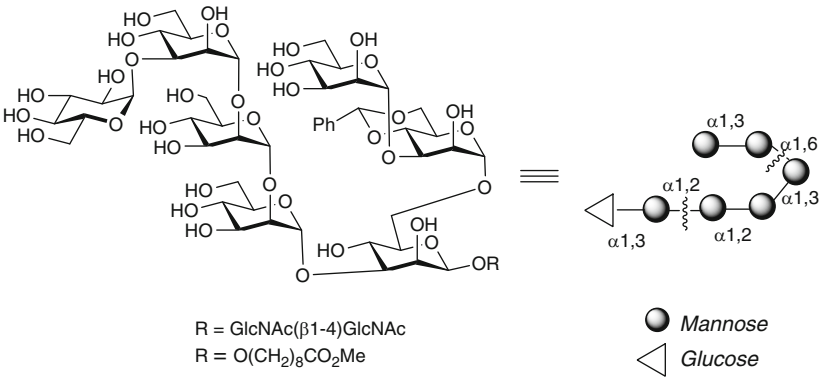


Fig. 9 The heptasaccharide of gp63 of *Leishmania mexicana amazonensis*

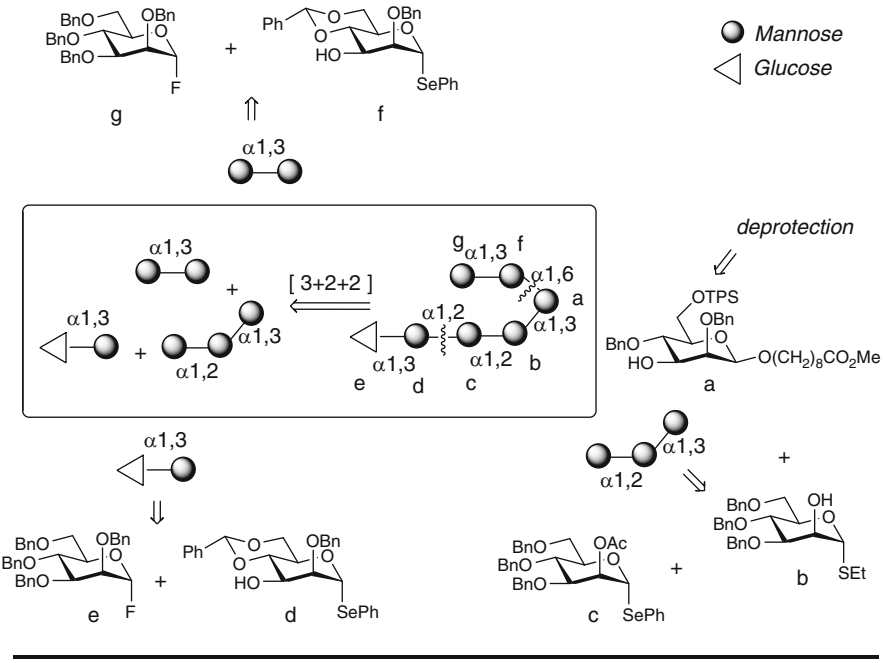


Fig. 10 Building blocks and retrosynthetic analyses for heptasaccharide of *N*-glycans of gp63

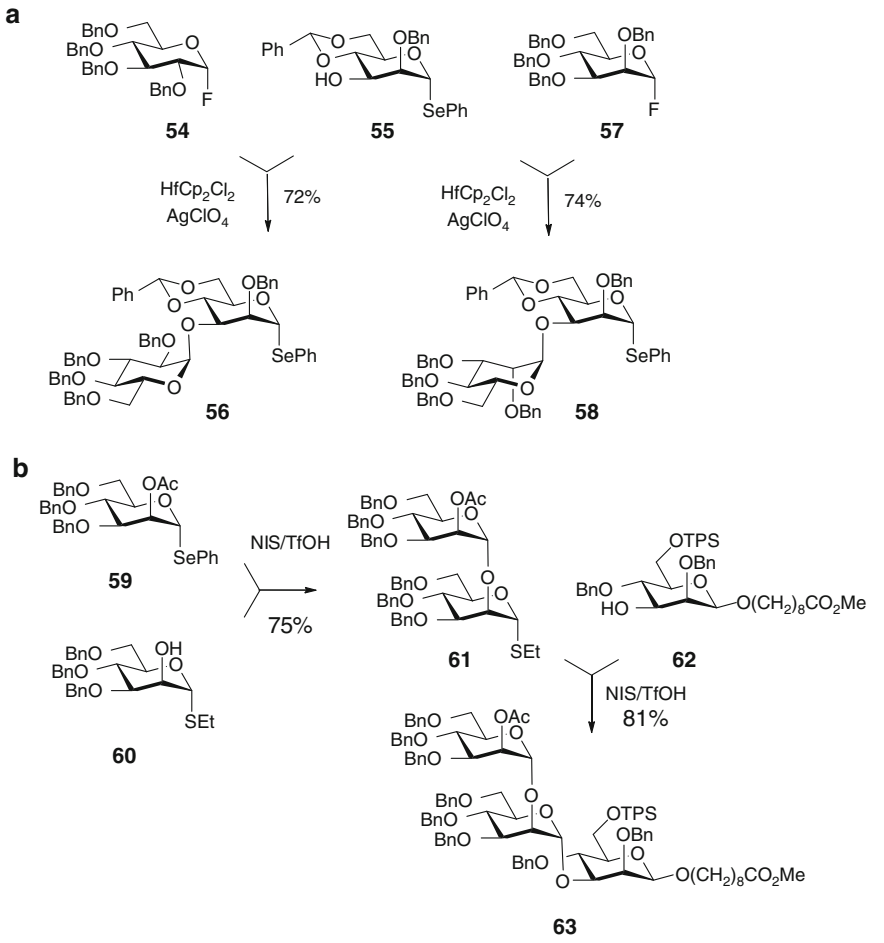
further derivatization of the final glycoconjugates for use in biosynthesis studies and/or preparation of neoglycolipids [119].

The entire synthetic strategy relied on the use of thioethyl, selenophenyl and glycosyl fluoride donors by stepwise addition and selective activation [120]. The synthesis was accomplished by Ley's group in a [2 + 3 + 2] fashion as depicted in Fig. 10.

The assembly began with the preparation of the α-1,3 linked disaccharides **56** and **58** (Scheme 13a). Each of the donors, 2,3,4,6-*O*-benzyl-α-D-mannopyranosyl fluoride **54** and 2,3,4,6-*O*-benzyl-α-D-glucopyranosyl fluoride **57**, upon coupling to the readily available benzylidene protected selenomannoside **55** under the selective agency of $HfCp_2Cl_2$–$AgClO_4$, gave the desired disaccharides **56** and **58**, respectively, as single isomers.

Meanwhile, the assembly of the central trisaccharide **63** was initiated by the selective activation of the more reactive seleno glycosyl donor **59** in the presence of the thioglycosyl donor **60** to provide the corresponding disaccharide **61** in 75% (Scheme 13b). The latter could be used directly as the glycosyl donor for the reaction with the central β-mannoside **62** under NIS/TfOH activation conditions to give the protected trisaccharide **63** in 81% yield on a gram scale.

To complete the construction of the α-1,3-arm of the target compound, standard deacetylation of **63** was followed by glycosidation of the resulting acceptor

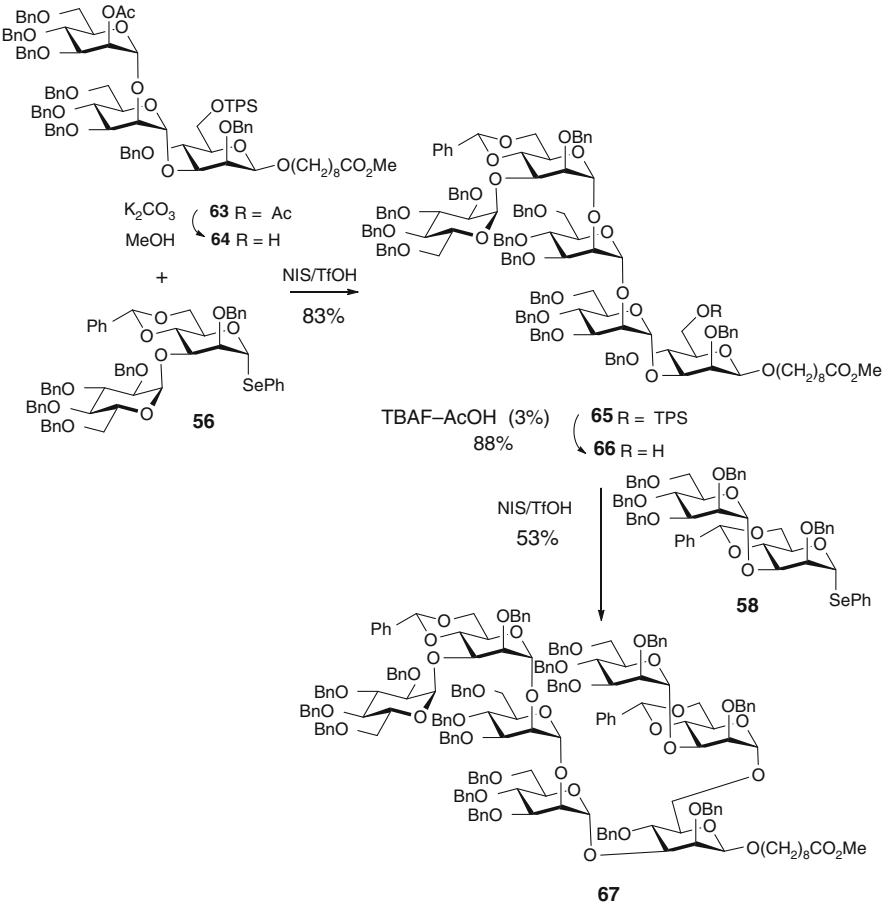


Scheme 13 Selective activation using three leaving groups

saccharide **64**, with the selenophenyl glycoside **56** under NIS–TfOH conditions to yield the desired pentasaccharide **65** in 83% yield (Scheme 14).

Desilylation of the fully protected glycoconjugate **65** was followed by the coupling of the resulting glycosyl acceptor **66** with the seleno glycoside **58** to complete the synthesis of the fully protected target molecule **67**. The moderate yield for the last glycosidation (53%) is acceptable considering the complexity of the product molecule.

Taking advantage of common structural motifs found in all the biantennary mannosaccharides of gp63, the same selective-activation based strategy was applied to the rapid assembly of the whole class of the major surface high mannosides from *L.m. amazonensis*. For full details readers are referred to the original papers [119, 120].



Scheme 14 Synthesis of the heptasaccharide of gp63 of *Leishmania mexicana amazonensis*

6.1 Selective Activation of Thioethyl, Selenophenyl and Fluoro Leaving Groups

The next advance came by combining these selective activation strategies with the concepts of reactivity tuning using 1,2-diacetals. The concept is illustrated in Fig. 11. Set 1 sugars comprise thioethyl and selenophenyl donors capable of activation with iodonium sources, whereas Set 2 sugars form an orthogonal set, with respect to the former, in which the activation may be achieved by hafnocene dichloride/silver triflate as the promoter system. The difference in reactivity between level 1 and level 2 is provided by torsional deactivation due to the appended diacetal protecting group. Anomeric deactivation, obtained by replacing selenium with sulfur, affords level 3.

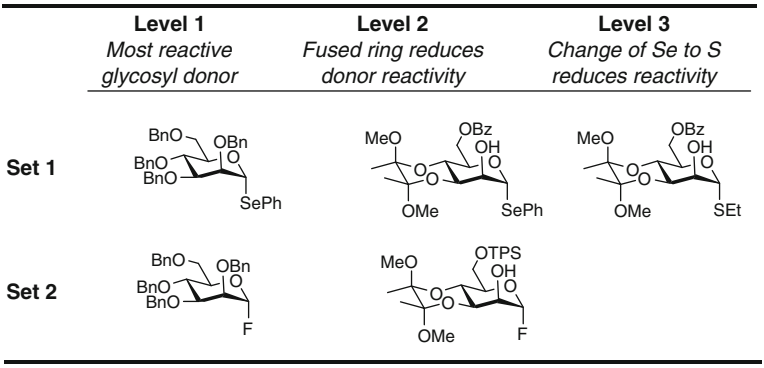


Fig. 11 Reactivity tuning of thioethyl, selenophenyl, and fluoro leaving groups

6.2 *One-Pot Preparation of Oligosaccharides Using Three Leaving Groups*

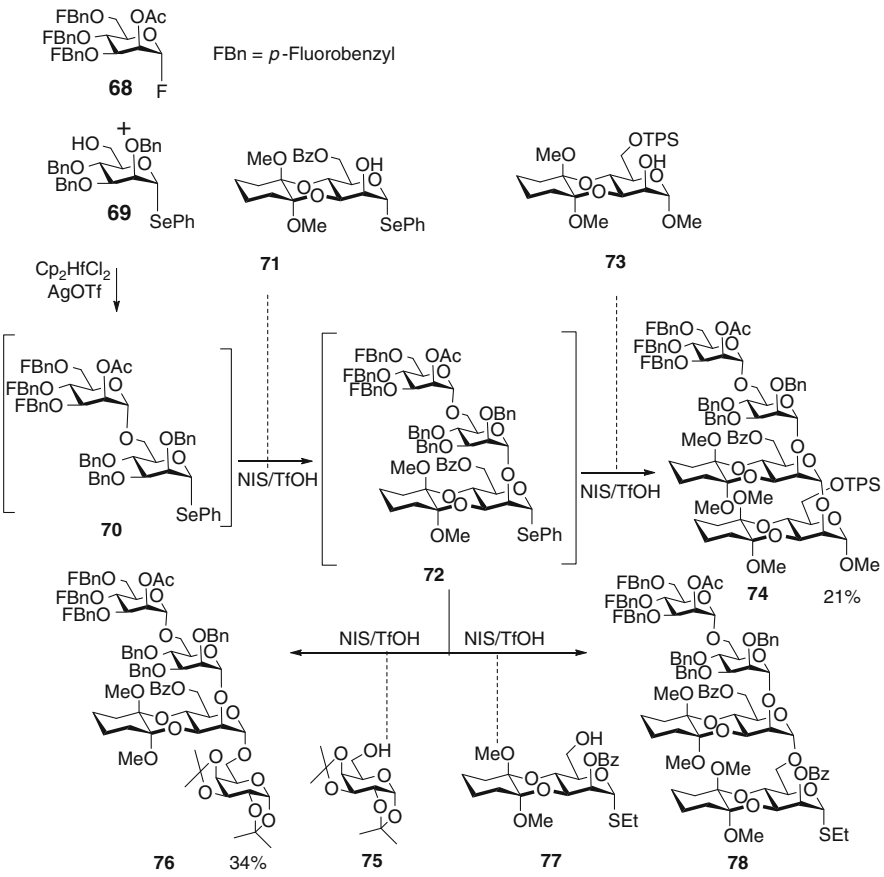
The first synthetic utility of this methodology was demonstrated by the one-pot preparation of linear tetrasaccharides which were assembled in a single reaction vessel from molar equivalents of monomeric building blocks [121].

Here, the fluoro donor **68** may be selectively activated in the presence of other leaving groups, such as the phenylseleno substituent, and consequently coupling with **69** can take place to give the disaccharide **70** (Scheme 15). The latter then glycosylates a CDA-detuned phenylseleno derivative **71** to afford the trisaccharide **72** which in turn can react with more NIS/TfOH and alkyl glycosides with free hydroxyl groups such as **73** or **75**, to give the corresponding tetrasaccharides **74** or **76** respectively. It should be mentioned that, if the acceptor contains an anomeric leaving group (e.g., thioglycoside **77**), the activation sequence can be continued.

Owing to the fact that the diacetal method is also applicable to the reactivity tuning of glycosyl fluorides, these one-pot processes can be extended even further to give linear pentamers (Scheme 16). Here a highly reactive fluoro donor **57** reacts with a BDA-detuned fluoro acceptor **79** to give a fluoro disaccharide **80** which, in turn, glycosylates a phenyseleno monomer **81** to give phenylseleno trisaccharide **82**. The latter then glycosylates a CDA-detuned phenyseleno derivative **71** to give phenyl selenotetrasaccharide **83**, which finally glycosylates thioethyl sugar acceptor **84** to give the final pentasaccharide **85**.

One-pot methods are not only limited to the preparation of linear sequences but branched isomers can also be obtained by adapting these methods to include diols as acceptors in the coupling process [122].

A number of branched pentamers have been prepared using these procedures, although even larger compounds may be obtained by judicious choice of the

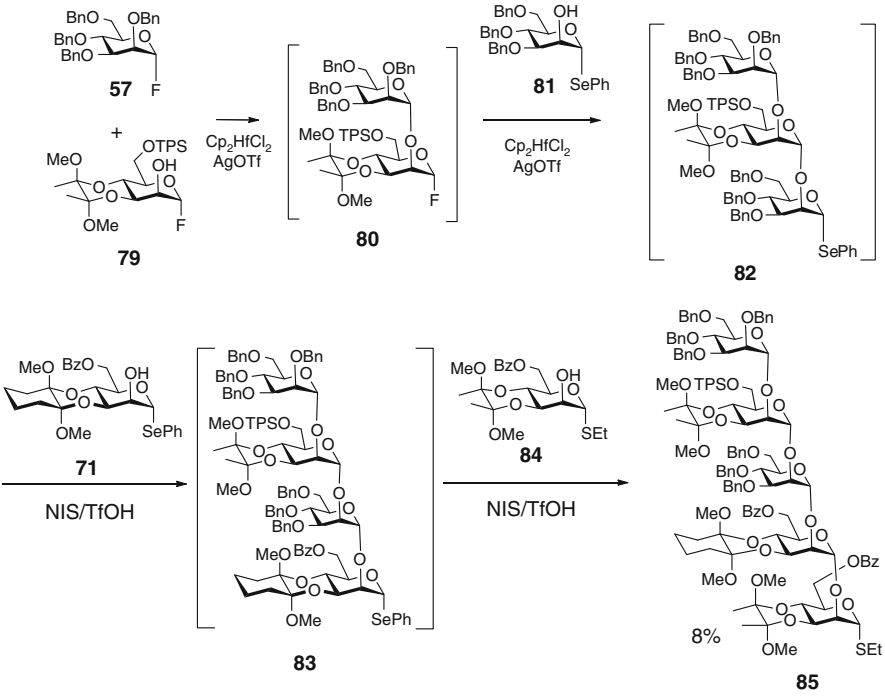


Scheme 15 One-pot preparation of linear tetrasaccharides using three leaving groups

coupling components. For example, Scheme 17 illustrates the preparation of two heptamers by splitting the reaction stream at the key linear trimer intermediate followed by its coupling with two different diol acceptors. For all these products, selective deprotection would lead to a wide range of compounds. These products can be further employed in a block coupling process to give large libraries of oligosaccharides. One-pot synthesis of glycoclusters has also been reported [123].

6.3 *Synthesis of GPI Anchor of* Saccharomyces cerevisiae

The synthetic potential of this methodology was further demonstrated by the one-pot synthesis of the core oligosaccharide of the GPI anchor of yeast (*Saccharomyces*



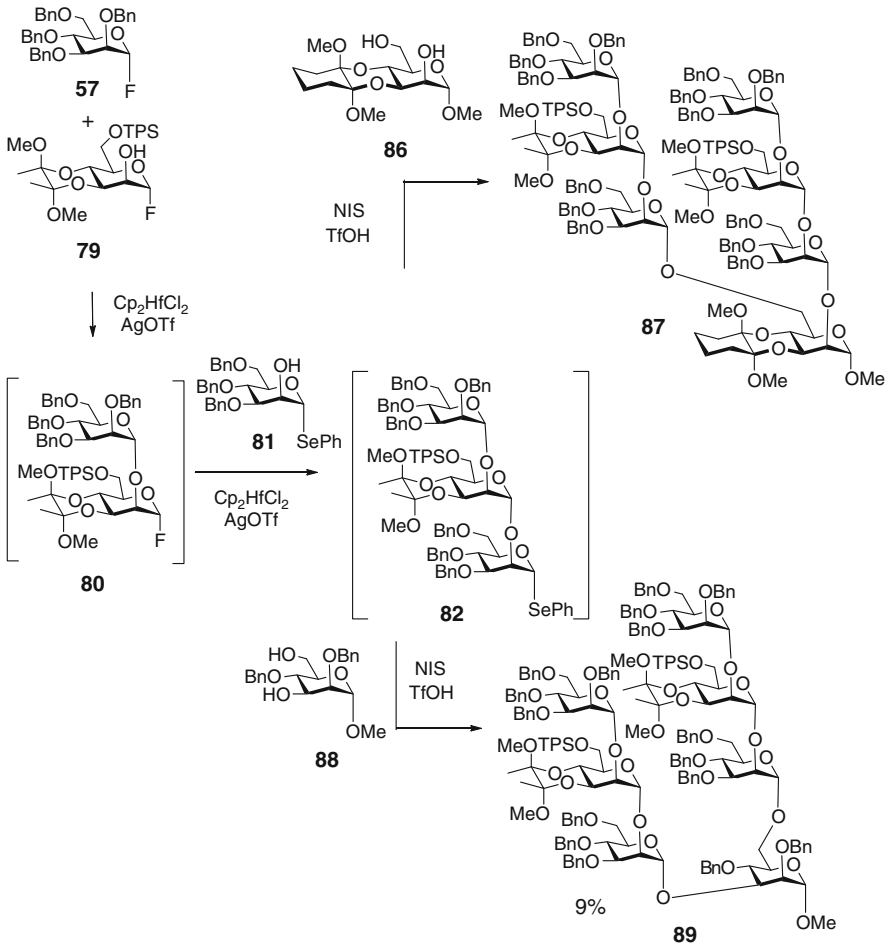
Scheme 16 One-pot preparation of a linear pentasaccharides using three leaving groups

cerevisiae) [124]. The design of the synthesis was such that in each set of orthogonal sugars, the protecting groups and the anomeric substituent of the building blocks would induce a decrease in reactivity of the donor functionality from the non-reducing to the reducing end of the pseudohexasaccharide (Fig. 12) [125].

Therefore, the selective activation of the more reactive fluoride **57** in the presence of diacetal detuned fluoride **90** using the $HfCp_2Cl_2$–$AgClO_4$ protocol furnished disaccharide **91** in good yield (Scheme 18). It should be mentioned that, when glycosylations were attempted with the analogous selenophenyl or thioethyl sugars, chemical yields were poor due to homocoupling of the acceptor. This result illustrates one advantage of glycosyl fluorides over the previous donors used – that their lower reactivity enables greater influence of the appended protecting groups.

On the other hand, the reactivity-tuned coupling of selenophenyl donor **92** and thioethyl glycoside **93**, mediated by NIS/TMSOTf, proceeded smoothly to give the disaccharide **94** as a single anomer in 77% yield. The Aloc group was selected to control the α-selectivity of the glycosylation reaction.

To complete the assembly of the core pseudohexasaccharide, selective removal of the Aloc protecting group in **94** was followed by coupling with glycosyl fluoride



Scheme 17 One-pot preparation of a branched heptasaccharide using three leaving groups

91 and thioglycoside **95**, using the Suzuki activation system (Scheme 18). Careful control of the concentration and mass of molecular sieves used was crucial to avoid decomposition of the donor **91**. Attention was then turned to the pivotal coupling of tetrasaccharide **96** and pseudodisaccharide **52**. In the previously discussed GPI anchor synthesis of the *Trypanosoma brucei* (see Scheme 10) an NIS/TfOH coupling allowed access to the required heptasaccharide core. However, initial reactions with the NIS/TMSOTf promoter system showed the coupling of **96** and **52** to be much more sensitive to the reaction conditions. Activation of **96** occurred immediately, but as the hydroxyl moiety in **52** is hindered, degradation pathways rather than glycosylation predominated. In this way, hexasaccharide core **97** could

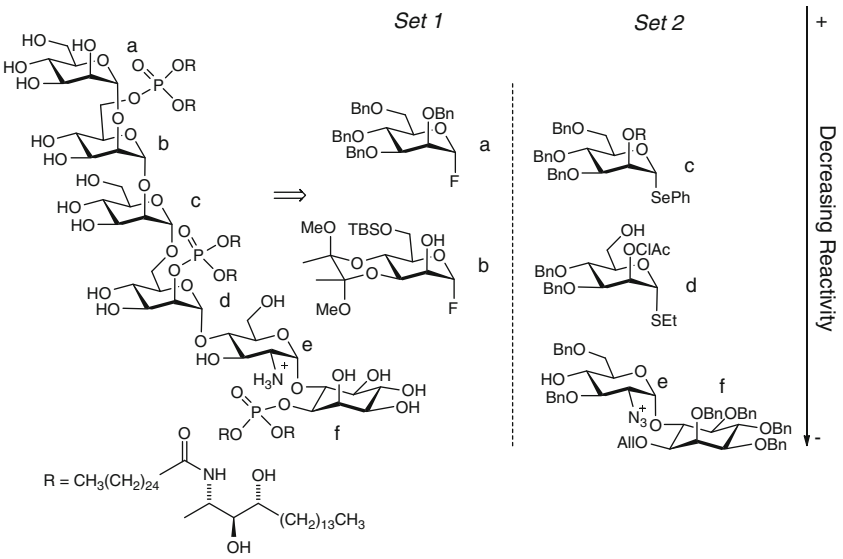
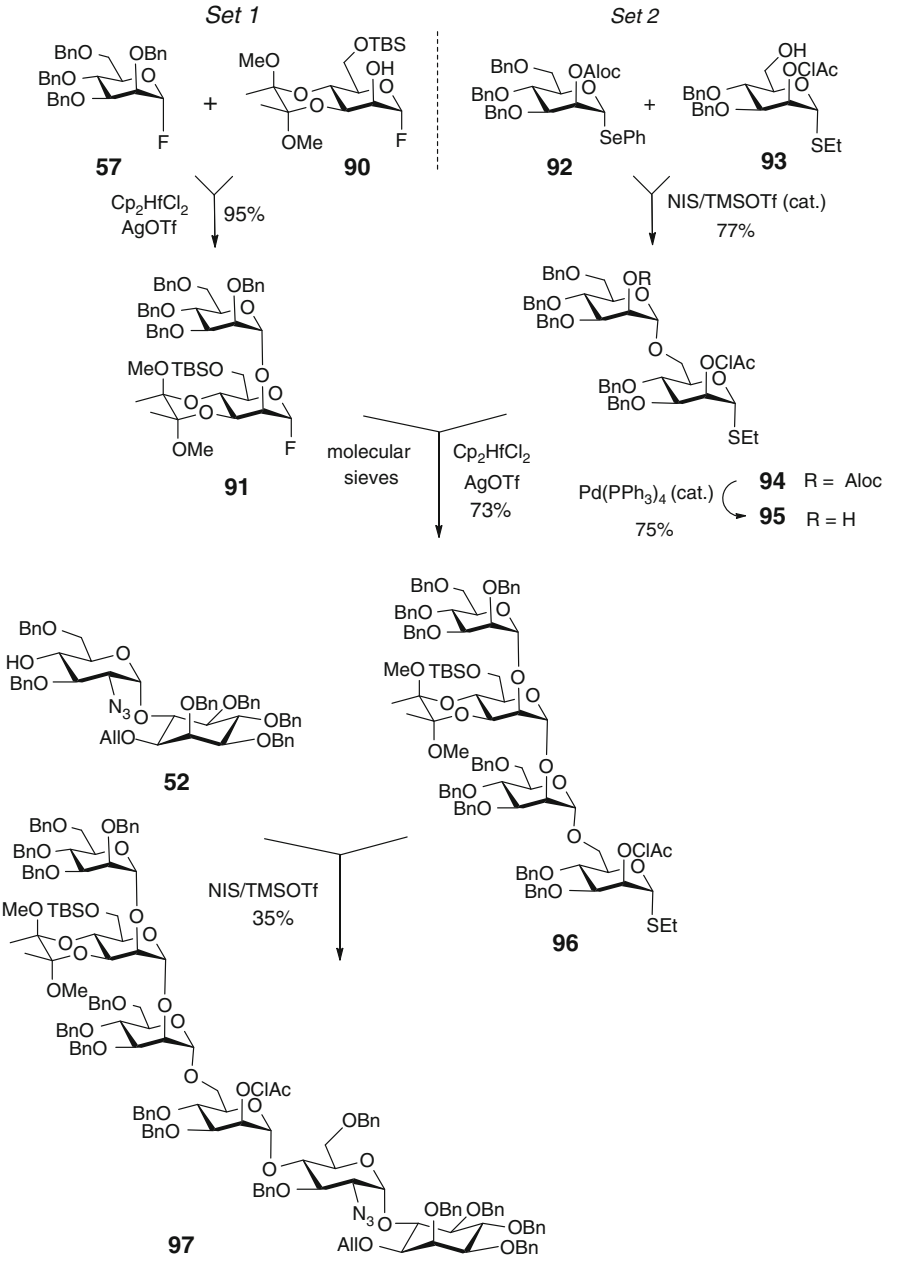


Fig. 12 Structure of *N*-glycans of GPI anchor of *Saccharomyces cerevisiae* and designed building blocks for its synthesis

be isolated in an unoptimized 35% yield. While the overall yield is not high in this particular case, it does demonstrate the potential of the method.

7 Conclusions

1,2-Diacetals, initially developed by Ley's group as selective protection for 1,2-diequatorial diols, have proved capable of "tuning" the reactivities of donors and acceptors with such efficiency that the number of steps needed to synthesize complex oligosaccharides can be considerably reduced. The presence of a 1,2-diacetal on a glycosyl donor enables chemoselective glycosylation processes; but further refinement of this 1,2-diacetal-mediated reactivity tuning comes from its use in combination with orthogonal glycosyl donors (thio-, selenoglycosides, and glycosyl fluorides). Thus by varying the possible combinations, up to four levels of reactivity can be attained. Strategic combination of reactivity tuning and chemoselective glycosyl activation makes possible the development of simplified synthetic strategies for complex oligosaccharides. For instance, the synthesis of a branched nonamannoside could be carried out in just five steps, and the assembly of the carbohydrate core of GPI took just six steps and included only one protecting group manipulation.



Scheme 18 Synthesis of GPI anchor of *Saccharomyces cerevisiae*

References

1. Vliegenhart JFG, Doorland L, Van Halbeek H (1983) Adv Carbohydr Chem Biochem 41:209
2. Dell A (1987) Adv Carbohydr Chem Biochem 45:21
3. Varki A (1993) Glycobiology 3:97
4. Sharon N, Lis H (1993) Sci Am 268:82
5. Montreuil J (1980) Adv Carbohydr Chem Biochem 37:157
6. Kobata A (1984) In: Ginsberg V, Robbins PW (eds) Biology of carbohydrates. Wiley, New York, p 87
7. Gottschalk A (ed) (1972) Glycoproteins. Elsevier, Amsterdam
8. Sharon N, Lis H (1991) Eur J Biochem 1:218
9. Lis H, Sharon N (1998) Chem Rev 98:637
10. Sharon N, Lis H (1981) Chem Eng News 59:21
11. Karlsson K-A (1991) Trends Pharmacol Sci 12:265
12. Karlsson KA (1989) Annu Rev Biochem 58:309
13. Rademacher TW, Parekh RB, Dwek RA (1988) Annu Rev Biochem 57:785
14. Goldstein EJ (1979) Carbohydrate protein interaction. ACS Symp Series, vol 88. American Chemical Society, Washington, DC
15. Feizi T (1985) Nature 314:53
16. Feizi T, Childs RA (1987) Biochem J 245:1
17. Kocienski PJ (2005) Protecting groups, 3rd edn. Georg Thieme, Stuttgart
18. Robertson J (2000) Protecting group chemistry. Oxford University Press, New York
19. Greene TWP, Wuts GM (1999) Protective groups in organic synthesis, 3rd edn. Wiley, New York
20. Hanson JR (1999) Protecting groups in organic synthesis. Sheffield Academic Press, New York
21. Ley SV, Downham R, Edwards PJ, Innes JE, Woods M (1995) Contemp Org Synth 2:365
22. Ley SV, Baeschlin DK, Dixon DJ, Foster AC, Ince SJ, Priepke HWM, Reynolds DJ (2001) Chem Rev 101:53
23. Ley SV, Polara A (2007) J Org Chem 72:5943
24. van Boeckel CAA, van Boom JH (1985) Tetrahedron 41:4567
25. Ziegler T (1994) Angew Chem Int Ed Eng 33:22
26. Ley SV, Woods M, Zanotti-Gerosa A (1992) Synthesis:52
27. Hughes AB, Ley SV, Priepke HWM, Woods M (1994) Tetrahedron Lett 35:773
28. Ley SV, Priepke HWM, Warriner SL (1994) Angew Chem Int Ed Engl 33:2290
29. Lemieux RU (1971) Pure Appl Chem 25:527
30. Juaristi E, Cuevas G (1992) Tetrahedron 48:5019
31. Entwistle DA, Hughes AB, Ley SV, Visentin G (1994) Tetrahedron Lett 33:777
32. Edwards PJ, Entwistle DA, Genicot C, Ley SV, Visentin G (1994) Tetrahedron Asymmetry 5:2609
33. Montchamp JL, Tian F, Hart ME, Frost JW (1996) J Org Chem 61:3897
34. Douglas NL, Ley SV, Osborn HMI, Owen DR, Priepke HWM, Warriner SL (1996) Synlett:793
35. Hense A, Ley SV, Osborn HMI, Owen DR, Poisson JF, Warriner SL, Wesson KE (1997) J Chem Soc Perkin Trans I:2023
36. Grice P, Ley SV, Pietruszka J, Priepke HWM, Warriner SL (1997) J Chem Soc Perkin Trans I:351
37. Paulsen H, Richter A, Sinnwell V, Stenzel W (1974) Carbohydr Res 38:312
38. Paulsen H (1982) Angew Chem Int Ed Engl 21:155
39. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B (1988) J Am Chem Soc 110:5583
40. Fraser-Reid B, Udodong U, Wu ZF, Ottosson H, Merritt JR, Rao CS, Roberts C, Madsen R (1992) Synlett: 927 and references therein
41. Veeneman GH, van Boom JH (1990) Tetrahedron Lett 31:275

42. Friesen RW, Danishefsky SJ (1989) J Am Chem Soc 111:6656
43. Barrena MI, Echarri R, Castillón S (1996) Synlett:675
44. Baeschlin DK, Chaperon AR, Charbonneau V, Green LG, Ley SV, Lucking U, Walther E (1998) Angew Chem Int Ed 37:3423
45. Hashimoto SI, Sakamoto H, Honda T, Abe H, Nakamura SI, Ikegami S (1997) Tetrahedron Lett 38:8969
46. Chiba H, Funasaka S, Kiyota K, Mukaiyama T (2002) Chem Lett:746
47. Kamat MN, Demchenko AV (2005) Org Lett 7:3215
48. Smoot JT, Pornsuriyasak P, Demchenko AV (2005) Angew Chem Int Ed 44:7123
49. Mydock LK, Demchenko AV (2008) Org Lett 10:2103
50. Mydock LK, Demchenko AV (2008) Org Lett 10:2107
51. Parameswar KT, AR DAV (2010) Org Lett 12:3078
52. Pedersen CM, Nordstrom LU, Bols M (2007) J Am Chem Soc 129:9222
53. Jensen HH, Pedersen CM, Bols M (2007) Chem Eur J 13:7576
54. Douglas NL, Ley SV, Lücking U, Warriner SL (1999) J Chem Soc Perkin Trans I:51
55. Green LG, Ley SV (2000) In: Ernst B, Hart GW, Sinaÿ P (eds) Carbohydrates in chemistry and biology. Wiley-VCH, Weinheim, p 427
56. Zhang Z, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) J Am Chem Soc 121:734
57. Lee J-C, Greenberg WA, Wong CH (2006) Nat Protoc 1:3143
58. Lahmann M, Oscarson S (2002) Can J Chem 80:889
59. Pedersen CM, Marinescu LG, Bols M (2008) Chem Commun:2645
60. Li X, Huang L, Hu X, Huang X (2009) Org Biomol Chem 7:117
61. Fraser-Reid B, Wu Z, Andrews CW, Skowronski E, Bowen JP (1991) J Am Chem Soc 113:1434
62. Andrews CW, Rodebaugh R, Fraser-Reid B (1996) J Org Chem 61:5280
63. Jensen HH, Nordstrom LU, Bols M (2004) J Am Chem Soc 126:9205
64. Boons G-J, Grice P, Leslie R, Ley SV, Yeung LL (1993) Tetrahedron Lett 34:8523
65. Wang Y, Ye XS, Zhang LH (2007) Org Biomol Chem 5:2189
66. Ley SV, Priepke HWM (1994) Angew Chem Int Ed Engl 33:2292
67. Grice P, Ley SV, Pietruszka J, Priepke HWM, Walther EPE (1995) Synlett:781
68. Lis H, Sharon N (1978) J Biol Chem 253:3468
69. Li E, Kornfeld S (1979) J Biol Chem 254:1600
70. Dorland L, van Halbeek H, Vliegenthart JFG, Lis H, Sharon N (1981) J Biol Chem 256:7708
71. Mizuochi T, Spellman MW, Larkin M, Solomon J, Basa LJ, FeiLi T (1988) Biochem J 254:599
72. Doores KJ, Bonomelli C, Harvey DJ, Vasiljevic S, Dwek RA, Burton DR, Crispin M, Scanlan CN (2010) Proc Natl Acad Sci USA 107:13800
73. Scanlan CS, Offer J, Zitzmann N, Dwek RA (2007) Nature 446:1038
74. Krauss IJ, Joyce JG, Finnefrock AC, Song HC, Dudkin VY, Geng X, Warren JD, Chastain M, Shiver JW, Danishefsky S (2007) J Am Chem Soc 129:11042
75. Sanders RW, Venturi M, Schiffner L, Kalyanaraman R, Katinger H, Lloyd KO, Kwong PD, Moore JP (2002) J Virol 76:7293
76. Calarese DA, Scanlan CN, Zwick MB, Deechongkit S, Mimura Y, Kunert R, Zhu P, Wormald MR, Stanfield RL, Roux KH, Kelly JW, Rudd PM, Dwek RA, Katinger H, Burton DR, Wilson IA (2003) Science 300:2065
77. Calarese DA, Lee H-K, Huang C-Y, Best MD, Astronomo RD, Stanfield RL, Katinger H, Burton DR, Wong C-H, Wilson IA (2005) Proc Natl Acad Sci USA 102:13372
78. Wang S-K, Liang P-H, Astronomo RD, Hsu T-L, Hsieh S-L, Burton DR, Wong C-H (2008) Proc Natl Acad Sci USA 105:3690
79. Joyce JG, Krauss IJ, Song HC, Opalka DW, Grimm KM, Nahas DD, Esser MT, Hrin R, Feng M, Dudkin VY, Chastain M, Shiver JW, Danishefsky S (2008) Proc Natl Acad Sci USA 105:15604
80. Grice P, Ley SV, Pietruszka J, Priepke HWM (1996) Angew Chem Int Ed 35:197
81. Grice P, Ley SV, Pietruszka J, Osborn HMI, Priepke HWM, Warriner SL (1997) Chem Eur J 3:431

82. Merritt JR, Naisang E, Fraser-Reid B (1994) J Org Chem 59:4443
83. Jiang L, Chan T-H, Nokami TK (2005) Can J Chem 83:693
84. Nokami T, Tsuyama H, Shibuya A, Nakatsutsumi T, Yoshida J (2008) Chem Lett 37:942
85. Adinolfi M, Iadonisi A, Ravidà A, Valerio S (2006) Tetrahedron Lett 47:2595
86. Jain RK, Liu X-G, Oruganti SR, Chandrasekaran EV, Matta KL (1995) Carbohydr Res 271:185
87. Takatani M, Ito Y (2006) Chem Asian J 1–2:64
88. Blattner R, Furneaux RH, Ludewig M (2006) Carbohydr Res 341:299
89. Lam SN, Gervay-Hague J (2005) J Org Chem 70:8772
90. Srivastava OP, Hindsgaul O (1987) J Org Chem 52:2869
91. Ratner DM, Plante OJ, Seeberger PH (2002) Eur J Org Chem:826
92. Du Y, Zhang M, Kong F (2001) Tetrahedron 57:1757
93. Jiang L, Chan T-H (2005) Can J Chem 83:693
94. Matsuo I, Wada M, Manabe S, Yamaguchi Y, Otake K, Kato K, Ito Y (2003) J Am Chem Soc 125:3402
95. Totani K, Ihara Y, Matsuo I, Koshino H, Ito Y (2005) Angew Chem Int Ed 44:7950
96. Xing Y, Ning J (2003) Tetrahedron Asymmetry 14:1275
97. Baeschlin DK, Chaperon AR, Charbonneau V, Green LG, Ley SV, Lücking U, Walther E (1998) Angew Chem Int Ed Engl 37:3423
98. Baeschlin DK, Chaperon AR, Green LG, Hahn MG, Ince SJ, Ley SV (2000) Chem Eur J 6:172
99. Ferguson MAJ, Homans SW, Dwek RA, Rademacher TW (1998) Science 239:753
100. Sharma DK, Smith TK, Weller CT, Crossman A, Brimacombe JS, Ferguson MA (1999) Glycobiology 9:415
101. Udenfriend S, Kodukula K (1995) Annu Rev Biochem 64:563
102. McConville MJ, Ferguson MAJ (1993) Biochem J 294:305
103. Ferguson MAJ (1997) Philos Trans R Soc London B 352:1295
104. Ali A, Vishwakarma RA (2010) Tetrahedron 66:4357
105. Shao N, Xue J, Guo Z (2004) Angew Chem Int Ed 43:1569
106. Yashunsky DV, Borodkin VS, Ferguson MAJ, Nikolaev AV (2006) Angew Chem Int Ed 45:468
107. Tailler D, Ferrieres V, Pekari K, Schmidt RR (1999) Tetrahedron Lett 40:679
108. Mayer TG, Schmidt RR (1999) Eur J Org Chem:1153
109. Mayer TG, Kratzer B, Schmidt RR (1994) Angew Chem Int Ed Engl 33:2177
110. Campbell AS, Fraser-Reid B (1995) J Am Chem Soc 117:10387
111. Madsen R, Udodong UE, Roberts C, Mootoo DR, Konradsson P, Fraser-Reid B (1995) J Am Chem Soc 117:1554
112. Roberts C, Madsen R, Fraser-Reid B (1995) J Am Chem Soc 117:1546
113. Murakata C, Ogawa T (1992) Carbohydr Res 235:95
114. Murakata C, Ogawa T (1992) Carbohydr Res 234:75
115. Murakata C, Ogawa T (1991) Tetrahedron Lett 32:671
116. Murakata C, Ogawa T (1990) Tetrahedron Lett 31:2439
117. Suzuki K, Matsumoto T (1993) J Syn Org Chem Jpn 51:718
118. Olafson RW, Thomas JR, Ferguson MAJ, Dwek RA, Chaudhuri M, Chang K-P, Rademacher TW (1990) J Biol Chem 265:12240
119. Düffels A, Green LG, Ley SV, Miller AD (2000) Chem Eur J 6:1416
120. Düffels A, Ley SV (1999) J Chem Soc Perkin Trans I:375
121. Cheung M-K, Douglas NL, Hinzen B, Ley SV, Pannecoucke X (1997) Synlett:257
122. Green L, Hinzen B, Ince SJ, Langer P, Ley SV, Warriner SL (1998) Synlett:440
123. Langer P, Ince SJ, Ley SV (1998) J Chem Soc Perkin Trans I:3913
124. Fankhauser C, Homans SW, Thomasoates JE, McConville MJ, Desponds C, Conzelmann A, Ferguson MAJ (1993) J Biol Chem 268:26365
125. Baeschlin DK, Green LG, Hahn MG, Hinzen B, Ince SJ, Ley SV (2000) Tetrahedron Asymmetry 11:173

Top Curr Chem (2011) 301: 69–108
DOI: 10.1007/128_2010_108

Published online: 5 February 2011

"Active–Latent" Thioglycosyl Donors and Acceptors in Oligosaccharide Syntheses

Tze Chieh Shiao and René Roy

Abstract The fine tuning of thioglycosides used as glycosyl donors occurs through careful manipulations of the aglycon's nucleofugality, for example, by using "active–latent" principles. In the first section, the control of the relative leaving group abilities will be discussed in terms of electronic factors, including electron-donating/withdrawing substituents. In the second section, the nucleofugality will be adjusted by steric factors. Quantitative reactivity relationships will then be documented followed by presentation of other controlling elements including locked conformations, solvents, and promoters that will be illustrated throughout.

Keywords Active–latent · Allyl glycosides · Carboxybenzyl glycoside · GM_3 · $Lewis^X$ · Oligosaccharides · Promoters · Sialic acid · Sulfoxides · Thioglycosides · Vinyl glycosides

Contents

T.C. Shiao and R. Roy (✉)
Pharmaqam – Groupe de Recherche en Chimie Thérapeutique, Université du Québec à Montréal, P.O. Box 8888, Succ. Centre-ville, Montréal, QC, Canada, H3C 3P8,
e-mail: roy.rene@uqam.ca

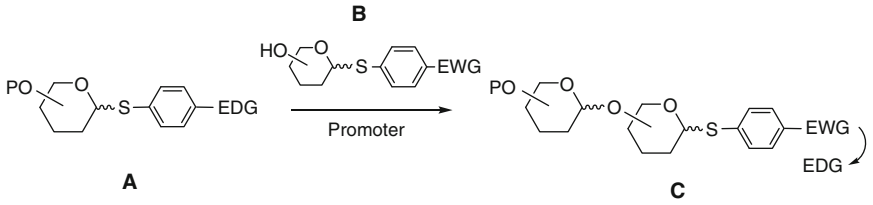
1 Introduction and Concept

The increasing awareness and biological significance of oligosaccharide containing natural products has stimulated significant progress in carbohydrate chemistry. However, efficient protocols for building complex oligosaccharides from monosaccharidic moieties still constitute a major challenge in the field. Several strategies have been developed for the efficient preparation of *O*-glycosides [1–21]. In the past, the most widely used glycosyl donors toward the synthesis of glycosides were glycosyl halides (bromides and chlorides) [1–4], but the conversion of synthetic oligosaccharide intermediates into such glycosyl donors represented difficult or challenging tasks. Several powerful alternatives have then followed, several of which are the subject of accompanying chapters in this book and fall outside the scope of this particular review. A major breakthrough in the field of oligosaccharide syntheses has been introduced by Fraser-Reid et al. [10] who unraveled the seminal observations leading to the concept of "armed" and "disarmed" glycosyl donors. The synthetic utility of this concept has proven to be an influential tool in the concise preparation of complex oligosaccharides that later stimulated additional improvements, including one-pot and solid-phase strategies [14, 15].

The concept of "armed" and "disarmed" glycosyl donors was found to be valid for most other types of glycosyl donors such as *n*-pentenyl, thioglycosides, sulfoxides, and glycals [6–9], including several more recent variations on this theme. Consequently, these observations have greatly contributed to the modern art of oligosaccharide syntheses. Other more subtle controlling elements have also been identified, some of which will be part of the discussion presented in this chapter.

This concept has also led our group to disclose a novel extension of this notion to the aglycon residues of thioglycosyl donors [22–25]. This novel and complementary approach was coined "active–latent" because it permitted a temporarily inactive (inert/latent) thioglycosyl donor to be transformed, by a simple chemical process, into an active form. This could be achieved by using electron-rich thioaryl glycosides serving as "active" glycosyl donors (**A**) while electron-poor thioaryl glycosides played the role of acceptors (**B**) leading to a "latent" disaccharidic thioglycosyl donor (**C**) that could be further activated. Hence, simple functional group interconversion allowed complex oligosaccharides build up using single thioglycosides precursors. This concept is illustrated in Scheme **1**.

Taking advantage of both "active–latent" and "armed–disarmed" concepts, the relative reactivities of the thioglycosyl donors and acceptors can be further modulated by changing both the substituent at the *para*-position of the thioaryl aglycons and the protecting group at the C-2 position. For instance, the reactivity order of thioglycosyl donors toward various thiophilic promoters should be active-armed



Scheme 1 "Active–latent" strategy in oligosaccharide syntheses. *EDG* Electron-donating group; *EWG* electron-withdrawing group. (**A**) "Active" thioglycosyl donor; (**B**) "latent" thioglycosyl acceptor; (**C**) "latent" oligosaccharide transformable into an "active" form

> active-disarmed > latent-armed > latent-disarmed. Thus, the reactivities of "active-armed" donors are much larger than that of "latent-disarmed" acceptors. This has expanded the reactivity differences of thioglycosyl donors and acceptors and thus provided greater flexibility toward complex oligosaccharide syntheses.

Although the initial concept was purely based on the differential reactivity of the reacting partners, conferred by the nature of the protecting groups and the intrinsic nucleophilicity of the thioglycosides toward the promoters, it became rapidly evident that the choice of the promoters themselves was also playing a critical role in the outcome of the reactions. Indeed, "disarmed" thioglycosides could be activated in the presence of powerful thiophilic promoter such as *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH) whereas they remained inactive in the presence of a weaker promoter such as iodonium dicollidine perchlorate (IDCP). So it became clear that, for successful glycosylations, the choice of appropriate promoters provided yet another important variable that needed to be added to other controlling elements such as conformational lock, solvents, etc. that are constantly evolving (see below and other chapters).

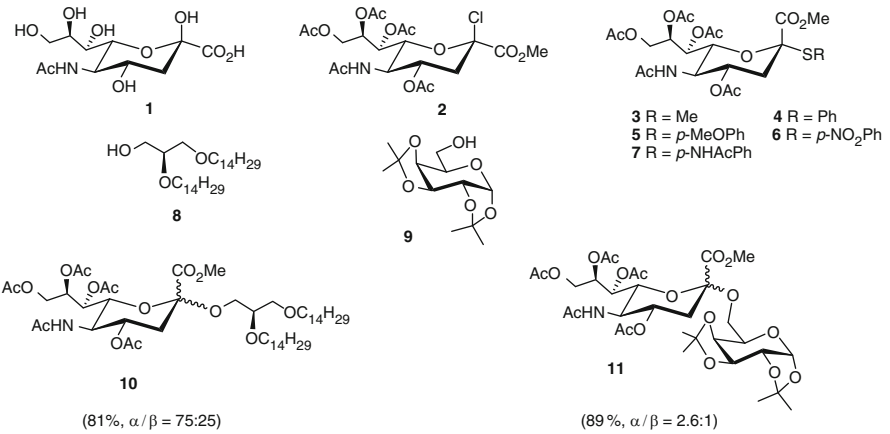
Thioglycosyl donors can be activated by various thiophilic promoters, including methyl triflate and dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) [8, 9]. The use of DMTST is well documented and gives excellent results. Methyl triflate is a potential carcinogen and is also highly toxic, whereas DMTST is prepared using carcinogenic methylating agents. Nicolaou and coworkers introduced a combination of *N*-bromosuccinimide (NBS) and triflic acid salts [17]. NBS/TfOH can also be used to activate armed thioglycosides [26]. However, the rates of glycosylation are usually not sufficiently high, and so the reagent has not been used frequently in practice. Furthermore, in extended glycosylation studies with thioglycosylation by the van Boom group, IDCP was found to be an appropriate promoter in the selective glycosylation reaction of an armed (benzyl) thioglycosyl donor and a disarmed (benzoate) thioglycosyl acceptor [27]. The powerful thiophilic promoter *N*-iodosuccinimide, together with triflic acid, was introduced by van Boom [28], Fraser-Reid [29], and coworkers independently. NIS/TfOH can effectively activate both armed and the less reactive disarmed thioglycosides, whereas NIS alone was not effective for disarmed thioglycosides. This acceleration effect is conceivably due to the formation of an iodonium sulfonate intermediate in which the iodonium ion is more electrophilic compared to the NIS/triflate intermediate which reacts rapidly with the glycosyl acceptors.

2 Application of the "Active–Latent" Concept in Oligosaccharide Syntheses

2.1 Syntheses of Sialosides: Proof of Concept

Remarkably, the initial successful demonstration of the "active–latent" glycosylation strategy was unambiguously demonstrated using the intractable chemistry related to sialic acid **1** [22]. To this end, the required α-thiosialosyl donors (**3–6**) were prepared under stereocontrolled inversion of configuration at the anomeric center using phase transfer catalyzed (PTC) conditions from acetochloroneuraminic acid **2** readily obtained from sialic acid **1** in a one-pot, two step reaction (Scheme 2) [23, 30, 31]. Then, the validity of the strategy was first demonstrated using the known 1,2-di-*O*-tetradecyl-*sn*-glycerol (**8**) [32] as model primary hydroxyl group-containing glycosyl acceptor. For comparison purposes, the β-chloride **2** [33, 34] and the methylthio-α-sialoside **3** [35] were used in glycosylation reactions. Thus, β-chloride **2** ($HgBr_2$/$HgCN_2$) and thioglycoside **3** using dimethyl(methylthio)sulfonium triflate (DMTST) [36] as promoter reacted with acceptor **8** in dichloromethane to provide an anomeric mixture (60:40) of the known sialosides **10** [22, 32, 37] in 62% and 82% yield, respectively (Table 1). The reaction of **3** with **8** was much faster than the reaction using the β-chloride **2**.

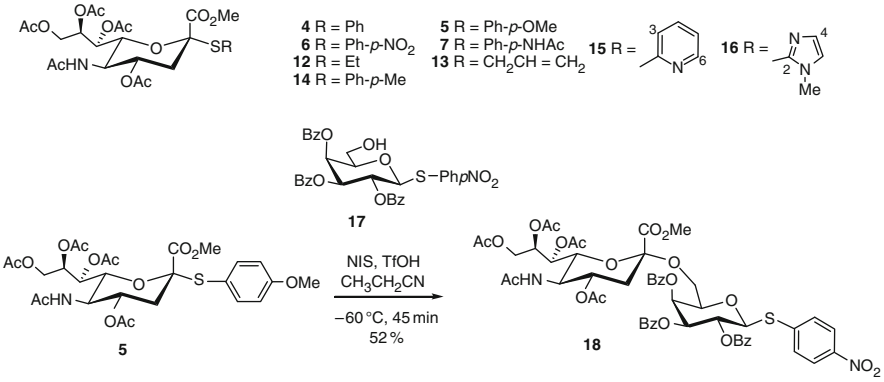
When the above glycosylation reactions were repeated with the "active" arylthio-α-sialosyl donors **4** and **5** [23] under the same reaction conditions (CH_2Cl_2, room temperature) the yields were similar and the stereoselectivity was only marginally reduced (entries 3 and 4 in Table 1). The reaction was faster for the more reactive donor **5** compared to **4**. Changing the solvent from CH_2Cl_2 to a 1:1 mixture of CH_3CN:CH_2Cl_2 had two beneficial effects (nitrilium effect) [38]. The reaction time



Scheme 2 Early demonstration of the "active–latent" glycosylation strategy using sialic acid glycosides [22]

Table 1 Sialylation of glycosyl acceptor **8** with sialosyl donors **2–7**

Entry	Donor	Solvent	Time (h)	Yield (%)	10 (α/β)
1	**2**	CH_2Cl_2	48	62	60:40
2	**3**	CH_2Cl_2	1	82	60:40
3	**4**	CH_2Cl_2	24	81	55:45
4	**5**	CH_2Cl_2	8	80	50:50
5	**5**	CH_3CN:CH_2Cl_2 (1:1)	0.5	73	70:30
6	**6**	CH_3CN:CH_2Cl_2 (1:1)	NR	–	–
7	**7**	CH_3CN:CH_2Cl_2 (1:1)	0.5	81	75:25



Scheme 3 Sialylation of galactoside using thioglycosyl donors [22]

was further reduced and the α-stereoselectivity was slightly increased (entries 4 and 5). Moreover, as anticipated, treatment of the "latent" (unreactive) 4-nitrophenylthio-α-sialosyl donor **6** with **8** under the above conditions (entry 6) gave no detectable formation of the corresponding sialosides **10**. However, transformation of the "latent" donor **6** into the "active" form **7** and glycosylation of **8** as above (entry 7) provided the sialoside **10** in 30 min (70% yield) with a slightly better α-stereoselectivity.

To demonstrate further the usefulness of the crystalline "active" thiosialosyl donor **5** in disaccharide synthesis, it was treated with the galactosyl acceptor **9** in a 2:1 mixture of CH_3CN:CH_2Cl_2 and NIS:TfOH as promoter (−15°C, 2 h) to provide the known [39, 40] disaccharides **11** (α/β = 2.6:1) in 89% yield after silica gel chromatography. Correspondingly, the "latent" sialosyl donor **6** was found inert under these conditions. The new strategy described above compared well with other sialylation methodologies [2, 41]. However, a recent report by Lönn and Stenvall [42] has reported better α-stereoselectivities from sialosyl xanthate, which is also obtainable in high yield under PTC conditions [30].

For the synthesis of Neu5Ac-α-(2–6)-D-Gal-β-*S*-Ar disaccharide using the above strategy, the required "latent" thioglycosyl acceptor, *p*-nitrophenyl 1-thio-β-D-galactopyranoside derivative **17** [23], was prepared under the mild PTC conditions. The usefulness of some of the α-thiosialosides **4–7** and **12–16** to act as efficient glycosyl donors was previously demonstrated (Scheme 3). Interestingly, thiopyridyl (**15**) and

N-methylimidazolyl (**16**) sialosides failed to react with any glycosyl acceptors when either methyl iodide or NBS was used as promoters. In the present situation, when the "active" arylthio sialosides **4** (SPh), **5** (SPh-*p*OMe), and **14** (SPh-*p*Me) were used as glycosyl donors and the "latent" (temporary inactive) *p*-nitrophenylthio galactoside (**17**) as acceptor using *N*-iodosuccinimide (NIS) and triflic acid (TfOH) as promoters, the resulting disaccharide **18** was obtained in good yield (52%) and α-stereoselectivity (Scheme 3). The "latent" *p*-nitrophenylthio sialoside **6** failed to react with acceptor **17** under the same conditions.

In conclusion, preliminary results confirmed the concept of using "active" and "latent" thioglycosyl donors in glycoside synthesis. The methodology is complementary to the "armed" and "disarmed" strategies [10] and should add another controllable variable in blockwise oligosaccharide syntheses.

To substantiate further the selectivity of the "active" and "latent" thioglycoside strategy, the previously inert sialosyl donor **6**, having a *p*-nitrophenyl electron-withdrawing group in the aglycon moiety, was transformed into an "active" donor **7** bearing a *p*-*N*-acetamidophenyl electron-donating group. Thus, the nitro group in **6** was reduced with $SnCl_2$ in refluxing ethanol [22] and the resulting *p*-aminophenylthio sialoside was immediately N-acetylated (pyridine, acetic anhydride) to provide the new sialosyl donor **7** in 87% overall yield. Preliminary results with **7** indicated its usefulness in oligosaccharide synthesis.

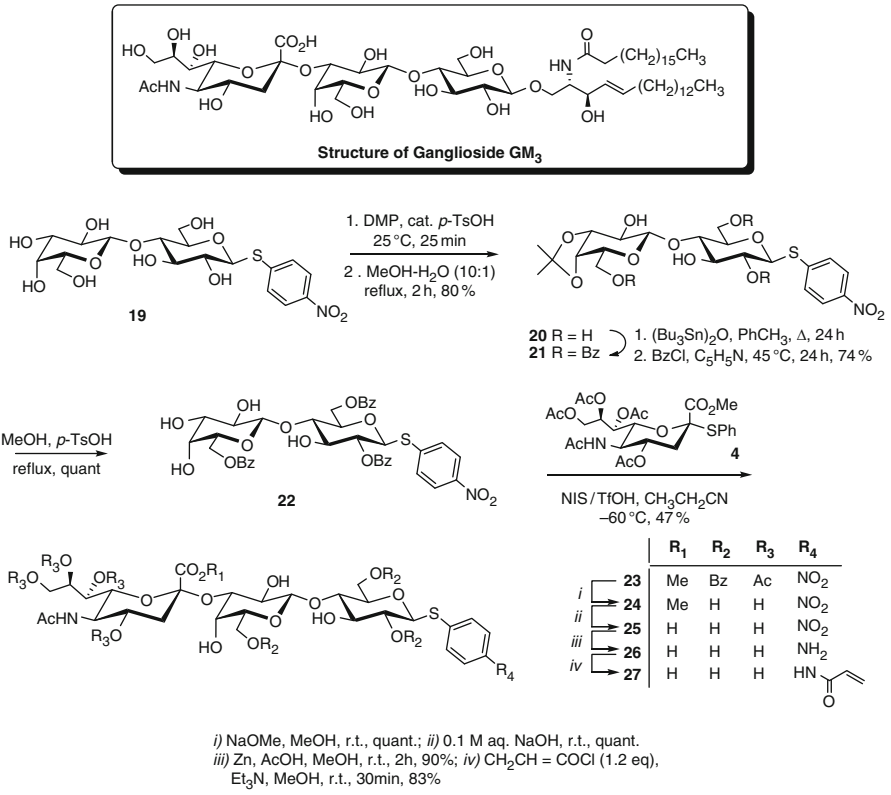
2.2 *Syntheses of Sialosides: GM_3 Oligosaccharide*

Sialic acid-containing glycoconjugates play critical roles in numerous biological phenomena such as cell–cell adhesion, malignancy, and cell growth regulation [43–45]. Of concern, and under active investigation, is ganglioside GM_3 which is over expressed on several tumor cells [44]. GM_3 is also known to modulate epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors [46]. It is therefore of prime interest to have access to glycoconjugates containing only the trisaccharide portion of the glycolipid in order to evaluate the intrinsic biological function played by the trisaccharide itself. Ideally, the glycoconjugates should be prepared in forms suitable for bio- and immunological investigations. Several successful chemo-enzymatic syntheses of ganglioside GM_3 and GM_3-trisaccharide derivatives have been reported [12, 41]. In addition, most of the earlier reported syntheses of GM_3 trisaccharide lacked the necessary anomeric functionality at the reducing glucosyl residue for direct processing to give glycoconjugates. Hence, lengthy anomeric group activation-transformations were necessary for useful functionalization. We demonstrated that the nitrophenyl aglycon could fulfill this criterion.

Another useful application of the "active–latent" glycosylation strategy [24] for the synthesis of GM_3 trisaccharide containing a conjugatable aglycon is described herein. The above strategy makes use of aryl 1-thioglycosides that can act as glycosyl donors or acceptors depending on the electron density of the aryl substituents.

For instance, "active" thiosialosyl donor **4** can be chemoselectively activated with suitable thiophilic promoters in the presence of *p*-nitrophenyl thiolactoside **22** acting as "latent" acceptor (Scheme 4). The resulting "latent" thiooligosaccharide (**23**) can be further transformed into an "active" form by a mild reduction–acetylation sequence. This new glycosylation strategy has been very useful in blockwise oligosaccharide syntheses [23–26].

Suitably protected lactosyl acceptor **22** was synthesized from readily available *p*-nitrophenyl 1-thio-β-D-lactoside (**19**) [24] obtained under phase transfer catalysis (PTC). Thus, treatment of **19** with 2,2-dimethoxypropane (DMP) in the presence of *p*-toluenesulfonic acid (TsOH) gave 3,4-*O*-isopropylidene derivative **20** in 80% yield after cleavage of the concomitant mixed 6′-acetal also formed during the process. Initial attempts of regioselective benzoylation at 2-, 6-, 6′-OH of **20** using benzoyl chloride gave a mixture of di-, tri-, and tetra-*O*-benzoylated products. However, dibutyltin oxide-mediated regioselective benzoylation afforded the desired *p*-nitrophenyl 2,6,6′-tri-*O*-benzoylated-1-thio-β-D-lactoside derivative **21** in 74% yield. Hydrolysis of the isopropylidene group in **21** afforded acceptor **22** quantitatively.



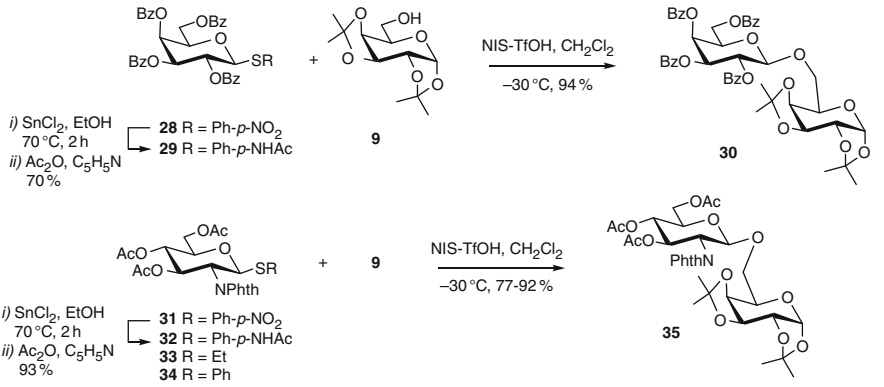
		R_1	R_2	R_3	R_4
i	**23**	Me	Bz	Ac	NO_2
ii	**24**	Me	H	H	NO_2
iii	**25**	H	H	H	NO_2
iv	**26**	H	H	H	NH_2
	27	H	H	H	HN–C(=O)–CH=CH$_2$

Scheme 4 "Active–latent" synthesis of GM_3 oligosaccharide [24]

Active thiosialyl donor **4**, also prepared under PTC conditions [23], was glycosidated with latent acceptor **22** (0.126 mmol) in the presence of *N*-iodosuccinimide (NIS, 0.252 mmol) and triflic acid (TfOH, 0.126 mmol) in propionitrile (5 mL, −60°C, 50 min) to provide partially protected GM_3 trisaccharide **23** in 47% yield. Neither cross-coupling nor β-linked trisaccharide by-products were detected under these mild glycosylation conditions. The α-configuration at the newly introduced anomeric center (Neu5Ac residue) was confirmed by ^{1}H- and ^{13}C-NMR spectroscopy. The remaining ester functionalities of trisaccharide **23** were hydrolyzed (NaOMe, MeOH, followed by 0.1 M NaOH) to provide **25** quantitatively. The *p*-nitrophenyl group was then reduced with zinc dust in a mixture of AcOH–MeOH (1:6, v/v) to give *p*-aminophenyl derivative **26** in 90% yield. N-Acryloylation of **26** (CH_2=CHCOCl, Et_3N, MeOH) afforded **27** suitable for glycoconjugate syntheses in 83% yield [47]. It is worth mentioning that when the reduction/N-acryloylation sequence was performed prior to the hydrolysis reactions, extensive 1,4-conjugate addition (1:2) of methoxide anions on the double bond occurred.

2.3 Qualitative Evaluation of Relative Reactivities

In order to appreciate fully the flexibility of the "active–latent" glycosylation strategy introduced by us [22–25], we next investigated the glycosylation behavior of different thioglycosyl donors with the acceptor 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) (Scheme 5). The thioglycosides chosen as donors were the fully benzoylated *p*-nitrophenyl 1-thio-β-D-galactopyranoside **28** and 4-nitrophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**31**), as well as the corresponding *p*-*N*-acetamidophenylthio glycosides **29** and **32**. Compound **28** was obtained by benzoylation (BzCl, pyridine, 89%) of known *p*-nitrophenyl 1-thio-β-D-galactopyranoside, whereas compound **31** was synthesized from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose by reaction with



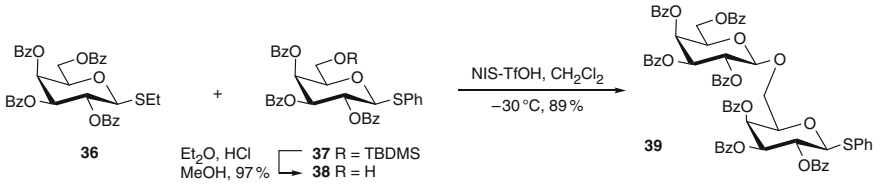
Scheme 5 Glycosylation of model acceptor **9** with varied "active-latent" thioglycosyl donors

p-nitrothiophenol under the catalytic action of tin(IV) chloride. Compounds **29** and **32** were obtained by reduction with $SnCl_2$ and acetylation of **28** and **31**, respectively. When active-disarmed *p*-*N*-acetamidophenyl thioglycosyl donors **29** and **32** were treated with glycosyl acceptor **9** using only a catalytic amount of TfOH (0.2 equiv) in dichloromethane, no glycosylation products were observed. However, formation of disaccharides **30** (94%) and **35** (80%), respectively, were rapidly achieved in high yields when TfOH was present in equimolar amounts with respect to the thioglycosyl donor. As expected, coupling latent-disarmed *p*-nitrophenyl thioglycosides **28** and **31** with the same acceptor **9** did not take place even when equimolar amounts of triflic acid were used.

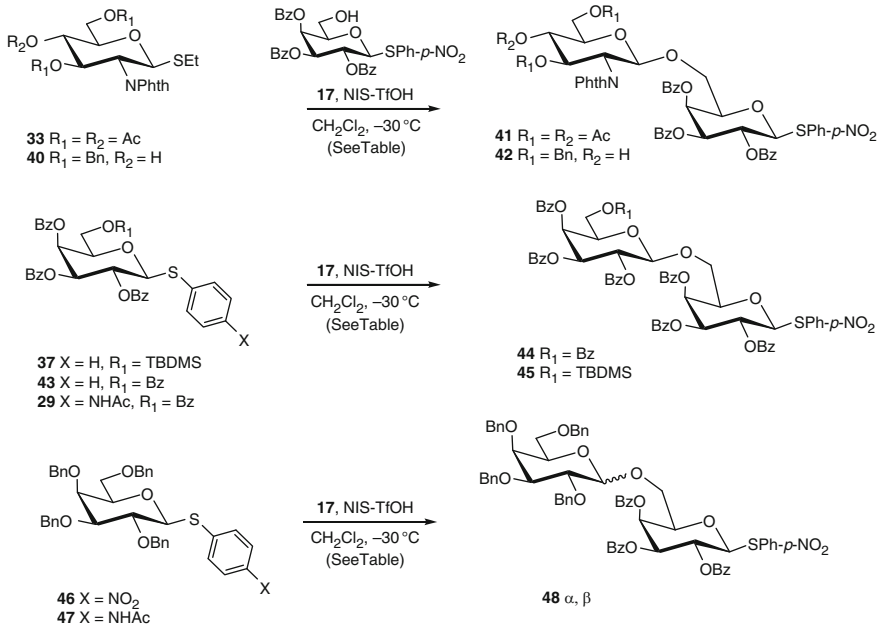
In order to assess further the "unreactivity" of disarmed *p*-nitrophenyl thioglycosides in glycosylation reactions, an equimolar mixture of **28** and **29** was treated with acceptor **9** under the same reaction conditions described above. Thin-layer chromatography of this competitive experiment revealed the rapid disappearance of the active donor **29** while its nitro counterpart **28** remained unchanged. The relative reactivity of the *p*-*N*-acetamidophenyl thioglycosides with respect to the widely used ethyl and phenyl thioglycosyl donors was then qualitatively evaluated. Ethyl 1-thio- and phenyl 1-thioglucosaminides **33** and **34** were synthesized from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose by reaction with ethanethiol or thiophenol, respectively, under the catalytic action of tin(IV) chloride in excellent yields and with complete stereocontrol. Glycosidations of **33** and **34** with **9** were performed using only catalytic amounts of TfOH. As judged from TLC, **33** reacted slightly faster than **34**, as expected (see discussion below).

The higher reactivity of ethyl thioglycosides than phenyl thioglycosides was further established by treating perbenzoylated ethyl 1-thio-β-D-galactopyranoside donor **36** with phenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside **38** as acceptor (Scheme 6). The reaction was complete within 5 min and disaccharide **39** was obtained in 89% yield. Self condensation or cyclization of the acceptor **38** was not detected. From these results, the relative reactivity of thioglycosyl donors was qualitatively established as SEt > SPh > SPhNHAc > $SPhNO_2$.

Considering the observed differences in reactivities between ethyl and phenyl thioglycosyl donors, it was anticipated that selective activation could also be achieved when active *p*-*N*-acetamidophenyl thioglycosyl donors were used in the presence of latent *p*-nitrophenyl thioglycosides acting as acceptors. For this purpose, *p*-nitrophenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside **17** was initially used as the acceptor (Scheme 7).



Scheme 6 Establishing reactivity order in thioglycosyl donors



Scheme 7 Relative reactivity of "active–latent" thioglycosyl donors

Table 2 Glycosylation reactions for compounds in Scheme 7

Entry	Donor	NIS-TfOH	Time (min)	Compounds (Yield %)	(α/β)
1	**33**	1.8/0.2	15	**41** (78)	β
2	**40**	1.8/0.2	10	**42** (89)	β
3	**43**	1.8/0.6	20	**44** (81)	β
4	**37**	1.8/0.6	25	**45** (79)	β
5	**29**	1.8/1.2	25	**44** (87)	β
6	**47**	1.8/1.2	25	**48** (92)	3:1
7	**46**	1.8/1.2	25	**48** (76)	4:1

First, ethyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside **33** and **40** and phenyl 1-thio-β-D-galactopyranoside derivatives **37** and **43** were arbitrarily chosen as disarmed-active donors to be used in the glycosylation reactions with latent-acceptor **17**. NIS-TfOH mediated glycosidation of donors **33**, **40**, **37**, and **43** with **17** afforded the corresponding disaccharides **41**, **42**, **44**, **45** in high yields (78%–89%) with complete β-stereocontrol (Table 2).

In the next steps, the relative reactivities of armed and disarmed (active) *p-N*-acetamidophenyl 1-thioglycosides were established using perbenzoylated *p*-nitrophenyl 1-thioglycoside **17** as the acceptor (disarmed-latent) (Scheme 7). To this end, fully benzoylated and benzylated *p-N*-acetamidophenyl 1-thio-β-D-galactopyranosides **29** and **47** were glycosylated with **17** using TfOH in a 1.5:1 M ratio relative to the acceptor. Similar to the results obtained from **37** and **43**,

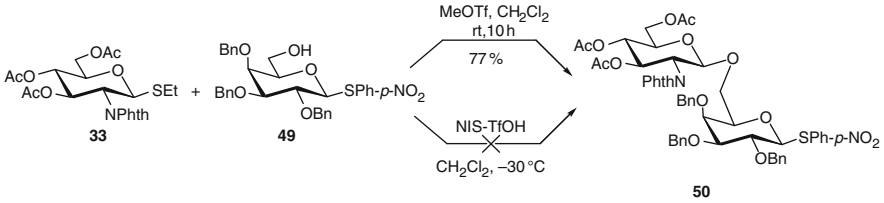
glycosidation of disarmed-active galactoside **29** with **17** gave disaccharide **44** in 87% yield (Table 2). Likewise, and as expected, armed donor **47** also allowed rapid formation of disaccharide **48** in high yield (92%) albeit as a 3:1 α/β anomeric mixture (Table 2).

To complete the evaluation of the relative reactivities of disarmed-latent *p*-nitrophenyl thioglycosyl acceptors, glycosidation of *p*-nitrophenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside **46** was examined using the acceptor **17**. Consumption of acceptor **17** took place within 1 h and, similar to its reaction with **47**, an anomeric mixture of disaccharide **48** was isolated (76% yield) as a 4:1 mixture of the α/β-anomers due to the nonparticipating effect of 2-*O*-benzyl ether.

Interestingly, none of the reactions performed using alcohol **17** as an acceptor and NIS-TfOH as promoters yielded detectable amounts of product resulting from self condensation or products containing the 1,6-anhydro functionality resulting from an intramolecular substitution. From the results obtained in the glycosylation reactions using **17** as acceptor, several conclusions can be drawn. Overall, these reactions showed that the decreased nucleophilicity of the sulfur atom in perbenzoylated (disarmed-latent) *p*-nitrophenyl 1-thioglycosides, such as **17**, allowed chemoselective activation of, not only disarmed-active ethyl 1-thio- and phenyl 1-thioglycosyl donors, but also armed *p*-*N*-acetamidophenyl 1-thioglycosyl donors and even of armed-latent *p*-nitrophenyl 1-thioglycosyl donors leading to the formation of disaccharides in high to excellent yields (76%–92%) when NIS-TfOH were used as promoters. These findings further extend similar observations by Sliedregt et al. [27, 48, 49] who recently studied the coupling of disarmed-latent 4-nitrophenyl 2,3,4,tri-*O*-benzoyl-1-thio-β-D-glucopyranoside with the corresponding armed ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside and disarmed ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside donors using IDCP and NIS-TfOH as promoters, respectively. In both cases, glycosylation products were observed but the coupling was efficient only in the second case.

In addition, it should be noted that the reaction between donor **46** and acceptor **17** constitutes the first example of coupling of two so-called "latent" thioaryl glycosides. This result further confirmed the validity of the "armed-disarmed" glycosylation strategy even when the nucleophilicity of both acceptor and donor is decreased by the presence of an electron-withdrawing nitro functionality in the aryl group of the aglycon. The ability of perbenzylated *p*-nitrophenyl 1-thioglycosides to work as glycosyl donors were previously observed [27, 48], but only with nonthioglycoside acceptors in glycosylation mediated by DMTST. These authors carried out the reaction of perbenzylated *p*-nitrophenyl 1-thio-β-D-glucopyranoside with acceptor **9** and isolated the corresponding disaccharide in 75% yield.

As demonstrated from reaction between **46** and acceptor **17** (entry 7, Table 2), compound **46** could be used directly as a glycosyl donor without manipulating the anomeric center in further glycosylation reactions with disarmed *p*-nitrophenyl thioglycosyl donors, allowing the preferential formation of a 1,2-*cis* linkage. On the other hand, disaccharide **45** is a versatile compound because chain-elongation can be performed at the nonreducing end (C-6′) by removing the silyl protecting group and also at the reducing-end (C-1) by conversion of the nitro group (latent)



Scheme 8 Mild promoters are required with "armed-latent" thioglycosyl donors

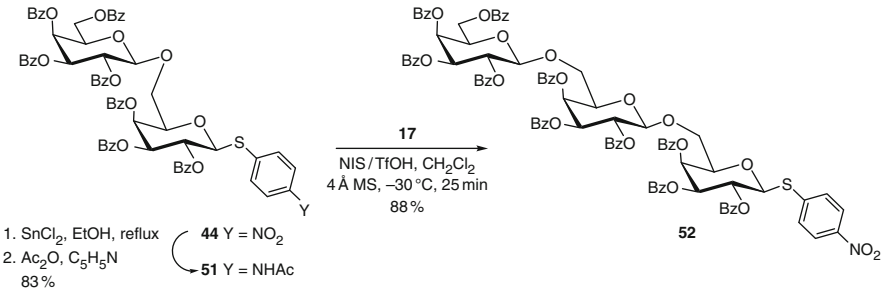
into an *N*-acetamido group (active). The above results further substantiate earlier observations reported by Garegg and coworkers [9, 50], who first described the usefulness and versatility of thioglycosides in oligosaccharide syntheses before the advent of the use of NIS-TfOH couple as promoters.

Considering these last results, glycosylation reactions with an "armed-latent" glycosyl acceptor were examined. This situation was previously addressed by Sliedregt et al. [48, 49] who studied the coupling of fully benzylated ("armed") and fully benzoylated ("disarmed") ethyl 1-thio-β-D-glucopyranoside with *p*-nitrophenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **49** using IDCP and NIS-TfOH as promoters, respectively. In both cases, they found that the corresponding disaccharides were formed but only in low yields and with concomitant intramolecular cyclization of the acceptor (1,6-anhydro derivative). *p*-Nitrophenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside **49** was synthesized to be used as "armed-latent" acceptor.

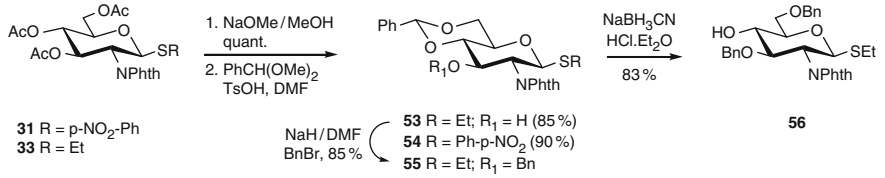
Attempts to prepare this compound using the method suggested by Ohrui et al. [51] were not successful in our hands because benzylation of 6-*O*-*tert*-butyldimethylsilyl galactoside led to concomitant cleavage of the 6-*O*-silyl group under the basic conditions giving perbenzylated galactoside as the major product. Thus, compound **49** was prepared starting from *p*-nitrophenyl 1-thio-β-D-galactopyranoside. Glycosylation of "disarmed" ethyl thioglycosyl donor **33** with acceptor **49** using NIS-TfOH as promoter led to a complex mixture that was not further investigated. However, the coupling took place smoothly when the less thiophilic methyl triflate promoter was used (CH_2Cl_2, r.t.) to give disaccharide **50** in 77% yield (Scheme 8).

2.4 *Usefulness of "Active–Latent" Strategy Toward Oligosaccharides*

The versatility of the "active–latent" glycosylation strategy in oligosaccharide synthesis was further illustrated by the synthesis of trisaccharide β-D-Gal*p*-(1–6)-β-D-Gal*p*-(1–6)-β-D-Gal*p* **52**. Again, the reactivity of the "latent" disaccharide **44** could be "turned on" by means of reduction of its nitro group into an *N*-acetamido group ($SnCl_2$, EtOH, reflux) and acetylation (Ac_2O, pyridine) to give "active" form **51**



Scheme 9 Synthesis of β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p* trisaccharide

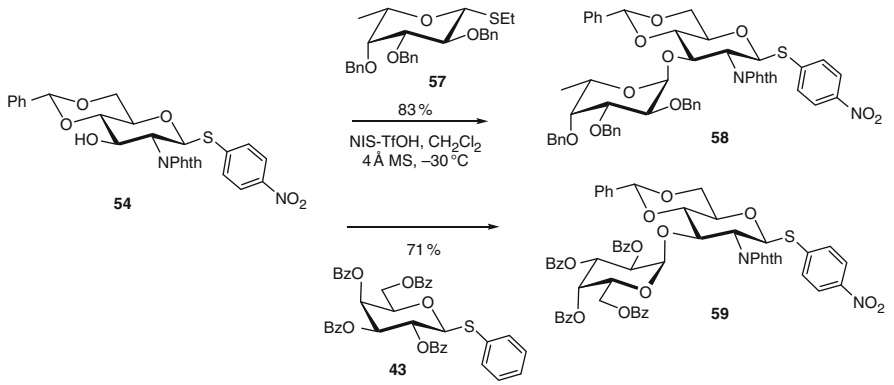


Scheme 10 Synthesis of partially protected 2-deoxy 2-phthalimido-1-thio-β-D-glucopyranosides

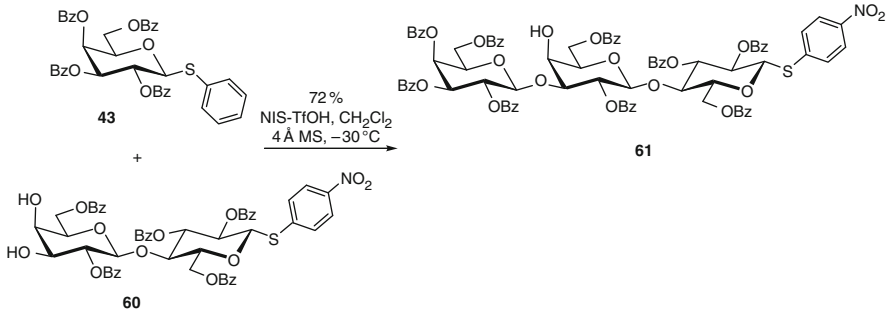
(Scheme 9). Successful glycosylation of "latent" glycosyl acceptor **17** with "active" disaccharide donor **51** was achieved in methylene chloride using NIS/TfOH as promoter to provide trisaccharide **52** in 88% yield. It is worthwhile mentioning that "latent" trisaccharide **52** could again be easily transformed to an "active" form by the method described above and can serve as a new glycosyl donor in following chain elongation.

The biological significance of β-1,4-linked oligomers of glucosamine (e.g., chitin) is well recognized [3, 52]. Also, the hydroxyl group at the C-4 position of GlcN is known to be relatively unreactive [3, 52–54]. Therefore, the construction of this type of oligosaccharide is a challenging task and is often used as a utility test for a given glycosylation method. To this end, partially protected D-GlcN derivatives were prepared as indicated in Scheme 10. The triol products of Zemplén de-*O*-acetylation of **31** and **33** were directly treated with α,α-dimethoxytoluene and *p*-TsOH in DMF solvent (or acetonitrile), to give the benzylidene derivatives **53** and **54** in 85% and 90% yields, respectively. Compound **53** was benzylated using benzyl bromide and sodium hydride in *N,N*-dimethylformamide, giving compound **55** in 85% yield. The 4,6-benzylidene acetal in **55** was regioselectively opened by treatment with sodium cyanoborohydride and HCl–diethyl ether in tetrahydrofurane [55], to give the alcohol **56** in 83% yield.

To demonstrate further the generality of "latent-active" glycosyl strategy in oligosaccharide synthesis, the more difficult β(1→ 3) linkage was next examined (Scheme 11). Glycosylation of "latent-disarmed" acceptor **54** with ethyl 1-thio-β-L-fucopyranoside **57** at −30°C in dichloromethane with 4 Å MS, promoted by NIS/TfOH, gave the desired α-(1→3) disaccharide **58** in 83% yield. Under similar



Scheme 11 Preparation of synthons for Le^X and Le^a syntheses

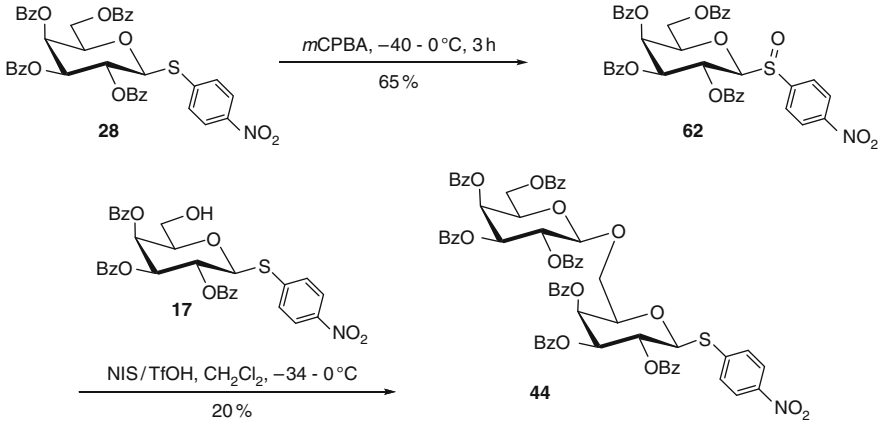


Scheme 12 Regioselective glycosylation of "disarmed-latent" lactoside acceptor **60**

reaction conditions, glycosylation of "latent-disarmed" acceptor **54** with "active-armed" β-D-galactopyranoside **43** afforded β-(1→3) linked disaccharide **59** in 71% yield. It is also worth mentioning that disaccharide **58** and **59** constitute versatile synthons toward the syntheses of Le^a and Le^X, respectively.

Condensation of phenyl 1-thio-D-galactopyranoside **43** with diol **60**, readily obtained from 4-nitrophenyl 3′,4′-*O*-isopropylidene-2,3,6,2′,6′-penta-*O*-benzoyl-1-thio-β-D-lactopyranoside by hydrolysis, gave β(1→3) linked trisaccharide **61** in 72% yield (Scheme 12). The newly introduced β-anomeric center in **61** was assigned from its ^{1}H NMR spectrum which showed a doublet for H-1 at δ 4.89 ppm ($J_{1''.2''} = 8.0$ Hz). The ^{1}H-NMR spectrum of **61** was less informative in confirming the regiochemistry of the newly introduced glycosidic linkage of **61**. However, the regiochemistry could be unambiguously confirmed from its ^{13}C NMR spectrum which showed a deshielded signal for C-3′ at δ 81.1 ppm (Δδ = +8.0 ppm) compared to δ 73.1 ppm for C-3′ of its precursor **60**.

The application of thioglycoside gained a new impetus by the finding of Kahne et al. [56] who observed that phenylsulfenyl glycosyl donors, readily accessible by oxidation (*m*CPBA) of phenyl thioglycosides, can be effectively glycosylated using



Scheme 13 Glycosylation of 4-nitrophenylsulfenyl glycoside **62** with latent acceptor **17**

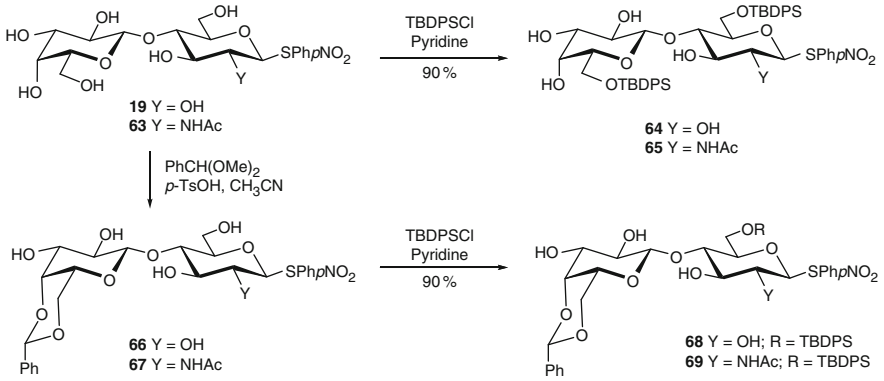
triflic anhydride as activator. It was revealed by the same group [57] that the glycosylation of phenyl thioglycosides with phenylsulfenyl glycoside occurs selectively under the influence of triflic acid (TfOH) and in the presence of methyl propiolate (MP) used as scavenger. The latter finding, together with the fact that the reactivity of phenylsulfenyl donors can be regulated by the introduction of EWG or EDG groups at the *para* position of the phenyl ring (reactivity order OMe > H > NO_2), enabled Kahne et al. [57] to assemble a precursor of the cyclamycin trisaccharide in a one-step synthesis (see below).

To widen the scope of *p*-nitrophenyl thioglycoside in oligosaccharide synthesis, the possibility of activating the *p*-nitrophenyl thioglycoside by means of the oxidation method used by Kahne et al. [56] was also explored. Initial attempts to condense perbenzoylated 4-nitrophenylsulfinyl glycoside **62**, prepared in 65% yield by oxidation of **28** [58] with *m*CPBA, with *p*-nitrophenyl thioglycosyl acceptor **17** using Tf_2O as promoter at −78°C failed. No trace of coupling product **44** could be detected. However, using NIS/TfOH as a promoter, disaccharide **44** was obtained in only 20% yield (Scheme 13). This preliminary observation, together with our previous data, revealed that to activate the "disarmed-latent" donor **28** by the oxidation method proved to be less effective than using the reduction–acetylation method, at least when ester protecting groups are present on O-2.

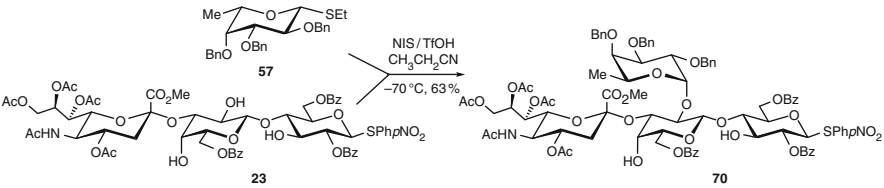
Several personal observations indicated that the sulfoxide method was best accomplished with armed donors.

2.5 *Highly Practical Synthesis of Lewis^X Trisaccharide*

Additional precursors in the use of the above strategy were prepared under two concise synthetic routes as outlined in Scheme 14. In the first approach, *p*-nitrophenyl thiolactoside **19** and *N*-acetyllactosamine derivative **63** were used as starting



Scheme 14 Selective protection of lactoside **19** and *N*-acetyllactosamine **63**



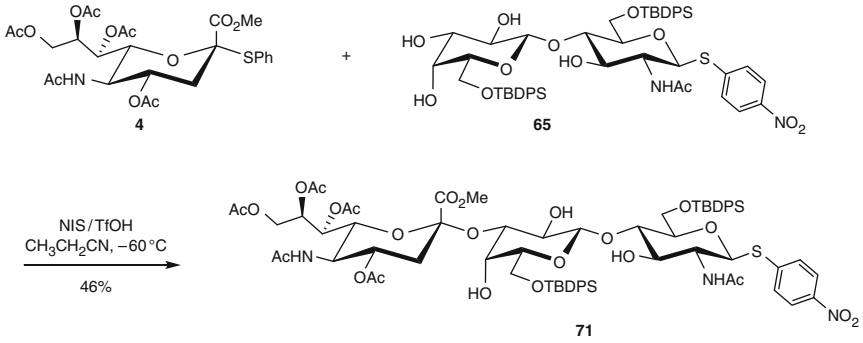
Scheme 15 Fucosylation of GM_3 toward sialyl Le^x

materials [54]. Hence, sequential treatment of **19** and **63** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in dry pyridine at room temperature for 6–8 h afforded 6,6′-di-*O*-silylated derivatives **64** and **65**. It is worth mentioning that evaporation of dry pyridine from the starting materials 2–3 times prior to the addition of the silylating reagent (TBDPSCl) resulted in significant improvement of yield (~90%).

In the second approach, treatment of lactoside derivatives **19** and **63** with benzaldehyde dimethylacetal in dry acetonitrile using *p*-toluenesulfonic acid as catalyst gave the 4′,6′-*O*-benzylidene derivatives **66** and **67** in 93% and 89% yield, respectively. Further derivatization of **23** (Scheme 4) was also considered in order to prepare sialyl Le^X as shown in Scheme 15. The "disarmed-latent" trisaccharide acceptor **23** was first coupled with ethylthio fucopyranosyl donor **57** in the presence of NIS/TfOH in dichloromethane at −70°C to give sialylated tetrasaccharide **70** in 63% yield together with recovered trisaccharide acceptor **23** (17%) and a minor unidentified regioisomer (less than 10%) (Scheme 15).

Finally, glycosylation of **65** with phenyl thiosialoside **4** (1.7 equiv) in propionitrile for 50 min at −60°C in the presence of NIS/TfOH (2:1 equiv relative to acceptor) gave the expected α-sialoside **71** in 46% yield (Scheme 16).

In conclusion, the "active–latent" glycosylation strategy discussed above offers the possibility to prepare complex oligosaccharides by a highly convergent reiterative



Scheme 16 Synthesis of Neu5Acα(2,3)βGal(1,4)βGlcNAc trisaccharide

approach and extends the "armed–disarmed" glycosylation strategy described by Fraser-Reid et al. [10].

Fully or partially protected *p*-nitrophenyl thioglycosides proved to be very versatile reagents for the intended goals. The potential usefulness of the "latent" nature of the nitro group was nicely illustrated by chemoselective glycosylation of partially benzoylated *p*-nitrophenyl thioglycosides with "active" thioglycosyl donors using NIS/TfOH as promoter. It was also established that a partially benzoylated *p*-nitrophenyl thioglycoside ("disarmed-latent" acceptor) could be condensed chemoselectively with a fully benzylated *p*-nitrophenyl thioglycosides ("armed-latent" donor) under the influence of NIS/TfOH. Therefore, the reactivity of a *p*-nitrophenyl thioglycoside toward glycosylation reaction could be regulated by the protecting group at C-2 (acyl type vs ether type) or can simply be "turned on" by transforming their electron-withdrawing thioaryl substituents into electron-donating groups. A simple reduction and acetylation could effectively transform "latent" *p*-nitrophenyl thioglycosides. The oxidation (*m*CPBA) to convert *p*-nitrophenyl thioglycosides into the corresponding phenylsulfinyl glycosyl donors had limited value, at least in the case of disarmed donors as stated above.

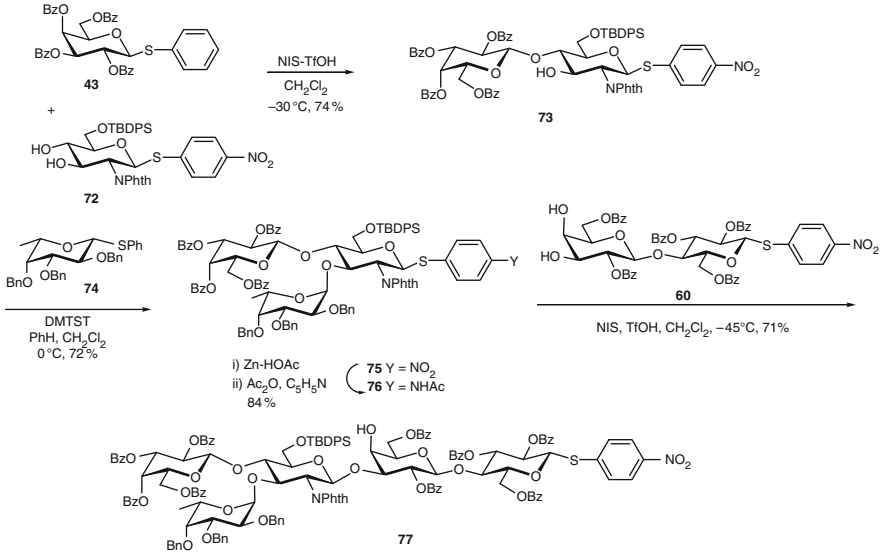
The results discussed in this chapter clearly indicated that NIS/TfOH is a valuable promoter system for the chemoselective glycosylation of "latent" acceptor with "active" thioglycosyl donors. Furthermore, this study revealed that the amount of triflic acid used was crucial for the selective activation of "active" thioglycosides over relatively "latent" thioglycosides.

As discussed above, the combination of "active–latent" and "armed–disarmed" glycosidation methodology made it possible to manipulate the reactivity of both the glycosyl donors and acceptors by means of changing the electron-withdrawing or electron-donating ability of the protecting groups at the anomeric center (active–latent) and at the C-2 position (armed–disarmed). The versatile chemistry allowed us to prepare complex oligosaccharide in a highly convergent manner.

In order to study further the usefulness of "active–latent" glycosylation strategy, we chose the synthesis of Lewis^X pentasaccharide which is widely distributed in many different human and animal tissues, and also in human milk oligosaccharides.

Retrosynthetic analysis of a suitable "active–latent" process toward the Le^X pentasaccharide led us to design the putative Le^X trisaccharide donor **76** that could be coupled with lactosyl acceptor **60**. The donor **76** and acceptor **60** were expected to be constructed from synthons derived from D-galactose, 2-amino-2-deoxy-d-glucose, l-fucose, and lactose, respectively (Scheme 17). The efficiency of the *tert*-butyldiphenylsilyl auxiliary group at O-6 of **72** was established in previous studies [54]. Utilization of this silyl group can regiospecifically control the formation of the desired β-(1–4) linked key intermediate disaccharide **73**.

Selective silylation of known 4-nitrophenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside at OH-6 with *tert*-butylchlorodiphenylsilane in pyridine gave 3,4-*O*-unprotected *p*-nitrophenyl acceptor (**72**) in 82% yield. Condensation of active thiophenyl donor **43** with latent acceptor **72** was performed using *N*-iodosuccinimide and trifluoromethanesulfonic acid as promoter at −30°C. The reaction afforded exclusively the desired β-(1–4)-linked disaccharide **73** in 74% yield (Scheme 17). No (1–3)-linked regioisomer was detected during the coupling reaction. Furthermore, the β-configuration of the resulting disaccharide **73** was deduced from its ^{1}H-NMR spectrum ($J_{1,2}$ 8.1 Hz) while its regiochemistry was proved by converting it into its corresponding 4-*O*-acetyl derivative. This seemingly unexpected result was attributed to the bulky 6-*O*-*tert*-butyldiphenylsilyl protecting group in acceptor **72** which played a key role for the regiospecificity. Under such reaction conditions, the very bulky protecting group could cover the top side (3,5-*cis*) of the OH-3 of the acceptor **72** and block the glycosyl donor from approaching the OH-3. This strategy, coupled with the steric hindrance imparted by the neighboring 2-phthalimido group on OH-3, concurred to the total regiospecificity of the glycosylation. Previous studies [3, 52]



Scheme 17 Synthesis of Lewis^X pentasaccharide [54]

have shown that the 2-phthalimido group alone could not be entirely responsible for the selectivity/specificity observed.

Further 3-*O*-fucosylation of disaccharide **73** with phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**74**) using DMTST as promoter at 0°C afforded Le^X trisaccharide **75** in good yield (72%). The α-anomeric configuration of the newly introduced anomeric center in **74** was assigned from its ^{1}H-NMR spectrum ($J_{1,2}$ 3.6 Hz). The *p*-nitrothiophenyl group of "latent" donor **74** was then reduced with zinc in acetic acid, and the resulting amine was N-acetylated to provide the key "active" *p*-acetamidothiophenyl donor **76** in 84% yield. The latent diol thiolactoside acceptor **60** was obtained through benzoylation and hydrolysis from the known 4-nitrophenyl 3,4-*O*-isopropylidene-1-thio-β-D-lactopyranoside. Condensation of *p*-acetamidothiophenyl donor **76** with the *p*-nitrothiophenyl acceptor **60** was performed using NIS and TfOH as promoter at −45°C. The reaction afforded exclusively the β-(1–3)-linked pentasaccharide **77** in 71% yield. The stereochemistry of the newly introduced β-anomeric center in **77** was assigned from its ^{1}H-NMR spectrum which showed a doublet for H-1 ($J_{1,2}$ 8.5 Hz).

In conclusion, the "active–latent" glycosylation strategy made it possible to manipulate the reactivity of both glycosyl donors and acceptors by means of changing the electron density of the aryl substituents at the anomeric center. This strategy provided a straightforward entry toward the synthesis of complex oligosaccharides in a highly convergent manner. Therefore, pentasaccharide **77** with its *p*-nitrothiophenyl aglycon can be reiteratively introduced into a new glycosylation cycle.

3 "Active–Latent" Oligosaccharide Syntheses: Steric Effects

As stated above, the chemoselective glycosylation strategy described above is amenable to further modifications by fine tuning other factors. For example, it has been conceived that, by varying the bulkiness of the glycosyl donors, one could decrease the access of typical promoters toward the aglyconic leaving groups and hence "activate" the least hindered glycosides while the most hindered ones would remain "inactive" and thus would serve as acceptors. Obviously, then, the "armed–disarmed" protecting groups would add yet another level of sophistication. Two such steric-controlling strategies have been published by Boons and coworkers [59–64] and by Crich and coworkers [65]. The first complementary approach to the one using electronic effects described the uses of sterically hindered thioglycosides while the second one capitalized on the use of *O*-vinyl (enol ethers) vs *O*-allyl glycosides.

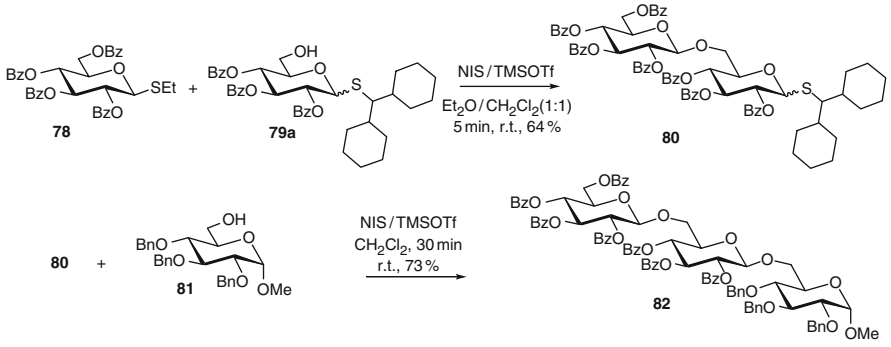
3.1 Sterically Hindered Thioglycosyl Donors

To demonstrate the concept, Boons and coworkers [59] initially conceived the synthesis of dicyclohexylmethyl thioglycosides serving as bulky (inactive) glycosyl donors [59–61]. The latter could be readily obtained under standard Lewis

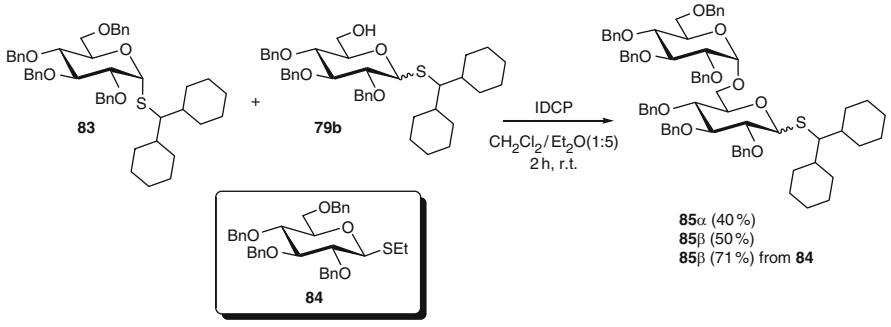
acid-catalyzed glycosidation of sugar peracetates using dicyclohexylmethanethiol (prepared from the corresponding commercially available alcohol in three steps [66]). Thus, by using disarmed SEt donor **78** and both sterically and electronically deactivated thioglycoside acceptor **79a** and using the powerful promoter NIS-TMSOTf, the disaccharide **80** was produced in 64% yield (Scheme 18). Latent thioglycoside **80** was next used as donor using inert methyl glucoside **81** to provide trisaccharide **82** in 73% yield.

They next examined the relative reactivity profile of the bulky dicyclohexylmethyl thioglycosides as either acceptor or donor. To this end, α-donor **83** was treated with acceptor **79b** (Scheme 19). Using the mild IDCP promoter, they observed a better yield of disaccharide **85** when the acceptor had the β-configuration (50%) as opposed to the α-anomer (40%). This result was attributed to the higher reactivity of the α-anomer, an observation already seen with glycosyl bromides [67]. As expected, the yield was significantly improved to 71% when the more reactive SEt donor **84** was used instead.

Finally, a combined application of both electronic and steric controlling elements permitted the generation of a wide range of thioglycosides possessing



Scheme 18 Chemoselective glycosylation of sterically hindered thioglycosyl acceptor [60]



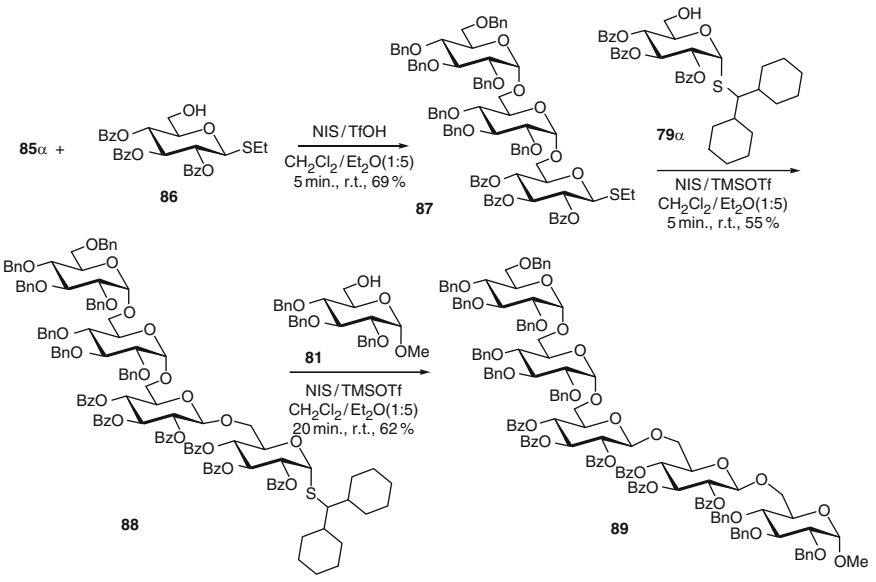
Scheme 19 Hindered thioglycoside as active donor

few distinct levels of anomeric activation, i.e., "active–latent," anomeric configuration and "armed–disarmed." When added to the choice of suitable promoters, the expanded strategy allowed for a complex oligosaccharide assembly without any protecting group manipulations.

Thus, "disarmed-latent" acceptor **86** was treated with "armed-bulky" thioglycosyl donor **85α** under NIS/TfOH activation to provide trisaccharide **87** in 69% yield (Scheme 20). Notably, even with a strong promoter, the activation of hindered dicyclohexylmethyl thioglycoside bearing armed-benzyl protecting group preceded that of the smaller disarmed ethylthio glycoside. Alternatively, **87** could be used as a donor in the presence of acceptor **79a** using NIS/TMSOTf as promoter (r.t., 5 min) to afford tetrasaccharide **88** in 55% yield. Lastly, completion of the pentasaccharide synthesis was achieved with inert acceptor **81** under the above conditions, albeit with slightly longer reaction time (20 min) to give **89** in 62% yield.

In a more recent application toward the synthesis of the complex heptasaccharide related to the jelly coat glycoprotein of the South African clawed toad *X. leavis*, Geurtsen and Boons [61] observed that chemoselective glycosylation of a poorly reactive ethyl thioglycosyl acceptor (axial C-4 OH) provided products resulting from self-condensation. They concluded that the self-condensed glycosides resulted from activation of the poorly reacting ethyl thioglycosides with oxacarbenium intermediates. The problem was however solved by the use of the more bulky dicyclohexylmethyl thioglycoside.

Armed glycosyl donor **90** reacted smoothly with **91** by its in situ transformation into an intermediate that was then activated with silver triflate to provide disaccharide

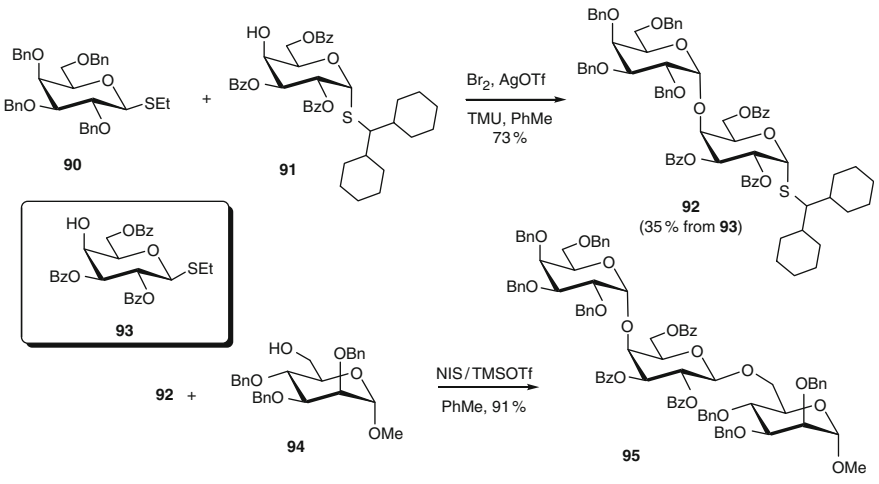


Scheme 20 Active–latent bulky thioglycoside in complex pentasaccharide synthesis [60]

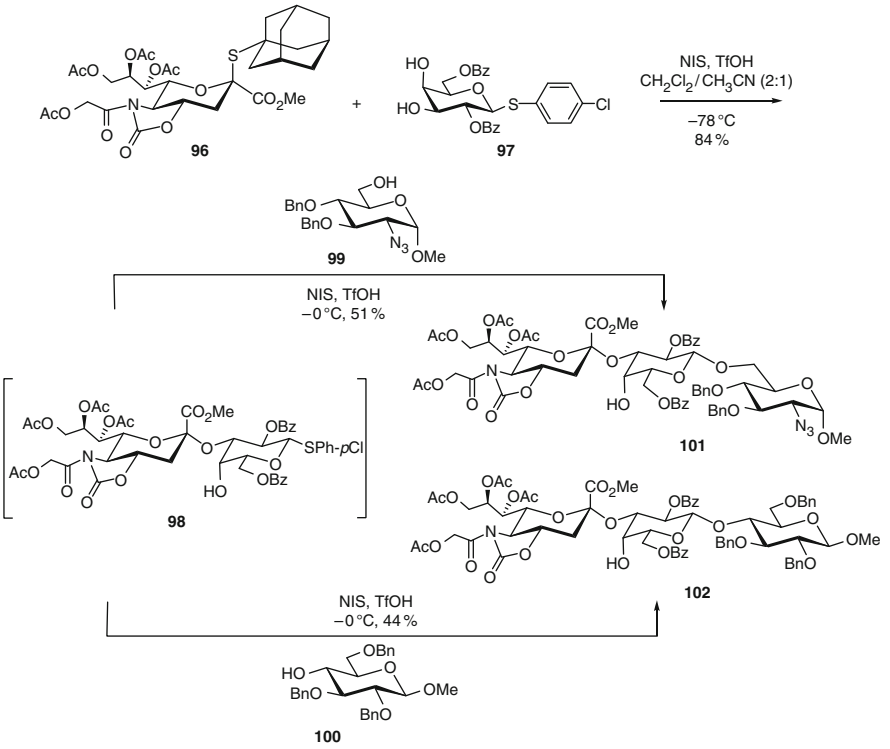
92 in 73% yield (Scheme 21). The use of the corresponding ethyl thioglycosides **93** afforded **92** in only 35% yield with concomitant formation of self-condensation.

In a recent paper, Crich and Wu elegantly explored the use of the very bulky *S*-adamantanyl thiosialoside together with locked *N*-acyloxazolidinone O-4/N-5 protecting group (**96**) to allow the highly stereoselective, one-pot multicomponent synthesis of α-sialylated oligosaccharides (Scheme 22) [65]. The analogous 5*N*-acetyl-5*N*,4*O*-oxazolidinone protected phenylthio sialoside has also been used previously as a stereocontrolling element from which the oxazolidinone group could be removed under mild basic hydrolysis leading directly to the naturally occurring *N*-acetyl oligosaccharides [68]. The α-selectivity of the phenylthio sialoside was further improved with the *S*-adamantanyl analog [69]. In the forthcoming description (Scheme 22), the *N*-glycolyl analog **96** was chosen because it was adequately armed to be utilized as the first component in a thioglycoside-based iterative one-pot oligosaccharide syntheses (see Sect. 6 below) and because the derived *N*-glycolyl α-sialosides have been identified as markers in a large number of human tumors [43–45].

Hence, *S*-adamantanylthio sialosyl donor **96** was treated with a panel of glycosyl acceptors, including "latent" thioglycosyl acceptors such as *p*-chlorophenylthio galactoside **97** to afford the α-sialylated disaccharide **98** in 84% yield using NIS/TfOH as promoter and the nitrilium effect provided by a mixture of acetonitrile and dichloromethane at −78°C (α/β = 6:1). To demonstrate further the "latent" nature of the resulting *p*-chlorophenylthio disaccharide intermediate, **98** was entered into a one-pot sequence of glycosidation leading to various trisaccharides such as **101** and **102** in close to 50% yields using NIS/TfOH at 0°C. Unfortunately, all attempts to remove selectively the oxazolidone moiety without concomitant cleavage of the glycolyl residue failed. Attempts to use the unprotected oxazolidinone derivative,



Scheme 21 Active–latent sterically congested thioglycoside in oligosaccharide synthesis [61]



Scheme 22 *S*-Adamantanyl thiosialoside in stereoselective one-pot *N*-glycolylneuraminic acid-containing oligosaccharide synthesis [65]

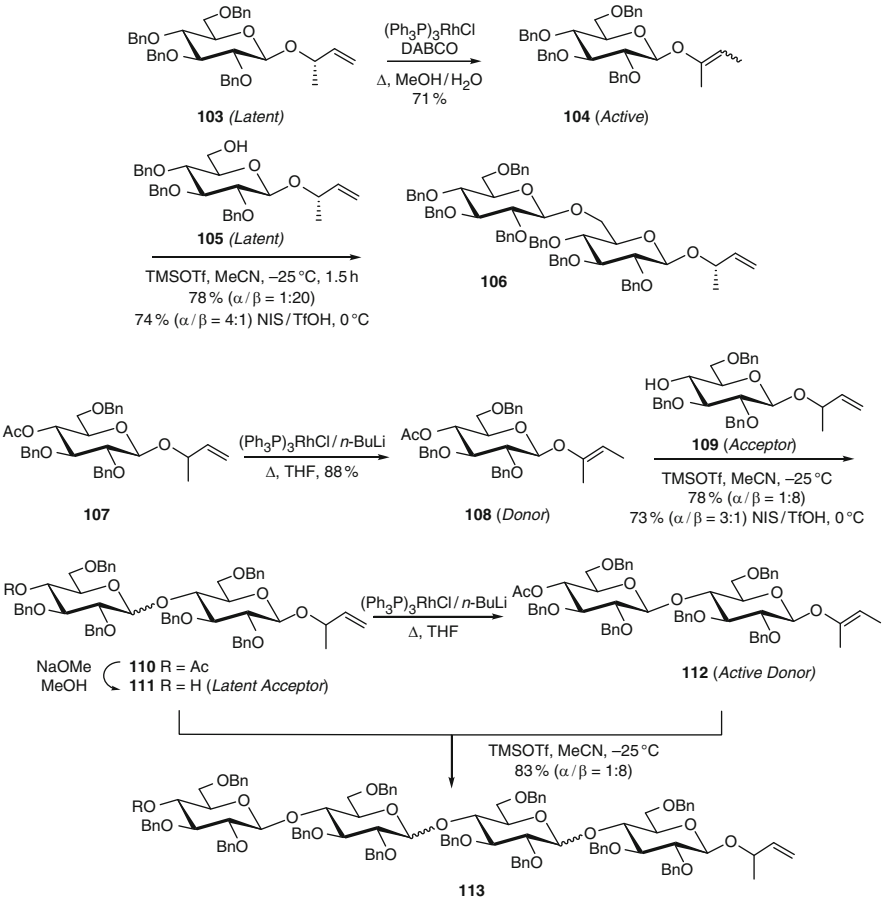
analogous to the work of Takahashi [70] and DeMeo [71] resulted in 1:1 mixture of anomers. Consequently, the authors necessitated the use of a three step protocol to restore fully the natural state of the required *N*-glycolyl sialosides (1: LiOH, EtOH-H_2O, 70°C; 2: acetoxyacetyl chloride MeCM-H_2O, $NaHCO_3$; 3: LiOH, H_2O) in yields ranging from 75% to 83%.

3.2 Vinyl vs Allyl Glycosyl Donors

In a series of papers directed at an extension of the electronic controlling aspects related to "active–latent" glycosylation principle using thioglycosides, Boons and coworkers [62–64] described the first examples wherein the controlling reactivities of glycosyl donors could be achieved using allyl ("latent") vs vinyl ("active") glycosides. To this end, they prepared 3-buten-2-yl glycosides as the inert component which could be activated into 2-buten-2-yl glycosides by a simple double bond isomerization using Wilkinson's catalyst (*tris*(triphenylphosphine)-rhodium(I) chloride) which in turn could undergo Lewis acid-catalyzed glycosidation.

The principle and application of this additional variant is described in Scheme 23 below. Synthesis of initial allyl glycosides such as **103** as a mixture of diastereoisomers was performed using racemic 3-buten-2-ol and standard procedures. However, the use of racemic alcohol, although with no direct consequence on the glycosylation outcome, complicated interpretation of NMR spectra all along. If desired, optically pure 3-buten-2-ol can be obtained in large quantity by resolution through its monophthalate ester using either (*S*)- or (*R*)-α-phenylethylamine salt [72].

Successful isomerization of latent **103** into its active vinylic form **104** was performed in 71% yield with Wilkinson's catalyst $(Ph_3P)_3RhCl$ and diazabicyclo [2.2.2]octane (DABCO) in refluxing methanol water [62, 63]. This critical step happened to be somewhat more difficult than initially anticipated and failed using other catalysts such as dihydrotetrakis(triphenylphosphine)ruthenium(II), *trans*-dichlorodiaminepalladium(II), or the more common 10% palladium on



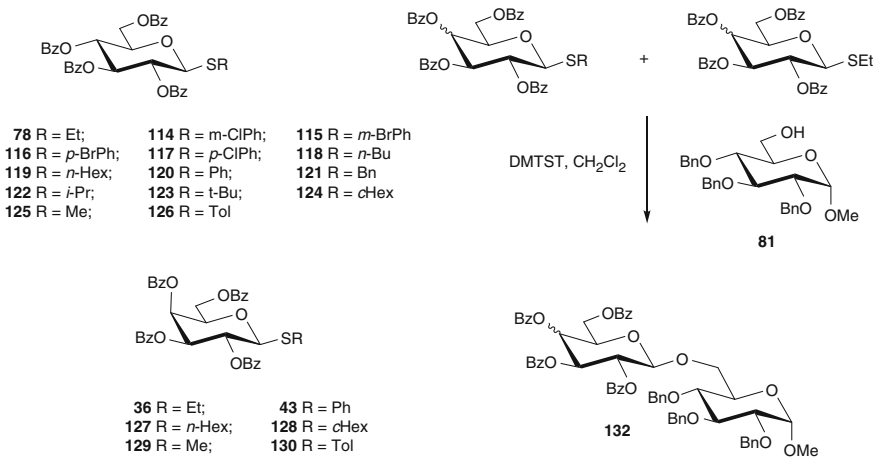
Scheme 23 Oligosaccharide synthesis using "active–latent" vinylic donors [63]

charcoal. Upon treatment with glycosyl acceptor **105**, disaccharide **106** could be obtained in varied anomeric ratios depending on the promoter used. With acetonitrile as solvent, the β-anomer was obtained as major product in 78% yield (20 β:1 α) due to the nitrilium effect [38] while the α-anomer was obtained as a major glycoside when NIS/TfOH was used as promoter in a mixture of CH_2Cl_2/Et_2O at 0°C.

An additional example was provided with the synthesis of β-(1–4)-linked tetrasaccharide **113** (Scheme 23). Toward this goal, allylic intermediate **107** was used as both precursor to the active donor form **108** and latent acceptor **109**. Compound **108** was obtained by isomerization into its vinylic state using this time, butyl lithium in refluxing THF (88% yield) while **109** was obtained by de-*O*-acetylated under usual Zemplén conditions (NaOMe, MeOH). It is noteworthy to mention that the 4-*O*-acetate in **107** resisted the harsher isomerization conditions. As described for disaccharide **106** above, the acid-catalyzed (TMSOTf or NIS/TfOH) glycosidation occurred uneventfully to provide intermediate disaccharide **110** in 78% (α/β = 1:8) and 73% (α/β = 3:1) yields, respectively. Reiteration of the process provided tetrasaccharide **113** in 83% yield using TMSOTf in acetonitrile (α/β = 1:8).

4 Quantitative Evaluation of Thioglycosyl Donors

In order to evaluate quantitatively the reactivity difference between thioglycosyl donors with variable aglycons, Lahman and Oscarson published a detailed account of their results [73]. Competitive glycosylations were performed using mainly ethyl thioglycosides (**Glc-78** or **Gal-36**) as reference donors and dimethyl(methylthio) sulfonium trifluoromethylsulfonate (DMTST) as promoter (Scheme 24) and the reaction mixtures were analyzed by HPLC. The results are summarized in Table 3.



Scheme 24 Panel of D-gluco- and D-galacto-thioglycosyl donors for quantitative structure activity relationship

Table 3 Relativity reactivity of thioglycosyl donors

Entry	Donor	Reference donor	Rel. react.
1	Gal-43 (Ph)	Gal-36 (Et)	<0.1
2	Glc-120 (Ph)	Glc-78 (Et)	0.1
3	Glc-126 (Tol)	Glc-78 (Et)	0.1
4	Gal-130 (Tol)	Gal-36 (Et)	0.2
5	Gal-43 (Ph)	Glc-78 (Et)	0.4
6	Glc-125 (Me)	Glc-78 (Et)	0.4
7	Gal-129 (Me)	Gal-36 (Et)	0.5
8	Glc-121 (Bn)	Glc-78 (Et)	0.7
9	Gal-130 (Tol)	Glc-78 (Et)	0.7
10	Glc-118 (*n*-Bu)	Glc-78 (Et)	0.7
11	Gal-127 (*n*-Hex)	Gal-36 (Et)	1.0
12	Glc-119 (*n*-Hex)	Glc-78 (Et)	1.0
13	Glc-122 (*i*-Pr)	Gal-36 (Et)	1.4
14	Gal-129 (Me)	Glc-78 (Et)	1.6
15	Glc-126 (Tol)	Glc-120 (Ph)	1.9
16	Gal-128 (cHex)	Gal-36 (Et)	2.1
17	Gal-127 (*n*-Hex)	Glc-78 (Et)	3.4
18	Glc-124 (*c*-Hex)	Glc-78 (Et)	3.6
19	Glc-125 (Me)	Glc-120 (Ph)	5.8
20	Glc-119 (*n*-Hex)	Glc-120 (Ph)	6.1
21	Gal-128 (cHex)	Glc-78 (Et)	10.3
22	Glc-123 (*t*-Bu)	Glc-78 (Et)	12.6 (Dec.)

As expected, the reactivity correlated well with the electronic density of the aglycon substituents. Interestingly, in comparison, tolyl (*p*-MePh) and phenyl glycosides were slow (Table 1, entries 1–4, 15, 19, and 20). This is important as this study nicely complements the thorough investigations performed by Wong and coworkers, who used tolyl thioglycosides for their "Programmable One-pot" oligosaccharide syntheses (see below) [74]. The differences were even more pronounced with halosubstituted phenyl derivatives, which were inert under the conditions used but known to be activated with better promoters such as NIS–AgOTf. Surprisingly, of the alkyl glycosides tested, the methyl derivative showed rather low reactivity (entries 6 and 7), whereas the *n*-butyl and benzyl glycosides were slightly faster (entries 8 and 10). The *n*-hexyl glycosides were comparable to the ethyl glycosides in reactivity (entries 11 and 12), while the branched alkyl glycosides, isopropyl and the previously unused cyclohexyl, were the most reactive donors with the cyclohexyl derivative being an effective donor (entries 13, 16, and 18). The *tert*-butyl glycoside disappeared fastest (entry 22), but mainly gave decomposition product of the donor and very little of the disaccharide. In contrast, the perbenzylated *tert*-butyl thioglucosyl donor was found to be an excellent donor.

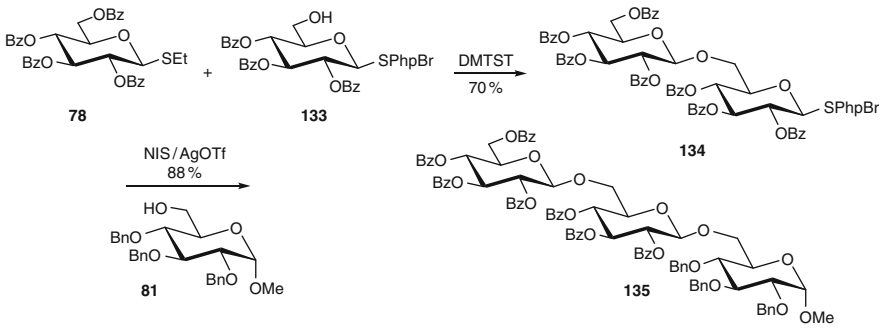
Competitive glycosylations between glucosyl and galactosyl donors showed the galactosides to be more reactive (Table **3**, entries 5, 9, 14, 17, and 21 compared with entries 2, 3, 6, 12, and 18, respectively). A good correlation between the different derivatives was obtained, with a reactivity difference of about three to four in favor of the galactoside, which is in good agreement with the results of Wong and

coworkers [74]. In general, one can state that the reactivity differences between thioglycosides differing only in their thiol aglycons are most often too small to allow efficient chemoselective couplings. However, as discussed above, *p*-nitrophenyl thioglycosides have been used as inert acceptors, but to function as donors they have to be activated by conversion of the nitro functionality into an *N*-acetamido group or by oxidation into the corresponding phenylsulfenyl donors.

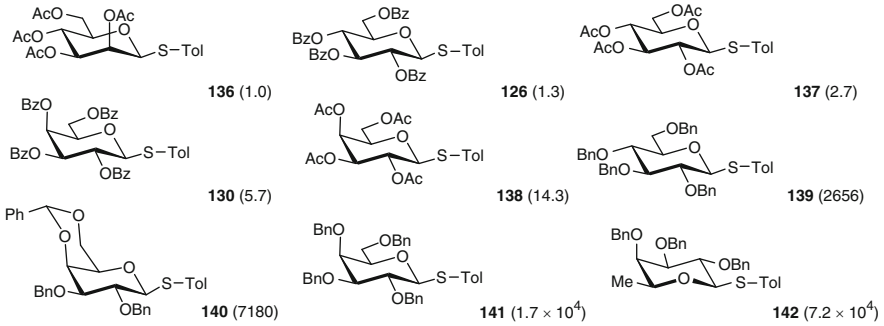
Couplings between some of the more reactive (cHex, *i*-Pr, Et) perbenzoylated glycosyl donors and less reactive acceptors (Ph, Tol, PhX, 4-OH, or 6-OH) were carried out, but were found to be ineffective due to concomitant activation of the supposed acceptor. The combination of thiocyclohexyl or thioethyl glycosides **78** or **124** as donors with thio *p*-Br-phenyl derivative **133** as acceptor, led however to efficient product formation (Scheme 25). The amount of promoter (DMTST) had to be reduced compared with those of standard conditions (1.5 equiv instead of 2–4 equiv), which not only slowed down the couplings but also effectively suppressed activation of the acceptor. The *p*-Br-phenyl group of the obtained disaccharide **134** could then be smoothly activated in a NIS–AgOTf promoted coupling with model acceptor **81** to produce trisaccharide **135** in high yield (88%) (Scheme 25).

To render accessible a "Programmable One-pot Oligosaccharide Synthesis" using thioglycosides, Wong and coworkers determined the relative reactivity values of a panel of thioglycosides using HPLC [30, 74]. A computerized program resulted from their findings and permitted the predictable assembly of two tetrasaccharides of biological interest. Scheme 26 below illustrates the range of reactivity observed from single *p*-methylphenyl thioglycosides (STol) extracted from a list of 50 different compounds. Other quantitative relative reactivity profiles of several glycosyl donors have been previously performed by NMR spectroscopy [75, 76].

From these data, it can be concluded that for fully acetylated STol donors, **Gal 138** (14.3) > **Glc 137** (2.7) > **Man 136** (1.0) and the trend is the same for the perbenzoylated species **Gal 130** (5.7) > **Glc 126** (1.3). The perbenzylated derivatives are, as expected, several times more reactive than their corresponding



Scheme 25 Programmable one-pot oligosaccharide syntheses using thioglycosyl donors of known relative reactivities



Scheme 26 Relative reactivity of various *S*-tolyl (*p*MePh) thioglycosides for programmable one-pot oligosaccharide syntheses [74]

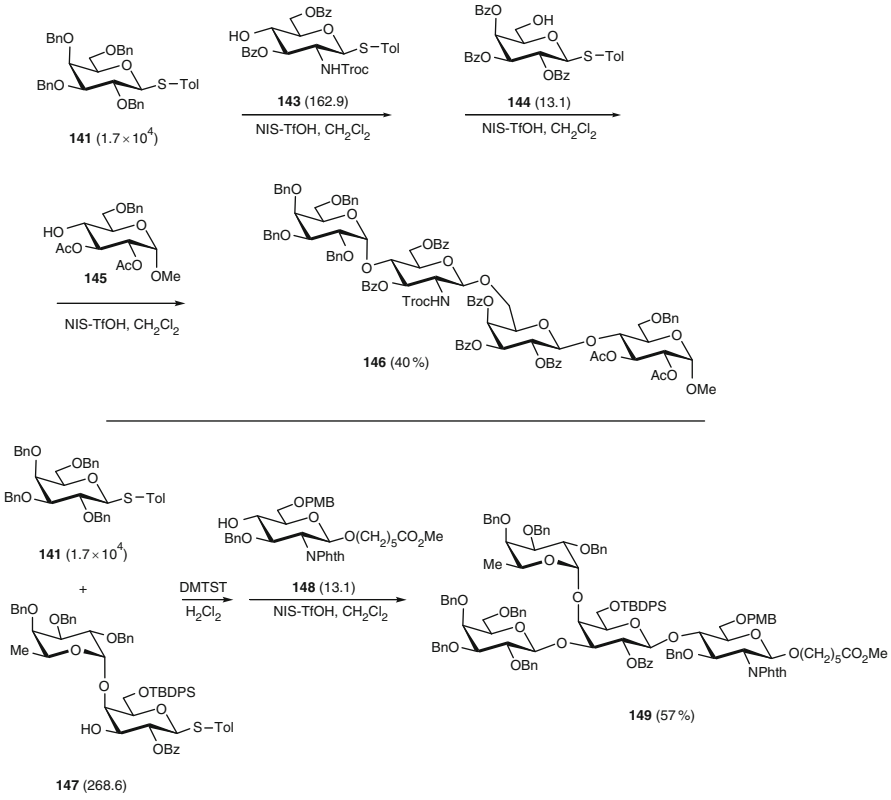
benzyl ethers **Gal 141** (1.7×10^4) > **Glc 139** (2656). Conformationally restricted benzylidene acetals are less reactive than their perbenzylated counterparts, i.e., **Gal 141** (1.7×10^4) > **Gal 140** (7180) and, 6-deoxy sugars (e.g., L-fucosides) represents extremely reactive species **Fuc 142** (7.2×10^4).

A practical extension of the use of thioglycosides in the arsenal of possible aglycons was provided by Sakairi and coworkers [77] who used dodecyl thioglycosides for another elegant synthesis of the Lewis[a] trisaccharide. The argument used in favor of their choice was the high boiling property of 1-dodecanethiol and hence odorless experimentation. They used 1-benzenesulfinyl piperidine (BSP) and triflic anhydride (Tf_2O) at −78°C for the coupling reactions (85%). An additional variant proposed the use of 5-nitro-2-pyridyl thioglycosides as stable and reactive acceptors which could resist glycosidation of disarmed thiomethyl glycoside acceptors [78]. Davis and coworkers have also identified that their mixed glycosyl disulfides (Sugar-SSR), normally used as glycoconjugate precursors, could also efficiently act as glycosyl donors in either armed (ether) or disarmed (ester) protected states [79] (Scheme 27).

5 Other Factors Controlling the Reactivity of Thioglycosides

5.1 Conformationally Locked Thioglycosyl Donors

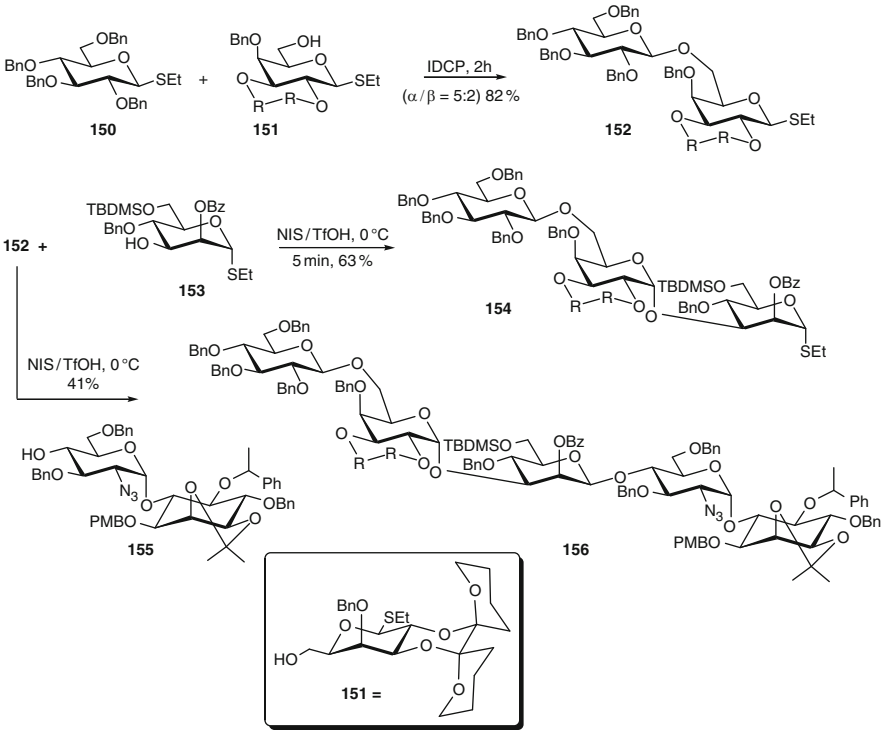
An additional useful controlling element in thioglycosides-based glycosylation, in close analogy to that obtained from "armed–disarmed" glycosyl donors, has been nicely introduced by the group of Ley [80, 81]. An exemplary application of conformationally locked dispiroketal ("dispoke acetal") has been used toward the synthesis of the pentasaccharide unit common to the surface glycoprotein of *Trypanosoma brucei* [81, 82].



Scheme 27 Representative cases of one-pot oligosaccharide syntheses [74]

In this powerful demonstration of the effect of protecting groups on the reactivity of thioglycosides, it was shown that benzylated thioethyl glucoside **150** could be used as the "active" donor, while the dispiroketal **151** served as the "latent" partner to provide disaccharide **152** (α/β = 5:2) in 82% yield using IDCP as promoter (Scheme 28). In return, dispiroketal **152** was subsequently used with either "disarmed" thioethyl glycoside acceptor **153** to give trisaccharide **154** in 63% yield with NIS/TfOH or alternatively with **155** to afford pentasaccharide-like structure **156** in 41% yield with the same potent promoter. It was thus concluded that dispiroketal-protected thioglycosides had reactivities between those of "armed" (ethers) and "disarmed" (esters) glycosyl donors (semidisarmed).

The usefulness of dispiroketal to act as practical glycosyl donors was further illustrated in a facile one-pot synthesis of a trisaccharide fragment from the capsular polysaccharide of Group B *Streptococci* [80]. In the following example (Scheme 29), "armed" perbenzylated ethyl 1-thio-α-L-rhamnopyranoside donor **157** was treated with "semidisarmed" dispiroketal **158** under IDCP promoted glycosylation to provide disaccharide **159** in 59% yield. Glycosidation of acceptor **159** with acceptor **160** with the more potent NIS/TfOH couple afforded protected

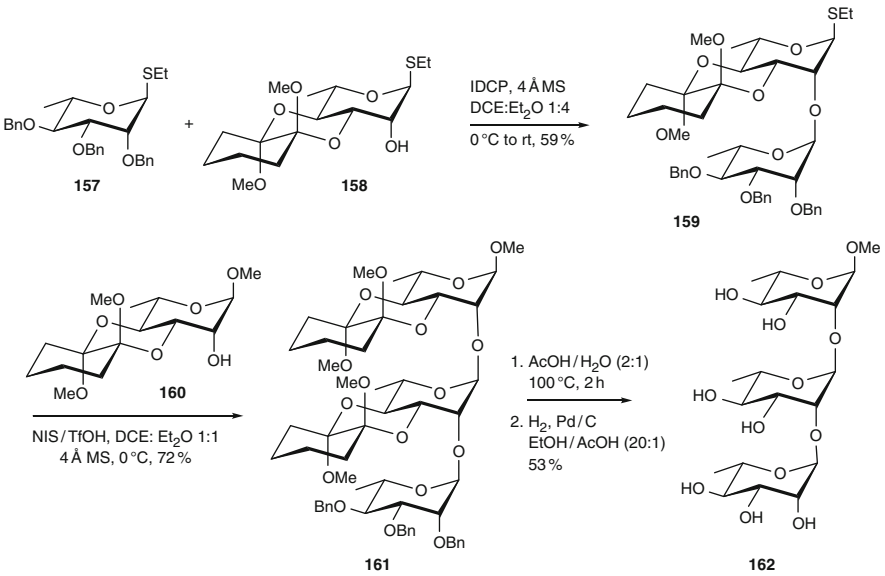


Scheme 28 Synthesis of GPI anchor of *Trypanosoma brucei* pentasaccharide using conformationally locked thioethyl glycosyl donors [81]

trisaccharide **161** which upon standard deprotection gave the target trisaccharide **162** in 53% overall yield.

In addition to dispiroketals, acetonide, and benzylidene acetals, conventionally used as "conformational locking" elements for the fine tuning reactivity of thioglycosides [65, 68, 69, 83–86] and other types of glycosyl donors, *trans*-2,3-cyclic carbonates, and analogs have also received consideration (see for instance Scheme 22) above. For instance, it has been demonstrated that *trans*-2,3-cyclic carbonates deactivated the anomeric center of thioglycosides both electronically and conformationally and that they had lesser reactivities than the corresponding ester-protected thioglycosyl donors [83]. Moreover, they were shown to provide, under suitable conditions, respectable α-anomeric selectivities.

Scheme 30 illustrates several applications of this additional strategy. Hence, carbonate-protected ethylthio glycosyl donor **163** reacted with various ethylthio glycosides bearing esters (**36** (Bz), **165** (Lev)) or *N*-phthalimide (**167**) by means of the effective promoter NIS/TMSOTf to provide disaccharides **164**, **166**, and **168** in yields ranging from 47% to 81%. Crucially, attempts to use these strongly disarmed ethylthio glycosides as glycosyl donors with strong promoters such as NIS/TMSOTf, MeOTf, and dimethyl(thiomethyl)sulfonium triflate (DMTST) [39]



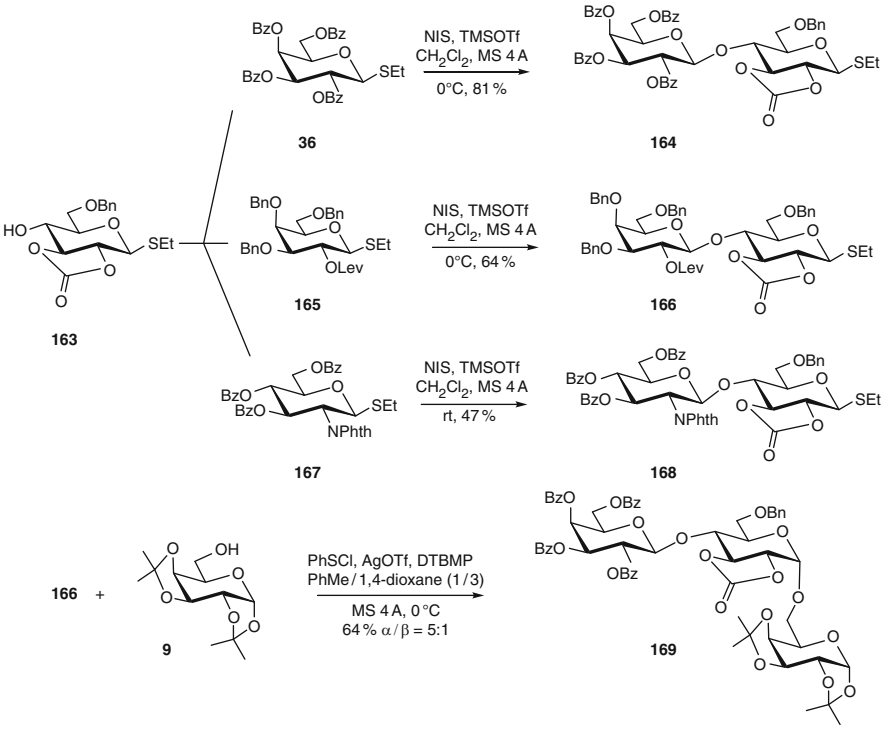
Scheme 29 A facile one-pot synthesis of rhamnoside trisaccharide fragment from the Group B Streptococci capsular polysaccharide antigen [80]

failed or gave complex reaction mixtures. Fortunately, PhSOTf, generated in situ from PhSCl and AgOTf [87] proved to be efficient and afforded trisaccharide **169** in 64% yield ($\alpha/\beta = 5{:}1$) with acceptor **9**.

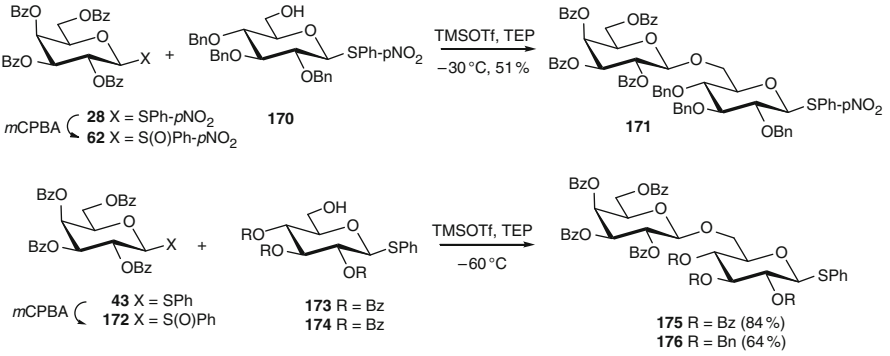
In conclusion, while 2,3-dispiroketals provided thioglycosyl donors of reactivities between those of ethers and esters, the *trans*-2,3-cyclic carbonates described above gave thioglycosyl of lesser reactivities than esters ("armed → disarmed = ethers > dispiroketals > esters > cyclic 2,3-carbonates").

5.2 Sulfoxides

As depicted above in Scheme 13, an additional aglycon transformation leading to "active" thioglycosyl donors issued from their "latent" precursors could also be achieved by oxidation [56, 57]. Van Boom and coworkers later helped confirming these observations by chemoselectively glycosylating two *p*-nitrophenylthio glycosides. Therefore, "disarmed-latent" ester-protected galactoside **28** was suitably activated as a "disarmed-active" donor **62** by *m*CPBA oxidation which in turn could be glycosidated with "armed-latent" acceptor **170** using TMSOTf/TEP in 51% yield (Scheme 31) [88]. Additionally, sulfoxide **172** could be similarly glycosidated employing either "disarmed" (**173**) or "armed" (**174**) acceptors to provide β-(1–6)-linked disaccharides **175** and **176** in 84% and 64% yield, respectively. It is worth mentioning that some of these transformations did not proceed well in the



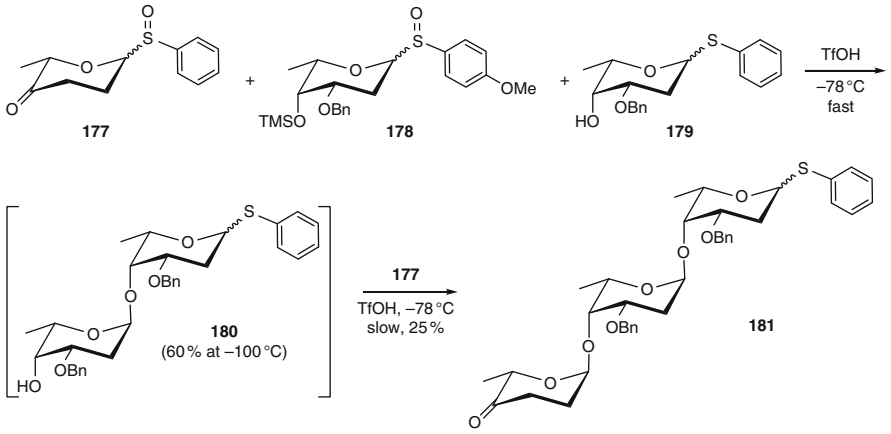
Scheme 30 Chemoselective glycosylations using thioglycosides protected as *trans*-2,3-cyclic carbonates [83]



Scheme 31 Chemoselective interplay of "armed–disarmed" thioglycosyl donors activated by oxidation into glycosyl sulfoxides [7]

absence of triethylphosphite (TEP) which was acting by deoxygenation of arylsulfenyl trimethylsilyl esters transiently formed through activation by TMSOTf.

Raghavan and Kahne used these principles to provide a one-step synthesis of the ciclamycin 0 trisaccharide **181** as depicted in Scheme 32 which further demonstrates



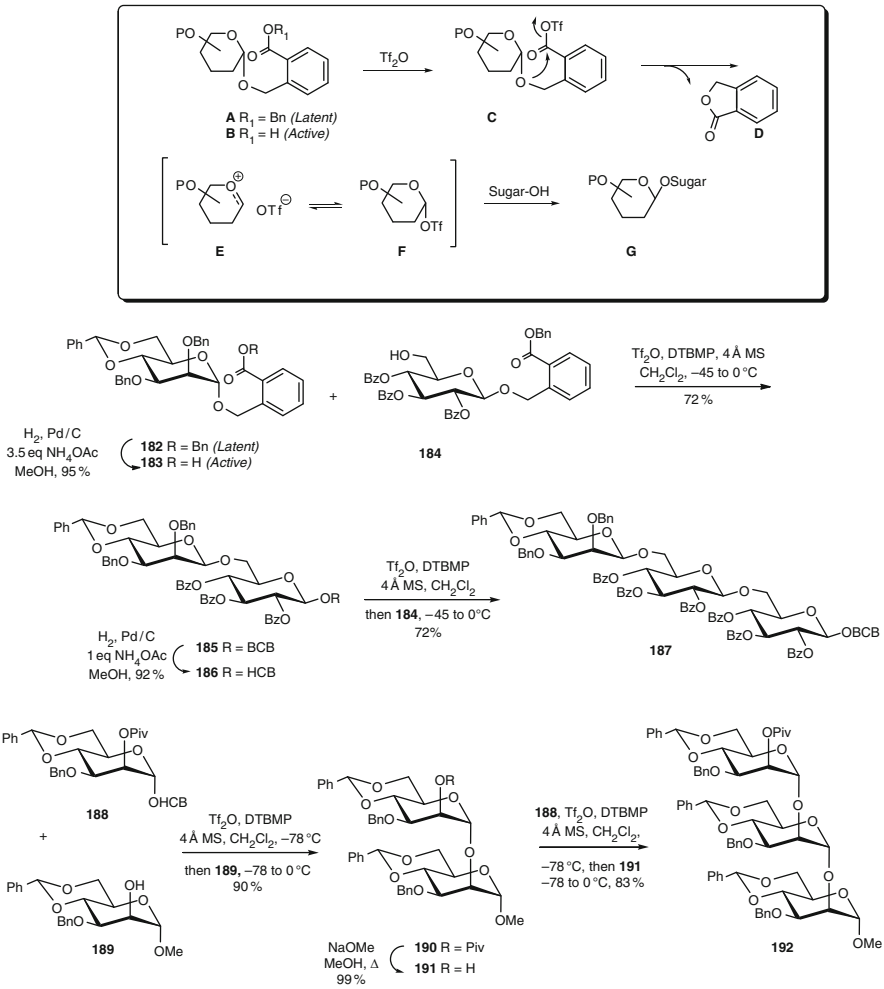
Scheme 32 One-pot synthesis of the ciclamycin 0 trisaccharide by the chemoselective arylsulfoxide method

the usefulness of the "active–latent" technology in the case of 2-deoxy sugars together with the relative reactivity profiles of phenylsulfoxide **177**, *p*-MeO-phenylsulfoxide **178**, and the phenylthio glycoside acceptor **179** [57]. Similarly, they later applied their strategy to the efficient syntheses of the blood group antigens Le^a, Le^b, and Le^x trisaccharides [89]. In these syntheses, the authors reported that the sulfoxide method could be used throughout the entire synthetic scheme, a situation rarely possible in such complex oligosaccharide syntheses. Thus, the three oligosaccharides were prepared using triflic anhydride (Tf_2O, DTBMP, CH_2Cl_2, −78°C to −30°C, 1 h) in approximately 80% yields. The same group also reported the efficient synthesis of the glycon portion of the powerful antibiotic Vancomycin [90].

5.3 2′-Carboxybenzyl Glycosides

Kim and coworkers elegantly further expanded the notion of active and latent aglycons by designing novel 2-(benzyloxycarbonyl)benzyl (BCB) glycosides that could be reiteratively transformed into active and latent forms using simple chemoselective debenzylation [91–101]. In this new strategy, an inactive form of the glycosyl donor (**A**) has its aglyconic benzyl ester hydrogenolyzed into the active acid form (**B**) (box in Scheme 33). By treatment with triflic anhydride (Tf_2O) and di-*tert*-butylmethylpyridine (DTBMP) at −78°C, the acid **B** is rapidly transformed into a mixed anhydride **C** that loses the neutral lactone **D** with the ensuing formation of the oxacarbenium ion **E**. At the low temperature of the reaction, oxacarbenium ion **E** is in equilibrium with the anomeric α-triflate **F** which undergoes typical glycosidation [102].

Two typical examples are illustrated in Scheme 33 [91] wherein latent BCB mannoside **182** is transformed into its active form **183** by the mild hydrogenolysis



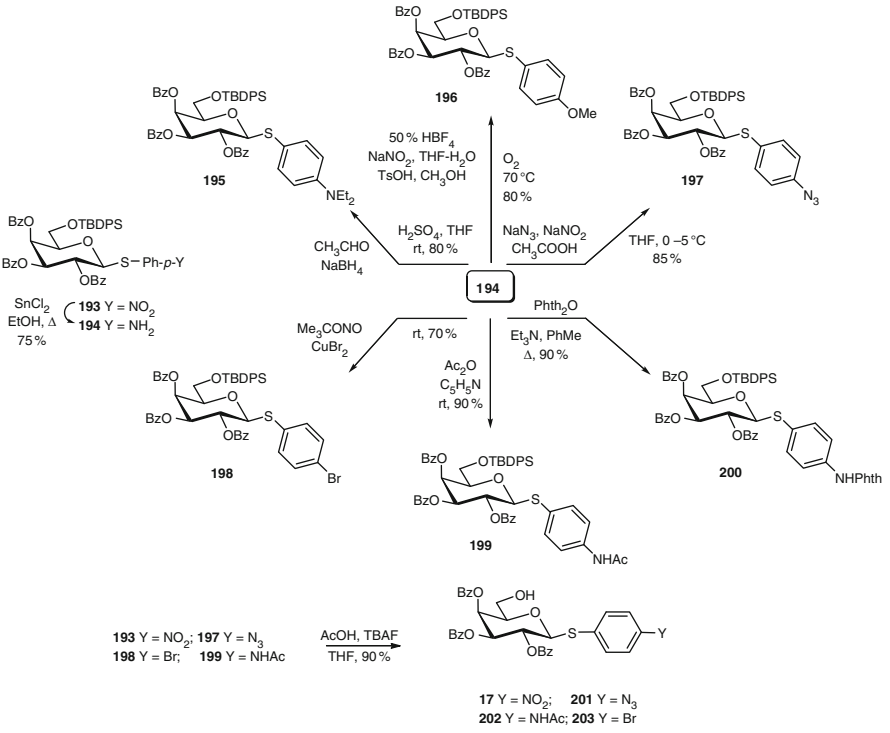
Scheme 33 "The active–latent" 2′-carboxybenzyl glycosides: concept and oligosaccharide syntheses [91]

of the aglyconic benzyl ester ensured by the suppressing presence of ammonium acetate [103]. When the active donor **183** was treated with the latent acceptor **184** using Tf_2O/DTBMP at −45°C, disaccharide **185** was obtained in 72% yield. Transformation of ester **185** into its reactive intermediate acid **186** (92%) followed by the one-pot activation through mixed anhydride formation and glycosidation with acceptor **184** yielded trisaccharide **187** as the expected β-anomer (72%) [104]. Similarly, treatment of active HCB glycosyl donor **188** with acceptor **189** under analogous conditions afforded disaccharide **190** (90%) which after depivaloylation (**191**, 99%) and glycosylation with **188** gave trisaccharide **192** in 83% yield. Subsequent work by the same group allowed access to mannosylated

tetrasaccharide [92], 2-deoxy glycosides [93], trisaccharide repeating unit of the O-antigen polysaccharide from Danish *Helicobacter pylori* [94, 100], octaarabinofuranoside repeating unit from arabinogalactan [96], antineoplastic glycosphingolipid agelagalastatin [97], C-glycosides [98], and the tetrasaccharide repeating unit of the O-antigen from *E. coli* 077 [99]. The work described by Kim's group has been highlighted in a recent review [101, 102].

6 One-Pot Oligosaccharide Syntheses Using the "Active–Latent" Thioglycoside Methodology

Huang and coworkers nicely exploited the general concept presented throughout this chapter by expanding the family of active arylthio glycosyl donors that could be efficiently used through postsynthetic modifications of the aglycons [105, 106]. In the above discussions, transformation of the "latent" nitro group into the "active" form was restricted to its *N*-acetamido derivative [32–34, 53, 54]. Scheme 34 illustrates further transformations by first reducing the nitro group in **193** into an amine **194** using tin(II) chloride as before. Three subgroups of glycosyl donors of increasing reactivities were then generated. Interestingly, and as expected [74], the

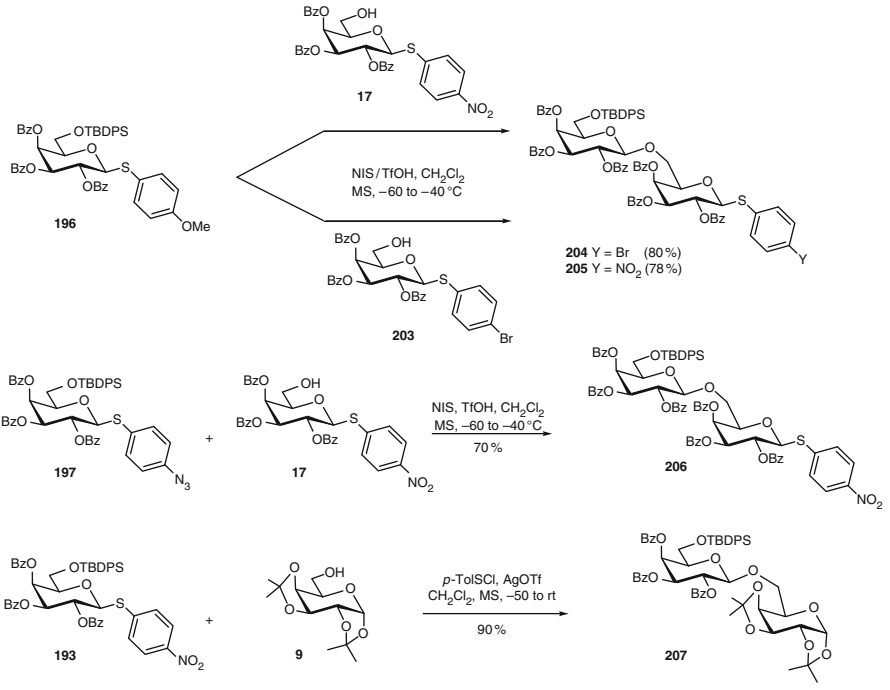


Scheme 34 Thioglycosides reactivity tuning by postsynthetic aglycon modifications [106]

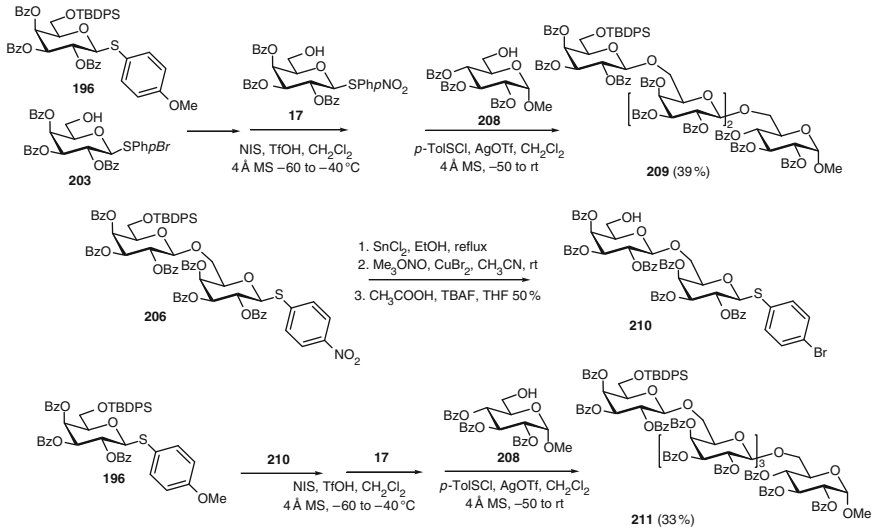
glycosidation potencies of the newly introduced donors matched well with the chemical shifts of the anomeric protons. As a general rule, it was anticipated that the electron-rich aryl glycosides (**195**, **196**, δ H-1 NMR 4.78 and 4.82 ppm) would be more reactive than the middle group (**197–199**, H-1 NMR 4.87 and 4.90 ppm) and even more reactive than the group bearing strongly electron-withdrawing substituents (**193**, **200**, δ H-1 NMR 5.05 and 5.08 ppm). The O-6 TMDPS-protecting group of compounds **193**, **197–199** was then removed with TBAF to generate acceptors **17**, **202** and **203**. Transformations of the *p*-nitrophenylthio galactosides into the other forms follow the details included in Scheme 34 [105, 106].

The most active *p*-methoxyphenylthio galactoside **196** was treated with acceptors **17** (*p*-NO_2) and **203** (*p*-Br) to give disaccharides **204** and **205** in 80% and 78% yields, respectively under NIS/TfOH promoted glycosidations (Scheme 35). Analog **197** (*p*-N_3) was also treated with acceptor **17** to provide disaccharide **206** in 70% yield under similar conditions. It was also found that the more poorly reactive "disarmed-latent" glycosyl donor **193**, known to be unreactive toward mild thiophilic reagents (see Scheme 8), could be efficiently activated with *p*-toluenesulfenyl triflate (*p*-TolOTf) [87] generated in situ from *p*-TolSCl and AgOTf to give, with acceptor **9**, the disaccharide **207** in 90% yield.

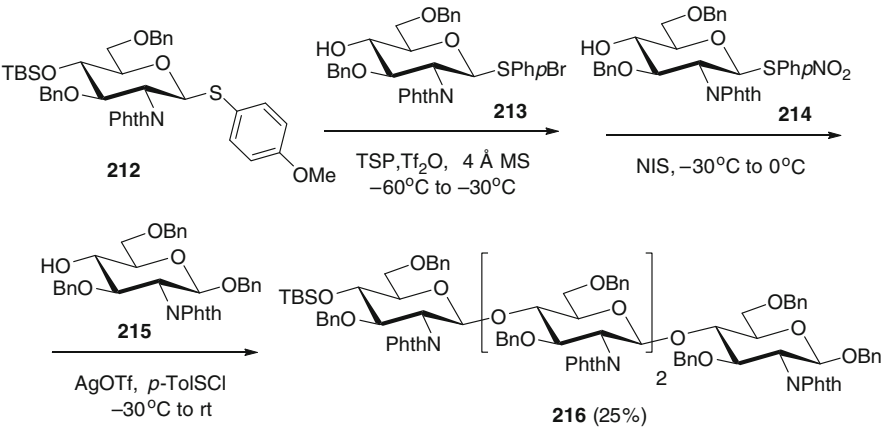
Having established the relative reactivity potential of the above donors and acceptors, the same group [107] then performed an efficient synthesis of oligosaccharides in a one-pot strategy through a single purification. The synthesis of tetra-



Scheme 35 Glycosidation of *p*-substituted arylthio galactosides [106]



Scheme 36 Glycosidation of *p*-substituted arylthio galactosides



Scheme 37 Glycosidation of *p*-substituted arylthio galactosides

209 and pentasaccharide **211** are depicted in Scheme 36. While tetrasaccharide **209** was obtained in 39% overall yield through a linear sequence, pentasaccharide **211** was obtained in 33% overall yield through a semiconvergent synthesis in order to demonstrate that the reactivity tuning could be achieved at the aglycon level. To this end, the nitro group in preformed disaccharide **206** was transformed into a bromide **210** of intermediate reactivity which underwent the one-pot process as above to afford **211**.

Finally, an analogous one-pot sequence was followed to prepare the chitinooligosaccharide **216** obtained in 25% overall yield (Schemes 36 and 37).

7 Conclusion and Perspectives

Given their ease of preparation with Lewis acids or under PTC conditions, the low cost of thiols, high storage stability, the large choice of promoters, and the possibility to merge electronic as well as steric controlling elements, thioglycosides still constitute appealing and practical glycosylating species that are barely met. They have been shown to be elegantly introduced into solid-phase and one-pot oligosaccharide syntheses. Moreover, novel promoters are constantly discovered and hence add to our arsenal of activating reagents, thus providing even more flexibilities into our synthetic design (for additional recent examples see [107–109]).

The fine tuning characteristics of solvents, protecting groups, and conformational locking functions all constitute additional powerful tools with which carbohydrate chemists can count on. The programmable one-pot synthesis put forward by the group of Wong [74] can obviously be extended to other families of thioglycosides. The finding that "latent" nitrophenyl groups can be transformed not only into "active" species by oxidation, reduction/N-acetylation but also into other varied electron-rich functionalities opens new directions and possibilities that further warrant exploration [105, 106].

Acknowledgments This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC). RR is especially grateful to the many coworkers, graduate students, and postdoctoral fellows, past and present, who have significantly contributed to his research activities and to NSERC and UQAM for generous supports through a Canadian Research Chair in Therapeutic Chemistry.

References

1. Paulsen H (1982) Angew Chem Int Ed Engl 21:155
2. Schmidt RR (1986) Angew Chem Int Ed Engl 25:212
3. Banoub J, Boullanger P, Lafont D (1992) Chem Rev 92:1167
4. Toshima K, Tatsuta K (1993) Chem Rev 93:1503
5. Schmidt RR, Kinzy W (1994) Adv Carbohydr Chem Biochem 50:1419
6. Danishefsky SJ, Bilodeau MT (1996) Angew Chem Int Ed Engl 35:1380
7. Boons GJ (1996) Tetrehedron 52:1095
8. Norberg T (1996) In: Khan SH, O'Neill RA (eds) Modern methods in carbohydrate synthesis. Harwood Academic, Amsterdam, p 82
9. Garegg PJ (1997) Adv Carbohydr Chem Biochem 52:179
10. Fraser-Reid B, Madsen R (1997) In: Hanessian S (ed) Preparative carbohydrate chemistry. Marcel Dekker, New York, pp 339–356
11. Davis B (2000) J Chem Soc Perkin Trans 1 2137
12. Boons GJ, Demchenko AV (2000) Chem Rev 100:4539
13. Hanessian S, Lou B (2000) Chem Rev 100:4443
14. Seeberger PH, Haase WC (2000) Chem Rev 100:4349
15. Koeller KM, Wong CH (2000) Chem Rev 100:4465
16. Oscarson S (2000) In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley, Weinheim, pp 93–116

17. Nicolaou KC, Mitchell HJ (2001) Angew Chem Int Ed Engl 40:1576
18. Demchenko AV (2003) Curr Org Chem 7:35
19. El Ashry ESH, Awad LF, Atta AI (2006) Tetrahedron 62:2943
20. Crich D (2007) ACS Symp Ser 960:60
21. Cai F, Wu B, Crich D (2009) Adv Carbohydr Chem Biochem 62:251
22. Roy R, Andersson FO, Letellier M (1992) Tetrahedron Lett 33:6053
23. Cao S, Meunier SJ, Andersson FO, Letellier M, Roy R (1994) Tetrahedron Asymmetry 5:2303
24. Cao S, Roy R (1996) Tetrahedron Lett 37:3421
25. Cao S, Hernández-Matéo F, Roy R (1998) J Carbohydr Chem 17:609
26. Sasaki M, Tachibana K, Nakanishi J (1991) Tetrahedron Lett 32:6873
27. Veeneman GH, van Boom JH (1990) Tetrahedron Lett 31:275
28. Veeneman GH, van Leeuwen SH, van Boom JH (1990) Tetrahedron Lett 31:1131
29. Konradsson P, Udolong UE, Fraser-Reid B (1990) Tetrahedron Lett 31:4313
30. Roy R, Tropper FD, Cao S, Kim JM (1997) ACS Symp Ser 659:163
31. Roy R (1997) In: Sasson Y, Neumann R (eds) Handbook of phase transfer catalysis, chap 7. Chapman and Hall, London, pp 244–275
32. Roy R, Letellier M, Fenske E, Jarell HC (1990) J Chem Soc Chem Commun 378
33. Kuhn R, Lutz P, McDonald DL (1966) Chem Ber 99:611
34. Roy R, Laferrière CA (1990) Can J Chem 68:2045
35. Murase T, Ishida H, Kiso M, Hasegawa A (1988) Carbohydr Res 184:C1
36. Fügedi P, Garegg PJ (1986) Carbohydr Res 149:C9
37. Ogawa T, Sugimoto M (1984) Carbohydr Res 128:Cl
38. Hasegawa A, Nagahama T, Ohki H, Hotta K, Ishida H, Kiso J (1991) J Carbohydr Chem 10:493
39. Kirchner E, Thiem F, Dernick R, Henkeshoren J, Thiem J (1988) J Carbohydr Chem 7:453
40. Paulsen H, Tietz H (1984) Carbohydr Res 125:47
41. Okamato K, Goto T (1990) Tetrahedron 46:5835
42. Lönn H, Stenvall K (1992) Tetrahedron Lett 33:115
43. Varki A (1993) Glycobiology 3:97
44. Chen X, Varki A (2010) ACS Chem Biol 5:163
45. Angata T, Varki A (2002) Chem Rev 102:439
46. Hanai N, Nores GA, MacLeod C, Torres-Mendez CR, Hakomori SJ (1988) Biol Chem 263:10915
47. Roy R (2002) J Carbohydr Chem 21:769
48. Sliedregt LAJM, Zegelaar-Jaarsveld K, van der Marel GA, van Boom JH (1993) Synlett 5:335
49. Sliedregt LAJM, van der Marel GA, van Boom JH (1994) Proc Indian Acad Sci 106:1213
50. Andersson F, Birberg W, Fugedi P, Garegg PJ, Nashed M, Pilotti A (1989) ACS Symp Ser 386:117
51. Ohrui H, Nishida Y, Itoh H, Meguro H (1991) J Org Chem 56:1726
52. Bongat AFG, Demchenko AV (2007) Carbohydr Res 342:374
53. Cao S (1996) Ph.D. Dissertation, University of Ottawa, Canada
54. Gan Z, Cao S, Wu Q, Roy R (1999) J Carbohydr Chem 18:755
55. Garegg PJ, Hultberg H, Wallin S (1982) Carbohydr Res 108:97
56. Kahne D, Walker S, Cheng Y, Engen D (1989) J Am Chem Soc 111:6881
57. Raghavan S, Kahne D (1993) J Am Chem Soc 115:1580
58. Blanc-Muesser M, Defaye J, Driguez H (1978) Carbohydr Res 67:305
59. Boons G-J, Geurtsen R, Holmes D (1995) Tetrahedron Lett 36:6325
60. Geurtsen R, Holmes DS, Boons G-J (1997) J Org Chem 62:8145
61. Geurtsen R, Boons G-J (2002) Tetrahedron Lett 43:9429
62. Boons GJ, Isles S (1994) Tetrahedron Lett 35:3593
63. Boons GJ, Isles S (1996) J Org Chem 61:4262
64. Boons GJ, Heskamp B, Hout F (1996) Angew Chem Int Ed Engl 35:2845
65. Crich D, Wu B (2008) Org Lett 10:4033

66. Strijtveen B, Kellog RM (1986) J Org Chem 51:3664
67. Lemieux RU, Hendriks KB, Stick RV, James K (1975) J Am Chem Soc 97:4056
68. Crich D, Li W (2007) J Org Chem 72:2387
69. Crich D, Li W (2007) J Org Chem 72:7794
70. Tanaka H, Nishiura Y, Takahashi T (2006) J Am Chem Soc 128:7124
71. Farris MD, DeMeo C (2007) Tetrahedron Lett 48:1225
72. Grattan TJ, Whitehurst JS (1990) J Chem Soc Perkin Trans 1 11
73. Lahmann M, Oscarson S (2002) Can J Chem 80:889
74. Zhang Z, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) J Am Chem Soc 121:745
75. Douglas NL, Ley SV, Lucking U, Warriner SL (1998) J Chem Soc Perkin Trans 1 51
76. Wu C-Y, Wong C-H (2011) Programmable one-pot glycosylation. In: Topics in current chemistry. Springer, Heidelberg. doi: 10.1007/128_2010_109
77. Son SH, Tano C, Furuike T, Sakairi N (2009) Carbohydr Res 344:285
78. Pastuch G, Wandzik I, Szeja W (200) Tetrahedron Lett 41:9923
79. Davis BG, Ward SJ, Rendle PM (2001) Chem Commun 189
80. Ley SV, Priepke HWM (1994) Angew Chem Int Ed Engl 33:2292
81. Boons G-J, Grice P, Leslie R, Ley SV, Yeung LL (1993) Tetrahedron Lett 34:8523
82. Gómez AM (2011) A survey of Ley's reactivity tuning in oligosaccharide synthesis. In: Topics in current chemistry. Springer, Heidelberg. doi: 10.1007/128_2010_112
83. Zhu T, Boons GJ (2001) Org Lett 3:4201
84. Crich D, Jayalath P (2005) J Org Chem 70:7252
85. Crich D, Subrammanian V, Hutton TK (2007) Tetrahedron 63:5042
86. Crich D, Sharma I (2008) Org Lett 10:4731
87. Martichonok V, Whitesides GM (1996) J Org Chem 61:1702
88. Sliedregt LAJM, van der Marel GA, van Boom JH (1994) Tetrahedron Lett 35:4015
89. Yan L, Kahne D (1996) J Am Chem Soc 118:9239
90. Thompson C, Ge M, Kahne D (1999) J Am Chem Soc 121:1237
91. Kim KS, Kim JH, Lee YJ, Lee YJ, Park J (2001) J Am Chem Soc 123:8477
92. Kim KS, Seo YS, Kim HJ, Lee YJ, Jeong K-S (2003) Synlett 9:1311
93. Kim KS, Park J, Lee YJ, Seo YS (2003) Angew Chem Int Ed 42:459
94. Kwon YT, Lee YJ, Lee K, Kim KS (2004) Org Lett 6:3901
95. Lee YJ, Lee K, Jung EH, Jeon HB, Kim KS (2005) Org Lett 7:3263
96. Lee YJ, Lee B-Y, Jeon HB, Kim KS (2006) Org Lett 8:3971
97. Lee YJ, Baek JY, Lee B-Y, Kang SS, Park H-S, Jeon HB, Kim KS (2006) Carbohydr Res 341:1708
98. Lee BR, Jeon JM, Jung JH, Jeon HB, Kim KS (2006) Can J Chem 84:506
99. Fulse DB, Jeon HB, Kim KS (2007) J Org Chem 72:9963
100. Kim KS, Jeon HB (2007) ACS Symp Ser 960:134
101. Kim KS, Suk DH (2011) Effect of electron-withdrawing protecting groups at remote positions of donors on glycosylation stereochemistry. In: Topics in current chemistry. Springer, Heidelberg. doi:10.1007/128_2010_107
102. Crich D (2010) Acc Chem Res 43:1144
103. Sajiki H (1995) Tetrahedron Lett 36:3465
104. Aubry S, Sasaki K, Sharma I, Crich D (2011) Influence of protecting groups on the reactivity and selectivity of glycosylation: chemistry of the 4,6-*O*-benzylidene protected mannopyranosyl donors and related species. In: Topics in current chemistry. Springer, Heidelberg. doi: 10.1007/128_2010_102
105. Huang L, Wang Z, Huang X (2004) Chem Commun 1960
106. Li X, Huang L, Hu X, Huang X (2009) Org Biomol Chem 7:117
107. Cura P, Aloui M, Kartha KPR, Field RA (2000) Synlett 9:1279
108. Tatai J, Fügedi P (2007) Org Lett 9:4647
109. Crich D, Cai F, Yang F (2008) Carbohydr Res 343:1858

Top Curr Chem (2011) 301: 109–140
DOI: 10.1007/128_2010_107

Published online: 13 January 2011

Effect of Electron-Withdrawing Protecting Groups at Remote Positions of Donors on Glycosylation Stereochemistry

Kwan Soo Kim and Dae-Hwan Suk

Abstract Here we review the equatorial β-directing effects of electron-withdrawing protecting groups at remote positions of mannopyranosyl donors, mannuronate donors, rhamnopyranosyl donors, and 2,6-dideoxyglucopyranosyl donors. We discuss the equatorial α-directing effect of an electron-withdrawing group at the N-5 position of sialyl donors. The proposed mechanism and origin of some of the equatorial β-directing effects are described. We also review the effects of potentially participating, electron-withdrawing protecting groups at remote positions of glycopyranosyl and glycofuranosyl donors on the glycosylation stereochemistries. Further, we present substantial evidence in favor of the remote participation by the electron-withdrawing protecting groups and also include reports that are opposed to remote participation.

Keywords Directing effect, Electron-withdrawing protecting groups, Glycosylation, Remote participation, Remote protecting group

Contents

K.S. Kim (✉) and D.-H. Suk
Center for Bioactive Molecular Hybrids and Department of Chemistry, Yonsei University, Seoul 120-749, Korea
e-mail: kwan@yonsei.ac.kr

1 Introduction

The selection of appropriate protecting groups is one of the most important steps in the synthesis of complex oligosaccharides. The protecting groups in the oligosaccharide synthesis are used to block selectively interfering functions as well as influence the reactivity and stereoselectivity in the glycosylation steps. One of the most useful stereoselective glycosylation strategies utilizing protecting groups has been 1,2-*trans* glycoside synthesis using the anchimeric assistance of a neighboring participating group, generally an acyl-protecting group at the O-2 position of the glycosyl donor [1–5]. The reactivity of the glycosyl donor is also influenced by the electronic effect of protecting groups at remote positions. Electron-withdrawing protecting groups such as acyl groups reduce the reactivity of donors as compared with alkyl protecting groups such as the benzyl group. Although oxygen atoms themselves around the glycosyl core are already electron-withdrawing, the electron-withdrawing protecting groups are on the oxygens of donor **A** would destabilize the oxocarbenium ion intermediate **B** so that the donor **A** bearing electron-withdrawing groups is more deactivated as compared with analogous electron-donating protecting groups (Fig. 1). Based on the reactivity difference of donors depending on their protecting groups, Fraser-Reid and co-workers established the armed–disarmed strategy for oligosaccharide synthesis [6–11].

The effects of electron-withdrawing protecting groups on glycosylation reactivity and glycosylation stereochemistry, in certain cases, may not be independent issues. Although the acyl groups at O-2 of donors give 1,2-*trans* glycosides through neighboring group participation, their electron-withdrawing effects on the glycosylation stereochemistry might not be properly recognized because of the overwhelming effect of the neighboring group participation. In fact, Schurech and co-workers

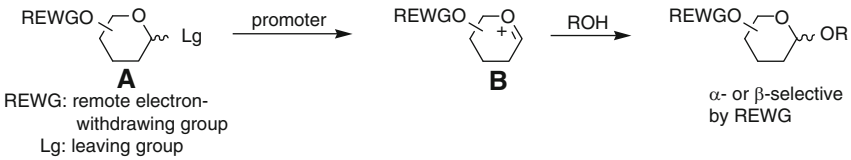


Fig. 1 Deactivation and directing effect by remote electron-withdrawing protecting groups of the donor

observed the effect of the nonparticipating electron-withdrawing groups, such as methanesulfonyl and benzylsulfonyl groups, at the O-2 positions of the donors on rhamnosylation stereochemistry [12–14]. Remote electron-withdrawing groups at O-3, O-4, and O-6 positions of pyranosyl donors or at O-3 and O-5 positions of furanosyl donors, which would reduce the reactivity of glycosyl donors, might also exert a direct effect on the stereochemistry of glycosylations.

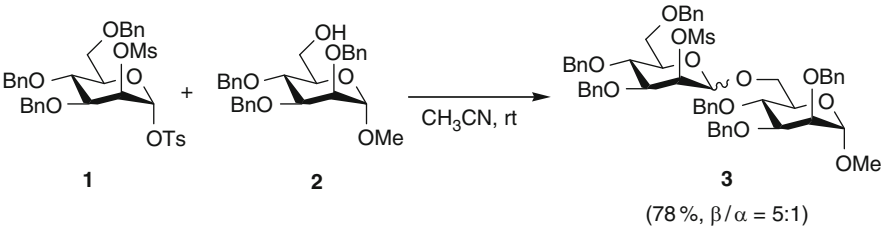
The magnitude of the directing effect from remote electron-withdrawing protecting groups may not be the same as that from protecting groups at the O-2 positions. Quantification of the deactivating effect of electron-withdrawing protecting groups at each position of several glycosyl donors has been reported by Ley [15] and Wong [16] and their co-workers. In addition, when the electron-withdrawing, potentially participating protecting groups are present at remote positions of glycosyl donors, it is difficult to distinguish between the electron-withdrawing and remote participation components of protecting groups on glycosylation stereochemistry.

Our discussion is restricted to the effect of electron-withdrawing protecting groups at remote positions on the glycosylation stereochemistry (Fig. 1). Since these electron-withdrawing groups include not only nonparticipating groups but also potentially participating groups, the directing effect by participation of the remote electron-withdrawing groups in glycosylations is included in this review. Before discussions on the main topics, we describe briefly the effect of nonparticipating electron-withdrawing groups at the O-2 position of donors on the glycosylation stereochemistry and the effect of remote electron-withdrawing protecting groups on the reactivity of donors in the Introduction.

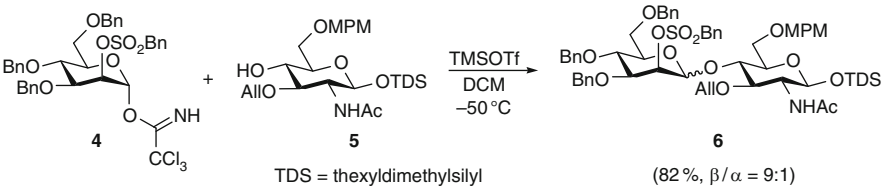
1.1 Effect of Nonparticipating Electron-Withdrawing Groups at the O-2 Position of Donors on the Glycosylation Stereochemistry

Glycosylations with donors possessing electron-withdrawing acyl groups at the O-2 position provide 1,2-*trans* glycosides through neighboring group participation of the acyl groups. This neighboring group participation pathway is so facile that the electron-withdrawing effect of the acyl groups on the glycosylation stereochemistry is usually not detected. In place of the participating acyl groups, if nonparticipating electron-withdrawing groups are introduced at the O-2 position of donors, the effect of electron-withdrawing groups at O-2 on the glycosylation stereochemistry would be appreciated.

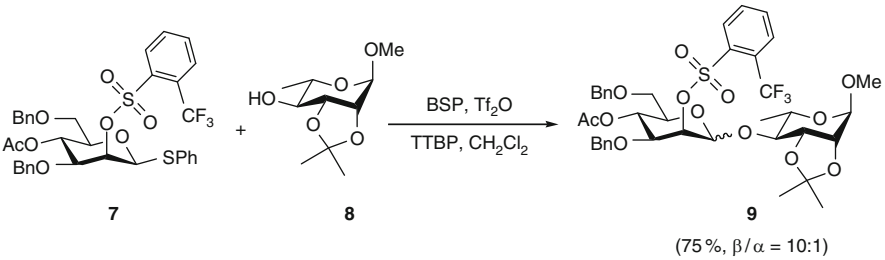
In fact, in 1980 Schuerch and co-workers introduced a nonparticipating, strongly electron-withdrawing group such as an alkyl or an aryl sulfonyl group at the O-2 position of mannosyl donors for stereoselective β-D-mannosylations and β-L-rhamnosylations [12–14]. As an example, the mannosylation of acceptor **2** with mannosyl donor **1** bearing a methanesulfonyl group at the O-2 position provided disaccharide **3** (β/α = 5:1) in 78% yield with an excess of the β-anomer (Scheme 1) [12].



Scheme 1



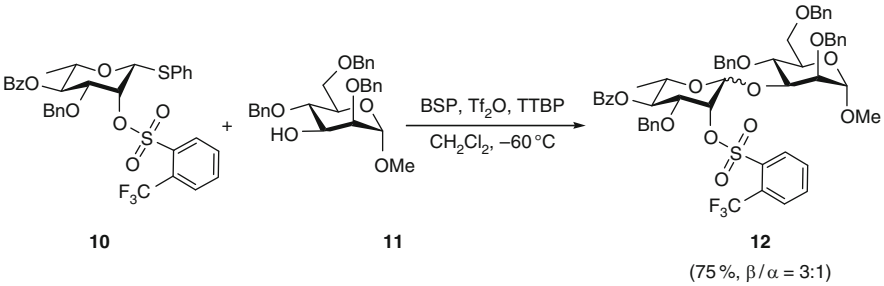
Scheme 2



Scheme 3

Recently, the scope and limitation of Schuerch's β-selective mannosylation were further investigated by other workers [17–19], and explanations for the β-selectivity were suggested. Schmidt and co-workers reported that the β-mannosylation of **5**, with mannopyranosyl trichloroacetimidate **4** as the donor possessing a nonparticipating, electron-withdrawing benzylsulfonyl group at the O-2 position, was β-selective, providing disaccharide **6** (β/α = 9:1) with an excess of the β-anomer (Scheme 2) [17]. They proposed that the strong dipole produced by the O-2 sulfonyl group would favor the formation of the mannosyl oxocarbenium ion in a twist-boat conformation over the half-chair conformation, and that the twist-boat oxocarbenium ion intermediate would be preferentially attacked by the acceptor from the β-side [17].

Crich and co-workers also reported that the mannopyranosylation of **8**, with thiomannopyranoside donor **7** bearing a nonparticipating, electron-withdrawing *o*-(trifluoromethyl)benzenesulfonyl group at the O-2 position, was β-selective, producing disaccharide **9** (β/α = 10:1) with an excess of the β-anomer (Scheme 3)



Scheme 4

[19]. They reasoned that the electron-withdrawing effect of the O-2 sulfonyl group would destabilize the oxocarbenium ion, thereby shifting the equilibrium toward a covalent α-mannosyl triflate, which would react with an acceptor in an S_N2-like fashion to generate the β-mannoside [19].

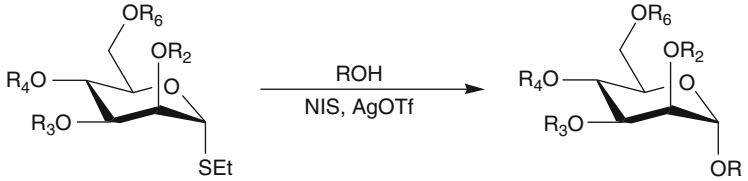
Stereoselective β-L-rhamnopyranosylations with donors bearing an electron-withdrawing group at the O-2 position were also reported: the rhamnosylation of **11** with 2-*O*-*o*-(trifluoromethyl)benzenesulfonyl thiorhamnoside **10** provided disaccharide **12** (β/α = 3:1) with a slight excess of the β-anomer (Scheme 4) [18].

1.2 Effect of Remote Electron-Withdrawing Protecting Groups on the Reactivity of Glycosyl Donors

Electron-withdrawing protecting groups such as acyl groups, either at the O-2 or at the remote position, reduce the reactivity of donors in glycosylations as compared with electron-donating protecting groups such as alkyl groups. The reduced reactivity of the donor possessing the electron-withdrawing group is ascribed to the enhanced transition state energy by destabilization of the oxocarbenium ion intermediate by the electron-withdrawing groups. Based on this reactivity difference of donors due to the electron-withdrawing and electron-donating protecting groups, Fraser-Reid and co-workers established an armed–disarmed strategy and applied it to the synthesis of oligosaccharides [6].

On the other hand, the magnitude of deactivation of glycosyl donors by electron-withdrawing groups at each position has been quantified by Ley and co-workers [15] and Wong and colleagues [16]. Ley and co-workers calculated deactivation factors by the electron-withdrawing benzoyl group at each position of thiomannosyl donors based on the data obtained from generating two differently protected glycosyl donors to compete for a standard glycosyl acceptor; the benzoyl group at the O-2 position was found to be the most deactivating and the deactivation factors of the others decreased in the order of $2 > 6 > 4 > 3$ (Table 1) [15]. Based on the data, they suggested that glycosylation transition states are destabilized more by the

Table 1 Deactivation factors for Bz-protecting groups at each position of galactosyl donor **13**



13 **14**

Position of benzoyl group[a]	Deactivation factor
2-Bz	33.6
3-Bz	1.1
4-Bz	5.0
6-Bz	8.2

[a]All other protecting groups are benzyl groups

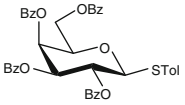
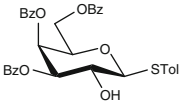
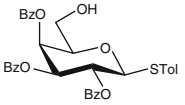
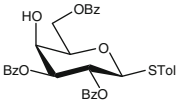
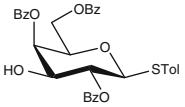
proximity of an electron-withdrawing group to the ring oxygen than by proximity to the anomeric center [15].

Wong and co-workers also characterized and quantified the influence on the reactivity of the benzoyl group for each position of galactosyl donors by comparing the reactivity of donor **15** bearing a benzoyl protecting group vs donors **16–19** bearing a hydroxy group at the same position; removal of the benzoyl group from the O-4 position caused the largest increase in the rate of reaction, and the observed influence of the positions of the benzoyl group was in the order of $4 > 3 > 2 > 6$ (Table 2) [16]. The strongest effect by the benzoyl group at the O-4 position was explained by the participation of the 4-oxygen of galactose in the stabilization of the putative cationic transition state [16].

There are some other remote protecting groups which are not the usual electron-withdrawing groups, but they still deactivate glycosyl donors: 4,6-benzylidene acetal, 3,4-cyclohexylidene diacetal (cyclohexane-1,2-diacetal; CDA), dispiroketal (dispoke), and butane diacetal (BDA) (Fig. 2).

In NBS-induced hydrolysis reactions of *n*-pentenyl glucosides **20** having 4,6-di-*O*-benzyl groups and **21** bearing a 4,6-*O*-benzylidene group, Fraser-Reid and co-workers found that the hydrolysis rate of the acetalated **21** was slower than that of its torsion-free analog **20** and thus the 4,6-*O*-benzylidene-protecting group was disarming the donor (Fig. 3) [20]. The calculated relative activation energies for the hydrolysis of **20** and **21**, considering solvation energies, were in agreement with the experimentally observed trends [21]. A torsional effect was ascribed to the reduced reactivity of **21**; the 4,6-*O*-benzylidene-protecting group raises the activation energy barrier by opposing the flattening that is required in the oxocarbenium ion intermediate, which is generated by the activation process [20, 21]. By employing the 4,6-*O*-benzylidene-protected mannosyl sulfoxides or thiomannopyranosides as mannosyl donors, Crich and a co-worker discovered a highly stereoselective β-mannosylation method [22–25]. The 4,6-*O*-benzylidene effect on the construction of β-mannosyl linkages was further demonstrated by other workers employing various mannosyl donors [26–31].

Table 2 Influence of positions of the benzoyl group over the hydroxyl group on the reactivity of thiogalactosyl donors

Galactosyl donors	Relative rate of reaction	Galactosyl donors	Relative rate of reaction
 **15**	1.0	 **18**	11.8
 **16**	3.1	 **19**	2.3
 **17**	5.1		

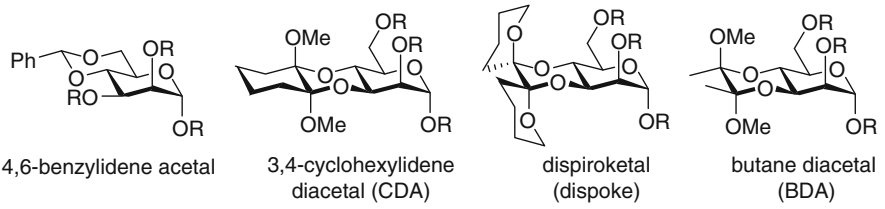


Fig. 2 Non-electron-withdrawing, deactivating protecting groups at remote positions

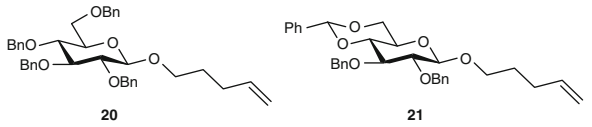
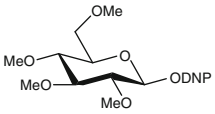
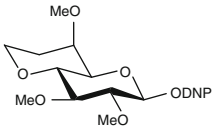
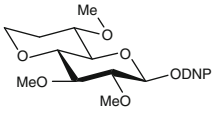
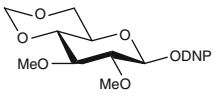


Fig. 3 *n*-Pentenyl tetra-*O*-benzyl glucoside **20** and *n*-pentenyl 4,6-*O*-benzylidene glucoside **21**

Recently, Bols and a co-worker demonstrated that the deactivating effect of the 4,6-benzylidene acetal is partially torsional and partially electronic by measuring the relative hydrolysis rate of dinitrophenyl glycosides **22**−**25** (Table 3); they showed that the glycoside **25**, in which the C5−C6 bond is restricted to a *tg* conformation by the 4,6-*O*-methylene group, was less reactive than the glycoside **22**, in which the C5−C6 bond is not restricted to a specific conformation, as well as the glycosides **23** and **24**, in which the C5−C6 bond is restricted to *gg* and *gt* conformations, respectively [32]. Thus, the 4,6-*O*-benzylidene group deactivates glycosyl donors more than the corresponding di-*O*-benzyl groups by locking the 6-alkoxymethyl group in the most electron-withdrawing *tg* conformation [32].

The 3,4-cyclohexylidene diacetal, which was introduced for the selective protection of *trans* diequatorial vicinal diols [33], is resistant to the flattening of carbohydrate ring required for the generation of an oxocarbonium ion intermediate and thus a torsionally disarming protecting group [15]. Similarly, the dispiroketal [15, 34]

Table 3 Relative hydrolysis rates of dinitrophenyl glycosides

Structure		Conformation of C5–C6 bond	Relative hydrolysis rate
	**22**	–	1
	**23**	*gg*	0.24
	**24**	*gt*	0.16
	**25**	*tg*	0.07

DNP Dinitrophenyl

and the butane diacetal [15] are also known as deactivating groups for the protection of *trans* diequatorial vicinal diols.

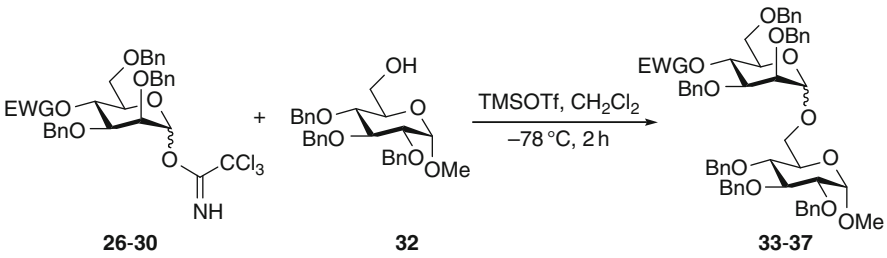
2 Directing Effect by Remote Electron-Withdrawing Groups of Donors in Glycosylations

The effect of remote electron-withdrawing protecting groups on the reactivity of glycosyl donors is substantial and the magnitude of the effect may be smaller than that of O-2 protecting groups as reviewed in the Introduction. There we also reviewed the β-directing effect of electron-withdrawing groups attached at the O-2 position of donors in mannosylations. In this section, the effect of an electron-withdrawing group at remote positions of donors, such as O-3, O-4, and O-6 positions, on glycosylation stereochemistry is discussed. Since the stereoselective β-mannosylation still remains one of the most challenging tasks in carbohydrate chemistry [35–37], the directing effects by electron-withdrawing groups in mannosylations and in other glycosylations are discussed separately in this section.

2.1 β-Directing Effect of Remote Electron-Withdrawing Protecting Groups of Donors in Mannopyranosylations

A systematic study on the effect of electron-withdrawing protecting groups such as sulfonyl and acyl groups at remote positions such as O-3, O-4, and O-6 of mannosyl donors on the mannosylation stereochemistry was reported recently by Kim and coworkers [38]. They reported that mannopyranosylations of acceptor **32** with mannosyl donors bearing strongly electron-withdrawing sulfonyl groups at O-4, including 4-*O*-(*o*-trifluoromethylbenzenesulfonyl)-tri-*O*-benzyl-mannosyl trichloroacetimidate **26**, and 4-*O*-benzylsulfonyl-tri-*O*-benzyl-mannosyl trichloroacetimidate **27**, were highly β-selective, yielding mannosyl disaccharides **33** (β/α = 15.5:1) and **34** (β/α = 10.7:1), respectively, with a large excess of β-anomers in high yields (Table 4) [38]. The acyl groups at O-4 of mannosyl trichloroacetimidate donors also made the mannosylation of **32** highly β-selective, although less pronounced than the 4-*O*-sulfonyl groups, and thus the reactions of **32** with **28**−**30** gave **35** (EWG = *p*-NO_2Bz, β/α = 7.2:1), **36** (EWG = Bz, β/α = 7.1:1), and **37** (EWG = Ac, β/α = 4.0:1), respectively, with an excess of β-anomers (Table 4). On the other hand, the mannosylation of the same acceptor **32** with donor **31**, which is a standard donor for comparison and thus possesses no electron-withdrawing protecting groups, was less β-selective, affording disaccharide **38** (β/α = 2.7:1) with a slight excess of the β-anomer. They also reported that mannosylations of other acceptors with mannosyl donors **26**−**30** were highly β-selective. As indicated by Kim and coworkers [38], it is noteworthy that the more strongly electron-withdrawing groups

Table 4 Mannosylations with trichloroacetimidate donors possessing electron-withdrawing groups at O-4



26-30 **32** **33-37**

Donor	EWG	Product (Yield, %)	Ratio β/α
26	SO_2Ph*o*-CF_3	**33** (81)	15.5:1
27	SO_2Bn	**34** (80)	10.7:1
28	Bz*p*-NO_2	**35** (91)	7.2:1
29	Bz	**36** (73)	7.1:1
30	Ac	**37** (85)	4.0:1
(**31**)[a]	(Bn)[a]	**38** (91)	2.7:1

[a]A standard donor for comparison

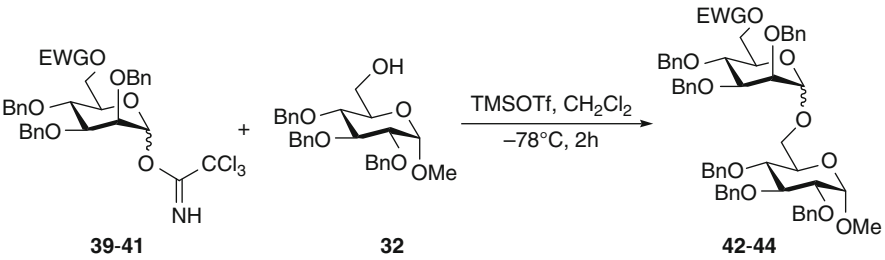
$SO_2C_6H_4$*o*-CF_3 and SO_2Bn exhibit a somewhat higher β-directing effect than the weakly electron-withdrawing acyl groups *p*-NO_2Bz, Bz, and Ac. As compared to the β-directing effect of electron-withdrawing groups at O-2 [17–19], the β-directing effect of those at O-4 is not smaller and is even greater in certain cases.

Kim and co-workers also reported that mannosylations of **32** with mannosyl donors **39**−**41** possessing an electron-withdrawing group at the O-6 position afforded disaccharides **42** (EWG = SO_2Bn, β/α = 13.8:1), **43** (EWG = *p*-NO_2Bz, β/α = 5.2:1), and **44** (EWG = Bz, β/α = 6.8:1), respectively, favoring β-anomers (Table 5) [38]. Like electron-withdrawing groups at O-4, the more strongly electron-withdrawing sulfonyl group exhibited a somewhat higher β-directing effect than the weakly electron-withdrawing acyl groups at the O-6 position.

Mannosylation of **32** with mannosyl donor **45** possessing an electron-withdrawing benzylsulfonyl group at the O-3 position was also highly β-selective, yielding mannosyl disaccharide **46** (β/α = 15.9:1) with a large excess of the β-anomer (Scheme 5) [38], whereas the mannosylation of **32** with the mannosyl donor possessing the electron-withdrawing acyl group at the O-3 position was α-selective, which is discussed in the next section on remote participation.

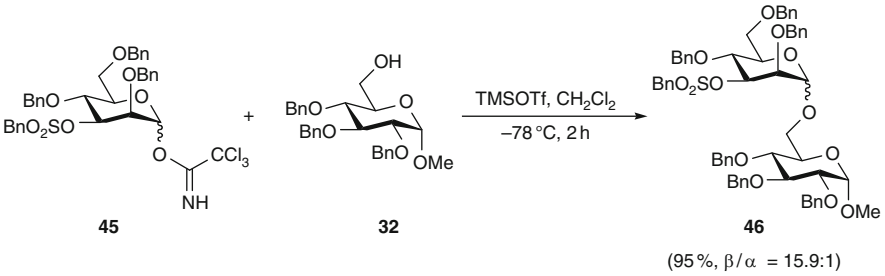
Kim and co-workers observed that the triflate anion, the counter anion of the mannosyl oxocarbenium ion, was essential for the β-selectivity; covalent α-mannosyl triflates with an electron-withdrawing group at O-3, O-4, or O-6 were detected by low temperature NMR [38]. They also observed that the strongly electron-withdrawing sulfonyl groups, which exhibit a higher β-directing effect in the mannosylation, made the α-mannosyl triflates more stable than the weakly electron-withdrawing acyl groups. Based on these observations, they proposed the following mechanism for β-mannosylation and the origin of the β-directing effect. Activation of donor **C** with

Table 5 Mannosylations with trichloroacetimidate donors possessing electron-withdrawing groups at O-6



Donor	EWG	Product (Yield %)	Ratio β/α
39	SO_2Bn	**42** (76)	13.8:1
40	Bz*p*-NO_2	**43** (83)	5.2:1
41	Bz	**44** (83)	6.8:1
(**31**)[a]	(Bn)[a]	**38** (91)	2.7:1

[a]A standard donor for comparison

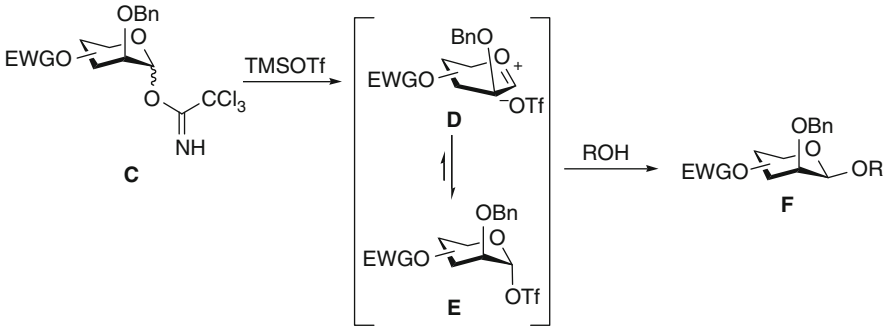


Scheme 5

TMSOTf generates mannosyl oxocarbenium ion **D**, which is in equilibrium with α-mannosyl triflate **E**. The electron-withdrawing group on the sugar ring stabilizes **E**, but might destabilize **D** so that the equilibrium shifts toward the α-mannosyl triflate **E**. Then **E**, or its contact ion pair, reacts with acceptor alcohol ROH in an S_N2-like fashion to give β-mannoside **F** (Scheme 6) [38].

2.2 Directing Effect of Remote Electron-Withdrawing Groups in Glycopyranosylations Other than Mannopyranosylations

van der Marel and co-workers found that glycosylations of various acceptors with 1-thiomannuronic acid ester donors, which have the carboxylate ester groups at the C-5 position, were also highly β-selective; the glycosylation of **32** with



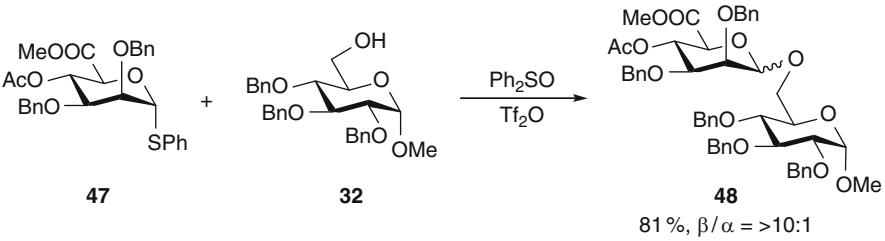
Scheme 6

mannuronate donor **47** afforded disaccharide **48** (β/α = >10:1) with a large excess of the β-anomer (Scheme 7) [39].

A mechanistic rationale for this β-selectivity was provided by van der Marel and co-workers based on the remote β-directing effect of the C-5 carboxylate ester; the C-5 carboxylate ester prefers to occupy an axial position in the oxocarbenium ion intermediate, thereby favoring the formation of the $^{3}H_{4}$ half-chair **G** over the $^{4}H_{3}$ conformer **H** and nucleophilic attack on the $^{3}H_{4}$ half-chair oxocarbenium ion **G** occurs in a β-fashion (Fig. 4) [40]. Woerpel's works [41–44] and van der Marel's result [45] indicate that all substituents in the $^{3}H_{4}$ conformer **G** are in their most favorable orientations so that the stabilization of **G** over **H** is large enough to overrule the unfavorable 1,3-pseudo-diaxial interactions of the substituents at C-3 and C-5 and the incoming acceptor nucleophile that develops upon attack of the acceptor on the $^{3}H_{4}$ conformer **G**.

Substitution of hydrogens at the C-6 position of rhamnopyranosyl donors by electron-withdrawing fluorine atoms resulted in a moderate increase of the β-selectivity in rhamnosylations. Crich and co-workers reported that glycosylations of diacetoneglucose **50** with thio-D-rhamnosyl donors **49** bearing two fluorine atoms, and with thio-L-rhamnosyl donor **52** bearing three fluorine atoms at the C-6 position, afforded disaccharides **51** (β/α = 2.3:1) and **53** (β/α = 5.3:1), respectively, favoring β-anomers (Scheme 8) [46]. They found that the stereochemical outcome of the glycosylations depends on the number of fluorine atoms present. Stabilization of covalent α-triflates by electron-withdrawing fluorine atoms at C-6 and then S_N2-like reactions of the resulting α-triflates with acceptors were ascribed to the enhanced β-selectivity of the rhamnosylations [46].

Stereoselective construction of equatorial β-2-deoxyglycosyl linkages is a difficult task in oligosaccharide synthesis [47–49]. Takahashi and co-workers reported β-selective glycosylations employing 2,6-dideoxyglucosyl donors bearing a strongly electron-withdrawing benzylsulfonyl group at the O-4 position; the glycosylation of the secondary alcohol acceptor **55** with 2,6-dideoxy-4-*O*-benzylsulfonyl-glucopyranosyl trichloroacetimidate **54** at −94 °C gave disaccharide **56** (β/α = >95:5) in 94% yield with an excellent β-stereoselectivity, while the



Scheme 7

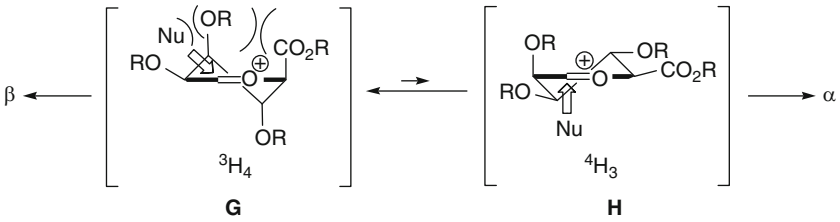
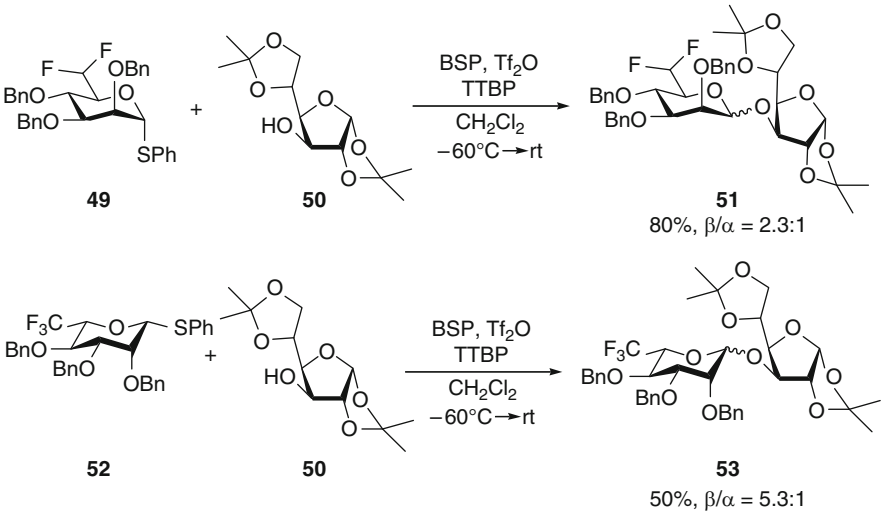


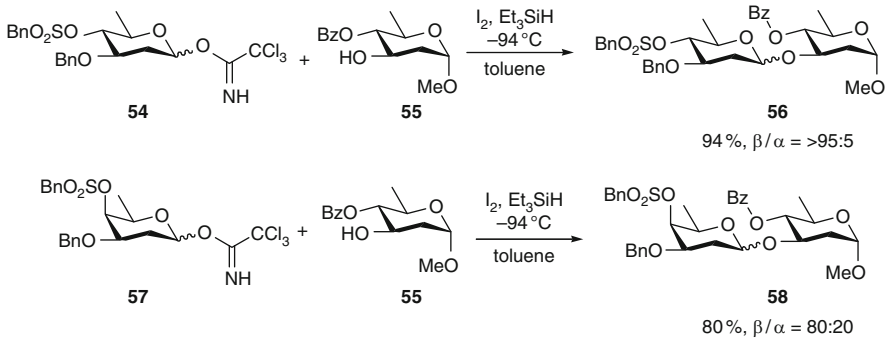
Fig. 4 Two half-chair conformers of mannuronate ester oxocarbenium ion



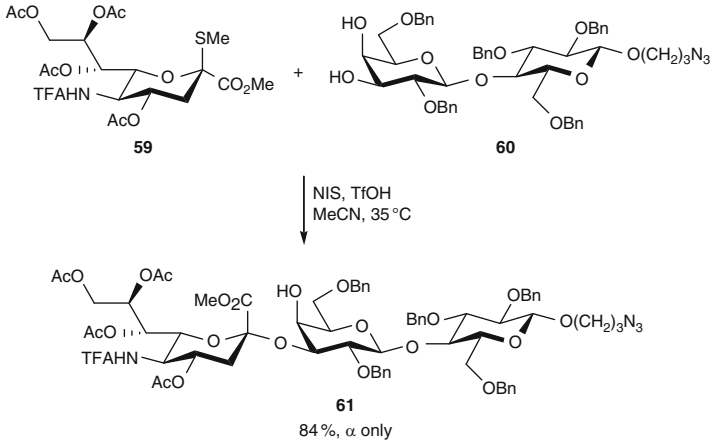
Scheme 8

glycosylation of **55** with of 2,6-dideoxy-4-*O*-benzylsulfonyl-galactopyranosyl trichloroacetimidate **57** was less β-selective than with **54,** but still afforded disaccharide **58** (β/α = 80:20) with an excess of the β-anomer (Scheme 9) [50].

Construction of the equatorial α-sialyl linkage still poses a challenge in oligosaccharide synthesis [51–53]. One way to enhance the α-selectivity in the sialylation is



Scheme 9



Scheme 10

the introduction of a strongly electron-withdrawing protecting group in place of 5-*N*-acetyl group of the sialyl donor. Boons and co-workers employed a sialyl donor bearing the trifluoroacetyl (TFA) group at the N-5 position for the α-selective sialylation; the sialylation of lactose acceptor **60** with TFA-protected sialyl donor **59** provided exclusively trisaccharide **61** having an α-sialyl linkage in 84% yield (Scheme 10) [54]. Similar sialylations with donors bearing the 5-*N*-acetyl group gave anomeric mixtures of sialosides in much lower yields [55]. Sialyl donors possessing diacetyl (Ac_2) groups [56–59] and a trichloroethoxycarbonyl (Troc) group [60–62] at the N-5 position have also been used for the equatorial α-selective sialylations. Although it has been suggested that the stronger electron-withdrawing group such as the trifluoroacetyl group would reduce the nucleophilicity of the amino group, thereby suppressing possible side reactions in sialylations [54], the origin of the enhanced α-selectivity by introducing a stronger electron-withdrawing group at the N-5 position is currently unclear.

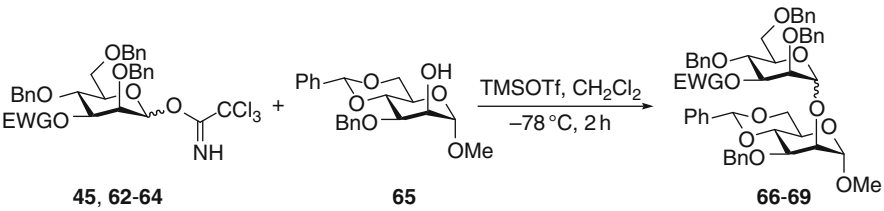
3 Directing Effect of Potentially Participating Groups at Remote Positions of Donors in Glycosylations

In the previous section, we discussed the directing effect of remote electron-withdrawing groups such as nonparticipating sulfonyl groups and potentially participating acyl groups of donors in glycosylations. Some of the directing effects by acyl groups might not be purely due to their electron-withdrawing ability, but rather, partially due to their participating ability from the remote position. It is, however, difficult to distinguish the effect of remote participation from the electron-withdrawing effect of the protecting groups on the outcome of the stereochemistry in glycosylations. Although numerous examples for glycosylations with electron-withdrawing, potentially participating groups at remote positions of glycosyl donors can be found in the literature, most of them do not discuss remote participation of the protecting groups in glycosylations. There have been reports both opposed to and in favor of the remote participation by protecting groups in glycosylations. As in the previous section, the remote participation in mannopyranosylations and that in other glycopyranosylations are discussed separately. In addition, the remote participation in glycofuranosylations is also discussed.

3.1 Directing Effect of Potentially Participating Groups at Remote Positions of Mannopyranosyl Donors

Recently, during their systematic study on the effect of electron-withdrawing groups including nonparticipating sulfonyl groups and potentially participating acyl groups at remote positions of donors on the mannosylation stereochemistry, Kim and co-workers found the strong α-directing effect by acyl groups at O-3 of donors in mannosylations [38]; mannosylations of secondary alcohol acceptor **65** with donor **62**, possessing the acetyl group at O-3, and with donor **63**, possessing the benzoyl group at O-3, yielded almost exclusively α-disaccharides **66** (β/α = 1:40.4) and **67** (β/α = 1:19.8), respectively, while the α-directing effect by *p*-nitrobenzoyl group at O-3 was less pronounced and thus the reaction of **64** and **65** gave disaccharide **68** (β/α = 1:3.8) with an excess of the α-anomer (Table 6) [38]. On the other hand, the mannosylation of the same acceptor **65** with donor **45**, possessing the nonparticipating, strongly electron-withdrawing benzylsulfonyl group at O-3, was highly β-selective, giving disaccharide **69** (β/α = 11.8:1) with a large excess of the β-anomer (Table 6) [38]. They also reported that mannosylations of other acceptors with mannosyl donors **62**–**64** were highly α-selective. Mannosylations with donors having the 3-*O*-acetyl group probably proceeded almost exclusively through the six-membered ring 2-methyl-1,3-dioxanylium ion intermediate, in which the sugar ring is in the $^1C_4$ conformation, resulting from the remote participation of the acetyl group (Fig. 5). Mannosylations with donors having the 3-*O*-benzoyl group might also have proceeded through the

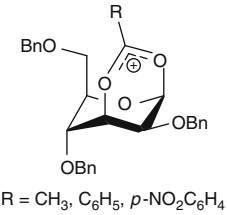
Table 6 Mannosylations with trichloroacetimidate donors possessing participating, electron-withdrawing groups at O-3



45, **62-64** **65** **66-69**

Donor	EWG	Product (Yield, %)	Ratio β/α
62	Ac	**66** (92)	1:40.4
63	Bz	**67** (91)	1:19.8
64	Bz*p*-NO_2	**68** (80)	1:3.8
(**45**)[a]	(SO_2Bn)[a]	**69** (85)	11.8:1

[a]A standard donor for comparison



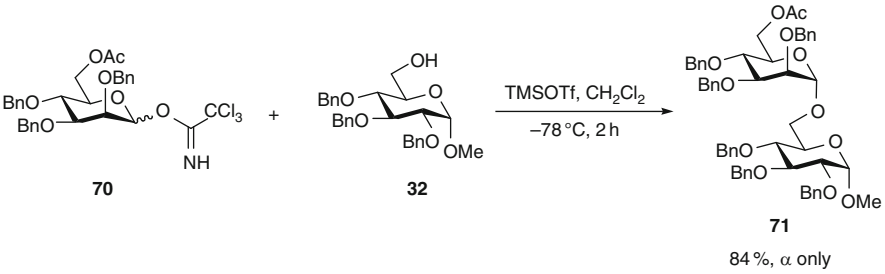
R = CH_3, C_6H_5, *p*-$NO_2C_6H_4$

Fig. 5 Possible dioxalynium ion intermediate by the remote participation of 3-*O*-acyl groups of mannosyl donors

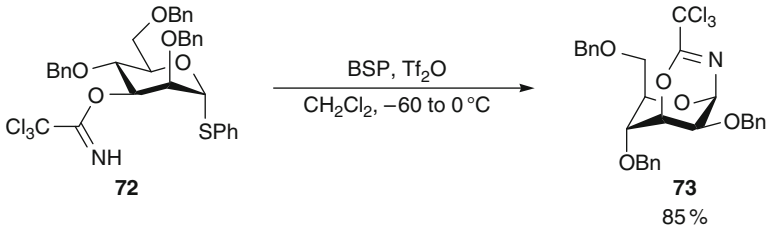
1,3-dioxanylium ion pathway by the remote participation of the benzoyl group, whereas the 3-*O*-*p*-nitrobenzoyl group might have participated only partially during the mannosylation.

The α-selective mannosylations of various acceptors with the donor bearing an acetyl group at the O-6 position were also reported by Kim and colleagues; the mannosylation of **32** with **70** provided exclusively α-mannosyl disaccharide **71** (Scheme 11) [38]. The α-directing effect by the acetyl group could be attributed to its remote participation from the O-6 position, which might generate a seven-membered dioxocarbenium ion intermediate, having the sugar ring in a chair conformation. Kim and co-workers, however, reported that there was no evidence for the remote participation of acyl groups at the O-4 position of donors in mannosylations. Based on their results it could be assumed that there is remote participation of 3-*O*-acyl and 6-*O*-acetyl groups, but not of 4-*O*-acyl groups, of donors in mannosylations.

To obtain more support for the remote participation of 3-*O*-acyl and 6-*O*-acetyl groups in mannosyl donors, Kim and co-workers carried out experiments to trap anomeric oxocarbenium ion intermediates by the intramolecular nucleophilic attack of the trichloroacetimidoyl group at the O-3 position of mannosyl donors; the activation of **72** with 1-benzenesulfinyl piperidine (BSP) and Tf_2O afforded



Scheme 11

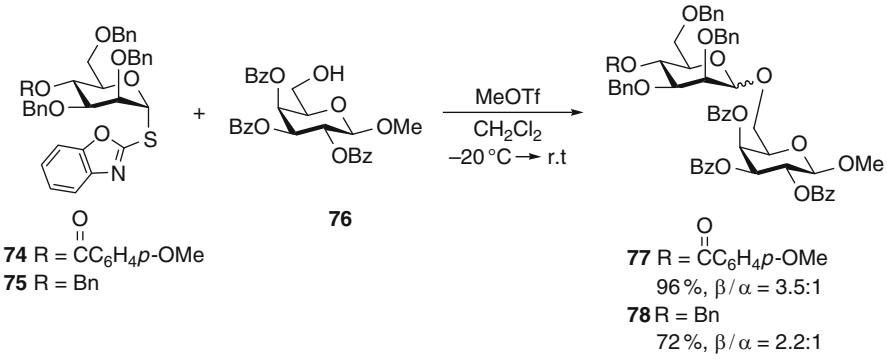


Scheme 12

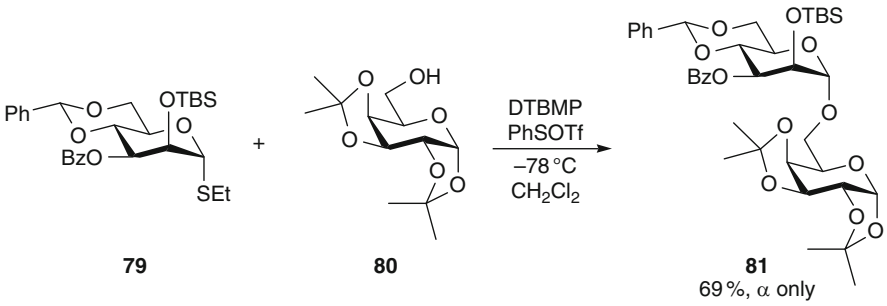
stable bicyclic product **73**, with a six-membered trichloromethyloxazine ring (Scheme 12) [38].

Demchenko and co-workers, on the other hand, reported that the mannosylation of **76** with donor **74**, having the *p*-methoxybenzoyl group at the O-4 position, gave disaccharide **77** (β/α = 3.5:1) while the mannosylation of **76** with tetra-*O*-benzyl-protected donor **75** provided disaccharide **78** (β/α = 2.2:1) (Scheme 13). They interpreted the slightly increased β-selectivity in the mannosylation of **76** with **74** compared to that with **75** as the result of the remote participation of the *p*-methoxybenzoyl group at the O-4 position of the donor **74** during the mannosylation [63].

Crich and co-workers reported that the mannosylation of acceptor **80** with donor **79**, having the benzoyl group at the O-3 position, provided exclusively α-disaccharide **81** (Scheme 14) and attributed the α-selectivity to the remote participation of the 3-*O*-benzoyl group, which can form the bridged cation in a $^{1}S_{5}$ twist conformation without imposing undue strain of the fused 4,6-*O*-benzylidene ring [64]. Recently, however, Crich and co-workers performed an experiment to trap anomeric oxocarbenium ion intermediates by the intramolecular nucleophilic attack of the *tert*-butoxycarbonyl (Boc) group at the O-3, O-4, and O-6 positions of mannosyl donors, and concluded that the neighboring group participations by acyl groups at O-3, O-4, and O-6 of mannosyl donors did not occur under typical glycosylation conditions because they did not observe the formation of any cyclic carbonate products which, they think, must be formed if remote participations of acyl groups are occurring [65].



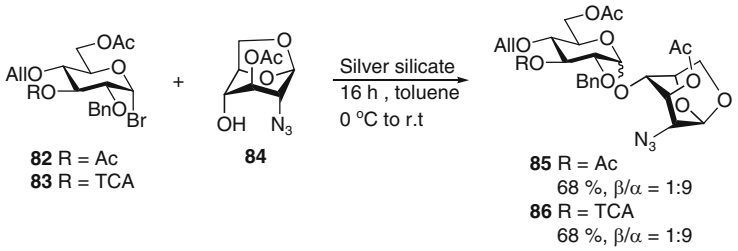
Scheme 13



Scheme 14

3.2 Directing Effect of Potentially Participating Groups at Remote Positions of Glycopyranosyl Donors Other than Mannopyranosyl Donors

van Boeckel and co-workers observed high α-selectivities in glucosylations with glucosyl donors bearing acyl groups at the O-3 position. Glucosylations of acceptor **84** with glucosyl donors **82** possessing a 3-*O*-acetyl group, and **83** possessing a 3-*O*-trichloroacetyl group, gave disaccharides **85** (β/α = 1:9) and **86**, (β/α = 1:9), respectively, favoring α-anomers (Scheme 15) [66]. However, they opposed the possibility of remote participation by the 3-*O*-acyl groups, even though glucosylations of **84** with **82** and **83** afforded more α-glucosides than the glucosylation of **84** with the corresponding donor bearing the 3-*O*-benzyl group, based on the fact that the glucosylation with donor **82** having the 3-*O*-acetyl group afforded the same ratio of the α- and β-glucosides as the glucosylation with donor **83** having the 3-*O*-trichloroacetyl group, which they believed to be a poor participating group [66].



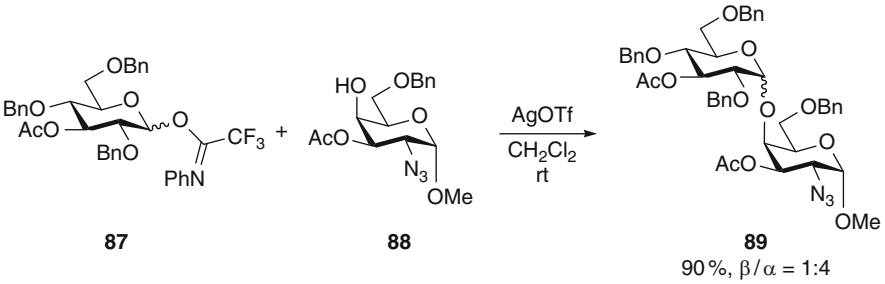
Scheme 15

Nifantiev and co-workers reported that the glucosylation of acceptor **88** with glucosyl donor **87** possessing an acetyl group at the O-3 position produced disaccharide **89** (β/α = 1:4) (Scheme 16) and was a little more α-selective than the glucosylation of **88** with a corresponding donor bearing a benzyl group at O-3 position, which gave a 1:2 (β:α) mixture of disaccharides [66]. They also reported that glycosylations of secondary alcohol acceptors with a D-glucuronyl bromide donor and a D-xylosyl trichloroacetimidate donor bearing an acetyl group at the O-3 position provided exclusively α-disaccharides. The α-selectivity was attributed to the remote stereocontrolling effect of the acetyl group at the O-3 position (**J** in Fig. 6) and the difference in the stabilization energy between oxocarbenium ion **I** and stabilized dioxocarbenium ion **J**, which was obtained by a calculation, and supported by experimental results (Fig. 6) [67].

Mukaiyama and colleagues published that glucosylations with glucopyranosyl fluoride donors possessing a diethylthiocarbamoyl group at the O-6 position were highly α-selective; the glucosylation of acceptor **32** with the fluoride donor **90** produced disaccharide **91** (β/α = 3:97) with an excellent α-stereoselectivity (Scheme 17) [68]. They also reported on galactosylations with galactopyranosyl fluoride donors possessing a diethylthiocarbamoyl group at the O-4 or O-6 position; the reaction of **32** and fluoride donor **92** having diethylthiocarbamoyl group at O-4 gave almost exclusively α-disaccharide **93** (β/α = 1:>99) (Scheme 17) [68].

The high α-stereoselectivity in the glucosylation of **32** with **90** was attributed to the bridged 1,6-participation intermediate **K** generated by the remote participation of the diethylthiocarbamoyl group at the O-6 position of the donor to the anomeric carbon (Fig. 7). The outstanding α-stereoselectivity in the galactosylation of **32** with **92** was ascribed to the effective formation of the bridged 1,4-participation intermediate **L** by the remote participation of the diethylthiocarbamoyl protecting group at O-4 to the anomeric carbon (Fig. 7) [68]. On the other hand, based on the lower α-stereoselectivity (β/α = 24:76) in the galactosylation of **32** with a galactopyranosyl fluoride donor bearing the diethylthiocarbamoyl group at O-6, Mukaiyama and co-workers indicated that the remote participation by the diethylthiocarbamoyl group at the O-6 position of the galactosyl donor might not work well [68].

Boons and co-workers investigated the effect of various electron-withdrawing groups including both potentially participating and nonparticipating groups at the



Scheme 16

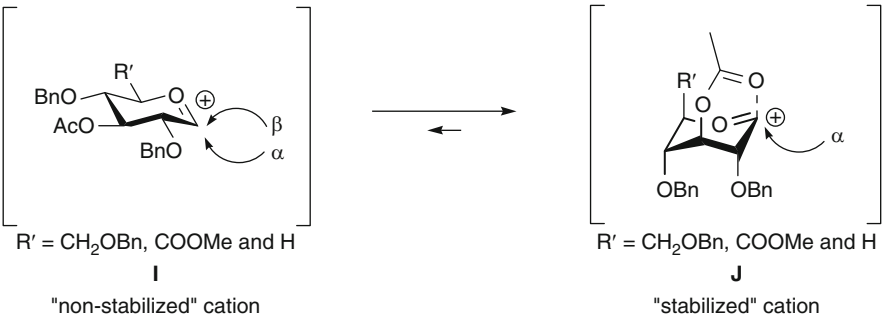
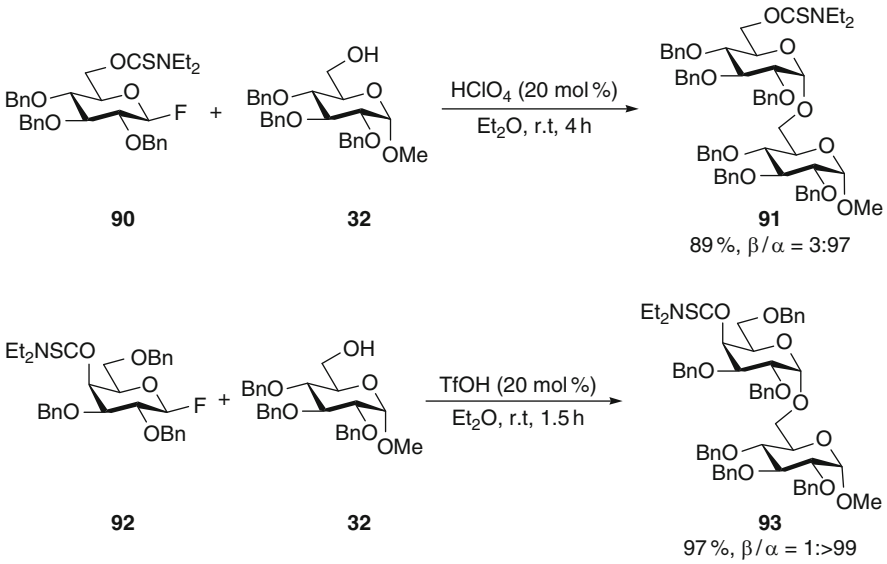


Fig. 6 Possible non-stabilized oxocarbenium ion **I** and stabilized dioxocarbenium ion **J** as intermediates in glycosylation with **87** and with related donors

O-4 position of donors on the galactosylation stereochemistry and confirmed that the remote participation of acyl groups at the O-4 position of the galactosyl donor was possible; galactosylations of acceptor **80** with galactosyl donors possessing potentially participating acyl groups at O-4, such as 4-*O*-acetyl thiosugar **94** and 4-*O*-benzoyl thiosugar **95**, afforded galactosyl disaccharides **101** (β/α = 1:7.2) and **102** (β/α = 1:17), respectively, with an excess of α-anomers (Table 7) [69]. The α-directing effect of the *p*-nitrobenzoyl group at O-4 of **96** was less pronounced than that of the benzoyl group while the α-directing effect of the *p*-methoxybenzoyl group at O-4 of **97** was observed to be higher than that of the benzoyl group. Thus, galactosylations of **80** with **96** and **97** provided **103** (R = *p*-NO_2Bz, β/α = 1:14) and **104** (R = *p*-OMeBz, β/α = 1:33), respectively. On the other hand, they found that galactosylations of **80** with galactosyl donors **98** and **99** bearing nonparticipating electron-withdrawing 4-*O*-(2,2,2-trifluoroethyl) and 4-*O*-trifluoroacetyl groups, respectively, showed almost the same α-selectivities as the galactosylation of **80** with **100** bearing the 4-*O*-benzyl group; the galactosylations afforded disaccharides **105** (R = CH_2CF_3, β/α = 1:2.3), **106** (R = $COCF_3$, β/α = 1:3.0), and **107** (R = Bn, β/α = 1:2.2), respectively (Table 7). Based on the results, Boons and coworkers



Scheme 17

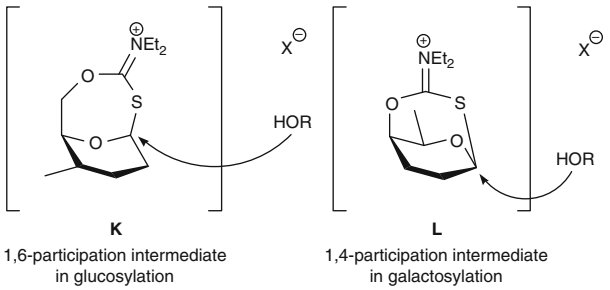


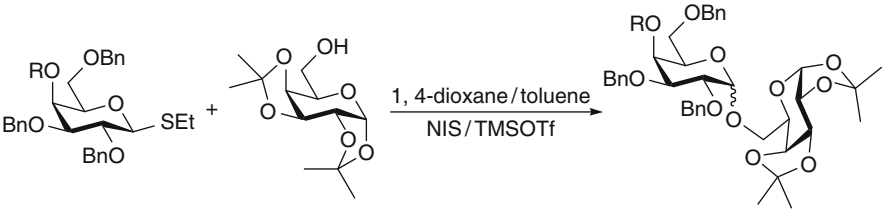
Fig. 7 Putative 1,6-participation intermediate in glucosylation and 1,4-participation intermediate in galactosylation

concluded that the 4-*O*-acyl groups of galactosyl donors can perform remote neighboring group participation during galactosylations [69].

Wong and co-workers reported that the galactosylation of trihydroxy sugar **109** with α-galactosyl phosphite donor **108** having an *O*-6 acetyl group produced disaccharide **110** (β/α = 15:85) with an excess of the α-anomer, which could be formed by the remote participation of the acetyl group at O-6 (Scheme 18) [70].

Lin and co-workers reported highly stereoselective α-galactosylations with galactopyranosyl donors possessing two potentially participating benzoyl groups at O-4 and O-6 positions; the galactosylation of **112** with the dibenzoyl phosphite donor **111** produced exclusively α-galactosyl disaccharide **113** (Scheme 19) [71]. They ascribed the high α-selectivity of the galactosylation to the remote participation of both benzoyl groups at the O-4 and O-6 positions (Fig. 8).

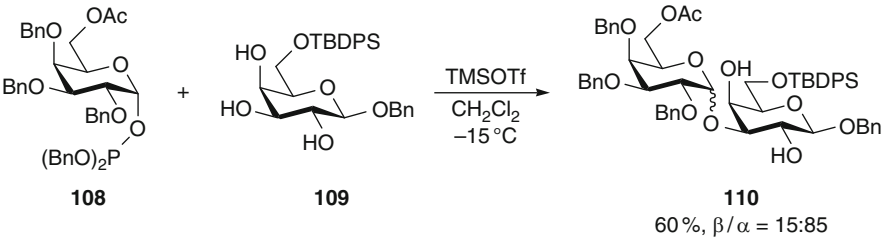
Table 7 Galactosylations of **80** with donors bearing electron-withdrawing groups at the O-4 position



94-100 **80** **101-107**

R		Product (Yield, %)	Ratio β/α
Ac	**94**	**101** (76)	1:7.2
Bz	**95**	**102** (72)	1:17
Bz(*p*-NO_2)	**96**	**103** (87)	1:14
Bz(*p*-OCH_3)	**97**	**104** (85)	1:33
CH_2CF_3	**98**	**105** (58)	1:2.3
$COCF_3$	**99**	**106** (71)	1:3.0
(Bn)[a]	**100**	**107** (91)	1:2.2

[a]A standard donor for comparison



108 **109** **110**
60 %, β/α = 15:85

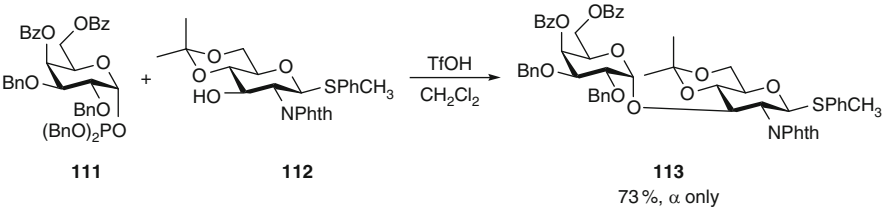
Scheme 18

Corey et al. reported a successful total synthesis of pseudopterosin E (**116**) through a crucial coupling reaction of 2-*O*-benzyl-3,4-di-*O*-*p*-methoxybenzoyl-α-L-fucosyl bromide (**115**) and catechol **114**; the fucosylation of **114** with **115** proceeded in the complete position-selective and α-stereoselective manner, providing exclusively α-fucoside **116** (Scheme 20), and the α-stereoselectivity of the reaction was ascribed to the internal 1,4-remote participation of the *p*-methoxybenzoyl group (Fig. 9) [72].

Nifantiev and co-workers investigated the effect of acyl groups at the O-4 position of donors on the fucosylation stereochemistry; fucosylations of acceptor **121** with fucosyl donors **118**–**120** having *p*-methoxybenzoyl, benzoyl, and *p*-nitrobenzoyl groups, respectively, at the O-4 position were α-selective and thus disaccharides **123** (R = Bz, β/α = 1:3.5), **124** (R = *p*-NO_2Bz, β/α = 1:2), and **125** (R = *p*-OMeBz, β/α = 1:5) were obtained, respectively, with an excess of α-anomers (Table 8) [73]. The α-selectivity was ascribed to the remote participation of the 4-*O*-acyl groups and the computational work on the difference in the total energy

between oxocarbenium ion **O** and stabilized dioxocarbenium ion **P** supported the presence of the 1,4-remote participation of the 4-*O*-acyl groups (Fig. 10) [73].

Nifantiev and co-workers also investigated the effect of the 3-*O*- and/or 4-*O*-benzoyl protecting group of donors in fucosylations; fucosylations of acetonide **121** with fucosyl donors **126** having a 3-*O*-benzoyl group and **127** having 3,4-di-*O*-benzoyl groups afforded disaccharides **129** (β/α = 1:13) and **130** (β/α = 1:20), respectively, with a large excess of α-anomers whereas the fucosylation of **121** with **128** having a 4-*O*-benzoyl group was much less α-selective, providing disaccharide **131** (β/α = 1:3.5), with a slight excess of the α-anomer (Table 9) [74]. The highly α-selective fucosylations was ascribed to remote participation of the benzoyl group at the O-3 position [74].



Scheme 19

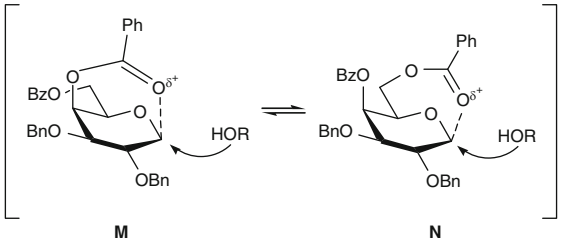
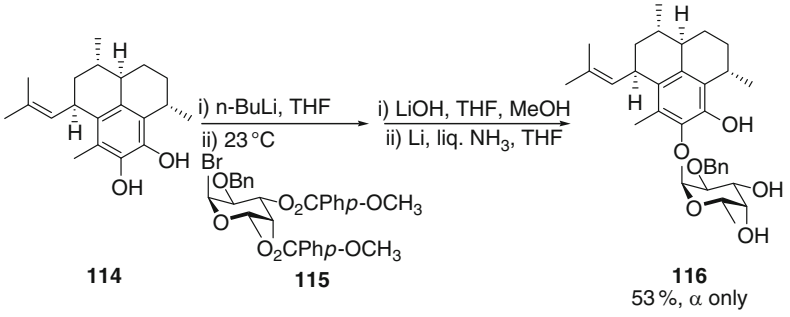


Fig. 8 Proposed remote participation by 4- and 6-*O*-benzoyl groups in galactosylations



Scheme 20

Crich and co-workers reported that the remote participation of esters at the O-3 position of allopyranosyl donors is possible in glycosylations based on the trapping experiment, in which the anomeric oxocarbenium ion intermediate generated by the activation of thioalloside **132** was trapped by the intramolecular nucleophilic attack of the *tert*-butoxycarbonyl (Boc) group at the O-3 axial position to afford stable cyclic carbonate **133** (Scheme 21) [65].

However, Crich and co-workers reported that there was no evidence to support the remote participation by an O-3 equatorial ester, by O-4 axial or equatorial esters, or by O-6 esters, and concluded that the remote participation by esters at these positions does not occur under typical glycosylation conditions [65].

Narasaka and co-workers reported a successful β-selective glycosylation, which is one of the key steps in the total synthesis of (−)-sordarin, by employing the remote participation of the O-3 axial *p*-methoxybenzoyl group of glycosyl donor **134**; the glycosylation of sordaricin ethyl ester **135** with **134** provided glycoside **136** (β/α = 6.5:1) with an excess of the β-anomer (Scheme 22) [75].

Nifantiev and co-workers reported that the glucuronylation of **121** with the donor **137** bearing the acetyl group at O-3 produced only α-linked disaccharide **138** (Scheme 23), and assumed that the α-stereoselectivity of the donor **137** resulted from the formation of a stabilized glycosyl cation intermediate generated by the remote participation of the acetyl group at O-3 (Fig. 11) [76].

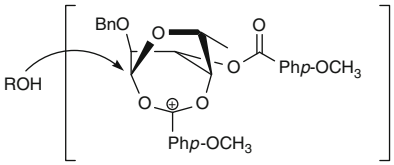
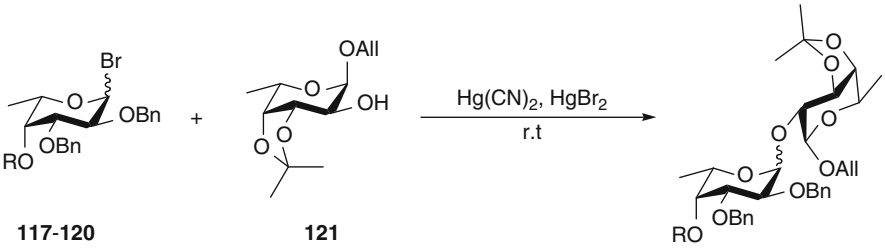


Fig. 9 The 1,4-remote participation in the fucosylation with donor **115** bearing 4-O-*p*-methoxybenzoyl group

Table 8 Fucosylations of **121** with donors bearing acyl groups at the O-4 position



117-120 **121** **122-125**

R		Product	Ratio β/α
(Bn)[a]	**117**	**122**	1:1
Bz	**118**	**123**	1:3.5
Bz(*p*-NO$_2$)	**119**	**124**	1:2
Bz(*p*-OCH$_3$)	**120**	**125**	1:5

[a]A standard donor for comparison

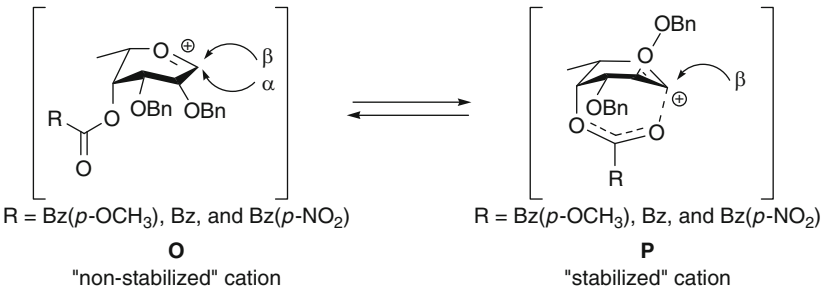
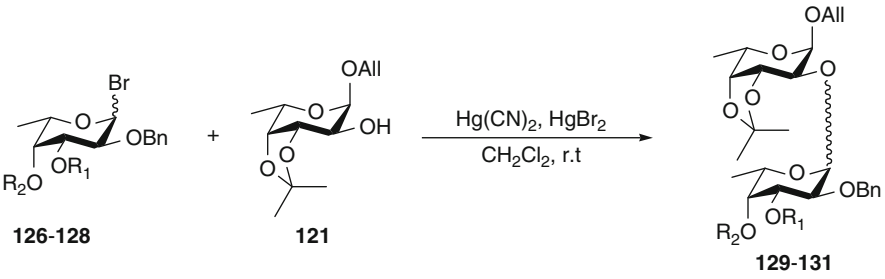


Fig. 10 Possible non-stabilized oxocarbenium ion **O** and stabilized dioxocarbenium ion **P** as intermediates in fucosylations with donors bearing 4-*O*-acyl groups

Table 9 Fucosylations of **121** with donors bearing benzoyl groups at O-3 and/or O-4 positions

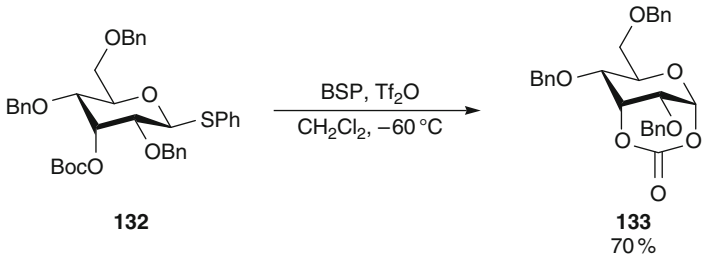


Fucosyl donor	R_1	R_2	Product	Ratio β/α
126	Bz	Bn	**129**	1:13
127	Bz	Bz	**130**	1:20
128	Bn	Bz	**131**	1:3.5

3.3 Directing Effect of Potentially Participating Groups at Remote Positions of Glycofuranosyl Donors

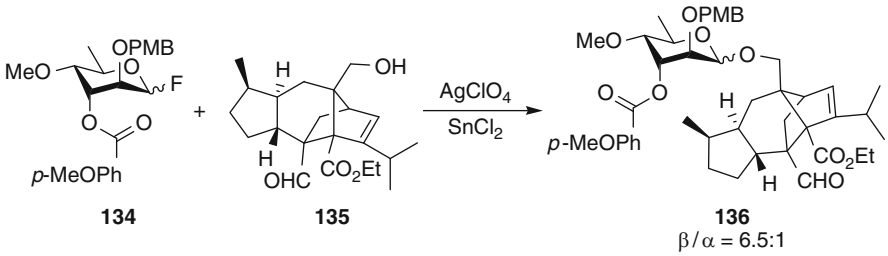
Mukaiyama and colleagues investigated N-glycofuranosylations of silylated pyrimidine nucleoside bases with 2-deoxy ribofuranosyl donors possessing a potentially participating group at the O-3 position; reactions of pyrimidine nucleobase **141** with 3-*O*-benzoyl ribofuranosyl donor **139** and with 3-*O*-diethylthiocarbamoyl ribofuranosyl donor **140** gave nucleosides **142** (β/α = 74:26) and **143** (β/α = 96:4), respectively, favoring β-anomers (Scheme 24) [77].

The high β-selectivity in the reaction between **140** and **141** was attributed to the reaction of the silylated nucleoside with the iminium ion intermediate, which resulted from the remote participation of the diethylthiocarbamoyl group at the O-3 position of **140** (Scheme 25) [77].



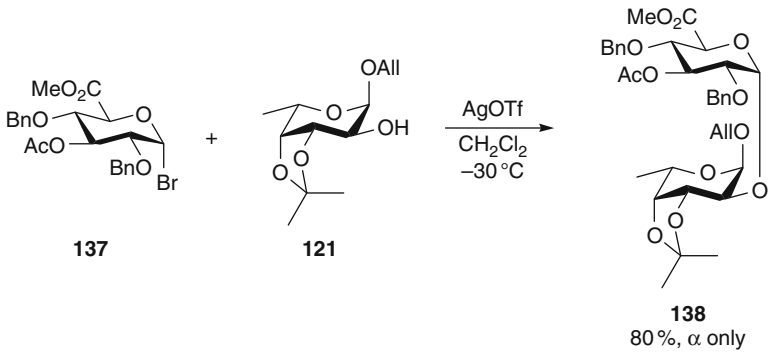
132 **133** 70 %

Scheme 21



134 **135** **136** β/α = 6.5:1

Scheme 22



137 **121** **138** 80 %, α only

Scheme 23

The 3-*O*-diethylthiocarbamoyl ribofuranosyl donor **140** was also utilized for the β-stereoselective C-glycosylation by Mukaiyama and co-workers; the reaction of **140** and carbon nucleophile **144** produced the coupling product **145** (β/α = 96:4) with an excellent β-selectivity, which presumably resulted from the remote participation of the thiocarbamoyl group at O-3 of **140** (Scheme 26) [78].

Mukaiyama and co-workers also reported that the diethylthiocarbamoyl group at the O-5 position of ribofuranosyl donors is capable of participating from the remote position during N- and C-glycosylations; glycosylations of silylated nucleoside base **147** and silyl enol ether **149** with 5-*O*-diethylthiocarbamoyl ribofuranosyl donor **146**

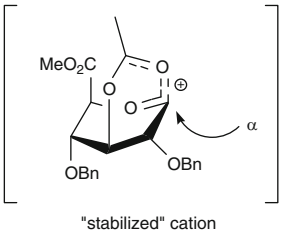
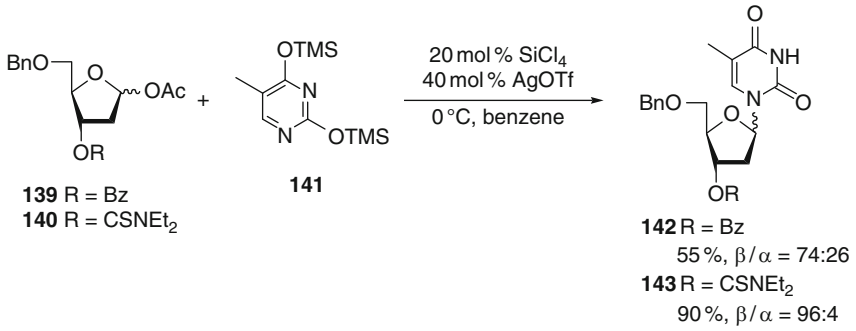


Fig. 11 Proposed stabilized dioxonium ion intermediate resulting from the remote participation of the 3-*O*-acetyl group of **137**

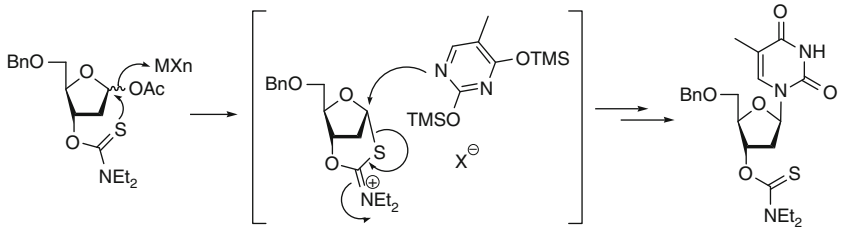


139 R = Bz
140 R = $CSNEt_2$

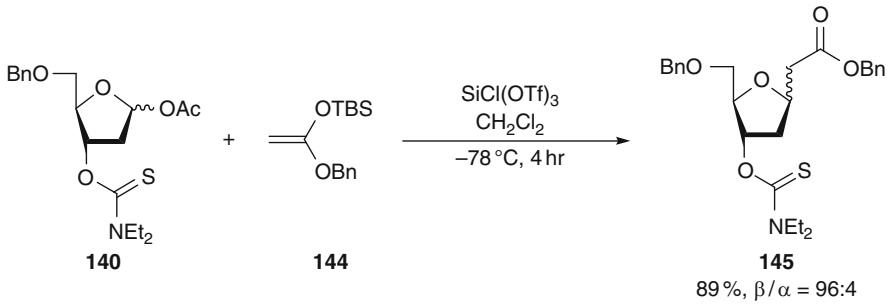
141

142 R = Bz
55 %, β/α = 74:26
143 R = $CSNEt_2$
90 %, β/α = 96:4

Scheme 24

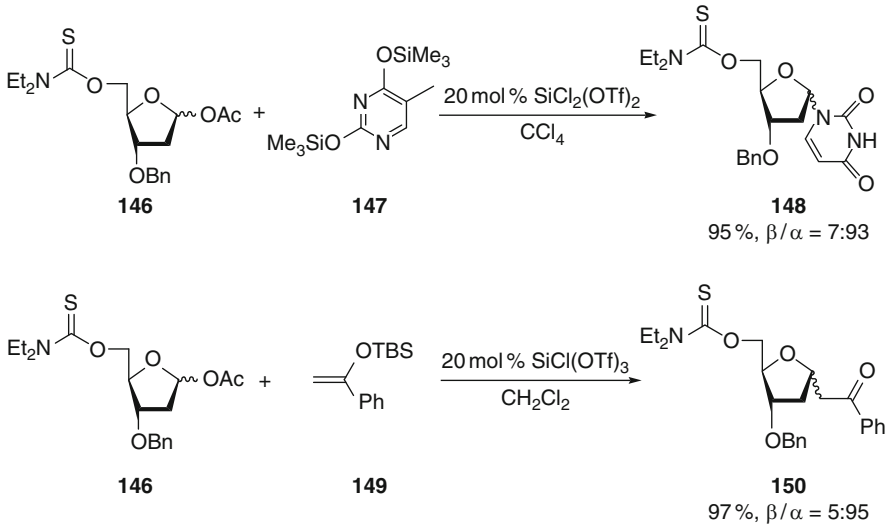


Scheme 25

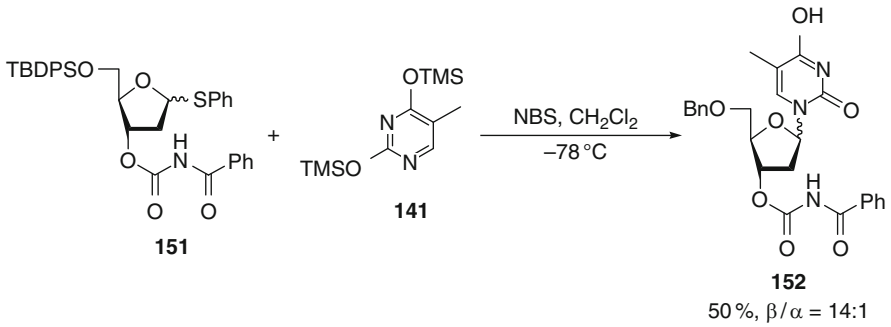


140 **144** **145**
89 %, β/α = 96:4

Scheme 26



Scheme 27

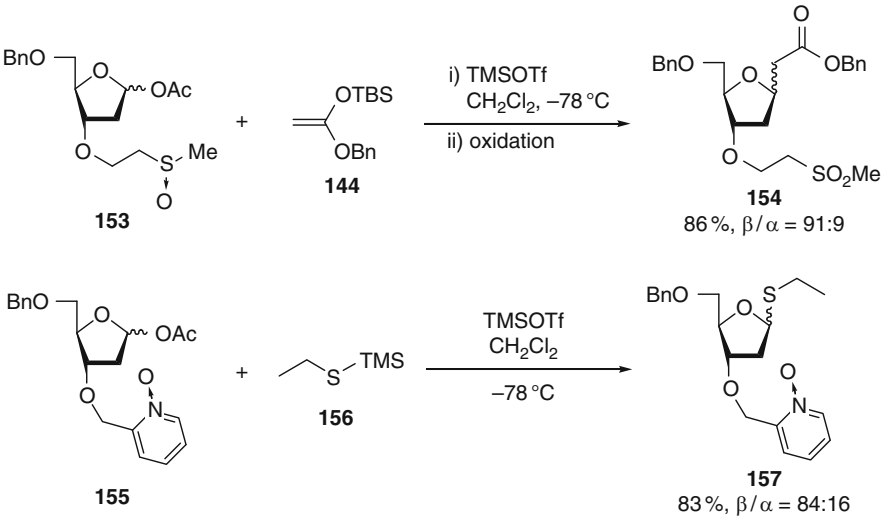


Scheme 28

afforded nucleoside **148** (β/α = 7:93) and *C*-ribofuranoside **150** (β/α = 5:95), respectively, favoring α-anomers (Scheme 27) [79].

Young and co-workers utilized the *N*-benzoylcarbamoyl group at the O-3 position of a 2-deoxyribofuranosyl donor as a directing group in N-glycosylations; the reaction of **151** and **141** produced deoxyribonucleoside **152** (β/α = 14:1) with a large excess of the β-anomer (Scheme 28), and the β-selectivity was attributed to the remote participation by the carbamoyl group at the O-3 position [80].

2-(Methylsulfinyl)ethyl group and 2-pyridylmethyl group at the O-3 position of 2-deoxyribofuranosyl donors were employed as directing groups by the remote participation in β-selective C- and S-glycosylations. Narasaka and colleagues reported that the reaction of silyl enol ether **144** with 3-*O*-[2-(methylsulfinyl) ethyl]-ribofuranosyl donor **153** and subsequent oxidation gave *C*-ribofuranoside



Scheme 29

154 (β/α = 91:9), while the reaction of 3-*O*-(2-pyridylmethyl)-ribofuranosyl donor **155** with trimethylsilyl sulfide **156** produced *S*-ribofuranoside **157** (β/α = 84:16) (Scheme 29) [81].

4 Conclusion and Perspectives

Although it has been relatively well established that remote electron-withdrawing groups affect the reactivity of donors, their simultaneous effect on the stereochemical outcome of glycosylations has not been recognized until recently. Here we reviewed the equatorial β-directing effects of remote electron-withdrawing groups of glycopyranosyl donors, including β-directing effects of sulfonyl and acyl groups at each remote position of mannosyl donors, the C-5 carboxylate ester of mannuronate donors, the C-6 fluorine atom of rhamnosyl donors, and the O-4 sulfonyl group of 2,6-dideoxyglycosyl donors. We also reviewed the enhanced equatorial α-directing effect by introduction of stronger electron-withdrawing protecting groups at the N-5 position of sialyl donors in the place of the 5-*N*-acetyl group. The proposed mechanism and origin of some of the equatorial β-directing effects were discussed.

Unlike the neighboring group participation by O-2 protecting groups, the existence of the remote participation by potentially participating groups at remote positions of glycosyl donors has been controversial. We reviewed reports that were opposed to and in favor of the remote participation. Nevertheless, results and evidence in favor of the remote participation are quite substantial, especially for

protecting groups at the following positions: the O-3 position of mannopyranosyl donors, allopyranosyl donors, and 2-deoxyribofuranosyl donors and the O-4 position of galactopyranoyl donors and fucopyranosyl donors.

Certainly, more careful systematic studies are required to observe α- or β-directing effects of electron-withdrawing protecting groups at remote positions of donors in glycosylations. In certain cases, as reviewed here, the directing effect by the remote electron-withdrawing groups could be observed clearly while it is difficult to discern the electron-withdrawing effect from effects by other factors such as the remote participation, the leaving group, and the counter anion of the oxocarbenium ion intermediate. Although the evidence supporting the remote participation from certain positions of donors has been presented, further studies are required to clarify which protecting groups and which positions of glycosyl donors are most effective for remote participation during glycosylations.

Acknowledgments Authors acknowledge the support by the National Research Foundation and the Ministry of Education, Science and Technology through the Center for Bioactive Molecular Hybrids (R11-2003-019-00000-0) and the BK 21 program.

References

1. Capon B (1969) Chem Rev 69:407
2. Nukada T, Berces A, Zgierski MZ, Whitfield DM (1998) J Am Chem Soc 120:13291
3. Demchenko AV (2008) In: Demchenko AV (ed) Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance. Wiley-VCH, Weinheim, p 1
4. Green LG, Ley SV, Ernst B, Hart GW, Sinay P (2000) In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, p 427
5. Capon B (1964) Q Rev Chem Soc 18:45
6. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B (1988) J Am Chem Soc 110:5583
7. Fraser-Reid B, Wu Z, Udodong UE, Ottosson H (1990) J Org Chem 55:6068
8. Fraser-Reid B, Udodong UE, Wu Z, Ottosson H, Merritt JR, Rao CS, Roberts C, Madsen R (1992) Synlett 927
9. Mootoo DR, Konradsson P, Fraser-Reid B (1989) J Am Chem Soc 111:8540
10. Merritt JR, Naisang E, Fraser-Reid B (1994) J Org Chem 59:4443
11. Ratcliffe AJ, Konradsson P, Fraser-Reid B (1990) J Am Chem Soc 112:5665
12. Srivastava VK, Schuerch C (1981) J Org Chem 46:1121
13. Awad LF, El Ashry ESH, Schuerch C (1986) Bull Chem Soc Jpn 59:1587
14. Srivastava VK, Schuerch C (1980) Carbohydr Res 79:C13
15. Douglas NL, Ley SV, Lücking U, Warriner SL (1998) J Chem Soc Perkin Trans 1 51
16. Zhang Z, Ollmann IR, Ye X-S, Wischnat R, Baasov T, Wong C-H (1999) J Am Chem Soc 121:734
17. Abdel-Rahman AAH, Jonke S, El Ashry ESH, Schmidt RR (2002) Angew Chem Int Ed 41:2972
18. Crich D, Picione J (2003) Org Lett 5:781
19. Crich D, Hutton TK, Banerjee A, Jayalath P, Picione J (2005) Tetrahedron Asymmetry 16:105
20. Fraser-Reid B, Wu ZC, Andrews CW, Skowronski E (1991) J Am Chem Soc 113:1434
21. Andrews CW, Rodebaugh R, Fraser-Reid B (1996) J Org Chem 61:5280
22. Crich D, Sun S (1996) J Org Chem 61:4506
23. Crich D, Sun S (1997) J Org Chem 62:1198

24. Crich D, Sun S (1998) J Am Chem Soc 120:435
25. Crich D, Sun S (1998) Tetrahedron 54:8321
26. Kim KS, Kim JH, Lee YJ, Park J (2001) J Am Chem Soc 123:8477
27. Baek JY, Choi TJ, Jeon HB, Kim KS (2006) Angew Chem Int Ed 45:7436
28. Kim KS, Fulse DB, Baek JY, Lee B-Y, Jeon HB (2008) J Am Chem Soc 130:8537
29. Weingart R, Schmidt RR (2000) Tetrahedron Lett 41:8753
30. Tanaka S-i, Takashina M, Tokimoto H, Fujimoto Y, Tanaka K, Fukase K (2005) Synlett 2325
31. Codée JDC, Hossain LH, Seeberger PH (2005) Org Lett 7:3251
32. Jensen HH, Nordstrøm LU, Bols M (2004) J Am Chem Soc 126:9205
33. Grice P, Ley SV, Pietruszka J, Priepke HWM, Warriner SL (1997) J Chem Soc Perkin Trans 1 351
34. Ley SV, Downham R, Edwards PJ, Innes JE, Woods M (1995) Contemp Org Synth 2:365
35. Barresi F, Hindsgaul O (1996) In: Khan SH, O'Neil RA (eds) Modern methods in carbohydrate synthesis. Harwood Academic Publishers, Amsterdam, p 251
36. Gridley JJ, Osborn HMI (2000) J Chem Soc Perkin Trans 1 1471
37. Demchenko AV (2003) Curr Org Chem 7:35
38. Baek JY, Lee B-Y, Jo MG, Kim KS (2009) J Am Chem Soc 131:17705
39. van den Bos LJ, Dinkelaar J, Overkleeft HS, van der Marel GA (2006) J Am Chem Soc 128:13066
40. Codée JDC, van den Bos LJ, de Jong A-R, Dinkelaar J, Lodder G, Overkleeft HS, van der Marel GA (2009) J Org Chem 74:38
41. Yang MT, Woerpel KA (2009) J Org Chem 74:545
42. Lucero CG, Woerpel KA (2006) J Org Chem 71:2641
43. Chamberland S, Ziller JW, Woerpel KA (2005) J Am Chem Soc 127:5322
44. Ayala L, Lucero CG, Romero JAC, Tabacco SA, Woerpel KA (2003) J Am Chem Soc 125:15521
45. Dinkelaar J, de Jong AR, van Meer R, Somers M, Lodder G, Overkleeft HS, Codée JDC, van der Marel GA (2009) J Org Chem 74:4982
46. Crich D, Vinogradova O (2007) J Am Chem Soc 129:11756
47. Marzabadi CH, Franck RW (2000) Tetrahedron 56:8385
48. Thiem J, Klaffke W (1990) Top Curr Chem 154:285
49. Veyrieres A (2000) In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim
50. Tanaka H, Yoshizawa A, Takahashi T (2007) Angew Chem Int Ed 46:2505
51. Halcomb RL, Chappell MD (2002) J Carbohydr Chem 21:723
52. Boons G-J, Demchenko AV (2000) Chem Rev 100:4539
53. Okamoto K, Goto T (1990) Tetrahedron 46:5835
54. Meo CD, Demchenko AV, Boons G-J (2001) J Org Chem 66:5490
55. Hasegawa A, Nagahama T, Ohki H, Hotta K, Ishida H, Kiso M (1991) J Carbohydr Chem 10:493
56. Demchenko AV, Boons G-J (1998) Tetrahedron Lett 39:3065
57. Tanaka K, Goi T, Fukase K (2005) Synlett 2958
58. Farris MD, De Meo C (2007) Tetrahedron Lett 48:1225
59. Crich D, Li W (2007) J Org Chem 72:2387
60. Ando H, Koike Y, Ishida H, Kiso M (2003) Tetrahedron Lett 44:6883
61. Adachi M, Tanaka H, Takahashi T (2004) Synlett 609
62. Tanaka H, Adachi M, Takahashi T (2005) Chem Eur J 11:849
63. De Meo C, Kamat MN, Demchenko AV (2005) Eur J Org Chem 706
64. Crich D, Cai W, Dai Z (2000) J Org Chem 65:1291
65. Crich D, Hu T, Cai F (2008) J Org Chem 73:8942
66. van Boeckel CAA, Beetz T, van Aelst SF (1984) Tetrahedron 40:4097
67. Ustyuzhanina N, Komarova B, Zlotina N, Krylov V, Gerbst A, Tsvetkov Y, Nifantiev N (2006) Synlett 921

68. Mukaiyama T, Suenaga M, Chiba H, Jona H (2002) Chem Lett 56
69. Demchenko AV, Rousson E, Boons G-J (1999) Tetrahedron Lett 40:6523
70. Lin C-C, Shimazaki M, Heck M-P, Aoki S, Wang R, Kimura T, Ritzen H, Takayama S, Wu S-H, Weitz-Schmidt G, Wong C-H (1996) J Am Chem Soc 118:6826
71. Cheng Y-P, Chen H-T, Lin C-C (2002) Tetrahedron Lett 43:7721
72. Corey EJ, Carpino P (1989) J Am Chem Soc 111:5472
73. Gerbst AG, Ustuzhanina NE, Grachev AA, Tsvetkov DE, Khatuntseva EA, Nifant'ev NE (1999) Mendeleev Commun 9:114
74. Gerbst AG, Ustuzhanina NE, Grachev AA, Khatuntseva EA, Tsvetkov DE, Whitfield DM, Berces A, Nifantiev NE (2001) J Carbohydr Chem 20:821
75. Chiba S, Kitamura M, Narasaka K (2006) J Am Chem Soc 128:6931
76. Zlotina NS, Ustyuzhanina NE, Grachev AA, Gerbst AG, Nifantiev NE (2008) J Carbohydr Chem 27:429
77. Mukaiyama T, Hirano N, Nishida M, Uchiro H (1996) Chem Lett 25:99
78. Mukaiyama T, Uchiro H, Hirano N, Ishikawa T (1996) Chem Lett 25:629
79. Mukaiyama T, Ishikawa T, Uchiro H (1997) Chem Lett 26:389
80. Young RJ, Shaw-Ponter S, Hardy GW, Mills G (1994) Tetrahedron Lett 35:8687
81. Ichikawa Y-i, Kubota H, Fujita Ki, Okauchi T, Narasaka K (1989) Bull Chem Soc Jpn 62:845

Top Curr Chem (2011) 301: 141–188
DOI: 10.1007/128_2010_102

Published online: 15 January 2011

Influence of Protecting Groups on the Reactivity and Selectivity of Glycosylation: Chemistry of the 4,6-*O*-Benzylidene Protected Mannopyranosyl Donors and Related Species

Sylvain Aubry, Kaname Sasaki, Indrajeet Sharma, and David Crich

Abstract The genesis and development of the 4,6-*O*-benzylidene acetal method for the preparation of β-mannopyranosides are reviewed. Particular emphasis is placed on the influence of the various protecting groups on stereoselectivity and these effects are interpreted in the framework of a general mechanistic scheme invoking a series of solvent-separated and contact ion pairs in dynamic equilibrium with a covalent α-glycosyl trifluoromethanesulfonate.

Keywords Acetal, Anomeric effect, Diastereoselectivity, Glycosylation, Ion pair, Kinetic isotope effect, Stereoelectronic effects

Contents

S. Aubry, K. Sasaki, and D. Crich (✉)
Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette, France
e-mail: david.crich@icsn.cnrs-gif.fr

I. Sharma and D. Crich
Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202 USA

1 Introduction and Background

Understandably in view of the very definition of organic chemistry and the carbon-based framework of organic compounds, the traditional focus of organic synthesis and methods development has been on the efficient stereocontrolled formation of carbon–carbon bonds. In many ways this has resulted in the sidelining of certain areas of the discipline as specialist areas, of which the formation of glycosidic C–O bonds is a paramount example. The prevailing attitude some years ago is summed up by the comment of a Nobel prize winner once known to one of the editors of this volume and, we suspect, to one of the authors of this chapter to the effect that "stabilization of the anomeric carbon by the ring oxygen constitutes half of carbohydrate chemistry" [1]. The situation has evolved tremendously since that era as, while carbohydrate nomenclature remains something of a quagmire for the uninitiated, modern chromatographic and analytical methods have rendered the isolation and structural elucidation of previously intractable saccharides and their conjugates open to all. Nevertheless, the chemical synthesis of the glycosidic C–O bond in general, and certain classes of it in particular, remains for the most part a highly challenging and most frequently empirical enterprise. This is nicely illustrated by reference to Hindsgaul and Barresi's compilation of the entire set of 734 glycosidic bond syntheses published in the calendar year 1994 when >10 types of glycosyl donor, and >10 types of leaving group were employed, not to mention the considerable variety of promoters, solvent, reaction times, and temperatures [2]. For example, even for the subgroup of the thioglycosides, more than 16 different promoters were used in the 173 examples tabulated. Certainly, in the ensuing 16 years considerable advances have been made but, as recent reviews make clear [3],

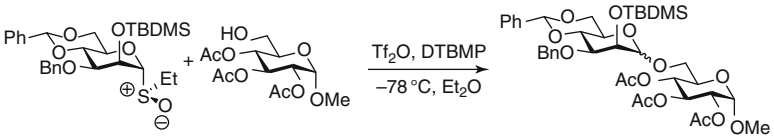
the field is still a difficult one and the challenge of stereocontrolled C–O bond formation is in many cases at least equal to that of C–C bond formation.

Since 1990 the Crich group has been actively involved in the search for methods for the efficient formation of the β-mannopyranosides, traditionally one of the three more difficult classes of glycosidic bond to form owing to the need to overcome the enhanced anomeric effect in the mannopyranose series, the shielding of the β-face by the C2–O2 bond and any protecting group blocking it, and the impossibility of recourse to traditional crutches such as neighboring group participation. Owing to these difficulties the most successful and reliable approaches to β-mannopyranoside formation were frequently indirect ones typically requiring formation of a more facile β-glucopyranoside followed, post-glycosylation, by correction of the stereochemistry at C2 [4–9]. In the early 1990s the Crich laboratory was no different from most others in this respect insofar as efforts were directed at the elaboration of cute but inefficient indirect methods for the elaboration of β-mannopyranosides [10–12]. Fortunately, however, a lucky choice of protecting groups allowed the serendipitous discovery to be made of the ability of a 4,6-*O*-acetal protecting group to direct simple mannopyranosylations to the formation of the β-isomer [13, 14]. The desire to understand this key phenomenon, and the many factors that influence it, has occupied a considerable amount of time in the intervening years and it is these investigations that are combined into a harmonious picture in this chapter. The parallel exploitation of the acetal-directed β-mannosylation in complex oligosaccharide synthesis will be reviewed elsewhere.

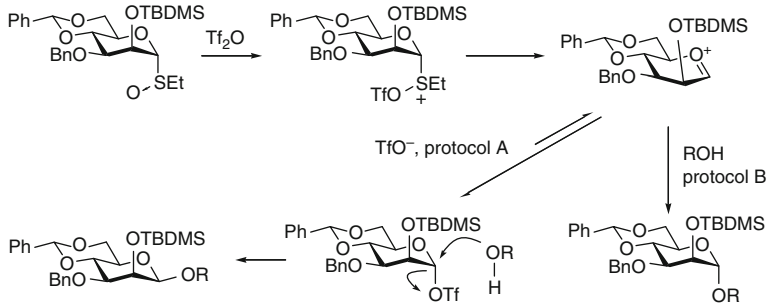
2 4,6-*O*-Benzylidene-Directed β-Mannopyranosylation

2.1 The Sulfoxide Method

In the course of the elaboration of an indirect method for β-mannopyranoside synthesis, the need to prepare an α-mannopyranoside arose [11]. Chance had it that a 4,6-*O*-benzylidene protecting group was selected for the donor and Kahne's sulfoxide method [15] for the glycosylation reaction, and that different coworkers inadvertently reversed the order of mixing of the reagents. Summarizing, it was found that in ether solution with a 4,6-*O*-benzylidene protected donor carrying a benzyl ether at O3 and a silyl ether at O2, premixing the donor and acceptor prior to addition of the triflic anhydride activating agent gave predominantly the α-mannopyranoside, whereas addition of the acceptor to the preformed mixture of the donor and the triflic anhydride resulted in the opposite stereoselectivity (Scheme 1) [13, 14]. These reactions are typically conducted in the presence of a weak non-nucleophilic base such as 2,6-di-*tert*-butyl-4-methylpyridine, or the easier to handle 2,4,6-tri-*tert*-butyl-pyrimidine [16], but this may be omitted with no detrimental consequences provided that the reaction is quenched with a suitable base before the introduction of water [17]. Subsequently it was found that reactions conducted in dichloromethane gave generally better β-selectivities than those carried out in ether, and the preactivation of the



Scheme 1 Inversion of selectivity with mixing order in ether



Scheme 2 The initial mechanistic hypothesis

donor in dichloromethane solution prior to addition of the acceptor has become the standard protocol [14, 18]. It must be noted, however, that it has been observed subsequently that 4,6-*O*-benzylidene protected mannopyranosyl sulfoxides and other related donors also give β-mannopyranosides under premixing conditions in dichloromethane solution, thereby emphasizing the influence of solvent (see Sect. 3.3) in these glycosylation reactions [19].

Subsequent work showed the novel β-mannosylation reaction to be independent of the stereochemistry at sulfur in the starting sulfoxide [20, 21], although rare examples of the opposite are known for the broader sulfoxide method [22], and independent of the anomeric configuration of the donor [21].

An initial hypothesis was formulated whereby reaction of the triflic anhydride with the sulfoxide leads to a highly active glycosyl sulfonium ion that collapses to a glycosyl oxocarbenium ion. When this carbenium ion is generated in the presence of the acceptor, it is trapped by the latter, leading directly to the α-mannoside. On the other hand, in the absence of an acceptor alcohol, the oxocarbenium ion combines with the triflate anion to give an α-glycosyl triflate, which on subsequent addition of the acceptor takes part in an S_N2-like process to give the β-mannoside (Scheme 2) [14, 18].

In elaborating this hypothesis it was assumed, and subsequently supported by calculations [23–25], that the intermediate oxocarbenium ion adopts a $^4H_3$ half-chair or ^4E envelope conformation and that attack on this electrophile takes place

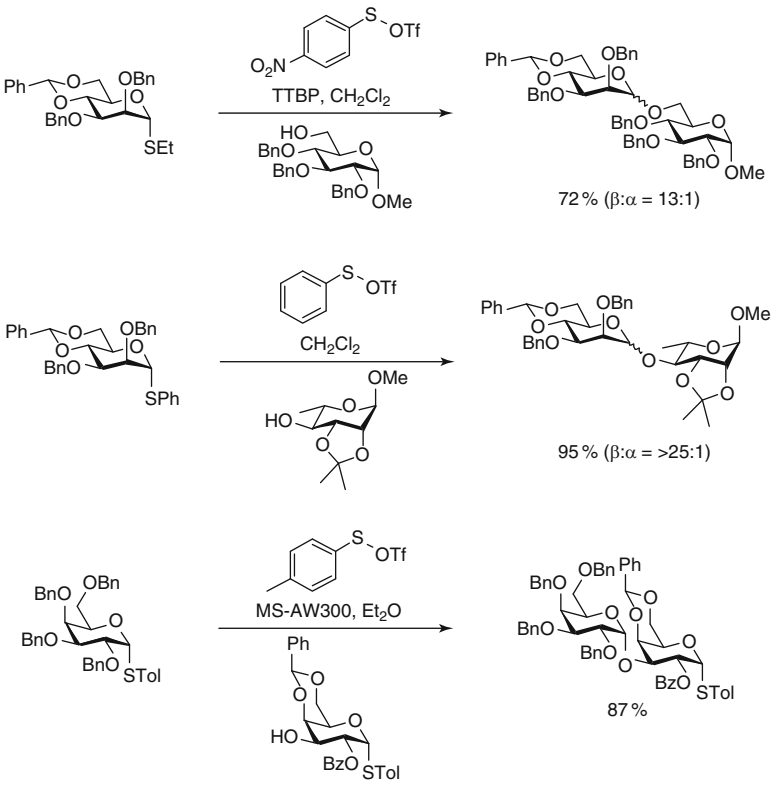
predominantly in the pseudo-axial direction to deliver either the α-glycoside or triflate directly in the chair conformation [26] in which it also benefits from the anomeric effect [27, 28].

2.2 The Thioglycoside Method

In the course of investigations of the reaction of the glycosyl phenyl sulfoxides with triflic anhydride [29], it was realized that a necessary byproduct of that reaction, benzenesulfenyl triflate, was capable of converting the glycosyl sulfoxides to the glycosyl triflates and, more importantly, of cleanly transforming thioglycosides into glycosyl triflates at low temperature. Using benzenesulfenyl triflate generated from benzenesulfenyl chloride and silver triflate, this discovery afforded the opportunity to prepare β-mannopyranosides directly from thioglycosides, without the need for their prior oxidation to the sulfoxide [30]. The sulfenyl triflate method for the activation of thioglycosides was subsequently developed by Huang and coworkers who preferred 4-toluenesulfenyl chloride as the precursor of choice [31], whereas the Crich group ultimately preferred 4-nitrobenzenesulfenyl chloride because of its shelf-stability and commercial availability (Scheme 3) [32].

The need to prepare the arenesulfenyl triflate in situ, and the heterogeneous nature of this preparation, prompted the search for alternative protocols for the synthesis of sulfenyl triflates. Based on work by Oae on the reaction of thiosulfinates with acetic anhydride [33], a method involving reaction of an electron rich thiosulfinate with triflic anhydride was developed (Scheme 4) [34]. This system was, however, less powerful than benzenesulfenyl triflate itself and could only activate armed thioglycosides, suggesting that an intermediate adduct between the thiosulfinate and the triflic anhydride was the true activating species rather than any sulfenyl triflate. Seeking to improve the reactivity of the system, attention was turned to the reaction of sulfinamides with triflic anhydride, resulting in the development of the reagent known as BSP (benzenesulfinyl piperidine) [35]. This reagent is more powerful than that derived from the thiosulfinate and activates all but strongly disarmed thioglycosides. However, it is nevertheless less potent that benzenesulfenyl triflate and so acts through an intermediate adduct with the anhydride (Scheme 4). Finally, van Boom and his coworkers introduced the combination of diphenyl sulfoxide with triflic anhydride for the conversion of even strongly disarmed thioglycosides into glycosyl triflates (Scheme 4) [36].

Subsequent variations on the theme include benzenesulfinyl pyrrolidine from the Crich laboratory, for use in low temperature NMR experiments because of its greater solubility than BSP [37], benzenesulfinyl morpholine by the Huang group [38], and *N*-(phenylthio) ε-caprolactam by Wong and coworkers [39]. Later, it was shown by Tatai and Fügedi that even the combination of dimethyl disulfide with triflic anhydride is a powerful system for the activation of thioglycosides at low temperature [40].

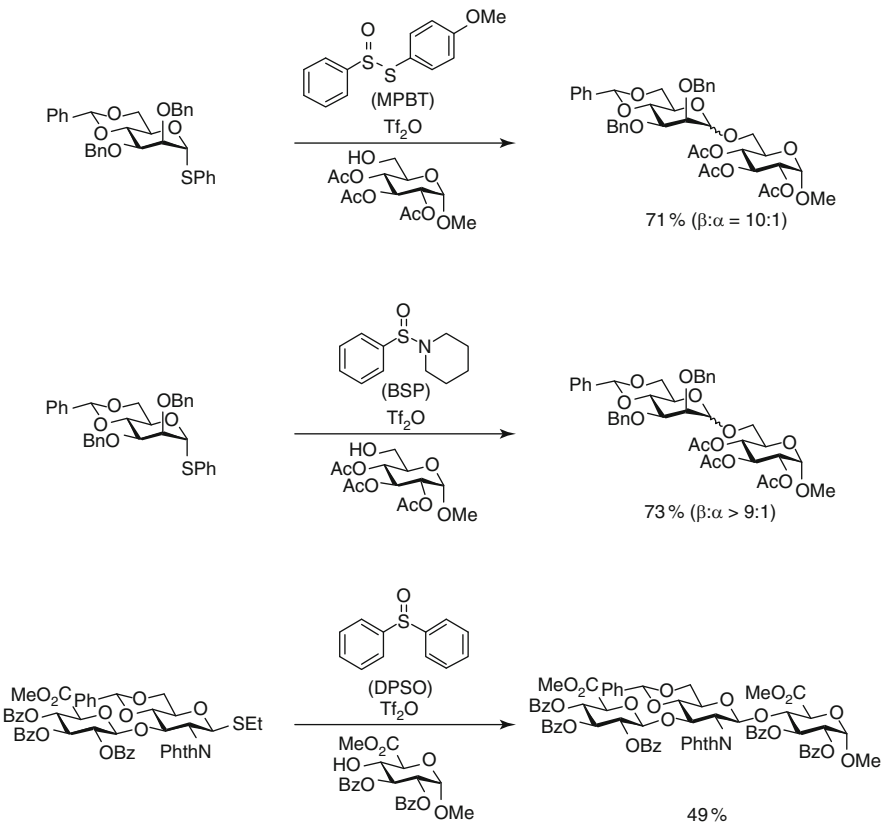


Scheme 3 Activation of thioglycosides with arenesulfenyl triflates

3 The General Mechanism

3.1 The Intermediacy of Glycosyl Triflates

Low temperature NMR work demonstrated that triflic anhydride converts glycosyl sulfoxides rapidly and cleanly to an intermediate species considered to be a α-glycosyl triflate at −78 °C in CD_2Cl_2 [29]. With a 4,6-*O*-benzylidene acetal protecting group and 2,3-di-*O*-methyl ethers as in the original work, this species is characterized by ^1H and ^{13}C chemical shifts of δ 6.20 and 104.6, respectively, and by an anomeric $^1J_{CH}$ coupling constant of 184.5 Hz. In subsequent work with benzyl ethers in the place of the methyl ethers, minor differences in chemical shift were observed, which are attributed to the change of protecting groups [41]. On warming, the 2,3-di-*O*-methyl-4,6-*O*-benzylidene protected mannosyl triflate displayed a decomposition temperature of ~ −10 °C [29]. As the decomposition temperature of a glycosyl triflate is an indirect measure of the stability of these

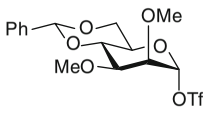
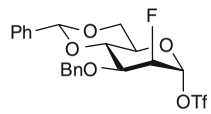
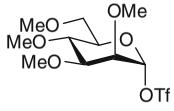
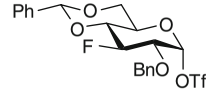
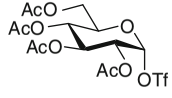
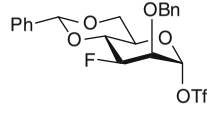
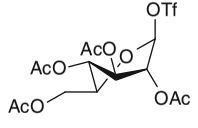
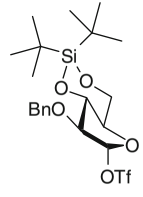
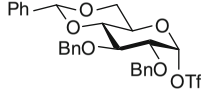
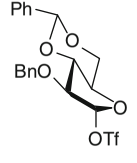


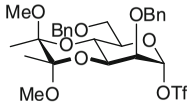
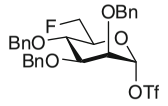
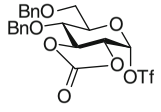
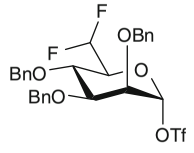
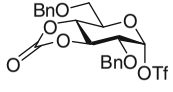
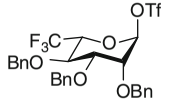
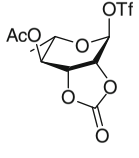
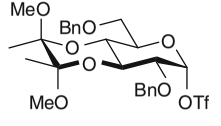
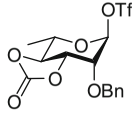
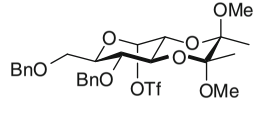
Scheme 4 Activation of thioglycosides with various S(IV) derivatives and triflic anhydride

species, a number of such measurements have been made in the intervening years and are collected here in Table 1 for convenience.

Previous attempts at forming glycosyl triflates by other workers from the reaction of anomeric hemiacetals with triflic anhydride resulted in the generation of 1,1′-disaccharides when the reaction was conducted in the absence of base, owing to the immediate glycosylation of a second aliquot of hemiacetal by the triflate [52–54]. The formation of glycosyl triflates as intermediates en route to glycosyl halides had also been quite reasonably postulated, but never demonstrated in the reaction of anomeric hemiacetals with triflic anhydride in the presence of collidine and tetrabutylammonium halides [55, 56]. Schuerch and coworkers studied the formation and reactions of glycosyl triflates produced by metathesis reactions of glycosyl chlorides and silver triflate but stressed the need to work under rigorously anhydrous conditions with the help of vacuum line techniques, such that the method was never exploited [57–61]. Along similar lines, a glycosyl fluoride was subsequently converted at low temperature to a glycosyl triflate through the action of trimethylsilyl triflate, as demonstrated by NMR spectroscopy [62]. The

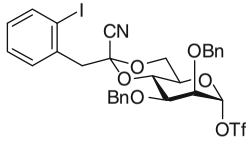
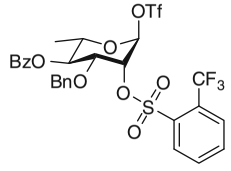
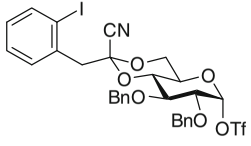
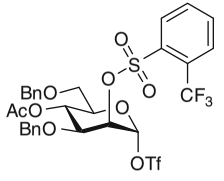
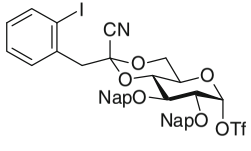
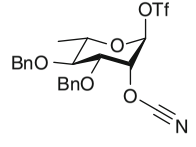
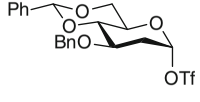
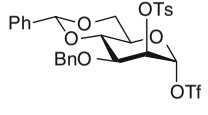
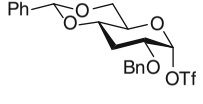
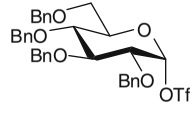
Table 1 Various glycosyl triflates and their decomposition temperatures

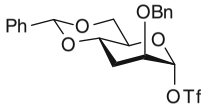
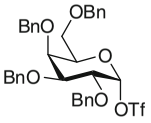
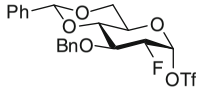
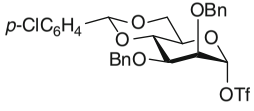
Entry	Glycosyl triflate	Decomp. temp. (°C)	Entry	Glycosyl triflate	Decomp. temp. (°C)
1 [29]		>−10	18 [42]		>25
2 [29]		−30	19 [42]		−10 to 0
3 [29]		0	20 [42]		−10 to 0
4 [29]		0	21 [43]		10
5 [44]		7 to 17[a]	22 [43]		−30

6 [45]		5 to 17	23 [46]		−10 to 0
7 [47]		~5	24 [46]		0 to 10
8 [47]		~5	25 [46]		10 to r.t.
9 [47]		~ −15	26 [48]		−5
10 [47]		30	27 [48]		−5

(*continued*)

Table 1 (continued)

Entry	Glycosyl triflate	Decomp. temp. (°C)	Entry	Glycosyl triflate	Decomp. temp. (°C)
11 [49]		0	28 [50]		10
12 [49]		>−10	29 [50]		−10
13 [49]		−50 to −20	30 [50]		−30
14 [51]		−30	31 [50]		20
15 [51]		−20 to −10	32 [41]		>−50

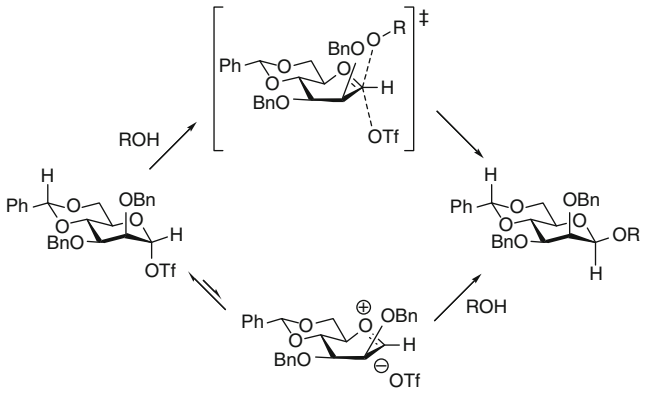
16 [51]		−20 to −10	33 [41]		>−60
17 [42]		>25	34 [41]		>−40

[a]In the light of entries 12 and 13 of this table this value appears to be abnormally high and is probably erroneous

advantage of the methods described in this chapter employing triflic anhydride and glycosyl sulfoxides, or triflic anhydride and thioglycosides, in conjunction with various sulfur(II) and (IV) reagents is their ability to generate the glycosyl triflate quickly and cleanly at low temperature.

3.2 The Kinetic Isotope Effect Experiment

The idea that the β-mannopyranosides were generated from the α-mannosyl triflate by an S_N2 reaction (Scheme 2) was never entirely satisfactory not least because the S_N2 reaction is stereospecific by definition and the observed selectivities, while high, were never total. For this reason, the displacement was generally referred to as being S_N2-like. Formally, S_N1 and S_N2 processes are distinguished on the basis of kinetics in addition to stereochemistry but the very rapid nature of the reaction [29], coupled with the relatively slow nature of the observation method (NMR), ruled out the possibility of direct kinetic measurements. Ultimately, we turned to the measurement of secondary deuterium kinetic isotope effects by a modification of the Singleton NMR method [63, 64]. For the reaction illustrated in Scheme 5, a KIE [65–67] of 1.2 was determined at −78 °C, which is equivalent to one of 1.1 at 25 °C, indicating an S_N1 process [63]. Gervay-Hague and coworkers have subsequently applied the same NMR KIE method to formation of β-mannosides from α-mannosyl iodides and found comparable results [68]. It having been estimated by Jencks and his followers that glycosyl oxocarbenium ions have only borderline existence in water and even less in organic solvents less capable of supporting charge separation [69], the alternative explanation is that of a bimolecular reaction with an exploded transition state [70], namely a very loose S_N2 reaction with substantial positive charge development at the anomeric carbon and very long bonds to both the leaving group and the nucleophile. As discussed elsewhere [71], consideration



Scheme 5 Mechanistic possibilities consistent with secondary deuterium kinetic isotope effect measurements

of the extrapolations made by Jencks [69], and NMR work on simpler oxocarbenium ions by Yoshida [72], suggest that predictions on the inability of glycosyl oxocarbenium ions to exist in organic solvents are likely erroneous and that it is only a matter of time and experimental design before one is detected experimentally. As such, the simple S_N1 pathway is considered here to remain a distinct possibility for the β-mannosylation reaction (Scheme 5).

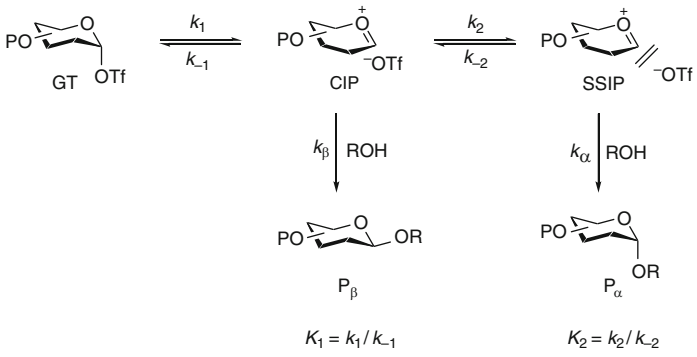
3.3 The Ion Pair Mechanism

The realization that even the β-mannosylation reactions proceed via an S_N1 reaction, or something very close to it, leads to the proposition of a general mechanism based on the concept of a series of equilibrating ion pairs [63]. According to this mechanism, the covalent α-glycosyl triflate acts as a reservoir for a transient contact ion pair, which is in turn in equilibrium with a solvent separated ion pair (Scheme 6). In the contact ion pair the triflate counterion is closely associated with the α-face of the oxocarbenium and effectively shields it, such that attack on this species leads to the β-glycoside. In the solvent-separated ion pair, on the other hand, the α-face of the oxocarbenium ion is exposed and attack takes place along the axial direction to give the α-glycoside directly in the chair conformation.

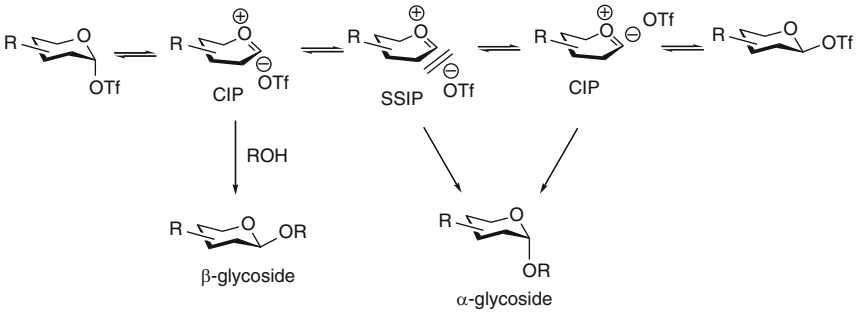
In this manner, extrapolating from Winstein [73], the product ratio can be expressed in terms of (1), whose derivation is given in the Appendix:

$$\frac{(\mathrm{d}[P_\beta])/\mathrm{d}t}{(\mathrm{d}[P_\alpha])/\mathrm{d}t} = \frac{k_\alpha}{k_2}[\mathrm{ROH}] + \frac{k_\beta}{k_\alpha K_2}[^{-}\mathrm{OTf}] \tag{1}$$

This concept of a series of equilibrating ion pairs in solvolysis [74] was first introduced into organic chemistry by Winstein in the 1950s [73], and was first applied to glycosylation reactions by Rhind-Tutt and Vernon in 1960 [75]. The concept was further elaborated for glycosylation by Scherch and coworkers



Scheme 6 Simplified general mechanistic hypothesis for glycosylation



Scheme 7 Complete mechanistic hypothesis

[57–59], and then considerably extended by Lemieux et al. in their seminal work on the formation of α-glycosides [76]. Extrapolating from the discussions of Vernon, Schuerch, and Lemieux, the ion pair mechanism for β-mannosylation potentially also includes a β-covalent glycosyl triflate, and a β-contact ion pair, which potentially serve as the source of the α-glycoside. The complete mechanism, therefore, is as pictured in Scheme 7. However, as will become clear, at least for the work described in this chapter, the β-triflate and the corresponding β-contact ion pair are not necessary to explain the experimental observations. Indeed, apart from the identification of a potential β-triflate derived from tetraacetyl glucosyl thioglycoside [29, 77], and a more recent observation by the van der Marel group in the mannuronic acid series [78], such species are mostly not observed. Taking the principle of Okham's razor [79] into consideration, such species are consequently no longer considered in this chapter.

Although it remains to be proved, it is logical to postulate that, if this most difficult of glycosylation reactions – the β-mannosylation – proceeds in a dissociative manner, such a pathway will operate for most other cases and the mechanism of Scheme 6, or its extended version in Scheme 7 will be general.

Consideration of Scheme 6 and of (1) leads directly to the hypothesis that the explanation of any factors affecting the stereochemistry of glycosylation reactions can be found in the manner in which these factors influence the equilibrium between the contact and solvent separated ion pairs. For example, polar solvents support charge separation better than nonpolar solvents and so are likely to shift the equilibrium toward the solvent separated ion pair and increase the proportion of α-glycoside formation. The difference in selectivity noted earlier between the use of diethyl ether and dichloromethane as solvent [14], as well as the increased β-selectivity with weaker nucleophiles in toluene solution (see Sect. 2.1) [80, 81], are thus readily understood. The importance of the concentration of the alcohol on selectivity is also apparent from (1) as is the expected influence of the concentration of the triflate counterion. To favor β-mannoside formation it is necessary to shift the contact ion pair-solvent separated ion pair equilibrium as far as possible toward the contact ion pair. However, any factors favoring the contact ion pair over the solvent separated ion pair are also likely to favor the covalent glycosyl triflate over the

ion pairs and consequently to retard the overall reaction. For example, according to (1), increasing the triflate concentration by addition of, e.g., tetrabutylammonium triflate will increase β-selectivity. However, it will also influence the position of the equilibrium between the glycosyl triflate and the contact ion pair and so will retard the overall reaction rate.

To a first approximation the stability of the covalent glycosyl triflate with respect to the oxocarbenium ion (pairs) will be reflected in the decomposition temperature of the triflate (Table 1). Thus, the tetra-*O*-methyl α-mannosyl triflate (Table 1, entry 2) has a decomposition temperature of −30 °C whereas the corresponding 4,6-*O*-benzylidene protected system decomposes at −10 °C (Table 1, entry 1) [29]. The equilibrium constant K_1 is therefore smaller for the benzylidene protected system than for a similar all-ether protected one. In agreement with this observation, the benzylidene protected system is more β-selective than the per-ether protected one. When an extra electron-withdrawing group is added to the 2-position of the benzylidene protected system, for example a sulfonate ester, the equilibrium constants K_1 and K_2 necessarily decrease further, leading to an observed decomposition temperature for the covalent triflate of ~25 °C and a general lack of reactivity (Table 1, entry 31) [50].

3.4 The Benzylidene Effect

3.4.1 The Torsional Hypothesis

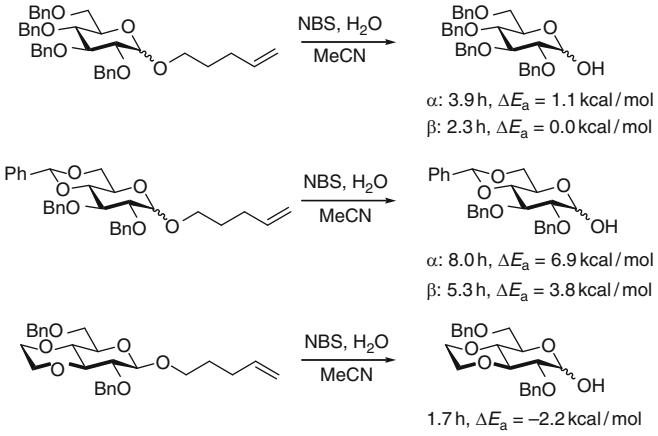
If the general mechanism of Scheme 6 is accepted then it follows that the explanation for the benzylidene effect can be found in the effect of this group on the equilibrium constant K_2, or more specifically in a reduction of K_2.

Fraser-Reid and coworkers found, working in the glucose series, that a 4,6-*O*-benzylidene protected pentenyl glycoside was hydrolyzed more slowly than the corresponding 4,6-di-*O*-benzyl system (Scheme 8) [82, 83].

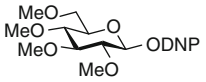
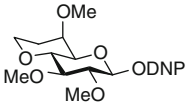
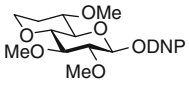
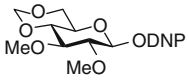
Based on computational work, Fraser-Reid and coworkers hypothesized that the benzylidene group is disarming due to the additional torsional strain its presence engenders as the covalent glycosyl donor collapses to the oxocarbenium ion [82, 83]. In other words, in this hypothesis the effect of the benzylidene acetal is due to the strain encountered as the chair–chair donor undergoes a conformational change to a chair–half-chair oxocarbenium ion. Accordingly, these workers coined the term torsionally disarming for the benzylidene acetal group [82, 83].

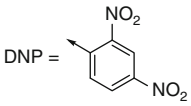
3.4.2 The Stereoelectronic Factor

In a subsequent study on the hydrolysis of a series of bicyclic glucosyl donors (Scheme 9), Bols and coworkers revealed that the presence of a six-membered ring



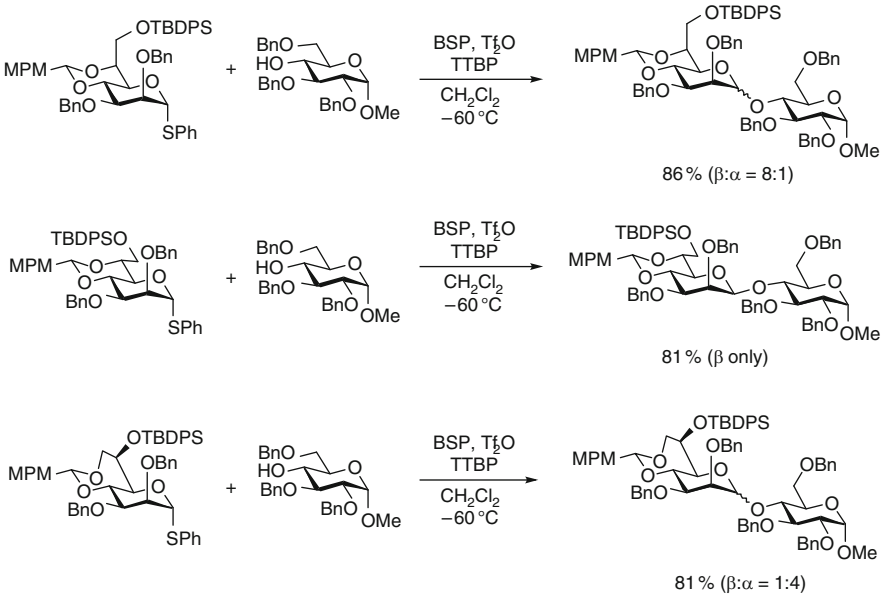
Scheme 8 Hydrolysis times and the disarming effect of a 4,6-*O*-benzylidene acetal

	E_a (kJ/mol)	ΔS (J/molK)	$k \times 10^7$ s^{-1} (37 °C)	Relative hydrolysis rate
	92.5 ± 4.5	22.8 ± 1.7	19.0	1
	113.5 ± 2.1	29.5 ± 0.8	4.6	0.24
	119.1 ± 2.7	30.1 ± 1.0	3.1	0.16
	107.3 ± 2.5	25.8 ± 0.9	1.3	0.07



Scheme 9 Relative hydrolysis rates of a series of dinitrophenyl glycosides

fused to the pyranose ring is not sufficient to retard hydrolysis and, therefore, that the benzylidene effect is not purely torsional [84]. These workers demonstrated that for the full magnitude of the effect to be observed it is necessary for the O6 to be in the second ring. They hypothesized that the effect arises from the locking of the C5–C6 bond in the *trans-gauche* (*tg*) [85] conformation with the 180° torsion angle for the O5–C5–C6–O6 system, which maximizes the electron-withdrawing effect



Scheme 10 Effect of acetal ring size on stereoselectivity

of O6. This maximization of the electron-withdrawing effect of O6 maximizes destabilization of the glycosyl oxocarbenium ion and thereby minimizes K_1 with respect to a system with a freely rotating C5–C6 bond.

Crich and Banerjee, in their studies on the preparation of β-mannoheptopyranosides, prepared a series of three donors, two bearing a 4,6-*O*-benzylidene acetal and either an axial or equatorial group at C6, and a third with a 4,7-*O*-benzylidene acetal (Scheme 10) [86]. The two 4,6-*O*-benzylidene acetals were highly β-selective, indicating that the extra substituent at C6 has little influence on the course of the reaction, and arguing against torsional factors. On the other hand, the more flexible seven-membered 4,7-*O*-benzylidene acetal, which does not hold the C5–C6 bond in the *tg* conformation, showed considerably reduced selectivity. Apparently, therefore, the locking of the C5–C6 bond in the *tg* conformation is important for both the control of stereochemistry as well as the retardation of the overall reaction rate.

3.4.3 Influence on the Contact Ion Pair-Solvent Separated Ion Pair Equilibrium

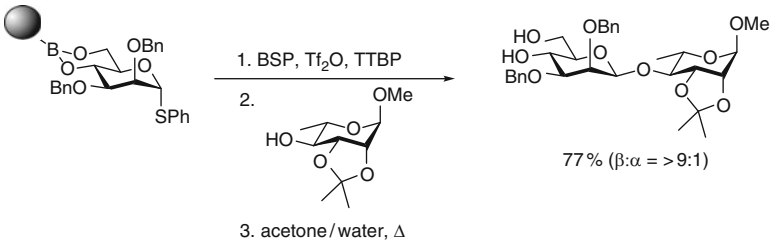
The experimental results of both the Fraser-Reid (Scheme 8) and Bols (Scheme 9) groups highlight the retarding influence of the benzylidene acetal on the overall reaction rate, i.e., on the covalent triflate – contact ion pair equilibrium and provide a basis on which to build a hypothesis for the effect on stereoselectivity. If the

benzylidene group retards reaction rate by destabilizing the glycosyl oxocarbenium ion, i.e., by reducing the magnitude of K_1 (Scheme 6), then it must increase β-selectivity by causing a similar reduction in K_2 [Scheme 6 and (1)]. In other words, the benzylidene acetal must destabilize the solvent separated ion pair more than it does the contact ion pair. Two explanations, that are not necessarily mutually exclusive, can be advanced for the effect on K_2. First, the oxocarbenium ion in the contact ion pair is stabilized by the proximity of the triflate counterion to a greater extent than it is in the solvent separated ion pair. Accordingly, it can be expected that the extra-destabilizing effect of the benzylidene acetal will be the greater for the more naked oxocarbenium ion in the solvent separated ion pair. Second, there exists the possibility of a conformational change of the oxocarbenium ion between the oxocarbenium ion in the contact ion pair and the solvent separated ion pair. Thus, the proximity of the counter ion in the contact ion pair may result in the retention of a degree of sp^3 character on the anomeric carbon, with corresponding less charge delocalization onto the ring oxygen, thereby effectively shielding it from the full effect of the benzylidene acetal. Such changes in the hybridization schemes of ion pairs according to the degree of separation of the constituent ions have been commented on and observed previously in other systems [87]. Extending this latter hypothesis to its logical conclusion, the transition state for the formation of the β-mannosides via the contact ion pair must resemble very closely the exploded transition state of Scheme 5.

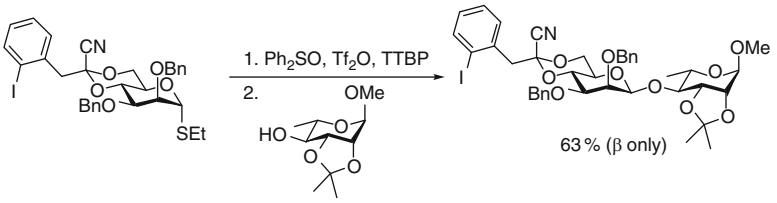
4 Substituent Effects

4.1 Alternatives to Benzylidene Acetals

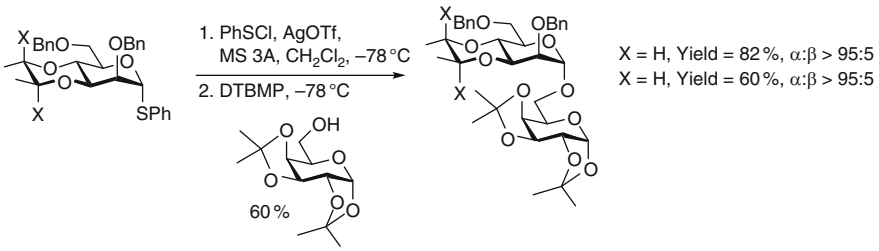
It follows that if the effect of the benzylidene acetal derives simply from the locking of the C5–C6 bond in the *tg* conformation, other groups able to do the same will have a similar effect. Indeed, a 4,6-*O*-phenylboronate group was shown to afford high β-selectivities in mannopyranosylation [88], and the use of a 4,6-*O*-polystyryl boronate enabled effective β-mannosylation with a polymer supported donor (Scheme 11) [88].



Scheme 11 Stereoselective glycosylation with a 4,6-*O*-polystyrylboronate protected donor



Scheme 12 Enhanced selectivity with an electron deficient 4,6-acetal



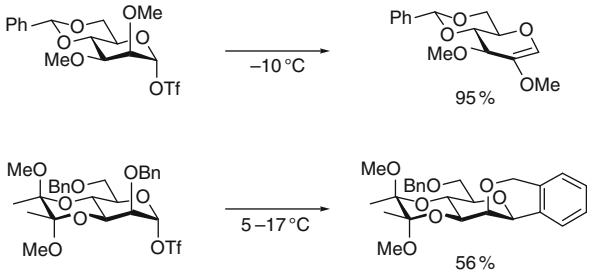
Scheme 13 α-Selective mannosylation with 3,4-dioxanyl type protecting systems

Acetals bearing either an axial thioester function [89] or a nitrile group [49] on the acetal carbon were also found to be highly β-selective donors. Indeed, these substituted acetals were generally observed to be more β-selective than the simple benzylidene acetals, and to be generally more disarming, as manifested by the need for the stronger activating system DPSO/Tf_2O (Scheme 12). Presumably, the very high β-selectivity observed in these cases arises from the electron-withdrawing nature of the substituent on the acetal carbon which further increases the electron-withdrawing ability of O6 and again reinforces the Bols hypothesis.

Although no experiments have been carried out to this effect, it is expected that groups such as a 4,6-*O*-silylene acetal, and a 4,6-*O*-carbonate, etc., will also lead to β-selective mannosyl donors.

4.2 Cyclic Bis(acetals) Spanning O3 and O4

The need for a six-membered cyclic protecting group that specifically spans O4 and O6 of the mannosyl donor is underlined by consideration of a series of donors in which O3 and O4 are bridged by a Ley-type cyclic bis-acetal [90]. Like the 4,6-*O*-benzylidene acetal, this group imposes a *trans*-decalin-like conformation on the donor and limits the number of conformations available to any glycosyl oxocarbenium ions. Glycosylations carried out with these donors, and with simplified derivatives lacking the two methoxyl groups (Scheme 13), were found to be



Scheme 14 Different decomposition products of glycosyl triflates as a function of protecting group

highly α-selective, which, with hindsight, obviously reflects the free rotation of the C5–C6 bond [45].

In their work on the hydrolysis of 4-pentenyl glucosides, Fraser-Reid and coworkers discovered that a related bis(acetal) type donor was hydrolyzed more readily even than a simple per-benzyl protected system (Scheme 8) [83], which, along with the very high α-selectivity observed with such protecting groups in the mannose series (Scheme 13), suggests that this system actually facilitates oxocarbenium ion formation. VT-NMR experiments of the type conducted in the benzylidene series indicated the formation of an α-mannosyl triflate (Table 1, entry 6) but which, with its decomposition temperature of >0 °C [45], does not conform to the general rule of thumb according to which an increased decomposition temperature correlates with increased β-selectivity. A clue to this anomaly is found in the differing nature of the decomposition products from the 4,6-*O*-benzylidene and 3,4-*O*-(bisacetal) protected series [45]. Thus, for the benzylidene acetal, thermal decomposition of the α-mannosyl triflate leads to the predominant formation of a 1,2-glycal (Scheme 14), whereas in the bisacetal series the major product is that intramolecular Friedel Crafts reaction onto the O2 protecting group. Apparently, therefore, the abnormally high decomposition temperature of the bisacetal-protected mannosyl triflate (Table 1, entry 6) is due to the retardation of the elimination pathway to give the glycal. This difference in ease of accommodation of the glycal system depending on the location of the six-membered cyclic protecting group recalls the greater stability of the *trans*-fused Δ^2-octalins over their Δ^1-isomers [91].

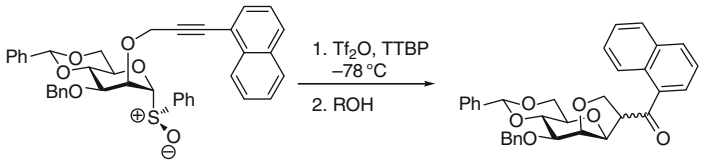
4.3 Substituents at O2

With the obvious exception of the carboxylate esters, which direct glycosylation alpha by means of classical neighboring group participation [92–96], the 4,6-*O*-benzylidene directed β-mannosylation reaction is remarkably insensitive to the nature of the protecting group at O2.

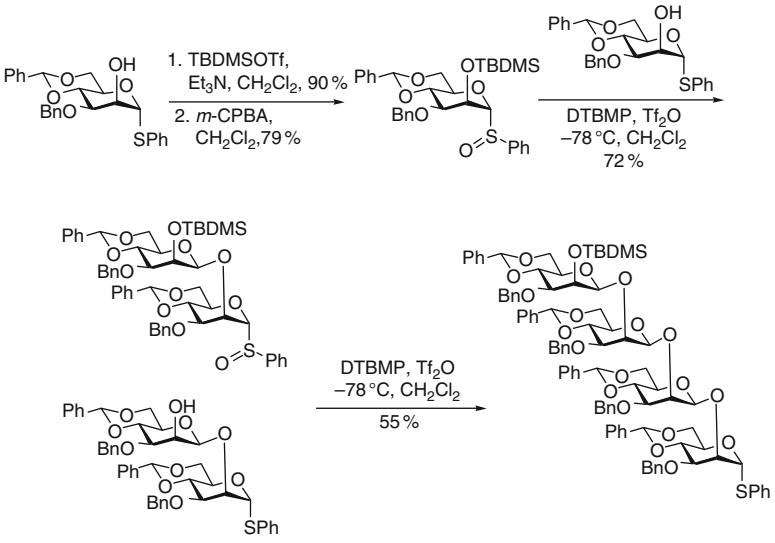
4.3.1 Ethers and Glycosides

A wide range of ether protecting groups, including allyl [97, 98], benzyl [14], *p*-methoxybenzyl [99], propargyl [100], and 3-(4-trifluoromethylphenyl)-propargyl [101], function admirably when the O3 position is also protected with a benzyl type ether. Attempted use of the electron-rich 3-(1-naphthyl)propargyl group, on the other hand, gave rise to complications resulting from cyclization of the intermediate glycosyl oxocarbenium ion onto the triple bond (Scheme 15) [102].

Most remarkable, however, is the relative indifference of the system to steric bulk at O2 as recorded for the 2-*O*-silyl ethers and subsequently for glycosidic substituents. A block synthesis of a β-(1→2)-tetramannan (Scheme 16), with a first coupling to a 2-*O*-TBDMS protected donor and a second to a 2-*O*-glycosyl donor, illustrates this phenomenon very nicely [103].



Scheme 15 Cyclization onto an activated propargyl ether



Scheme 16 Block synthesis of a tetramannan underscoring tolerance of steric bulk at O2

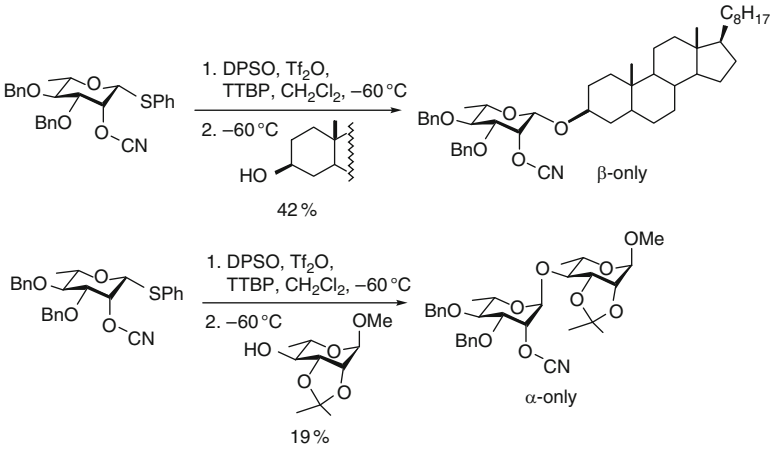
4.3.2 Electron-Withdrawing Groups at O2

To a first approximation, on the basis of the general mechanism (Scheme 6) the installation of a non-participating but electron-withdrawing protecting group on a mannosyl donor is expected to destabilize the oxocarbenium ion, shift the key ion pair equilibrium further toward the contact ion pair, increase the decomposition temperature of the covalent triflate, and increase the β-selectivity. However, as discussed above, the combination of a 4,6-*O*-benzylidene acetal and a 2-*O*-sulfonyl group is simply too disarming and results in an over-stabilized and somewhat unreactive glycosyl triflate [50]. In spite of this, the use of a non-participating, electron-withdrawing protecting group on O2 in the absence of the benzylidene acetal group potentially provides an attractive entry into the β-rhamnosides (6-deoxy-β-mannosides). A range of electron-withdrawing protecting groups have been assayed in this context, including sulfonate and phosphonate esters, vinylogous esters, cyanate, and nitrate esters. Unfortunately, while such systems give good selectivities with simple alcohols as acceptors, they fail with the less reactive and more sterically demanding carbohydrate-based acceptors (Scheme 17) [50, 60, 61, 104].

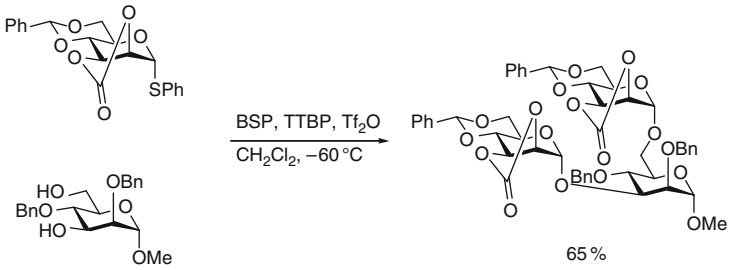
4.4 Electron-Withdrawing Groups at Other Positions

4.4.1 The 2,3-*O*-Carbonates and the 3,4-*O*-Carbonates

Classically, one of the more successful systems for β-mannoside generation was based on the activation of a 2,3-*O*-carbonate protected mannopyranosyl halide by



Scheme 17 Influence of a 2-*O*-cyanate ester on rhamnopyranosylation as a function of acceptor reactivity

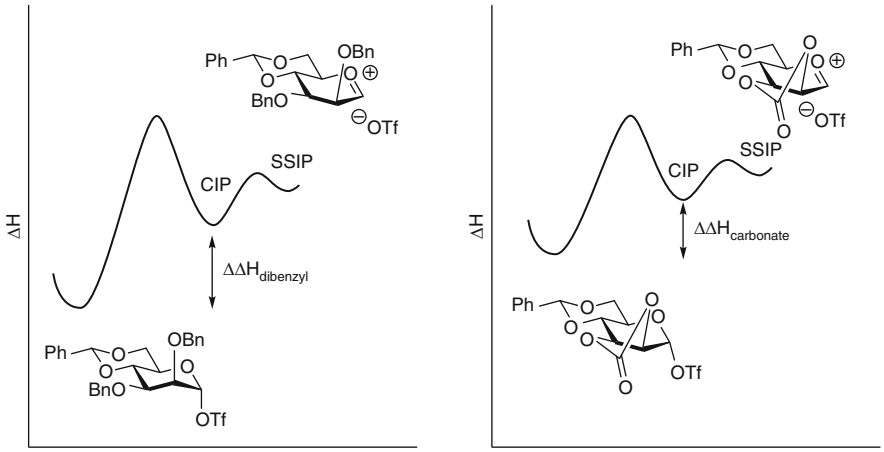


Scheme 18 The influence of a 2,3-*O*-carbonate on homogeneous mannosylation reactions

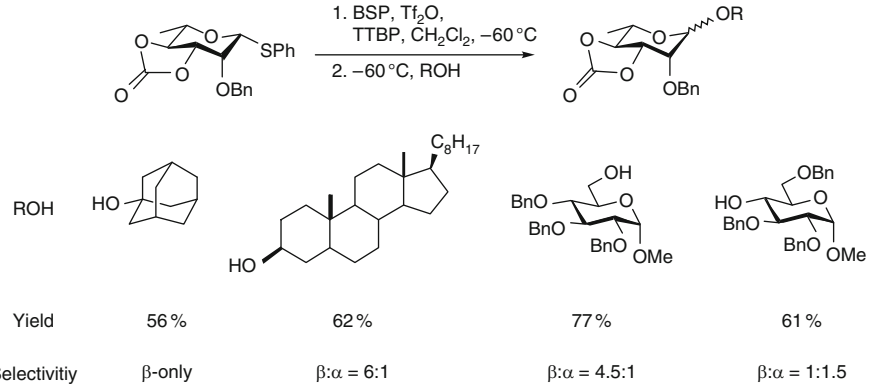
an insoluble silver salt [105]. The application of the 2,3-*O*-carbonate group in this manner, and its extension to the synthesis of β-rhamnopyranosides, was long considered to be due to the strongly electron-withdrawing but non-participating character of the cyclic carbonate group, allied with the hetereogenous nature of the coupling system. The combination of a 4,6-*O*-benzylidene acetal with a 2,3-*O*-carbonate was therefore initially considered likely to lead to a highly β-selective mannosylation system [45]. However, it was found that under standard conditions in homogeneous solution such a system gave very high α-selectivity (Scheme 18) [35, 36, 45].

Exactly analogous results were found in the rhamnopyranose series with a 2,3-*O*-carbonate donor being fully α-selective in homogeneous solution [106]. Accordingly, it was concluded that the *cis*-fused 2,3-*O*-carbonate as a matter of fact exerts an arming effect on glycosyl donors and consequently that the β-selectivity observed when using an insoluble promoter [105, 107] is uniquely a surface phenomenon. This latter conclusion also accords with the observation that 2,3-*O*-ketal protected mannosyl and rhamnosyl donors show β-selectivity when activated in an heterogeneous silver-based system. Consideration of NMR and crystallographic data leads to the assignment of a half-chair conformation for a series of *cis*-fused 2,3-*O*-carbonate protected mannosyl and rhamnopyranosyl donors and coupled products and, by extension, the intermediate glycosyl triflates [108, 109]. The hypothesis was therefore advanced that the *cis*-fused 2,3-*O*-carbonate functions by imposing on the glycosyl triflate a conformation closely related to that of the derived glycosyl oxocarbenium ion and thereby reduces the energetic penalty to the formation of the latter. In other words, the *cis*-fused carbonate acts on the equilibrium constants K_1 and K_2 by increasing the energy of the substrate – a case of ground state destabilization (Scheme 19).

Extrapolation of this line of reasoning resulted in the synthesis of a rhamnopyranosyl donor carrying a *trans*-fused carbonate group bridging the 3- and 4-positions as a system likely to impede rather than promote oxocarbenium ion formation [106]. Under the standard coupling conditions this donor gave good to excellent β-selectivity with simple acceptors, but it was inadequate for coupling to



Scheme 19 Rationale for α-mannoside formation from 2,3-*O*-carbonates



Scheme 20 β-Rhamnopyranosylation with a 3,4-*O*-carbonate protected donor

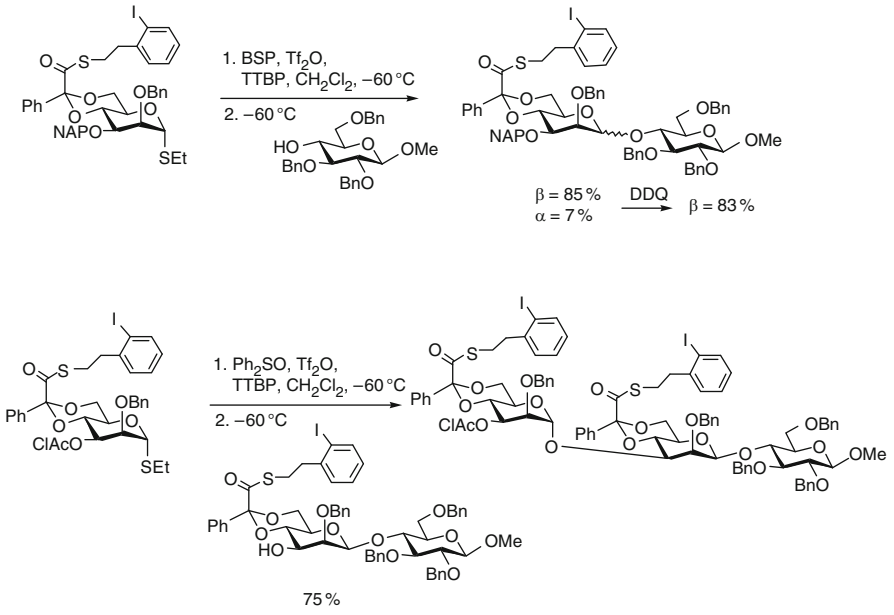
carbohydrate secondary alcohols when mixtures were observed (Scheme 20). The contrast between the stereodirecting properties of the 2,3- and 3,4-*O*-carbonates is nevertheless clear and, at first pass, is reflected in the decomposition temperatures of the two intermediate glycosyl triflates with the β-selective system possessing the more stable triflate (Table 1, entries 9 and 10) in accordance with the general mechanistic hypothesis [106].

Comparison of the 3,4-*O*-carbonate protected system and the fully α-selective 3,4-*O*-bisacetal is also appropriate [45], as is comparison with a 3,4-*O*-isopropylidene system that was α-selective [106]. Evidently, it is the combination of the *trans*-fused five-membered cyclic protecting group and its strong electron-withdrawing properties that are responsible for the unique properties of the 3,4-*O*-carbonate.

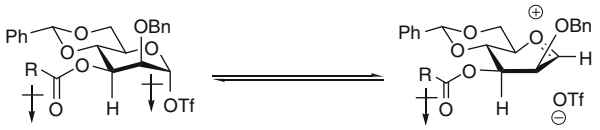
4.4.2 The 3-*O*-Esters

In a further attempt to increase the β-selectivity of the 4,6-*O*-benzylidene protected mannosyl donors, a system carrying an ester group at O3 was studied, based on the expectation that such a group would be electron-withdrawing and non-participating. In the event, however, complete α-selectivity was observed under the typical glycosylation conditions [45]. This observation was subsequently exploited in synthesis and is illustrated by the synthesis of a trisaccharide in which the two donors employed sequentially differ only in the nature of the O3 protecting group but give diametrically opposite selectivities (Scheme 21) [89].

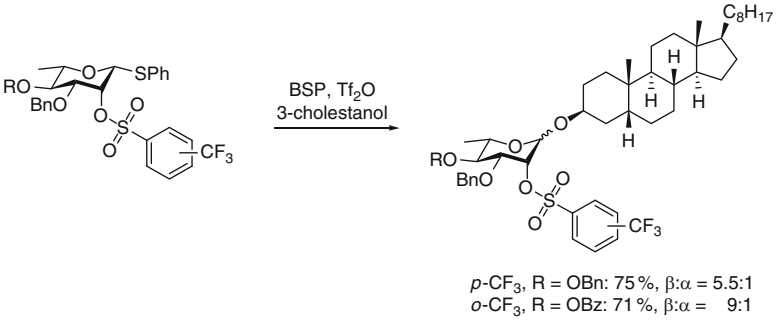
Despite claims to the contrary employing an unrepresentative probe [110], neighboring group participation through a six-membered cyclic intermediate as an explanation for this effect seems unlikely on several grounds. First, a *tert*-butyloxycarbonate ester on O3 was found to be equally α-directing and not to undergo fragmentation with loss of the *tert*-butyl cation as would have been expected from a bridging intermediate in this case [111]. Second, such participation would require the pyranose ring to adopt a twist boat conformation that appears unlikely in the presence of the 4,6-*O*-benzylidene acetal, and third, such participation would necessarily deliver the product in a boat or a half-chair conformation. A plausible explanation builds upon the well-established preferred conformation of the ester group that aligns the dipole of the C=O bond parallel with that of the anomeric C–O bond in the covalent glycosyl triflate, thereby destabilizing the latter (Scheme 22) [112, 113]. This perturbation of the stability of the covalent triflate,



Scheme 21 Selectivity as a function of the O3 protecting group



Scheme 22 Destabilization of the α-glycosyl triflate by the 3-*O*-ester



Scheme 23 Enhancement of β-selectivity by a 4-*O*-ester

effectively a second example of ground state destabilization, influences the equilibrium constants K_1 and K_2 and increases the concentration of the various ion pairs leading to the α-selective reaction. Viewed in this manner the, at first surprising, effect of the 3-*O*-ester falls squarely in the purview of the general mechanistic hypothesis.

4.4.3 Esters at O4

Although the use of esters as protecting groups at the 4-position is clearly incompatible with the presence of the 4,6-*O*-benzylidene acetal, their electron-withdrawing nature should generally enhance β-selectivity for other donors. That such is the case is clear from this study of the 2-*O*-sulfonate protected rhamnopyranosyl donors, which alone gave only modest β-selectivity but which, when used in conjunction with a 4-*O*-benzoate group, showed considerably improved performance (Scheme 23) [50, 114].

It has been proposed that O4 esters in the mannopyranosyl series exert their modest stereodirecting effect by participation through a bicyclic intermediate with the pyranose ring in a $B_{1,4}$ [115] conformation. However, as a series of probes failed to detect such an intermediate [111], and as it would also deliver the product in a boat conformation, such an effect is considered unlikely. Rather, the effect is best interpreted as one of a simple electron-withdrawing group destabilizing the glycosyl oxocarbenium ion in the solvent separated ion pair and negatively influencing K_2 [116]. Indeed, donors bearing a 4-*O*-sulfonate ester have been found to enhance

β-selectivity in a series of 2,6-dideoxyglucosyl donors [117] as well as in mannopyranosyl donors [110].

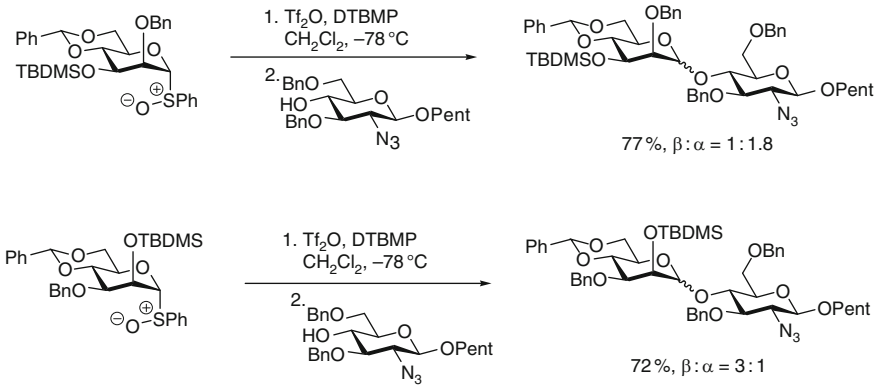
4.5 *The Effect of Bulky Substituents at O3*

Interestingly, particularly in view of the relatively minor effect of silyl ethers and glycosidic bonds at O2, the 4,6-*O*-benzylidene directed β-mannosylation reaction is highly sensitive to steric bulk in the protecting group for O3 [118]. Thus, a 2-*O*-benzyl-3-*O*-TBDMS protected donor was found to be considerably less selective than the 3-*O*-benzyl-2-*O*-TBDMS regioisomer toward a common acceptor (Scheme 24) [19, 118].

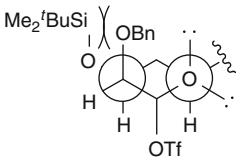
This effect, which was explained in terms of a buttressing interaction between the O3 and O2 protecting groups forcing the O2 protecting group to shield the β-face of the donor more than is typically the case (Scheme 25), extends to other bulky groups at O3, particularly glycosidic bonds [118–121].

The detrimental effect of glycosidic substituents at O3 of the donor on coupling stereoselectivity is a potentially serious hindrance to the application of this chemistry to the synthesis of β-(1→3)-mannans by convergent or block methods [119–121]. The explanation advanced suggested a solution in the form of a protecting group for O2 exhibiting minimal steric bulk so as to limit both the buttressing phenomenon and the shielding of the β-face of the donor. The 2-*O*-propargyl ether (Table 2), but not the larger allyl ether (Table 2), was found to be adequate for the task within certain limits as illustrated in Scheme 26 [100, 120].

Most interestingly, attempted use of the simple propargyl ether as a protecting group for O3 in a mannosyl donor resulted in a very considerable reduction of β-selectivity (Scheme 27), while the application of a 2,3-di-*O*-propargyl system gave intermediate values (Scheme 27) [100]. These observations may be rationalized



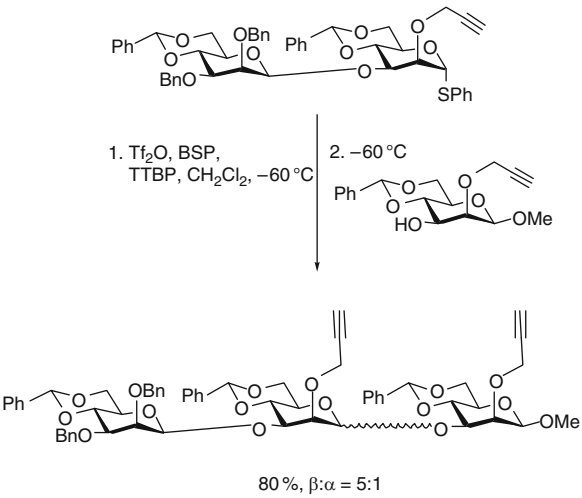
Scheme 24 Detrimental effect of steric bulk at O3



Scheme 25 Buttressing effect due to a bulky O3 group increases steric hindrance at this anomeric center

Table 2 Steric A-values for selected protecting groups

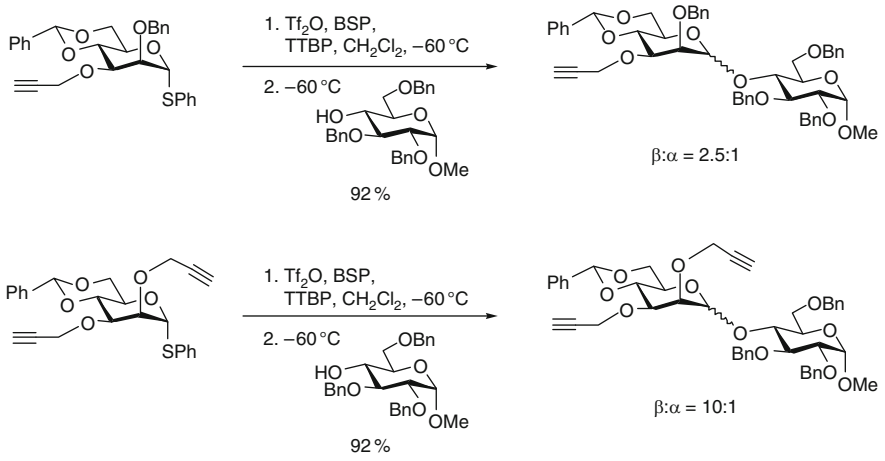
Substituent	Steric A-value	References
Propargyloxy	1.10	[100]
Allyloxy	1.25	[100]
Benzyloxy	1.39	[100]
Azido	0.45–0.62	[122, 123]
Fluoride	0.25–0.42	[122, 124–128]
tert-Butyldimethylsilyloxy	1.50	[100]



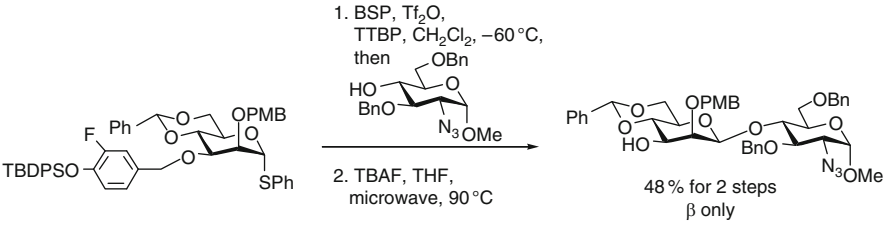
Scheme 26 Use of a 2-*O*-propargyl ether to overcome the effect of steric bulk at O3

in terms of the torsional interactions between the O2 and O3 substituents which are covered in greater detail in Sect. 6.2.

The standard two step deprotection protocol required for the removal of the propargyl ether function stimulated the development of alternative sterically minimal protecting groups cleavable in a single step. Thus, the 3-(1-naphthyl)propargyl protecting group cleavable under oxidative conditions with dichlorodicyanoquinone [102, 120], and the 3-(4-trifluoromethylphenyl)propargyl system removable with lithium naphthalide [101], were introduced to glycochemistry. The need



Scheme 27 Effect of a 3-*O*-propargyl ether and of a 2,3-di-*O*-propargyl system



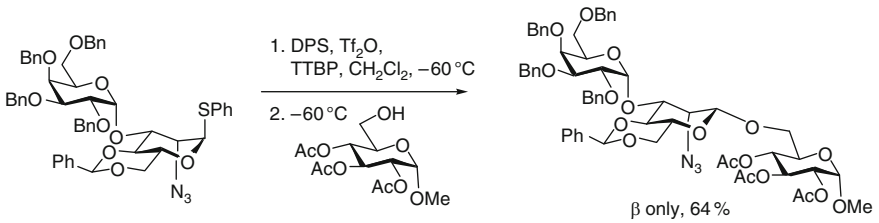
Scheme 28 Application of a benzyl ether cleavable under desilylation conditions

evident from Scheme 24 for a 3-*O*-protecting group having the steric characteristics of a benzyl ether but cleavable under desilylation conditions provoked the development of the 4-*O*-*tert*-butyldimethylsilyl-3-fluorobenzyl ether (Scheme 28) [129] and of the (triisopropylsilyl)oxymethyl ether [19].

4.6 The Aminodeoxy Systems

4.6.1 At the 2-Position

A 2-azido-2-deoxy mannopyranosyl donor protected with a 4,6-*O*-benzylidene acetal has been prepared and studied by the van Boom group. Owing to the strongly electron-withdrawing properties of the azide group, the powerful diphenyl sulfoxide/triflic anhydride system was required for activation and excellent β-selectivities were observed (Scheme 29) [36]. This system is especially interesting in view of the presence of the glycosidic linkage at O3 and the above discussion (Sect. 4.5).



Scheme 29 Beneficial influence of a 2-azido group on a disaccharide donor

Presumably the β-selectivity arises from the combination of the relatively small size of the azido group (Table 2), which enables it to escape from the buttressing phenomenon, and its electron-withdrawing nature that helps stabilize the intermediate glycosyl triflate.

4.6.2 At the 3-Position

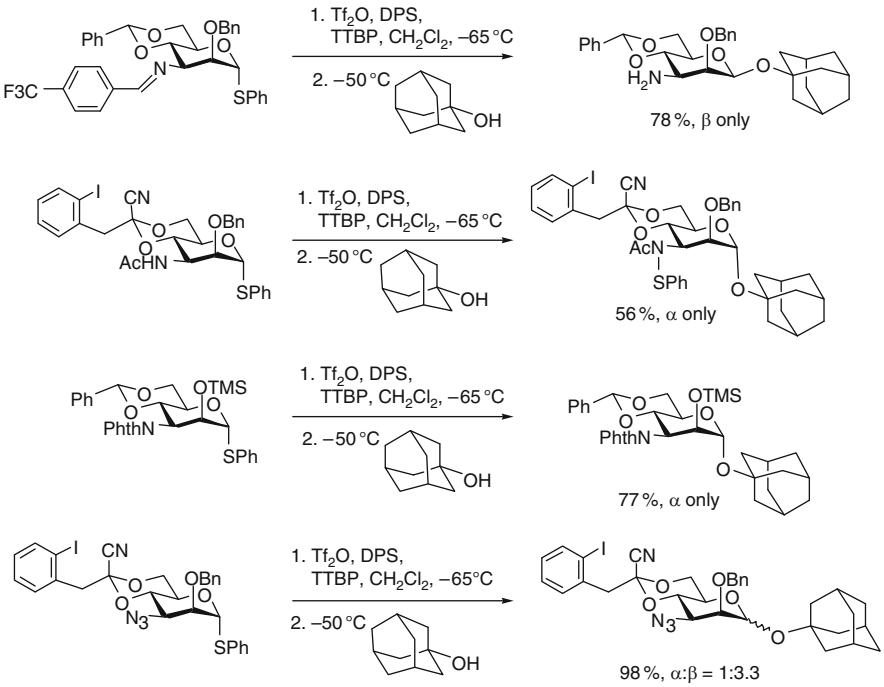
A number of donors bearing protected amines were prepared and their coupling reactions studied. Selectivities ranged from very high β- with a benzylidene imine that best mimics the steric properties of the benzyloxy group, to complete α- in the case of an acetamide and a phthalimide (Scheme 30), with the latter two systems clearly functioning in the same manner as 3-*O*-ester (Sect. 4.4.2) [130]. A 3-azido-3-deoxy system gave only moderate selectivity and recalls the disappointing selectivity observed with the 3-*O*-propargyl system discussed above (Sect. 4.5).

4.7 Substitution at the 6-Position

As is clear from Scheme 10, the standard 2,3-di-*O*-benzyl-4,6-*O*-benzylidene protected mannosyl donors tolerate the inclusion of an extra substituent, either axial or equatorial, on C6. This section is therefore concerned with the replacement of O6 by other heteroatoms.

4.7.1 The 6-Deoxy-6-Thia Series

The replacement of O6 by a sulfur atom, even held within the framework, of a benzylidene thioacetal poses several potential problems [131]. The first of these is the compatibility of the thioacetal functionality with the conditions employed to activate the anomeric thioglycoside in a glycosylation reaction, or with the reagents employed to oxidize the anomeric thioglycoside to the corresponding sulfoxide. The second is the reduced electronegativity of sulfur with respect to oxygen, which can be anticipated to favor oxocarbenium ion formation, and the third is the greater conformational flexibility of the oxathiane ring with respect to the dioxane

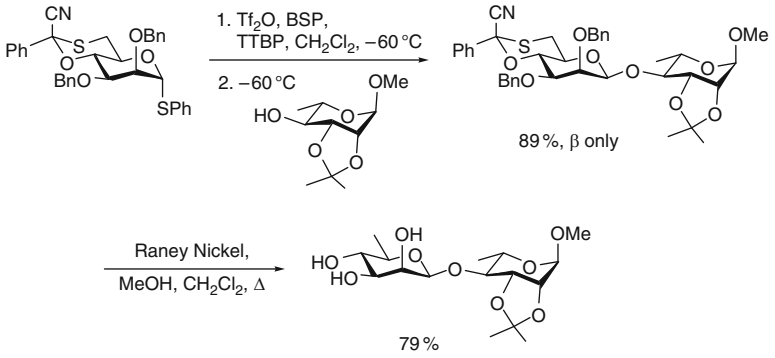


Scheme 30 Selectivity as a function of nitrogen substitution at C3

ring owing to the longer C–S bonds, which results in a less strict imposition of the *tg* conformation on the C5–C6 bond. Indeed, initial work with a simple replacement of O6 by a sulfur atom resulted in complicated reaction mixtures [131]. The situation can be salvaged, however, by use of the cyanobenzylidene acetal whose greater electron-withdrawing properties enabled the various deficiencies to be overcome and high yielding β-selective reactions to be conducted (Scheme 31). After glycosylation, treatment with Raney nickel in hot methanol served to effect desulfurization and concomitant removal of all benzyl ether protecting groups (Scheme 31). In this manner, effective synthesis of the β-rhamnopyranosides in both the D- and L-series were effected [131].

4.7.2 The 6-Deoxy-6-Mono-, Di-, and Tri-Fluoro Series

A series of 6-deoxy-6-mono-, di-, and tri-fluoromannopyranosyl donors (6-fluor-orhamnopyranosyl donors) were prepared in order to investigate the effect of increasing electron-deficiency at C6 on glycosylation stereochemistry [46]. All three donors were converted cleanly to observable glycosyl triflates and the thermal stability of these latter species increased with increasing fluorine content at the



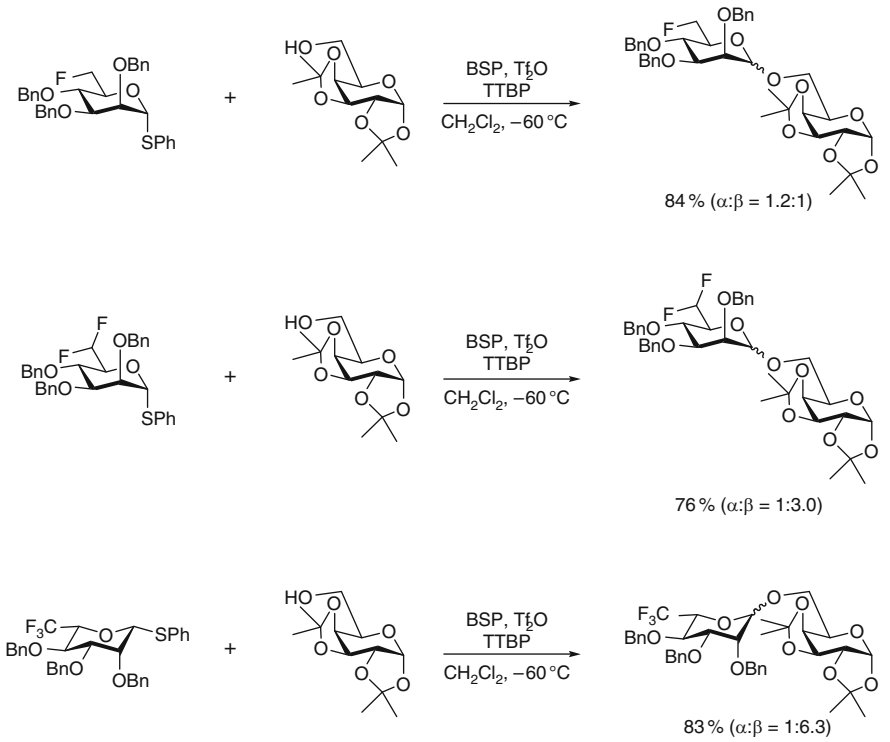
Scheme 31 Effective synthesis of a β-rhamnopyranoside by means of an acetal-protected *6*-deoxy-*6*-thia donor

6-position (Table 1, entries 23–25). In coupling reactions to a standard glycosyl acceptor, the β-selectivity also increased with increasing fluorine content (Scheme 32) [46]. With the caveat that one of these couplings involved a donor of opposite absolute configuration and may be influenced by the phenomenon of double diastereodifferentiation (Sect. 7.1), these results are consistent with the Bols hypothesis for the reasons underlying the influence of the 4,6-*O*-benzylidene acetal on glycosylation reactions.

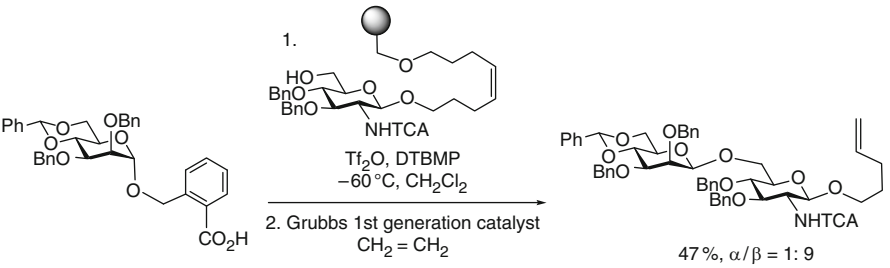
5 Polymer-Supported β-Mannosylation

While it is usually considered most efficient to conduct polymer-supported glycosylation by an acceptor-bound strategy [132, 133], consideration of the hydrolytic and thermal instability of the mannosyl triflate intermediates initially led to the development of a donor-bound strategy for the supported synthesis of the β-mannopyranosides. Thus, a polystyrylboronate resin was employed to capture a 4,6-diol leading to a resin bound donor that was activated and coupled under the standard BSP conditions. Excellent β-selectivities were obtained and the products cleaved from the resin with aqueous acetone (Scheme 11) [88].

Taking a more contemporary acceptor-bound approach to the problem, Seeberger and coworkers initially prepared a disaccharide donor containing a β-mannopyranoside linkage in the solution phase. Conventional methods were then applied to incorporate this unit into the growing polymer-supported oligosaccharide chain [134]. Subsequently, however, using the 2-carboxybenzyl mannopyranosides as donors with activation by triflic anhydride in the presence of a resin-bound acceptor, the same group was able to construct successfully β-mannosides linkages directly on the polymeric support (Scheme 33) with moderate to good β-selectivities [19].



Scheme 32 The effect of fluorination at C6 on selectivity

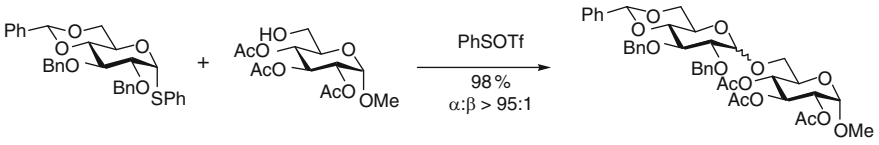


Scheme 33 Acceptor-bound approach to polymer-supported β-mannoside synthesis

6 The Glucose Series

6.1 4,6-O-Benzylidene Protected Glucopyranosyl Donors

Initial attempts at the extrapolation of the 4,6-*O*-benzylidene protected mannopyranosylation to the glucopyranosyl series led to the observation of the preferential formation of α-glucosides (Scheme 34) [44, 135]. Low temperature NMR



Scheme 34 α-Glucoside formation with a 4,6-*O*-benzylidene-protected donor

measurements indicated the clean formation of an α-glucosyl triflate intermediate and showed it to have a decomposition temperature lower than that of the corresponding mannosyl triflate (Table 1, entries 5 and 13) [44].

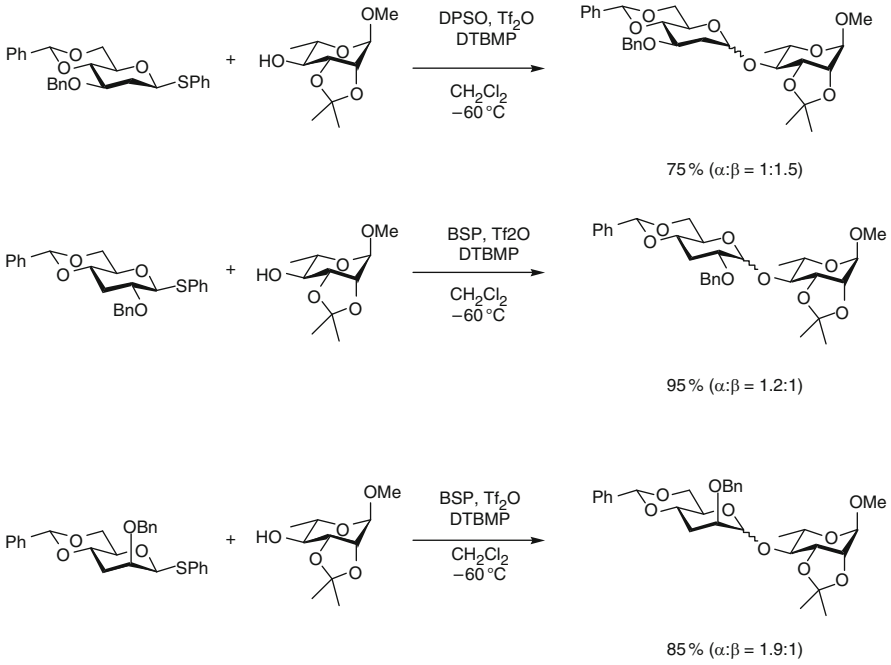
This result was unexpected as, on the basis of the classical work on the hydrolysis of glycopyranosides, it is generally considered that the relative order of reactivity in glycopyranosides is galactosides > mannopyranosides > glucosides [136, 137]. However, and perhaps more relevant to the chemistry of the glycosyl triflates, the Withers group have observed that in the spontaneous hydrolysis of the 2,4-dinitrophenyl glycopyranosides the α-mannoside is cleaved some five times more slowly than the corresponding α-glucoside [138]. Also noteworthy in this context is the work of Kirby and co-workers who reported the spontaneous hydrolysis of a 2,3,4,6-tetradeoxy-2,3,4,-trimethyl-α-glucopyranosyl *p*-nitrobenzoate to proceed more rapidly than that of the corresponding manno-configured compound [139].

6.2 2- and 3-Deoxy-4,6-O-Benzylidene Series and Their 2- and 3-Fluoro Congeners

In an attempt to understand the above glucose/mannose paradox, a series of three donors were prepared lacking the C–O bond in the 2- or 3-positions. Glycosylation with these donors under the standard conditions led in each case to considerably lower stereoselectivity (Scheme 35) [51].

The more highly armed nature of these deoxy donors, however, renders any interpretation of these results ambiguous. To palliate this deficiency a further series of four 2- and 3-deoxy-fluoro donors were prepared and studied. In this series, too, activation was clean and led to a series of glycosyl triflates that were observable by NMR spectroscopy. The glycosylation reactions of these triflates also showed considerably lower selectivities than those of the standard 2,3-di-*O*-benzyl manno and glucopyranosyl series (Scheme 36) [42].

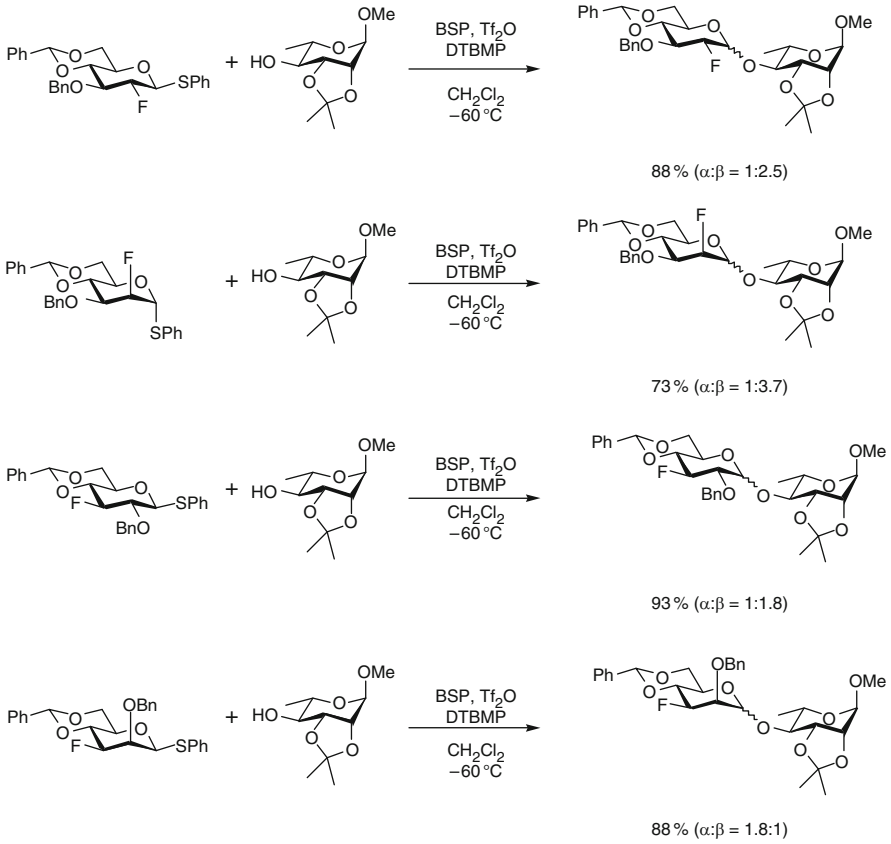
Setting aside any improbable hypotheses based on participation by the fluoro substituents [140, 141], and taking into account their strongly electron-withdrawing nature and small size, it is apparent that the reversal of selectivity between the standard manno- and glucopyranosyl series must be in large part due to a steric effect operating between O2 and O3. Consideration of the evolving torsional



Scheme 35 Reduced stereoselectivity with deoxygenation at O2 or O3

interactions between O2 and O3 as the $^4C_1$ chair conformers of the covalent glycosyl triflates collapse to the oxocarbenium ions, for each of which two quasi equi-energetic conformations are found computationally [24], is revealing. Thus, in the mannose series this torsional angle is compressed if the $^4H_3$ conformation is adopted by the oxocarbenium ion and remains unchanged if the ^4E conformation is preferred (Scheme 37). This effect can be viewed as operating between the covalent glycosyl triflate and the contact ion pair and between the contact and solvent separated ion pairs if, as discussed in Sect. 3.4.3, the contact ion pair is considered to retain a measure of sp^3 hybridization.

On the other hand, in the gluco series the O2–C2–C3–O3 torsion angle opens up irrespective of the conformation adopted by the oxocarbenium ion (Scheme 37). In energetic terms, in the mannose series, there is a penalty to pay for increased torsional interactions that has to be added to that generally required for formation of the ion pair, whereas in the glucose series this penalty is absent. Essentially, the passage from the covalent glycosyl triflate to the oxocarbenium ion, and particularly the solvent separated one, is less endothermic in glucose than in mannose (Scheme 38), resulting in a shift in the key equilibria in favor of the solvent separated ion pair in the glucose series. When the torsional penalty is removed, or at least reduced, as in the deoxy and deoxy fluoro series the difference in behavior between the mannose and glucose series is much reduced. These results



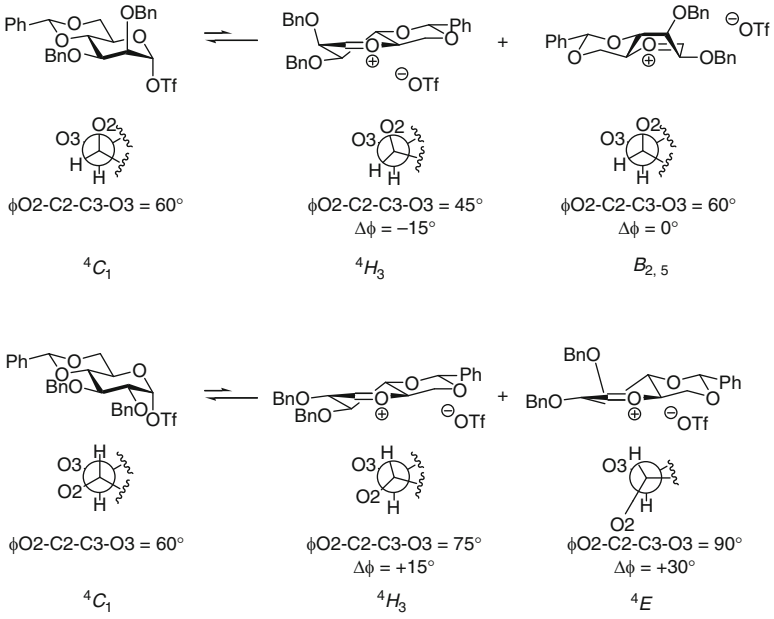
Scheme 36 Glycosylation with 2- and 3-deoxy-fluoro donors

also serve to emphasize the importance of the substituent at C3 and are thus clearly related to the discussion of Sect. 4.5.

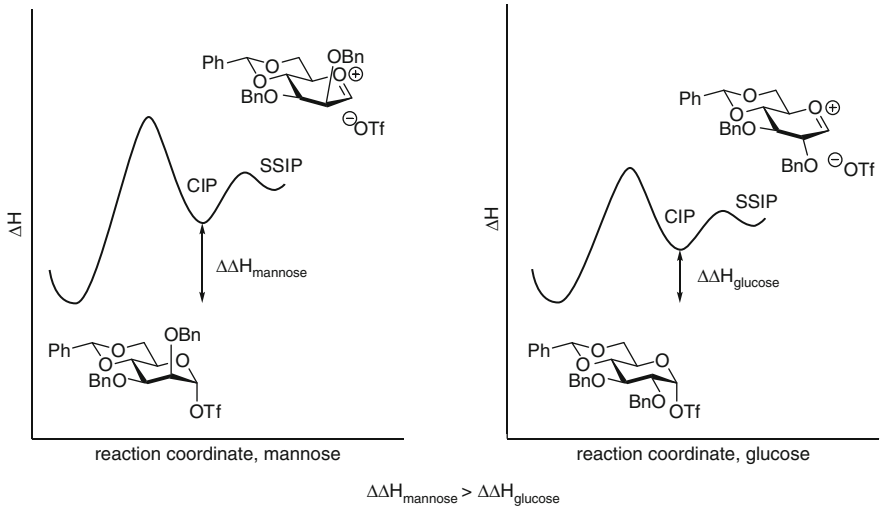
6.3 2,3- and 3,4-Bisacetals

Glucopyranosyl donors carrying 2,3- and 3,4-*O*-bisacetal protecting systems were prepared and studied under the standard conditions. The 2,3-*O*-bisacetal donor showed modest β-selectivity (Scheme 39). However, as the level was insufficient for synthetic purposes and as the corresponding manno-configured bisacetal is not available for comparison, the 2,3-series was not studied further [48].

The 3,4-*O*-acetal was more interesting as with simple alcohols it showed excellent β-selectivity and retained modest β-selectivity even with hindered secondary alcohols (Scheme 40) [48]. This selectivity, of course, stands in stark contrast to the high α-selectivity discussed above for the 3,4-*O*-bisacetal protected

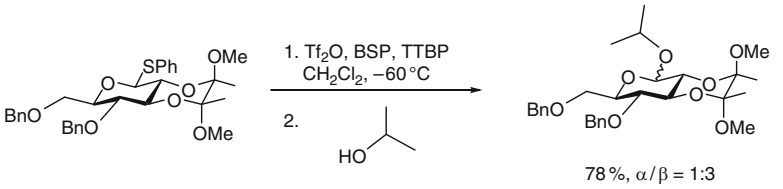


Scheme 37 Change in the O2–C2–C3–O3 torsion angle with oxocarbenium ion formation

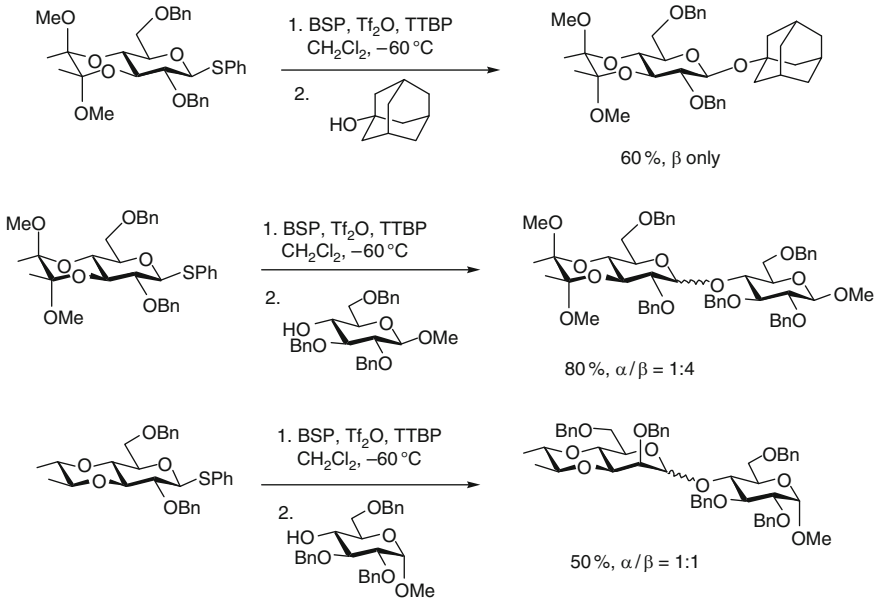


Scheme 38 Rationale for the gluco-mannose paradox

mannopyranosyl donors (Sect. 4.2). Continuing the glucose/mannose paradox even further, a reduction in selectivity was found in a contiguous 3,4-*O*-cyclic dioxanyl donor lacking the two methoxy groups (Scheme 40) [48].



Scheme 39 Stereoselective coupling with a 2,3-*O*-bisacetal protected glucosyl donor

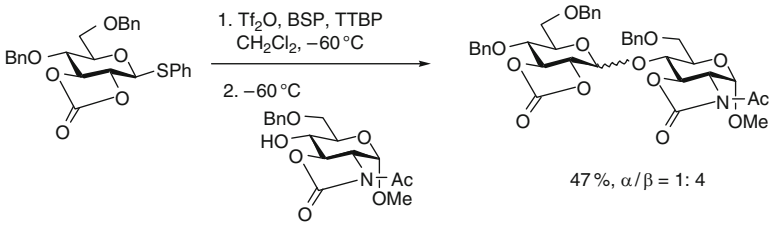


Scheme 40 Couplings with 3,4-*O*-dioxanyl-protected glucopyranosyl donors

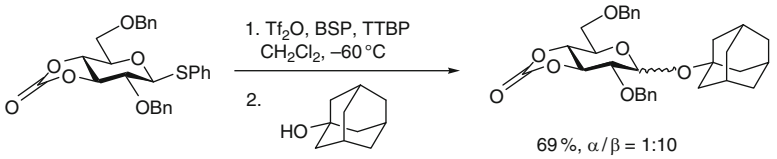
Overall, it is clear that the 3,4-*O*-bisacetal protecting system has opposing effects in the gluco- and manno-series and that these differing effects must arise from the manner in which the constrained C3–O3 bond interacts with the C2–O2 bond as the covalent glycosyl triflates collapse to the corresponding oxocarbenium ions. Once again, therefore, the importance of the O2–C2–C3–O3 torsional interaction is invoked even if further studies are required to pinpoint the precise origin of the difference in this instance.

6.4 2,3- and 3,4-O-Carbonates

As in the manno- and/or rhamnopyranosyl series, glucopyranosyl donors were prepared bearing cyclic carbonate groups spanning the O2,O3 and O3,O4-diols. The 2,3-*O*-carbonate being strongly electron-withdrawing, non-participating and, by



Scheme 41 β-Selective couplings with a 2,3-*O*-carbonate protected glucosyl donor



Scheme 42 β-Selective couplings with a 3,4-*O*-carbonate protected glucosyl donor

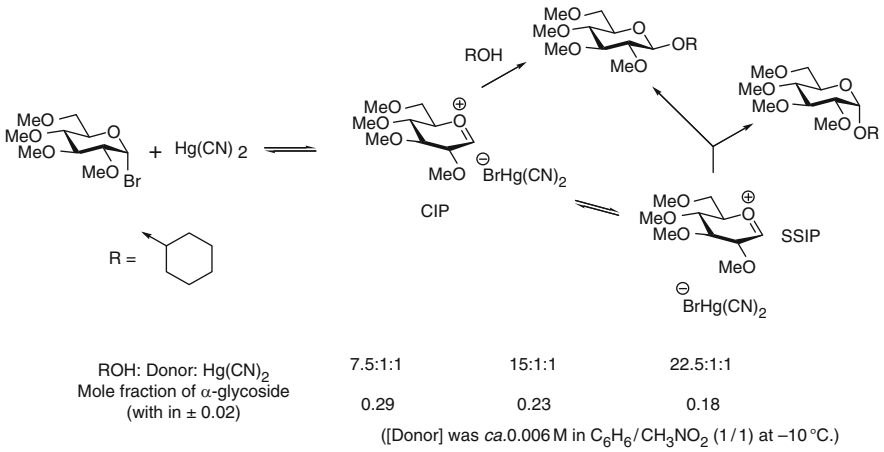
virtue of its *trans*-fused nature opposing further flattening of the pyranose ring, destabilizes any oxocarbenium ion and gave moderate β-selectivity (Scheme 41) [47].

The 3,4-*O*-carbonate gave only modest β-selectivity with simple alcohols (Scheme 42). These selectivities were lower than those observed with the corresponding rhamnopyranosyl series (Sect. 4.4.1) but also lower than those observed subsequently with a glucopyranosyl 3,4-*O*-bisacetal (Scheme 40). The β-selectivity had been anticipated on the basis of the electron-withdrawing, non-participating effect of the cyclic carbonate coupled with its *trans*-fused nature, but its smaller than anticipated size compared to the rhamnopyranosyl system again points to the importance of the O2–C2–C3–O3 torsional interaction in these glycosylation reactions. The reduced selectivity as compared to the gluco-configured 3,4-*O*-bisacetal must indicate a lower endothermicity for the formation of the glucosyl oxocarbenium ion in the dioxabicyclo[4.3.0]nonane system than in the dioxabicyclo[4.4.0]decane framework.

7 The Effect of the Acceptor

7.1 Double Diastereoselectivity

Although glycosylation is largely viewed here as a dissociative process with rate determining formation of an oxocarbenium ion intermediate, the involvement of the acceptor in the product determining step cannot be escaped. This involvement of the acceptor is all the clearer if one inclines to the exploded transition state interpretation of the mechanism of glycosylation. On this basis it is not surprising that the stereochemical outcome of a glycosylation reaction is influenced by the



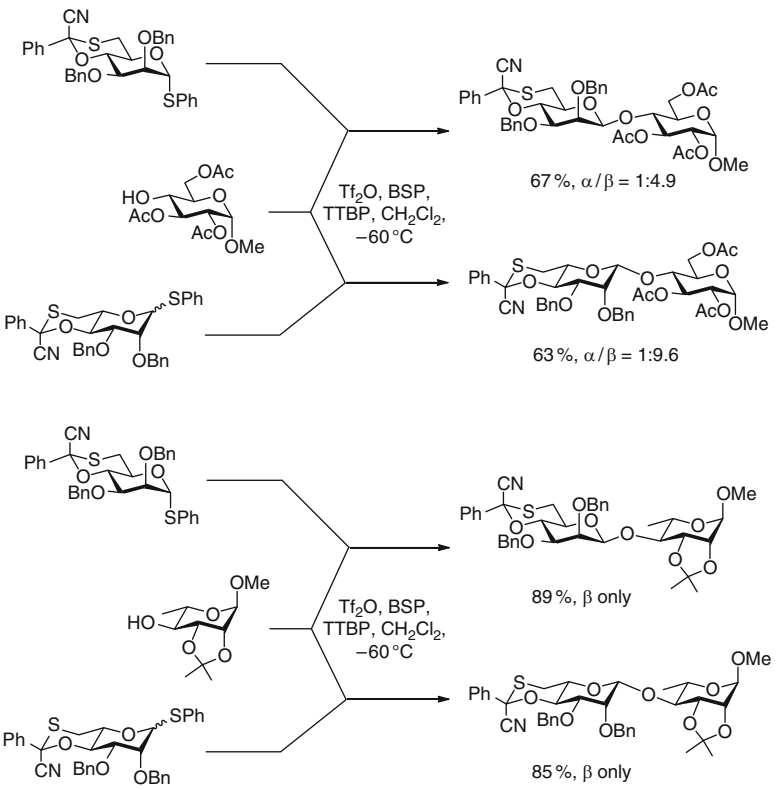
Scheme 43 Early evidence for the dependence of stereoselectivity on the acceptor concentration

acceptor. Evidence of this influence was provided early by Wallace and Schroeder [142] who noted the effect of acceptor concentration on the selectivity, but not on the kinetics, of a mercuric ion promoted glycosylation (Scheme 43).

The corollary of such an effect is that the stereochemistry of the acceptor alcohol will influence the stereochemical outcome of a glycosylation reaction, i.e., that the phenomenon of double diastereoselectivity will be evident [143, 144]. That such is the case was first determined by Spijker and van Boeckel [145], with many examples being uncovered subsequently [146]. A relevant example is that of reaction of both enantiomers of a mannopyranosyl donor with methyl 2,3,6-tri-*O*-acetyl-D-gluopyranoside, when widely differing stereoselectivities were observed (Scheme 44) [131]. The dependence of such phenomena on the acceptor alcohol is clearly brought home by the comparison of Scheme 44 with the reaction of the same pair of enantiomeric donors with methyl 2,3-*O*-isopropylidene-L-rhamnopyranoside as acceptor under the same conditions when both couplings were completely β-selective [131]. More striking examples of the phenomenon exist including, in some cases, the complete reversal in the selectivity of the coupling according to the relative chirality of a donor/acceptor pair, just as other examples exist in which the effect is negligible. As discussed elsewhere [146], if glycosylation is viewed as a continuum of mechanisms spanning all the way from pure S_N1 on the one hand to pure S_N2 on the other, the likelihood of observing such effects will increase with the tightness of the transition state, i.e., with proximity to the S_N2 side of the mechanistic spectrum.

7.2 Thiols as Nucleophiles

In the light of the above, and with thiols generally being better nucleophiles than alcohols, it is not surprising that carbohydrate based thiols give excellent



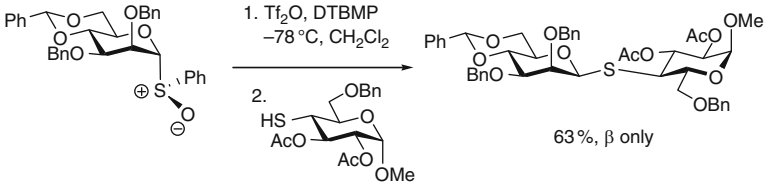
Scheme 44 The phenomenon of double diastereoselectivity in mannosylation

β-selectivities in the 4,6-*O*-benzylidene directed β-mannosylation. For example, the 4-deoxy-4-thio-D-gluopyranosyl acceptor gave a good yield of the β-thiomannoside with selectivity much greater than that seen with corresponding alcohols (Scheme 45) [147].

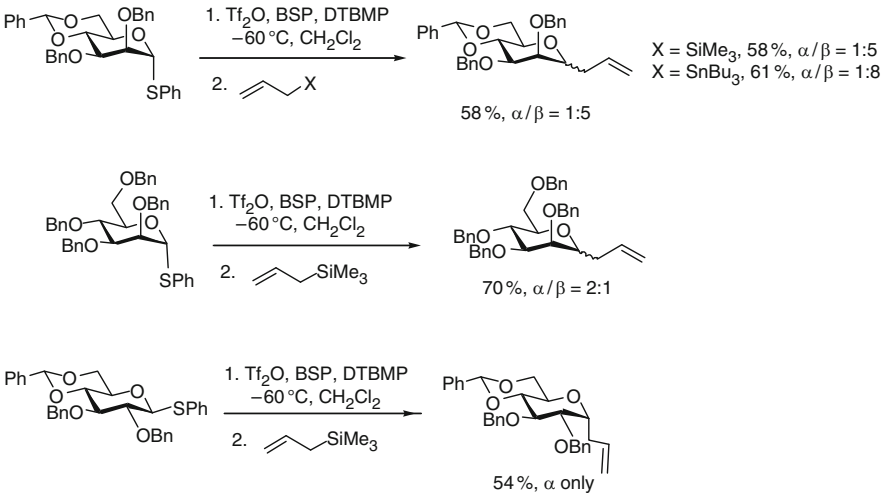
7.3 C-Nucleophiles

Most interestingly, allylsilanes, stannanes, and silyl enolethers function as nucleophiles in the reactions described here and are subject to the same stereochemical preferences as alcohols [148, 149]. Thus, unselective reactions are observed with a per-*O*-benzyl mannopyranosyl donor, β-selective couplings are seen with a 4,6-*O*-benzylidene protected mannopyranosyl donor, and α-selective reactions with the corresponding glucopyranosyl donor (Scheme 46).

In this chemistry, better β-selectivities were observed for mannopyranosylation with the allylstannane than with the silane (Scheme 46) and essentially complete β-selectivity was observed with the silyl enolethers, consistent with the better



Scheme 45 Generation of a β-thiomannoside



Scheme 46 Stereoselectivity in *C*-glycoside formation

nucleophiles reacting through a tighter transition state. On the whole, the parallel observations for *C*- and *O*-nucleophiles as to the influence of the benzylidene acetal and the configuration at C2 of the donor tend to suggest a commonality of mechanism in the two series and, thus, to rule out the need for any hypothesis [25] including donor–acceptor H-bonding as an explanation of stereoselectivity in the *O*-glycosides.

8 Return to Mechanism

The serendipitous discovery of the 4,6-*O*-benzylidene directed β-mannosylation reaction and the subsequent attempts to apply, extend, and understand it led to a number of other fascinating and mostly unexpected discoveries. Of importance among these were the reversal of selectivity seen with the corresponding 4,6-*O*-benzylidene protected glucopyranosyl donors, the α-directing effect of the *cis*-fused 2,3-*O*-carbonate in homogeneous mannosylation and rhamnosylation

reactions, and the α-directing effect of esters at the 3-position. A consistent theme that was revealed over time was the considerable influence of the substituent on the 3-position of the donor and the importance of its mainly steric interplay with the substituent at the 2-position. Ultimately, essentially all the experimental observations reconcile with the general mechanism of Scheme 6 with the shifts between α- and β-selectivity being understood in terms of the influence of the various substituents and/or pairs of substituents on the equilibrium constant K_2. The O2–C2–C3–O3 torsional interaction and above all its influence on the covalent donor-oxocarbenium ion equilibrium plays a significant role in determining the stereochemistry of these reactions, through subtle but important variation of the enthalpy of oxocarbenium ion formation. In general, substituents at the 3-position having the approximate steric bulk of a benzyloxy group are optimal with both larger and smaller groups provoking a reduction in stereoselectivity. Finally, at least for the systems studied here with the uncatalyzed loss of a negatively charged leaving group from a covalent glycosyl donor, the standard reactivity order of mannose > glucose, derived from classical experiments on acid catalyzed hydrolyses of glycosides, appears to be reversed as is the case with other systems involving spontaneous hydrolysis of glycosides.

One of the most important lessons taken from this body of work has been the excellence of carbohydrates as a teaching ground for many of the fundamental concepts of modern organic chemistry, including the concepts of ion pairs, of transient intermediates, of neighboring group participation and of its sister anchimeric assistance, of torsional strain and interactions, of so-called stereoelectronic effects, and of double diastereoselection.

Overall it appears increasingly likely to the authors of this chapter that, as the editor's cryptic Nobel prize winner stated, half of carbohydrate chemistry is the stabilization of the anomeric cation by the ring oxygen. What our common mentor failed to state is that it is the many subtleties of the chemistry of the glycosyl oxocarbenium ion that make the subject so fascinating and instructive. Paradoxically, however, it is important to note that an actual glycosyl oxocarbenium ion has yet to be observed [71]!

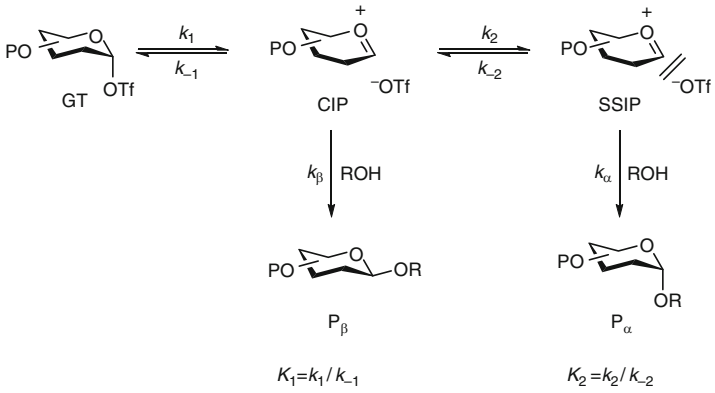
9 Parallels with Enzymic Hydrolysis

In parallel with the gradual revealing of the importance of the O2–C2–C3–O3 torsional interaction in the chemical synthesis of the mannopyranosides, the important role of the substrate 3-OH group in the hydrolysis of mannopyranosides by mannosidase enzymes has become increasingly clear thanks to the work of Davies and co-workers. Thus, for example, it has been determined through X-ray crystallographic means that retaining β-glucosidase and β-mannosidase enzymes transfers the discrimination between their *gluco*- and *manno*-configured substrates from the 2- to the 3-position as the transition state for formation of the bound intermediate

is approached [150]. Recalling the function of the 2,3-*O*-carbonate group in directing homogeneous glycosylation to the α-stereochemistry, and taking the parallel even further [151], it is suggested in recent work that the metal ion in a series of calcium dependent α-mannosidases serves to co-ordinate to both O2 and O3 and to distort the ground state toward a half-chair conformation that facilitates oxocarbenium ion formation.

Acknowledgments D.C. is especially grateful to the many co-workers, graduate students, and postdoctoral fellows, past and present, who have contributed significantly to the mannose project. He is equally grateful to the many colleagues, most notably Michael L. Sinnott, for their insightful comments and encouragement over the years.

Appendix



$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{GT}] = -k_1[\mathrm{GT}] + k_{-1}[\mathrm{CIP}]$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{CIP}] = k_1[\mathrm{GT}] - (k_{-1} + k_2 + k_\beta[\mathrm{ROH}])[\mathrm{CIP}] + k_{-2}[\mathrm{SSIP}][^{-}\mathrm{OTf}]$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{SSIP}] = k_2[\mathrm{CIP}] - (k_{-2}[^{-}\mathrm{OTf}] + \mathrm{k}_\alpha[\mathrm{ROH}])[\mathrm{SSIP}]$$

By the steady state approximation,

$$\frac{\mathrm{d}}{\mathrm{d}t}[P_\beta] = \frac{k_\beta k_1(k_\alpha[\mathrm{ROH}] + k_{-2}[^{-}\mathrm{OTf}])[\mathrm{GT}]}{k_\alpha k_\beta[\mathrm{ROH}]^2 + (k_\alpha k_{-1} + k_\alpha k_2 + k_\beta k_{-2}[^{-}\mathrm{OTf}])[\mathrm{ROH}] + \mathrm{k}_{-1}\mathrm{k}_{-2}[^{-}\mathrm{OTf}]}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[P_\alpha] = \frac{k_\alpha k_1 k_2[\mathrm{GT}]}{k_\alpha k_\beta[\mathrm{ROH}]^2 + (k_\alpha k_{-1} + k_\alpha k_2 + k_\beta k_{-2}[^{-}\mathrm{OTf}])[\mathrm{ROH}] + \mathrm{k}_{-1}\mathrm{k}_{-2}[^{-}\mathrm{OTf}]}$$

$$\frac{(\mathrm{d}[P_\beta])/\mathrm{d}t}{(\mathrm{d}[P_\alpha])/\mathrm{d}t} = \frac{k_\alpha}{k_2}[\mathrm{ROH}] + \frac{k_\beta k_{-2}}{k_\alpha k_2}[^{-}\mathrm{OTf}]$$

$$\frac{(\mathrm{d}[P_\beta])/\mathrm{d}t}{(\mathrm{d}[P_\alpha])/\mathrm{d}t} = \frac{k_\alpha}{k_2}[\mathrm{ROH}] + \frac{k_\beta}{k_\alpha K_2}[^{-}\mathrm{OTf}]$$

References

1. Fraser-Reid B (1975) Acc Chem Res 8:192
2. Barresi F, Hindsgaul O (1995) J Carbohydr Chem 14:1043
3. Zhu X, Schmidt RR (2009) Angew Chem Int Ed 48:1900
4. Gridley JJ, Osborn HMI (2000) J Chem Soc Perkin Trans 1:1471
5. Demchenko AV (2003) Curr Org Chem 7:35
6. Demchenko AV (2003) Synlett 1225
7. Barresi F, Hindsgaul O (1996) In: Khan SH, O'Neill RA (eds) Modern methods in carbohydrate synthesis. Harwood Academic Publishers, Amsterdam, p 251
8. Pozsgay V (2000) In: Ernst B, Hart GW, Sinaÿ P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, p 319
9. Ito Y, Ohnishi Y (2001) In: Fraser-Reid B, Kuniaki T, Thiem J (eds) Glycoscience: chemistry and chemical biology, vol 2. Springer-Verlag, Berlin, p 1589
10. Brunckova J, Crich D, Yao Q (1994) Tetrahedron Lett 35:6619
11. Crich D, Sun S, Brunckova J (1996) J Org Chem 61:605
12. Crich D, Hwang J-T, Yuan H (1996) J Org Chem 61:6189
13. Crich D, Sun S (1996) J Org Chem 61:4506
14. Crich D, Sun S (1997) J Org Chem 62:1198
15. Kahne D, Walker S, Cheng Y, Engen DV (1989) J Am Chem Soc 111:6881
16. Crich D, Smith M, Yao Q, Picione J (2001) Synthesis 323
17. Crich D, Li H (2002) J Org Chem 67:4640
18. Crich D, Sun S (1998) Tetrahedron 54:8321
19. Codée JDC, Kröck L, Castagner B, Seeberger PH (2008) Chem Eur J 14:3987
20. Crich D, Mataka J, Zakharov LN, Rheingold AL, Wink DJ (2002) J Am Chem Soc 124:6028
21. Crich D, Lim LBL (2004) Org React 64:115
22. Ferrieres V, Joutel J, Boulch R, Roussel M, Toupet L, Plusquellec D (2000) Tetrahedron Lett 41:5515
23. Nukada T, Bérces A, Wang L, Zgierski MZ, Whitfield DM (2005) Carbohydr Res 340:841
24. Nukada T, Berces A, Whitfield DM (2002) Carbohydr Res 337:765
25. Whitfield DM (2009) Adv Carbohydr Chem Biochem 62:83
26. Stevens RV (1984) Acc Chem Res 17:289
27. Kirby AJ (1983) The anomeric effect and related stereoelectronic effects at oxygen. Springer-Verlag, Berlin
28. Deslongchamps P (1983) Stereoelectronic effects in organic chemistry. Pergamon, Oxford
29. Crich D, Sun S (1997) J Am Chem Soc 119:11217
30. Crich D, Sun S (1998) J Am Chem Soc 120:435
31. Huang X, Huang L, Wang H, Ye X-S (2004) Angew Chem Int Ed 43:5221
32. Crich D, Cai F, Yang F (2008) Carbohydr Res 343:1858
33. Morishita T, Furukawa N, Oae S (1981) Tetrahedron 37:3115
34. Crich D, Smith M (2000) Org Lett 2:4067
35. Crich D, Smith M (2001) J Am Chem Soc 123:9015

36. Codée JDC, van den Bos LJ, Litjens REJN, Overkleeft HS, van Boeckel CAA, van Boom JH, van der Marel GA (2004) Tetrahedron 60:1057
37. Crich D, Banerjee A, Li W, Yao Q (2005) J Carbohydr Chem 24:415
38. Wang C, Wang H, Huang X, Zhang L-H, Ye X-S (2006) Synlett 2846
39. Durón SG, Polat T, Wong C-H (2004) Org Lett 6:839
40. Tatai J, Fügedi P (2007) Org Lett 9:4647
41. Nokami T, Shibuya A, Tsuyama H, Suga S, Bowers AA, Crich D, Yoshida J-i (2007) J Am Chem Soc 129:10922
42. Crich D, Li L (2007) J Org Chem 72:1681
43. Crich D, Pedersen CM, Bowers AA, Wink DJ (2007) J Org Chem 72:1553
44. Crich D, Cai W (1999) J Org Chem 64:4926
45. Crich D, Cai W, Dai Z (2000) J Org Chem 65:1291
46. Crich D, Vinogradova O (2007) J Am Chem Soc 129:11756
47. Crich D, Jayalath P (2005) J Org Chem 70:7252
48. Crich D, Subramanian V, Hutton TK (2007) Tetrahedron 63:5042
49. Crich D, Bowers AA (2006) J Org Chem 71:3452
50. Crich D, Hutton TK, Banerjee A, Jayalath P, Picione J (2005) Tetrahedron: Asymmetry 16:105
51. Crich D, Vinogradova O (2006) J Org Chem 71:8473
52. Pavia AA, Rocheville JM, Ung SN (1980) Carbohydr Res 79:79
53. Lacombe JM, Pavia AA, Rocheville JM (1981) Can J Chem 59:473
54. Pavia AA, Ung-Chhun SN (1981) Can J Chem 59:482
55. Leroux J, Perlin AS (1978) Carbohydr Res 67:163
56. Leroux J, Perlin AS (1976) Carbohydr Res 47:C8
57. Kronzer FJ, Schuerch C (1973) Carbohydr Res 27:379
58. Lucas TJ, Schuerch C (1975) Carbohydr Res 39:39
59. Marousek V, Lucas TJ, Wheat PE, Schuerch C (1978) Carbohydr Res 60:85
60. Srivastava VK, Schuerch C (1980) Carbohydr Res 79:C13
61. Srivastava VK, Schuerch C (1981) J Org Chem 46:1121
62. Garcia BA, Gin DY (2000) J Am Chem Soc 122:4269
63. Crich D, Chandrasekera NS (2004) Angew Chem Int Ed 43:5386
64. Singleton DA, Thomas AA (1995) J Am Chem Soc 117:9357
65. Westaway KC (2006) Adv Phys Org Chem 41:217
66. Peters KS (2007) Chem Rev 107:859
67. Horenstein NA (2006) Adv Phys Org Chem 41:275
68. El-Badri MH, Willenbring D, Tantillo DJ, Gervay-Hague J (2007) J Org Chem 72:4663
69. Amyes TL, Jencks WP (1989) J Am Chem Soc 111:7888
70. Zechel DL, Withers SG (2000) Acc Chem Res 33:11
71. Bohé L, Crich D (2011) CR Chimie 14: in press
72. Matsumoto K, Ueoka K, Suzuki S, Suga S, Yoshida J-i (2009) Tetrahedron 65:10901
73. Winstein S, Clippinger E, Fainberg AH, Heck R, Robinson GC (1956) J Am Chem Soc 78:328
74. Richard JP, Amyes Tl, Toteva MM, Tsuji Y (2004) Adv Phys Org Chem 39:1
75. Rhind-Tutt AJ, Vernon CA (1960) J Chem Soc 4637
76. Lemieux RU, Hendriks KB, Stick RV, James K (1975) J Am Chem Soc 97:4056
77. Zeng Y, Wang Z, Whitfield D, Huang X (2008) J Org Chem 73:7952
78. Walvoort MTC, Lodder G, Mazurek J, Overkleeft HS, Codée JDC, van der Marel GA (2009) J Am Chem Soc 131:12080
79. Hoffmann R, Minkin VI, Carpenter BK (1996) Bull Soc Chim Fr 133:117
80. Crich D, Dudkin V (2000) Org Lett 2:3941
81. Crich D, Dudkin V (2002) J Am Chem Soc 124:2263
82. Fraser-Reid B, Wu ZC, Andrews W, Skowronski E (1991) J Am Chem Soc 113:1434
83. Andrews CW, Rodebaugh R, Fraser-Reid B (1996) J Org Chem 61:5280
84. Jensen HH, Nordstrom M, Bols M (2004) J Am Chem Soc 126:9205

85. Bock K, Duus JO (1994) J Carbohydr Chem 13:513
86. Crich D, Banerjee A (2006) J Am Chem Soc 128:8078
87. Reich HJ, Dykstra RR (1993) J Am Chem Soc 115:7041
88. Crich D, Smith M (2002) J Am Chem Soc 124:8867
89. Crich D, Yao Q (2004) J Am Chem Soc 126:8232
90. Ley SV, Baeschlin DK, Dixon DJ, Foster AC, Ince SJ, Priepke HWM, Reynolds DJ (2001) Chem Rev 101:53
91. Thompson HW, Gaglani KD (1993) J Chem Soc Perkin Trans 2:967
92. Olsson JDM, Landstroem J, Roennols J, Oscarson S, Widmalm G (2009) Org Biomol Chem 7:162
93. Kajimoto T, Ishioka Y, Katoh T, Node M (2006) Bioorg Med Chem Lett 16:5736
94. Hanashima S, Inamori K-i, Manabe S, Taniguchi N, Ito Y (2006) Chem Eur J 12:3449
95. El Alaoui A, Schmidt F, Monneret C, Florent J-C (2006) J Org Chem 71:9628
96. Chevalier R, Esnault J, Vandewalle P, Sendid B, Colombel J-F, Poulain D, Mallet JM (2006) Tetrahedron 61:7669
97. Crich D, Dai Z, Gastaldi S (1999) J Org Chem 64:5224
98. Crich D, Barba GR (1998) Tetrahedron Lett 39:9339
99. Crich D, de la Mora MA, Cruz R (2002) Tetrahedron 58:35
100. Crich D, Jayalath P, Hutton TK (2006) J Org Chem 71:3064
101. Crich D, Karatholuvhu MS (2008) J Org Chem 73:5173
102. Crich D, Wu B (2006) Org Lett 8:4879
103. Dromer F, Chevalier R, Sendid B, Improvisi L, Jouault T, Robert R, Mallet JM, Poulain D (2002) Antimicrob Agents Chemother 46:3869
104. Bedini E, Carabellese A, Barone G, Parrilli M (2005) J Org Chem 70:8064
105. Gorin PAJ, Perlin AS (1961) Can J Chem 39:2474
106. Crich D, Vinod AU, Picione J (2003) J Org Chem 68:8453
107. Backinowskii LV, Balan NF, Shashkov AS, Kochetkov NK (1980) Carbohydr Res 84:225
108. Crich D, Vinod AU, Picione J, Wink DJ (2005) ARKIVOC vi:339
109. Manabe S, Ishii K, Hashizume D, Ito Y (2007) Acta Crystallogr E63:o3028
110. Baek JY, Lee B-Y, Jo MG, Kim KS (2009) J Am Chem Soc 131:17705
111. Crich D, Hu T, Cai F (2008) J Org Chem 73:8942
112. Gonzalez-Outeiriño J (2005) J Org Chem 70:2486
113. Schweitzer WB, Dunitz JD (1982) Helv Chim Acta 65:1547
114. Crich D, Picione J (2003) Org Lett 5:781
115. De Meo C, Kamat MN, Demchenko AV (2005) Eur J Org Chem 706
116. van Boeckel CAA, Beetz T, van Aelst SF (1984) Tetrahedron 40:4097
117. Tanaka H, Yoshizawa A, Takahashi T (2007) Angew Chem Int Ed 46:2505
118. Crich D, Dudkin V (2000) Tetrahedron Lett 41:5643
119. Crich D, Li W, Li H (2004) J Am Chem Soc 126:15081
120. Crich D, Wu B, Jayalath P (2007) J Org Chem 72:6806
121. Crich D (2007) In: Demchenko AV (ed) ACS symposium series, vol 960. American Chemical Society, Washington, p 60
122. Schneider H-J, Hoppen V (1978) J Org Chem 43:3866
123. Sülze D, Gatial A, Karlsson A, Klaeboe P, Nielsen CJ (1988) J Mol Struct 174:207
124. Jensen FR, Bushweller CH, Beck BH (1969) J Am Chem Soc 91:344
125. Bugay DE, Bushweller CH, Danehy CT, Hoogasian S, Blersch JA, Leenstra WR (1989) J Phys Chem 93:3908
126. Subbotin OA, Sergeyev NM (1975) J Am Chem Soc 97:1080
127. Chu P-S, True NS (1985) J Phys Chem 89:5613
128. Jensen FR, Bushweller CH (1971) Adv Alicycl Chem 3:139
129. Crich D, Li L, Shirai M (2009) J Org Chem 74:2486
130. Crich D, Xu H (2007) J Org Chem 72:5183
131. Crich D, Li L (2009) J Org Chem 74:773

132. Castagner B, Seeberger PH (2007) Top Curr Chem 278:289
133. Seeberger PH (2001) Solid support oligosaccharide synthesis and combinatorial carbohydrate libraries, Wiley Interscience, New York, p 308
134. Ratner DM, Swanson ER, Seeberger PH (2003) Org Lett 5:4717
135. Bousquet E, Khitri M, Lay L, Nicotra F, Panza L, Russo G (1998) Carbohydr Res 311:171
136. Sinnott ML (2007) Carbohydrate chemistry and biochemistry. RSC Publishing, Cambridge
137. Green LG, Ley SV (2000) In: Ernst B, Hart GW, Sinaÿ P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, p 427
138. Namchuk MN, McCarter JD, Becalski A, Andrews T, Withers SG (2000) J Am Chem Soc 122:1270
139. Dean KES, Kirby AJ, Komarov IV (2002) J Chem Soc Perkin Trans 2:337
140. Ford GP, Raghuveer KS (1988) Tetrahedron 44:7489
141. Olah GA, Prakash GKS, Krishnamurthy VV (1983) J Org Chem 48:5116
142. Wallace JE, Schroeder LR (1976) J Chem Soc Perkin Trans 2:1632
143. Horeau A, Kagan H-B, Vigneron JP (1968) Bull Soc Chim Fr 3795
144. Masamune S, Choy W, Peterson JS, Sita LR (1985) Angew Chem Int Ed 24:1
145. Spijker NM, van Boeckel CAA (1991) Angew Chem Int Ed 30:180
146. Bohé L, Crich D (2010) Trends Glycosci Glycotech 22:1
147. Crich D, Li H (2000) J Org Chem 56:801
148. McGarvey GJ, LeClair CA, Schmidtmann BA (2008) Org Lett 10:4727
149. Crich D, Sharma I (2008) Org Lett 10:4731
150. Ducros VM-A, Zechel DL, Murshudov GN, Gilbert HJ, Szabo L, Stoll D, Withers SG, Davies GJ (2002) Angew Chem Int Ed 41:2824
151. Zhu Y, Suits MDL, Thompson AJ, Chavan S, Dinev Z, Dumon C, Smith N, Moremen KW, Xiang Y, Siriwardena A, Williams SJ, Gilbert HJ, Davies GJ (2010) Nature Chem Biol 6:125

Top Curr Chem (2011) 301: 189–221
DOI: 10.1007/128_2010_106

Published online: 1 December 2010

Superarmed and Superdisarmed Building Blocks in Expeditious Oligosaccharide Synthesis

Hemali D. Premathilake and Alexei V. Demchenko

Abstract Traditional strategies for oligosaccharide synthesis often require extensive protecting and/or leaving group manipulations between each glycosylation step, thereby increasing the total number of synthetic steps while decreasing both the efficiency and yield. In contrast, expeditious strategies allow for the rapid chemical synthesis of complex carbohydrates by minimizing extraneous chemical manipulations. The armed–disarmed approach for chemoselective oligosaccharide synthesis is one such strategy that addresses these challenges. Herein, the significant improvements that have recently emerged in the area of chemoselective activation are discussed. These advancements have expanded the scope of the armed–disarmed methodology so that it can now be applied to a wider range of oligosaccharide sequences, in comparison to the original concept. Surveyed in this chapter are representative examples wherein these excellent innovations have already been applied to the synthesis of various oligosaccharides and glycoconjugates.

Keywords Armed–disarmed strategy, Carbohydrates, Chemoselective activation, Expeditious synthesis, Glycoconjugates, Glycosylation, Oligosaccharides, Synthetic strategy

Contents

H.D. Premathilake and A.V. Demchenko (✉)
Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, MO 63121, USA
e-mail: demchenkoa@umsl.edu

Abbreviations

1,2-DCE	1,2-Dichloroethane
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CDA	Cyclohexane 1,2-diacetal
DMTST	Dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (triflate)
Et	Ethyl
IDCP	Iodonium(di-δ-collidine)perchlorate
LG	Leaving group
NIS	*N*-Iodosuccinimide
PFBz	Pentafluorobenzoyl
Ph	Phenyl
Phth	Phthalimido
Pic	Picolinyl
RRV	Relative reactivity value
SBox	*S*-Benzoxazolyl
STaz	*S*-Thiazolinyl
TBDMS	*tert*-Butyldimethylsilyl (also TBS)
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate (triflate)
TESOTf	Triethylsilyl trifluoromethanesulfonate (triflate)
TfOH	Trifluoromethanesulfonic acid
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate (triflate)
Tol	Tolyl

1 Introduction

1.1 Background

Complex carbohydrates (polysaccharides or complex glycoconjugates in which oligosaccharides are connected to peptides, proteins, or fatty acids) are involved in a variety of biological processes [1]. Throughout the past two decades, the main scientific effort in the field of glycoscience has remained centered upon those carbohydrates associated with diseases that consistently rank among the leading causes of death worldwide, such as cardiovascular disease, cancer, septicemia, bacterial, viral, and parasitic infections. The driving force behind this tremendous scientific and industrial effort is the belief that a comprehensive knowledge of the structural, conformational, and other general properties of these carbohydrates will help scientists understand the pathogenesis of the associated diseases. Consequently, this could lead to the development of new and effective strategies for the prevention, diagnosis, and treatment of these diseases. Over the years, glycoscientists have mastered the techniques necessary for isolating only certain classes of naturally occurring carbohydrates. Therefore, the availability of pure natural isolates cannot satisfy all of the challenges presented by modern glycoscience. As a result, glycoscientists have turned to both chemical and enzymatic synthesis as a means for accessing complex carbohydrates. While enormous progress in the areas of synthetic, biological, and analytical chemistry has made many classes of organic compounds readily accessible through broadly applicable methods, carbohydrates of even moderate complexity still represent a significant challenge. A few representative examples of such oligosaccharide sequences are shown in Fig. 1.

1.2 Principles of Chemical O-Glycosylation

Poly- or oligosaccharide sequences are constructed by connecting monosaccharide units via O-glycosidic bonds. In nature this linkage is formed by a coupling reaction known as glycosylation, the course and selectivity of which is controlled by glycosyltransferases. In the chemical laboratory, glycosylation typically involves a promoter- (or activator)-assisted nucleophilic displacement, wherein a leaving group (LG = halogen, OH, *O*-alkenyl/imidoyl, *S*-alkyl/aryl/imidoyl, etc.) on the glycosyl donor is displaced by a hydroxyl moiety of the glycosyl acceptor (Scheme 1a) [2]. Remaining functional groups on both the glycosyl donor and acceptor are temporarily masked with protecting groups (P, T), which, along with strategies for their installation and removal (protection-deprotection), have become essential components of chemical syntheses of oligosaccharide molecules. Although protecting groups were initially applied to reduce unwanted side reactions by masking additional sites of reactivity, they can also affect the glycosylation in a variety of other ways; in other words, they "do more than protect" [3]. Since the

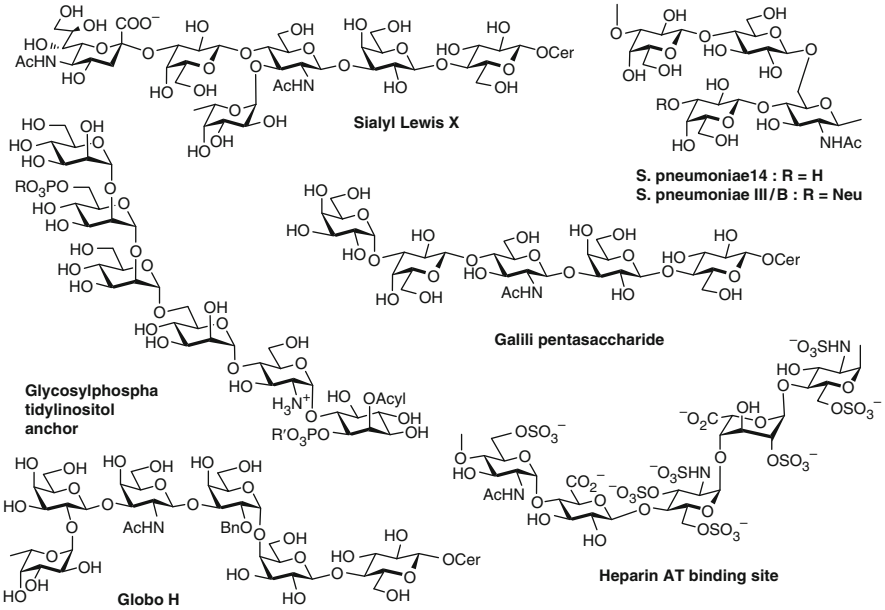
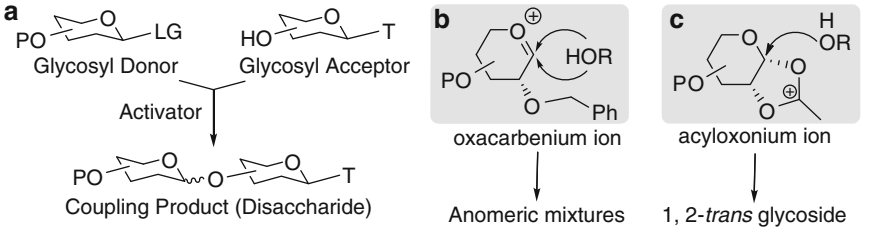


Fig. 1 Representative examples of natural poly- and oligosaccharide sequences



Scheme 1 Outline of chemical glycosylation

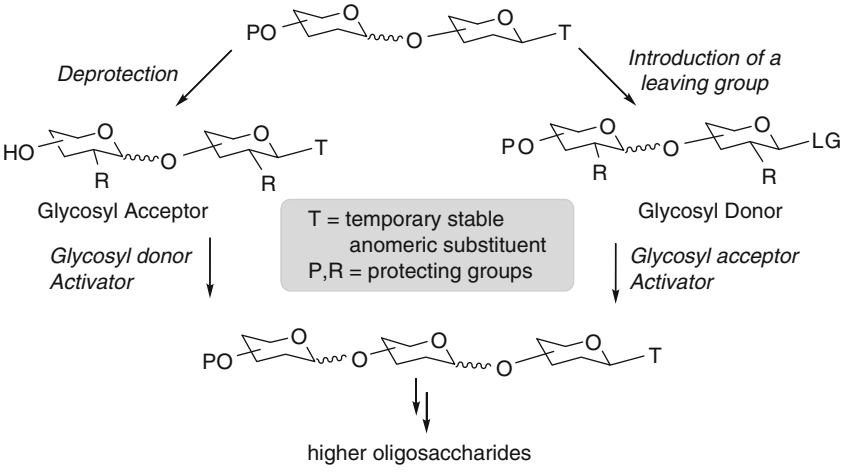
anomeric center is chiral, particular care has to be taken with regard to the stereoselectivity of glycosylation. Despite the significant progress made in the area of glycoside synthesis [2], the necessity of forming either a 1,2-*cis*- or a 1,2-*trans*-glycosidic bond with high stereocontrol remains the main reason that chemical O-glycosylation is ranked among the most critical challenges of modern synthetic chemistry.

Although mechanistic rationalizations of the glycosylation reaction lack generality and consistency, and although studies dedicated to the reaction mechanism are still scarce, some conventions have already been well established [4]. For instance, in the case of ether-type non-participating substituents, glycosylation proceeds via a flattened oxacarbenium ion [5] (Scheme 1b), often leading to anomeric mixtures favoring 1,2-*cis* glycosides [6, 7] (for D-gluco/galacto series) due to the influence of

the anomeric effect [8, 9]. Thus, variable factors such as temperature, pressure, structure, conformation, solvent, promoter, steric hindrance, protecting or leaving group are exceedingly important in influencing the stereoselectivity of glycosylation. Amongst these, neighboring group participation [10] is one of the most prominent effects dictating the stereochemical outcome of the glycosylation reaction (protecting groups do more than protect), as it is well established that 1,2-*trans* glycosides can be obtained from 2-acylated glycosyl donors. This selectivity arises from the acyloxonium intermediate formed as a result of the anchimeric assistance from the neighboring C-2 group (Scheme 1c).

1.3 Oligosaccharide Synthesis

The development of new leaving groups and efficient glycosylation methods is largely responsible for the progress that has been made in the area of oligosaccharide synthesis. When the arsenal of glycosylation techniques was limited to the Fischer (LG = OH) [11] and Koenigs–Knorr (LG = Cl, Br) [12, 13] approaches (or their variations) [14, 15], oligosaccharide assembly was limited to inefficient stepwise linear techniques. However, as more stable glycosyl donors, such as fluorides [16], thioglycosides [17], and *O*-alkenyl glycosides were developed [18], the possibility of selective and/or chemoselective activation of one leaving group over another emerged. In linear oligosaccharide synthesis, the disaccharide product formed from the single step glycosylation reaction (see Scheme 1) is then converted into either a second-generation glycosyl acceptor or donor; this is accomplished via the liberation of a specific hydroxyl group or installation of a suitable leaving group, respectively (Scheme 2). These second generation



Scheme 2 conventional (linear) oligosaccharide synthesis

disaccharide building blocks are then allowed to react with an appropriate monosaccharide glycosyl donor or acceptor, resulting in the formation of a trisaccharide. The protecting/leaving group manipulation and glycosylation sequence can be then reiterated until an oligosaccharide of the desired chain length is obtained.

It soon became apparent, however, that both the linear and convergent [19–21] approaches were too inefficient, due to the extensive protecting or leaving group manipulations between each glycosylation step. Consequently, the past two decades have witnessed a dramatic improvement of the methods and strategies used for oligosaccharide synthesis, as scientists have persistently aimed to answer the key question: can oligosaccharides be obtained more expeditiously through the elimination of these unnecessary synthetic steps? The first attempts to address this challenge emerged in the mid-1980s and 1990s, which resulted in the development of a number of revolutionary approaches. Many of these innovative strategies involve selective activations, wherein different leaving groups are sequentially activated, minimizing the need for protecting group manipulations between glycosylation steps; selective activation [19, 22], two-step activation [19, 23–25], and the active-latent concept [26–29] are just a few classifications of such approaches. One specific example, the orthogonal approach, makes use of two chemically distinct glycosyl donors, wherein one of the leaving groups is selectively activated while the other remains intact, and vice versa, offering significant flexibility [30]. This activation sequence can then be reiterated to give straightforward access to larger oligosaccharides.

Another direction in expeditious oligosaccharide synthesis emerged with the discovery of the so-called armed–disarmed approach by Fraser-Reid and coworkers [31]. This strategy, based on the chemoselectivity principle, utilizes only one class of leaving group; thus, glycosyl donor reactivity is modulated entirely through the choice of protecting group (protecting groups do more than protect). This effect allows for direct chemoselective coupling between an activated (armed) glycosyl donor and a deactivated (disarmed) glycosyl acceptor, and the resulting disaccharide can then be used directly in subsequent glycosidation.

With the main focus on the armed–disarmed concept, this chapter discusses the recent progress that has been made in the area of chemoselective oligosaccharide synthesis. The classic *armed–disarmed approach,* developed by Fraser-Reid, has created a solid basis for extensive studies and applications, and all strategies discussed in this chapter are directly related to (or derived from) this elegant concept. As recent improvements have significantly expanded the scope of the original chemoselective concept, a series of building blocks, the reactivity of which extends beyond the traditional armed–disarmed definition, have additionally been introduced. These “superarmed” and “superdisarmed” building blocks have helped to expand the scope of the original methodology so that it can now be applied to the synthesis of a much broader range of complex oligosaccharide sequences, in comparison to that of the classic armed–disarmed concept. These excellent innovations have already been applied to the synthesis of various oligosaccharides and glycoconjugates, and some representative examples are presented herein.

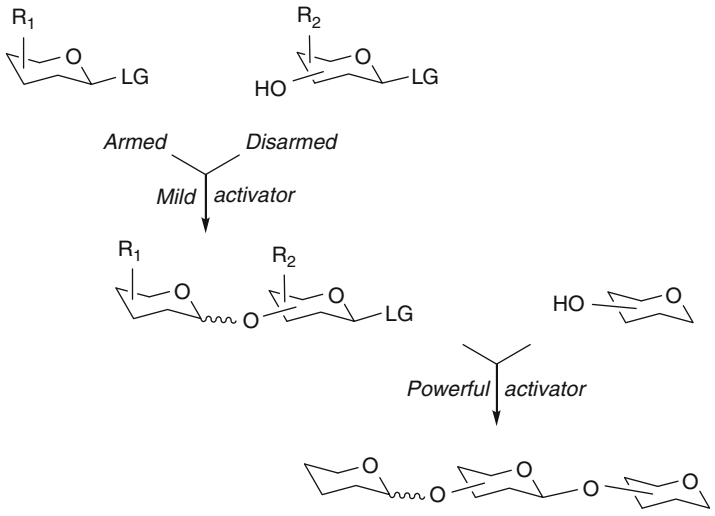
2 Armed–Disarmed Strategy for Oligosaccharide Synthesis

The chemoselective approach and its variations discussed in this section make use of only one class of leaving group for both reaction components, which are either activated (armed donor) or deactivated (disarmed acceptor) by the influence of the protecting groups (R_1, R_2, Scheme 3). Usually, the protecting groups in both reaction components have to be taken into consideration to allow for direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. As both components bear the same type of LG, the key factor for an armed–disarmed activation to take place is finding suitable reaction conditions that can efficiently differentiate between the activated and deactivated building blocks. In most cases, the differentiation is achieved by the choice of promoter, temperature, or solvent [32].

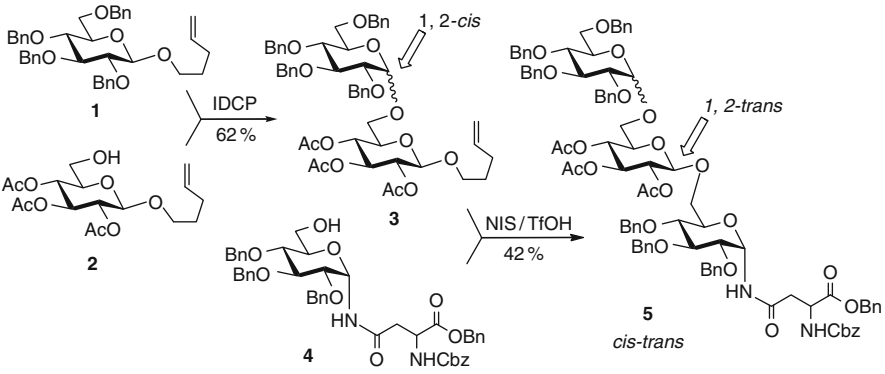
As already mentioned, the majority of strategies discussed in this subsection allow for efficient oligosaccharide assembly without the need to perform additional synthetic steps between the glycosylation steps. Accordingly, the disarmed leaving group of the resulting disaccharide can be activated directly, although a more powerful promoter or elevated temperatures are typically required.

2.1 *Classic Concept: Electron-Withdrawing Substituents and the Synthesis of* cis–trans*-Patterned Oligosaccharides*

Although the effect of protecting groups on reactivity had been noted [20], it was Fraser-Reid who described, in 1988, a new manner by which the differential



Scheme 3 Armed–disarmed strategy outline



Scheme 4 Armed (**1**) and disarmed (**2**) *O*-pentenyl glycosides: synthesis of *cis–trans*-patterned trisaccharide **5**

properties of protecting groups could be exploited, termed the "armed–disarmed strategy" [33]. It was noticed that ester-type protecting groups (OAc, OBz, etc.) strongly reduced, i.e., "disarmed," the reactivity of the *n*-pentenyl glycosyl donor, in comparison to that of its alkylated (benzylated, OBn) "armed" counterpart.

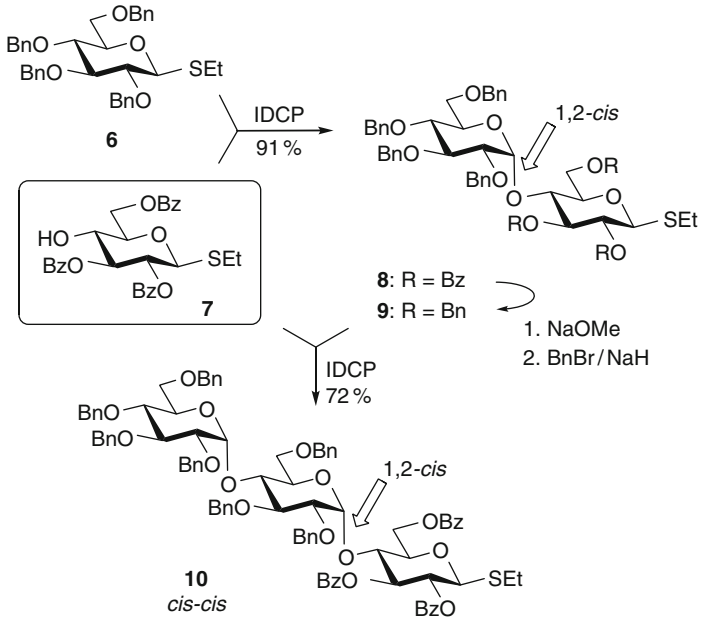
One justification for such an observation is that the increased electron-withdrawing ability of ester protecting groups decreases the electron density (nucleophilicity) of the anomeric heteroatom, which translates into a diminished ability to interact with the electrophilic promoter. As a result, the armed leaving group reacts faster, with the disarmed leaving group reacting either much more slowly or not at all. In order to achieve an efficient differentiation in reactivity, mild promoters have an advantage, as they are able to offer a more controlled activation. For example, iodonium(di-γ-collidine)perchlorate (IDCP) was found to be a suitable mild electrophilic activator for *O*-pentenyl glycosyl donor **1**, and corresponding disaccharide **3** was isolated in 62% yield (Scheme 4) [33]. As the anomeric configuration of the product is influenced by the protective group at O-2, a 1,2-*cis*-linked disaccharide is preferentially obtained in the first step, due to the use of the non-participating, ether-type (*O*-benzyl) arming substituent.

Furthermore, the leaving group of disarmed building blocks (such as **2** or **3**) can also be activated, but this would typically require more time, higher temperature, and/or stronger promoters. For instance, the direct glycosidation of disaccharide **3** was readily achieved in the presence of a strong promoter system, NIS/TfOH. This glycosylation step was performed with glycosyl acceptor **4**, resulting in the stereoselective formation of a 1,2-*trans* glycosidic linkage. As mentioned before, glycosidation of 2-acylated glycosyl donors typically proceeds via the formation of the bicyclic acyloxonium intermediate, which coordinates the 1,2-*cis* face of the ring. As a result of this two-step activation sequence, a *cis–trans*-patterned trisaccharide (**5**) is obtained, wherein the monosaccharide units are sequentially connected via a 1,2-*cis* and 1,2-*trans* linkage (Scheme 4).

Although this discovery was made using *n*-pentenyl glycosides, this electronic effect ultimately proved to be of a general nature, and as such can be applied to nearly any class of glycosyl donor. This concept was further explored for the chemoselective glycosidations of thioglycosides [34], selenoglycosides [35], fluorides [36], phosphoroamidates [37], substituted thioformimidates [38], glycals [39], and thioimidates [40, 41]. The usefulness of this approach was realized in application toward expeditious oligosaccharide synthesis, as it circumvents the need for protecting group manipulations at the anomeric center [42].

2.2 Strategic Updates to the Original Armed–Disarmed Method

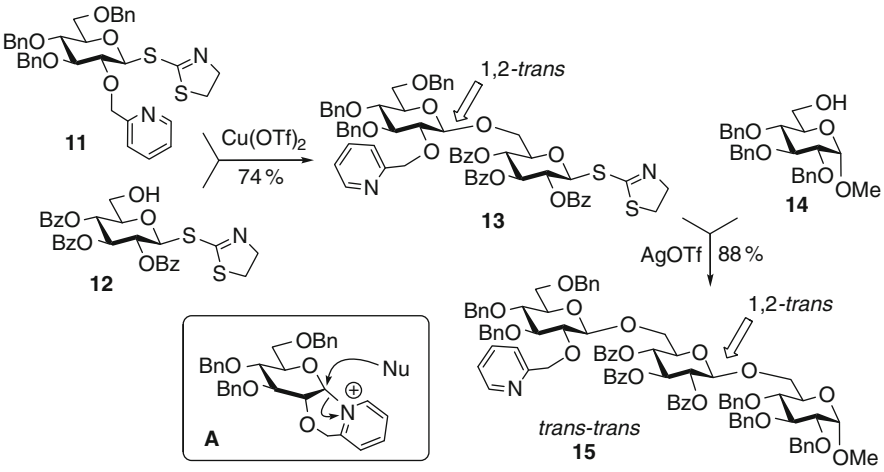
Synthesis of the cis–cis-Patterned Oligosaccharides Using Reprotection of the Intermediate Disaccharide. To address the major limitation that the armed–disarmed strategy could only be applied to the synthesis of oligosaccharides having a *cis–trans* glycosylation pattern, van Boom and co-workers designed a method whereby the synthesis of *cis–cis*-linked derivatives could also be achieved [34]. In the first synthetic step the classic armed–disarmed activation was performed; however, the resulting disaccharide was then reprotected (OBz → OBn) prior to subsequent glycosidation. A representative example of this strategy is shown in Scheme 5.



Scheme 5 Synthesis of *cis–cis*-patterned trisaccharide **10**, via the modified armed–disarmed approach [34]

Armed thioglycoside donor **6** was selectively activated over disarmed glycosyl acceptor **7** in the presence of IDCP to provide the disarmed 1,2-*cis*-linked disaccharide (**8**) in 91% yield. The latter was then subjected to a two-step debenzoylation-benzylation sequence, whereupon the resulting disaccharide donor (**9**) was glycosidated with disarmed acceptor **7**, to afford the *cis–cis*-linked trisaccharide (**10**) in 72% yield. The conversion of the second generation glycosyl donor **8** into the armed state **9** also allowed for the second coupling step to be performed with the mild promoter IDCP.

Synthesis of trans–trans Patterned Oligosaccharides Using Picolinyl Arming Participating Group. Demchenko et al. [41] demonstrated that with the use of an *O*-picolyl substituent as an "arming participating group" at C-2 of the glycosyl donor, a 1,2-*trans* glycosidic linkage can be chemo- and stereo-selectively introduced in the first glycosylation step. For example, glycosidation of armed glycosyl donor **11** with disarmed acceptor **12** in the presence of $Cu(OTf)_2$, produced 1,2-*trans*-linked disaccharide **13** in 74% yield (Scheme 6). Due to the opposite stereochemical outcome of this glycosylation, in comparison to the 1,2-*cis* linkage formed in the first step of the classic armed–disarmed approach, this approach was called the *inverse armed–disarmed* strategy. Subsequent glycosidation of disarmed disaccharide **13** with the standard glycosyl acceptor **14** could then be achieved in the presence of a more powerful activator AgOTf, and the resulting *trans–trans*-linked trisaccharide **15** was obtained in 88% yield [41]. NMR experiments were utilized, showing the presence of the anticipated cyclic compound **A** as the key reaction intermediate (Scheme 6).

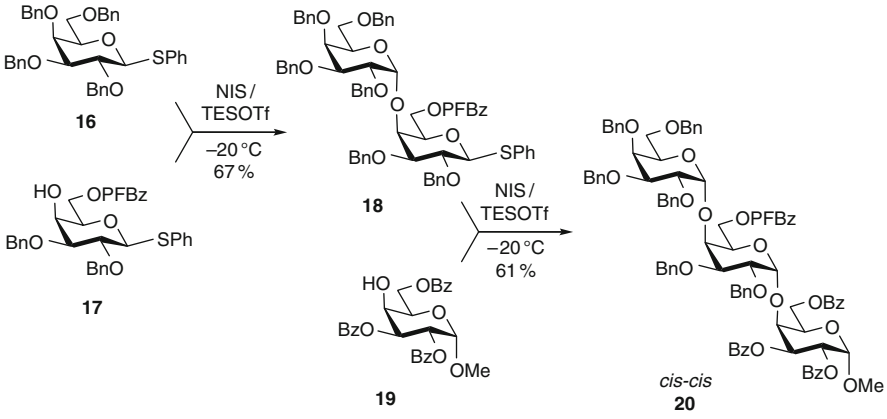


Scheme 6 Arming participating picolinyl group mediated synthesis of *trans–trans*-patterned trisaccharide **15**

2.3 Conceptual Updates to the Original Armed–Disarmed Method

Deactivation by a Remote Protecting Group Capable of Powerful Electron-Withdrawal. Madsen et al. [43] clearly demonstrated that a single electron-withdrawing moiety at the remote C-6 position will sufficiently disarm the leaving group of a glycosyl acceptor, in comparison to the per-alkylated glycosyl donor. This effect was especially pronounced with the use of a pentafluorobenzoyl (PFBz) ester, capable of a very powerful electron-withdrawal [44]. For example, armed benzylated thioglycoside **16** could be chemoselectively activated over the disarmed 6-*O*-pentafluorobenzoyl acceptor **17** in the presence of NIS/TESOTf to provide disaccharide **18** (Scheme 7). The latter could then be glycosidated with glycosyl acceptor **19** the presence of NIS/TESOTf to give trisaccharide **20** in 61% yield. It is important to highlight that this approach allows for the *cis–cis* oligosaccharide sequence to be obtained directly, without deprotection/reprotection of the intermediate disaccharide, as previously discussed for the synthesis reported by van Boom (see Scheme 5).

Crich et al. [45] also investigated the influence of the electron-withdrawal at the C-6 position on the reactivity of glycosyl triflates and stereoselectivity of their glycosidations. In exploring a series of mono-, di-, and tri-fluorinated 6-deoxy rhamnosides, a clear correlation between the strength of electron-withdrawal at C-6 and stability of the anomeric triflates was established. While common rhamnosyl triflates undergo rapid decomposition at temperatures above −60°C, it was shown that their 6,6,6-trifluorinated counterparts remained stable at temperatures up to +10°C. Many related studies have further demonstrated that the arming/disarming effect of the protecting groups may also be highly

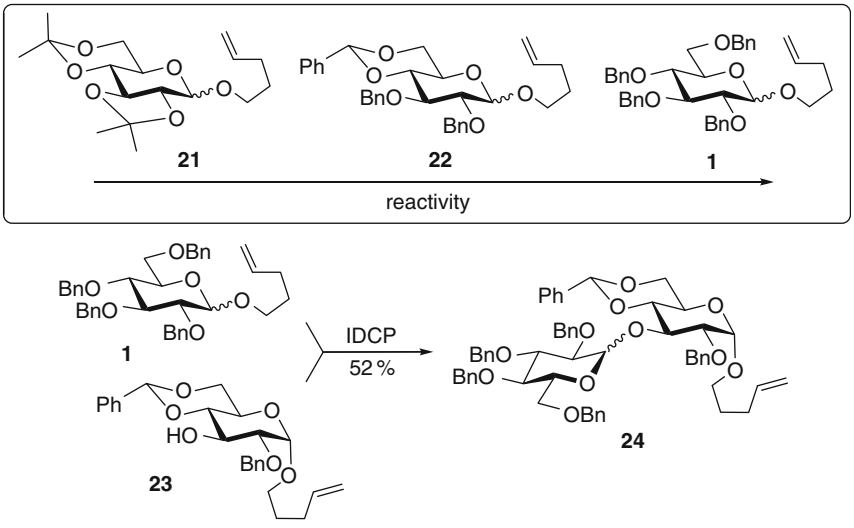


Scheme 7 Disarming the glycosyl acceptor with the remote 6-*O*-pentafluorobenzoyl moiety: direct synthesis of *cis–cis*-patterned trisaccharide **20**[44]

dependent upon their location (see Schemes 11 and 12), geometry, and core donor structure [46, 47].

Deactivation with Cyclic Ketals/Acetals: Torsional and Electronic Effects. Fraser-Reid and co-workers discovered that the deactivation of glycosyl donors could also be achieved through the strategic placement of cyclic acetal/ketal substituents that would lock the pyranose ring in the $^4C_1$ chair conformation. This type of deactivating effect was attributed to the increased rigidity of the fused ring system, prohibiting the oxacarbenium ion intermediate from achieving the requisite planar geometry about the (C-2)-(C-1)-(O-5)-(C-5) atoms [48]. As depicted in Scheme 8, in a series of *O*-pentenyl glycosides, reactivity was noted to increase from the tricyclic 2,3:4,6-diacetone ketal **21** to the bicyclic 4,6-benzylidene acetal **22** with the traditional armed *O*-pentenyl glycoside (**1**) being the most reactive. This relative reactivity trend was proven by direct chemoselective activation of armed glycosyl donor **1** over benzylidene-protected glycosyl acceptor **23**. As in the case of the traditional armed–disarmed approach, IDCP was found to be a suitable promoter that allowed for efficient differentiation of the reactivity levels between the armed and torsionally disarmed building blocks (**1** and **23**, respectively). As a result, disaccharide **24** was isolated in 52% yield, with no observed by-products resulting from the self-condensation of glycosyl acceptor **23**. These results suggested that the disarming could be achieved by acetal/ketal protecting groups exclusively.

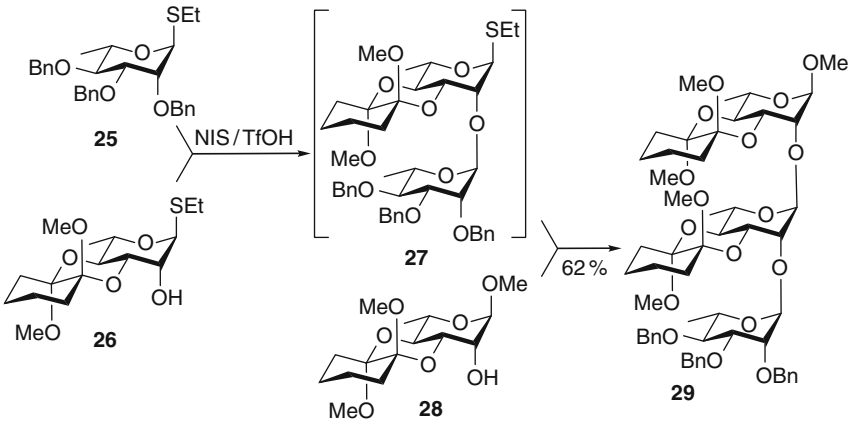
This concept was expanded upon by Ley and co-workers, who clearly demonstrated that similar deactivation could be effectively achieved with the use of a variety of cyclic 1,2-diacetal/diketal systems [49]. And the example below highlights one such application, in which a two-step sequential activation was



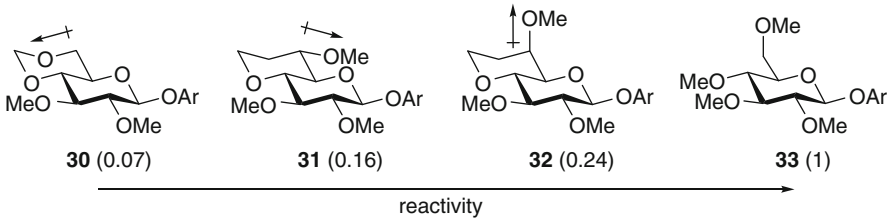
Scheme 8 The disarming of building blocks can be achieved with a benzylidene acetal or isopropylidene ketal [48]

accomplished using a one-pot synthetic strategy. The one-pot approach allows for two (or more) sequential glycosylation reactions to be performed in a single flask (pot) without isolation and purification of the intermediate [50]. Thus, armed glycosyl donor **25**, of the L-rhamno series, was chemoselectively activated over torsionally disarmed rhamnosyl acceptor **26** in the presence of NIS/TfOH (Scheme 9). The resulting disaccharide (**27**, not isolated) was then reacted directly with rhamnosyl acceptor **28**, and the final trisaccharide **29** was isolated in 62% yield over the two-step activation sequence. Clearly, one-pot strategies offer the fastest pathway to oligosaccharides, although to ensure successful isolation of the final product, all steps need to proceed with particularly high diastereoselectivity and yield [50, 51].

It should be noted, that the ester and acetal/ketal groups disarm building blocks following different considerations and mechanisms. Whereas ester disarming effect is purely electronic, benzylidene/isopropylidene groups were initially assumed to disarm exclusively through torsional strain. In further mechanistic probing, Bols and co-workers proposed that the disarming effect of the 4,6-acetal may also be due to the orientation of the electron-withdrawing C-6 substituent [52]. From a series of model experiments, it was found that a basic torsional disarming effect does exist; however, the data suggested that the substituent configuration (stereoelectronic effect) also plays a significant role in the overall degree of disarming. For example, the reactivity of torsionally disarmed compound **32** (with an axially oriented 6-methoxy substituent) falls between that of per-methylated armed building block **33** and compounds **30/31** (in which the equatorially oriented 6-O-substituents are capable of more a geometrically directed electron-withdrawal, Fig. 2). Based on relative rates of hydrolysis (Fig. 2), it was concluded that conformational restriction and stereoelectronics (charge-dipole interactions) were almost equally responsible for the observed disarming effect.



Scheme 9 One-pot synthesis of trisaccharide **29** via torsional deactivation with cyclohexane 1,2-diacetal (CDA)



Ar = 2,4-dinitrophenyl (values in parentheses represent relative rate of hydrolysis)

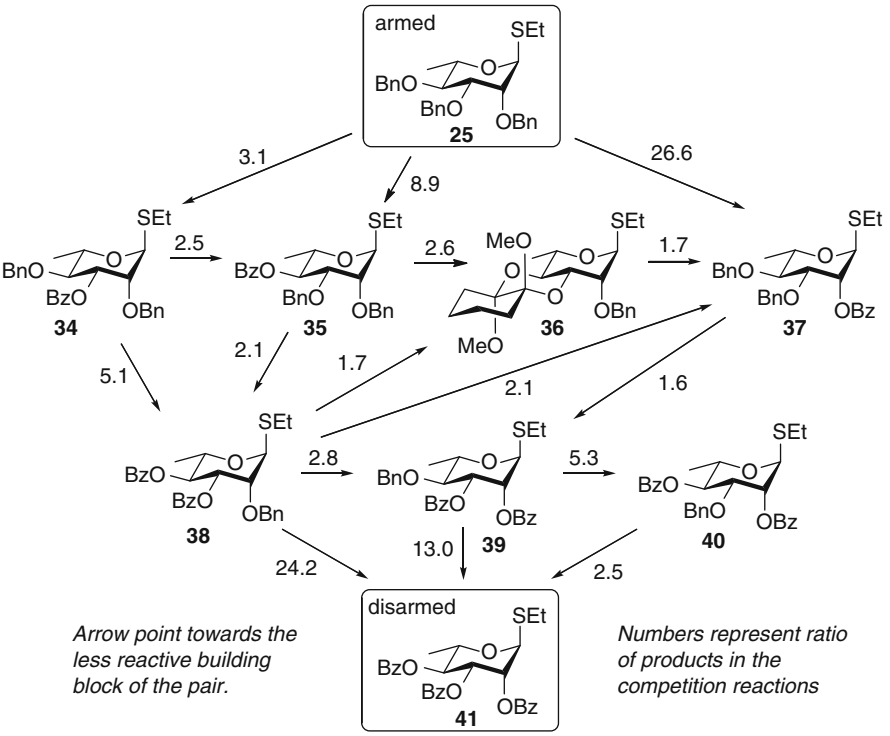
Fig. 2 The disarming effects of the cyclic ketal/acetal are both conformational and electronic

2.4 Going Beyond the Simple Armed and Disarmed Building Block Combination

Many Different Reactivity Levels Revealed. Further progress in the area of chemoselective oligosaccharide synthesis emerged with the development of a programmable oligosaccharide strategy, which stemmed from the studies pioneered in Fraser-Reid's, van Boom's, Ley's, and Wong's groups. Subsequently, attempts to classify, and even predict, the outcome of a glycosylation reaction (or a sequence) led to the further development of approaches that attempted to quantify the reactivity of building blocks [46–48, 53, 54]. Following Fraser-Reid's study on the *n*-pentenyl glycoside-based methodology for determining the relative reactivities of variously protected pairs of glycosides [53], Ley et al. developed an approach wherein building block reactivity could be "tuned" [46]. In a series of competitive experiments, wherein two glycosyl donors were competing for one glycosyl acceptor, a series of relative reactivity ratios was established. Additionally, these ratios were found to correspond to various protecting group patterns. For instance, an important relationship between the position of benzoyl groups and their effect on reactivity surfaced from these studies (Scheme 10).

Thus, the greatest disarming effect was seen from the 2-benzoyl substituent in compound **37**, followed by the 4-benzoyl and 3-benzoyl substituents (in compounds **34** and **35**, respectively). In addition, cyclic ketal **36** was found closer in reactivity to the mono-benzoylated rather than the di-benzoylated series of compounds. Not surprisingly, reactivity levels recorded for the mono-benzoylated (**34**, **35**, **37**), di-benzoylated (**38–40**), and torsionally disarmed (**36**) glycosyl donors fell in between the traditional per-benzylated armed rhamnoside **25** and its disarmed per-benzoylated counterpart **41**.

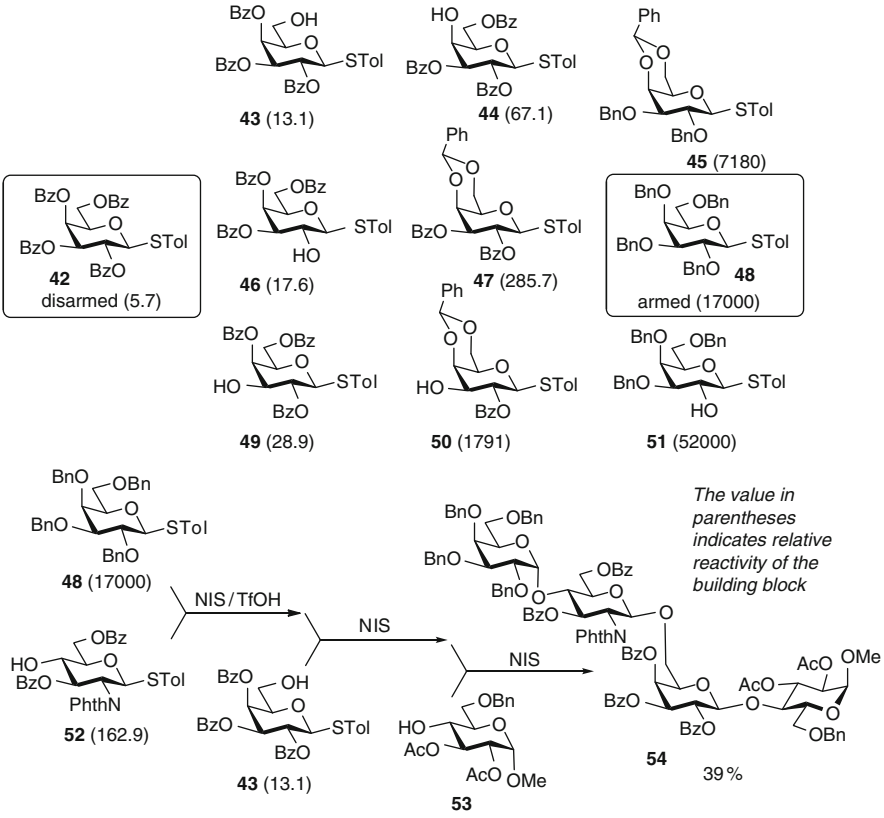
Wong et al. devised a mathematical approach, assigning relative reactivity values (RRVs) to a wide library of building blocks [47]. The determination of RRVs was made in standardized reaction conditions, tolyl thioglycoside donors in the presence of an NIS/TfOH promoter system. The cumulative reactivity data was then compiled into a predictive computer program called Optimer [47]. Various intermediate reactivity levels were revealed during these studies, with nearly all



Scheme 10 The reactivity of a series of partially benzoylated rhamnosides falls between the traditional armed (**25**) and disarmed (**41**) building blocks

compounds clearly situated between the armed (**42**) and disarmed (**48**) building blocks (Scheme 11). Similar to Ley's findings, the acetal-protected building blocks were also positioned between the armed and disarmed building blocks, being closer in reactivity to the former. For example, 4,6-benzylidene-2,3-dibenzoyl derivative **47** was approximately 50 times more reactive than its per-benzoylated disarmed counterpart **42** (Scheme 11).

Following these studies, a well-rounded technology for one-pot oligosaccharide synthesis based on RRVs emerged. A representative example is depicted in Scheme 11, wherein armed glycosyl donor **48** was chemoselectively activated over glycosyl acceptor **52** in the presence of NIS/TfOH. The resulting disaccharide intermediate was then reacted with added disarmed glycosyl acceptor **43** to form a trisaccharide intermediate that was then glycosidated with added glycosyl acceptor **53** to provide tetrasaccharide **54** in 39% overall yield [47]. The reactivity difference between similarly protected sugars of different series has also to be taken into consideration. For example, the reactivity ratio between perbenzylated tolyl thioglycosides of the 6-deoxy-L-*galacto*, D-*galacto*, and D-*gluco* series was found to be 27.1/6.4/1 respectively [47]. Ley's studies also showed a similar correlation



Scheme 11 Relative reactivity levels of differently protected galactosides. Synthesis of tetrasaccharide **54** via the programmable one-pot strategy [47]

between the reactivity of building blocks of different series [49, 55]. Accumulation of comparison data for reactivity of building blocks of 2-amino-2-deoxysugars and their neutral counterparts has also began to emerge [54, 56–60].

3 Superdisarmed Building Blocks

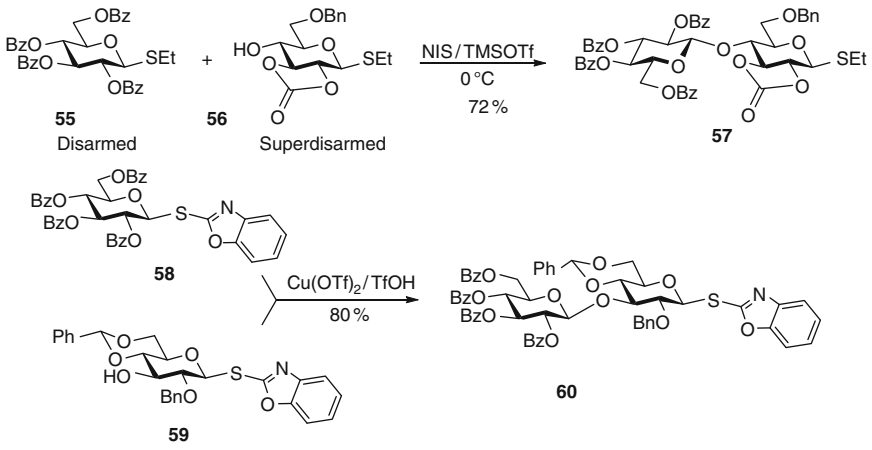
Although most reactivity levels in Fraser-Reid's, Ley's, and Wong's studies fall between the traditional armed and disarmed building blocks, Wong's study revealed a number of building blocks that were extended beyond this boundary. For example, 2-hydroxyl galactoside **51** was found to be three times more reactive than the traditional armed galactoside **48** (Scheme 11). Indirectly, this discovery opened up a new avenue for studying building blocks that are either more reactive than armed ones (superarmed) or less reactive than disarmed ones (superdisarmed);

the studies arising from these two directions are surveyed below. In this section, those building blocks possessing a lower reactivity than their conventional per-acylated (per-benzoylated) disarmed counterparts will be discussed.

3.1 Superdisarming by Torsional Effect

As mentioned before, Fraser-Reid [48], Ley [61], and Bols [52] found that anomeric deactivation can be achieved by the combination of the torsional and electronic effects of cyclic acetal/ketal protecting groups. The combination of two separate effects could lead one to believe that such systems would be less reactive than the pure-electronically disarmed, acylated building blocks. However, in the majority of cases investigated and surveyed in the previous section, the acetal/ketal-protected derivatives were found to be of intermediate reactivity, falling between the traditional armed and disarmed building blocks (see Schemes 10 and 11). It was not until more recent studies by Boons [62] that it became apparent that thioglycosides protected with the cyclic 2,3-carbonate group could be even less reactive (super-disarmed) than traditional disarmed acylated derivatives. The following example clearly illustrates this finding. Thus, disarmed per-benzoylated thioglycoside donor **55** was chemoselectively activated over superdisarmed glycosyl acceptor **56** in the presence of NIS/TMSOTf (Scheme 12).

Along similar lines, Demchenko et al. performed the direct chemoselective activation of the electronically disarmed SBox glycoside **58** over torsionally/electronically disarmed (superdisarmed) glycosyl acceptor **59**. This direct chemoselective coupling resulted in the formation of disaccharide **60**, proving that even



Scheme 12 Chemoselective activation of disarmed donors **55** or **58** over superdisarmed acceptors **56** or **59**, respectively

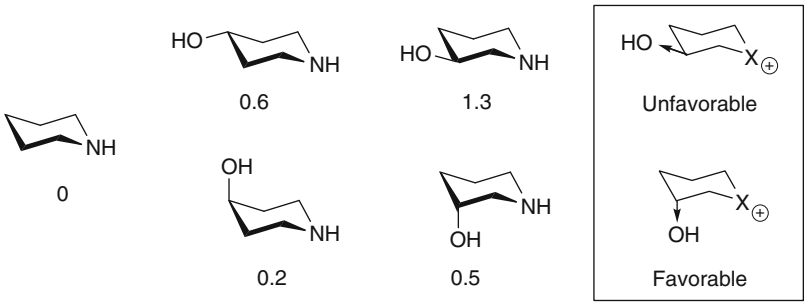


Fig. 3 Effect of axial and equatorial electron-withdrawing substituents on basicity of piperidines

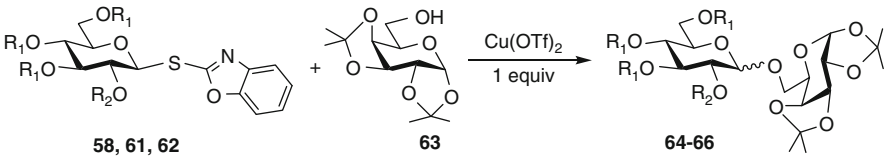
traditional benzylidene systems can superdisarm building blocks of the SBox series. It appears that there is a certain inconsistency between this result and the comprehensive programmable approach which showed benzylidene derivatives to be more reactive than their disarmed counterparts. Although a direct investigation of these two findings is not yet available, studies reported by Bols [63] offer the explanation that the disparity could be simply explained by the benzylidene orientation; axial – galactose (Wong et al.) vs equatorial – glucose (Demchenko et al.).

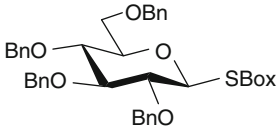
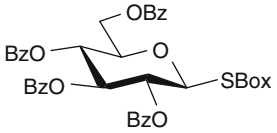
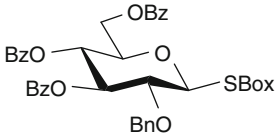
In order to access the electronic effects of various ring substituents, Bols et al. designed the following model study which showed equatorial substituents to be significantly more electron-withdrawing (destabilizing, disarming) than their axial counterparts (Fig. 3). The values shown are in pH units, and reflect the amount by which the pKa of the substituted amine decreases with respect to piperidine. It is believed that this result can help to rationalize different relative reactivity found amongst 4,6-benzylidene building blocks of different series (gluco vs galacto in this case). However, a more systematic study of this phenomenon, and perhaps a series of side-by-side chemoselective coupling experiments, would be needed to draw a more direct conclusion.

3.2 Superdisarming by Electronic Effects

Demchenko et al. also reported that a mixed protecting group pattern can unexpectedly and profoundly affect the glycosyl donor reactivity [40]. Upon investigating *S*-benzoxazolyl (SBox) glycosides containing an "arming" benzyl group at C-2 and "disarming" acyl groups at the remaining hydroxyls, it was expected that reactivity would fall somewhere between that of the armed (per-benzylated) and the disarmed (per-benzoylated) glycosyl donors; similar to the results found in Ley's studies for building blocks of the L-rhamnose series, as discussed above. However, the results acquired with the SBox glycosides of the D-gluco series revealed that these "mixed-patterned" glycosyl donors were the least reactive amongst the building blocks investigated (Table 1) [40].

Table 1 Comparative activation of differently protected SBox glycosides **58**, **61**, and **62**



Entry	Donor	Product	Yield	α/β ratio
1	 **61**	**64**	89%	5.4/1
2	 **58**	**65**	70%	β only
3	 **62**	**66**	No reaction	–

Thus, the reaction of armed SBox donor **61** with glycosyl acceptor **63** in the presence of copper(II) trifluoromethanesulfonate proceeded smoothly, and product **64** was isolated in a good yield of 89% (Entry 1, Table 1). Along similar lines, it was discovered that disarmed perbenzoylated SBox glycoside **58** also reacted readily, although this glycosylation was marginally slower in comparison to that of the armed per-benzylated building block **61**, never fully going to completion, resulting in a slightly lower, 70% yield of the disaccharide **65**. Interestingly, when essentially the same reaction conditions were applied to the glycosidation of 2-*O*-benzyl-tri-3,4,6-*O*-benzoyl protected SBox glucoside **62**, no formation of the expected disaccharide **66** was detected.

As Lemieux's halide stability theory [64–66], Fraser-Reid's armed–disarmed concept rationale [31, 33], Ley's tuning reactivity studies [46], and Wong's programmable oligosaccharide synthesis [47] all predicted 2-*O*-benzylated glycosyl donor **62** to be more reactive than its per-benzoylated counterpart **58**, these

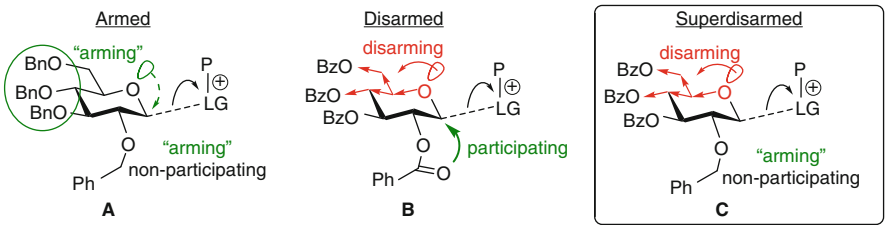


Fig. 4 O-2/O-5 Cooperative effect in glycosidation of the superdisarmed building blocks

unanticipated results necessitated further studies. This finding implies that a combination of electronic effects, beyond the recognized inductive effects of the C-2 protecting group, may exist. The observed reactivity pattern was rationalized by the occurrence of the so-called "O-2/O-5 Cooperative Effect" [40]. Thus, in addition to the "arming/disarming" nature of the protecting group at O-2, stabilization of the glycosyl cation intermediate must also be taken into consideration. First, this stabilization can be achieved from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) as in the armed glycosyl donor **A**, shown in Fig. 4. However, if electron-withdrawing protecting groups are placed near the O-5 ring oxygen (C-4 and C-6, as in the disarmed donors **B** or **C**), the electron density on O-5 will be decreased, effectively suppressing oxacarbenium ion formation. In this case, the ability of the system to stabilize via other plausible internal modes may become increasingly important.

A second type of stabilization may arise based on the availability of the lone electron pair on an acyl type protecting group at O-2, which is capable of providing stabilization via the formation of an acyloxonium ion intermediate, as in disarmed glycosyl donor **B**. Crich et al. [67] emphasized that the anchimeric assistance was particular to the 1,2-*trans* orientation of the 2-*O*-acyl and 1-SBox leaving group, as stabilization presumably takes place via the concerted displacement of the leaving group. However, if no source of secondary stabilization is available, as in case of 2-*O*-benzyl substituent in **C**, this combination will give rise to the overall "superdisarming" protecting group pattern.

4 Superarmed Building Blocks

In contrast to superdisarmed building blocks, possessing reactivity even lower than that of the peracylated disarmed building blocks, other, super reactive glycosyl donors have also been discovered. The term superarmed was first coined by Bols for describing the reactivity of conformationally armed building blocks. Herein, however, we apply the term superarmed to all building blocks that are more reactive than conventional per-alkylated armed building blocks.

4.1 Superarming by Conformational Effects

As was previously noted, the substituent orientation can have a strong effect on the reactivity of a molecule. A model study of the relative pK_a values for protonated heterocyclic amines showed that equatorial substituents are significantly more deactivating than their axial counterparts (compare **67** and **68** in Fig. 5) [63]. Further revealed by these findings was that a perturbation of the equilibrium between ring conformations may also occur upon protonation of the heterocyclic amine [68]. This was found to result from the desire for substituents to reside axially, as they have a greater ability to provide charge stabilization through charge-dipole interactions. For example, cyclic amine derivative **68** was found to exist predominantly in the conformation wherein the electron-withdrawing hydroxyl substituents are axial. This study further suggests that positively charged oxocarbenium ion intermediates may also spontaneously undergo conformational changes in an attempt to maximize the number of axial substituents. If so, this conformational change would be made easier if the starting material already had a number of axial substituents [69]; for example, galactose has long been known to be more reactive than glucose (compare hydrolysis rates for compounds **69** and **70**, Fig. 5).

Furthermore, when conformationally restricted 3,6-anhydroglucoside **71**, having all-axial hydroxyl groups, was investigated, it was shown to hydrolyze much faster than its all-equatorial counterpart **69** [70].

This result implies that if all-equatorial glucosyl donors were converted into their all-axial counterparts, the reactivity could be dramatically increased. Based on the knowledge that steric congestion at the equatorial C-3 and C-4 positions causes conformational changes [71, 72], Bols and co-workers were able to exploit this phenomenon [70, 73, 74]. However, when TBS protection was applied to glucose derivative **72**, the product **73** was found to exist in more of a skew-boat conformation [75] (Scheme 13) rather than the anticipated $^1C_4$ conformation

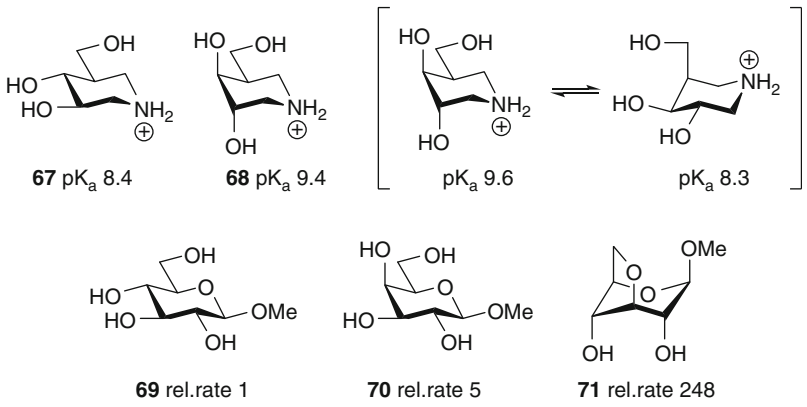
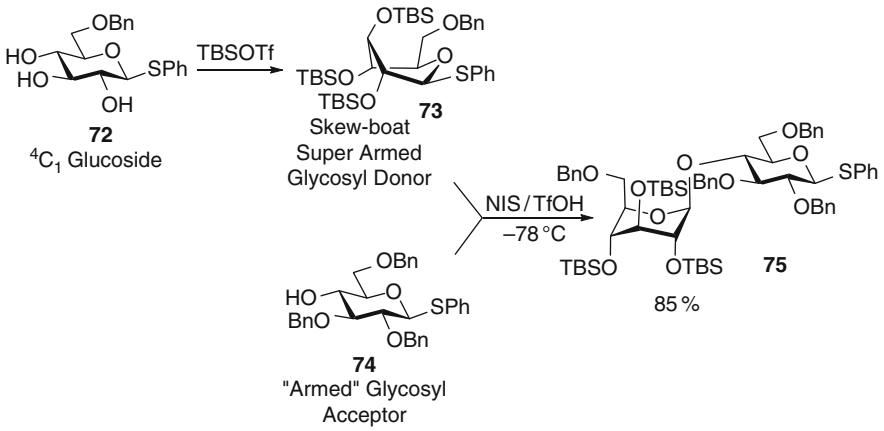


Fig. 5 Basicity and reactivity increase with the increase of the number of axial hydroxyls: conformational change to increase reactivity



Scheme 13 Chemoselective activation of the conformationally superarmed glycosyl donor **73** over armed glycosyl acceptor **74**

adopted by analogous xylopyranose derivatives [76], perhaps due to the added steric bulk of the substituent at C-5. Nevertheless, a sufficient conformational change was induced, reconfiguring the substituents perpendicular to the sugar ring. As such, this conformationally superarmed glucosyl donor **73** showed a dramatic 20-fold increase in reactivity, relative to the traditional armed benzylated derivatives, as shown by direct competition experiments [73]. Furthermore, superarmed glycosyl donor **73** could be successfully coupled with "armed" acceptor **74** to afford the resulting disaccharide **75** in 85% yield [77]. Similar observations have also been made with glycosyl donors of the manno, rhamno, and galacto series [74].

Interestingly, Bols et al. showed that while the 4,6-dialkylsilylene protection disarms the glycosyl donor, the 3,6-dialkylsilylene tethering is able to arm glycosyl donors [77]. As a matter of fact, the axial-rich 3,6-tethered glycosyl donor demonstrated superarming properties that have been proven in the direct competition experiments with traditional armed glycosyl donor [77].

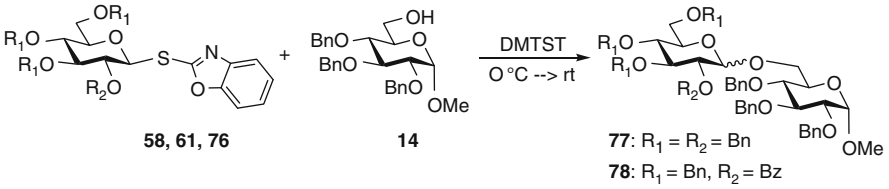
4.2 Superarming by Electronic Effects

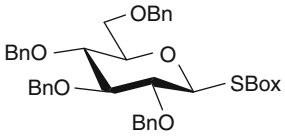
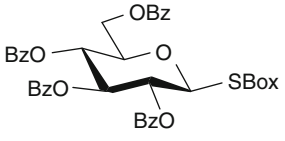
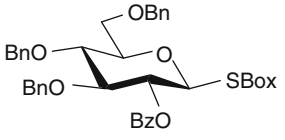
As mentioned before, a mixed protecting group pattern could unexpectedly and profoundly affect glycosyl donor reactivity [40]. Along these lines, a glycosyl donor containing a participating benzoyl group at C-2 and electron donating groups at the remaining positions was also investigated. Interestingly, these glycosyl donors proved to be even more reactive (superarmed) than their armed per-benzylated counterparts [78, 79]. Thus, the reaction of armed SBox donor **61** with glycosyl acceptor **14** in the presence of dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (DMTST) proceeded smoothly, and product **77** was

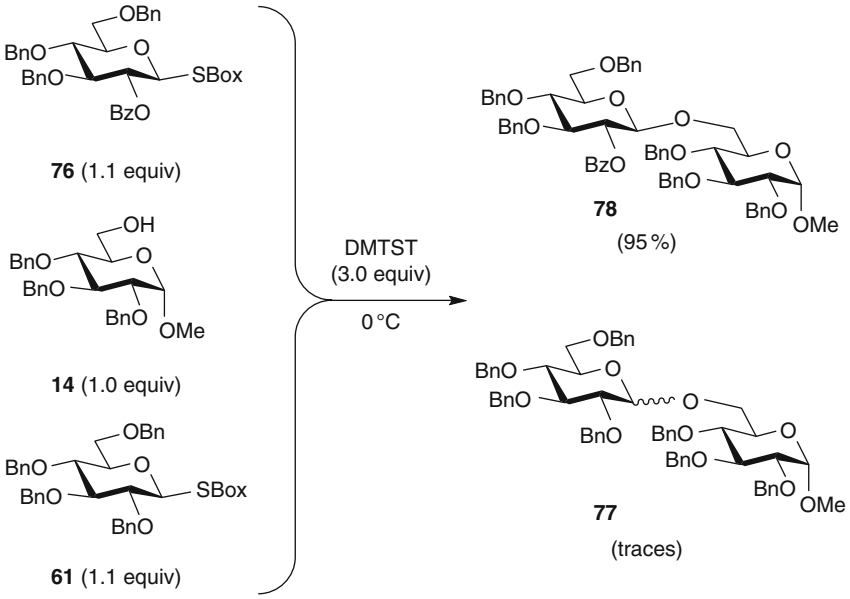
isolated in 91% yield (Entry 1, Table 2). Furthermore, it was discovered that the disarmed perbenzoylated SBox glycoside **58** failed to react under essentially the same reaction conditions. Unexpectedly, the glycosidation of 2-*O*-benzoyl-tri-3,4,6-*O*-benzyl protected SBox glucoside **76** proceeded almost instantaneously, and disaccharide **78** was obtained in 90% yield (for comparison, the glycosidation of armed donor **61** took 2 h).

The reactivity of the superarmed donors was illustrated in a direct competitive glycosylation experiment, wherein both the superarmed and armed donors (**76** and **61**, respectively), were placed in the same reaction vessel with glycosyl acceptor **14**. As depicted in Scheme 14, superarmed glycosyl donor **76** proved to be significantly more reactive than its per-benzylated analog **61**; this was reflected in the formation of disaccharide **78** (95%) with only trace amounts of disaccharide **77** present (<5%). In addition, unreacted glycosyl donor **61** was recovered in 87%

Table 2 Comparative glycosidations of glycosyl donors **58**, **61**, and **76**



Entry	Donor	Time	Product	Yield	α/β ratio
1	 **61**	2 h	**77**	91%	1.2/1
2	 **58**	16 h	–	No reaction	–
3	 **76**	< 5 min	**78**	90%	β only



Scheme 14 Superarmed (**76**) and armed (**61**) glycosyl donors in competitive glycosylation

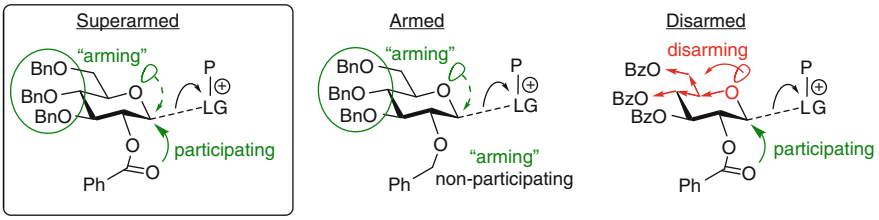


Fig. 6 O-2/O-5 Cooperative effect in glycosidation of the superarmed building blocks

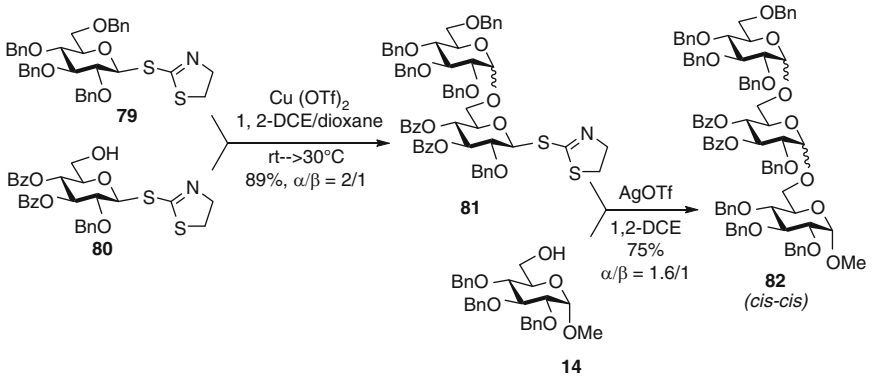
yield. Furthermore, this concept was found to be universal and applicable to glycosidation of *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl, and *S*-thiazolinyl building blocks [80]. This observed reactivity pattern was also rationalized by the occurrence of the "O-2/O-5 Cooperative Effect" [40].

As described in Fig. 6, stabilization of the glycosyl cation can be achieved either from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) or from the lone electron pair on an acyl type protecting group at O-2, as it is capable of providing stabilization via the formation of the acyloxonium ion intermediate. If both sources of stabilization are available, as in the case of 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl, this combination gives rise to an overall "superarming" protecting group pattern. Alternatively, this type of superarmed glycosyl donor may also be viewed as an armed donor, capable of a 1,2-*trans* stereoselective glycosylation, allowing for the chemoselective introduction of a 1,2-*trans* linkage prior to other linkages.

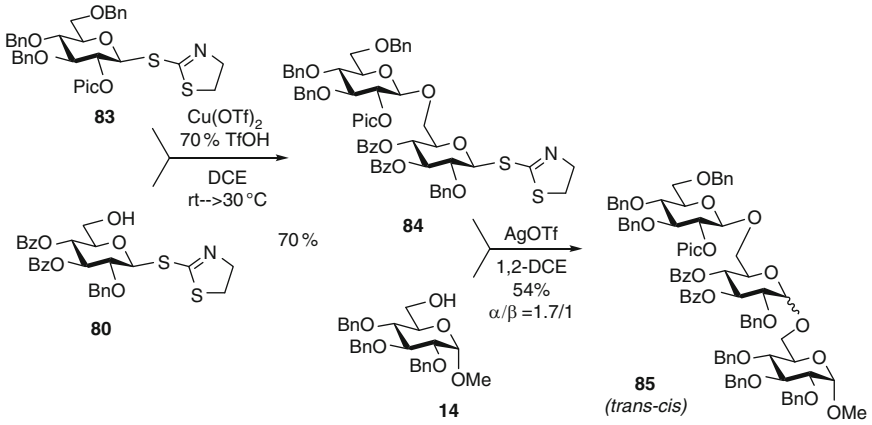
5 The Involvement of Superdisarmed and Superarmed Building Blocks in Oligosaccharide Synthesis

The expeditious preparation of complex oligosaccharides remains a significant challenge to synthetic organic chemistry. The combined demands of regio- and stereo-selectivity in glycosidic bond formation has led to complex synthetic schemes and extensive protecting group manipulations. As mentioned before, the use of a chemoselective activation strategy avoids such extraneous manipulations, thus offering significant advantages for expeditious glycoside synthesis. Combining the strategic and conceptual updates to the original Fraser-Reid strategy for armed–disarmed oligosaccharide synthesis with the novel concepts for superarming and superdisarming of building blocks has expanded the applicability of chemoselective synthesis to encompass a variety of oligosaccharide sequences. For example, utilization of the cooperative effect allows for the acquisition of *cis–cis*-linked oligosaccharides, similar to that discussed previously (see Scheme 7). As shown in Scheme 15, armed STaz glycosyl donor **79** was chemoselectively activated over superdisarmed 3,4-di-*O*-benzoyl-2-*O*-benzyl protected STaz glycosyl acceptor **80** in the presence of $Cu(OTf)_2$ to give disaccharide **81** in 89% yield [81]. Superdisarmed disaccharide **81** was then glycosidated with standard glycosyl acceptor **14** in the presence of AgOTf to give the desired *cis–cis*-linked trisaccharide **82** in 75% yield.

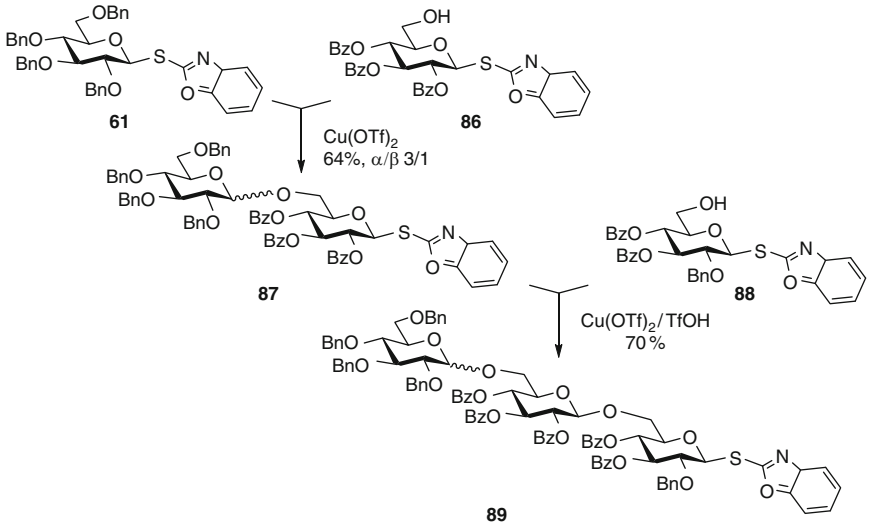
Along similar lines, it was demonstrated that a combination of the *trans*-directing picolyl functionality of armed glycosyl donor **83** and the *cis*-directing functionality of its subsequent superdisarmed disaccharide **84**, led to a *trans–cis* glycosylation pattern, inverse to that of the classic armed–disarmed approach which gives a *cis–trans* pattern [81]. The coupling between building blocks **83** and **80** was performed in the presence $Cu(OTf)_2$/TfOH to give *trans*-linked disaccharide **84** in 70% yield (Scheme 16). The superdisarmed disaccharide **84** was then coupled with



Scheme 15 Sequential activation of armed → superdisarmed building blocks for direct synthesis of *cis–cis*-linked oligosaccharide **82**



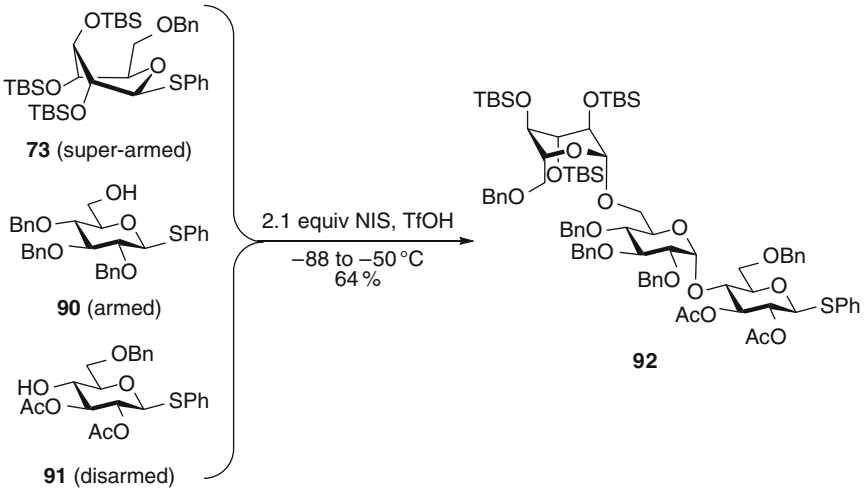
Scheme 16 Sequential activation of picolylated armed → superdisarmed building blocks: synthesis of *trans–cis*-linked trisaccharide **85**



Scheme 17 Sequential activation of armed → disarmed → superdisarmed building blocks **61**, **86**, **88**, respectively [40]

glycosyl acceptor **14** in the presence of AgOTf, affording the desired inverse-patterned *trans–cis* trisaccharide **85** in 54% yield.

It was also demonstrated that disarmed disaccharide **87** (obtained by classic armed–disarmed approach from building blocks **61** and **86**, Scheme 17) could be further chemoselectively activated over superdisarmed building block **88**.



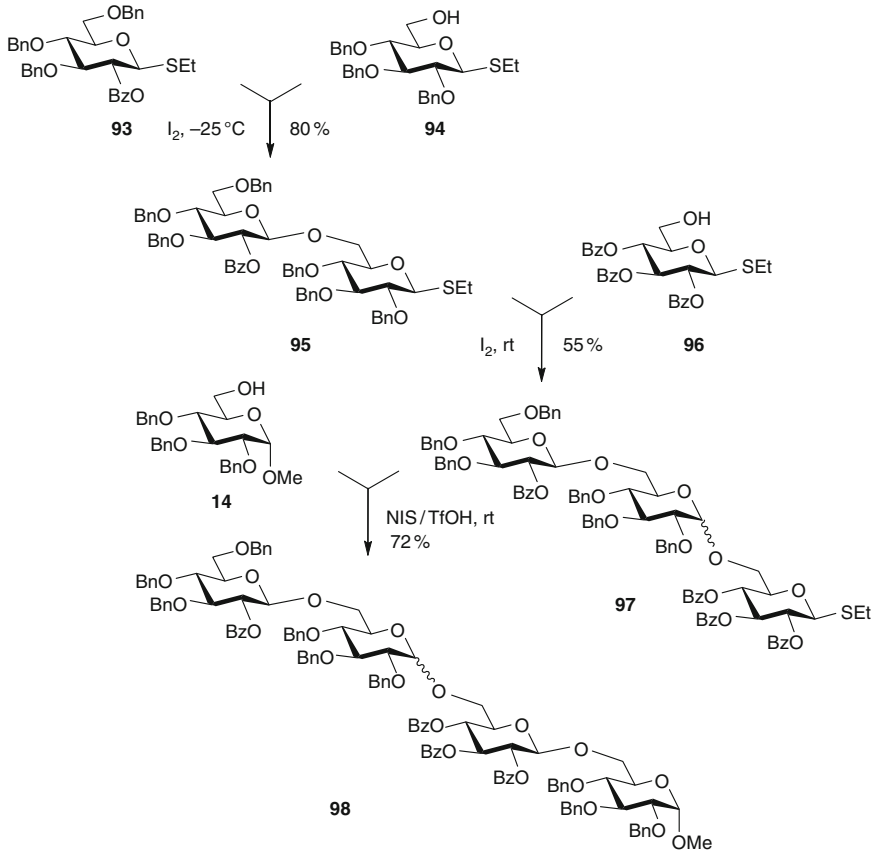
Scheme 18 Superarmed → armed → disarmed activation for the synthesis of trisaccharide **92** in one-pot

Thus, disarmed disaccharide **87** was activated in the presence of $Cu(OTf)_2$/TfOH to produce trisaccharide **89** in 70% yield [40].

This concept of conformational superarming was clearly demonstrated by performing a one-pot coupling wherein all three reaction components (thioglycosides **73**, **90**, and **91**) were mixed from the beginning (Scheme 18) [74]. This type of one-pot technique requires differentiation between the reactivity levels of both glycosyl donors (**73** and **90**) and both glycosyl acceptors (**90** and **91**), while all bearing the same anomeric leaving group (phenylthio). The first reaction took place between the superarmed glycosyl donor **73** and the more reactive primary (and also more electron rich due to the neighboring benzyl substituents) glycosyl acceptor **90**. The resulting disaccharide derivative then reacted with the remaining glycosyl acceptor **91**. As a result of this one-pot coupling in the presence of NIS/TfOH, trisaccharide **92** was obtained in 64% yield.

A similar sequence, yet with the execution of the traditional stepwise approach, was explored with the electronically superarmed glycosyl donors. Thus, the superarmed glycosyl donor **93** was activated over "armed" acceptor **94** in the presence of iodine to provide disaccharide **95** in 80% yield (Scheme 19). This disaccharide was then glycosidated with the disarmed acceptor **96** to provide trisaccharide **97** in 55% yield. The resultant trisaccharide was glycosidated with glycosyl acceptor **14** to obtain the target tetrasaccharide **98** in which monosaccharide residues are connected via alternating *trans–cis–trans* linkages.

In principle, examples of using electronically superarmed building blocks are rather abundant; however, these building blocks were chosen for the convenience of their protecting group pattern rather than in appreciation of the superarmed properties. These examples include the synthesis of HIV viral protein gp120 glycopeptide fragment [82], the synthesis of core tetrasaccharide corresponding to GPI-related



Scheme 19 Synthesis of tetrasaccharide **98** using superarmed → armed → disarmed sequential activations [80]

mucins of *Trypanosoma cruzi* Y-strain [83], the synthesis of a complex branched oligosaccharide of F1α antigen 9 [84], etc. [85, 86]. The involvement of super-disarmed glycosyl donors in electrochemical glycosylations was also investigated [87, 88].

6 Conclusions and Outlook

It is critical to make complex carbohydrates more accessible to general chemical, biochemical, and industrial researchers to keep pace with the exploding area of glycobiology. This aim can only be achieved by the development of methods and strategies for efficient oligosaccharide synthesis that would be applicable for both laboratory and industrial preparation. A number of excellent strategies that offer a reasonably efficient route to oligosaccharide assembly have already emerged and

the armed–disarmed approach for chemoselective oligosaccharide synthesis is undoubtedly amongst them. Although recent advancements discussed herein have expanded the scope of the armed–disarmed methodology, it is clear that further development of efficient and general methods for the expeditious synthesis of complex carbohydrates will remain an important and active arena for scientific endeavors during the twenty-first century.

Other remarkable improvements in oligosaccharide synthesis have also emerged, including one-pot protection [89] and glycosylation strategies [50, 51, 90], polymer-supported [91–93] and automated synthesis [94, 95], fluorous tag assisted synthesis in microreactors [96], and surface-tethered iterative carbohydrate synthesis (STICS) [97]. The chemoselective strategy, however, is still occupying an important niche in the arsenal of available methods. In the coming years, glycoscientists are expected to have developed simple, efficient, and flexible approaches to oligosaccharide assembly that will complement existing methodologies and bring our ability to obtain complex oligosaccharides up to a significantly higher level.

Acknowledgements Dr. Laurel K. Mydock is thanked for critical reading of this chapter and providing valuable suggestions. The authors are indebted to the National Institute of General Medical Studies (Award # GM077170) for providing generous support for their research efforts in the area of expeditious oligosaccharide synthesis.

References

1. Varki A (1993) Biological roles of oligosaccharides: all of the theories are correct. Glycobiology 3(2):97–130
2. Demchenko AV (2008) Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance. Wiley-VCH, Weinheim
3. Fraser-Reid B, Jayaprakash KN, López JC, Gómez AM, Uriel C (2007) Protecting groups in carbohydrate chemistry profoundly influence all selectivities in glycosyl couplings. In: Demchenko AV (ed) Frontiers in modern carbohydrate chemistry, ACS symposium series, vol 960. Oxford University Press, Oxford, pp 91–117
4. Mydock LK, Demchenko AV (2010) Mechanism of chemical O-glycosylation: from early studies to recent discoveries. Org Biomol Chem 8:497–510
5. Whitfield DM (2009) Computational studies of the role of glycopyranosyl oxacarbenium ions in glycobiology and glycochemistry. Adv Carbohydr Chem Biochem 62:83–159
6. Demchenko AV (2003) Stereoselective chemical 1, 2-cis O-glycosylation: from "Sugar Ray" to modern techniques of the 21st century. Synlett (9):1225–1240
7. Demchenko AV (2003) 1, 2-cis O-Glycosylation: methods, strategies, principles. Curr Org Chem 7(1):35–79
8. Juaristi E, Cuevas G (1995) The anomeric effect. CRC Press, Boca Raton, pp 1–48, 95–112, 173–194, and references therein
9. Tvaroska I, Bleha T (1989) Anomeric and exo-anomeric effects in carbohydrate chemistry. Adv Carbohydr Chem Biochem 47:45–123
10. Goodman L (1967) Neighboring-group participation in sugars. Adv Carbohydr Chem Biochem 22:109–175
11. Fischer E (1893) Über die Glucoside der Alkohole. Ber Dtsch Chem Ges 26:2400–2412
12. Igarashi K (1977) The Koenigs-Knorr reaction. Adv Carbohydr Chem Biochem 34:243–283

13. Koenigs W, Knorr E (1901) Über einige Derivate des Traubenzuckers und der Galactose. Ber Deutsch Chem Ges 34:957–981
14. Ryan DA, Gin DY (2008) Glycoside synthesis from 1-oxygen substituted glycosyl donors: hemiacetals and O-acyl/carbonyl derivatives. In: Demchenko AV (ed) Handbook of chemical glycosylation. Wiley-VCH, Weinheim, pp 95–143
15. Kulkami SS, Gervay-Hague J (2008) Glycosyl chlorides, bromides and iodides. In: Handbook of chemical glycosylation. Wiley-VCH, Weinheim, pp 59–93
16. Shoda S-i (2008) Glycoside synthesis from anomeric halides: glycosyl fluorides. In: Handbook of chemical glycosylation. Wiley-VCH, Weinheim, pp 29–59
17. Zhong W, Boons G-J (2008) Glycoside synthesis from 1-sulfur/selenium-substituted derivatives: thioglycosides in oligosaccharide synthesis. In: Demchenko AV (ed) Handbook of chemical glycosylation. Wiley-VCH, Weinheim, pp 261–303
18. Kim K-S, Jeon H-B (2008) Anomeric transglycosylation. In: Demchenko AV (ed) Handbook of chemical glycosylation. Wiley-VCH, Weinheim, pp 185–223
19. Koto S, Uchida T, Zen S (1973) Syntheses of isomaltose, isomaltotetraose, and isomaltooctaose. Bull Chem Soc Jpn 46:2520–2523
20. Paulsen H (1982) Advances in selective chemical syntheses of complex oligosaccharides. Angew Chem Int Ed Engl 21(3):155–173
21. Ogawa T, Yamamoto H, Nukada T, Kitajima T, Sugimoto M (1984) Synthetic approach to glycan chains of a glycoprotein and proteoglycan. Pure Appl Chem 56:779–795
22. Nicolaou KC, Ueno H (1997) Oligosaccharide synthesis from glycosyl fluorides and sulfides. In: Hanessian S (ed) Preparative carbohydrate chemistry. Marcel Dekker, New York, pp 313–338
23. Nicolaou KC, Dolle RE, Papahatjis DP, Randall JL (1984) Practical synthesis of oligosaccharides. Partial synthesis of avermectin B1a. J Am Chem Soc 106:4189–4192
24. Nicolaou KC, Caulfield T, Kataoka H, Kumazawa T (1988) A practical and enantioselective synthesis of glycosphingolipids and related compounds. Total synthesis of globotriaosylceramide (Gb_3). J Am Chem Soc 110:7910–7912
25. Williams LJ, Garbaccio RM, Danishefsky SJ (2000) Iterative assembly of glycals and glycal derivatives: the synthesis of glycosylated natural products and complex oligosaccharides. In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, pp 61–92
26. Roy R, Andersson FO, Letellier M (1992) "Active" and "latent" thioglycosyl donors in oligosaccharide synthesis. Application to the synthesis of α-sialosides. Tetrahedron Lett 33(41):6053–6056
27. Boons GJ, Isles S (1994) Vinyl glycosides in oligosaccharide synthesis. Part 1: a new latent-active glycosylation strategy. Tetrahedron Lett 35:3593–3596
28. Allen JG, Fraser-Reid B (1999) n-Pentenyl glycosyl orthoesters as versatile intermediates in oligosaccharide synthesis. The proteoglycan linkage region. J Am Chem Soc 121:468–469
29. Kim KS, Kim JH, Lee YJ, Lee YJ, Park J (2001) 2-(Hydroxycarbonyl)benzyl glycosides: a novel type of glycosyl donors for highly efficient β-mannopyranosylation and oligosaccharide synthesis by latent-active glycosylation. J Am Chem Soc 123:8477–8481
30. Kanie O, Ito Y, Ogawa T (1994) Orthogonal glycosylation strategy in oligosaccharide synthesis. J Am Chem Soc 116:12073–12074
31. Fraser-Reid B, Wu Z, Udodong UE, Ottosson H (1990) Armed/disarmed effects in glycosyl donors: rationalization and sidetracking. J Org Chem 55:6068–6070
32. Lahmann M, Oscarson S (2000) One-pot oligosaccharide synthesis exploiting solvent reactivity effects. Org Lett 2(24):3881–3882
33. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B (1988) "Armed" and "disarmed" n-pentenyl glycosides in saccharide couplings leading to oligosaccharides. J Am Chem Soc 110:5583–5584
34. Veeneman GH, van Boom JH (1990) An efficient thioglycoside-mediated formation of α-glycosidic linkages promoted by iodonium dicollidine perchlorate. Tetrahedron Lett 31(2):275–278

35. Baeschlin DK, Chaperon AR, Charbonneau V, Green LG, Ley SV, Lucking U, Walther E (1998) Rapid assembly of oligosaccharides: total synthesis of a glycosylphosphatidylinositol anchor of Trypanosoma brucei. Angew Chem Int Ed Engl 37(24):3423–3428
36. Barrena MI, Echarri R, Castillon S (1996) Synthesis of disaccharides by selective metallocene promoted activation of glycosyl fluorides. Synlett 675–676
37. Hashimoto SI, Sakamoto H, Honda T, Abe H, Nakamura SI, Ikegami S (1997) "Armed-disarmed" glycosidation strategy based on glycosyl donors and acceptors carrying phosphoroamidate as a leaving group: a convergent synthesis of globotriaosylceramide. Tetrahedron Lett 38(52):8969–8972
38. Chiba H, Funasaka S, Kiyota K, Mukaiyama T (2002) Catalytic and chemoselective glycosylation between armed and disarmed glycosyl p-trifluoromethylbenzylthio-p-trifluoromethylphenyl formimidates. Chem Lett 746–747
39. Friesen RW, Danishefsky SJ (1989) On the controlled oxidative coupling of glycals: a new strategy for the rapid assembly of oligosaccharides. J Am Chem Soc 111:6656–6660
40. Kamat MN, Demchenko AV (2005) Revisiting the armed-disarmed concept rationale: chemoselective activation of the S-benzoxazolyl glycosides in oligosaccharide synthesis. Org Lett 7:3215–3218
41. Smoot JT, Pornsuriyasak P, Demchenko AV (2005) Development of an arming participating group for stereoselective glycosylation and chemoselective oligosaccharide synthesis. Angew Chem Int Ed Engl 44:7123–7126
42. Smoot JT, Demchenko AV (2009) Oligosaccharide synthesis: from conventional methods to modern expeditious strategies. Adv Carbohydr Chem Biochem 62:161–250
43. Clausen MH, Madsen R (2003) Synthesis of hexasaccharide fragments of pectin. Chem Eur J 9:3821–3832
44. Schmidt T, Madsen R (2007) Glycosylations directed by the armed-disarmed effect with acceptors containing a single ester group. Eur J Org Chem 2007:3935–3941
45. Crich D, Vinogradova O (2007) Synthesis and glycosylation of a series of 6-mono-, di-, and trifluoro S-phenyl 2, 3, 4-tri-O-benzylthiorhamnopyranosides. Effect of the fluorine substituents on glycosylation stereoselectivity. J Am Chem Soc 129:11756–11765
46. Douglas NL, Ley SV, Lucking U, Warriner SL (1998) Tuning glycoside reactivity: new tool for efficient oligosaccharides synthesis. J Chem Soc Perkin Trans 1:51–65
47. Zhang Z, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) Programmable one-pot oligosaccharide synthesis. J Am Chem Soc 121:734–753
48. Fraser-Reid B, Wu Z, Andrews CW, Skowronski E (1991) Torsional effects in glycoside reactivity: saccharide couplings mediated by acetal protecting groups. J Am Chem Soc 113:1434–1435
49. Ley SV, Baeschlin DK, Dixon DJ, Foster AC, Ince SJ, Priepke HWM, Reynolds DJ (2001) 1, 2-Diacetals: a new opportunity for organic synthesis. Chem Rev 101:53–80
50. Wang Y, Ye XS, Zhang LH (2007) Oligosaccharide assembly by one-pot multi-step strategy. Org Biomol Chem 5:2189–2200
51. Parameswar AR, Demchenko AV (2009) One-pot oligosaccharide synthesis. In: Nifantiev NE (ed) Progress in the synthesis of complex carbohydrate chains of plant and microbial polysaccharides. Transworld Research Network, Kerala, pp 463–488
52. Jensen HH, Nordstrom LU, Bols M (2004) The disarming effect of the 4, 6-acetal group on glycoside reactivity: torsional or electronic? J Am Chem Soc 126:9205–9213
53. Wilson BG, Fraser-Reid B (1995) n-Pentenyl glycoside based methodology for determining the relative reactivities of variously protected pairs of glycosides. J Org Chem 60:317–320
54. Fridman M, Solomon D, Yogev S, Baasov T (2002) One-pot synthesis of glucosamine oligosaccharides. Org Lett 4(2):281–283
55. Green LG, Ley SV (2000) Protecting groups: effects on reactivity, glycosylation specificity and coupling efficiency. In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, pp 427–448

56. Hansson J, Garegg PJ, Oscarson S (2001) Syntheses of anomerically phosphodiester-linked oligomers of the repeating units of the *Haemophilus influenzae* types C and F capsular polysaccharides. J Org Chem 66:6234–6243
57. Ritter TK, Mong K-KT, Liu H, Nakatani T, Wong C-H (2003) A programmable one-pot oligosaccharide synthesis for diversifying the sugar domains of natural products: a case study of vancomycin. Angew Chem Int Ed Engl 42(38):4657–4660
58. Yamada T, Kinjyo S, Yoshida J, Yamago S (2005) Chem Lett 34:1556–1557
59. Bongat AFG, Kamat MN, Demchenko AV (2007) S-Benzoxazolyl (SBox) approach to the synthesis of glycosides of 2-deoxy-2-aminosugars. J Org Chem 72:1480–1483
60. Kamkhachorn T, Parameswar AR, Demchenko AV (2010) Comparison of the armed/disarmed building blocks of the D-gluco and D-glucosamino series in the context of chemoselective oligosaccharide synthesis. Org Lett 12:3078–3081
61. Boons GJ, Grice P, Leslie R, Ley SV, Yeung LL (1993) Dispiroketals in synthesis (part 5): a new opportunity for oligosaccharide synthesis using differentially activated glycosyl donors and acceptors. Tetrahedron Lett 34(52):8523–8526
62. Zhu T, Boons GJ (2001) Thioglycosides protected as trans-2, 3-cyclic carbonates in chemoselective glycosylations. Org Lett 3(26):4201–4203
63. Jensen HH, Lyngbye L, Bols M (2001) A free-energy relationship between the rate of acidic hydrolysis of glycosides and the pK_a of isofagomines. Angew Chem Int Ed Engl 113(18): 3555–3557
64. Lemieux RU (1954) Some implications in carbohydrate chemistry of theories relating to the mechanisms of replacement reactions. Adv Carbohydr Chem Biochem 9:1–57, and references therein
65. Lemieux RU (1971) Effects of unshared pairs of electrons and their solvation on conformational equilibria. Pure Appl Chem 25:527–548, and references therein
66. Lemieux RU, Hendriks KB, Stick RV, James K (1975) Halide ion catalyzed glycosylation reactions. Syntheses of α-linked disaccharides. J Am Chem Soc 97(14):4056–4062, and references therein
67. Crich D, Li M (2007) Revisiting the armed-disarmed concept: the importance of anomeric configuration in the activation of S-benzoxazolyl glycosides. Org Lett 9:4115–4118
68. Jensen HH, Bols M (2006) Stereoelectronic substituent effects. Acc Chem Res 39:259–265
69. Edward JT (1955) Stability of glycosides to acid hydrolysis. Chem Ind 36:1102–1104
70. McDonnell C, Lopez O, Murphy P, Bolanos JGF, Hazell R, Bols M (2004) Conformational effects of glycoside reactivity: study of the high reactive conformer of glucose. J Am Chem Soc 126:12374–12385
71. Hosoya T, Ohashi Y, Matsumoto T, Suzuki K (1996) On the stereochemistry of aryl C-glycosides: unusual behavior of bis-TBDMS protected aryl C-olivosides. Tetrahedron Lett 37:663–666
72. Kozlowski JS, Marzabadi CH, Rath NP, Spilling CD (1997) Carbohydr Res 300:301–313
73. Pedersen CM, Nordstrom LU, Bols M (2007) "Super armed" glycosyl donors: conformational arming of thioglycosides by silylation. J Am Chem Soc 129:9222–9235
74. Jensen HH, Pedersen CM, Bols M (2007) Going to extremes: "super" armed glycosyl donors in glycosylation chemistry. Chem Eur J 13:7576–7582
75. Okada Y, Nagata O, Taira M, Yamada H (2007) Highly β-stereoselective and direct formation of 2-O-glycosylated glucosides by ring restriction into twist-boat. Org Lett 9:2755–2758
76. Abe H, Shuto S, Matsuda A (2001) Highly α- and β-selective radical C-glycosylation reactions using a controlling anomeric effect based on the conformational restricrion strategy. A study on the conformation – anomeric effect – stereoselectivity relationship in anomeric radical reactions. J Am Chem Soc 123:11870–11882
77. Pedersen CM, Marinescu LG, Bols M (2008) Conformationally armed glycosyl donors: reactivity quantification, new donors and one pot reactions. Chem Commun 2465–2467
78. Mydock LK, Demchenko AV (2008) Application of the superarmed glycosyl donor to chemoselective oligosaccharide synthesis. Org Lett 10:2107–2110

79. Mydock LK, Demchenko AV (2008) Superarming the S-benzoxazolyl glycosyl donors by simple 2-O-benzoyl-3, 4, 6-tri-O-benzyl protection. Org Lett 10:2103–2106
80. Premathilake HD, Mydock LK, Demchenko AV (2010) Superarming common glycosyl donors by simple 2-O-benzoyl-3, 4, 6-tri-O-benzyl protection. J Org Chem 75:1095–1100
81. Smoot JT, Demchenko AV (2008) How the arming participating moieties can broaden the scope of chemoselective oligosaccharide synthesis by allowing the inverse armed-disarmed approach. J Org Chem 73:8838–8850
82. Geng X, Dudkin VY, Mandal M, Danishefsky SJ (2004) Angew Chem Int Ed Engl 43: 2562–2565
83. Hederos M, Konradsson P (2005) Synthesis of the core tetrasaccharide of Trypanosoma cruzi glycoinositolphospholipids: Manp(α1–>6)-Manp(α1–> 4)-6-(2-aminoethylphosphonic acid)-GlcNp(α1–>6)-myo-Ins-1-PO4. J Org Chem 70(18):7196–7207
84. Hashihayata T, Ikegai K, Takeuchi K, Jona H, Mukaiyama T (2003) Bull Chem Soc Jpn 76:1829–1848
85. Ravidà A, Liu X, Kovacs L, Seeberger PH (2006) Synthesis of glycosyl phosphates from 1, 2-orthoesters and application to in situ glycosylation reactions. Org Lett 8:1815–1818
86. Ziegler T, Lemanski G, Hurttlen J (2001) Prearranged glycosides. Part 14: intramolecular glycosylation of non-symmetrically tethered glycosides. Tetrahedron Lett 42:569–572
87. Drouin L, Compton RG, Fietkau N, Fairbanks AJ (2007) Protecting groups and solvent effects in electrochemical glycosylation. Synlett 2711–2717
88. Drouin L, Compton RG, Fairbanks AJ (2008) Electrochemical glycosylation in the presence of a catalytic chemical mediator. J Phys Org Chem 21:516–522
89. Wang CC, Lee JC, Luo SY, Kulkarni SS, Huang YW, Lee CC, Chang KL, Hung SC (2007) Regioselective one-pot protection of carbohydrates. Nature 446:896–899
90. Huang X, Huang L, Wang H, Ye XS (2004) Iterative one-pot synthesis of oligosaccharides. Angew Chem Int Ed Engl 43:5221–5224
91. Osborn HMI, Khan TH (1999) Recent developments in polymer supported syntheses of oligosaccharides and glycopeptides. Tetrahedron 55(7):1807–1850
92. Krepinsky JJ, Douglas SP (2000) Polymer-supported synthesis of oligosaccharides. In: Ernst B, Hart GW, Sinay P (eds) Carbohydrates in chemistry and biology, vol 1. Wiley-VCH, Weinheim, pp 239–265
93. Seeberger PH, Haase WC (2000) Solid-phase oligosaccharide synthesis and combinatorial carbohydrate libraries. Chem Rev 100(12):4349–4393
94. Plante OJ, Palmacci ER, Seeberger PH (2001) Automated solid-phase synthesis of oligosaccharides. Science 291(5508):1523–1527
95. Seeberger PH (2003) Automated carbohydrate synthesis to drive chemical glycomics. Chem Commun 1115–1121
96. Carrel FR, Geyer K, Codée JDC, Seeberger PH (2007) Oligosaccharide synthesis in microreactors. Org Lett 9:2285–2288
97. Pornsuriyasak P, Ranade SC, Li A, Parlato MC, Sims CR, Shulga OV, Stine KJ, Demchenko AV (2009) STICS: surface-tethered iterative carbohydrate synthesis. Chem Commun 1834–1836

Top Curr Chem (2011) 301: 223–252
DOI: 10.1007/128_2010_109

Published online: 3 February 2011

Programmable One-Pot Glycosylation

Chung-Yi Wu and Chi-Huey Wong

Abstract In oligosaccharide synthesis, protecting groups, possible participating groups, promoters/catalysts, reaction conditions, and donor leaving groups and acceptors must all be carefully designed in order to generate the correct regio- and stereochemistry for the new glycosidic bond. Programmable one-pot synthesis has been developed to address the above problems. This strategy is based on the sequential use of thioglycoside building blocks to form glycosidic bonds based on the reactivity difference of the building blocks. The activation of the anomeric leaving group can be attenuated through modification of the protecting group strategy and neighboring group participation. This reactivity-based strategy has been applied to one-pot glycosylation reactions where a series of building blocks with identical leaving groups react sequentially in one vessel without laborious intermediate purification steps. It provides rapid access to oligosaccharides with a wide-range of molecular diversity. In this chapter we outline the recent development of this strategy that can be applied to synthesize a wide variety of oligosaccharides and glycoconjugates that are associated with infectious diseases or carbohydrate-based cancer antigens.

Keywords Carbohydrates · Oligosaccharides · One-pot · OptiMer · Relative reactivity values · Thioglycosides

Contents

C.-Y. Wu (✉) and C.-H. Wong (✉)
Genomics Research Center, Academia Sinica, 128 Academia Road, Section 2, Nankang, Taipei 115, Taiwan
e-mail: cyiwu@gate.sinica.edu.tw, chwong@gate.sinica.edu.tw

Abbreviations

°C	Degrees Celsius
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Bn	Benzyl
BOM	Benzyloxymethyl
BSA	Bovine serum albumin
BSP	1-(Benzensulfinyl)piperidine
Bz	Benzoyl
Cbz	Bezyloxycarbonyl
ClBn	*ortho*-Chlorobenzyl
CSA	Camphorsulfonic acid
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
EA	Ethyl acetate
Et	Ethyl
g	Gram
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HSTol	*p*-Toluenethiol
Lev	Levulinate
mAb	Monoclonal antibodies
Man	Mannose
Me	Methyl
MeOH	Methanol
MS	Molecular sieve
N_3	Azide
NaOMe	Sodium methoxide
NBz	*p*-Nitrobenzoyl
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
Phth	Phthalimido
Py	Pyridine
RRVs	Relative reactivity values
rt (RT)	Room temperature
SSEA-4	Stage-specific embryonic antigen-4
TBAI	Tetrabutylammonium iodide
TBS (TBDMS)	*tert*-Butyldimethyl silyl
TEA	Triethylamine
TES	Triethylsilane

Tf	Trifluoromethanesulfonyl (triflic)
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
Troc	2,2,2-Trichloroethoxyl carbonyl

1 Introduction

Beyond the traditionally accepted roles of carbohydrates as energy sources and structural polymers, it is now well established that glycoconjugates play important structural and functional roles in numerous physiological processes, such as various disease states [1–4]. The recognition of carbohydrates as a medicinally relevant class of biomolecules further prompted development of therapeutic agents based on either glycan structure or mimics thereof [3]. For example, cancer cell metastasis [5] and cell–cell adhesion in the inflammatory response [6] depend on cell surface presentation of specific glycans. Therefore, synthetic carbohydrate-based cancer vaccines [7–11], sialidase inhibitors for influenza virus treatment [12–14], and small molecules selectin inhibitors [15] have been studied for drugs or potential medicinal agents. Moreover, the initial stages of bacterial or viral infection often rely on the recognition of host cell glycoconjugates by the invading organism [16]. Thus, both naturally occurring and designed synthetic antibiotics frequently contain carbohydrate structures to disrupt the deleterious interactions [17]. The biological activities involved in these processes are typically linked not to monosaccharide units but to oligosaccharide structures of glycoconjugates. However, it is very difficult to obtain adequate, pure oligosaccharides from natural sources for studies. Consequently, the synthesis of oligosaccharides becomes an essential tool in studying the biochemistry and biology of vital processes.

Nucleic acids can be synthesized via chemical and biological methods with the aid of the polymerase chain reaction and protein sequences, which are encoded by DNA and therefore can be easily determined, produced, and manipulated through recombinant DNA technology. In addition, automatic synthesizers are available to synthesize these linear polymers (polynucleotides and polypeptides) using a single protecting group strategy in the iterative process. Saccharides, however, are often branched and made with diverse set of enzymes; therefore, there is no information carrier that encodes a particular saccharide sequence [18]. Traditional synthesis of saccharides requires multiple protection and deprotection steps and stereocontrol in each glycosylation reaction [19]. Although advancements in automatic saccharide synthesis have been reported [19–22], the efficiency does not compare to the synthesis of nucleic acids and polypeptides. Scientists still could not create libraries of saccharides with methods similar to protein mutagenesis.

The lack of convenient, synthetic tools for research in glycobiology has slowed down its development, and the discovery of carbohydrates functions has thus been relatively slow when compared with proteins. In addition, synthesis of complex

glycoconjugates, especially glycoproteins, could not employ the conventional approaches, considering the practicality of large-scale synthesis and the enormous molecular diversity that can be assembled from the nine common monosaccharides found in humans [23, 24]. A new synthesis strategy based on the fusion of chemical and enzymatic methods in a programmable one-pot approach has thus been developed to tackle this major problem [25].

2 Strategy for Programmable One-Pot Oligosaccharide Synthesis

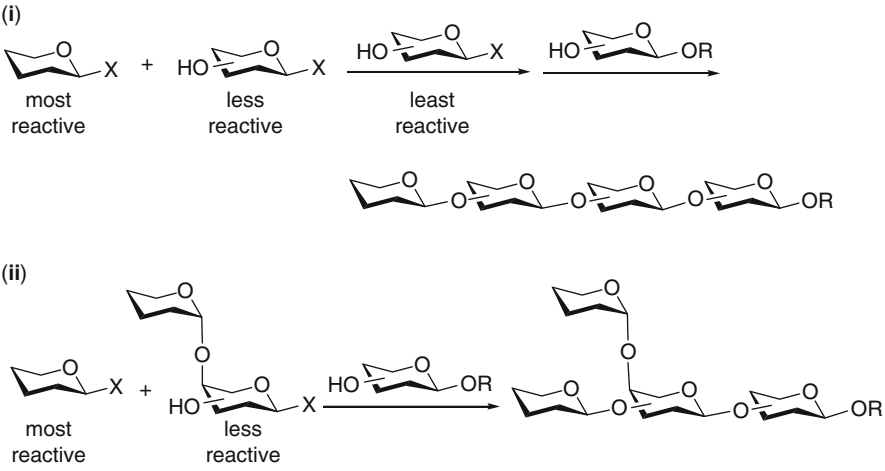
Our original strategy for one-pot methods utilized common anomeric leaving groups and a common activator. We chose *p*-methylphenyl thioglycosides (STol) as our donor species not only because of their easy preparation and stability toward carbohydrate manipulation, such as standard protection/deprotection reactions, but also for three reasons:

1. Thioglycosides can be activated by numerous strategies [26–29]
2. The thiotoluoyl group offers a convenient spectroscopic handle
3. The reagents have significant shelf lives

Our goals for assembling carbohydrate libraries included (1) methods that did not rely on protecting group manipulations during synthesis, (2) the preparation of a significant pool of reagents, and (3) building blocks that afforded simple, branched carbohydrates with both α and β linkages. To accomplish this strategy under competitive reaction (one-pot) condition, we take advantage of the reaction in which the reactivity of donors decreases over the course of the reaction; that is, we began at the nonreducing end and performed glycosylations up to the reducing end, and this strategy is shown schematically as applied to the synthesis of linear and simple branched targets (Scheme 1).

For this strategy to be successful, relative reactivities of a variety of donors are needed. Previously, most one-pot syntheses had been carried out with the general knowledge of the reactivity difference between ether and ester protecting groups; however, no reactivity number was involved in synthesis designs. We envisioned that a greater diversity of targets could be prepared if reactivity values were collected and used. Thus, we calculated and compared relative reactivity values (RRVs) of the most reactive donors (high values) and the least reactive donor (1.0).

Relative reactivities describe the ratio of products between two glycosyl donors for an acceptor. Professor Ley first constructed such relationships for fully protected mannoside and rhamnoside donors to rationalize the results of his one-pot syntheses employing cyclic diketals [30]. Ley showed that these relationships need not be measured for every potential combination of donors but rather the multiplicative relationship between these donors held with only small discrepancies. Throughout his work, Ley reports deactivation factors, which described the



Scheme 1 Synthesis of (**i**) linear and (**ii**) branched oligosaccharides

decreased reactivity of a donor in comparison with the perbenzylated species. As such, larger numbers imply lesser reactivity. Alternatively, we normalize reactivities to the least reactive donor; hence, larger numbers in our series represent greater reactivity. In any case, these reactivity differences are determined by competition experiments. Ley's group [30] used NMR to determine RRVs. Subsequently, our group took an alternative and convenient route to quantitatively determining glycosyl donor reactivity by a competitive HPLC experiment based on some modifications of method that was first reported by Fraser-Reid's group [25, 31].

RRVs were obtained by monitoring the disappearance of donor with respect to a standard. We obtained these rates by HPLC identification of the starting materials and did not rely on identification of the product. Each donor was added to an excess of acceptor, methanol (5.0 eq.), in dichloromethane. We used methanol as an acceptor to eliminate the steric effect on the glycosylation reaction. Activation was accomplished by adding a solution of NIS in acetonitrile (1.0 eq.) followed by TfOH (0.1 eq.). After 2 h, the reaction was worked up with saturated sodium thiosulfate and sodium bicarbonate; then, organic phases were evaporated to dryness. The resulting residue was suspended and subjected to HPLC analysis. To accommodate the wide range in relative reactivities, four reference molecules were selected [25]. From the competition experiments, the reactivity coefficients were tabulated in a database (currently containing around 600 monomers).

The quantification of reactivity for these donors revealed several interesting trends [25]:

1. *Pyranosides show reactivities that differ as a function of sugar.* Among commonly protected pyranosides (i.e., perbenzylated), reactivity decreases in the order fucose > galactose > mannose > glucose > sialic acid. These differences in reactivity are not significant. Fucose is approximately four times

more active than galactose, which is approximately six times more active than glucose. These observations are consistent with the rates of hydrolysis of their corresponding glycosyl halides and glycosides [32, 33].

2. *The reactivity of aminosugars can be tuned by choice of the N-protecting group.* We investigated the ability of different N-protecting groups on glucosamine and galactosamine in order to generate donors for early (reactive) or later (less reactive) stages of a synthetic protocol. As expected, we found that the nature of the protecting group influences the reaction. The reactivity decreases in the order NHCbz > NHTroc > NHPhth > N_3 > NHAc. Aminosugars bearing phthalimide groups showed very little reactivity (1.0–3.5) in comparison with those bearing the Troc (trichloroethoxycarbonyl) group (28.6). Given the large effect of the C2 group on the overall reactivity of a donor, the range of reactivities (1–28.6) is small and may determine where these molecules should be incorporated into targets. This strategy cannot be applied to all targets until more is known about the effects on reactivities through alternate C2 groups or other hydroxyl protecting groups.
3. *A general trend in protecting group effects.* For galactose, we found that the C2 substituent plays a significant role in deactivating the pyranose. Reactivity is most reduced by OClAc > OBz > OAc > NHTroc > OBn >> OH > OSilyl > H. This phenomenon largely came from electronic effects. One elegant review by Fraser-Reid et al. described protecting group effects in more detail [34]. The commonly accepted belief is that benzylated derivatives are always significantly more reactive than their benzoylated counterparts. In addition, the overall glycosyl donor reactivity is presumed to be in direct correlation with the total number of benzyl substituents [32]. However, this phenomenon was challenged by Demchenko et al. recently [35–38]. They found that, when *S*-benzoxazolyl glycosides were used as donors, C2 benzoyl group increased the reactivity and benzyl group reduced the reactivity (Fig. 1).
4. *The position that affects pyranoside reactivity most is not always the same for all sugars.* While Ley reported that the C2 position had the greatest effect on reactivity for mannose (followed by C6 > C4 > C3), we found that the order is C4 > C3 > C2 > C6 for galactose.
5. *The magnitude of any effect is influenced by its position on the pyranoside.* While the substituents affect the reactivity in a predictable manner, the magnitude of this effect depends on the position of the group in most cases (similarly observed by Ley). This trend is most easily observed in the tribenzylated thiogalactoside bearing one free hydroxyl group. Reactivity increases, as the hydroxyl group is available at the C6 (2.3) < C2 (3.1) < C3 (5.1) < C4 (11.8)

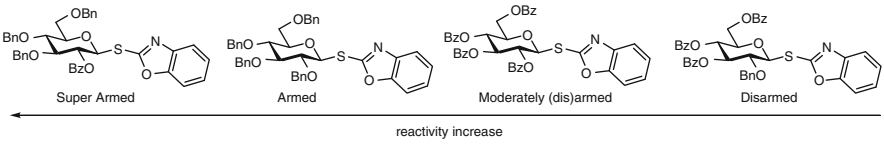


Fig. 1 C2 benzoyl group increases reactivity

positions. It seems likely that steric factors as well as electronic factors are playing a role.

6. *Conformational effects (torsional effects)*. More O-substituents on the axial position will increase the reactivity of thioglycoside donors. Recently, the groups of Bols [39–41] and Yamada [42, 43] independently used bulky silyl protecting groups to adopt a twisted boat conformation to arm glycosyl donors by forcing the oxygen substituents into an axial position (Fig. 2). Bols et al. also calculated the reactivity of these "superarmed" donors and incorporated them into reactivity based one-pot glycosylation to synthesize a trisaccharide in 64% yield (Scheme 2).
7. *Influence of leaving group*:
   (a) Steric effects: altering the size of the anomeric group can tune the reactivity of the glycosyl donor. Boons et al. were the first to describe the influence of steric effects of thioglycosides on glycosyl reactivity [44, 45] and found that more bulky groups reduce the reactivity.

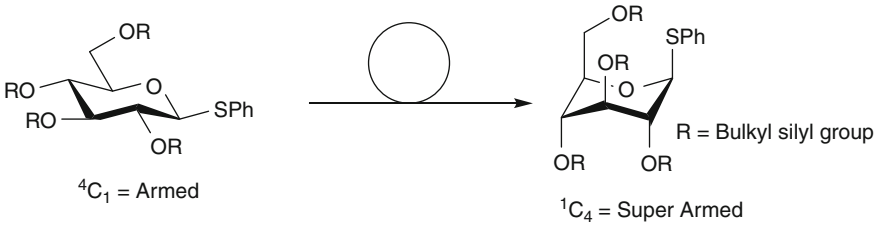
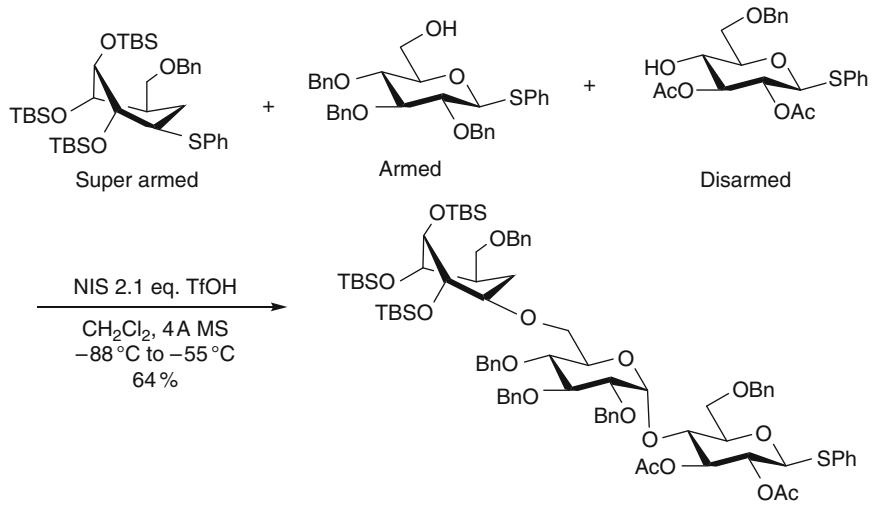
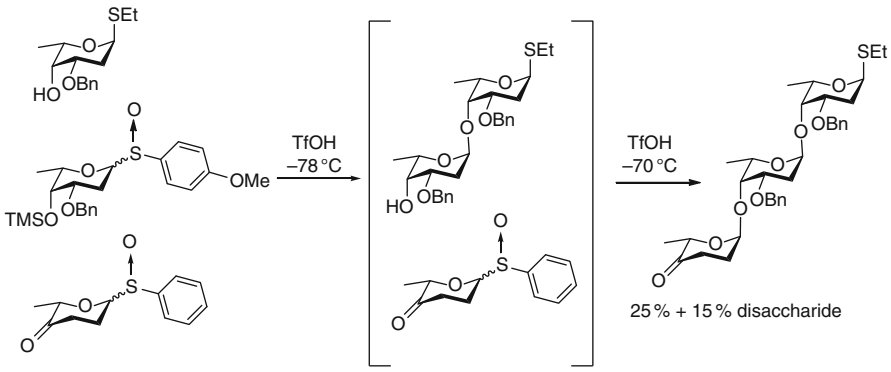


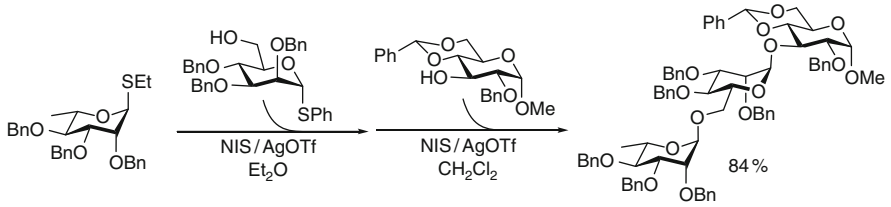
Fig. 2 More O-substituents on the axial position increase the reactivity of thioglycoside donors



Scheme 2 To incorporate "superarmed" donor into reactivity based one-pot glycosylation



Scheme 3 One-pot glycosylation of ciclamycine 0 trisaccharide



Scheme 4 Solvent effect on the one-pot glycosylation

(b) Electronic effects: the reactivity of the glycosyl donor can be influenced by the nature of the *para* position substituent of the phenyl ring with reactivity order OMe > H > NO_2. The reactivity difference between OMe and H is sufficient for one-pot glycosylation to synthesize ciclamycine 0 trisaccharide (Scheme 3) [46].

More recently, Huang et al. have systematically investigated the reactivity of the thio-arylglycosides with various aglycon *para*-substituents. The reactivity trend for thioglycoside is OMe > NHAc > N_3 > Br > NO_2 [47].

8. *Solvent effect*. The Oscarson group found that the reactivity of donor can be tuned by different solvent systems. By using different solvents, they performed the first glycosylation in Et_2O (low glycosylation rate) and the second in CH_2Cl_2/Et_2O (higher glycosylation rate). Thus, a trisaccharide can be synthesized in high yield (Scheme 4) [48].

3 OptiMer

With the reactivities of many donors and donor-acceptors (e.g., the building blocks with one hydroxyl group unprotected) available, one can use the database to conduct one-pot synthesis of a desired oligosaccharide. From our experience, to

achieve a convenient high-yield coupling and minimize byproduct formation without changing the reaction conditions, the leaving group should be the same and the reactivity difference for each coupling should be larger than 100. In order to optimize the reaction to create a greater diversity, a computer program is essential to select the appropriate building blocks for the one-pot synthesis. Our first version of the computerized database and search engine, OptiMer, was created using FileMaker Pro 4.0 (Filemaker Inc.). The database contains the name of the residue, the position of unprotected hydroxyl groups, and the information on whether the C2 substituent directs the glycosylation to α or β positions. The database also stores the reference for preparation and a picture of the compound. Once a user has selected an oligosaccharide structure, the program lists the best combination of building blocks for its preparation (Fig. 3).

With the OptiMer database, oligosaccharides containing three to six monosaccharides are rapidly assembled in minutes or hours by sequential addition of thioglycoside building blocks with the most reactive one being added first. No intermediate workup or purification procedures are required. OptiMer has been successfully applied to assemble designed linear and branched oligosaccharide structures as well as construction of a 33-membered oligosaccharide library [25, 49].

The programmable one-pot synthesis of oligosaccharides has the potential to affect many areas of drug discovery, as it provides scientists of all fields with access to complex carbohydrate structures without the need to consult a carbohydrate chemist. For example, carbohydrate-associated cancer antigens Lewis^y that are expressed on surfaces in colon-rectal adenocarcinoma and heptacellular carcinomas, can be prepared through the one-pot coupling of two fucosyl and two lactosaminyl building blocks [50]. For the OptiMer analysis of Lewis^y hapten, the sequence of this saccharide was first entered into the computer system installed with the OptiMer program. Three building blocks – **1** (RRV = 7.2×10^4), **2** (RRV = 1.2×10^4), and **3** (RRV = 0) – with appropriate reactivity profiles were suggested for use in a one-pot synthesis. This one-pot synthetic operation was performed in the presence of the NIS/TfOH promoter system (Scheme 5). The first glycosylation

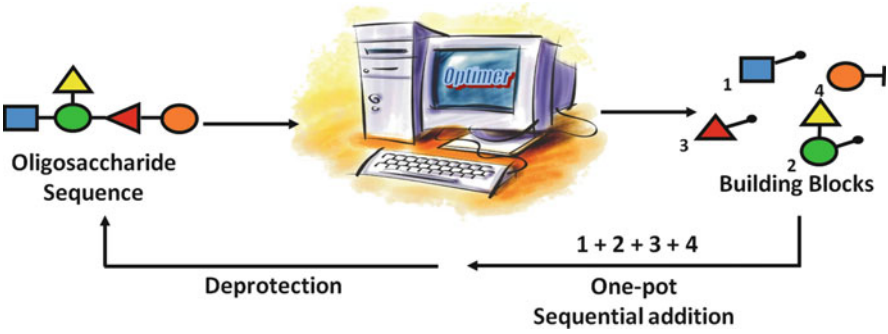
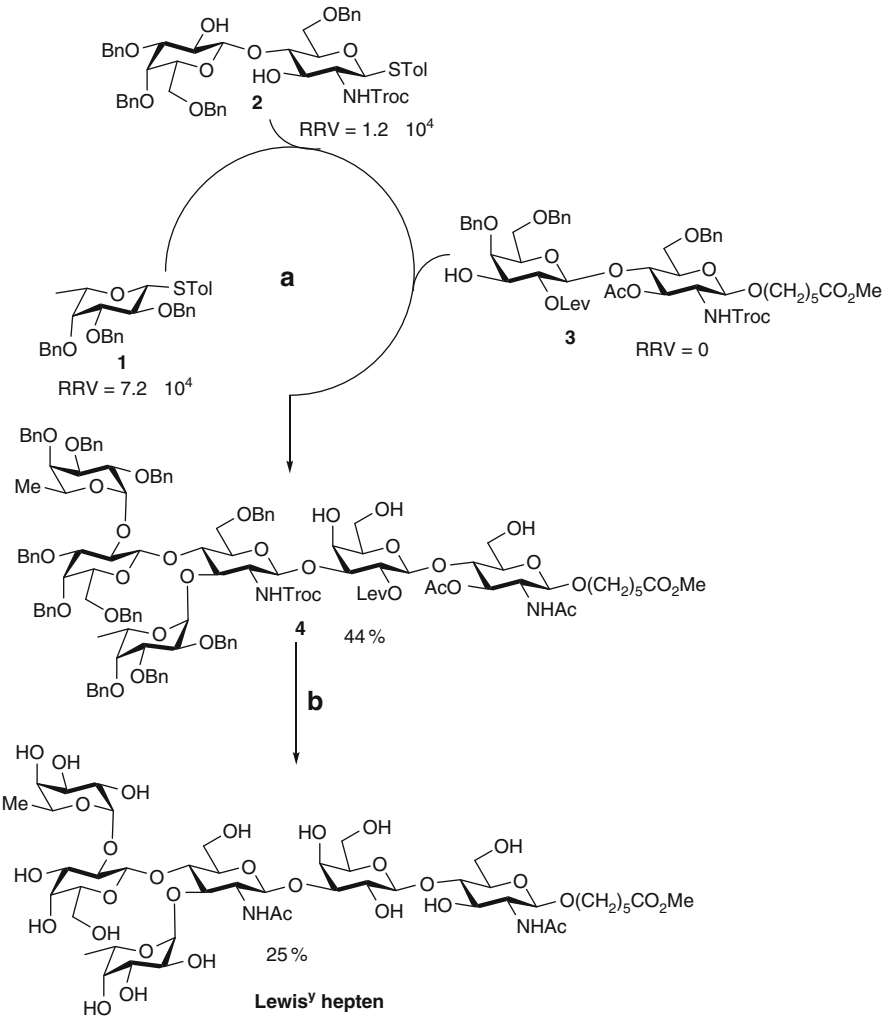


Fig. 3 Programmable one-pot glycosylation strategy



Scheme 5 One-pot synthesis of the Lewis^y hapten **4** and its deprotected compound. (a) (i) NIS, cat. TfOH, MS (AW300), −70°C; (ii) **3**, NIS, cat. TfOH, −25°C, 44%; (b) (i) Zn dust, Ac_2O; (ii) NaOMe, MeOH/CH_2Cl_2; (iii) Pd-black, H_2, MeOH/AcOH, 25% for three steps. *NHAc* N-acetamido

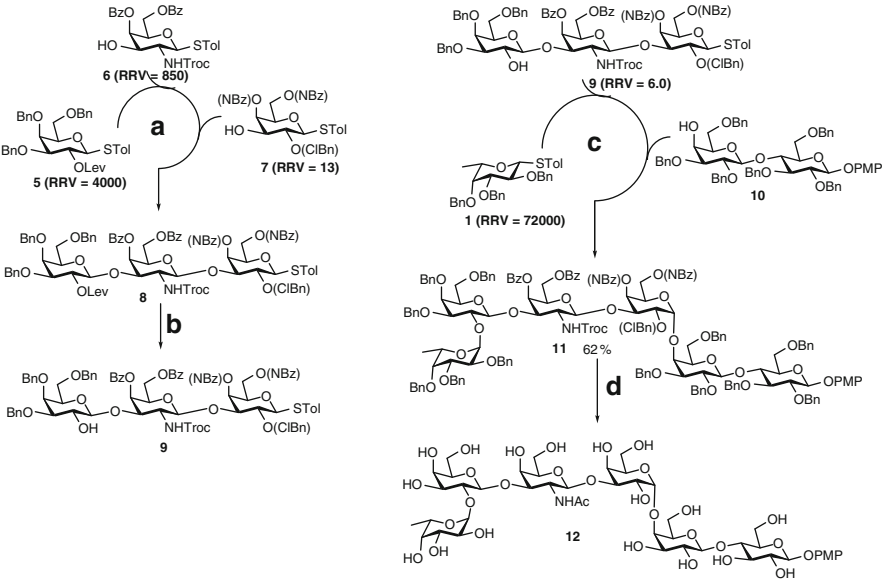
between the fucosyl donor **1** and the functional bridging lactosaminyl unit **2** was performed at −70°C, whereas the second glycosylation required a higher temperature (−25°C). The lower temperature for the first glycosylation suppressed the formation of undesired succinimide by-product. In addition, low temperature favors the formation of the α glycosidic linkage [51]. The second glycosylation involves the coupling of two large sugar fragments for which a higher temperature was necessary for a practical reaction. The yield of fully protected determinant **4** was 44%, which was equivalent to 81% per glycosylation. Global deprotection of **4** was performed in three steps: (1) zinc dust in acetic anhydride removed the two trichloroethyl carbamate

protecting functions (Troc) on **4** and reacetylated the free amino groups simultaneously, (2) the remaining levulinoate and acetyl protecting functions were cleaved by Zemplen deacylation, and (3) the final debenzylation was accomplished by a palladium-black catalyzed hydrogenolysis. The targeted Lewis^y hapten was obtained in 25% yield from **4** (Scheme 5).

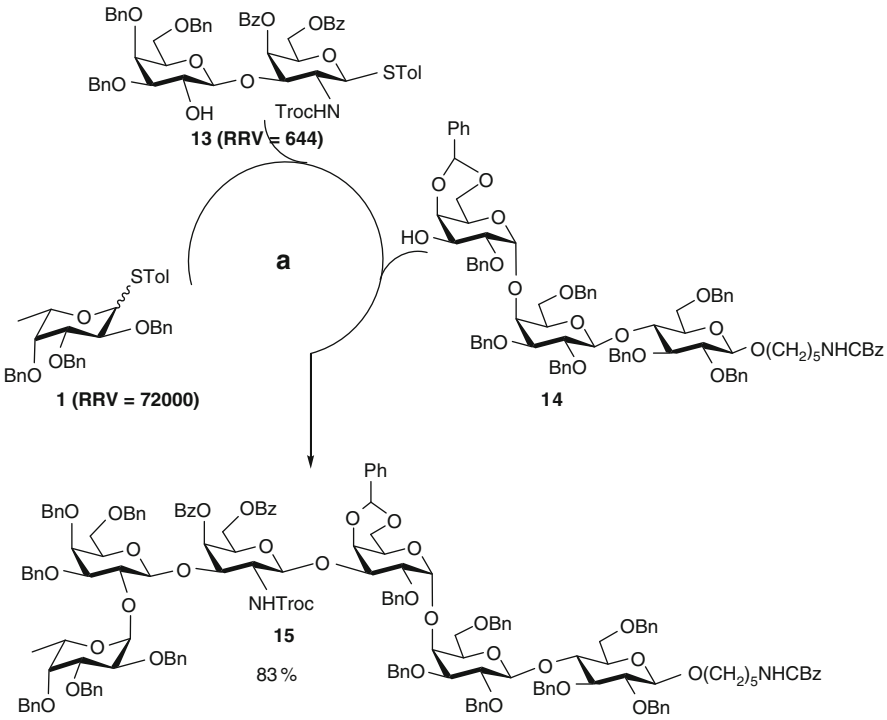
By using the same strategy, the hexasaccharide of Globo H, a glycosyl ceramide found on a variety of epithelial tumors such as colon, ovarian, gastric, pancreatic, endometrial, lung, prostate, and breast cancers, but not on the immune-accessible normal tissues [52–55], can be readily assembled by two one-pot glycosylation reactions. The first one-pot reaction will create the inter-trisaccharide **9,** which is then used to form the protected Globo H saccharide in a second (1+3+2) one-pot reaction (Scheme 6) [56].

Recently, the programmable one-pot synthesis of Globo H has been further refined to a [1+2+3] approach, which overcomes the most difficult Galα1→4Gal linkage and improves the yield to 83% compared to previous 62% in the [1+3+2] approach (Scheme 7) [57].

More recently, Globo H and its fragments were synthesized and used to create a Globo H based glycan array for use in measuring the level of antibodies against a tumor-associated glycan antigen, Globo H, and related structures [57–59]. These results have shown that two mAbs (MBr1 and VK-9) bound to the terminal



Scheme 6 One-pot synthesis of Globo H by [1+3+2] strategy. (a) (i) NIS, cat. TfOH, MS (AW300), −20°C; (ii) **7**, NIS, cat. TfOH, −20°C, 67%; (b) H_2NNH_2, HOAc, THF, 0°C; (c) NIS, cat. TfOH, −40°C→RT, 62%; (d) (i) Zn, AcOH; (ii) Ac2O-pyridine; (iii) NaOMe-MeOH; (iv) H2-Pd/C, 45%. *Bn* benzyl, *Bz* benzoyl, *ClBn ortho*-chlorobenzyl, *Lev* levulinate, *NBz para*-nitrobenzoyl, *NHTroc* 2,2,2-trichloroethylcarbamate, *NIS N*-iodosuccinamide, *PMP para*-methoxyphenyl, *Tf* triflate = trifluoromethanesulfonyl, *Tol* tolyl = *para*-methylphenyl



Scheme 7 One-pot synthesis of Globo H by [1+2+3] strategy. (a) (i) NIS, TfOH, −40°C; (ii) NIS, TfOH, −30°C, 83% from **1**

tetra-saccharide to the same degree as the full Globo H hexasaccharide and the fucose residue is essential for mAb recognition. Therefore, the implication is that a smaller oligosaccharide analog may have the same immunogenic properties as the Globo H hexasaccharide. Moreover, when compared with the normal individuals, breast cancer patients had higher levels of anti-Globo-H antibodies in their blood, suggesting a new application in diagnosis of Globo-H antigen [58]. A glycan-based vaccine composed of Globo H hexasaccharide linked to a KLH protein carrier is currently in clinical trials for the treatment of metastatic breast cancer. For detection of Globo H antibody, this glycan array has been shown to be $10^5 \sim 10^6$ times more sensitive than the traditional ELISA method [58]. It is a powerful tool to monitor the immune response after the patient is vaccinated by Globo H vaccine (Fig. 4).

4 Promoter Effect

One-pot glycosylation used NIS as a promoter. However, the glycosylation yield can often be reduced by the formation of undesired succinimide by-product. Although formation of such by-products can be suppressed at lower reaction

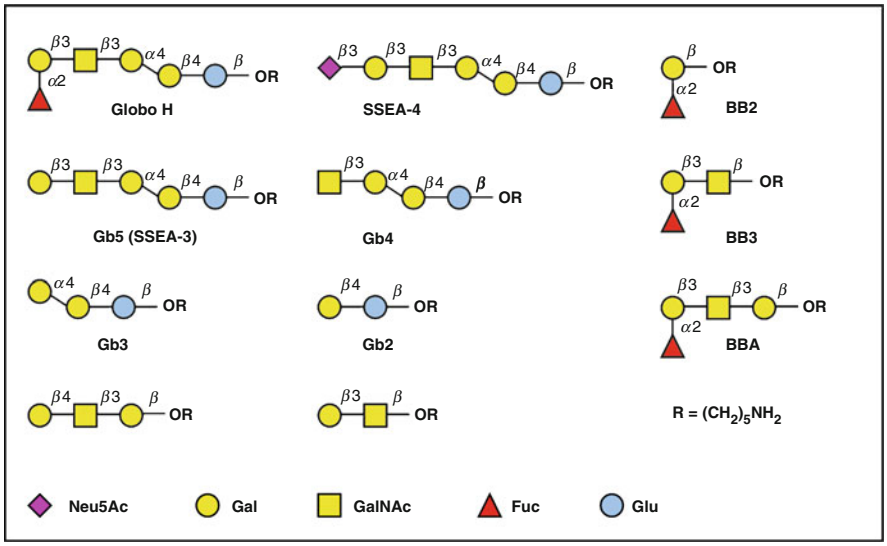
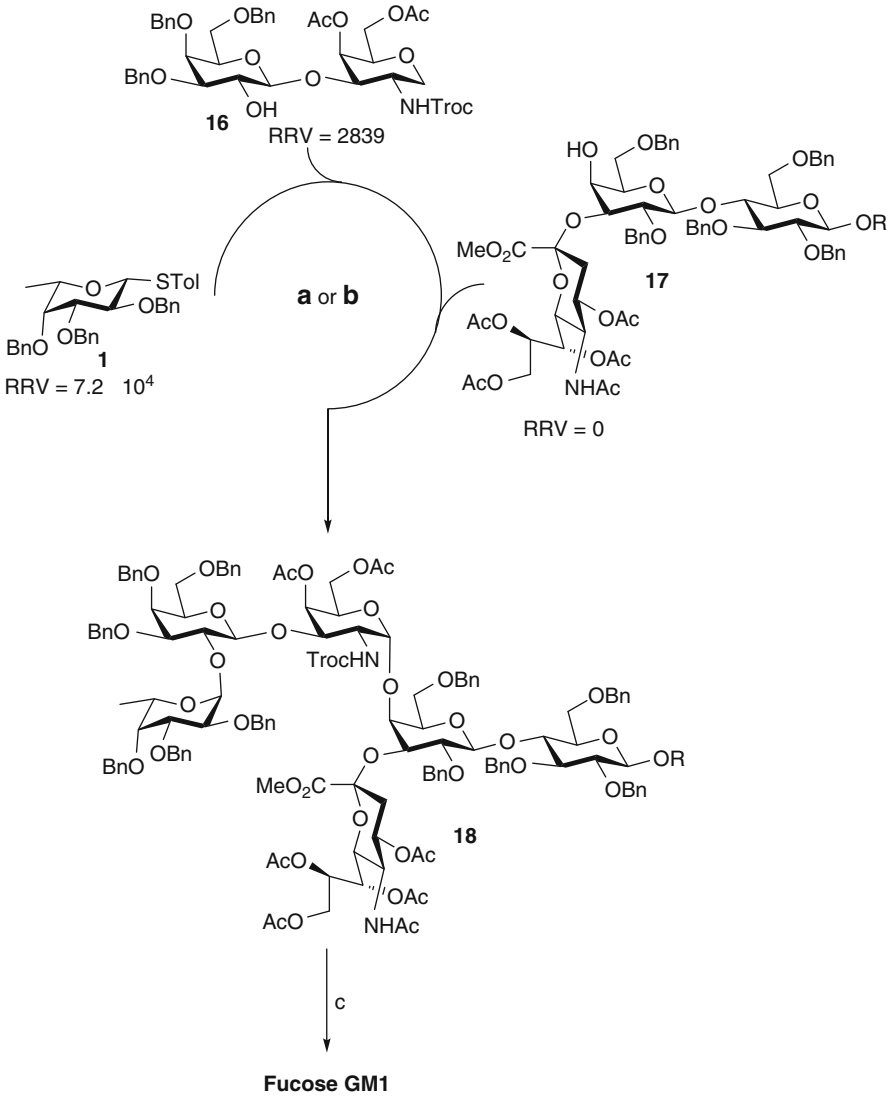


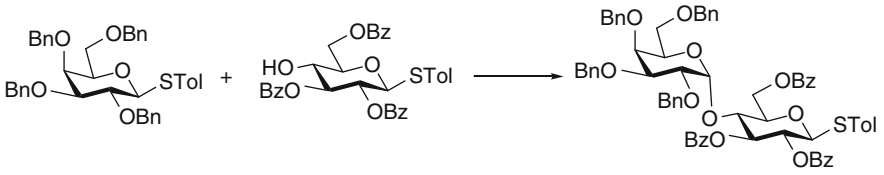
Fig. 4 Structures of Globo H and its fragments and derivatives

temperatures, the formation of succinimide is unavoidable when more than 2 glycosidation steps or less reactive acceptors are used. In such cases a new promoter may be used. For example, in the one-pot glycosylation of Fucosyl GM1, when 1-(benzensulfinyl)piperidine-trifluoromethanesulfonic anhydride (BSP/Tf_2O) developed by Crich [60] was used as the promoter, the product yield was improved (from 13% to 22% for the one-pot glycosylation to assemble whole protective Fucosyl GM1). In addition the reaction time was reduced (from 1 day to 5 h) in comparison with the *N*-iodosuccinimide-trifluoromethanesulfonic acid- and dimethyl (thiomethyl) sulfonium trifluoromethanesulfonate-promoted systems [61, 62]. By using the BSP/TfOH promoter system, tumor-associated antigen N3 minor octasaccharide was also synthesized in 11% yield (Scheme 8) [63].

Although NIS/TfOH, DMTST, and BSP/Tf_2O promoters are convenient for the assembly of oligosaccharides, we have encountered several drawbacks and limitations mainly due to side reactions with by-products resulting from the promoters. In identifying a better promoter, several requirements are critical. The new reagent must be thiophilic, amenable to the reactivity-based one-pot strategy, and, most importantly, must not generate by-products that will interfere with the course of the reaction. It is known that benzenesulfenyl triflate is an extremely powerful thiophilic reagent that can couple thioglycosides with various acceptors [64, 65]. Though a potent electrophile, it remains problematic due to its instability and its requirement for in situ preparation from benzenesulfinyl chloride and silver trifluoromethane sulfonate. A new reagent is needed to complement benzenesulfenyl triflate which offers features of stability and convenient accessibility. Recently,



Scheme 8 One-pot synthesis of Fucose GM1 by using NIS/TfOH or BSP/Tf_2O as a promoter system. Reagents and conditions for NIS/Tf_2O- and DMTST-promoted one-pot reaction: route a (i) NIS, TfOH, CH_2Cl_2, −70°C, 36%; (ii) DMTST, 0°C, 36%. Reagents and conditions for BSP, Tf_2O-promoted one-pot reaction: route b (i) BSP, Tf_2O, CH_2Cl_2, −70°C to −10°C, 47%; (ii) BSP, Tf_2O, CH_2Cl_2, −70°C to 0°C, 47%. Reagents and conditions for global deprotection: route c (i) Zn dust, acetic anhydride/CH_2Cl_2, 4-(dimethylamino)pyridine; (ii) NaOMe, CH_2Cl_2/MeOH; (iii) NaOH, THF/MeOH/H_2O; (iv) Pd-black, MeOH with 10 vol% formic acid, H_2 (1 atm), 44% over four steps

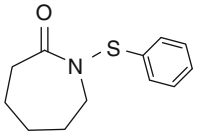


entry	promoter system	yield[a]
1	*N*-(thiophenyl)caprolactam/Tf_2O	83%[b]
2	Benzenesulfinyl piperidine/Tf_2O	<15%[c]
3	*N*-iodosuccinimide/TfOH	75%

[a] Conditions: 1:1:1 donor/acceptor/promoter, room temperature, 10 min. [b] Buffering reaction with TTBP gave comparable yields. [c] It rationalized that BSP yields electrophilic byproducts, which serve to further activate the products. When using 0.5 equiv of BSP, the yield was 63%.

Scheme 9 Room-temperature glycosylation with **19** and other promoters

N-(phenylthio)caprolactam **19** [66] has been applied as a new promoter for the activation of thioglycosides. Then **19** reacts with trifluoromethansulfonic anhydride, which subsequently activates the thioglycoside for glycosidic bond formation (Scheme 9). Notably, the reaction proceeds efficiently at room temperature and is adaptable to our reactivity-based one-pot oligosaccharide synthesis. This overcomes some limitations of the current methods and, more importantly, proceeds efficiently at room temperature, which is very helpful for the development of one-pot glycosylation machine.



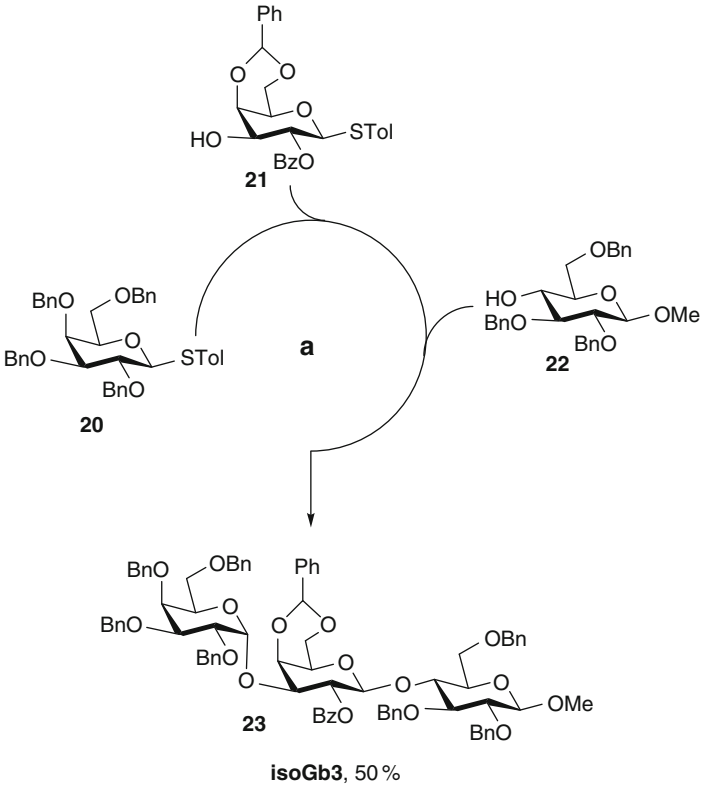
N-(thiophenyl)caprolactam

19

Recently, Ye et al. used the same promoter to synthesize Gb3 and *iso*Gb3 in 47% and 50%, respectively (Scheme 10) [67].

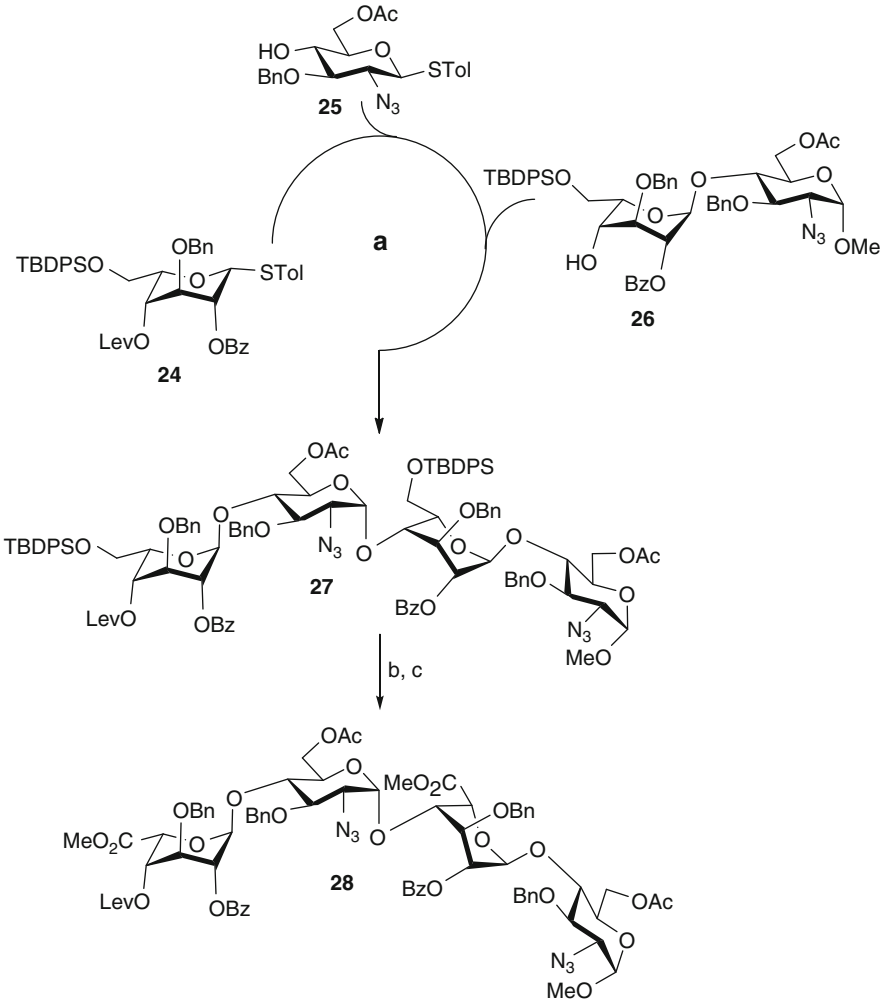
5 Heparins

Besides the neutral oligosaccharides, negatively charged oligosaccharides can also be synthesized by the reactivity-based one-pot glycosylation strategy. Recently, syntheses of heparin and heparan sulfate oligosaccharides utilizing thioglycosides with well-defined reactivity as building blocks were reported [68]. Heparin and



Scheme 10 One-pot synthesis of isoGb3 by using **19** as a promoter. (a) (i) **19**/Tf_2O, CH_2Cl_2; (ii) **22**, **19**/Tf_2O, CH_2Cl_2, 50%

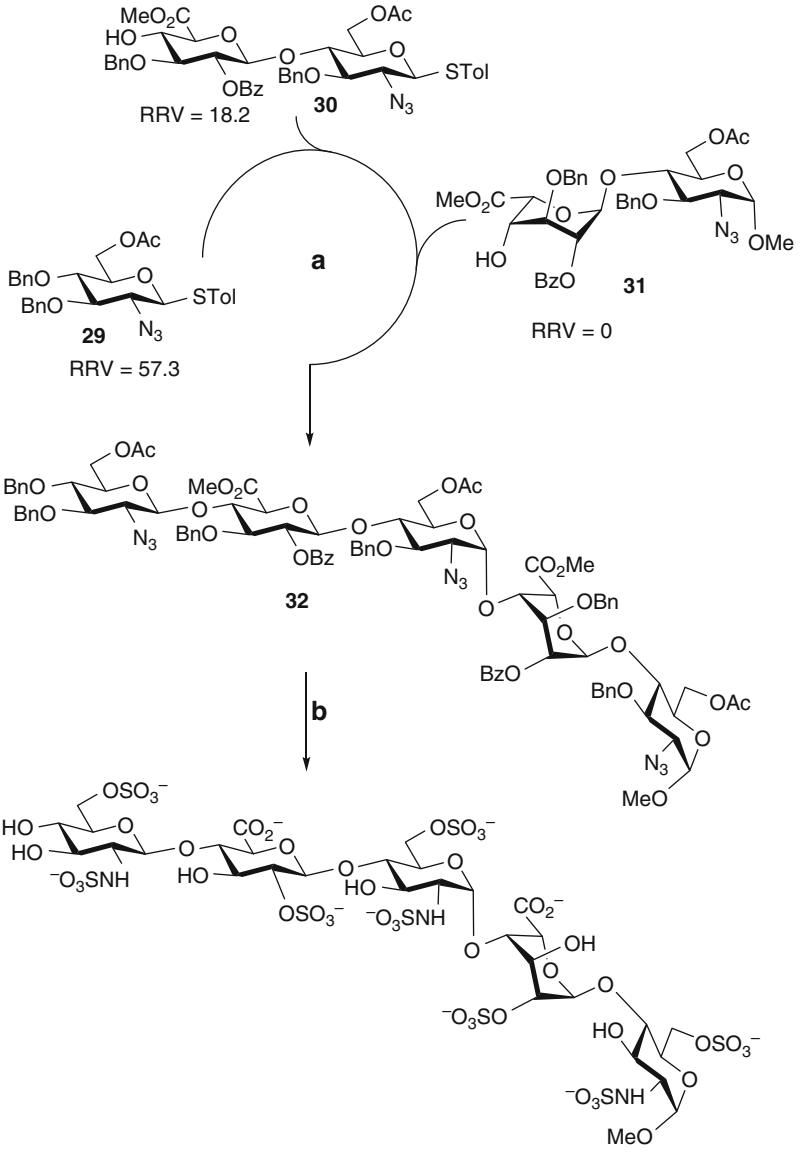
heparan sulfate are the most widely studied members of glycosaminoglycans (GAGs) family. They are composed of repeating disaccharide units of 1→4 linked uronic acid and D-glucosamine. However, the application of uronic acid building blocks as glycosyl donors [69, 70] is limited and often avoided [71–74], because uronic acids are prone to epimerization, exhibit low reactivity owing to the C-5 carboxyl group, and complicate protecting group manipulations. Thus, in our synthetic approach, the formation of uronic acids by selective oxidation at the C-6 hydroxyl group was processed after assembly of oligosaccharides. To this end, the hydroxyl groups to be sulfated were protected as acyl (acetyl and benzoyl) groups. The primary hydroxyl groups to be selectively oxidized to uronic acids were protected as *tert*-butyldiphenylsilyl ethers. Thus, L-idopyranosyl, D-glucopyranosyl, and azidoglucosyl thioglycosides were designed and prepared using the above synthetic strategy. For the one-pot tetrasaccharide synthesis (Scheme 11), fully protected idopyranosyl donor **24** was first coupled with azidoglucosyl acceptor **25** in the presence of NIS/TfOH at −45°C followed by slow warming to room



Scheme 11 One-pot synthesis of heparin tetrasaccharide. (a) NIS, TfOH, CH_2Cl_2, −45°C to room temperature, 35%; (b) HF/Pyr, THF, 87%; (c) (i) TEMPO, KBr, NaOCl, CH_2Cl_2, H_2O; (ii) MeI, $KHCO_3$, DMF, 68% in two steps

temperature. After 3 h, α-methyl disaccharide acceptor **26** was added, followed by the addition of NIS/TfOH at the same temperature. The fully protected tetrasaccharide **27** was obtained in 35% yield. Desilyl reaction followed using HF, and the obtained primary hydroxyl groups were selectively oxidized to uronic acids and protected as ester **28** (Scheme **11**).

For the one-pot pentasaccharide synthesis (Scheme 12), azidoglucosyl donor **29** (RRV, 53.7) was first coupled with disaccharide acceptor **30** (RRV, 18.2) and then α-methyl disaccharide acceptor **31** was added to the reaction mixture. Under these



Scheme 12 One-pot synthesis of heparin pentasaccharide. (a) (i) NIS, TfOH, CH_2Cl_2, −45°C to room temperature; (ii) NIS, TfOH, CH_2Cl_2, −45°C to room temperature, 20%; (b) (i) LiOH, THF; (ii) $Et_3N.SO_3$, DMF; (iii) H_2, Pd/C; (iv) Pyr. SO_3, H_2O, 33%

conditions, the fully protected pentasaccharide **32** was obtained in 20% yield. The heparin pentasaccharide derivative can be obtained, after global deprotection and sulfation.

6 Human Immunodeficiency Virus

Antibody 2G12 was found to have broadly neutralizing anti-HIV activity [75, 76] and shown to protect against infection in vivo in monkey models [77]. However, the structure of 2G12 binding sites has been proven to be difficult to characterize. It is well known that the heavily glycosylated gp120 on the surface of HIV can increase immune evasion by shielding peptide epitopes from immune surveillance as well as promote infection by interaction with dendritic cells. Moreover, the conserved dense cluster of oligomannose on gp120 has been recognized as the epitope for the broadly-neutralizing 2G12 antibody. As a result, this unique oligomannose cluster has been targeted for chemical synthesis in order to elicit 2G12-like antibodies. Recently, our group synthesized the trimannose Manα1-2Manα1-2Man, the D1 arm of $Man_9GlcNAc_2$. Analysis of the RRVs of mannose building blocks for the one-pot synthesis, showed that D-mannose thioglycosides are less reactive than other thioglycosides, such as fucose and galactose [25]. In addition, 2-hydroxymannose thioglycosides are in general much more reactive than the corresponding 2-protected derivatives [25], which makes a one-pot synthesis with a universal leaving group difficult to carry out. To tackle this problem, a one-pot strategy was developed [78] based on the most reactive monomer undergoing self-condensation to give a less-reactive dimer. The dimer then serves as an acceptor for another monomer molecule, which leads to formation of the trimer (Fig. 5).

Screening on several 2-hydroxymannose thioglycosides showed that compound **33** with nonpolar *tert*-butyldimethylsilyl protecting group on C3 had the best result, and optimal glycosylation can be obtained when promoter NIS was used in 0.6 eq. at −40°C (Scheme 13) [78].

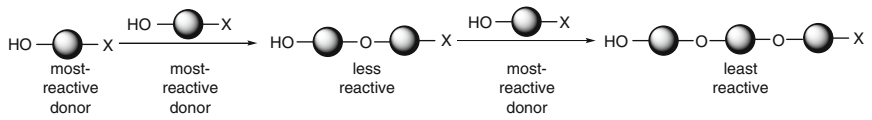
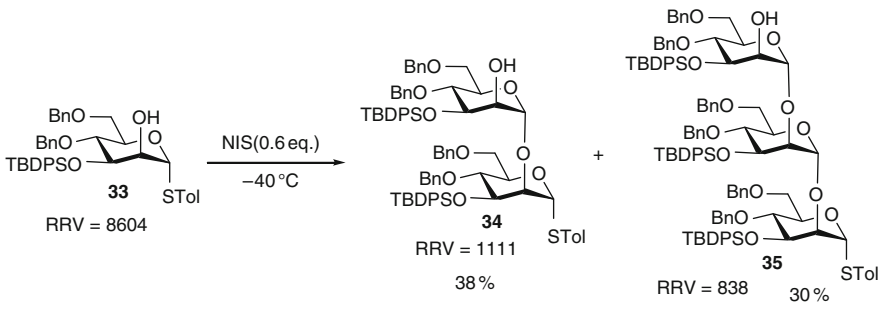


Fig. 5 One-pot self-condensation reaction



Scheme 13 Synthesis of di- and tri-mannose donors by one-pot self-condensation

By using di- or trisaccharide as glycosylation donor, several high mannose structures like Man4, Man5, Man7, Man8, and Man9 can be easily synthesized. Recently, by using these synthetic high mannose structures, multivalent Man4 or Man9 glycodendron (3-, 9-, 27-mer) were prepared, and the synthetic glycodendron, especially the $(Man9)_9$-dendron, exhibited promising inhibition abilityof both gp120-mAb 2G12 and gp120-DC-SIGN in a nanomolar range [79]. The results indicated the potential ability of synthetic glycodendron to inhibit dendritic cell-mediated HIV infection as both antiviral therapeutic and vaccine candidate. In addition, it was also reported that the Man4 of D1 arm can inhibit 2G12 binding to gp120 as efficiently as $Man_9(GlcNAc)_2$ using the glycan array analysis, indicating the potential use of Man4 as a minimum recognition immunogen [80]. However, the synthetic Man4-BSA conjugated vaccine induced elicited IgG in rabbits can only bind to Man4 but not cross-react with gp120 [81].

7 Sialosides

N-Acetyl neuraminic acid (Neu5Ac) is most frequently found at the terminal end of glycoconjugates on the cell surface. This terminally exposed position allows Neu5Ac-containing conjugates to be exploited as receptors for viruses and bacteria, in addition to governing a wide variety of biological processes such as tumor metastasis, cell differentiation, and cell–cell interactions [15, 82, 83]. In naturally occurring sialosides, Neu5Ac is linked to galactosides through the α(2→3) or α(2→6) linkage in *N*-linked and O-linked glycoproteins and also to *N*-acetyl-galactosamine through the α(2→6) linkage in O-linked glycoproteins. In addition, polysialosides formed via the α(2→8) or α(2→9) linkages are constituents of glycoproteins and glycolipids [4, 84, 85]. The biological significance of sialoside receptors has prompted research to design more efficient syntheses. However, high yielding α-selective sialylation is still problematic due to the presence of the C-1 electron-withdrawing carboxyl group at the tertiary anomeric center and the lack of a participating group at C-3 to direct the stereochemical outcome of glycosylation. Sialic acid thioglycosides have limitations in our programmable reactivity-based one-pot strategy due to their poor and narrow range of relative reactivity values (RRVs) [86, 87].

To tackle these problems, we converted the carboxyl group of sialic acid to the hydroxymethyl group **37** and prepared derivatives **38–42** for the investigation. RRVs of known and new sialic acid donors **36–42** were measured (Fig. 6). The reactivity difference between per-O-benzylated sialoside **41** and per- O-acetylated sialoside **36** was less than 100, compared to $\sim 1 \times 10^5$ for the corresponding thioglycosides of other sugars [25]. Reduction of the carboxyl group did increase the reactivity by $>1 \times 10^4$, but the α-selectivity was completely diminished and gave mainly the undesirable β−glycoside product, probably due to a significant anomeric effect [87].

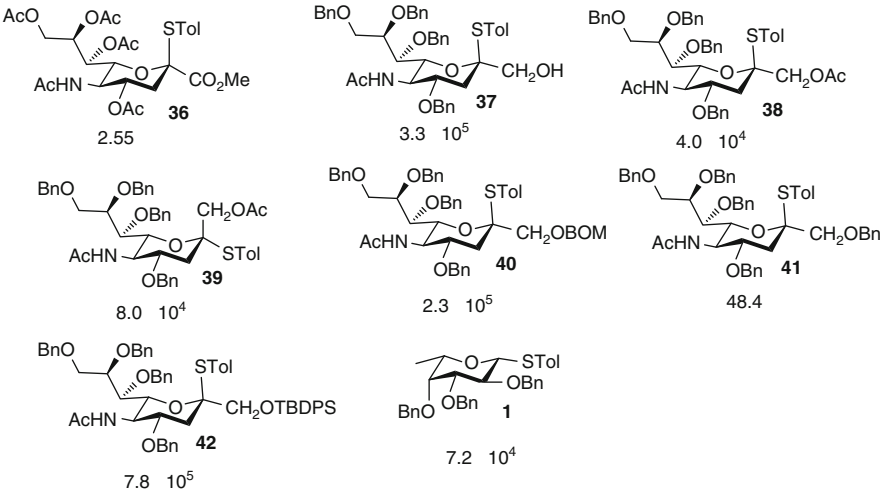
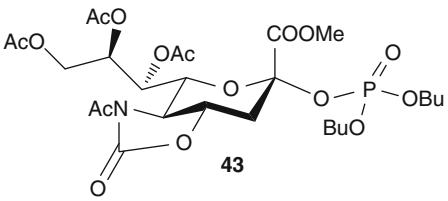


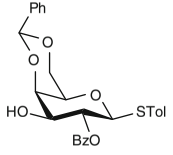
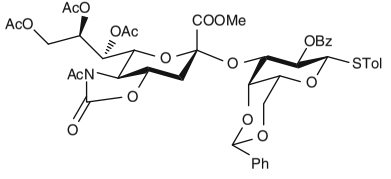
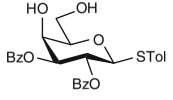
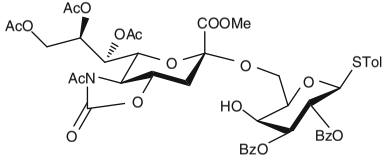
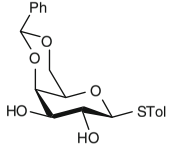
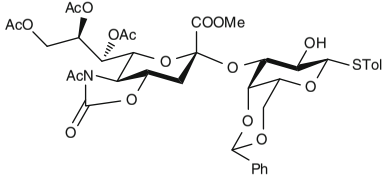
Fig. 6 The relative reactivity values (in parentheses) of sialic acid thioglycosides

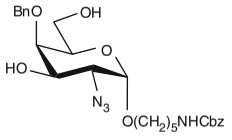
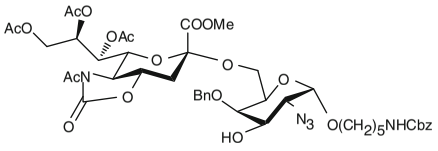
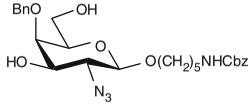
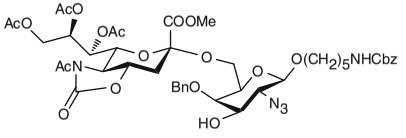
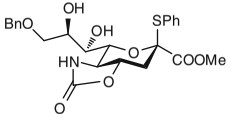
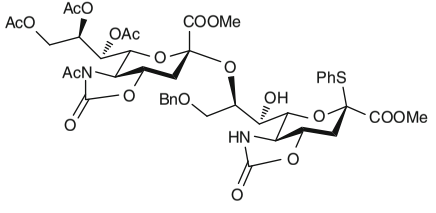
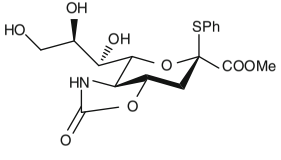
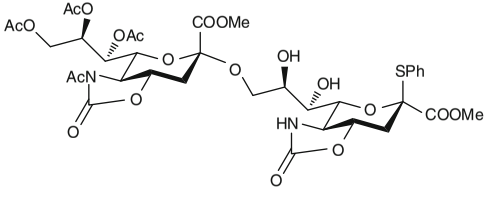
Due to their poor and narrow range of relative reactivity values (RRVs), the sialic acid thioglycosides have limitations in our programmable reactivity-based one-pot strategy. To tackle this problem, a new strategy using sialylated disaccharides as building blocks in the one-pot synthesis was developed [88], as the reactivity of a disaccharide or trisaccharide glycosyl donor is mainly determined by the reducing end unit. However, application of this strategy is limited by the lack of an efficient α-selective sialic acid donor that possesses a leaving group orthogonal to the thioglycoside. Recently, we have developed a new sialyl phosphate compound **43** that employs an *N*-acetyl-5-*N*,4-*O*-carbonyl protection with dibutyl phosphate as the leaving group and a new sialylation donor [89]. With this donor, several kinds of acceptors were tested and it was found that this method is efficient for the α-selective synthesis of major natural occurring α(2,6)-, α(2,3)-, α(2,8)-, and α(2,9)-sialosides (Table 1) [89].



To extend the synthetic method to a programmable one-pot strategy, the RRVs of the sialylated disaccharides **45–47** were measured. Disaccharide **45** showed the highest reactivity among the three building blocks. Compound **47**, containing the extra C-4 O-benzylation, is 1.7-fold more reactive than **46**. In general, the sialylation of a thioglycoside results in a modest deactivation of the anomeric reactivity of the acceptor, as exemplified by comparison of **44** and **45**.

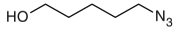
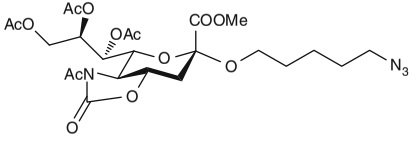
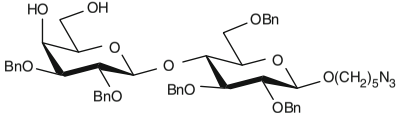
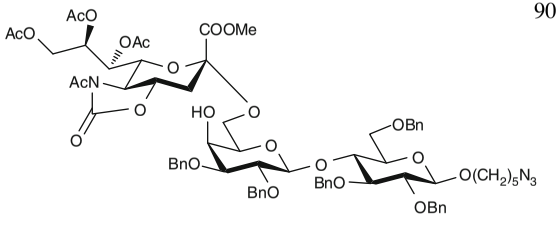
Table 1 Results of sialylation by using the *N*-acetyl-5-*N*,4-*O*-carbonyl protected sialyl phosphate **43**

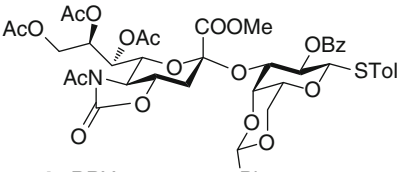
Entry	Acceptor	Product	Yield	α:β ratio	δ_{C1} (ppm)	$^{3}J_{C1\text{-}H3eq}$ (Hz)
1			83	α only	168.9	5.5
2			85	α only	168.4	5.7
3			41	α only	168.6	6.3

4			71	α only	168.3	6.2
5			70	α only	168.3	6.0
6			67	α only	168.7	6.0
7			82	α only	168.5	6.0

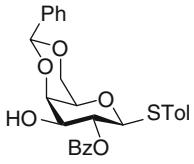
(*continued*)

Table 1 (continued)

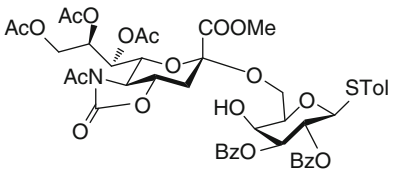
Entry	Acceptor	Product	Yield	α:β ratio	δ_{C1} (ppm)	$^{3}J_{C1\text{-}H3eq}$ (Hz)
8			91	α only	168.8	6.0
9			90	α only	168.3	6.4



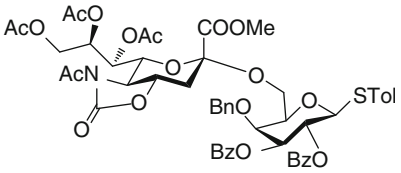
45 RRV = 1462



44 RRV = 1791

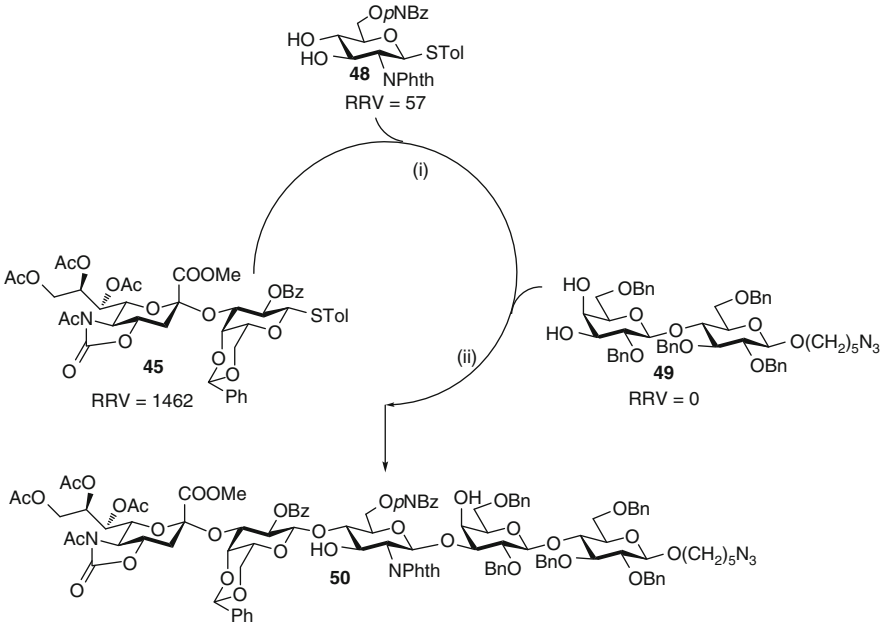


46 RRV = 127



47 RRV = 218

To demonstrate the synthetic application of sialylated disaccharides as building blocks, a representative reactivity-based one-pot synthesis of α(2→3)-linked sialylated pentasaccharide **50** was conducted. The RRVs of these three building units, **45** (RRV = 1,462), **48** (RRV = 57), and **49** (RRV = 0), presented an appropriate reactivity profile for one-pot synthesis. The one-pot synthetic operation was performed in the presence of NIS/TfOH promoter system (Scheme 14). The second

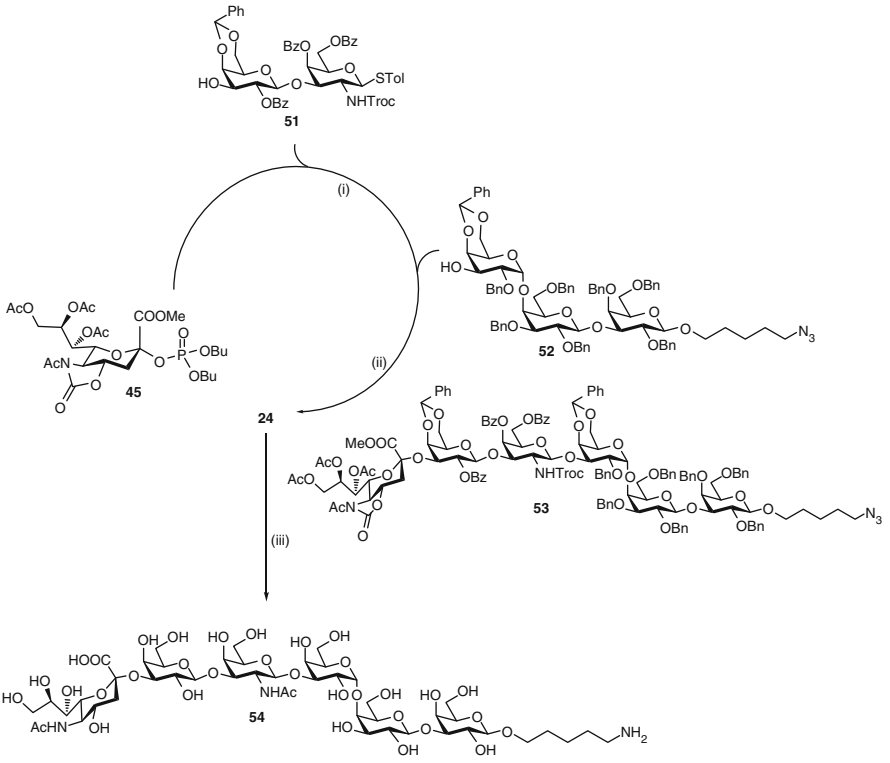


Scheme 14 Reactivity-based one-pot glycosylation of sialo pentasaccharide **50**. (i) NIS, TfOH, 4 A molecular sieves,CH_2Cl_2, −78°C; (ii) NIS, TfOH, −20°C to RT. 48%. *Phth* phthaloyl

glycosylation between **48** and **49** required higher temperature (−20°C to room temperature). The high-yield one-pot glycosylation product (48%) indicated that the sialylated disaccharides with Neu5Ac as terminal residue can be used as building blocks for the programmable one-pot synthesis of oligosaccharides [89].

It was also found that the sialyl phosphate donor **45** is a good donor for the orthogonal one-pot synthesis of sialosides. The power of this method was further demonstrated by the synthesis of tumor-associated antigen SSEA-4 [90, 91] hexasaccharide, which belongs to the globo series of gangliosides. The SSEA-4 derivative **24** was synthesized in 78% yield by using the one-pot procedure, and after global deprotection, the SSEA-4 hexasaccharide **25** was obtained in 30% yield (Scheme 15).

Using this new sialyl phosphate donor **45**, more than 50 different sialosides have been synthesized by combining several strategies (Fig. 7) that allow stereoselective, one-pot multicomponent synthesis of α-sialo oligosaccharides. These sialosides were further used in the preparation of a glycan array for the quantitative and



Scheme 15 One-pot synthesis of SSEA-4 hexasaccharide **54**. (i) TMSOTf, MS 4 A, CH_2Cl_2, −78°C; (ii) NIS, overall 78%; (iii) (a) NaOMe, MeOH; (b) Zn, AcOH, THF; (c) Ac_2O, pyridine, DMAP; (d) 0.1N NaOH; (e) $Pd(OH)_2$, H_2, THF/MeOH/AcOH/H_2O 10:8:1:0.7

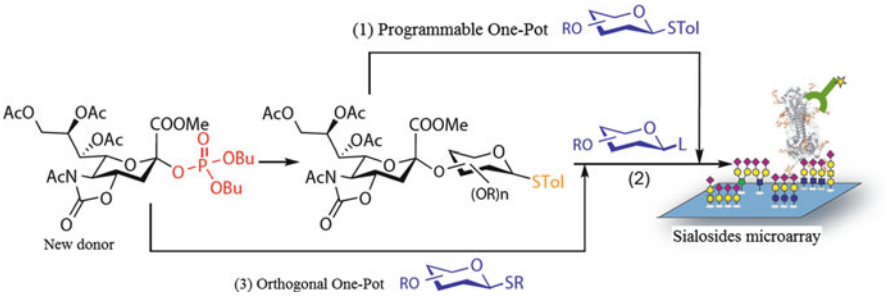


Fig. 7 Strategies for sialosides syntheses

high-throughput analysis of influenza hemagglutinins with regard to their binding specificity and energetics.

8 Conclusions

The "programmable" one-pot method is a rational (and, ideally, computer-aided and automated) approach to polysaccharide synthesis [25]. In addition, the one-pot approach has also been used in modification of the sugar moiety of natural products (such as aminoglycosides, vancomycin, and macrolides) for the development of new antibiotics. A protocol of four steps was carried out to reduce the synthesis of complex carbohydrates to a routine: (1) the sequence of interest is keyed into a computer, (2) the computer selects appropriate reagent combinations, (3) a laboratory worker (human or robotic) prepares the reagent containers for the delivery to the reaction vessel, and (4) the synthesis is executed and a crude reaction product is delivered. Subsequent purification affords the oligosaccharide of interest. Although there is a big advancement in complicated oligosaccharides synthesis using programmable one-pot or automatic solid phase methods, no automatic machine is available on the market now. Although more than 600 building blocks have been prepared so far, they were not optimized for the OptiMer guided one-pot synthesis. As more oligosaccharides are made by these methods with the designed building blocks being tested, the programmable one-pot method could become a method of choice for the rapid assembly of oligosaccharides.

References

1. Dwek RA (1996) Chem Rev 96:683
2. Paulson JC, Blixt O, Collins BE (2006) Nat Chem Biol 2:238
3. Sears P, Wong CH (1998) Cell Mol Life Sci 54:223
4. Varki A (1993) Glycobiology 3:97

5. Hakomori S, Zhang YM (1997) Chem Biol 4:97
6. Kansas GS (1996) Blood 88:3259
7. Danishefsky SJ, Allen JR (2000) Angew Chem Int Ed 39:836
8. Buskas T, Thompson P, Boons GJ (2009) Chem Commun 5335
9. Guo ZW, Wang QL (2009) Curr Opin Chem Biol 13:608
10. Zhu JL, Warren JD, Danishefsky SJ (2009) Expert Rev Vaccines 8:1399
11. Astronomo RD, Burton DR (2010) Nat Rev Drug Discov 9:308
12. Vonitzstein M, Wu WY, Kok GB, Pegg MS, Dyason JC, Jin B, Phan TV, Smythe ML, White HF, Oliver SW, Colman PM, Varghese JN, Ryan DM, Woods JM, Bethell RC, Hotham VJ, Cameron JM, Penn CR (1993) Nature 363:418
13. Kim CU, Lew W, Williams MA, Liu HT, Zhang LJ, Swaminathan S, Bischofberger N, Chen MS, Mendel DB, Tai CY, Laver WG, Stevens RC (1997) J Am Chem Soc 119:681
14. Magano J (2009) Chem Rev 109:4398
15. Simanek EE, McGarvey GJ, Jablonowski JA, Wong CH (1998) Chem Rev 98:833
16. Karlsson KA (1995) Curr Opin Struct Biol 5:622
17. Williams DH, Bardsley B (1999) Angew Chem Int Ed 38:1173
18. Wong CH (2005) J Org Chem 70:4219
19. Nicolaou KC, Mitchell HJ (2001) Angew Chem Int Ed 40:1576
20. Danishefsky SJ, McClure KF, Randolph JT, Ruggeri RB (1993) Science 260:1307
21. Liang R, Yan L, Loebach J, Ge M, Uozumi Y, Sekanina K, Horan N, Gildersleeve J, Thompson C, Smith A, Biswas K, Still WC, Kahne D (1996) Science 274:1520
22. Seeberger PH, Haase WC (2000) Chem Rev 100:4349
23. Koeller KM, Wong CH (2000) Chem Rev 100:4465
24. Sears P, Wong CH (2001) Science 291:2344
25. Zhang ZY, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) J Am Chem Soc 121:734
26. Toshima K, Tatsuta K (1993) Chem Rev 93:1503
27. Garegg PJ (1997) Advances in carbohydrate chemistry and biochemistry, vol 52. Academic Press Inc, San Diego, p 179
28. Smoot JT, Demchenko AV (2009) Advances in carbohydrate chemistry and biochemistry, vol 62. Elsevier Academic Press Inc, San Diego, p 161
29. Zhu XM, Schmidt RR (2009) Angew Chem Int Ed 48:1900
30. Douglas NL, Ley SV, Lucking U, Warriner SL (1998) J Chem Soc Perkin Trans 1 51
31. Wilson BG, Fraserreid B (1995) J Org Chem 60:317
32. Paulsen H (1982) Angew Chem Int Ed Engl 21:155
33. Miljkovic M, Yeagley D, Deslongchamps P, Dory YL (1997) J Org Chem 62:7597
34. Fraser-Reid B, Jayaprakash KN, Lopez JC, Gomez AM, Uriel C (2007) In: Demchenko AV (ed) Frontiers in modern carbohydrate chemistry, vol 960. American Chemical Society, Washington, p 91
35. Kamat MN, Demchenko AV (2005) Org Lett 7:3215
36. Mydock LK, Demchenko AV (2008) Org Lett 10:2103
37. Mydock LK, Demchenko AV (2008) Org Lett 10:2107
38. Premathilake HD, Mydock LK, Demchenko AV (2010) J Org Chem 75:1095
39. Jensen HH, Pedersen CM, Bols M (2007) Chem Eur J 13:7577
40. Pedersen CM, Nordstrom LU, Bols M (2007) J Am Chem Soc 129:9222
41. Pedersen CM, Marinescu LG, Bols M (2008) Chem Commun 2465
42. Okada Y, Mukae T, Okajima K, Taira M, Fujita M, Yamada H (2007) Org Lett 9:1573
43. Okada Y, Nagata O, Taira M, Yamada H (2007) Org Lett 9:2755
44. Boons GJ, Geurtsen R, Holmes D (1995) Tetrahedron Lett 36:6325
45. Geurtsen R, Holmes DS, Boons GJ (1997) J Org Chem 62:8145
46. Raghavan S, Kahne D (1993) J Am Chem Soc 115:1580
47. Li XN, Huang LJ, Hu XC, Huang XF (2009) Org Biomol Chem 7:117
48. Lahmann M, Oscarson S (2000) Org Lett 2:3881

49. Ye XS, Wong CH (2000) J Org Chem 65:2410
50. Mong KKT, Wong CH (2002) Angew Chem Int Ed 41:4087
51. Yin HF, D'Souza FW, Lowary TL (2002) J Org Chem 67:892
52. Zhang S, Cordon-Cardo C, Zhang HS, Reuter VE, Adluri S, Hamilton WB, Lloyd KO, Livingston PO (1997) Int J Cancer 73:42
53. Perrone F, Menard S, Canevari S, Calabrese M, Boracchi P, Bufalino R, Testori S, Baldini M, Colnaghi MI (1993) Eur J Cancer 29A:2113
54. Mariani-Costantini R, Barbanti P, Colnaghi MI, Menard S, Clemente C, Rilke F (1984) Am J Pathol 115:47
55. Zhang S, Zhang HS, Reuter VE, Slovin SF, Scher HI, Livingston PO (1998) Clin Cancer Res 4:295
56. Burkhart F, Zhang ZY, Wacowich-Sgarbi S, Wong CH (2001) Angew Chem Int Ed 40:1274
57. Huang CY, Thayer DA, Chang AY, Best MD, Hoffmann J, Head S, Wong CH (2006) Proc Natl Acad Sci USA 103:15
58. Wang CC, Huang YL, Ren CT, Lin CW, Hung JT, Yu JC, Yu AL, Wu CY, Wong CH (2008) Proc Natl Acad Sci USA 105:11661
59. Liang CH, Wang CC, Lin YC, Chen CH, Wong CH, Wu CY (2009) Anal Chem 81:7750
60. Crich D, Smith M (2001) J Am Chem Soc 123:9015
61. Mong TKK, Lee HK, Duron SG, Wong CH (2003) Proc Natl Acad Sci USA 100:797
62. Lee JC, Greenberg WA, Wong CH (2006) Nat Protoc 1:3143
63. Lee JC, Wit CY, Apon JV, Siuzdak G, Wong CH (2006) Angew Chem Int Ed 45:2753
64. Effenberger F, Russ W (1982) Chem Ber -Recl 115:3719
65. Martichonok V, Whitesides GM (1996) J Org Chem 61:1702
66. Sergio D, Polat T, Wong CH (2004) Org Lett 6:839
67. Wang CN, Li Q, Wang HS, Zhang LH, Ye XS (2006) Tetrahedron 62:11657
68. Polat T, Wong CH (2007) J Am Chem Soc 129:12795
69. Tabeur C, Machetto F, Mallet JM, Duchaussoy P, Petitou M, Sinay P (1996) Carbohydr Res 281:253
70. Krog-Jensen C, Oscarson S (1998) Carbohydr Res 308:287
71. Kovensky J, Duchaussoy P, Bono F, Salmivirta M, Sizun P, Herbert JM, Petitou M, Sinay P (1999) Bioorg Med Chem 7:1567
72. Haller M, Boons GJ (2001) J Chem Soc Perkin Trans 1 814
73. Ichikawa Y, Monden R, Kuzuhara H (1988) Carbohydr Res 172:37
74. Vanboeckel CAA, Beetz T, Vos JN, Dejong AJM, Vanaelst SF, Vandenbosch RH, Mertens JMR, Vandervlugt FA (1985) J Carbohydr Chem 4:293
75. Burton DR, Pyati J, Koduri R, Sharp SJ, Thornton GB, Parren PW, Sawyer LS, Hendry RM, Dunlop N, Nara PL et al (1994) Science 266:1024
76. Trkola A, Purtscher M, Muster T, Ballaun C, Buchacher A, Sullivan N, Srinivasan K, Sodroski J, Moore JP, Katinger H (1996) J virol 70:1100
77. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, Beary H, Hayes D, Frankel SS, Birx DL, Lewis MG (2000) Nat Med 6:207
78. Lee HK, Scanlan CN, Huang CY, Chang AY, Calarese DA, Dwek RA, Rudd PM, Burton DR, Wilson IA, Wong CH (2004) Angew Chem Int Ed 43:1000
79. Wang SK, Liang PH, Astronomo RD, Hsu TL, Hsieh SL, Burton DR, Wong CH (2008) Proc Natl Acad Sci USA 105:3690
80. Calarese DA, Lee HK, Huang CY, Best MD, Astronomo RD, Stanfield RL, Katinger H, Burton DR, Wong CH, Wilson IA (2005) Proc Natl Acad Sci USA 102:13372
81. Astronomo RD, Lee HK, Scanlan CN, Pantophlet R, Huang CY, Wilson IA, Blixt O, Dwek RA, Wong CH, Burton DR (2008) J Virol 82:6359
82. Lis H, Sharon N (1998) Chem Rev 98:637
83. Varki A (2007) Nature 446:1023
84. Reglero A, Rodriguezaparicio LB, Luengo JM (1993) Int J Biochem 25:1517

85. Inoue Y, Inoue S (1999) Pure Appl Chem 71:789
86. Yu CS, Niikura K, Lin CC, Wong CH (2001) Angew Chem Int Ed 40:2900
87. Ye XS, Huang XF, Wong CH (2001) Chem Commun 974
88. Zhang ZY, Niikura K, Huang XF, Wong CH (2002) Can J Chem -Rev Can Chim 80:1051
89. Hsu CH, Chu KC, Lin YS, Han JL, Peng YS, Ren CT, Wu CY, Wong CH (2010) Chem Eur J 16:1754
90. Katagiri YU, Ohmi K, Katagiri C, Sekino T, Nakajima H, Ebata T, Kiyokawa N, Fujimoto J (2001) Glycoconj J 18:347
91. Wenk J, Andrews PW, Casper J, Hata JI, Pera MF, Vonkeitz A, Damjanov I, Fenderson BA (1994) Int J Cancer 58:108

Top Curr Chem (2011) 301: 253–289
DOI: 10.1007/128_2010_111

Published online: 11 January 2011

Uronic Acids in Oligosaccharide and Glycoconjugate Synthesis

Jeroen D.C. Codée, Alphert E. Christina, Marthe T.C. Walvoort, Herman S. Overkleeft, and Gijsbert A. van der Marel

Abstract This chapter describes the assembly of uronic acid containing oligosaccharides and glycoconjugates. Two strategies are available to access these target molecules, namely a pre-glycosylation oxidation approach, in which uronic acid building blocks are used, and a post-glycosylation oxidation strategy, which employs an oxidation step after the assembly of the oligosaccharide chain. Because uronic acid building blocks are generally considered to be less reactive than their non-oxidized counterparts, the latter approach has found most application in carbohydrate synthesis. With the aid of selected examples of recent syntheses of biologically relevant oligosaccharides and glycoconjugates, the reactivity of different uronic acid building blocks is evaluated. From these examples it is apparent that the generally assumed low reactivity of uronic acids does not a priori rule out an efficient assembly of these target compounds. Besides influencing the reactivity of a given pyranoside, the C-5 carboxylic acid function can also have a profound effect on the stereochemical course of a glycosylation reaction, which can be exploited in the stereoselective formation of glycosidic bonds.

Keywords Glycosylation, Reactivity, Stereoselectivity, Uronic acids

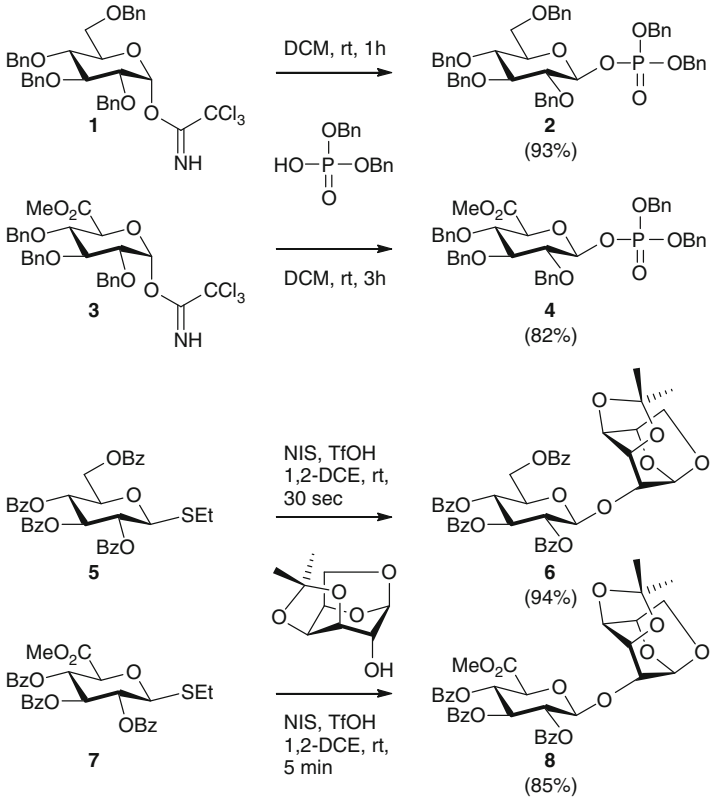
Contents

J.D.C. Codée (✉), A.E. Christina, M.T.C. Walvoort, H.S. Overkleeft and G.A. van der Marel (✉)
Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands
e-mail: jcodee@chem.leidenuniv.nl; marel_g@chem.leidenuniv.nl

1 Introduction

Uronic acids are defined as aldoses of which the primary alcohol is oxidized to a carboxylic acid function [1]. They are widespread in nature, where they constitute key components of oligo- and polysaccharides and glycoconjugates found in all life forms. As such they play a role in numerous biological processes and therefore the synthesis of uronic acid containing oligosaccharides and glycoconjugates has received considerable attention from the synthetic organic chemistry community [2, 3]. For the assembly of uronic acid containing oligosaccharides, two strategies can be followed which differ in the timing of the introduction of the uronic acid carboxylate function. In a post-glycosylation oxidation approach, the oligosaccharide chain is assembled using non-oxidized glycosyl building blocks, after which the carboxylate groups are introduced at the oligomer level. In the alternate pre-glycosylation oxidation strategy, uronic acid building blocks are used for the construction of the oligosaccharide chain. Because uronic acid building blocks are generally less reactive than their non-oxidized counterparts (see below), the former approach has been applied most extensively. A drawback of this approach is that extra steps are required at the oligomer level and that often an extra orthogonal protecting group has to be used to mask selectively the primary alcohol to be oxidized. In the pre-glycosylation oxidation approach, the reduced reactivity of uronic acid building blocks, both as donor and acceptor, has to be dealt with, as well as possible side reactions originating from the presence of the C-5 carboxylic acid, such as epimerization and β-elimination.

The lower reactivity of glycuronic acids was acknowledged by Schmidt and co-workers in their studies on glucuronic acid trichloroacetimidates, which required significantly longer reaction times than their non-oxidized counterparts as depicted in Scheme 1 [4, 5]. Veeneman and Van Boom reported a similar trend in their early work on *N*-iodosuccinimid (NIS)/triflic acid (TfOH) mediated couplings of thioglycosides [6]. A milestone in understanding and harnessing glycoside reactivity was set by Fraser-Reid and co-workers who introduced the armed–disarmed concept to denote reactivity differences between per-benzylated and per-benzoylated *n*-pentenyl glycosides [7]. Subsequently this concept was translated to other types of donors including thioglycosides [8]. To get a more precise overview of glycoside reactivity, the groups of Ley [9] and Wong [10, 11] started to quantify the reactivity of thioglycosides. At present, the reactivity of hundreds of thioglycosides has been mapped and the armed–disarmed concept has evolved from a system in which a donor was termed either armed or disarmed into a system in which donor reactivity is regarded as a continuum. The reactivity of uronic acid thioglycoside



Scheme 1 Early reports highlighting the reactivity difference between oxidized and non-oxidized glucosyl donors

donors, however, has not been quantified (the influence of carboxylic acid ester functions on the p*K*a-value of piperidines has been quantified by Bols and co-workers. It has been revealed that the presence of a C-5 CO_2Me function lowers the p*K*a-value of a given piperidine by 0.7 p*K*a-units with respect to a CH_2OH moiety. See [12]).[1]

In this chapter we will present an overview of the synthesis of uronic acid containing oligosaccharides and glycoconjugates. We have divided the chapter into six sections, focusing on major classes of uronic acid containing biomolecules, namely (1) glucuronides, (2) saponins, (3) glycosaminoglycans, (4) bacterial polysaccharides, (5) pectins, and (6) alginates. All sections present one or more examples of how uronic acids can be introduced in the target molecules using either a post-glycosylation oxidation or pre-glycosylation oxidation approach, detailing both the advantages and disadvantages of the followed synthetic strategies and

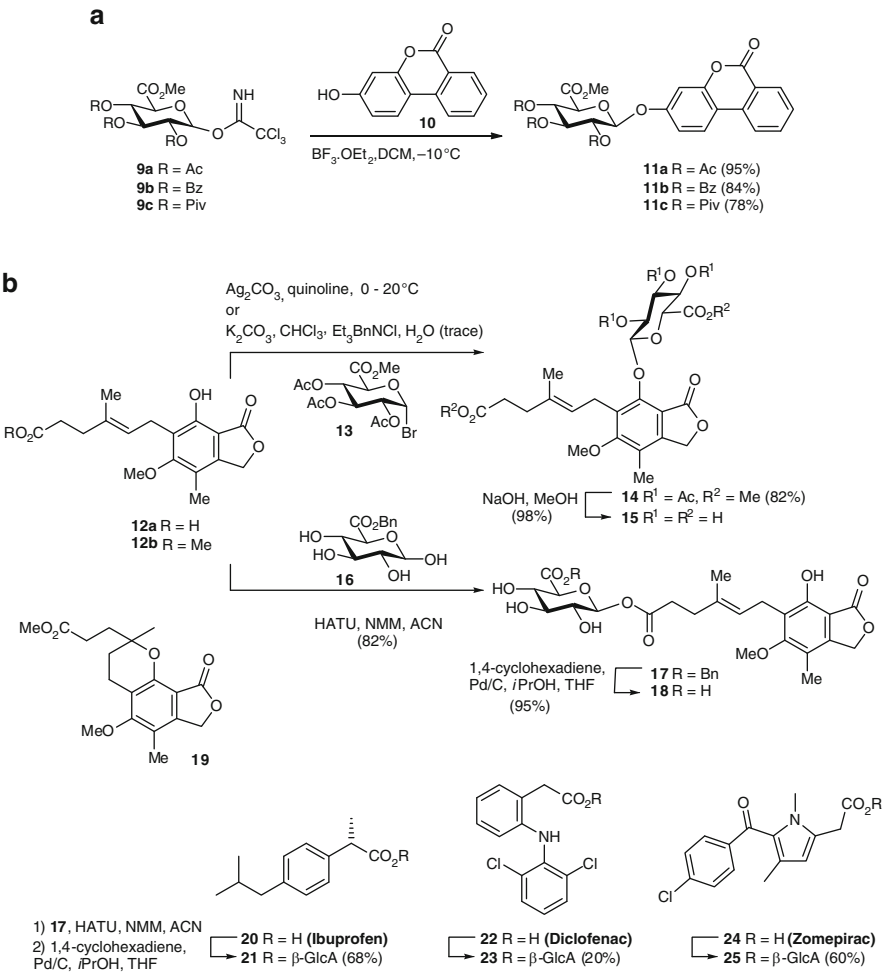
[1]This work is currently in progress in our laboratory.

thereby illustrating how the reactivity/unreactivity of uronic acid building blocks impacts oligosaccharide/glycoconjugate synthesis.

2 Glucuronylation

Glucuronylation is a major metabolizing pathway, by which endobiotics and xenobiotics are transformed into more water soluble molecules to be excreted from the human body [13, 14]. Glucuronylation is catalyzed by the family of uridine diphosphate (UDP) glucuronosyltransferases (UGTs) and entails the transfer of glucuronic acid from UDP-glucuronic acid to a nucleophilic site on the acceptor molecule. Originally considered as a solely favorable detoxification process it gradually became evident that glucuronide metabolites can be reactive and have biological effects too. The finding that many drugs are metabolized as glucuronides stimulated the determination of the pharmacological and toxicological properties of these metabolites. Several synthetic procedures have been developed to deliver sufficient amounts of well-defined *O*-, *N*-, *S*-, and *C*-glucuronides, and these have previously been reviewed [15–17]. Generally, suitably protected glucuronic ester donors are applied to minimize the number of reaction steps after glycosylation. Especially in the case of labile glucuronides, such as the *O*-acyl and quaternary ammonium conjugates, the amount of synthetic steps should be kept to a minimum. Traditional methods to synthesize glucuronides involve the use of bromosugars under Koenings–Knorr conditions or basic phase transfer conditions. Since its introduction, the trichloroacetimidate method has been widely used to obtain glucuronides. For example, in a route of synthesis to glucuronylated dietary phenols, such as urolithin-B (**10**, Scheme 2a), differentially protected glucuronic acid trichloroacetimidates (**9a–c**) were explored in combination with different Lewis acid promoters [18]. It was found that in the glucuronylation of **10**, the acetylated donor **9a** performed best under the agency of $BF_3 \cdot OEt_2$, to give the target product in excellent yield. No sign of ortho-ester formation or the undesired α-anomer was observed.

The intrinsic reactivity of acyl glucuronides, such as their ability to act as acylating agents, requires the use of mildly removable protecting groups. Interestingly, recently several approaches have been developed, in which protection of the pyranosyl hydroxyls can be omitted. Juteau et al. have shown that otherwise unprotected allyl glucuronates can be condensed with carboxylic acids under Mitsunobu conditions [19]. Unfortunately, this procedure often leads to the production of anomeric mixtures. Contrarily, acylation of allyl glucuronides under the influence of the condensing reagent 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and *N*-methylmorpholine (NMM) as base proceeds both in a regioselective and stereoselective manner to give the β-configured allyl esters [20]. The stereoelectronic enhancement of the nucleophilicity of the 1β-alkoxide by virtue of the kinetic anomeric effect has been brought forward to explain the stereoselectivity of this anomeric acylation. Stachulski and-



Scheme 2 Selected examples of glucuronylation reactions

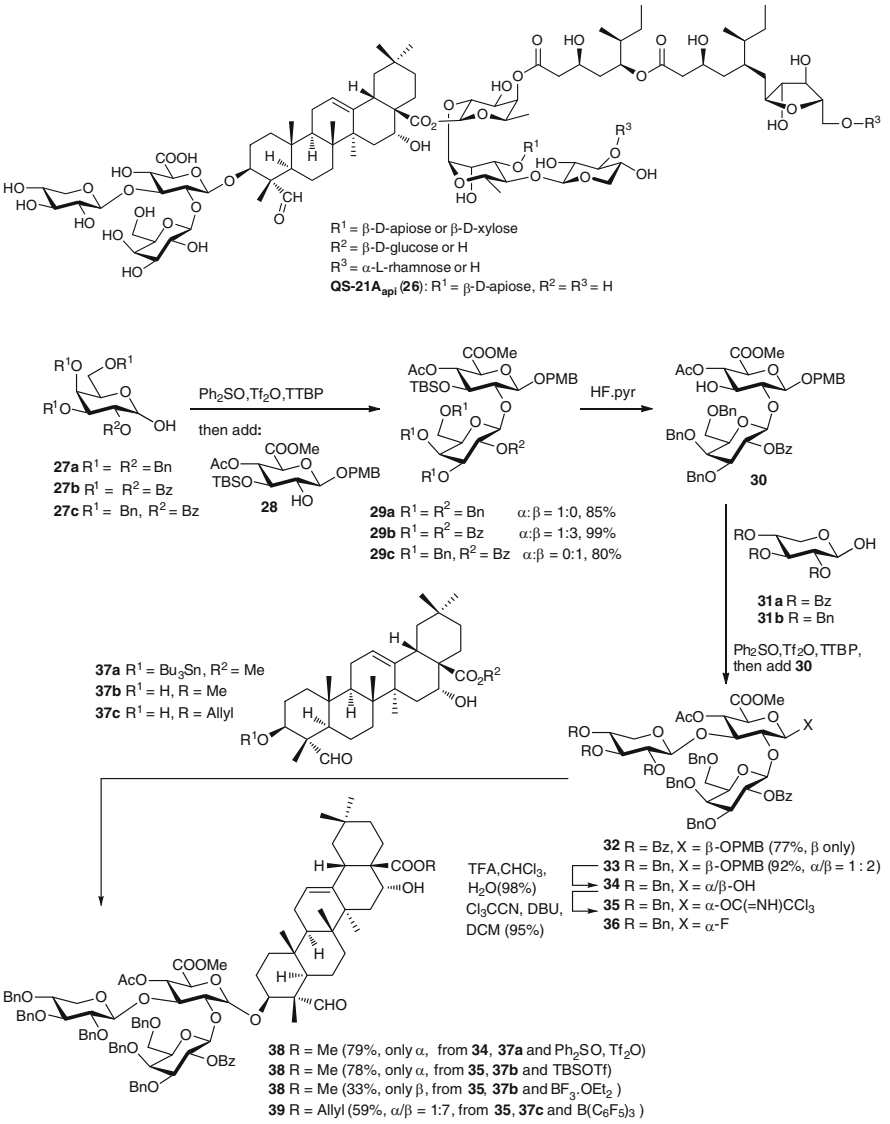
coworkers have described the glucuronylation of various nonsteroidal antiinflammatory drugs, including mycophenolic acid **12a** (Scheme 2b) [21, 22]. Both the phenol- and the acyl glucuronides of **12a** were synthesized. The aryl glucuronide **14** could be prepared from mycophenolic acid methyl ester **12b** using the bromosugar **13** and Ag_2CO_3 catalysis. When the corresponding trichloroacetimidate donor **9a** was used in combination with $BF_3 \cdot OEt_2$ only cyclized acceptor **19** was obtained. Alternatively, a phase transfer alkylation could be realized, in which the use of solid K_2CO_3 in chloroform with a minimal amount of water (1:1 with respect to the bromosugar) delivered **14** in 82% yield. Cleavage of all acetyl groups and methyl esters was accomplished under Zemplèn conditions with excess base, to give the phenol glucuronide **15** in excellent yield. For the construction of acyl glucuronide

18, glucuronic acid benzyl ester **16** was used in combination with HATU and NMM. After optimization of reaction conditions, the β-acylglucuronide **17** was obtained in 82% yield as the sole anomer. The use of the glucuronic acid benzyl ester was preferred over its allyl counterpart [22], because deprotection of the latter could lead to the persistence of Pd traces in the end product. Removal of the benzyl ester in **17** was accomplished using hydrogen transfer reduction in THF-*i*PrOH. The use of this solvent system prevented reduction of the trisubstituted internal double bond. Following a similar strategy, the glucuronides of various carboxylic acid containing drugs, including ibuprofen (**20**), diclofenac (**22**), and zomepirac (**24**), have been synthesized [21].

3 Saponins

Saponins are amphipathic plant glycosides of steroids and triterpenes, which occur in an enormous structural diversity, and which are traditionally used as detergents and emulsifiers [23, 24]. Many plant saponin extracts have been used as folk medicine to treat various human diseases. Since it is often difficult to acquire well-defined, homogeneous saponins from natural sources to establish structure-activity relationships, considerable attention has been devoted to their synthesis over the last two decades. Some of these efforts have recently been reviewed [25, 26].

Although D-glucose is the most common monosaccharide constituent of saponins, D-glucuronic acid also frequently occurs in saponin structures. Relevant examples are represented by the complex triterpene saponins found in extracts from the South American tree *Quillaja saponaria Molina*, which have been reported to display remarkable adjuvant activity [27–29]. The group of Gin explored the synthesis of these complex triterpene saponins, such as QS-21A$_{api}$ **26** depicted in Scheme 3 [30–33]. The QS-21A$_{api}$ structure contains an all β-linked branched trisaccharide subunit composed of a central D-glucuronate and peripheral D-galactopyranose and D-xylopyranose residues attached to the C-2 and C-3 hydroxyls respectively. In an impressive total synthesis of QS-21A$_{api}$ **26** [30], Gin and co-workers assembled the fully protected trisaccharide **33** prior to the attachment to the triterpene aglycon as depicted in Scheme 3. The synthesis of trimer **33** started with the introduction of the β-glycosidic linkage between GlcA acceptor **28** and galactoside **27**, the stereochemical outcome of which proved to be highly dependent on the protective group pattern of the donor galactoside [30, 31]. Tetrabenzylgalactose **27a** provided solely the α-linked disaccharide, while its tetrabenzoyl counterpart **27b** gave the disaccharide in a 1:3 α/β ratio. This stereochemical outcome was postulated to be the result of the anchimeric influence of the C-4-benzoate in the donor. The use of the more reactive galactoside, 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-D-galactose **27c**, exclusively produced the β-product using the sulfoxide-mediated dehydrative glycosylation procedure. After HF · pyridine-mediated removal of the TBS group the



Scheme 3 Part of the total synthesis of QS-21A$_{api}$

β-xyloside linkage could be installed by a similar dehydrative glycosylation event using 2,3,4-tri-*O*-benzoyl-D-xylose **31a** as donor. Interestingly, the use of tri-*O*-benzyl xylose **31b** also led to the preferential formation of β-linked trisaccharide (92%, α/β = 1:2). To circumvent multiple simultaneous saponifications in a far-advanced intermediate later on in the synthesis, Gin and co-workers proceeded with tri-*O*-benzyl xylosyl saccharide **33**. The condensation of the

branched trisaccharide with the triterpene fragment turned out to be a challenging task because of the sterically demanding array of C-2- and C-3-carbohydrate appendages on the donor glucuronide in combination with the neo-pentylic nature of acceptor alcohol **37**. In addition, anchimeric assistance could not be used to secure the desired β-linkage in this crucial glycosylation. Attempts to attain a productive β-selective dehydrative glycosylation using trisaccharide **34** failed. Interestingly, the use of the triterpene 3-stannyl ether **37a** did give an efficient glycosylation but led stereoselectively to the α-adduct **38**. The use of various other classes of glycosyl donors such as anomeric sulfides, phosphites, and fluorides also met with limited success. When α-trichloroacetimidate **35** was condensed with the triterpene alcohol under the agency of the powerful Lewis acidic catalyst TMSOTf, again the α-linked product **38** was obtained as the sole product. Changing to the milder $BF_3 \cdot OEt_2$ promoter did lead to the desired β-product, albeit in rather low yield. The anomeric fluoride **36** was obtained as a major side product in this glycosylation reaction. Therefore tris(pentafluorophenyl) borane ($B(C_6F_5)_3$) [34], having a similar reactivity as $BF_3 \cdot OEt_2$ but lacking the reactive B–F bond, was investigated. Glycosylation of alcohol **37c** using 3 mol% of $B(C_6F_5)_3$ as the catalyst gave the desired glycoconjugate **39** in 59% yield and a 1:7 α/β-ratio.

The successful total synthesis of QS-21A_{api} clearly shows that complex uronic acid building blocks can be effectively used in the construction of intricate glycoconjugates.

4 Glycosaminoglycans

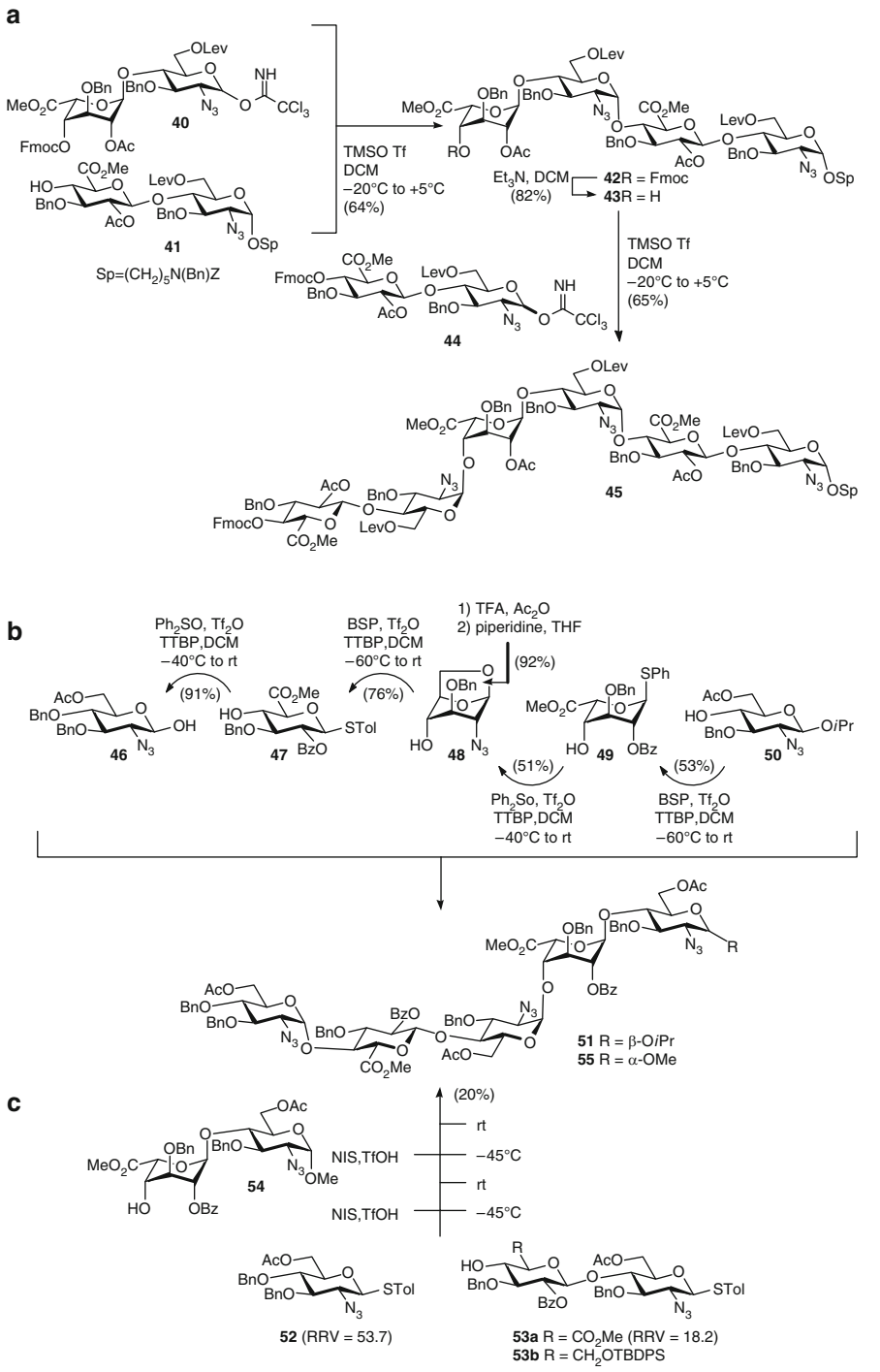
The glycosaminoglycans (GAGs) are a class of linear, anionic glycopolymers, build up from disaccharide repeats. The GAG-family consists of hyaluronic acid (hyaluronan/HA, poly-[β-D-GlcA-(1→3)-β-D-GlcNAc-(1→4)-]), chondroitin sulfate (CS, poly-[β-D-GlcA-(1→3)-β-D-GalNAc-(1→4)-]), dermatan sulfate (DS, poly-[α-L-IdoA-(1→3)-β-D-GalNAc-(1→4)-]), keratan sulfate (KS, poly-[β-D-Glc-(1→4)-β-D-GlcNAc-(1→3)-]), and heparin/heparin sulfate (H/HS, poly-[β-D-GlcA/α-L-IdoA-(1→4)-α-GlcNAc-(1→4)-]). The negative charge in these polymers comes from either the presence of uronic acid moieties (D-GlcA or L-IdoA) and/or sulfate groups, often randomly distributed on the carbohydrate chain. GAG synthesis is an intensive area of research because of the plethora of biological functions these molecules perform and the difficulty in obtaining pure, well-defined samples from natural sources [35–37]. Several reviews dealing with the synthesis of GAGs have appeared over the years [38–41], most of which focus on the assembly of heparin and heparin sulfates [38–40], the structurally most diverse member of the GAG-family. It is beyond the scope of this chapter to cover all the reported strategies on the assembly of GAGs and therefore selected examples will be described to illustrate to what extent the reactivity of the uronic acid building blocks impacts the synthesis of these molecules.

4.1 Heparin/Heparan Sulfate

All possible strategies (pre- and post-glycosylation oxidation in donor and acceptor building blocks) have been used for the synthesis of heparin/heparin sulfate (H/HS) fragments. Most recent synthetic efforts have been focused on the development of modular approaches in which dimer building blocks are used for the construction of higher oligomers. The uronic acid moieties have been placed on both the donor (i.e., the reducing) and the acceptor (i.e., the non-reducing) ends of these building blocks. Both glucuronic and iduronic acids have been incorporated, although the latter have been studied more intensely. Iduronic acid is the predominant uronic acid in the "regular sequence" heparin and the connection of a glucosazide donor to an iduronic acid ester acceptor proceeds in a highly stereoselective manner due to double stereodifferentiation in the glycosylation reaction transition state [38–40, 42, 43]. A recent example is presented by the work of Boons and co-workers, who reported the construction of a collection of 16 [uronic acid–glucosamine] building blocks, which were synthesized using non-oxidized *S*-ethyl glucosyl or *S*-ethyl idosyl donors and glucosazide acceptors (two dimer building blocks are depicted in Scheme 4a) [44]. Oxidation of the disaccharides was accomplished using the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/bisacetoxyiodobenzene (BAIB) reagent combination [45, 46]. The dimer building blocks were used for the assembly of a small library of six tetrasaccharides and one hexasaccharide using trichloroacetimidate technology. All couplings proceeded in similar yields (51–65%) and with excellent stereoselectivity. The protecting group strategy followed used Fmoc carbonates as temporary protecting groups at the uronic acid ester C-4 hydroxyls, levulinoyl esters at the hydroxyls to be sulfated in the end product, and acetyl and benzyl ethers as permanent protecting groups.

We have described a modular strategy for the construction of H/HS oligomers using monomeric building blocks (Scheme 4b) [47]. To ensure an efficient assembly process monomeric 1-hydroxyl glucosazide and 1-thio uronic acid ester were combined in a sequential glycosylation procedure. The key 1-thioglucuronic and iduronic acid esters, **47** and **49** respectively, were effectively accessed using a chemo- and regioselective TEMPO/BAIB mediated oxidation of partially protected thioglycosides [46]. Both the 1-hydroxyl and 1-thio glycosides were activated using sulfonium activator systems (Ph_2SO/Tf_2O) and 1-benzenesulfinyl piperidine (BSP)/Tf_2O respectively. For the activation of the 1-thio uronic acid ester donors both sulfonium systems could be used but only the latter activation system led to productive couplings. Currently there is no adequate explanation for this discrepancy, but the difference in reactivity has later also been observed in the construction of oligomannuronic acids (see below).

Polat and Wong reported a one-pot synthesis of pentasaccharide **55** employing glucuronic acid ester and iduronic acid ester acceptor coupling partners as depicted in Scheme 4c [48]. The one-pot glycosylation sequence commenced with the NIS/TfOH mediated condensation of *S*-toluyl glucosazide **52** (having a relative reactivity value (RRV) of 53.7) and glucuronic acid–glucosazide dimer **53a**

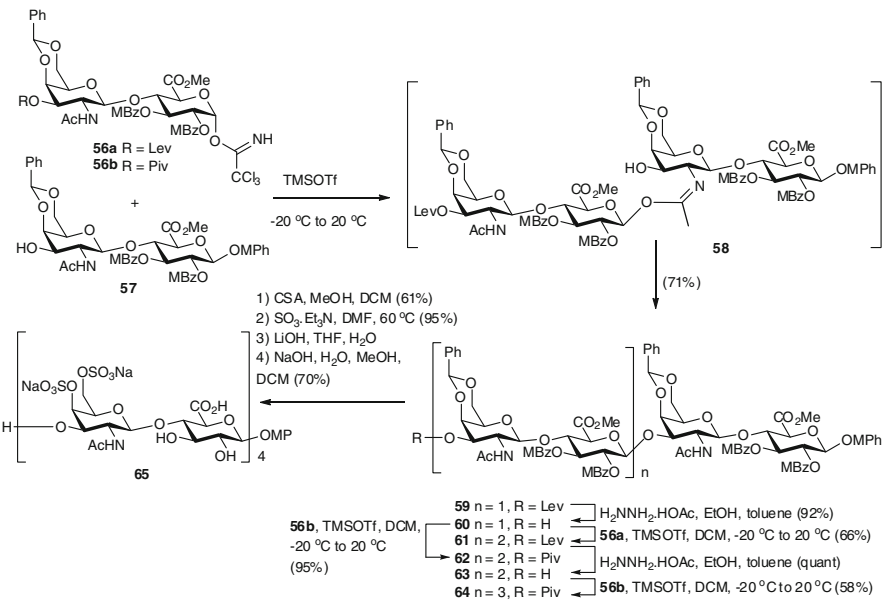


Scheme 4 Assembly of protected heparin oligosaccharides

(RRV = 18.2). In the second stage of the sequence the terminal iduronic acid–glucosamine disaccharide **54** was added, along with extra activator to provide the target pentasaccharide **55** in 20% yield. It is worth noting that the first condensation failed when the non-oxidized dimer building block **53b**, bearing a C-6'-*O*-TBDPS ether, was used. This observation was explained by the bulkiness of the silyl protecting group.

4.2 Chondroitin Sulfate

Modular approaches employing disaccharide building blocks have also been employed in the synthesis of chondroitin sulfate (CS) fragments. Both [GlcA-GalN]- and [GalN-GlcA]-dimers have been used. Tamura and co-workers have reported the synthesis of CS fragments up to the octamer level using [GalNAc-GlcA] disaccharides, bearing an *N*-acetyl group on the galactosamine and having a glucuronic acid reducing end with two methylbenzoate esters at the C-2 and C-3 hydroxyls (see Scheme 5) [49, 50]. The use of these building blocks is notable because glucuronic acids bearing electron-withdrawing protecting groups are considered to be unreactive donor glycosides and the presence of *N*-acetyl groups in glycosyl acceptors generally leads to low coupling yields [51]. In the coupling of

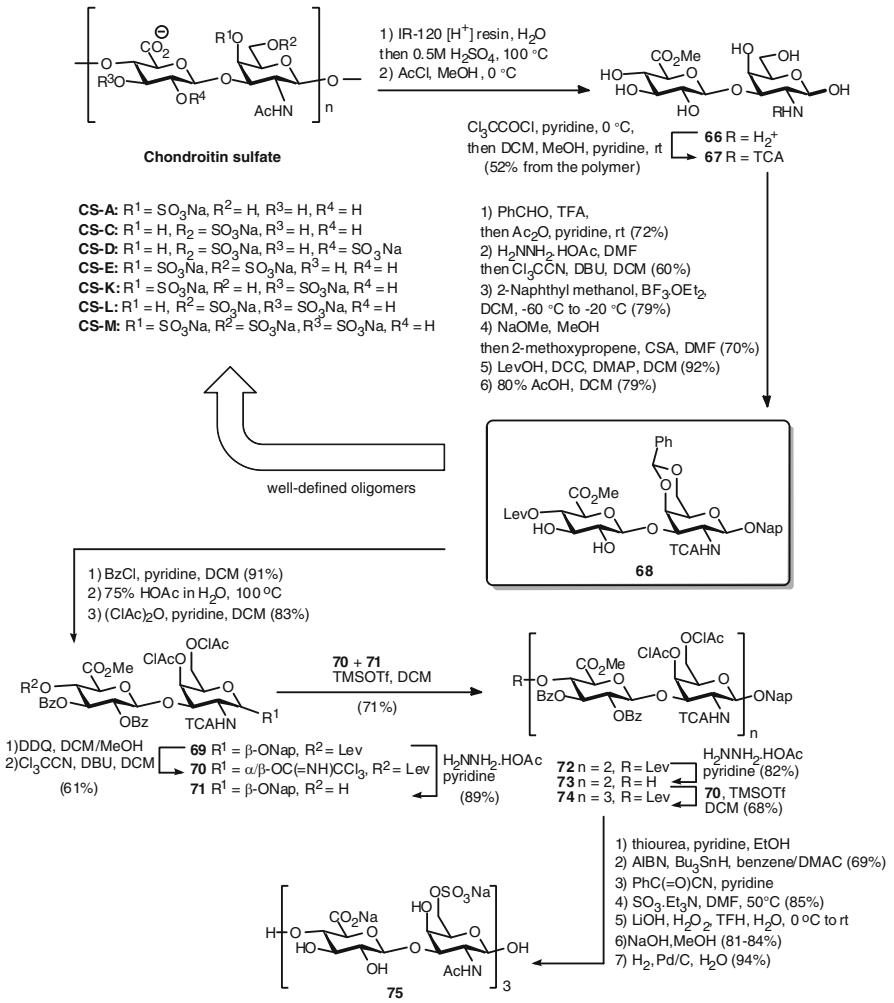


Scheme 5 Assembly of CS-E octamer **65**

[GalNAc-GlcA] dimer **56a** with acceptor **57**, imidate intermediate **58**, resulting from attack of the GalNAc *N*-acetyl group on the activated donor **56a**, was initially formed which slowly rearranged into the desired tetrasaccharide product **59** in 71% yield. After delevulinoylation, the tetramer was extended with the same dimer donor under analogous conditions to give the hexasaccharide **61** in 66% yield. Delevulinoylation then provided the hexamer acceptor **63**. When the pivaloylated donor **56b** was coupled with tetramer acceptor **60**, hexamer **62** was obtained in 95% yield. Glycosylation of hexamer alcohol **63** with pivaloyl dimer **56b** proceeded in 58% yield to give the fully protected CS-octamer **64**, which was transformed into the sulfated CS-E octamer **65** by removal of the benzylidene acetals, sulfation of the liberated hydroxyls, and global basic deprotection.

An interesting approach to obtain synthetic CS-fragments was recently reported by Jacquinet and co-workers, who fragmented CS-polymer into glucuronic acid-galactosamine disaccharides, which in turn were used to build up CS-oligomers [52–54]. Based on the pioneering works of Levene [55] and of Davidson and Meyer [56], they reported an optimized protocol for the acid mediated degradation of CS-polymer. As depicted in Scheme 6, acid treatment of the CS-polymer leads to complete desulfation, fragmentation and N-deacetylation. Acid mediated esterification and ensuing trichloroacetylation of the galactosamine nitrogen (in a two-step procedure) then gave disaccharide **67** in 50–55% yield from the polymer. This dimer was transformed into key CS-building block **68**, which was used as a single starting material for the construction of all known CS-sulfoforms (CS-A, C, D, E, K, L and M). Briefly, the C-4 and C-6 galactosamine hydroxyls in **67** were protected with a benzylidene functionality, after which the remaining hydroxyls were acetylated. Selective anomeric de-acetylation and subsequent imidate formation then set the stage for the $BF_3 \cdot OEt_2$ mediated introduction of the anomeric 2-naphthylmethyl group. It was noted that the use of the more reactive Lewis acid TMSOTf led to the formation of a significant amount of α-linked product [57]. Global deacetylation was followed by the installation of an isopropylidene group on the C-2 and C-3 hydroxyls of the GlcA moiety under kinetic conditions, after which levulinoylation provided the fully protected CS-dimer. Selective cleavage of the isopropylidene ketal gave CS-building block **68**.

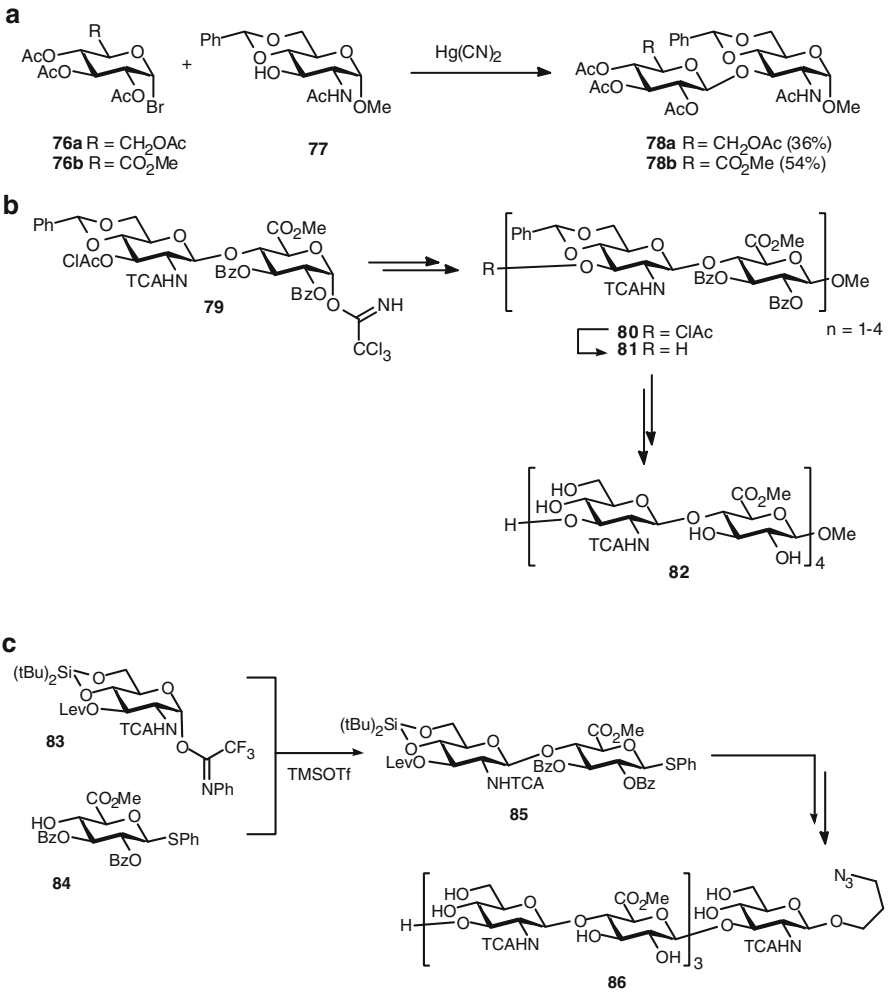
A representative synthesis of a CS-A hexamer is depicted in Scheme 6. Dimer **68** was benzoylated, after which the benzylidene functionality was replaced by two chloroacetyl groups to provide the fully protected building block **69**. Cleavage of the anomeric naphthyl ether and trichloroacetimidate formation led to disaccharide donor **70** and acceptor dimer **71** was obtained by delevulinoylation of **69**. Dimers **70** and **71** were combined in a TMSOTf-catalyzed condensation to provide the tetrasaccharide in 71% yield. Removal of the levulinoyl group in **72** and subsequent coupling with dimer **70** gave the fully protected hexasaccharide **74** (68%). Transformation of this oligomer into CS-A hexamer **75** was accomplished by removal of all chloroacetyl groups with thiourea, radical mediated reduction of the *N*-trichloroacetyls, selective benzoylation of the primary alcohols using benzoylcyanide, sulfation of the GalNAc C-4 hydroxyls, saponification of all methyl esters and benzoyl groups, and final reduction of the anomeric naphthyl group.



Scheme 6 Depolymerization of CS-polymer in the synthesis of well-defined CS-fragments

4.3 Hyaluronan

From a structural point of view, hyaluronan is the simplest member of the GAG superfamily. The first synthesis of hyalobiuronic acid, the [β-D-GlcA-(1→3)-β-D-GlcNAc-(1→4)-]-disaccharide repeating unit of HA, was reported as early as 1962, and was accomplished using 1-bromo glucuronic acid methyl ester **76b** (Scheme 7a) [58]. The yield of the Koenings–Knorr glycosylation of uronic acid **76b** and acceptor **77** was significantly higher than the yield for the analogous condensation using bromoglucoside **76a**. Several modular approaches towards the assembly of larger

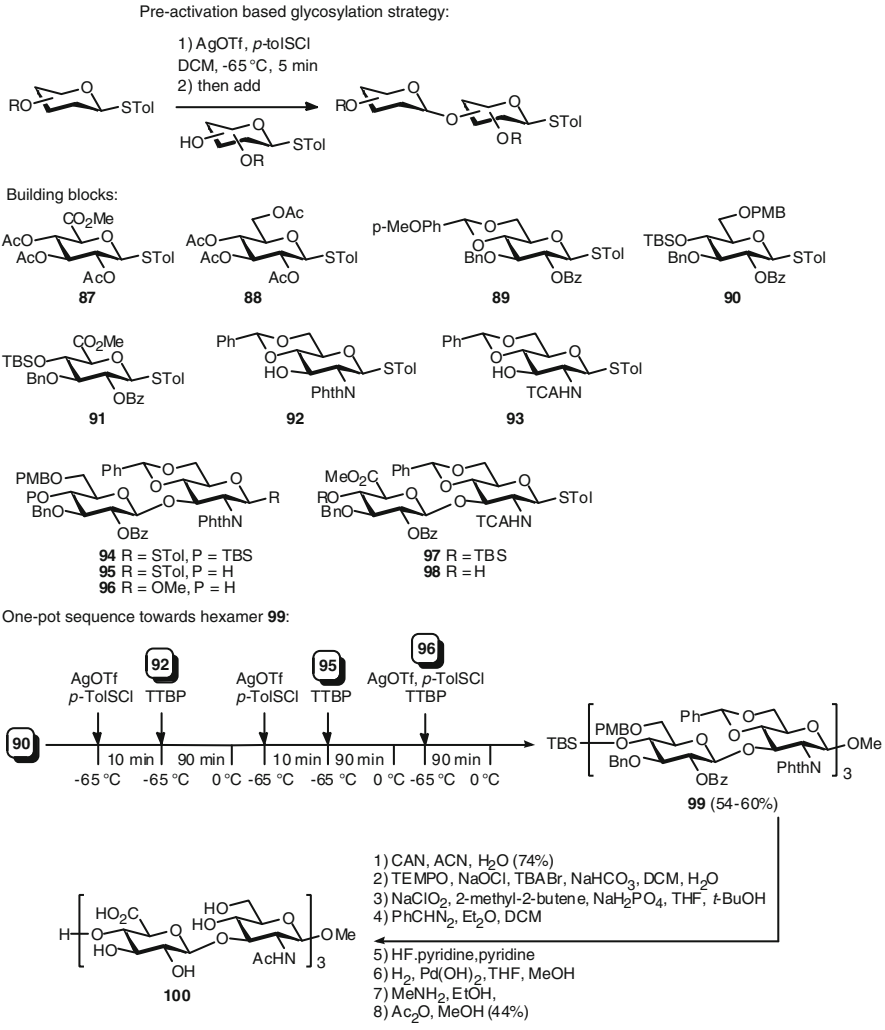


Scheme 7 Assembly of HA-oligomers

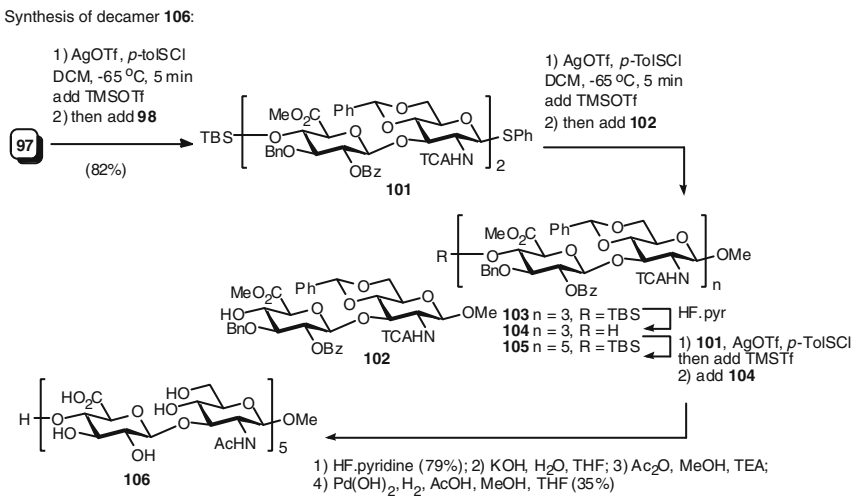
HA-fragments have been reported since. Jacquinet described the synthesis of HA-fragments up to the octamer level using dimer **79**, having a 2,3-di-*O*-benzoyl-glucuronic acid methyl ester trichloroacetimidate donor part (Scheme 7b) [59]. The building blocks were connected in high yielding TMSOTf-catalyzed reactions (87–93% yield). We have reported on the use of an analogous thiophenyl disaccharide **85**, which was equipped with a di-*tert*-butylsilylene ketal to mask the glucosamine C-4 and C-6 hydroxyls [60]. The silylene group was employed because the corresponding benzylidene functionality proved to be less stable under the (Lewis) acidic reaction conditions used for the glycosylations (Scheme 7c) [61]. The thiodisaccharide **85** was synthesized following an orthogonal glycosylation strategy from

N-phenyltrifluoroacetimidate glucosamine and 1-thio glucuronic acid monomers, **83** and **84** respectively. Starting from a spacer containing GlcN-acceptor, HA-heptamer **86** was synthesized using NIS-TfOH as promoter. Deprotection of the oligomer was effected by desilylation (HF · pyridine), saponification of all esters and trichloroacetyl groups and reacetylation of the resulting free amino functions.

To streamline the assembly of HA-oligomers, Huang and co-workers developed a pre-activation based iterative glycosylation strategy (Scheme 8) [62, 63]. In this strategy a thioglycoside donor is pre-activated with *p*-toluenesulfenyltriflate (*p*-TolSOTf, generated from AgOTf and *p*-TolSCl) and then condensed with a thioglycoside



Scheme 8 (continued)



Scheme 8 Pre-activation based glycosylation strategy towards HA oligomers

acceptor [64, 65]. The resulting thioglycoside product can then immediately be used in the next glycosylation event. In their first attempt towards a pre-activation based glycosylation strategy they found that glucuronic acid **87** did not provide a productive coupling with *N*-phthaloyl glucosamine **92**, and therefore they switched to the use of non-oxidized thioglucosides. The disarmed per-acetylated glucoside **88** could not be condensed with a range of glucosamine acceptors and that the use of *p*-methoxybenzylidene glucose donor **89** was also unproductive. The more reactive *tert*-butyldimethyl silyl containing *S*-tolyl glucoside **90** on the other hand gave a productive coupling with glucosamine **92** and the *S*-tolyl disaccharide **94** was obtained in 75% yield. Desilylation of this dimer provided a dimer building block **95** which could be used as an acceptor. Combination of the dimer building blocks in an iterative one-pot glycosylation sequence delivered the HA-hexasaccharide **100** in 54–60% yield. Transformation of the three PMB-ethers into three carboxylic acids proved to be a challenge. After significant experimentation it was discovered that the presence of the TBS-moiety was required for a productive cleavage of the PMB-groups, since treatment of the desilylated hexamer with either DDQ or CAN led to multiple decomposition products. Next, transformation of the liberated alcohol functions into the desired carboxylate groups required a carefully optimized two-step oxidation protocol to ensure complete oxidation of all three alcohols [66]. Protection of the resulting carboxylates as benzyl esters then allowed the purification of the fully protected HA-hexamer. Transformation of this hexamer into HA-fragment **100** was accomplished by desilylation, reduction of the benzyl esters, ethers and benzylidene acetals, transamination of the benzoyl and phthaloyl groups, and finally selective acetylation of the glucosamine nitrogens.

In the assembly of longer HA-fragments, Huang and co-workers discovered that removal of the PMB ethers failed in the final stage of an HA-decasaccharide

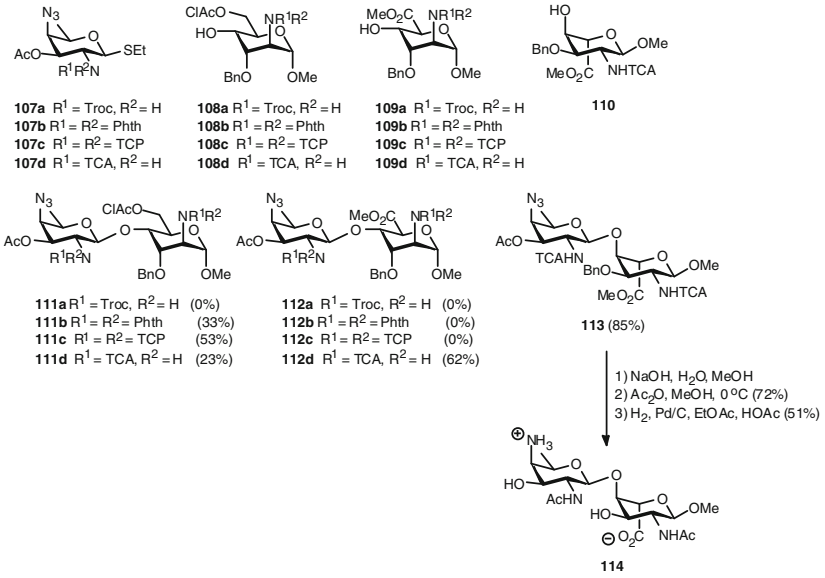
synthesis and therefore they returned to the use of oxidized dimer building blocks [63]. Fully protected disaccharide **97** could be obtained by condensation of trichloroacetyl protected glucosamine **93** and the previously used TBS-glucoside **90**, subsequent removal of the C-6' PMB ether, and uronic ester formation. Interestingly, dimer **97** could also be accessed from TBS-protected glucuronic acid ester **91** [67]. The per-acetylated glucuronide **87**, on the other hand, failed to give a productive glycosylation with acceptor **93** under the pre-activation conditions used. This result contrasts with results obtained using analogous trichloroacetimidate (e.g., **79**), 1-hydroxyl [60] or *S*-phenyl glucuronate donors (e.g., **85**), which could be condensed with very similar TCA-GlcN acceptors. The unsuccessful glycosylation of donor **87** can therefore not adequately be explained by its inherent low reactivity. After significant experimentation, Huang and co-workers were able to combine disaccharides **97** and **98** in a high yielding pre-activation based glycosylation to provide tetramer **101**. Addition of a catalytic amount of TMSOTf after pre-activation of the donor glycoside was required to prevent oxazoline formation of the activated TCA-protected donors. Tetrasaccharide **101** was elongated with terminal dimer building block **102** to provide hexamer **103**, which, after desilylation, served as an acceptor in a [4+6]-condensation to give the decamer **105**. Deprotection of this decamer started with removal of the TBS-group. Next, all esters and trichloroacetyls were saponified over a period of 5 weeks, after which *N*-acetylation and reductive removal of the benzyl ethers delivered HA-decamer **106**.

From the presented examples above it is clear that uronic acid building blocks have found widespread application both as donor and acceptor glycosides in the assembly of GAG-oligomers, notwithstanding their relatively low reactivity. In fact, the efficient synthesis of large oligomers has been made possible through the use of uronic acid esters.

5 Bacterial (Capsular) Polysaccharides

Many bacteria, both Gram-positive and Gram-negative, are covered with polysaccharides as part of LPS structures and/or a thick polysaccharide capsule [68–71]. The structural variation in these LPS and capsular polysaccharides (CPSs) is almost unlimited and they often contain rare monosaccharide and uronic acid building blocks. The synthesis of bacterial polysaccharides has attracted considerable attention in the context of modern vaccine development [72–74]. As with the other classes of uronic acid containing oligosaccharides and glycoconjugates described in this chapter, both post- and pre-oxidation glycosylation strategies have been employed for the assembly of acidic bacterial oligosaccharide structures.

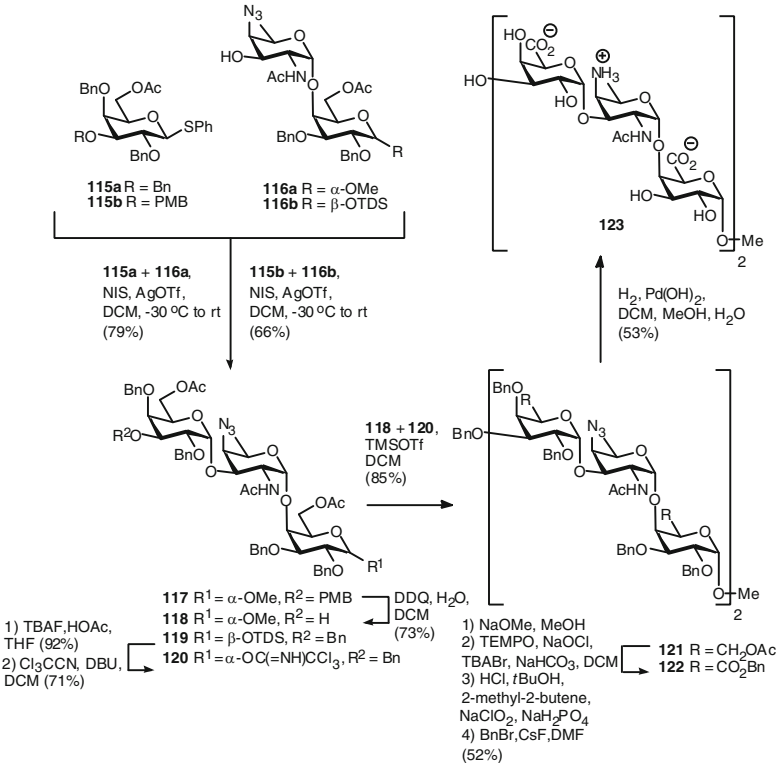
As part of a program directed at the synthesis of *Shigella sonnei* oligomers, Lipták and co-workers have conducted a detailed study of the glycosylation behavior of both oxidized and non-oxidized altrosyl acceptors (Scheme 9) [75–77]. The O-specific polysaccharide of *Shigella sonnei* Gram-negative bacteria, causing



Scheme 9 Synthesis of *Shigella sonnei* disaccharides

diarrhea and dysentery, comprises the virulence factor of this bacterium and is composed of diamino-D-fucose-L-altruronic acid dimer repeats [78]. Because the route of synthesis of L-altruronic acid started from the relatively expensive L-glucose, the first glycosylation studies towards a set of dimer saccharides used the enantiomeric D-altrosyl building blocks, obtained from D-glucose [75]. As depicted in Scheme 9, four *S*-ethyl diamino-D-fucosyl donors **107a–d**, differing in the protecting on the C-2 amino function, were probed with four D-altrosyl/altruronic acid acceptor pairs (**108a–d/109a–d**) in NIS/TfOH-mediated condensations. Use of the trichloroethoxycarbonyl-protected building blocks did not lead to any disaccharide formation, irrespective of the oxidation state at C-5 of the altrosyl coupling partner. When the phthaloyl- and tetrachlorophthaloyl-protected building blocks were used, the non-oxidized altrosyl acceptors provided the most productive condensation reactions. For the trichloroacetyl masked monosaccharides, on the other hand, the outcome was reversed and the TCA-protected altruronic acid acceptor **109d** gave the highest yielding glycosylation in the series. When the enantiomeric altruronic acid ester **110** was employed under similar conditions with a small excess of donor **107d** (1.8 equivalents), the fully protected *Shigella* disaccharide **113** was obtained in 85% yield. Deprotection of this dimer was accomplished by saponification of the methyl ester, *O*-acetyl and *N*-trichloroacetyl groups, *N*-acetylation, and final hydrogenolysis of the benzyl ether and azide functions in 36% overall yield.

An example of the use of a post-glycosylation oxidation strategy is presented by the recent synthesis of monomeric and dimeric repeats of the zwitterionic Type 1 capsular polysaccharide from *Streptococcus pneumonia* (Sp1) depicted in

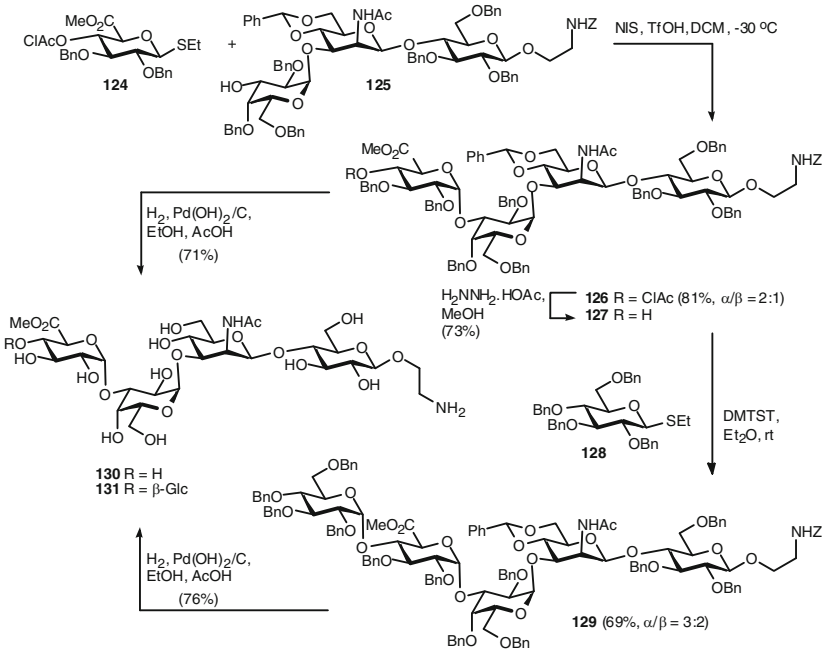


Scheme 10 Synthesis of a Sp1-hexamer fragment

Scheme 10 [79]. The Sp1-zwitterionic polysaccharide (ZP) is composed of trimeric [α-D-GalA-(1→3)-α-D-Fuc(4-N)NAc-(1→4)-α-D-GalA-(1→3)] repeats, containing negatively charged carboxylate groups on each of the GalA residues and a positively charged amino group on the rare 4-amino-*N*-acetyl fucosamine moiety [80]. The synthetic challenges presented by the structure of this ZP include the introduction of all *cis*-glycosidic linkages, the presence of the rare diaminofucose residue, and the difficult reactivity of the GalA residues (see section on Pectin). To circumvent the low reactivity of GalA derivatives, Bundle and co-workers followed a route in which the carboxylate functions were introduced in the penultimate step of the synthesis. The hexamer **121** was assembled using a [3+3] coupling strategy as depicted in Scheme 9. The trimer building blocks were constructed by the condensation of *S*-phenyl galactosyl donors **115a/b** and FucNAc-Gal dimers **116a/b** (both obtained in 22 steps from glucosamine), respectively. The high degree of stereoselectivity in these NIS/AgOTf mediated glycosylations was attributed to remote stereoelectronic effects of the C-6-*O*-acetyl function (condensation of galactosyl donors and galactosyl C-3-OH acceptors often proceed with a high degree of α-selectivity. See for example [81]). Trimer **117** was transformed into acceptor **118** by treatment with DDQ (73%) and donor **120** was constructed from trisaccharide

119 by removal of the anomeric thexyldimethylsilyl group and subsequent trichloroacetimidate formation. The union of the two trisaccharide parts required careful tuning of the reaction conditions (temperature, donor equivalents and amount of Lewis acid activator) and was accomplished in 85% yield. The fully protected hexasaccharide was deacetylated to give the tetraol, which was oxidized in a two-step procedure to provide the tetracarboxylate. Immediate benzylation then gave hexamer **122** in 52% over the last steps. Hydrogenolysis of all benzyl ethers and esters and the two azide groups gave the zwitterionic target compound **123**.

An example of the use of uronic acid building blocks in the assembly of a bacterial CPS is shown in Scheme 11. To investigate the immunogenicity of *Streptococcus pneumonia* Type 9 CPSs, Alpe and Oscarson synthesized tetra- and pentasaccharide fragments of the CPS [82, 83]. In the condensation of trisaccharide acceptor **125** with thioglucuronic acid ester **124** it was found that the promoter system had a profound effect on the stereochemical outcome of the reaction. Where DMTST gave predominantly the undesired β-isomer, the use of NIS/TfOH led to the preferential formation of the α-product (81% total yield, $\alpha/\beta = 2{:}1$). This condensation presents yet another example in which an *N*-acetyl containing acceptor is condensed with a disarmed uronic acid ester donor (see GAG section). The chloroacetyl group in **126** was readily removed by hydrazine acetate in MeOH to furnish tetrasaccharide acceptor **127**. The stereoselective introduction of the final α-glucosidic linkage also proved to be challenging and the use of DMTST in Et_2O



Scheme 11 Assembly of an *S. pneumonia* Type 9A tetra- and pentasaccharide

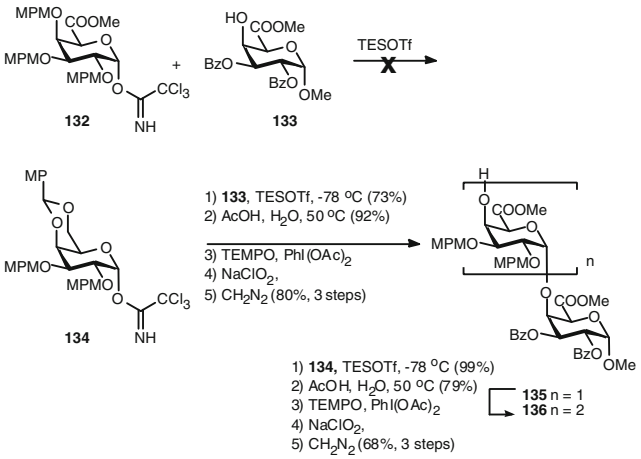
was found to give the best result: pentamer **129** was obtained in 69% yield and a 3:2 α/β ratio. Global reduction of the benzyl ethers and benzyloxycarbonyl groups in **127** and **129** gave the *S. pneumonia* type 9A tetra- and pentasaccharides **130** and **131** in their methylated form.

6 Pectin

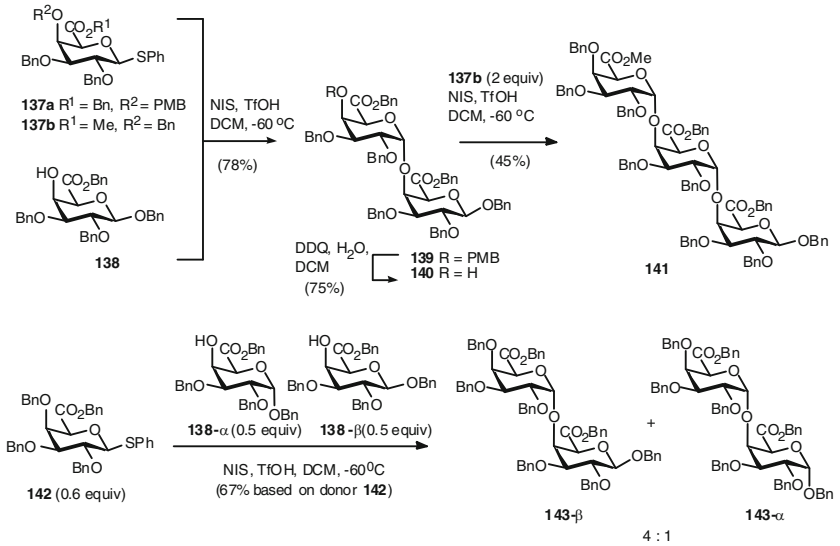
Pectin is an anionic polysaccharide which occurs in the primary cell wall of higher plants and is composed of homogalacturonan (HGA), rhamnogalacturonan (RG-I and RG-II), xylogalacturonan (XGA), and apiogalacturonan (AGA) regions [84]. Galacturonic acid is the most abundant hexose constituent of pectin, and it makes up approximately 90% of the uronic acid content. The pectin HGA part is characterized by linear α-1,4 linked oligomers of D-galacturonic acid, which occur either as the free carboxylic acid or the methyl ester. The RG-I regions are built up from α-D-galacturonic acid-(1→4)-α-L-rhamnosyl-(1→2) dimers, of which the rhamnosyl residues can be provided with neutral side chains, typically composed of D-galactose and D-arabinose. RG-II is a highly substituted galacturonan which is adorned with various complex oligosaccharides. The XGA and AGA regions in pectin are built up from HGA chains, which are substituted with monomeric or dimeric xylopyranosyl or apiosyl residues at the GalA C-2 position. Knowledge of the precise structure and function of pectin is crucial to elucidate the role of these polysaccharides in plant cell growth and defense mechanisms as well as their role in traditional medicine. Therefore they have attracted significant interest from the synthetic carbohydrate community.

The synthesis of homogalacturonan fragments has been investigated using different synthetic strategies, many of which point to the difficult reactivity of galacturonic acid building blocks. With the aim of studying the enzyme endo-polygalacturonase, Yamamoto et al. prepared a trigalacturonic acid and the corresponding *S*-glycosidic analog [85]. En route to these compounds it turned out that glycosylations between galacturonic acid ester C-4 hydroxyl acceptor **133** and donor galacturonate **132** under the agency of triethylsilyltriflate failed (Scheme 12). Therefore, an alternative strategy was devised, in which the mono- and dimeric galacturonic acceptors were coupled with galactosyl donor **134**, after which the non-reducing end galactose residues were oxidized. Condensation of the galacturonyl acceptors **133** and **135** with imidate **134** gave the α-linked products in high yield. After removal of the 4-methoxybenzylidene acetal, oxidation with TEMPO/BAIB led to the formation of the corresponding aldehydes. Further oxidation with sodium chlorite and ensuing treatment with diazomethane gave the methyl esters **135** and **136** in good yield.

In their preparation of homogalacturonan fragments, Doutheau and co-workers noticed a difference in the reactivity of α- and β-galacturonic ester C-4 alcohol acceptors (Scheme 13) [86, 87]. *S*-Phenyl donor **137a** was efficiently condensed with galacturonic acid acceptor **138**, at low temperature under the agency of



Scheme 12 Synthesis of a pectin trisaccharide

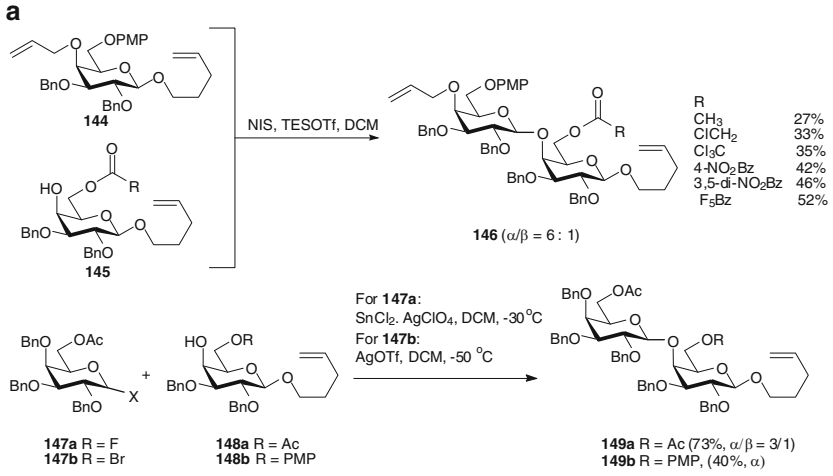


Scheme 13 Difference in reactivity between α- and β-galacturonic acid ester C-4-OH acceptors

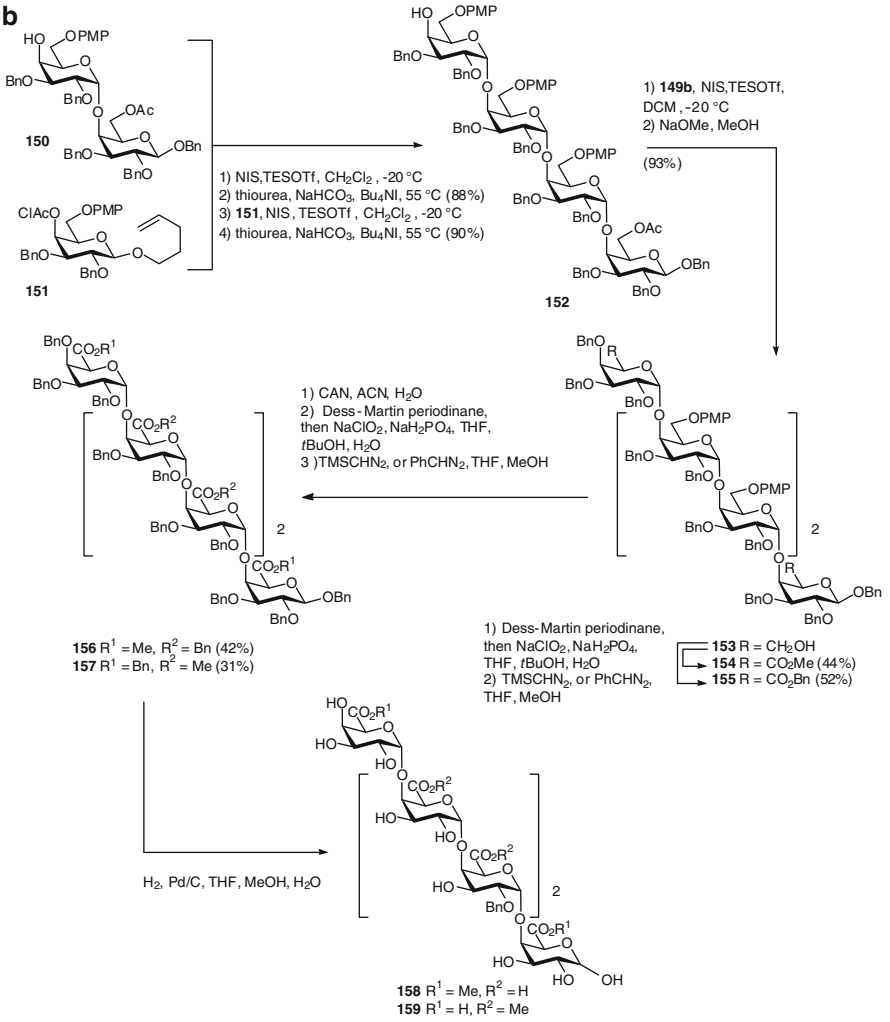
NIS/TfOH to provide disaccharide **139** in good yield and excellent stereoselectivity. When they tried to elongate disaccharide **140**, obtained after DDQ-mediated liberation of the C-4″hydroxyl, they noted that the coupling of disaccharide acceptor **140** with donor **137b** required more strenuous conditions. Higher reaction temperatures (−10 °C vs −60 °C), a larger excess of donor galactoside (2 vs 1.2 equivalents) and longer reaction times (4 h vs 1.4 h) were needed and the condensation

proceeded in lower yield (45% vs 78%) compared to the analogous reaction between monomeric acceptor **138** and donor **137a**. To investigate the nature of this reactivity difference, competition experiments were performed in which **138-α** (0.5 eq.) and **138-β** (0.5 eq.) were coupled with thiophenyl donor **142** (0.6 eq.) using NIS/TfOH as the promoter system [88]. A mixture of dimers **143** was formed in a ratio of 4:1, indicating that the β-anomer **138-β** was more reactive than its α-counterpart **138-α**. It was hypothesized that the absence of the anomeric effect in the β-configured acceptors makes the basicity of pyranosyl ring oxygen in these galacturonides greater than in the α-isomers. Therefore, intramolecular hydrogen bonding between the C-4-OH and the pyranosyl ring oxygen would be stronger in the β-anomers than in the α-anomers and as a consequence the C-4-OH of the β-anomers is more nucleophilic. Similar experiments with glucuronic ester derivatives, in which internal hydrogen bond formation is prevented by the equatorial orientation of the 4-OH, showed a less pronounced reactivity difference between the α- and β-acceptor (1:1.2). The residual enhanced nucleophilicity of the β-anomer C-4-OH was ascribed to an increase of the electron density at C-4 by the delocalization of the ring-oxygen nonbonding electrons into the σ* orbital of the C-4–C-5 bond (a similar effect was observed for C-4-OH mannuroic acid acceptors [89]).

To circumvent the use of galacturonic acid building blocks, Madsen's group explored the use of suitably protected galactose building blocks in the synthesis of partly methyl-esterified fragments of the homogalacturonan polysaccharide (Scheme 14) [90]. Methyl and benzyl carboxylic ester functions were introduced at the level of the fully protected oligosaccharides, which were assembled employing an orthogonal protective group strategy in which acyl protective groups were used in combination with *p*-methoxyphenyl ethers. To access dimer building blocks, chemoselective and orthogonal glycosylation strategies



Scheme 14 (continued)



Scheme 14 Assembly of partly methylated HGA-pectin fragements

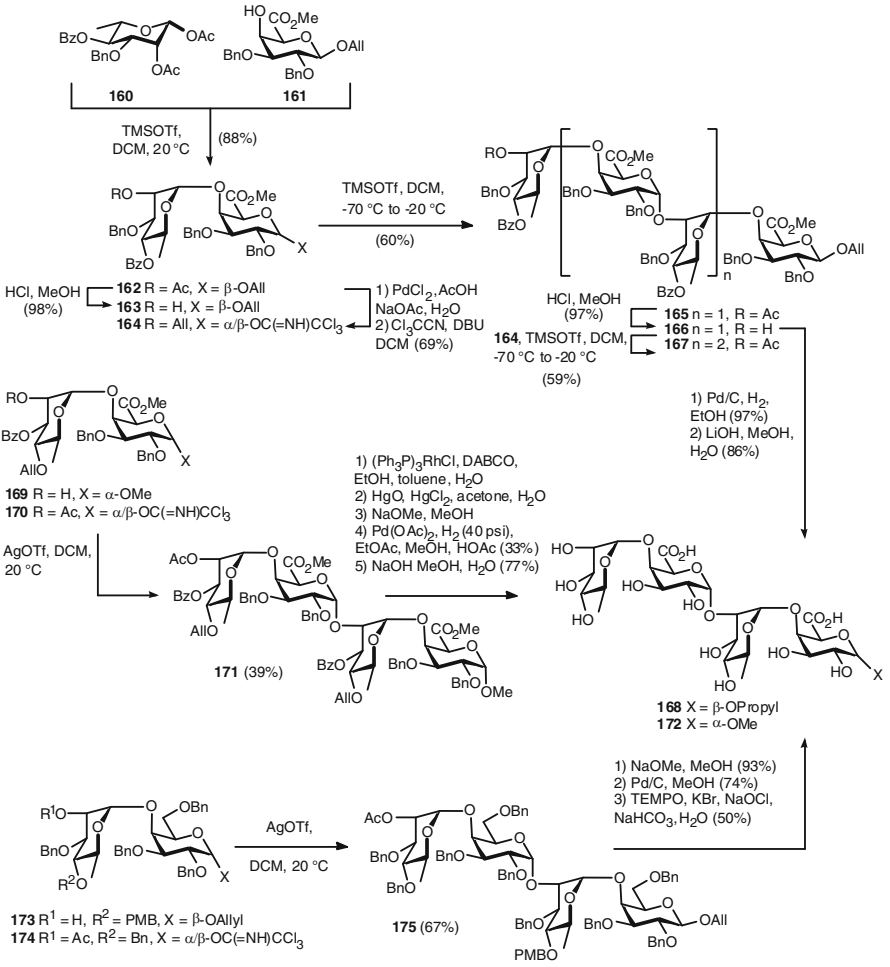
were carried out with *n*-pentenyl glycosyl donors. As depicted in Scheme 14a, the small reactivity difference between *n*-pentenyl donor **144** and various ester protected *n*-pentenyl acceptors **145** could be exploited to attain a productive chemoselective glycosylation. It was revealed that an increase in the electron-withdrawing capacity of the acyl group resulted in a higher yield of the disaccharides, while the anomeric ratio persisted (α:β = 6:1). Because a chemoselective glycosylation strategy was not suitable to construct dimer building blocks with the same C-6 hydroxyl protecting group, orthogonal condensations of *n*-pentenyl

acceptor **148a** with fluoride and bromide donors **147a/b** were explored. Whereas the glycosylation of **147a** and **148a** under Mukaiyama conditions afforded an anomeric mixture of digalactosides **149a**, only trace amounts of the β-anomer **149b** were formed in the coupling of acceptor **148a** with bromide **147b**. The latter donor was also used in the construction of dimer **150** from acceptor **148b**. The *n*-pentenyl monomer **151** and dimer donor **149b** were used in ensuing NIS/TESOTf-mediated glycosylation events to give uneventfully solely the α-configured tri-, tetra-, and hexamers in good to excellent yields (Scheme 14b). To attain the target pectin fragments selected 6-OH functions in the oligomers were unmasked, oxidized, and esterified. This sequence of reactions is illustrated for hexagalacturonate **158** and **159**. Dess–Martin periodinane oxidation of the primary alcohols in **153** gave the intermediate di-aldehyde and subsequent sodium chlorite oxidation furnished the carboxylic acids. It was observed that ensuing esterification with cesium carbonate and methyl iodide or benzyl bromide was accompanied by degradation. Considerable improvement could be made by the use of trimethylsilyl diazomethane and phenyl diazomethane under neutral conditions to give the methyl- and benzyl di-esters **154** and **155** in 44% and 52% yield respectively. Oxidative cleavage of the *p*-methoxyphenyl ethers with CAN then gave the tetraol, which could be transformed into either the benzyl or methyl esters (**156** and **157**, 42% and 31% respectively). Hydrogenolysis of hexamers **156** and **157** provided the tetramethyl ester **158** and dimethyl ester **159**.

The viability of galacturonic acid acceptors and donors in the assembly of rhamnogalacturonan I fragments has been explored by the group of Vogel [91]. Tetra- and hexasaccharide fragments of rhamnogalacturonan were prepared using α-L-Rha-(1→4)-GalA dimer building blocks (Scheme 15). Thus, TMSOTf mediated condensation of rhamnose acetate **160** and galacturonate **161** provided dimer **162**. Transformation of this disaccharide into glycosyl acceptor **163** was accomplished using methanolic hydrochloric acid, while deallylation of **162** and subsequent introduction of the trichloroacetimidate function furnished donor **164**. The two dimer building blocks were combined in a TMSOTf mediated glycosylation to give stereoselectively tetrasaccharide **165** in 60% yield. Deacetylation of this tetrasaccharide then set the stage for the next glycosylation event in which hexamer **167** was assembled in a [2+4] fashion in 59% yield. Deprotection of the fully protected tetrasaccharide was accomplished using a hydrogenation-saponification sequence, delivering RG-I tetramer **168**.

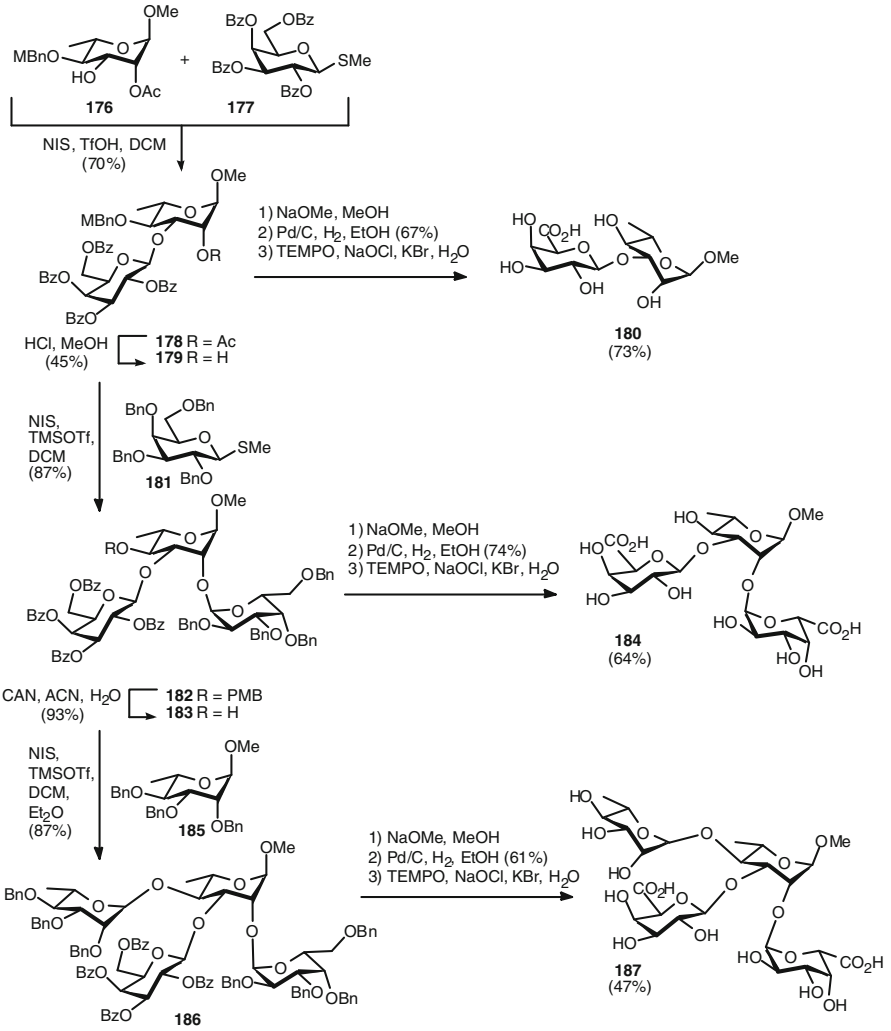
A very similar tetrasaccharide was synthesized by Reiffarth and Reimer (Scheme 15) [92]. They reported that the glycosylation of dimer acceptor **169** with donor **170**, which mainly differ from **163** and **164** in the protecting group pattern on the rhamnosyl residues, proceeded rather problematically. The best result with building blocks **169** and **170** was obtained using AgOTf as a promoter and led to tetramer **171** in 39% yield. Deprotection of this tetramer required a sequence of reactions, involving deallylation, transesterification, hydrogenolysis, and saponification to lead to the deprotected tetrasaccharide **172**.

RG-I tetrasaccharide **168** has also been synthesized following an approach in which the carboxylic acid functions are installed at the end of the synthesis



Scheme 15 Assembly of RG-pectin fragments

(Scheme 15) [93]. Coupling of α-L-rhamnopyranosyl-(1→4)-D-galactopyranosyl trichloroacetimidate **174** with allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside **173**, using AgOTf as a promoter, gave stereoselectively the tetrasaccharide **175** in 67% yield. Two-step removal of the protecting groups was followed by oxidation of the primary alcohol functions with TEMPO/NaOCl to give the target acidic tetrasaccharide **168**. Recently Davis and co-workers used an analogous approach in which they used an [Rha-Gal]-thioglycoside donor to synthesize RG-I tetrasaccharides having either two free carboxylic acids or one methyl ester in the final products [94].



Scheme 16 Late stage oxidation in the synthesis of RG-II sidechain fragments

Field's group studied the synthesis of a trisubstituted rhamnoside, which constitutes a tetrasaccharide fragment of rhamnogalacturonan-II (Scheme 16) [95]. Using non-oxidized galactosyl building blocks a methyl rhamnoside acceptor was functionalized by β-galactosylation of the C-3 hydroxyl, α-galactosylation of the C-2 OH, and α-fucosylation of the remaining C-4 alcohol. After removal of all protecting groups from the di- (**179**), tri- (**183**), and tetrasaccharide (**186**), the galactosyl residues were oxidized to provide the corresponding galacturonic acids using the TEMPO/NaOCl/KBr reagent combination. A decrease in yield with

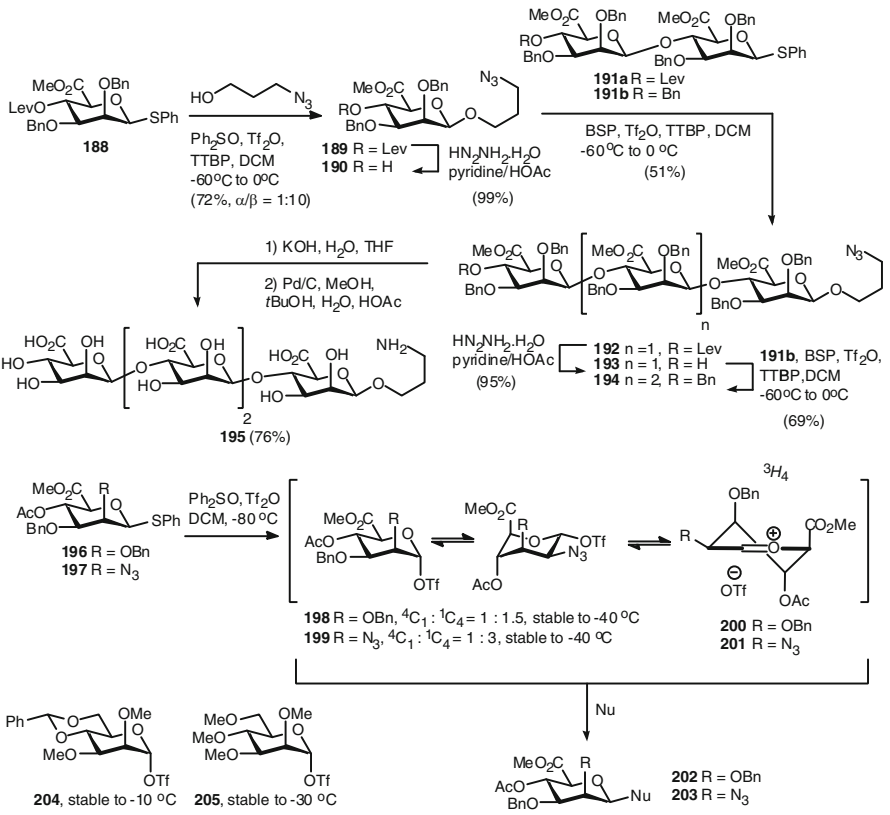
increasing complexity of the oxidation targets was observed, which was explained by the increased steric bulk of the substrates.

In summary, the combined work on the synthesis of pectin fragments has shown that strategies in which oxidized or non-oxidized galactose building blocks both can lead to productive routes of synthesis towards pectin oligomers. The non-oxidized building blocks are generally more reactive than their oxidized counterparts, which can lead to higher glycosylation yields. However, the oxidation in the final steps of the synthesis can be challenging, thereby counterbalancing this advantage. From the examples in which GalA building blocks have been used, it is clear that the lower reactivity of these building blocks does not a priori rule out an efficient condensation reaction. Especially when used in combination with a reactive coupling partner and activator system, productive glycosylation yields can be obtained.

7 Alginates

Alginates are linear unbranched polymers, built up from (1→4) linked β-D-mannuronic and α-L-guluronic acids, occurring in homouronate (poly-ManA or polyGulA) and alternating (ManA-GulA) stretches [96]. Alginate polymers are isolated from marine brown algae (Phaeophyta) and have found wide application in the food, textile, and pharmaceutical industries because of their gelling properties. Certain pathogenic bacteria, such as *Pseudomonas aerigunosa*, also produce alginate polymers as exopolysaccharides and small alginate fragments have been implied to have immunostimulatory activity [97, 98]. The synthesis of alginate oligomers has attracted recent interest in investigating the latter biological effects [99–103]. The main synthetic challenge posed by these structures is the repetitive installation of the 1,2-*cis*-linkages to build the oligosaccharide chain. Oligomers of mannuronic acid have been assembled using oxidized and non-oxidized mannosidic building blocks, whereas GulA-oligomers have only been assembled using a post-glycosylation oxidation strategy.

We have investigated the glycosylation behavior of mannuronic acids, and have disclosed that various mannuronic acid building blocks can effectively be used to install β-mannuronic acid linkages in a highly stereoselective fashion [89, 99, 100, 104]. As depicted in Scheme 17, ManA pentamer **195** was assembled using monomeric and dimeric *S*-phenyl ManA building blocks. As mentioned previously in the section on GAG synthesis, significant differences were observed between the BSP/Tf_2O and Ph_2SO/Tf_2O activated glycosylations, with the former sulfonium activator giving superior yields over the latter. The stereoselectivity in condensations of ManA donors can be explained to arise from the intermediacy of a relatively stable α-triflate, in analogy to the triflate intermediates in Crich's benzylidene β-mannosylation protocol [105]. In this case the electron-withdrawing carboxylic ester serves to stabilize the anomeric triflate relative to the (solvent separated) oxacarbenium ion. To investigate the intermediacy of anomeric triflates, low-temperature NMR experiments were performed to detect possible reactive intermediates. β-*S*-Phenyl mannuronic acid **196** was consumed instantaneously



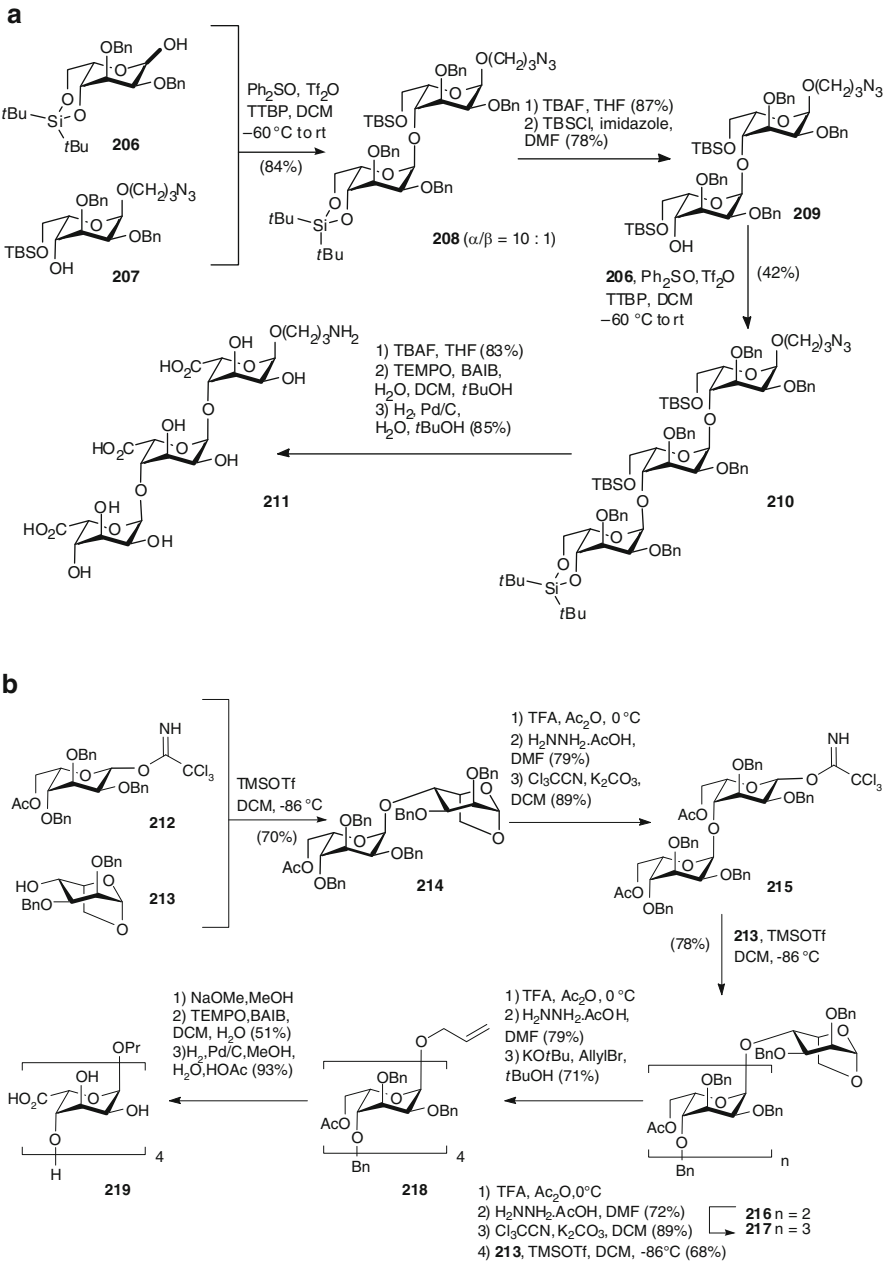
Scheme 17 Mannuronic acid building blocks in the synthesis 1,2-*cis* linked oligomers

upon treatment with Ph_2SO/Tf_2O at −80 °C and transformed into a mixture of anomeric triflates **198** [104]. Interestingly, the equatorial $^1C_4$-triflate is energetically slightly favored over its axial $^4C_1$-counterpart, even though the former structure places three substituents in an axial fashion and does not benefit from the anomeric effect. This effect was even more pronounced in the case of mannosaziduronic acid triflate **199**, which existed as a 3:1 mixture of chair conformers. We have postulated that the C-5 carboxylate is at the basis of this unexpected behavior. Because the anomeric center in **198** and **199** is so electron depleted it assumes a conformation which approaches the structure of the $^3H_4$-oxacarbenium ion **200/201**, which presents the most stable mannuronic acid oxacarbenium ion half chair. Nucleophilic attack on the β-face of oxacarbenium ion **200/201** can also provide an adequate explanation for the observed 1,2-*cis*-selectivities observed with mannuronates **196** and **197**. Interestingly, decomposition of anomeric triflates **198** and **199** occurred at significantly lower temperature (−40 °C) than the decomposition of benzylidene mannosyl triflate **204**, which was stable up to −10 °C. Even tetra-*O*-methyl mannosyl triflate **205** has been shown to decompose at higher

temperature (−30 °C) than triflates **198**/**199** [105]. These decomposition data suggest that mannuronates **198** and **199** are not as stable as would be expected based on the presence of the electron-withdrawing C-5 carboxylate.

The synthesis of L-guluronic acid oligomers has been successfully accomplished using non-oxidized building blocks. We have explored the use of guluronic acid building blocks, but it was found that the combination of a guluronic acid donor and acceptor did not lead to a productive glycosylation reaction, which we attributed to the low nucleophilicity of the guluronic acid C-4 alcohol [102]. The use of non-oxidized building blocks was more efficient, and gulose dimer **208** was obtained stereoselectively in 84% from monomers **206** and **207** (see Scheme 18a).[2] Elongation of the disaccharide proved to be more challenging and triguloside **210** was formed in a [1+2]-coupling of donor **206** and acceptor **209** in 42% yield. These results parallel the results of Doutheau and co-workers in their work on pectin oligomers (see above). Transformation of trimer **210** into triguluronic acid **211** was accomplished by global desilylation, TEMPO/BAIB mediated oxidation of the primary alcohols in a DCM/H_2O/*t*BuOH solvent system and finally hydrogenolysis of the benzyl ethers and concomitant reduction of the spacer azide. Hung and co-workers also noted the poor reactivity of the gulosyl C-4 alcohol and therefore investigated the use of 1,6-anhydrogulose **213**, which places the C-4 hydroxyl in an accessible equatorial fashion because of the inverted chair structure [103]. This acceptor functioned as adequate nucleophile and gulose oligomers up to the tetramer level were assembled as depicted in Scheme 18b. Gulosyl trichloroacetimidate **212** was condensed with anhydrogulose acceptor **213** to give the diguloside **214** in 70% yield. Transformation of this dimer into a suitable donor was accomplished by cleavage of the anhydro-bridge in **214**, followed by anomeric deacetylation and imidate formation. Elongation of the disaccharide donor with anhydro gulose **213** then gave triguloside **216**, again in good yield and excellent selectivity. After conversion of **216** into the corresponding imidate, following the three-step sequence outlined above, and a [1+3]-coupling using building block **213**, tetramer **217** was obtained. Because it was found that coupling with a primary alcohol spacer did not lead to a stereoselective construction of the desired α-gulosidic bond, an anionic glycosylation was used to cap the tetrasaccharide with a simple alkyl spacer. Clean formation of the α-allyl tetramer **218** was accomplished using KO*t*Bu as a base and allybromide as electrophile. The stereoselectivity in this reaction can be explained by the profitable chelation of the potassium cation between O-1 and O-3, which makes formation of the α-alkoxide favored over the generation of the corresponding β-isomer. After removal of the acyl functions in **218**, the primary alcohols were oxidized using the TEMPO/BAIB reagent combination to provide the tetracarboxylate. Removal of the benzyl ethers and concomitant reduction of the allyl into a propyl group completed the synthesis of guluronate **219**.

[2]We have postulated that the unusually high α-selectivity observed for condensations of gulosyl donors originates from the α-selective axial attack of the gulosyl $^3H_4$-cation. See [102].



Scheme 18 Synthesis of L-guluronic acid oligomers

8 Conclusions

Although not as extensively used as their non-oxidized counterparts, uronic acids have found wide application in the synthesis of a broad pallet of uronic acid containing oligosaccharides and glycoconjugates. It is now clear that most uronic acid building blocks are less reactive than their reduced equivalents, but this does not a priori rule out their effective use in synthesis. Depending on the protecting groups on the uronic acid building block, the strength of the electrophilic promoter system used, and the reactivity of the coupling partner, highly efficient condensation reactions can be achieved. Furthermore, the oxidation state of C-6 can have a strong influence on the stereochemical outcome of a glycosylation reaction as recently disclosed in the synthesis of alginate oligomers.

References

1. Lindberg B, Kenne L (1985) The polysaccharides. Academic, New York
2. Van den Bos LJ, Codée JDC, Litjens REJN, Dinkelaar J, Overkleeft HS, Van der Marel GA (2007) Uronic acids in oligosaccharide synthesis. Eur J Org Chem 3963–3976
3. Hassan H (2007) Present status in the chemistry of hexuronic acids found in glycosaminoglycans and their mimetic aza-sugars analogues. Mini-Rev Org Chem 4:61–74
4. Schmidt RR, Grundler G (1981) Simple synthesis of β-D-glucopyranosyluronates. Synthesis 885–887
5. Schmidt RR, Stumpp M, Michel J (1982) Glycosylimidates 4. α-D-Glucopyranosyl and β-D-glucopyranosyl phosphates from O-α-D-glucopyranosyl trichloroacetimidates. Tetrahedron Lett 23:405–408
6. Veeneman GH, Van Leeuwen SH, Van Boom JH (1990) Iodonium ion promoted reactions at the anomeric center 2. An efficient thioglycoside mediated approach toward the formation of 1, 2-trans linked glycosides and glycosidic esters. Tetrahedron Lett 31:1331–1334
7. Fraser-Reid B, Wu ZF, Udodong UE, Ottosson H (1990) Armed-disarmed effects in glycosyl donors – rationalization and sidetracking. J Org Chem 55:6068–6070
8. Veeneman GH, van Boom JH (1990) An efficient thioglycoside-mediated formation of α-glycosidic linkages promoted by iodonium dicollidine perchlorate. Tetrahedron Lett 31:275–278
9. Douglas NL, Ley SV, Lucking U, Warriner SL (1998) Tuning glycoside reactivity: new tool for efficient oligosaccharide synthesis. J Chem Soc Perkin Trans 1:51–65
10. Zhang ZY, Ollmann IR, Ye XS, Wischnat R, Baasov T, Wong CH (1999) Programmable one-pot oligosaccharide synthesis. J Am Chem Soc 121:734–753
11. Koeller KM, Wong CH (2000) Synthesis of complex carbohydrates and glycoconjugates: enzyme-based and programmable one-pot strategies. Chem Rev 100:4465–4493
12. Jensen HH, Lyngbye L, Jensen A, Bols M (2002) Stereoelectronic substituent effects in polyhydroxylated piperidines and hexahydropyridazines. Chem Eur J 8:1218–1226
13. Shipkova M, Wieland E (2005) Glucuronidation in therapeutic drug monitoring. Clin Chim Acta 358:2–23
14. Shipkova M, Armstrong VW, Oellerich M, Wieland E (2003) Acyl glucuronide drug metabolites: toxicological and analytical implications. Ther Drug Monit 25:1–16
15. Stachulski AV, Harding JR, Lindon JC, Maggs JL, Park BK, Wilson ID (2006) Acyl glucuronides: biological activity, chemical reactivity, and chemical synthesis. J Med Chem 49:6931–6945

16. Stachulski AV, Jenkins GN (1998) The synthesis of O-glucuronides. Nat Prod Rep 15:173–186
17. Kaspersen FM, Van Boeckel CAA (1987) A review of the methods of chemical synthesis of sulfate and glucuronide conjugates. Xenobiotica 17:1451–1471
18. Lucas R, Alcantara D, Morales JC (2009) A concise synthesis of glucuronide metabolites of urolithin-B, resveratrol, and hydroxytyrosol. Carbohydr Res 344:1340–1346
19. Juteau H, Gareau Y, Labelle M (1997) A convenient synthesis of β-acyl glucuronides. Tetrahedron Lett 38:1481–1484
20. Perrie JA, Harding JR, Holt DW, Johnston A, Meath P, Stachulski AV (2005) Effective synthesis of 1-β-acyl glucuronides by selective acylation. Org Lett 7:2591–2594
21. Jones AE, Wilson HK, Meath P, Meng XL, Holt DW, Johnston A, Oellerich M, Armstrong VW, Stachulski AV (2009) Convenient syntheses of the in vivo carbohydrate metabolites of mycophenolic acid: reactivity of the acyl glucuronide. Tetrahedron Lett 50:4973–4977
22. Bowkett ER, Harding JR, Maggs JL, Park BK, Perrie JA, Stachulski AV (2007) Efficient synthesis of 1-β-O-acyl glucuronides via selective acylation of allyl or benzyl D-glucuronate. Tetrahedron 63:7596–7605
23. Vincken J-P, Heng L, Groot AD, Gruppen H (2007) Saponins, classification and occurrence in the plant kingdom. Phytochemistry 68:275–297
24. Hostettmann K, Marston A (1995) Saponins. Cambridge University Press, Cambridge
25. Yu BA, Sun JS (2009) Current synthesis of triterpene saponins. Chem Asian J 4:642–654
26. Yu B, Zhang YC, Tang PP (2007) Carbohydrate chemistry in the total synthesis of Saponins. Eur J Org Chem 5145–5161
27. Kensil CR (1996) Saponins as vaccine adjuvants. Crit Rev Ther Drug Carrier Syst 13:1–55
28. Cleland JL, Kensil CR, Lim A, Jacobsen NE, Basa L, Spellman M, Wheeler DA, Wu JY, Powell MF (1996) Isomerization and formulation stability of the vaccine adjuvant QS-21. J Pharm Sci 85:22–28
29. Jacobsen NE, Fairbrother WJ, Kensil CR, Lim A, Wheeler DA, Powell MF (1996) Structure of the saponin adjuvant QS-21 and its base-catalyzed isomerization product by H-1 and natural abundance C-13 NMR spectroscopy. Carbohydr Res 280:1–14
30. Kim YJ, Wang PF, Navarro-Villalobos M, Rohde BD, Derryberry J, Gin DY (2006) Synthetic studies of complex immunostimulants from Quillaja saponaria: synthesis of the potent clinical immunoadjuvant QS-21A(api). J Am Chem Soc 128:11906–11915
31. Kim YJ, Gin DY (2001) Synthesis of the trisaccharide portion of the immunologic adjuvant QS-21A via sulfonium-mediated oxidative and dehydrative glycosylation. Org Lett 3:1801–1804
32. Deng K, Adams MM, Damani P, Livingston PO, Ragupathi G, Gin DY (2008) Synthesis of QS-21-xylose: establishment of the immunopotentiating activity of synthetic QS-21 adjuvant with a melanoma vaccine. Angew Chem Int Ed 47:6395–6398
33. Adams MM, Damani P, Perl NR, Won A, Hong F, Livingston PO, Ragupathi G, Gin DY (2010) Design and synthesis of potent quillaja saponin vaccine adjuvants. J Am Chem Soc 132:1939–1945
34. Ishihara K, Yamamoto H (1999) Arylboron compounds as acid catalysts in organic synthetic transformations. Eur J Org Chem 527–538
35. Gallagher JT, Turnbull JE (1992) Heparan-sulfate in the binding and activation of fibroblast growth-factor. Glycobiol 2:523–528
36. Spillmann D, Lindahl U (1994) Glycosaminoglycan protein interactions: a question of specificity. Curr Opin Struct Biol 4:677–682
37. Capila I, Linhardt RJ (2002) Heparin-protein interactions. Angew Chem Int Ed 41:391–412
38. Noti C, Seeberger PH (2005) Chemical approaches to define the structure-activity relationship of heparin-like glycosaminoglycans. Chem Biol 12:731–756
39. Codée JDC, Overkleeft HS, van der Marel GA, van Boeckel CAA (2004) The synthesis of well-defined heparin and heparan sulfate fragments. Drug Discov Today Technol 1: 317–326

40. Karst NA, Linhardt RJ (2003) Recent chemical and enzymatic approaches to the synthesis of glycosaminoglycan oligosaccharides. Curr Med Chem 10:1993–2031
41. Yeung BKS, Chong PYC, Petillo PA (2002) Synthesis of glycosaminoglycans. J Carbohydr Chem 21:799–865
42. Spijker NM, Van Boeckel CAA (1991) Double stereodifferentiation in carbohydrate coupling reactions – the mismatched interaction of donor and acceptor as an unprecedented factor in governing the α/β ratio of glycoside formation. Angew Chem Int Ed Engl 30:180–183
43. Spijker NM, Basten JEM, Van Boeckel CAA (1993) Unexpected phenomena in glycosylations of acceptors with L-idose configuration. Rec Trav Chim Pays-Bas 112:611–617
44. Arungundram S, Al-Mafraji K, Asong J, Leach FE III, Amster IJ, Venot A, Turnbull JE, Boons G-J (2009) Modular synthesis of heparan sulfate oligosaccharides for structure-activity relationship studies. J Am Chem Soc 131:17394–17405
45. De Mico A, Margarita R, Parlanti L, Vescovi A, Piancatelli G (1997) A versatile and highly selective hypervalent iodine (III)/2,2,6,6-tetramethyl-1-piperidinyloxyl-mediated oxidation of alcohols to carbonyl compounds. J Org Chem 62:6974–6977
46. Van den Bos LJ, Codee JDC, Van der Toorn JC, Boltje TJ, Van Boom JH, Overkleeft HS, Van der Marel GA (2004) Thioglycuronides: synthesis and application in the assembly of acidic oligosaccharides. Org Lett 6:2165–2168
47. Codée JDC, Stubba B, Schiattarella M, Overkleeft HS, van Boeckel CAA, van Boom JH, van der Marel GA (2005) A modular strategy toward the synthesis of heparin-like oligosaccharides using monomeric building blocks in a sequential glycosylation strategy. J Am Chem Soc 127:3767–3773
48. Polat T, Wong CH (2007) Anomeric reactivity-based one-pot synthesis of heparin-like oligosaccharides. J Am Chem Soc 129:12795–12800
49. Tamura J, Tokuyoshi M (2004) Synthesis of chondroitin sulfate E hexasaccharide in the repeating region by an effective elongation strategy toward longer chondroitin oligosaccharide. Biosci Biotech Biochem 68:2436–2443
50. Tamura JI, Nakada Y, Taniguchi K, Yamane M (2008) Synthesis of chondroitin sulfate E octasaccharide in a repeating region involving an acetamide auxiliary. Carbohydr Res 343:39–47
51. Crich D, Dudkin V (2001) Why are the hydroxyl groups of partially protected N-acetylglucosamine derivatives such poor glycosyl acceptors, and what can be done about it? A comparative study of the reactivity of N-acetyl, N-phthalimido, and 2-azido-2-deoxyglucosamine derivatives in glycosylation. 2-Picolinyl ethers as reactivity-enhancing replacements for benzyl ethers. J Am Chem Soc 123:6819–6825
52. Lopin C, Jacquinet JC (2006) From polymer to size-defined oligomers: an expeditious route for the preparation of chondroitin oligosaccharides. Angew Chem Int Ed Engl 45:2574–2578
53. Vibert A, Lopin-Bon C, Jacquinet JC (2009) From polymer to size-defined oligomers: a step economy process for the efficient and stereocontrolled construction of chondroitin oligosaccharides and biotinylated conjugates thereof: part 1. Chem Eur J 15:9561–9578
54. Jacquinet JC, Lopin-Bon C, Vibert A (2009) From polymer to size-defined oligomers: a highly divergent and stereocontrolled construction of chondroitin sulfate A, C, D, E, K, L, and M oligomers from a single precursor: part 2. Chem Eur J 15:9579–9595
55. Levene PA (1941) On chondrosin. J Biol Chem 140:267–277
56. Davidson EA, Meyer K (1954) Structural studies on chondroitin sulfuric acid: the nature of chondrosin. J Am Chem Soc 76:5686–5689
57. Belot F, Jacquinet JC (2000) Unexpected stereochemical outcome of activated 4,6-O-benzylidene derivatives of the 2-deoxy-2-trichloroacetamido-D-galacto series in glycosylation reactions during the synthesis of a chondroitin 6-sulfate trisaccharide methyl glycoside. Carbohydr Res 325:93–106
58. Jeanloz RW, Flowers HM (1962) Isolation and synthesis of methyl ester-methyl α-glycoside of 3-β-D-glucuronosyl-N-acetyl-D-glucosamine (hyalobiuronic acid). J Am Chem Soc 84:3030

59. Blatter G, Jacquinet JC (1996) The use of 2-deoxy-2-trichloroacetamido-D-glucopyranose derivatives in syntheses of hyaluronic acid-related tetra-, hexa-, and octa-saccharides having a methyl β-D-glucopyranosiduronic acid at the reducing end. Carbohydr Res 288:109–125
60. Dinkelaar J, Gold H, Overkleeft HS, Codee JDC, van der Marel GA (2009) Synthesis of hyaluronic acid oligomers using chemoselective and one-pot strategies. J Org Chem 74:4208–4216
61. Dinkelaar J, Codee JDC, van den Bos LJ, Overkleeft HS, van der Marel GA (2007) Synthesis of hyaluronic acid oligomers using Ph_2SO/Tf_2O-mediated glycosylations. J Org Chem 72:5737–5742
62. Huang LJ, Huang XF (2007) Highly efficient syntheses of hyaluronic acid oligosaccharides. Chem Eur J 13:529–540
63. Lu X, Kamat MN, Huang L, Huang X (2009) Chemical synthesis of a hyaluronic acid decasaccharide. J Org Chem 74:7608–7617
64. Codée JDC, Litjens REJN, Van den Bos LJ, Overkleeft HS, Van der marel GA (2005) Thioglycosides in sequential glycosylation strategies. Chem Soc Rev 34:769–782
65. Wang Y, Ye XS, Zhang LH (2007) Oligosaccharide assembly by one-pot multi-step strategy. Org Biomol Chem 5:2189–2200
66. Huang LJ, Teumelsan N, Huang XF (2006) A facile method for oxidation of primary alcohols to carboxylic acids and its application in glycosaminoglycan syntheses. Chem Eur J 12:5246–5252
67. Zeng YL, Wang Z, Whitfield D, Huang XF (2008) Installation of electron-donating protective groups, a strategy for glycosylating unreactive thioglycosyl acceptors using the preactivation-based glycosylation method. J Org Chem 73:7952–7962
68. Leone S, Silipo A, Nazarenko EL, Lanzetta R, Parrilli M, Molinaro A (2007) Molecular structure of endotoxins from Gram-negative marine bacteria: an update. Mar Drugs 5:85–112
69. Ovodov YS (2006) Bacterial capsular antigens. Structural patterns of capsular antigens. Biochemistry-Moscow 71:937–954
70. Schaffer C, Messner P (2005) The structure of secondary cell wall polymers: how Gram-positive bacteria stick their cell walls together. Microbiology 151:643–651
71. Nazarenko EL, Komandrova NA, Gorshkova RP, Tomshich SV, Zubkov VA, Kilcoyne M, Savage AV (2003) Structures of polysaccharides and oligosaccharides of some Gram-negative marine Proteobacteria. Carbohydr Res 338:2449–2457
72. Astronomo RD, Burton DR (2010) Carbohydrate vaccines: developing sweet solutions to sticky situations? Nat Rev 9:308–324
73. Pozsgay V (2008) Recent developments in synthetic oligosaccharide-based bacterial vaccines. Curr Top Med Chem 8:126–140
74. Jones C (2005) Vaccines based on the cell surface carbohydrates of pathogenic bacteria. Ann Acad Bras Cienc 77:293–324
75. Medgyes A, Bajza I, Farkas E, Pozsgay V, Liptak A (2000) Synthetic studies towards the O-specific polysaccharide of Shigella sonnei. J Carbohydr Chem 19:285–310
76. Toth A, Medgyes A, Bajza I, Liptak A, Batta G, Kontrohr T, Peterffy K, Pozsgay V (2000) Synthesis of the repeating unit of the O-specific polysaccharide of Shigella sonnei and quantitation of its serologic activity. Bioorg Med Chem Lett 10:19–21
77. Gyemant G, Toth A, Bajza I, Kandra L, Liptak A (2001) Identification and structural analysis of synthetic oligosaccharides of Shigella sonnei using MALDI-TOF MS. Carbohydr Res 334:315–322
78. Binns MW, Vaugham S, Timmis KN (1985) O-Antigens are essential virulance factors of Shigella sonnei and Shigella dysenteriae 1. ZBL Bakt Mik Hyg B 181:197–205
79. Wu X, Cui L, Lipinski T, Bundle DR (2010) Synthesis of monomeric and dimeric repeating units of zwitterionic type 1 capsular polysaccharide from Streptococcus pneumonia. Chem Eur J 16:3476–3488
80. Tzianabos AO, Wang JY, Kaspar DL (2003) Biological chemistry of immunomodulation by zwitterionic polysaccharides. Carbohydr Res 338:2531–2538

81. Dinkelaar J, De Jong AR, Van Meer R, Somers M, Lodder G, Overkleeft HS, Codée JDC, Van der Marel GA (2009) Stereodirecting effect of the pyranosyl C-5 substituent in glycosylation reactions. J Org Chem 74:4982–4991
82. Alpe M, Oscarson S (2003) Synthesis of tetra- and pentasaccharides corresponding to the capsular polysaccharide of Streptococcus pneumoniae type 9A&L, 9N and 9A. Carbohydr Res 338:2605–2609
83. Alpe M, Oscarson S (2002) Synthesis of oligosaccharides corresponding to Streptococcus pneumoniae type 9 capsular polysaccharide structures. Carbohydr Res 337:1715–1722
84. Caffall KH, Mohnen D (2009) The structure, function, and biosynthesis of plant cell wall pectic polysaccharides. Carbohydr Res 344:1879–1900
85. Yamamoto K, Watanabe N, Matsuda H, Oohara K, Araya T, Hashimoto M, Miyairi K, Okazaki I, Saito M, Shimizu T, Kato H, Okuno T (2005) Design, synthesis, and enzymatic property of a sulfur-substituted analogue of trigalacturonic acid. Bioorg Med Chem Lett 15:4932–4935
86. Magaud D, Grandjean C, Doutheau A, Anker D, Shevchik V, Cotte-Pattat N, Robert-Baudouy J (1998) Synthesis of the two monomethyl esters of the disaccharide 4-O-α-D-galacturonosyl-D-galacturonic acid and of precursors for the preparation of higher oligomers methyl uronated in definite sequences. Carbohydr Res 314:189–199
87. Magaud D, Grandjean C, Doutheau A, Anker D, Shevchik V, Cotte-Pattat N, Robert-Baudouy J (1997) An efficient and highly stereoselective α-(1→4) glycosylation between two D-galacturonic acid ester derivatives. Tetrahedron Lett 38:241–244
88. Magaud D, Dolmazon R, Anker D, Doutheau A, Dory YL, Deslongchamps P (2000) Differential reactivity of α- and β-anomers of glycosyl accepters in glycosylations. A remote consequence of the endo-anomeric effect? Org Lett 2:2275–2277
89. Codée JDC, De Jong AR, Dinkelaar J, Overkleeft HS, Van der Marel GA (2009) Stereoselectivity of glycosylations of conformationally restricted mannuronate esters. Tetrahedron 65:3780–3788
90. Clausen MH, Madsen R (2003) Synthesis of hexasaccharide fragments of pectin. Chem Eur J 9:3821–3832
91. Nemati N, Karapetyan G, Nolting B, Endress HU, Vogel C (2008) Synthesis of rhamnogalacturonan I fragments by a modular design principle. Carbohydr Res 343:1730–1742
92. Reiffarth D, Reimer KB (2008) Synthesis of two repeat units corresponding to the backbone of the pectic polysaccharide rhamnogalacturonan I. Carbohydr Res 343:179–188
93. Maruyama M, Takeda T, Shimizu N, Hada N, Yamada H (2000) Synthesis of a model compound related to an anti-ulcer pectic polysaccharide. Carbohydr Res 325:83–92
94. Scanlan EM, Mackeen MM, Wormald MR, Davis BG (2010) Synthesis and solution-phase conformation of the RG-I fragment of the plant polysaccharide pectin reveals a modification-modulated assembly mechanism. J Am Chem Soc. doi:10.1021/ja9090963
95. Chauvin AL, Nepogodiev SA, Field RA (2005) Synthesis of a 2,3,4-triglycosylated rhamnoside fragment of rhamnogalacturonan-II side chain a using a late stage oxidation approach. J Org Chem 70:960–966
96. Moe ST, Draget KI, Skjåk-Bræk G, Smidsrød O (1995) Food polysaccharides and their applications. Marcel Dekker, New York
97. Iwamoto M, Kurachi M, Nakashima T, Kim D, Yamaguchi K, Oda T, Iwamoto Y, Muramatsu T (2005) Structure–activity relationship of alginate oligosaccharides in the induction of cytokine production from RAW264.7 cells. FEBS Lett 579:4423–4429
98. Flo TH, Ryan L, Latz E, Takeuchi O, Monks BG, Lien E, Halaas Ø, Akira S, Skjåk-Bræk G, Golenbock DT, Espevik T (2002) Involvement of toll-like receptor (TLR) 2 and TLR4 in cell activation by mannuronic acid polymers. J Biol Chem 38:35489–35495
99. Codée JDC, Van den Bos LJ, De Jong AR, Dinkelaar J, Lodder G, Overkleeft HS, Van der Marel GA (2009) The stereodirecting effect of the glycosyl C5-carboxylate ester: stereoselective synthesis of β-mannuronic acid alginates. J Org Chem 74:38–47

100. van den Bos LJ, Dinkelaar J, Overkleeft HS, van der Marel GA (2006) Stereocontrolled synthesis of β-D-mannuronic acid esters: synthesis of an alginate trisaccharide. J Am Chem Soc 128:13066–13067
101. Jiang ZH, Xu RS, Wilson C, Brenk A (2007) Synthesis of β-1, 4-di-D-mannuronic acid glycosides as potential ligands for toll-like receptors. Tetrahedron Lett 48:2915–2918
102. Dinkelaar J, van den Bos LJ, Hogendorf WFJ, Lodder G, Overkleeft HS, Codee JDC, van der Marel GA (2008) Stereoselective synthesis of L-guluronic acid alginates. Chem Eur J 14: 9400–9411
103. Chi FC, Kulkarni SS, Zulueta MML, Hung SC (2009) Synthesis of alginate oligosaccharides containing L-guluronic acids. Chem Asian J 4:386–390
104. Walvoort MTC, Lodder G, Mazurek J, Overkleeft HS, Codee JDC, van der Marel GA (2009) Equatorial anomeric triflates from mannuronic acid esters. J Am Chem Soc 131: 12080–12081
105. Crich D (2002) Chemistry of glycosyl triflates: synthesis of β-mannosides. J Carbohydr Chem 21:667–690

Index