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Methodology Development and Physical Organic Chemistry: A Powerful Combination for the Advancement of Glycochemistry

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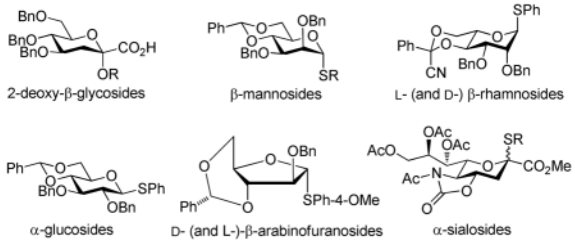
Abstract



This perspective article outlines work in the Crich group on the diastereoselective synthesis of the so-called difficult classes of glycosidic bond; the 2-deoxy-β-glycopyranosides, the β-mannopyranosides, the α-sialosides, the α-glucopyranosides and the β-arabinofuranosides with an emphasis on the critical interplay between mechanism and methodology development.

Introduction

A recent report from the National Research Council highlights the importance of the burgeoning area of glycoscience and draws attention to the need for improved chemical methods for the synthesis of oligosaccharides and glycans.[1] The size of the human glycome,[2] the growing importance of carbohydrates in medicinal chemistry,[3] the appearance on the market of the first totally synthetic oligosaccharide-based drug,[4] and well-known problems with the reliability of oligosaccharide-based medicines isolated from biological sources,[5] all combine to provide many opportunities and challenges for chemists in the field of synthetic oligosaccharide and glycoconjugate research.[6]

The central reaction around which all synthetic projects in the area revolve, and the focus of this Perspective, is that of glycosidic bond formation. The difficulties inherent in this process are apparent from the highly empirical nature of the field and the proliferation of obscure terminology describing strategies for oligosaccharide synthesis. Hindsgaul's excellent 1995 paper in which are tabulated all glycosylation reactions published in the calendar year 1994 helps to put the problem in context.[7] The more than 700 glycosidic bond forming reactions listed for the one year attest to the vigor of the field, but the enormous variety of donors, promoters, solvents, and temperatures used to achieve them cannot but focus attention on the high level of empiricism that prevails. Certainly, advances have been made in the 17 years since the publication of Hindgaul's paper, and many of these have been covered in several recent review articles,[6a,8] but one suspects that a similar compilation

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constructed for the year 2010 would contain a comparable diversity of methods and conditions.

Although other creative methods exist,[9] glycosidic bonds are usually formed[8f] by the reaction of a glycosyl donor with a glycosyl acceptor aide d by a promoter, perhaps with the intermediacy of a glycosyl oxocarbenium ion (Scheme 1).

Among the various classes of glycosidic bonds, three are commonly reputed as being particularly difficult to prepare stereoselectively, namely the 2-deoxy-α-glycopyranosides, the β-mannopyranosides (and the closely related β-rhamnopyranosides), and the α-sialosides (Fig. 1). All are equatorial glycosides and thus thermodynamically disfavored as they do not benefit from anomeric stabilization to the same extent as their axial epimers. Two of the three are deoxy sugars, generally meaning that they are activated toward oxocarbenium ion formation, and one is tertiary with all the additional complications arising from the need to conduct substitution at a congested center. The β-mannospyranosides suffer from the complication of the axial C2-O2 bond that hinders approach of the acceptor to the β-face of the donor and which precludes the use of any type of participating protecting group at that position. The other classes of difficult glycosidic bond (Fig 1) are the α-glucopyranosides, which cannot be prepared with the help of participation by neighboring ester in the classical manner, and the β-arabinofuranosides, ie, the furanoside equivalent of the β-mannopyranosides. The primary focus of this Perspective is on the three main classes – the 2-deoxy-β-glycosides, the β-mannopyranosides, and the α-sialosides - as studied in the author's laboratory over a period of 25 years, with minor diversions into both the α-glucopyranosides and the β-arabinofuranosides as appropriate. Not covered here are ketosides[10] and the mannuronic acid glycosides[11] for which much interesting chemistry also has been developed.

As complete newcomers to the glycosylation field, we were struck by the strong reliance of most practitioners of the art,[12] as continues to be the case today,[8a,8f] on variations on the classical approach that derives its origins in the venerable Koenigs-Knorr and Helferich reactions of a century or more ago. We were equally struck by the less than perfect anomeric selectivities observed in the majority of cases and by the bewildering diversity of conditions reported in the literature. Rather than trying to carve out a niche in a well-surveyed area, we elected to investigate alternative methods of setting the stereochemistry of glycosidic bonds with the perhaps naïve hope that a fresh look at the field would yield useful results. We also deliberately chose to focus on the more difficult classes of glycosidic bond generally feeling that any meaningful success here could be readily applied to the supposedly more routine classes of linkage.

2-Deoxy-β-glucopyranosides

Our first goal was the 2-deoxy-β-glycosides[13] for which we designed methods based on an intended stereoselective hydrogen atom transfer to an alkoxyglycosyl radical, following pioneering work on diastereselective α-C-glycoside formation from simple anomeric radicals by the Baldwin, Giese, and Vasella laboratories.[14] With respect to the alkoxyanomeric radicals, the Beckwith and Ingold groups had shown by esr spectroscopy that simple conformationally locked 2-alkoxytetrahydropyran-2-yl radicals were rapidly inverting sp^3-hybrized species in which the singly occupied orbital predominantly adopted an axial position. More pertinently, the same workers demonstrated that axial hydrogen atom abstraction from the 2-position of 2-alkoxytetrahydropyrans by alkoxy and related radicals took place some 8 times more rapidly than that of the corresponding equatorial hydrogens. Applying the principle of microscopic reversibility, it was therefore reasonable to expect that hydrogen atom transfer to 2-alkoxytetrahydropyran-2-yl radicals by suitable

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donors would show a strong preference for axial delivery. Although not our first choice,[15] we selected simple ulosonic acid glycosides as the precursors to the alkoxy glycosyl radicals by means of the Barton decarboxylation reaction.[16] The principle was rapidly established and a number of simple 2-deoxy-β-glycosides were accessed with good selectivity in this manner (Scheme 2).[17] In parallel work Kahne and coworkers accessed the analogous radicals, and demonstrated comparable selectivity in their quenching, by the reaction of tributylstannane with anomeric monothioorthoesters.[1819]

The methodology was extended to the synthesis of 2-deoxy-β-C-glycosides[20] and to that of β-glucosides,[21] the latter of which revealed an interesting reversal of anomeric selectivity in the presence of a 1,2-*O*-isopropylidene group. Thus, while radical decarboxylation of the fully ether-protected system **5** gave the β-glucoside **6** with excellent selectivity, application of the same reaction conditions to a system **7** bearing a 1,2-*O*-acetonide resulted in the formation of a product **8** arising from radical trapping on the β-face (Scheme 3).[22] This intriguing result suggests that the preference of the dioxolane ring for *cis*-fusion to a six-membered ring, well-known in carbohydrate chemistry, largely outweighs the preference of the alkoxy anomeric radical to place the singly occupied orbital in a pseudo-axial site.

Finally, the decarboxylative radical approach to 2-deoxy-β-glycosides was applied to the synthesis of the olivomycin C disaccharide[23] in the course of which a mixture of four diastereomers was converted into largely a single stereoisomer through a radical process (Scheme 4).

While the diastereoselective radical reactions described in Schemes 2 and 4 vindicated the design principle they could not be described as practical solutions to the problem of 2-deoxy-β-glycoside synthesis as they simply side stepped the issue and converted it into one of the equally difficult synthesis of 3-deoxyulosonic acid glycosides – congeners of the sialic acid glycosides to which we turn later in this Perspective.

β-Mannopyranosides

We returned briefly to the problem of the synthesis of the ulosonic acid glycosides in the mid-1990's as we turned our attention from the 2-deoxy-β-glycosides to the β-mannosides and again found excellent selectivity in the decarboxylation reaction (Scheme 5) but, again, the complexity of the synthesis of the ulosonic acid glycoside **11** conspired against any practical use of this radical approach.[24]

The excellent stereoselectivity in the quenching of the alkoxyglycosyl radicals, however, inspired us to search for other entries to these reactive intermediates. In particular we examined an approach to the β-mannosides **14** based on intramolecular 1,5-hydrogen atom from the anomeric position of an α-mannoside **13** by a radical tethered to mannose O2 followed by intermolecular hydrogen atom transfer with inversion of stereochemistry.[25] This on paper simple approach was complicated by the unanticipated competing 1,4-hydrogen abstraction from the 2-position leading to **16** (Scheme 6). Intramolecular hydrogen atom abstraction reactions, while typically preferring 6-membered cyclic transition states, are subject to subtle conformational factors that can have a major impact on regioselectivity.[26] In this respect it is apparent that the rigid bicyclic framework imposed by the presence of the 4,6-*O*-benzylidene acetal combines with the presence of the β-oxygen bond at C2,[27] that retards hydrogen atom abstraction by destabilization of the polar transition state,[28] to slow abstraction from the anomeric position to an extent that the unusual 1,4-abstraction is able to compete. Curran and coworkers contemporaneously adopted a parallel approach to the inversion of α- to β-mannosides based on 1,6-hydrogen atom abstraction with a benzyl radical precursor located on O2 and encountered the analogous problem, namely competing 1,5-hydrogen abstraction from the 2-position.[29]

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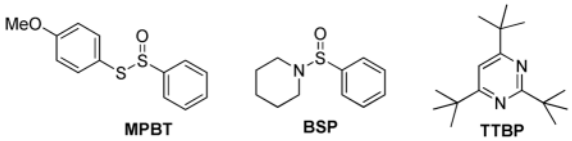
In seeking to optimize this process and above all to extend it beyond the commercial methyl α-mannopyranoside we needed to prepare more complex α-mannosides whose anticipated accessibility, in view of the very widely reported difficulty of accessing the β-anomers by classical glycosylation reactions,[9g,30] was a key design principle in the radical inversion route to the β-mannosides. To accomplish this task we selected Kahne's excellent sulfoxide glycosylation reaction because of its ability to introduce a sugar moiety onto even the most hindered of alcohols.[31] For simple reasons of ease of regioselective protection, necessary for installation of the tethered radical precursor to O2, we elected to make use of the 4,6-*O*-benzylidene acetal as a protecting group and were surprised to find that in diethyl ether as solvent at −78 °C the selectivity of the coupling reaction was variable and depended on the order of addition of the reagents. When triflic anhydride was added to a cold, premixed solution of a glycosyl acceptor, the sulfoxide **17**,[32] and a hindered non-nucleophilic base the α-mannoside 20 was obtained as anticipated.[25b] On the other hand, when triflic anhydride was added to a mixture of the sulfoxide **17** and base, followed by addition of the acceptor, the β-mannoside **22** was obtained directly with good to excellent selectivity.[33] We hypothesized that activation of the sulfoxide **17** in the presence of the acceptor resulted in direct quenching of an intermediate glycosyl oxocarbenium ion **19** by the acceptor itself, leading to the α-mannoside **20**, whereas preactivation of the sulfoxide **17** by triflic anhydride led to the formation of an α-mannosyl triflate **21** that was displaced in an S_N2-like manner on subsequent addition of the acceptor to give the β-mannoside **22** (Scheme 7). The obvious importance of this discovery, coupled with the (at the time) controversial postulation of the intermediacy of glycosyl triflates stimulated us to employ low and variable temperature NMR techniques to demonstrate the existence and probe the stability of the glycosyl triflates.[34] Such methods have proved critical in much of our subsequent work in the area[35] and have been widely adopted by the community.

Our desire to characterize all reaction products from the sulfoxide glycosylation reaction led us to the understanding that benzenesulfenyl triflate activates the glycsoyl sulfoxide more rapidly even than triflic anhydride,[34] and is capable of converting thioglycosides rapidly and cleanly to the glycosyl triflates.[33c,36] The instability of benzenesulfenyl triflate at room temperature, and the consequent need to prepare it in situ from silver triflate and benzenesulfenyl chloride,[37] itself only moderately stable at room temperature, prompted us to search for alternatives such as the combination of the stable and commercially available 4-nitrobenzenesulfenyl chloride and silver triflate.[38] Initially, however, the work of Oae on the reaction of trifluoroacetic anhydride with thiosulfinates[39] led us to examine the reaction of these latter species with triflic anhydride and resulted in the development of the **MPBT** reagent for the activation, in conjunction with triflic anhydride, of thioglycosides.[40] The modest reactivity of the **MPBT** combination and mechanistic considerations led us to introduce the more potent **BSP** reagent,[41] which has subsequently enjoyed wide success. Building on earlier work by Gin and coworkers on the use of hemiacetals as glycosyl donors,[42] the van Boom group subsequently showed the combination of diphenyl sulfoxide and triflic anhydride to be an even more potent reagent for thioglycoside activation at low temperature.[43] Numerous related reagents have subsequently been developed by other groups.[44] In terms of practical improvements we also introduced **TTBP** as a less hygroscopic, more crystalline and less volatile alternative to the widely employed non-nucleophilic 2,6-di-*tert*-butylpyridine bases.[45]



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With respect to the mechanism of the β-mannosylation reaction following formation of the α-mannosyl triflate **23**, the rapidity of the substitution on addition of the acceptor at −78 °C precluded us from carrying out standard kinetic measurements with the tools available to us at the time and drove us to apply a modification of Singleton's NMR method for the measurement of kinetic isotope effects. A secondary deuterium KIE of 1.2 at −78 °C, corresponding to 1.1 at room temperature, led us to the conclusion the reaction is dissociative in nature and involves either a contact ion pair (CIP) **24** or at best an "exploded transition state"[46] **25** in which the nucleophile and the leaving group are both loosely associated with the putative glycosyl oxocarbenium ion (Scheme 8).[47] Recent computational work supports this conclusion.[48]

On this basis we developed a mechanistic hypothesis according to which the β-mannosides are formed by attack on the CIP and any α-mannosides by reaction with the solvent separated ion pair (SSIP) with which it is in equilibrium,[35b] and a kinetic expression to account for the mixture of isomers formed[35c] that derives from Winstein's ion pair theory for solvolysis reactions.[49] This mechanistic scheme, which closely resembles that advocated earlier for glycosylation in general by Rhind-Tutt and Vernon, by Fréchet and Schuerch, and by Lemieux and coworkers (Scheme 9),[50] requires the inclusion of a second CIP and a covalent β-glycosyl triflate for completeness even if our NMR experiments to date have provided no evidence for such species in the mannose series. It must be noted, however, that β-glycosyl triflates have been observed spectroscopically in the mannuronic acid series.[11a,51]

Consideration of this mechanism leads to the hypothesis that the explanation of any factors affecting the stereochemistry of glycosylation reactions is related to the manner in which they influence the contact and solvent separated ion pair equilibria. Thus, polar solvents support charge separation better than non-polar solvents and are expected to shift the equilibrium toward the solvent separated ion pair and increase the extent of α-glycoside formation. The difference in selectivity between the use of diethyl ether and dichloromethane as solvent,[33b] and the increased selectivity for β-mannoside formation with weaker nucleophiles in toluene [52] are readily understood on this basis. The importance of alcohol concentration on selectivity is also apparent from the kinetic expression as is that of triflate ion concentration. 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 will likely favor the covalent glycosyl triflate over the ion pairs and will therefore retard the overall reaction. The stability of the covalent glycosyl triflate with respect to the oxacarbenium ion (pairs) will be reflected, to a first approximation, in the decomposition temperature of the covalent triflate. In agreement with this postulate tetra-*O*-methyl α-mannosyl triflate has a decomposition temperature of −30 °C whereas the corresponding β-selective 4,6-*O*-benzylidene protected system decomposes at −10 °C.[34]

Although glycosyl oxocarbenium ions form a central part of our mechanistic reasoning (Scheme 9), and indeed of almost all glycosylation mechanisms presented in the literature, it is important to note that even the simplest such cation has yet to be observed in organic solution.[53] Physical organic chemists have estimated by indirect methods the lifetimes in aqueous solution of the glucosyl cation[54], the 2-deoxyglucosyl cation,[54a] and of the sialyl cation presented in Fig 2,[54–55] but very little work has been done in organic solution.

Attempts to detect protected glycosyl cations in organic solvents have focused on NMR methods and, while very simple acyclic and cyclic systems can be observed in deuteriodichloromethane at low temperatures (Fig 3),[56] the permethyl glucosyl cation has so far evaded detection owing to its high reactivity and its immediate capture by nucleophiles

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such as triflate,[57] tetrafluoroborate (by fluoride abstraction),[56] and perchlorate, etc.[58] Even the use of the extremely non-nucleophilic counterion tetrakis(pentafluorophenyl)borate (BARF) did not allow detection of the glycosyl cation owing to its reaction with a diaryl disulfide generated in the course of activation.[59] Moreover, even in highly polar solvents such as ionic liquids it has been observed that glycosyl triflates exist as covalent entities rather than as ionic species.[60]

Although actual glycosyl cations have yet to be observed, mechanistic work has revealed zero order kinetics for the alcohol in several glycosylation systems[50a,6162] and we are forced to the conclusion[53] that glycosyl oxocarbenium ions most likely do have a real existence, however fleeting, in organic media. Indeed, some of the most elegant and convincing explanations of stereoselectivity in C- and O-glycoside formation in general derive from the conformational analyses of glycosyl oxocarbenium ions presented by the Woerpel and other groups.[63]

A similar problem exists in the computation of glycosyl oxocarbenium ions to that of their actual experimental observation. Thus, while numerous very helpful computational studies on glycosyl oxocarbenium ions in the absence of counterions have been reported,[64] attempts to compute ion pairs are thwarted by collapse to the covalent species unless artificial means are resorted to. Very recent in work in this direction, however, provides a possible solution making use of a combination of quantum mechanical and molecular dynamics methods.[65]

Whatever the finer points of the mechanism, the 4,6-*O*-benzylidene directed β-mannosylation reaction has been applied successfully to other glycosylation methods[66] beyond the glycosyl sulfoxides and thioglycosides and has found application in the synthesis of numerous glycosides, glycoconjugates, and oligosaccharides. Much of this synthetic work has been reviewed[67] and we limit ourselves here to a single example taken from the recent work of the Kobayashi group on the synthesis of the antibiotic TMC 151C (Scheme 10).[68] The intramolecular aglycone delivery method provides a useful alternative in many cases to the benzylidene directed mannosylation and has also been widely applied in synthesis, but it does require the extra step of tethering the donor to the acceptor prior to glycosylation.[9e–i,69] The use of more conformationally labile β-mannosyl donors lacking the benzylidene acetal also continues to be explored in numerous groups around the world. However, with the exception of small reactive acceptors[70] and of well-matched pairs,[71] selectivities are mostly moderate and require the use of multiple electron-withdrawing protecting groups[72] in line with our earlier work on rhamnopyranosyl donors to which we return below.

While the synthesis of many β-mannopyranosides has become almost routine by the 4,6-*O*-benzylidene directed method, as always it is the exceptions to the rule that are all the more interesting and that continue to give pause for thought. Perhaps one of the more important issues that has come to light, and that one pertains to the much broader question of stereoselective glycosylation in general especially when conducted in an automated manner so as to provide large arrays for screening, is that of matched and mismatched donor acceptor pairs. A report of apparent matching in the synthesis of a mannan fragment has appeared in the literature,[71] but, as we have discussed elsewhere,[73] it is the growing number of examples of mismatching[74] that sound the warning bells.

More interesting from a mechanistic point of view are the strongly α-directing effects of a 2,3-*O*-carbonate group and a 3-*O*-carboxylate group both of which completely override the β-directing effect of the 4,6-*O*-benzylidene acetal.[75]

The effect of the 2,3-*O*-carbonate group may be understood in terms of the half-chair conformation that the *cis*-fused cyclic protecting group imposes on the pyranoside ring at the level of the thioglycoside and, by extrapolation, of the glycosyl triflate.[76] The

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conformational barrier to formation of the glycosyl oxocarbenium ion from the glycosyl triflate is therefore essentially removed by the presence of the 2,3-*O*-carbonate and the effect is seen to be a manifestation of ground state destabilization that has the effect of causing the chemistry of the oxocarbenium ion (SSIP) to predominate over that of the glycosyl triflate. The α-selective nature of the 2,3-*O*-carbonate donor **30** is clearly seen from the synthesis of the branched trisaccharide unit **32** of the common core pentasaccharides presented in Scheme 11.[41] 2,3-*O*-Carbonates in the glucose series on the other hand are *trans*-fused and promote the modestly selective formation of β-glucopyranosides in the absence of neighboring group participation, presumably by opposing oxocarbenium ion formation.[77] It is fascinating that nature appears to use a related strategy in a group of α-mannosidase enzymes in which a Ca^{2+} ion is bound between O2 and O3 of the substrate thereby distorting it toward the transition state for hydrolysis.[78]

When the carbonate group is relocated to span the 3- and 4-positions it affords a moderately β-selective donor, eg, **33**, that can be advantageously employed in β-rhamnoside synthesis (Scheme 12).[76c] This selectivity depends on the combination of both the strong electron-withdrawing power of the cyclic carbonate group and the conformational rigidity it imposes on the pyranose ring, as its replacement by either two acetyl groups[76c] or by a Ley-type cyclic bis-acetal system[75] does not afford any β-selectivity.

Like the 2,3-*O*-carbonate group, a single 3-*O*-carboxylate ester completely overrides the β-directing effect of a 4,6-*O*-acetal and results in a highly α-selective coupling reactions. Although we originally inclined toward to a mechanism involving participation by the ester,[35a,75] subsequent work in our laboratory using a 3-*O*-*tert*-butyloxycarbonate protected donor, that also gave high α-selectivity, strongly indicates that this is not the case.[79] Kim and coworkers have subsequently argued strongly in favor of a participation mechanism for the directing effect of esters at the 3-position and even at the 6-position,[72e,80] however, on the basis of what we suggest[35b,35c] to be an overly nucleophilic probe that is a poor mimic of a carboxylate ester. The question of the origin of the directing effect of the 3-*O*-ester is therefore an open one that is being actively addressed in our and other laboratories.[81] Whatever the origin, the effect is a powerful one as is apparent from the complete reversal of selectivity in the two couplings presented in Scheme 13 simply on changing the 3-*O*-protecting group in an otherwise common donor.[82]

β-Rhamnopyranosides

The critical need for the benzylidene acetal or its surrogate[83] in β-mannosylation reactions, best explained by Bols in terms of the locking of the C5-C6 bond in the *tg* (trans-gauche)[84] conformation that maximizes the electron-withdrawing ability of the C6-O6 bond,[85] is also the main limitation of the method and has been the driving force for further methodological development. This limitation is most apparent in the synthesis of the 6-deoxy-β-mannosides, otherwise known as the β-rhamnosides,[67b,69e,86] a class of glycosides that are commonly found, in the form of either enantiomer, in bacterial capsular and lipopolysaccharides. We considered that the use of a 4,6-*O*-benzylidene protected donor followed by regioselective deoxygenation after β-selective glycosylation, by a modification of either the Hanessian-Hullar[87] or the Roberts'[88] acetal fragmentation chemistries, would be a suitable way to address this problem. We devised a method based on earlier work[89] for the generation of a benzylidene centered radical by a cascade of reactions beginning with cyclization of a stannane-generated aryl radical onto the sulfur center of a thioester followed by loss of carbon monoxide.[90] Once the benzylidene radical is accessed it undergoes highly selective contrathermodynamic fragmentation of the primary C6-O6 bond (rather than of the secondary C4-O4 bond), because of a less-strained transition state as explained by Roberts, to bring about the required regioselective deoxygenation.[88] Following cleavage of the

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chloroacetate ester from **39** the method was applied to the saccharide **40** to give a trisaccharide **41** containing both an α- and a β-D-rhamnopyranoside (Scheme 14).[82]

A second generation method was subsequently developed that features replacement of the thioester radical precursor by a more robust cyanoacetal **42**, activated for radical fragmentation by a Beckwith radical cyano group migration to a suitably placed aryl radical (Fig 4).[91] This methodology, which has been reviewed,[67b,92] was subsequently applied to the synthesis of a β-1,3-D-rhamnan[93] and to the 6-deoxy-β-D-mannoheptosides.[94] Seeking a perhaps more practical third generation method we turned to 6-deoxy-6-thia mannosyl donors with the 4,6-hydroxythiol unit tied up in a monothioacetal. Bearing in mind the existence of both the D- and L-rhamnosides in bacteria we developed syntheses of the two enantiomeric donors **43** and **44** (Fig 4) and demonstrated that they gave excellent β-selectivity in glycosylation reactions on activation with BSP and triflic anhydride in the usual manner. After glycosylation treatment with Raney nickel in hot methanol cleanly affected desulfurization to give the β-rhamnosides while at the same time removing any benzyl protecting groups.[92,95] The cyano group present in the monothioacetal function of donors **43** and **44** is a critical component and functions to prevent activation of the cyclic thioacetal by the BSP and triflic anhydride mixture used for glycosylation while at the same time improving stereoselectivity because of its electron-withdrawing nature.[92,95]

An alternative approach to the β-rhamnosides (and indeed to the β-mannosides themselves) not requiring the use of a cyclic protecting group spanning positions 4 and 6 focuses on the use of non-participating but electron-withdrawing protecting groups on the donor. Following early but seminal work by Schuerch and coworkers,[72f–h,96] we surveyed a number of such groups of which the best were the 2-*O*-sulfonate esters and particularly those bearing an electron-withdrawing trifluoromethyl group.[97] These systems gave the best selectivities when used in conjunction with an additional electron-withdrawing group at O4 such as a benzoate ester as in donor **45**.[97a] Unfortunately, as we and other groups have found, such systems rarely afford the same level of selectivity as the 4,6-*O*-benzylidene acetals.[72e,80,97–98,99]

Our work on the rhamnopyranosides also provided perhaps one of the clearest demonstrations of the influence of remote protecting groups on glycosylation stereochemistry in a system in which nucleophilic participation is unambiguously excluded. Thus, a set of three rhamnosyl donors **46** substituted with one, two, or three fluorine atoms at the 6-position were prepared and their stereoselectivities in coupling to a standard alcohol examined. The trifluoro system gave the highest β-selectivity and the mono the lowest consistent with increased destabilization of the oxocarbenium ion with increased fluorine substitution. This conclusion was also supported by the trend in the decomposition temperatures of the intermediate glycosyl triflates which increased with increasing fluorine content (Scheme 15).[100]

β-Glucopyranosides

Undeniably one of the more interesting and ultimately one of the more informative discoveries made in the course of our attempts to extrapolate the 4,6-*O*-benzylidene directed β-mannosylation was realization that the same protecting group is strongly α-directing when applied in the glucopyranose series.[101] This type of donor, whose chemistry also involves an intermediate α-glycosyl triflate, provides an interesting and very straightforward entry into the highly stereoselective synthesis of the α-glucopyranosides, for which other elegant solutions have been devised recently,[102] and has been applied in synthesis to such ends (Scheme 16).[103]

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Seeking to understand the reasons underlying the contrasting selectivities obtained with the 4,6-*O*-benzylidene protected mannosyl and glucosyl donors we prepared a number of 2-deoxy and 2-deoxy-2-fluoro donors as well as the corresponding 3-deoxy and 3-fluoro donors in both the mannose and glucose series (Fig 5).[104]

None of these donors showed the same level of selectivity as their simple manno- and gluco-counterparts leading us to the realization of the importance of the C3 substituent and to conclude that the difference between the β-selective mannosyl donors and their α-selective glucosyl diastereomers is a function of the differing interactions between the C2-O2 and C3-O3 bonds as the glycosyl triflates (in the $^4C_1$ conformation) are converted to the oxocarbenium ions (in either the $^4H_3$, $B_{2,5}$, or ^4E conformations).[35b,35c,104b] Thus, as the mannosyl triflate is converted to the oxocarbenium the O2-C2-C3-O3 torsion angle is compressed from 60° to 45° if the latter adopts the $^4H_3$ conformation computed for it,[64,105] or remains unchanged if the more or less degenerate $B_{2,5}$ form is taken up (Scheme 17). On the other hand the same torsion angle in the glucose series is expanded from 60° to either 75° or 90° as the glycosyl triflate fragments to either the $^4H_3$ or the ^4E conformations of the oxocarbenium that are preferred according to computational studies (Scheme 17).[64,105] The difference in these key torsional interactions between the mannose and the glucose series is reflected in the energy barrier for the conversion of the glycosyl triflates to the oxocarbenium ions and thus in the extent to which the chemistry is dominated by the oxocarbenium ion; the barrier is lower in glucose resulting in an increased role for the oxocarbenium ion and α-selectivity.[35b,35c,104b]

The importance of the C3-substituent is also apparent in the 3-amino-3-deoxy series of mannosyl donors, when only a benzylidene imine protecting system gives rise to high β-selectivity,[106] and in the influence of the bulk of the O3 protecting group with silyl groups being overly large and considerably eroding selectivity.[107] We and others have implemented a number of novel protecting groups for O2 and/or O3 to counteract the effect of steric bulk at the O3 position,[108] such as the propargyl ether **28** used to good effect by the Kobayashi group in their synthesis of TMC 151C illustrated above (Scheme 10).[68] It is again fascinating that the C3 substituent also plays an important role in substrate recognition by glycosidase enzymes.[109]

β-Arabinofuranosides

The obvious parallels between the β-mannopyranosides and the β-arabinofuranosides led us to hypothesize that a benzylidene acetal or related group spanning the 3- and 5-positions of the latter would assist in stereoselective glycosylation.[110] However, it rapidly became apparent that the 3,5-*O*-benzylidene furanosides are very different in nature to the 4,6-*O*-benzylidene pyranosides. Thus, we encountered considerable difficulty in the installation of a 3,5-*O*-benzylidene acetal onto arabinofuranosyl thioglycosides by the usual methods applied in the pyranoside series thereby explaining the absence of such species from the literature at the time. Eventually we succeeded in this task, albeit by a roundabout route, and established the structure of the acetal **62** crystallographically. Interestingly, this acetal (Fig 6) was considerably less stable than the 4,6-*O*-benzylidene acetals in the pyranoside series, thereby explaining the initial difficulties in its installation. We also prepared a rather more accessible and stable 3,5-*O*-di(*tert*-butyl)silylene acetal **63** (Fig 6) and examined glycosylation reactions of the benzylidene and silylene protected species under the standard BSP/triflic anhydride conditions, only to find very poor selectivity.

Curiously, oxidation of the silylene protected thioglycoside to the corresponding sulfoxide **66** followed by application of a preactivation strategy with triflic anhydride before addition of the alcohol resulted in acceptable β-selective coupling reactions with a range of primary

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alcohols (Scheme 18).[110] In the same timeframe, Boons and coworkers investigated the activation of the silylene-protected arabinofuranoside donors **63** (Fig 6) with NIS and silver triflate and found generally very good selectivities,[111] while Ito and coworkers studied a set of siloxane-protected donors **64** (Fig 6) and found moderate to good selectivites.[112] Perhaps most interestingly, Kim and coworkers reported excellent β-selectivities with a perbenzyl arabinofuranosyl donor **65** (Fig 6) based on their carboxylbenzyl glycoside system that is activated at low temperature with triflic anhydride.[113]

The Boons group explain their selectivities based on 1,2-*cis*-attack on an E_3 conformer of the L-arabinofuranosyl oxocarbenium ion imposed by the presence of the cyclic acetal (Fig 7). In particular *cis*-attack avoids the strong eclipsing interaction with the C2-H2 bond. Ito and coworkers also advanced a rationale for their β-selectivity based on minimization of torsional strain during attack on a furanosyl oxocarbenium ion following an earlier proposal of Woerpel in his work on C-glycoside formation.[114] On the basis that furanosides are generally more susceptible to hydrolysis than comparable pyranosides,[115] and that sp^2 centers are more easily accommodated in five rather than six-membered rings,[116] proposals such as these for furanosylation involving naked furanosyl oxocarbenium ions are reasonable and also provide a suitable explanation for our results (Scheme 18).

C-Glycosides

Just as donors, acceptors play a critical role to play in any glycosylation reaction.[63c,73] To this end we demonstrated early on that carbohydrate-based thiols are excellent acceptors in the 4,6-*O*-benzylidene directed β-mannosylation process.[117] Less predictably, as we have showed recently, simple carbon-based nucleophiles such as allyl silanes and stannanes and silyl enol ethers show the same selectivity patterns as alcohols in these glycosylation reactions. Thus, in the glucose series high α-selectivity is seen while in the mannose series high β-selectivity is observed when the donors carry ether protecting groups on O2 and O3 (Scheme 19).[118] Even more interesting is the fact that a 4,6-*O*-benzylidene protected mannoyl donor **71** carrying a 3-*O*-ester results in the formation of the α-C-glycoside **72** (Scheme 19)[119] exactly as with alcohols as acceptors. It is the common pattern of stereochemical outcomes shared by O- and C-glycosyl acceptors that cause us to downplay the influence of donor-acceptor hydrogen advocated by some[64] as a stereodetermining factor in glycosylation.

Derivatives of *N*-Acetylglucosamine

Our interest in the influence of acceptors and their substituents inevitably brought us to examine the well-known case of the poor reactivity of the 4-OH group in the *N*-acetylglucosamine series. We provided evidence that intermolecular hydrogen bonding between amide groups is part of the problem and offered suggestions as to how to disrupt this.[120] Similar hypotheses and conceptually related solutions have been advanced recently to explain the poor reactivity of donors in the *N*-acetylneuraminic acid series.[121] Ultimately however, the best explanation for the low reactivity of the *N*-acetylglucosamine 4-OH is that of Auzanneau and coworkers who, following an early report by Sinaÿ,[122] demonstrated that the amide group captures either the electrophilic promoter for the glycosylation reaction or the glycosyl donor itself through formation of an imidate.[123] In our laboratory we devised a practical solution to the problem based on the tying back of the O3 protecting group away from the 4-OH to be glycosylated. We achieved this through the formation of an oxazolidinone between N2 and O3, and acetylated the oxazolidinone nitrogen so as to preclude the possibility of its taking place in any hydrogen bonding network. So-protected acceptors, eg, **73**, proved considerably more reactive toward a bank of a glycosyl donors than the standard 3-*O*-benzyl ethers of *N*-acetylglucosamine (Scheme 20).[124] Kerns and

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coworkers reported a closely related oxazolidinone protected glucosamine also to be a good glycosyl acceptor but noted that glycosylation of the oxazolidinone NH was an important competing reaction, thereby underlining the importance of the *N*-acetyl group in our system.[125] Interestingly, when the β-anomer of the *N*-acetyl acceptor was employed the oxazolidinone could be cleaved selectively with barium hydroxide leaving the acetamide in place, while no such selectivity could be coaxed out of the α-epimer causing us to resort to exhaustive saponification followed by reintroduction of the amide (Scheme 20). We rationalized this difference of reactivity toward saponification according to the anomeric configuration by a change in the manner of substrate coordination to the Ba^{2+} cation (Scheme 20).[124]

In the course of the preparation of the oxazolidinone protected acceptors we also noted the unusually facile anomerization of a β- to an α-glycoside of an *N*-acetyloxazolidinone protected glucosamine derivative on reduction of a benzylidene acetal with sodium cyanoborohydride and hydrogen chloride in ether (Scheme 21),[124b] conditions which normally do not affect the anomeric position.[126]

Oscarson and coworkers demonstrated the *N*-acetyloxazolidinone protected glucosyl donor **76** (Fig 8) to be highly β-selective in coupling reactions when promoted with a catalytic quantity of silver triflate, and that the kinetic β-anomer isomerized cleanly to its thermodynamic α-epimer on continued exposure to the silver salt, for which they proposed a mechanism involving endocyclic ring cleavage.[127] On the basis of an X-ray crystal structure of the donor the possibility that the kinetic β-selectivity arose from neighboring group participation by the acetyl group was excluded.[127b] Related observations on the kinetic nature of the β-product with subsequent anomerization to the α-anomer were reported by Ye.[128] The use of various oxazolidinone protected glucosamine derivatives as glycosyl donors had been previously investigated by the Kerns with selectivities that depended on the nitrogen protecting group and on the reactivity of the acceptor (**77**).[125,129] Ito and coworkers showed the *N*-benzyloxazolidinone protected glucosamine donor **78** (Fig 8) to be unselective at low temperatures and α-selective at room temperature and, like Oscarson, came to the conclusion that this was the result of an equilibration process involving endocyclic cleavage.[130]

α-Sialosides

Our successful application of the *N*-acetyloxazolidinone protecting in the glucosamine series coupled with the knowledge that a *trans*-fused 3,4-*O*-carbonate ester exerts a significant influence on rhamnopyranosyl donors (Scheme 12) stimulated us to investigate the 4-*O*,5-*N*-acetyloxazolidinone protecting group system for the formation of sialic acid glycosides.[131] A great deal of effort has been devoted to the synthesis of the α-sialosides but their stereocontrolled synthesis still represents a formidable challenge to the synthetic chemist. The area has been reviewed a number of times[132] and we concentrate here only on recent advances using cyclic protecting groups.

We began, however, with an attempt to detect intermediates in sialidation reactions by low temperature NMR spectroscopy. Attempts to detect intermediates in sialidations are plagued by their relative instability and the facility with which elimination to give the 2,3-glycal typically occurs. This latter process is such that neither sialyl sulfoxides nor sialyl trichloroacetimidates have been described in the literature; fortunately, in recent years the Yu group demonstrated that stable *N*-phenyl trifluoroacetimidates of sialic acid derivatives could be prepared and employed.[133] Adapting Gin's dehydrative glycosylation method,[134] as generally developed for thioglycoside activation by the van Boom group,[43a] we were able to activate sialyl thioglycosides in dichloromethane solution with combinations of diaryl

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sulfoxides and triflic anhydride.[135] Working with a single equivalent of sulfoxide and in the absence of an acceptor the 2,3-glycal **79** was the only observed product, pointing to the instability of any putative glycosyl triflate intermediates and of the oxocarbenium ion. However, on activation with three equivalents of sulfoxide and one of triflic anhydride followed by the addition of the acceptor alcohol goods yields of glycosides were obtained with moderate selectivities without the need for the use of a nitrile solvent. Inspection of reaction mixtures by low temperature NMR spectroscopy prior to the addition of the acceptor revealed the formation of two isomeric species, tentatively assigned to the glycosyloxy sulfonium salts **80** (Fig 9).[135–136] With respect to other intermediates acetonitrile, by far the most common solvent for sialidation reactions,[37,137] is generally considered to afford selectivity through the formation of an intermediate axial nitrilium ion **81** although such an intermediate has yet to be demonstrated convincingly (Fig 9).[137c,138]

In terms of the influence of protecting groups on sialidation reactions, in the last decade it became apparent that strongly electron-withdrawing groups on N5 of sialyl donors enhance α-selectivity for reactions conducted in the presence of acetonitrile. Such groups include *N*,*N*-diacetyl systems,[139] *N*-trifluoroacetamides,[140] *N*-trichloroethylcarbamates,[141], trichloroacetamides,[142] phthalimido groups,[141c] and azides,[143] and progress in this area has been reviewed,[144] and useful comparative studies made.[141a,141c] Based on computational work, Fukase and coworkers suggested that the *N*-Troc group interacts electrostatically more strongly with the sialyl oxocarbenium ion than the simple acetamide and thereby more effectively shields the β-face from attack by the acceptor.[141c] For the phthalimido system the same workers proposed that the fixed dipole of the phthalimido group, which lies in the mean plane of the oxocarbenium ion, interacts with and stabilizes one or both of the oxocarbenium ion or the nitrilium ion through dipole-dipole interactions – a similar effect is expected for the *N*,*N*-diacetate but of reduced magnitude owing to the two conformations, and hence dipoles, possible for this imide.[141c] Alternatively, Kononov and coworkers suggested that the *N*,*N*-diacetyl and phthalimido effects arise from disruption of an intermolecular hydrogen bonding network present for the simple acetamide,[121a] and went on to demonstrate that the addition of external imides, such as *N*-methylacetimide had a beneficial effect on glycosylations conducted with simple *N*-acetyl sialyl thioglycosides.[121a145] This thought-provoking concept related to that we had advanced earlier for the low reactivity of the *N*-acetyl glucosamine-based acceptors,[120] however, does not provide a complete explanation as typical KDN donors, sialic acids lacking the amide function, suffer most of the same problems as their more common and better studied *N*-acetyl neuraminic acid analogs.

Taking into account the beneficial effect of cyclic protecting groups in many glycosylation systems[146] and that of electron-withdrawing groups on N5 discussed above, the groups of Takahashi[147] and De Meo[148] introduced the O4,N5-oxazolidinone protecting group for sialyl donors **82** and **83** to good effect (Fig 10).[149] In our laboratory the advantages of the oxazolidinone and of the *N*,*N*-diacetyl system were combined in the *N*-acetyl-*O*4,*N*5-oxazolidinone donor **84** that associated the advantages of high α-selectivity in most cases with selective cleavage of the oxazolidinone under mild conditions that left the acetamide group in place.[150] The main disadvantage of this latter system, as with most other systems based on sialic acid thioglycosides, arises from the lack of reactivity of the thioglycoside toward the NIS/TfOH activating system in the presence of acetonitrile much below −30 °C. Indeed, this lack of reactivity had previously prevented the use of sialic acid thioglycosides in Wong-type one pot glycosylation protocols,[151] thereby necessitating the use of orthogonal systems based on the activation of the sialyl thioglycoside in the presence of a glycosyl fluoride-based acceptor alcohol.[141a] On the basis of work by Lahman and Oscarson showing secondary alkyl thioglycosides to be more reactive than primary alkyl ones,[152] we next developed the tertiary adamantanyl thioglycoside **85** of the *N*-acetyl oxazolidinone protected

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sialyl donor (Fig 10). This system could be activated at −78 °C in mixtures of dichloromethane and acetonitrile by the NIS/TfOH system when it generally gave excellent α-selectivities.[153] Tackling the same problem of the poor reactivity of sialic acid thioglycosides, Wong and coworkers[154] subsequently converted the *N*-acetyloxazolidinone-protected tolylthio glycoside to the corresponding dibutylphosphates **86** by treatment with dibutylphosphoric acid in the presence of NIS and TfOH (Fig 10). Interestingly, the two anomeric phosphates prepared in this manner could be separated and displayed different reactivity, with the axial β-isomer being somewhat more reactive at −78 °C on activation with TMS triflate in dichloromethane. Under these conditions excellent α-selectivity was obtained from both the α- and β-phosphates in their reactions with a broad range of glycosyl acceptors without the need for added acetonitrile. An important feature of the oxazolidinone protected sialic acid donors, in addition to the high α-selectivity they typically employ is the virtual absence of formation of the 2,3-glycal side product that is an inevitable feature of almost all other systems.

We demonstrated the applicability of the sialyl adamantyl thioglycosides in one pot glycosylation by the preparation of a series of trisaccharides, eg, **90**, in which the first step was the activation of an adamantyl *N*-glycolyl neuraminate ester thioglycoside protected with an oxazolidinone ring **88** (Scheme 22).[155] In the example given an overall yield of 55% was obtained for the two glycosylation reactions with excellent selectivity at both anomeric centers.

Subsequently, in our laboratory we employed an analogous O4,O5 cyclic carbonate protected donor in the KDN series **91** and found it to give excellent α-selectivities in contrast to the diacetate protection usually employed at that locus (Scheme 23)[156] As with the oxazolidinone protected sialic acid donors, these systems were essentially free from the formation of the 2,3-glycal of which a sample was obtained by elimination from a glycosyl sulfoxide.

Overall, it is evident that a five-membered cyclic protecting group spanning positions 4 and 5-of the sialic acid framework (either an oxazoldinone for the neuraminic acids or a carbonate for KDN) permit the highly selective synthesis of many α-sialosides. The same groups also have the significant advantage in terms of reaction yield of very largely suppressing the formation of the 2,3-glycals that plagues most other sialidation methods. Thus, many years after our initial foray into the area en route to the 2-deoxy-β-glycosides, an effective solution to this problem is now at hand. Clearly, the *trans*-fused five membered ring severely limits the conformational space available to any intermediate oxocarbenium ion, but it is tempting to suggest that the directing influence arises from the existence of a single strong dipole in the plane of the pyranose ring that destabilizes any glycosyl oxocarbenium ions and leads to the formation of tighter and more selective ion pairs (Fig 11). It will be noted that the dipole imposed by the presence of the carbonate and/or oxazolidinone is oriented in the opposite direction to that due to the presence of the phthalimido system discussed above[141c] and must therefore act in a different manner.

The X-ray crystallographic structure of an *N*-acetyl oxazoldinone protected sialyl thioglycoside **84**[150] shows the pyranose ring to adopt an almost perfect chair conformation,[150] and that such remains the case in solution is indicated by the large trans-diaxial coupling constant between H's 4 and 5 in both the oxazolidinone and carbonate systems.[150,153a,156] The reasons underlying the absence of 2,3-glycal formation are not clear at the present time, but might be related to increased strain due to the presence of the oxazolidinone or carbonate.[157] Alternatively, it may simply be that in the case of the more common acetate protected systems the pseudo-axial acetate at O4 acts as a general base to catalyze deprotonation of the oxocarbonium ion.

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An alternative cyclic protecting group for *N*-acetylneuraminic acid, the N5,O7 oxazinone system, **94** and **95**, introduced by our[158] and the Ando groups,[159] was designed to mimic the 4,6-*O*-benzylidene system that is so beneficial in mannopyranosylation, but was generally found to afford β-sialosides preferentially (Fig 12), perhaps because of the pseudo-axial orientation imposed on the pendant side chain. Taking the concept a step further, Hanashima and coworkers studied a series of doubly locked donors, eg, **96**, in which, in addition to the oxazolidinone bridging O4 and N5 a *tert*-butylsilylene group was used to bridge N5 and O7 (Fig 12). In a series of coupling reactions conducted in dichloromethane at −40 °C using the NIS/TfOH activating system good to excellent α-selectivities were observed depending on the acceptor alcohol.[160]

Conclusion

In conclusion, what began as an exercise in demonstrating diastereoselectivity in radical reactions, evolved into a career-long fascination with the stereocontrolled formation of the glycosidic bond and with understanding the factors controlling reactivity at the anomeric center in general. This exercise has resulted in the development of practical solutions to the synthesis of two of the more difficult classes of glycosidic bond; the β-mannopyranosides and the α-sialosides. It is clear from the work described above that fundamental work on the mechanisms of glycosylation reactions has had and will continue to have an important role in the development of improved glycosylation methods. In the broader context, carbohydrates are an excellent teaching ground for the principles of reactivity and conformational analysis for both the specialist and the non-specialist. It is equally clear that, although enormous progress has been made in controlling anomeric stereochemistry over the last twenty five years by many groups worldwide, glycosidic bonds are very rarely formed with perfect, or even near-perfect, stereocontrol and that unpleasant surprises await the unwary particularly in the form of mismatched donor/acceptor pairs. It is evident therefore that many challenges remain to tax the creativity and imagination of organic chemists, and even that our initial premise of the need for alternative approaches to glycosidic bonds, and of novel mimics of them, remains valid today. The work presented in this Perspective relies heavily on the use of protecting groups, not only to block hydroxyl and other functionalities, but to control reactivity and stereoselectivity; the development of new systems for glycosidic bond formation with minimal use of protecting groups, in keeping with the general need in organic synthesis to reduce our dependence on such expensive systems,[161] is one obvious major and largely unmet need that would benefit from wider attention.[162] Finally, important parallels have emerged in recent years between factors controlling stereoselectivity in chemical glycosylation reactions and those operative, at least in some instances, in glycosidase enzymes and certainly merit closer attention.

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References

1. Martin McGowan, ED.; Bowman, K. Background Paper on Glycosciences and Glycomics in the United States. National Research Council; 2010.
2. a) Cummings RD. Mol Biosys. 2009; 5:1087–1104.b) Adibekian A, Stallforth P, Hecht ML, Werz DB, Gagneux P, Seeberger PH. Chem Sci. 2011; 2:337–344.c) Gabius, H-J., editor. The Sugar Code. Wiley-VCH; Weinheim: 2009.

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3. a) Galan MC, Benito-Alifonsoa D, Watt GM. Org Biomol Chem. 2011; 9b) Murrey HE, Hsieh-Wilson LC. Chem Rev. 2008; 108:1708–1731. [PubMed: 18452339]
4. Petitou M, van Boeckel CAA. Angew Chem Int Ed. 2004; 43:3118–3133.
5. Zhang Z, Weiwer M, Li B, Kemp MM, Daman TH, Linhardt RJ. J Med Chem. 2008; 51:5498–5501. [PubMed: 18754653]
6. a) Boltje TJ, Buskas T, Boons GJ. Nature Chemistry. 2009; 1:611–622.b) Wu CY, Wong CH. Chem Commun. 2011; 47:6201–6207.
7. Barresi F, Hindsgaul O. J Carbohydr Chem. 1995; 14:1043–1087.
8. a) Zhu X, Schmidt RR. Angew Chem Int Ed. 2009; 48:1900–1934.b) Mydock LK, Demchenko AV. Org Biomol Chem. 2010; 8:497–510. [PubMed: 20090962] c) Pedersen CM, Marinescu LG, Bols M. Comptes Rendus Chimie. 2011; 14:17–43.d) Codee JDC, Ali A, Overkleeft HS, van der Marel GA. Comptes Rendus Chimie. 2011; 14:178–193.e) Demchenko, AV., editor. Frontiers in Modern Carbohydrate Chemistry. American Chemical Society; Washington, DC: 2007. f) Demchenko, AV., editor. Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance. Wiley-VCH; Weinheim: 2008.
9. a) Schmidt RR. Angew Chem Int Ed. 1986; 25:212–235.b) Vasella A. Pure Appl Chem. 1991; 63:507–518.c) Vasella A. Pure Appl Chem. 1993; 65:731–752.d) Hodosi G, Kovac P. J Am Chem Soc. 1997; 119:2335–2336.e) Barresi F, Hindsgaul O. J Am Chem Soc. 1991; 113:9376–9377.f) Stork G, Kim G. J Am Chem Soc. 1992; 114:1087–1088.g) Cumpstey I. Carbohydr Res. 2008; 343:1553–1573. [PubMed: 18533138] h) Ito Y, Ogawa T. Angew Chem Int Ed. 1994; 33:1765–1767.i) Ishiwata A, Lee YJ, Ito Y. Org Biomol Chem. 2010; 8:3596–3608. [PubMed: 20585666]
10. a) Krog-Jensen C, Oscarson S. J Org Chem. 1996; 61:4512–4513. [PubMed: 11667372] b) Krog-Jensen C, Oscarson S. J Org Chem. 1996; 61:1234–1238.c) Krong-Jensen C, Oscarson S. J Org Chem. 1998; 63:1780–1784.d) Oscarson S, Sehgelmeble FW. J Am Chem Soc. 2000; 122:8869–8872.
11. a) Codée JDC, Christina AE, Walvoort MTC, Overkleeft HS, van der Marel GA. Top Curr Chem. 2011; 301:253–290. [PubMed: 21222193] b) Dinkelaar J, de Jong AR, van Meer R, Somers M, Lodder G, Overkleeft HS, Codée JDC, van der Marel GA. J Org Chem. 2009; 74:4982–4991. [PubMed: 19489535]
12. a) Paulsen H. Angew Chem Int Ed. 1982; 21:155–224.b) Paulsen, H. Selectivity α Goal for Synthetic Efficiency. Bartmann, W.; Trost, BM., editors. Verlag Chemie; Weinheim: 1984. p. 169-190.c) Bochkov, AF.; Zaikov, GE. Chemistry of the O-Glycosidic Bond. Pergamon; Oxford: 1979.
13. a) Thiem J, Klaffke W. Topics Curr Chem. 1990; 154:285–332.b) Marzabadi CH, Franck RW. Tetrahedron. 2000; 56:8385–8417.c) Hou D, Lowary TL. Carbohydr Res. 2009; 344:1911–1944. [PubMed: 19716123] d) De Lederkremer RM, Marino C. Adv Carbohydr Chem Biochem. 2008; 61:143–216. [PubMed: 17931551]
14. a) Adlington RM, Baldwin JE, Basak A, Kozyrod RP. J Chem Soc, Chem Commun. 1983:944–945.b) Giese B, Dupuis J. Angew Chem Int Ed. 1983; 22:622–623.c) Baumberger F, Vasella A. Helv Chim Acta. 1983; 66:2210–2222.
15. Crich D, Ritchie TJ. Tetrahedron. 1988; 44:2319–2328.
16. Barton DHR, Crich D, Motherwell WB. Tetrahedron. 1985; 41:3901–3924.
17. a) Crich D, Ritchie TJ. J Chem Soc, Chem Commun. 1988:1461–1463.b) Crich D, Ritchie TJ. J Chem Soc, Perkin Trans 1. 1990:945–954.
18. Kahne D, Yang D, Lim JJ, Miller R, Paguaga E. J Am Chem Soc. 1988; 110:8716–8717.
19. For practical improvements on Kahne's synthesis of the anomeric monothioorthoesters see: a) Hurzeler M, Bernet B, Vasella A. Helv Chim Acta. 1993; 76:995–1012.b) Wilkinson BL, Fairbanks AJ. Tetrahedron Lett. 2008; 49:4941–4943.
20. Crich D, Lim LBL. J Chem Soc, Perkin Trans 1. 1991:2205–2208.
21. Crich D, Lim LBL. J Chem Soc, Perkin Trans 1. 1991:2209–2214.
22. Both the substrate and the product adopted a twist boat conformation in solution
23. Crich D, Hermann F. Tetrahedron Lett. 1993; 34:3385–3388.
24. Crich D, Hwang JT, Yuan H. J Org Chem. 1996; 61:6189–6198. [PubMed: 11667454]

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25. a) Brunckova J, Crich D, Yao Q. Tetrahedron Lett. 1994; 35:6619–6622.b) Crich D, Sun S, Brunckova J. J Org Chem. 1996; 61:605–615. [PubMed: 11666981]
26. a) Barton DHR, Beaton JM. J Am Chem Soc. 1961; 83:4083–4089.b) Barton DHR, Basu NK, Day MJ, Hesse RH, Pechet MM, Starratt AN. J Chem Soc, Perkin Trans 1. 1975:2243–2247.
27. Crich D, Beckwith ALJ, Chen C, Yao Q, Davison IGE, Longmore RW, Anaya de Parrodi C, Quintero-Cortes L, Sandoval-Ramirez J. J Am Chem Soc. 1995; 117:8757–8768.
28. Brunckova J, Crich D. Tetrahedron. 1995; 51:11945–11952.
29. Yamazaki N, Eichenberger E, Curran DP. Tetrahedron Lett. 1994; 35:6623–6626.
30. a) Barresi, F.; Hindsgaul, O. Modern Methods in Carbohydrate Synthesis. Khan, SH.; O'Neill, RA., editors. Harwood Academic Publishers; Amsterdam: 1996. p. 251-276.b) Pozsgay, V. Carbohydrates in Chemistry and Biology. Ernst, B.; Hart, GW.; Sinaÿ, P., editors. Vol. 1. Wiley-VCH; Weinheim: 2000. p. 319-343.c) Gridley JJ, Osborn HMI. J Chem Soc, Perkin Trans 1. 2000:1471–1491.d) Ito, Y.; Ohnishi, Y. Glycoscience: Chemistry and Chemical Biology. Fraser-Reid, B.; Kuniaki, T.; Thiem, J., editors. Vol. 2. Springer-Verlag; Berlin: 2001. p. 1589-1619.e) Demchenko AV. Synlett. 2003:1225–1240.f) El Ashry ESH, Rashed N, Ibrahim ESI. Curr Org Synth. 2005; 2:175–213.
31. a) Kahne D, Walker S, Cheng Y, Engen DV. J Am Chem Soc. 1989; 111:6881–6882.b) Taylor, CM. Solid Support Oligosaccharide Synthesis and Combinatorial Libraries. Seeberger, PH., editor. Wiley Interscience; New York: 2001. p. 41-65.c) Crich D, Lim LBL. Org React. 2004; 64:115–251.d) Crich, D.; Bowers, AA. Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance. Demchenko, AV., editor. Wiley; Weinheim: 2008. p. 303-329.
32. In the mannopyranose series the axial thioglycosides are oxidized to essentially a single diasteromeric sulfoxide with the stereochemistry indicated: a) Crich D, Mataka J, Sun S, Lam KC, Rheingold AR, Wink D. J Chem Commun. 1998:2763–2764.b) Crich D, Mataka J, Zakharov LN, Rheingold AR, Wink DJ. J Am Chem Soc. 2002; 124:6028–6036. [PubMed: 12022836] c) Liang H, MacKay M, Grindley TB, Robertson KN, Cameron TS. Can J Chem. 2010; 88:1154–1174.
33. a) Crich D, Sun S. J Org Chem. 1996; 61:4506–4507. [PubMed: 11667369] b) Crich D, Sun S. J Org Chem. 1997; 62:1198–1199.c) Crich D, Sun S. Tetrahedron. 1998; 54:8321–8348.
34. Crich D, Sun S. J Am Chem Soc. 1997; 119:11217–11223.
35. a) Crich D. J Carbohydr Chem. 2002; 21:663–686.b) Crich D. Acc Chem Res. 2010; 43:1144–1153. [PubMed: 20496888] c) Aubry S, Sasaki K, Sharma I, Crich D. Top Curr Chem. 2011; 301:141–188. [PubMed: 21240602]
36. Crich D, Sun S. J Am Chem Soc. 1998; 120:435–436.
37. Martichonok V, Whitesides GM. J Org Chem. 1996; 61:1702–1706. [PubMed: 11667039]
38. Crich D, Cai F, Yang F. Carbohydr Res. 2008; 343:1858–1862. [PubMed: 18374318]
39. Morishita T, Furukawa N, Oae S. Tetrahedron. 1981; 37:3115–3120.
40. Crich D, Smith M. Org Lett. 2000; 2:4067–4069. [PubMed: 11112645]
41. Crich D, Smith M. J Am Chem Soc. 2001; 123:9015–9020. [PubMed: 11552809]
42. a) Garcia BA, Poole JL, Gin DY. J Am Chem Soc. 1997; 119:7597–7598.b) Garcia BA, Gin DY. J Am Chem Soc. 2000; 122:4269–4279.c) Gin, DY. Glycochemistry Principles, Synthesis, and Applications. Wang, P.; Bertozzi, CR., editors. Dekker; New York: 2001. p. 33-52.d) Boebel TA, Gin DY. J Org Chem. 2005; 70:5818–5826. [PubMed: 16018673]
43. a) Codée JDC, Litjens REJN, den Heeten R, Overkleeft HS, van Boom JH, van der Marel GA. Org Lett. 2003; 5:1519–1522. [PubMed: 12713313] b) Codée JDC, van den Bos LJ, Litjens REJN, Overkleeft HS, van Boeckel CAA, van Boom JH, van der Marel GA. Tetrahedron. 2004; 60:1057–1064.c) Codée JDC, Litjens REJN, Van den Bos LJ, Overkleeft HS, Van der Marel G. Chem Soc Rev. 2005; 34:769–782. [PubMed: 16100617]
44. a) Yun M, Shin Y, Chun KH, Jen S. Bull Chem Soc Kor. 2000; 21:562–566.b) Durón SG, Polat T, Wong CH. Org Lett. 2004; 6:839–841. [PubMed: 14986988] c) Peng, P.; Ye, X-S. Org Biomol Chem. 2010. d) Wang C, Wang H, Huang X, Zhang LH, Ye XS. Synlett. 2006:2846–2850.e) Tatai J, Fügedi P. Org Lett. 2007; 9:4647–4650. [PubMed: 17910468]
45. Crich D, Smith M, Yao Q, Picione J. Synthesis. 2001:323–326.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

46. a) Zechel, DL.; Withers, SG. Comprehensive Natural Products Chemistry. Barton, DHR.; Nakanishi, K.; Meth-Cohn, O., editors. Vol. 5. Pergamon; Oxford: 1999. p. 279-314.b) Davies, GJ.; Sinnott, ML.; Withers, SG. Comp Biol Catalysis. Sinnott, ML., editor. Vol. 1. Academic Press; London: 1998. p. 119-209.c) Gloster TM, Davies GJ. Org Biomol Chem. 2010:305–320. [PubMed: 20066263]
47. Crich D, Chandrasekera NS. Angew Chem Int Ed. 2004; 43:5386–5389.
48. Li Z. Carbohydr Res. 2010; 345:1952–1957. [PubMed: 20615497]
49. Winstein S, Clippinger E, Fainberg AH, Heck R, Robinson GC. J Am Chem Soc. 1956; 78:328–335.
50. a) Rhind-Tutt AJ, Vernon CA. J Chem Soc. 1960:4637–4644.b) Frechet JM, Schuerch C. J Am Chem Soc. 1972; 94:604–609.
51. Walvoort MTC, Lodder G, Mazurek J, Overkleeft HS, Codée JDC, van der Marel GA. J Am Chem Soc. 2009; 131:12080–12081. [PubMed: 19663422]
52. a) Crich D, Dudkin V. Org Lett. 2000; 2:3941–3943. [PubMed: 11101459] b) Crich D, Dudkin V. J Am Chem Soc. 2002; 124:2263–2266. [PubMed: 11878980]
53. Bohé L, Crich D. Comptes Rendus Chimie. 2011; 14:3–16.
54. a) Zhu J, Bennet AJ. J Org Chem. 2000; 65:4423–4430. [PubMed: 10891147] b) Amyes TL, Jencks WP. J Am Chem Soc. 1989; 111:7888–7900.
55. a) Horenstein BA, Bruner M. J Am Chem Soc. 1998; 120:1357–1362.b) Chou DTH, Watson JN, Scholte AA, Borgford TJ, Bennet AJ. J Am Chem Soc. 2000; 122:8357–8364.c) Horenstein NA. Adv Phys Org Chem. 2006; 41:275–314.
56. Matsumoto K, Ueoka K, Suzuki S, Suga S, Yoshida J-i. Tetrahedron. 2009; 65:10901–10907.
57. Nokami T, Shibuya A, Tsuyama H, Suga S, Bowers AA, Crich D, Yoshida J-i. J Am Chem Soc. 2007; 129:10922–10928. [PubMed: 17696345]
58. Igarashi K, Honma T, Irisawa J. Carbohydr Res. 1970; 15:329–337.
59. Saito K, Ueoka K, Matsumoto K, Suga S, Nokami T, Yoshida J-i. Angew Chem Int Ed. 2011; 50:5153–5156.
60. Rencurosi A, Lay L, Russo G, Caneva E, Poletti L. Carbohydr Res. 2006; 341
61. a) Wallace JE, Schroeder LR. J Chem Soc, Perkin Trans 2. 1976:1632–1636.b) Bülow A, Meyer T, Olszewski TK, Bols M. Eur J Org Chem. 2004:323–329.
62. Note, however, that a number of studies also clearly show S_N2 kinetics for the glucosylation of powerful nucleophiles, even in aqueous solution: a) footnote 50a b) Paulsen H, Richter A, Sinnvell V, Stenzel W. Carbohydr Res. 1978; 64:339–364.c) Banait NS, Jencks WP. J Am Chem Soc. 1991; 113:7951–7958.
63. a) Smith DM, Woerpel KA. Org Biomol Chem. 2006; 4:1195–1201. [PubMed: 16557303] b) Beaver MG, Billings SB, Woerpel KA. Eur J Org Chem. 2008:771–781.c) Beaver MG, Woerpel KA. J Org Chem. 2010; 75:1107–1118. [PubMed: 20108907] d) Chamberland S, Ziller JW, Woerpel KA. J Am Chem Soc. 2005; 127:5322–5323. [PubMed: 15826161] e) Krumper JR, Salamant WA, Woerpel KA. J Org Chem. 2009; 74:8039–8050. [PubMed: 19813702] f) Yang MT, Woerpel KA. J Org Chem. 2009; 74:545–553. [PubMed: 19072093] g) Walvoort MTC, Dinkelar J, van den Bos LJ, Lodder G, Overkleeft HS, Codée JDC, van der Marel GA. Carbohydr Res. 2010; 345:1252–1263. [PubMed: 20347068]
64. Whitfield DM. Adv Carbohydr Chem Biochem. 2009; 62:83–159. [PubMed: 19501705]
65. Satoh H, Hansen HS, Manabe S, van Gunsteren WF, Hunenberger PH. J Chem Theor Comput. 2010; 6:1783–1797.
66. a) Weingart R, Schmidt RR. Tetrahedron Lett. 2000; 41:8753–8758.b) Tsuda T, Sato S, Nakamura S, Hashimoto S. Heterocycles. 2003; 59:509–515.c) Kim KS, Fulse DB, Baek JY, Lee BY, Jeon HB. J Am Chem Soc. 2008; 130:8537–8547. [PubMed: 18528988] d) Kim KS, Kim JH, Lee YJ, Lee YJ, Park J. J Am Chem Soc. 2001; 123:8477–8481. [PubMed: 11525654] e) Codée JDC, Hossain LH, Seeberger PH. Org Lett. 2005; 7:3251–3254. [PubMed: 16018633] f) Baek JY, Choi TJ, Jeon HB, Kim KS. Angew Chem Int Ed. 2006; 45:7436–7440.g) Tanaka K, Mori Y, Fukase K. J Carbohydr Chem. 2009; 28:1–11.h) Tanaka, S-i; Takashima, M.; Tokimoto, H.; Fujimoto, Y.; Tanaka, K.; Fukase, K. Synlett. 2005:2325–2328.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

67. a) Crich, D. ACS Symp Ser. Demchenko, AV., editor. Vol. 960. American Chemical Society; Washington: 2007. p. 60-72.b) Cai, F.; Wu, B.; Crich, D. Adv Carbohydr Chem Biochem. Horton, D., editor. Vol. 62. Elsevier; 2009. p. 251-309.
68. Matsui R, Seto K, Sato Y, Suzuki T, Nakazaki A, Kobayashi S. Angew Chem Int Ed. 2011; 50:680–683.
69. a) Jung KH, Muller M, Schmidt RR. Chem Rev. 2000; 100:4423–4442. [PubMed: 11749353] b) Ziegler T, Lemanski G. Angew Chem Int Ed. 1998; 37:3129–3132.c) Chayajarus K, Chambers DJ, Chughtai MJ, Fairbanks AJ. Org Lett. 2004; 6:3797–3800. [PubMed: 15469352] d) Ishiwata A, Munemura Y, Ito Y. Eur J Org Chem. 2008:4250–4263.e) Lee YJ, Ishiwata A, Ito Y. J Am Chem Soc. 2008; 130:6330–6331. [PubMed: 18433121]
70. a) Dabideen DR, Gervay-Hague J. Org Lett. 2004; 6:973–975. [PubMed: 15012078] b) E-Badri MH, Willenbring D, Tantillo DJ, Gervay-Hague J. J Org Chem. 2007; 72:4663–4672. [PubMed: 17539683] c) Marsh SJ, Kartha KPR, Field RA. Synlett. 2003:1370–1372.
71. Doores KJ, Davis BG. Org Biomol Chem. 2008; 6:2692–2696. [PubMed: 18633526]
72. a) Hashihayata T, Mandai H, Mukaiyama T. Bull Chem Soc Jpn. 2004; 77:169–178.b) Hashihayata T, Mukaiyama T. Heterocycles. 2003; 61:51–57.c) De Meo C, Kamat MN, Demchenko AV. Eur J Org Chem. 2005:706–711.d) Mandai H, Mukaiyama T. Bull Chem Soc Jpn. 2006; 79:479–488.e) Baek JY, Lee BY, Jo MG, Kim KS. J Am Chem Soc. 2009; 131:17705–17713. [PubMed: 19908841] f) Awad LF, El Ashry ESH, Schuerch C. Bull Chem Soc Jpn. 1986; 59:1587–1592.g) El Ashry ESH, Schuerch C. Carohydr Res. 1982; 105:33–43.h) Srivastava VK, Schuerch C. J Org Chem. 1981; 46:1121–1126.
73. Bohé L, Crich D. Trends Glycosci Glycotech. 2010; 22:1–15.
74. Spijker NM, van Boeckel CAA. Angew Chem Int Ed. 1991; 30:180–183.
75. Crich D, Cai W, Dai ZJ. Org Chem. 2000; 65:1291–1297.
76. a) Crich, D.; Vinod, AU.; Picione, J.; Wink, DJ. ARKIVOC. 2005. p. 339-344.b) Manabe, S.; Ishii, K.; Hashizume, D.; Ito, Y. Acta Cryst. Vol. E63. 2007. p. o3028c) Crich D, Vinod AU, Picione J. J Org Chem. 2003; 68:8453–8458. [PubMed: 14575470]
77. Crich D, Jayalath P. J Org Chem. 2005; 70:7252–7259. [PubMed: 16122245]
78. 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. Nature Chem Biol. 2010; 6:125–132. [PubMed: 20081828]
79. Crich D, Hu T, Cai FJ. Org Chem. 2008; 73:8942–8953.
80. Kim KS, Suk DH. Top Curr Chem. 2011; 301:109–140. [PubMed: 21229347]
81. Fügedi, P. 16th European Carbohydrate Symposium; Sorrento. 2011. p. OL 128
82. Crich D, Yao Q. J Am Chem Soc. 2004; 126:8232–8236. [PubMed: 15225064]
83. Crich D, Smith M. J Am Chem Soc. 2002; 124:8867–8869. [PubMed: 12137540]
84. Bock K, Duus JO. J Carbohydr Chem. 1994; 13:513–543.
85. Jensen HH, Nordstrom M, Bols M. J Am Chem Soc. 2004; 126:9205–9213. [PubMed: 15281809]
86. El Ashry ESH, Rashed N, Ibrahim ES. Tetrahedron. 2008; 64:10631–10648.
87. a) Failla DL, Hullar TL, Siskin SB. J Chem Soc, Chem Commun. 1966:716–717.b) Hanessian S. Carbohydr Res. 1966; 2:86–88.
88. a) Cai Y, Dang HS, Roberts BP. J Chem Soc, Perkin Trans 1. 2002:2449–2458.b) Dang HS, Roberts BP, Sekhon J, Smits TM. Org Biomol Chem. 2003; 1:1330–1341. [PubMed: 12929663]
89. Crich D, Yao QJ. Org Chem. 1996; 61:3566–3570.
90. Crich D, Yao Q. Org Lett. 2003; 5:2189–2191. [PubMed: 12790561]
91. Crich D, Bowers AA. J Org Chem. 2006; 71:3452–3463. [PubMed: 16626126]
92. Picard S, Crich D. Chimia. 2011; 65:59–64. [PubMed: 21469447]
93. Crich D, Bowers AA. Org Lett. 2006; 8:4327–4330. [PubMed: 16956218]
94. Crich D, Banerjee A. J Am Chem Soc. 2006; 128:8078–8086. [PubMed: 16771524]
95. Crich D, Li L. J Org Chem. 2009; 74:773–781. [PubMed: 19132946]
96. a) Eby R, Schuerch C. Carbohydr Res. 1974; 34:79–90.b) Srivastava VK, Schuerch C. Carbohydr Res. 1980; 79:C13–C16.c) Srivastava VK, Schuerch C. Carbohydr Res. 1982; 100:411–417.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

97. a) Crich D, Picione J. Org Lett. 2003; 5:781–784. [PubMed: 12605514] b) Crich D, Hutton TK, Banerjee A, Jayalath P, Picione J. Tetrahedron: Asymmetry. 2005; 16:105–119.

98. Bedini E, Carabellese A, Barone G, Parrilli M. J Org Chem. 2005; 70:8064–8070. [PubMed: 16277328]

99. A report of very high β-selectivity obtained with a mannosyl trichloroacetimidate donor protected with benzyl ethers at positions 3,4, and 6 and carrying a 2-O-benzylsulfonyl group has been shown to be erroneous. a) Abdel-Rahman AA-H, Jonke S, El Ashry ESH, Schmidt RR. Angew Chem Int Ed. 2002; 41:2972–2974.b) Crich D, Li M, Jayalath P. Carbohydr Res. 2009; 344:140–144. [PubMed: 18954867]

100. Crich D, Vinogradova O. J Am Chem Soc. 2007; 129:11756–11765. [PubMed: 17725351]

101. a) Crich D, Cai W. J Org Chem. 1999; 64:4926–4930. [PubMed: 11674572] b) Bousquet E, Khitri M, Lay L, Nicotra F, Panza L, Russo G. Carbohydr Res. 1998; 311:171–181. [PubMed: 9825520]

102. a) Kim JH, Yang H, Park J, Boons GJ. J Am Chem Soc. 2005; 127:12090–12097. [PubMed: 16117550] b) Boltje TJ, Kim JH, Park J, Boons GJ. Nature Chemistry. 2010; 2:552–557.c) Fascione MA, Turnbull WB, Beilstein J. Org Chem. 2010; 610.3762/bjoc.6.19d) Fascione MA, Adshead SJ, Stalford SA, Kilner CA, Leach AG, Turnbull WB. Chem Commun. 2009:5841–5843.

103. Lourenço EC, Maycock CD, Ventura MR. Carbohydr Res. 2009; 344:2073–2078. [PubMed: 19691955]

104. a) Crich D, Vinogradova O. J Org Chem. 2006; 71:8473–8480. [PubMed: 17064022] b) Crich D, Li L. J Org Chem. 2007; 72:1681–1690. [PubMed: 17266375]

105. Nukada T, Bérces A, Wang L, Zgierski MZ, Whitfield DM. Carbohydr Res. 2005; 340:841–852. [PubMed: 15780250]

106. Crich D, Xu H. J Org Chem. 2007; 72:5183–5192. [PubMed: 17567072]

107. Crich D, Dudkin V. Tetrahedron Lett. 2000; 41:5643–5646.

108. a) Crich D, Jayalath P. Org Lett. 2005; 7:2277–2280. [PubMed: 15901188] b) Crich D, Jayalath P, Hutton TK. J Org Chem. 2006; 71:3064–3070. [PubMed: 16599600] c) Crich D, Wu B. Org Lett. 2006; 8:4879–4882. [PubMed: 17020326] d) Crich D, Karatholuvhu MS. J Org Chem. 2008; 73:5173–5176. [PubMed: 18529028] e) Crich D, Li L, Shirai M. J Org Chem. 2009; 74:2486–2493. [PubMed: 19243158] f) Codée JDC, Kröck L, Castagner B, Seeberger PH. Chem Eur J. 2008; 14:3987–3994.

109. Ducros VMA, Zechel DL, Murshudov GN, Gilbert HJ, Szabo L, Stoll D, Withers SG, Davies GJ. Angew Chem Int Ed. 2002; 41:2824–2827.

110. Crich D, Pedersen CM, Bowers AA, Wink DJ. J Org Chem. 2007; 72:1553–1565. [PubMed: 17286432]

111. a) Zhu X, Kawatkar SP, Rao Y, Boons GJ. J Am Chem Soc. 2006; 128:11948–11957. [PubMed: 16953636] b) Joe M, Bai Y, Nacario RC, Lowary TL. J Am Chem Soc. 2007; 129:9885–9901. [PubMed: 17655235] c) Nacario RC, Lowary TL, McDonald R. Acta Crystallographica, Section E: Structure Reports Online. 2007; E63(2):o498–o500.

112. Ishiwata A, Akao H, Ito Y. Org Lett. 2006; 8:5525–5528. [PubMed: 17107063]

113. Lee YJ, Lee K, Jung EH, Jeon HB, Kim KS. Org Lett. 2005; 7:3263–3266. [PubMed: 16018636]

114. Smith DM, Tran MB, Woerpel KA. J Am Chem Soc. 2003; 125:14149–14152. [PubMed: 14611253]

115. a) Capon B. Chem Rev. 1969; 69:407–498.b) BeMiller JN. Adv Carbohydr Chem Biochem. 1967; 22:25–108. [PubMed: 4890502] c) Sinnott, ML. Carbohydrate Chemistry and Biochemistry. RSC Publishing; Cambridge: 2007.

116. a) Brown HC, Brewster JH, Shechter H. J Am Chem Soc. 1954; 76:467–474.b) Prelog V, Kobelt M. Helv Chim Acta. 1949; 32:1187.

117. Crich D, Li H. J Org Chem. 2000; 56:801–805. [PubMed: 10814013]

118. a) Crich D, Sharma I. Org Lett. 2008; 10:4731–4734. [PubMed: 18826233] b) McGarvey GJ, LeClair CA, Schmidtmann BA. Org Lett. 2008; 10:4727–4730. [PubMed: 18826234]

119. Crich D, Sharma I. J Org Chem. 2010; 75:8383–8391. [PubMed: 21070063]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

120. Crich D, Dudkin V. J Am Chem Soc. 2001; 121:6819–6825. [PubMed: 11448186]
121. a) Kononov LO, Malysheva NN, Kononova EG, Orlova AV. Eur J Org Chem. 2008:3251–3254.b) Kononov LO, Malysheva NN, Orlova AV. Eur J Org Chem. 2009:611–616.
122. Pougny JR, Sinaÿ P. Carbohydr Res. 1976; 47:69–79.
123. a) Liao L, Auzanneau FI. Org Lett. 2003; 5:2607–2610. [PubMed: 12868870] b) Liao L, Auzanneau FI. J Org Chem. 2005; 70:6265–6273. [PubMed: 16050686] c) Liao L, Robertson V, Auzanneau FI. Carbohydr Res. 2005; 340:2826–2832. [PubMed: 16242677]
124. a) Crich D, Vinod AU. Org Lett. 2003; 5:1297–1300. [PubMed: 12688743] b) Crich D, Vinod AU. J Org Chem. 2005; 70:1291–1296. [PubMed: 15704963]
125. Kerns RJ, Zha C, Benakli K, Liang YZ. Tetrahedron Lett. 2003; 44:8069–8072.
126. Garegg PJ, Hultberg H, Wallin S. Carbohydr Res. 1982; 108:97–101.
127. a) Boysen M, Gemma E, Lahmann M, Oscarson S. ChemComm. 2005:3044–3046.b) Olsson JDM, Eriksson L, Lahmann M, Oscarson S. J Org Chem. 2008; 73:7181–7188. [PubMed: 18712923]
128. Geng YL-HZ, Ye X-S. ChemComm. 2008:597–599.
129. Wei P, Kerns RJ. J Org Chem. 2005; 70:4195–4198. [PubMed: 15876119]
130. a) Manabe S, Ishii K, Ito Y. J Am Chem Soc. 2006; 128:10666–10667. [PubMed: 16910646] b) Manabe S, Ishii K, Ito Y. Eur J Org Chem. 2011:497–516.c) Satoh H, Manabe S, Ito Y, Luthi HP, Laino T, Hutter J. J Am Chem Soc. 2011; 133:5610–5619. [PubMed: 21417469]
131. Note that the 3,4-position in hexopyranosides is equivalent to the 4,5-position in the sialic acids.
132. a) Boons GJ, Demchenko AV. Chem Rev. 2000; 100:4539–4565. [PubMed: 11749357] b) Boons, G-J.; Demchenko, AV. Carbohydrate-Based Drug Discovery. Wong, C-H., editor. Vol. 1. Wiley-VCH; Weinheim: 2003. p. 55-102.
133. Cai S, Yu B. Org Lett. 2003; 5:3827–2830. [PubMed: 14535720]
134. Haberman JM, Gin DY. Org Lett. 2003; 5:2539–2541. [PubMed: 12841775]
135. Crich D, Li W. Org Lett. 2006; 8:959–962. [PubMed: 16494484]
136. Ye D, Liu W, Zhang D, Feng E, Jiang H, Liu H. J Org Chem. 2009; 74:1733–1735. [PubMed: 19152263]
137. a) Murase T, Kameyama A, Kartha KPR, Ishida H, Kiso M, Hasegawa A. J Carbohydr Chem. 1989; 8:265–283.b) Hasegawa A, Nagahama T, Ohki H, Hotta K, Ishida H, Kiso M. J Carbohydr Chem. 1991; 10:493–498.c) De Meo C, Farris M, Ginder N, Gulley B, Priyadarshani U, Woods M. Eur J Org Chem. 2008:3673–3677.d) Marra A, Sinay P. Carbohydr Res. 1990; 195:303–308.e) Martin TJ, Schmidt RR. Tetrahedron Lett. 1992; 33:6123–6126.f) Kondo H, Ichikawa Y, Woing CH. J Am Chem Soc. 1992; 114:8748–8750.
138. Majumdar, D.; Boons, G-J. Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis. Crich, D., editor. Wiley; Chichester: 2005. p. 11-15.
139. Demchenko AV, Boons GJ. Tetrahedron Lett. 1998; 39:3065–3068.
140. a) Komba S, Galustian C, Ishida H, Feizi T, Kannagi R, Kiso M. Angew Chem Int Ed. 1999; 38:1131–1133.b) De Meo C, Demchenko AV, Boons GJ. J Org Chem. 2001; 66:5490–5497. [PubMed: 11485473]
141. a) Tanaka H, Adachi M, Takahashi T. Chem Eur J. 2005; 11:849–862.b) Tanaka H, Nishiura Y, Adachi M, Takahashi T. Heterocycles. 2006; 67:107–112.c) Tanaka K, Goi T, Fukase K. Synlett. 2005:2958–2962.
142. Sun B, Srinivasan B, Huang X. Chem Eur, J. 2008; 14:7072–7081.
143. a) Yu CS, Niikura K, Lin CC, Wong CH. Angew Chem Int Ed. 2001; 40:2900–2903.b) Mukaiyama T, Mandai H, Jona H. Chem Lett. 2002:1182–1183.
144. De Meo C, Priyadarshani U. Carbohydr Res. 2008; 343:1540–1552. [PubMed: 18452900]
145. Interestingly, while additives such as N-methylacetimide can have a substantial effect on the yield of sialylations achieved by the thioglycoside method with activation by Niodosuccinimide, they had essentially no effect on the stereoselectivity. The authors hypothesized that regardless of the additive the hydrogen bonding network evolves during the course of the reaction owing to the generation of the strong hydrogen bond donating succinimide and that in the later stages of the

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reaction succinimide plays a dominant role. This in turn led to the prediction and demonstration of changing stereoselectivity of sialylations conducted under these conditions with the extent of reaction; reactions stopped at a relatively early stage of conversion showed significantly higher α-selectivities than those allowed to proceed closer to completion.

146. Litjens REJN, van den Bos LJ, Codée JDC, Overkleeft HS, van der Marel G. Carbohydr Res. 2007; 342:419–429. [PubMed: 17007825]
147. Tanaka H, Nishiura Y, Takahashi T. J Am Chem Soc. 2006; 128:7124–7125. [PubMed: 16734441]
148. Farris MD, De Meo C. Tetrahedron Lett. 2007; 48:1225–1227.
149. Tanaka H, Nishiura Y, Takahashi T. J Org Chem. 2009; 74:4383–4386. [PubMed: 19413275]
150. Crich D, Li W. J Org Chem. 2007; 72:2387–2391. [PubMed: 17338570]
151. Zhang Z, Niikura K, Huang XF, Wong CH. Can J Chem. 2002; 80:1051–1054.
152. Lahman M, Oscarson S. Can J Chem. 2002; 80:889–893.
153. a) Crich D, Li W. J Org Chem. 2007; 72:7794–7797. [PubMed: 17824651] b) Liang FF, Chen L, Xing GW. Synlett. 2009:425–428.
154. Hsu CH, Chu KC, Lin YS, Han JL, Peng YS, Ren CT, Wu CY, Wong CH. Chem Eur J. 2010; 16:1754–1760.
155. Crich D, Wu B. Org Lett. 2008; 10:4033–4035. [PubMed: 18715011]
156. Crich D, Navuluri C. Angew Chem Int Ed. 2010; 49:3049–3052.
157. Note that in order obtain an authentic sample of the carbonate protected glycal it was necessary to heat a sample of a sialyl sulfoxide to 45 °C overnight in the presence of Hunig's base, whereas in simpler systems sialyl sulfoxides have never been previously isolated owing to facile decomposition at low temperature
158. Crich D, Wu B. Tetrahedron. 2008; 64:2042–2047. [PubMed: 19247426]
159. Tanaka H, Ando H, Ishihara H, Koketsu M. Carbohydr Res. 2008; 343:1585–1593. [PubMed: 18502408]
160. Hanashima SKS, Ito Y, Yamaguchi Y. Eur J Org Chem. 2009:4215–4220.
161. Gaich T, Baran PS. J Org Chem. 2010; 75:4657–4673. [PubMed: 20540516]
162. For promising recent developments see a) Lee D, Taylor MS. J Am Chem Soc. 2011; 133:3724–3727. [PubMed: 21355584] b) Chan L, Taylor MS. Org Lett. 2011; 13:3090–3093. [PubMed: 21591630] c) Gouliaras C, Lee D, Chan L, Taylor MS. J Am Chem Soc. 2011; 133:13926–13929. [PubMed: 21838223] and references therein.

Biography

David Crich studied for his doctorate with Derek Barton in the field of radical reactions. He is currently the Schaap chair of organic chemistry at Wayne State University, the editor-in-chief of the Electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS) and has wide ranging interests in organic and bioorganic chemistry.

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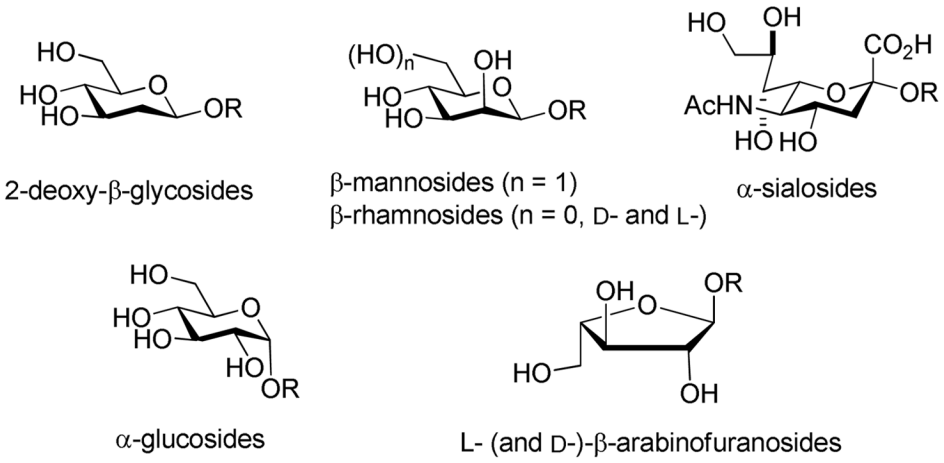

Fig. 1.
The difficult classes of glycosidic bond

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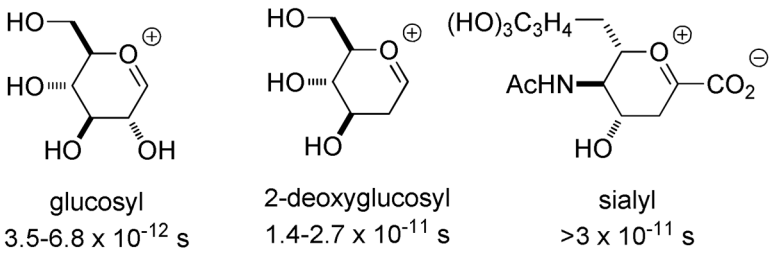

Fig. 2.
Estimated Lifetimes of Glycosyl Oxocarbenium Ions in Water

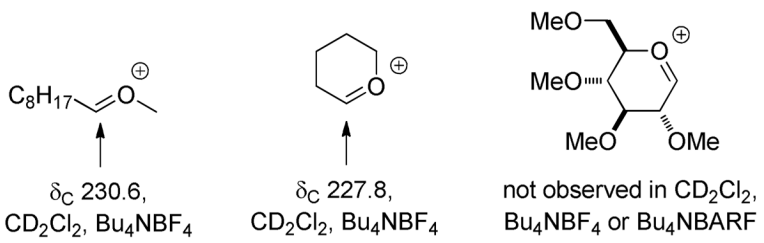

Fig. 3.
NMR Detectable and non-detectable oxocarbenium ions with their supporting electrolyte at −78 °C

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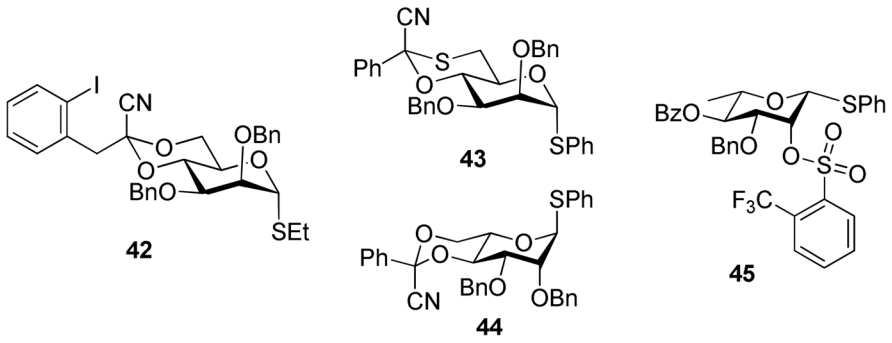

Fig. 4.

Second and Third Generation Precursors to β-Rhamnosides via β-Mannosides and a Direct β-Rhamnosyl Donor

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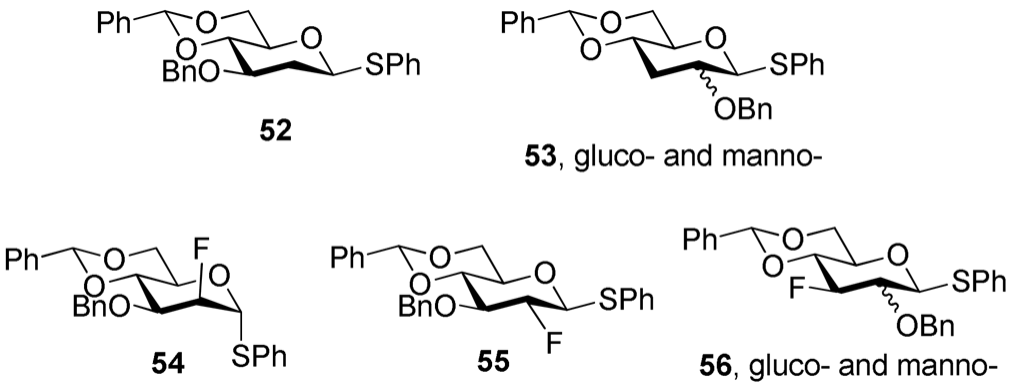

Fig. 5.
Deoxy and deoxyfluoro donors used to probe the glucose:mannose paradox

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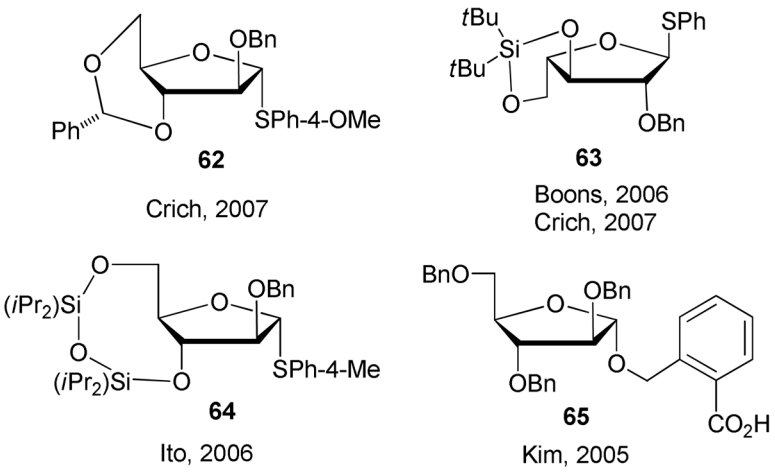

Fig. 6.
Examples of β-selective D- and L-arabinofuranosyl donors

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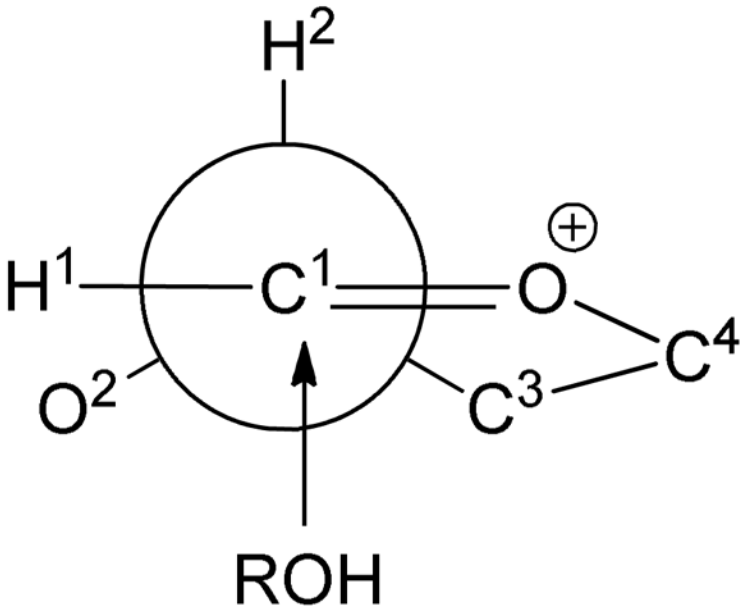

Fig. 7.
Preferred mode of attack on an L-arabinofuranosyl oxocarbenium ion according to Boons

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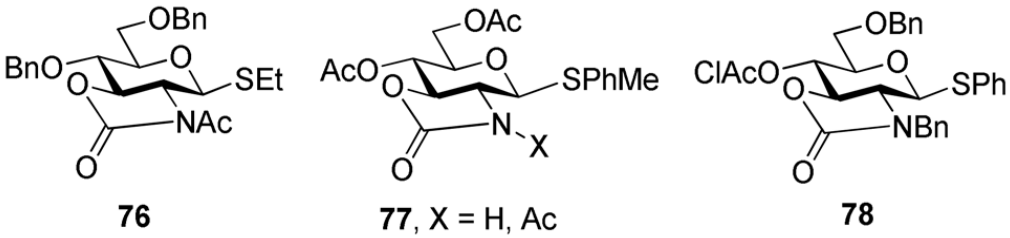

Fig. 8.
Examples of oxazolidinone-protected glucosamine donors from the Kerns, Oscarson and Ito groups α-Sialosides

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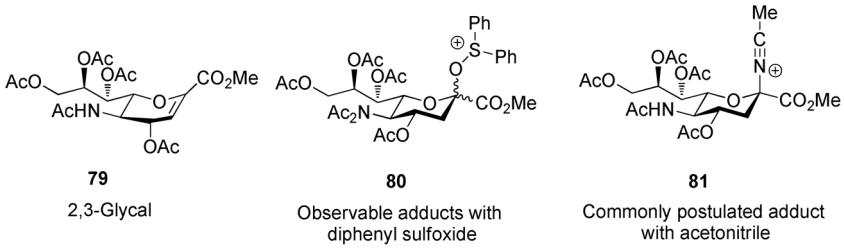

Fig. 9.

The sialyl 2,3-glycal and sulfoxonium and nitrilium adducts of sialyl oxocarbenium ions

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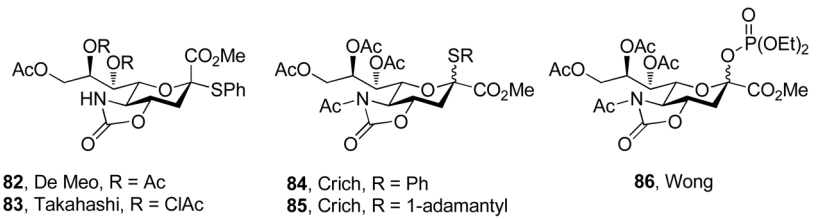

82, De Meo, R = Ac
83, Takahashi, R = ClAc

84, Crich, R = Ph
85, Crich, R = 1-adamantyl

86, Wong

Fig. 10.
α-Selective oxazolidinone-protected sialyl donors

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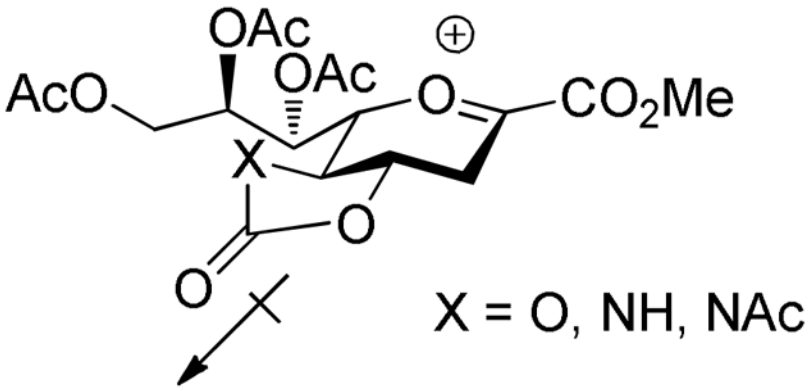

Fig. 11.
Oxocarbenium ion destabilization by a cyclic carbonate or oxazolidinone

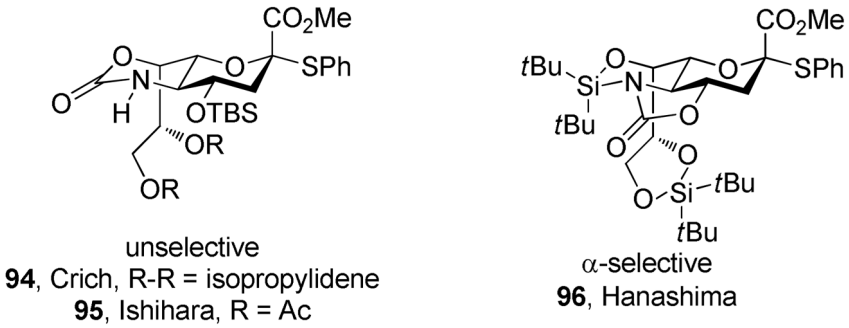

Fig. 12.
Sialyl donors with cyclic protecting groups spanning positions 5 and 7.

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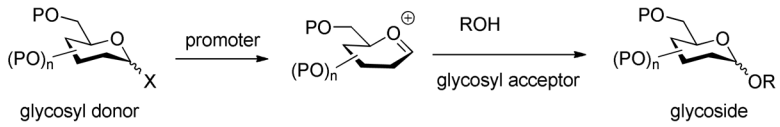

Scheme 1.
Standard approach to glycoside formation

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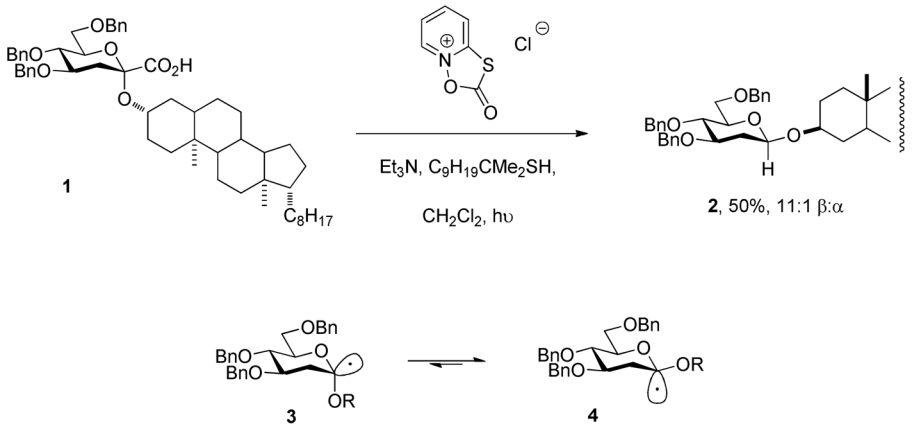
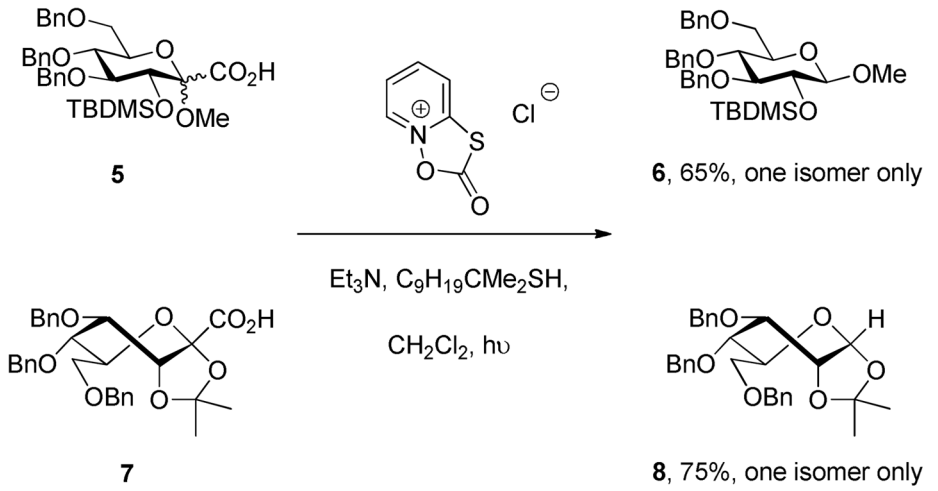


Scheme 2.

Synthesis of a 2-deoxy-β-glycoside by radical decarboxylation of a 3-deoxyulosonic acid glycoside and the key inversion of an alkoxyglycosyl radical



Scheme 3.
Differing anomeric radical selectivity in glucopyranosyl radicals according to the anomeric functionality

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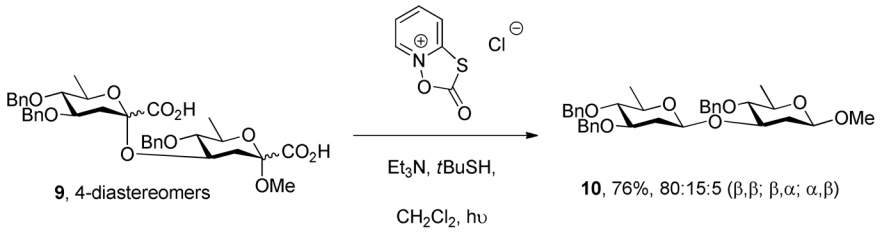

Scheme 4.
Synthesis of the Olivomycin A C–D disaccharide

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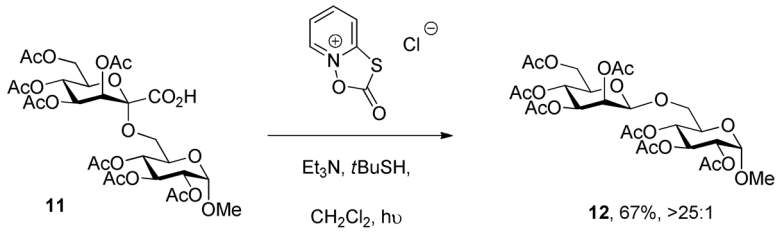

Scheme 5.
β-Mannoside synthesis by radical decarboxylation

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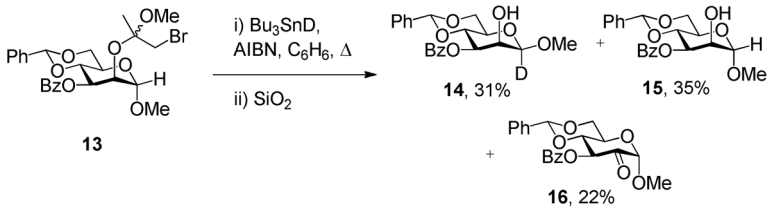

Scheme 6.
Attempted β-mannoside synthesis by inversion of an α-mannoside

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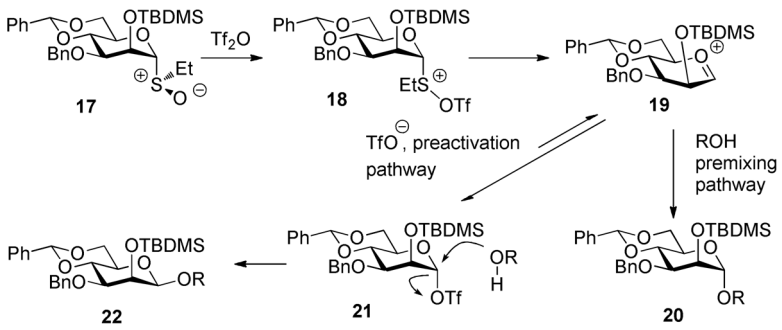

Scheme 7.
Early hypothesis for benzylidene-directed β-mannosylation

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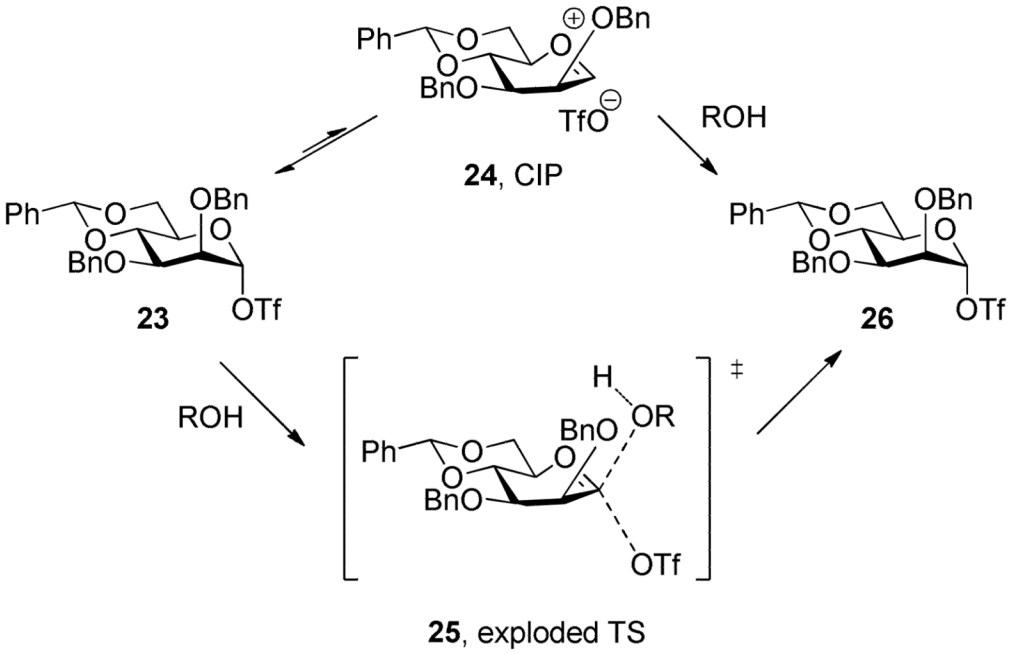
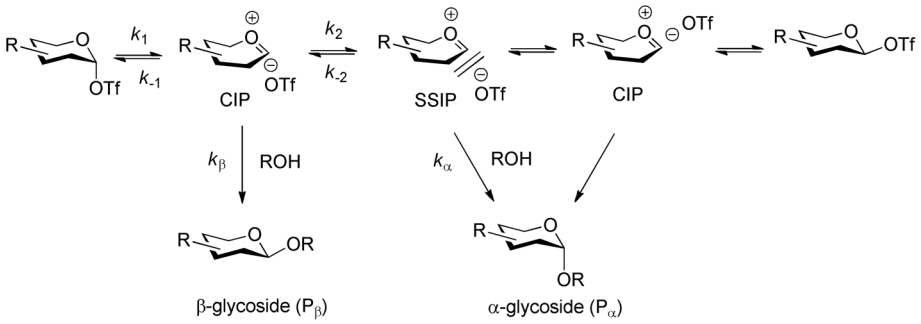


Scheme 8.
Mechanistic Possibilities Consistent with Secondary Deuterium Kinetic Isotope Effect Measurements for β-Mannosylation



Scheme 9.
The ion pair mechanism for glycosidic bond formation

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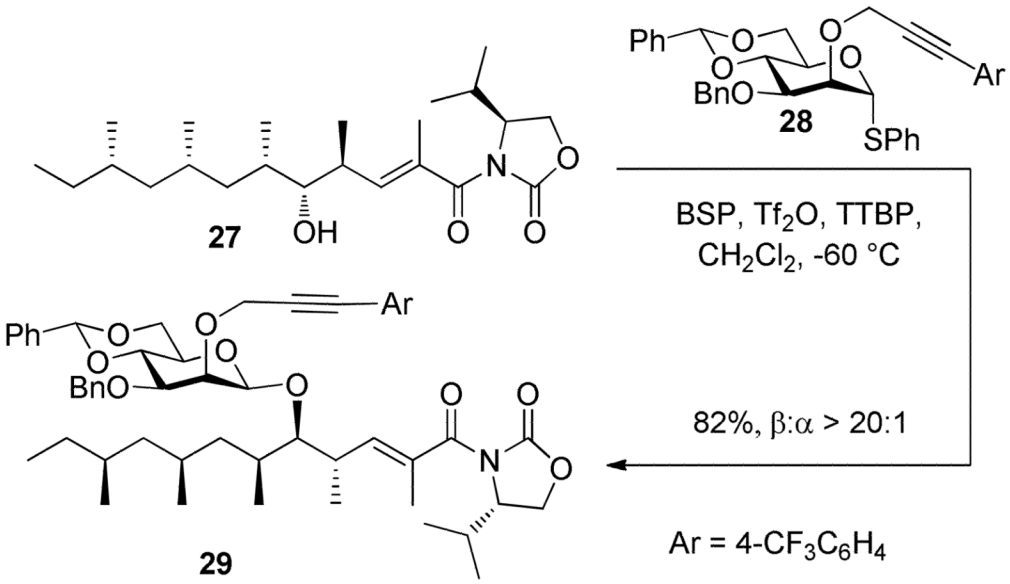
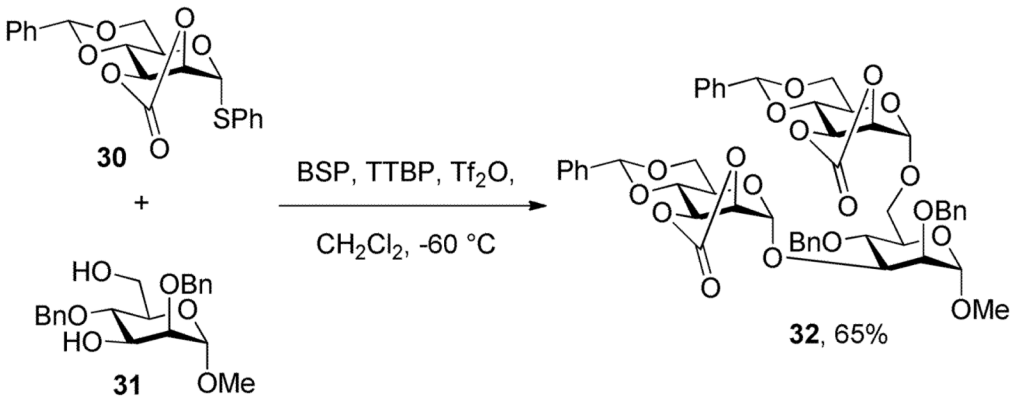


Scheme 10.
β-Mannosylation in the synthesis of (+)-TMC-151C



Scheme 11.
α-Selective mannosylation directed by the 2,3-*O*-carbonate group.

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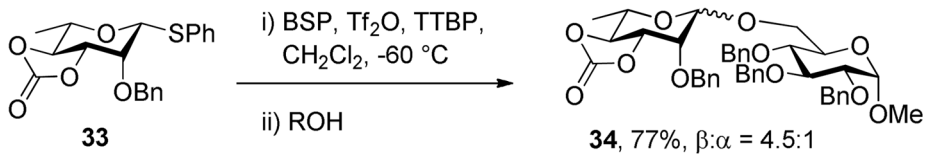

Scheme 12.

β-Selective glycosylation directed by a 3,4-*O*-carbonate

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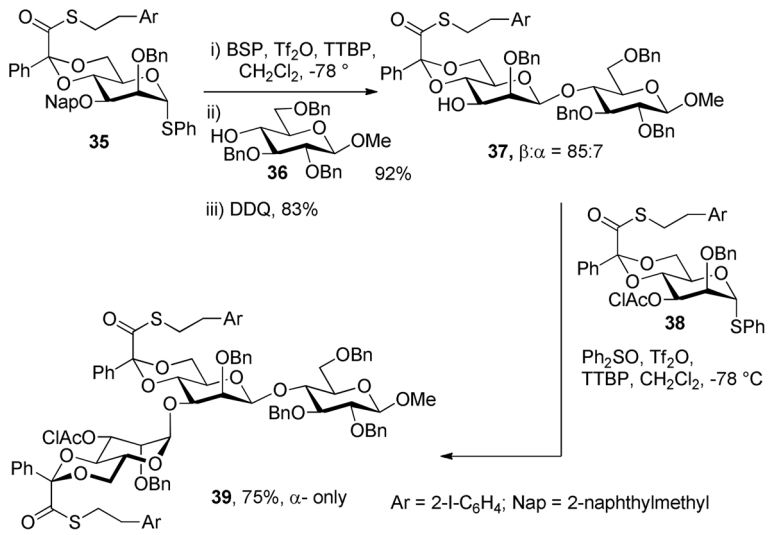

Scheme 13.
Effect of a 3-*O*-ester on coupling selectivity

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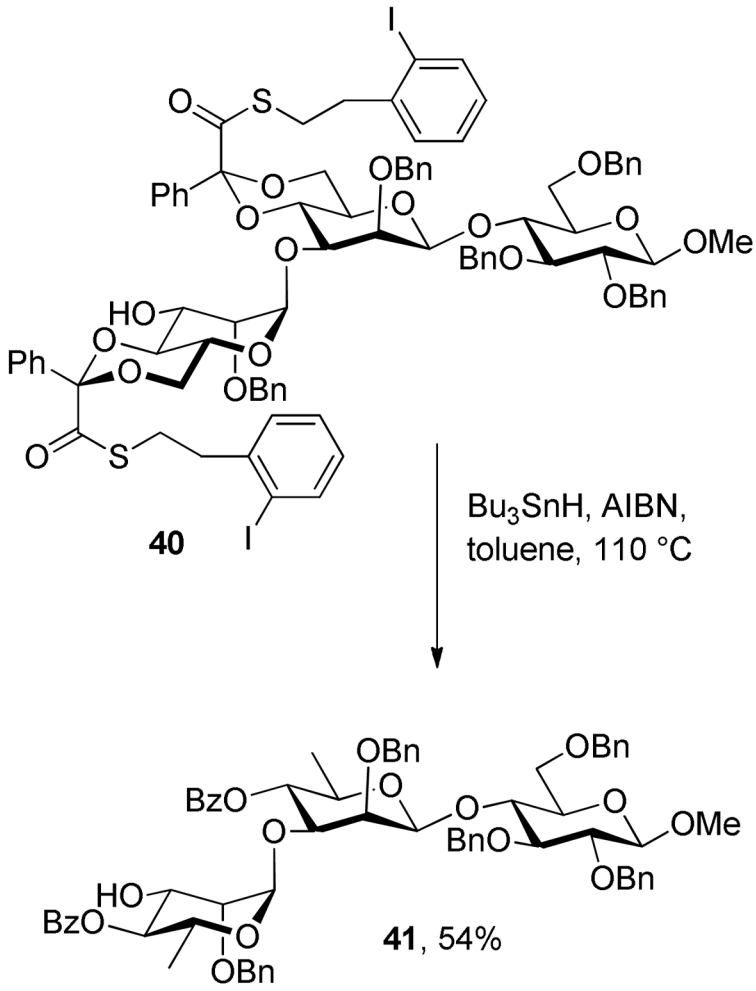

Scheme 14.
Radical fragmentation in the synthesis of a rhamnose-containing trisaccharide

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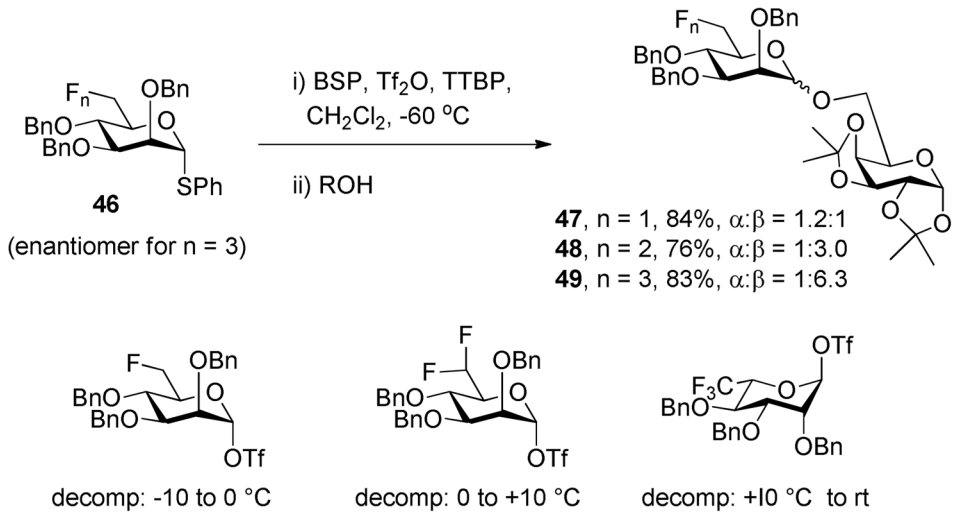
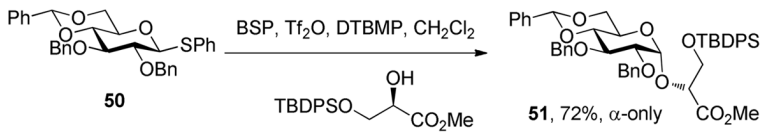


Scheme 15.

Effect of fluorine substitution at C6 on selectivity and triflate stability (NB: the enantiomeric L-donor was used for n = 3 for synthetic reasons)



Scheme 16.
Benzylidene acetal-directed synthesis of an α-glucopyranoside

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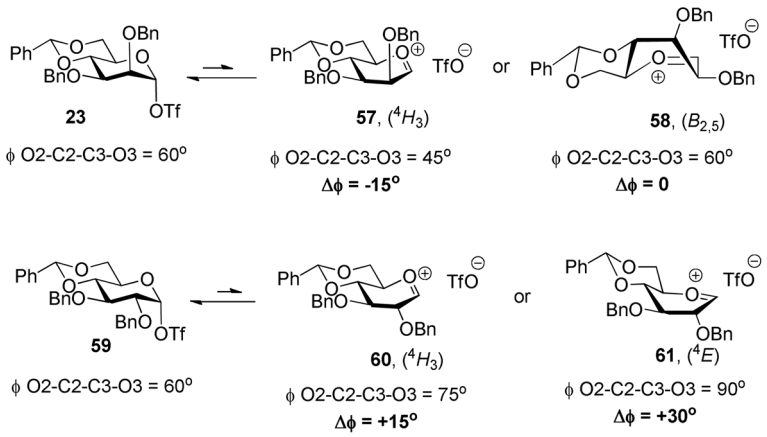

Scheme 17.

Evolution of the O2-C2-C3-O3 torsion angle with oxocarbenium ion formation in the mannose and glucose series

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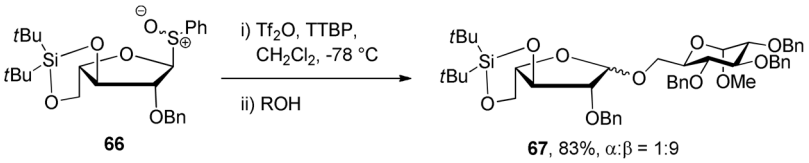

Scheme 18.
Formation of a β-L-arabinofuranoside

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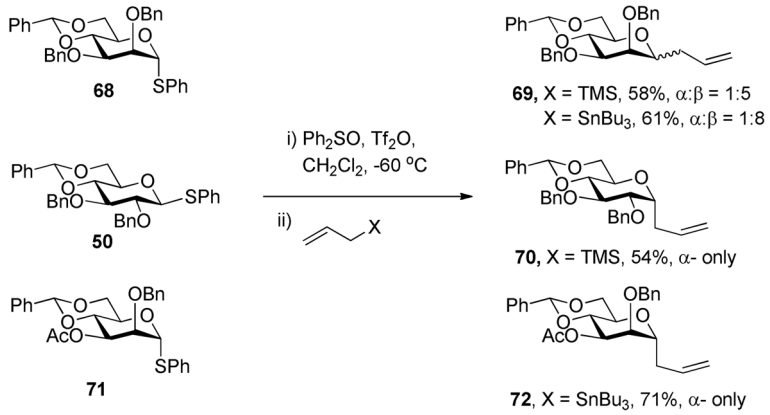

Scheme 19.

Stereoselectivity of C-glycoside formation and its dependence on configuration and protecting groups

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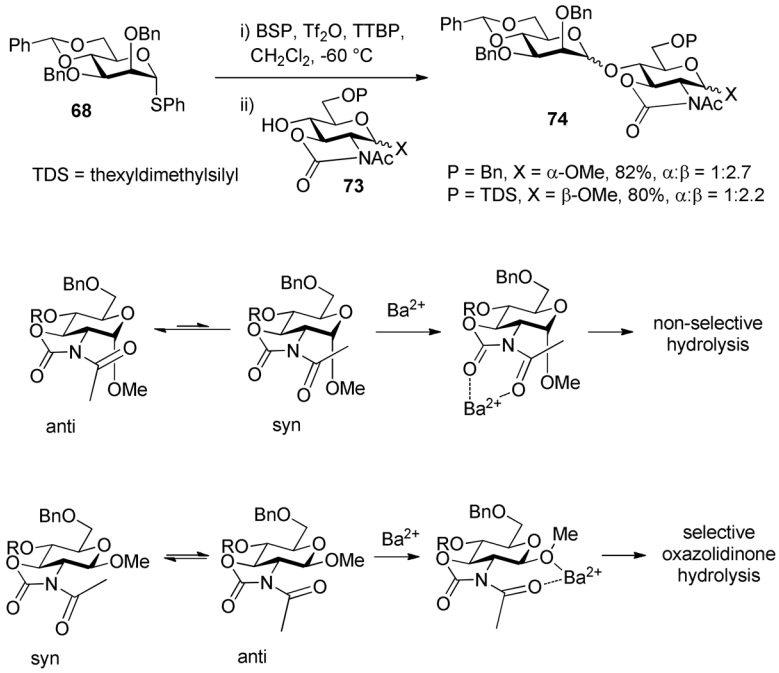
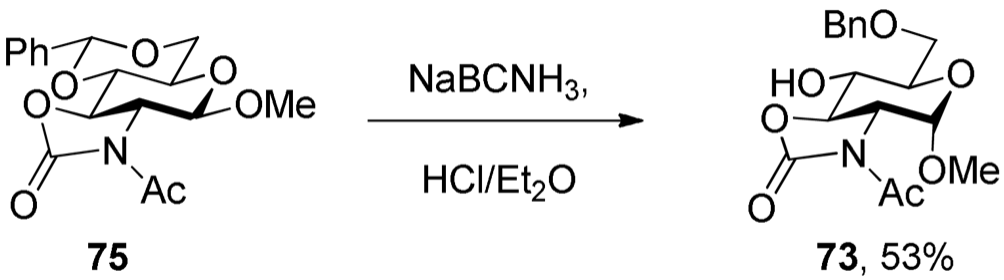


Scheme 20.

Use of the *N*-acetyloxazolidinone protected glucosamines as acceptors and dependence of oxazolidinone hydrolysis on anomeric stereochemistry



75 **73**, 53%

Scheme 21.
Facile anomeric inversion in an *N*-acetylglucsoamine oxazolidinone

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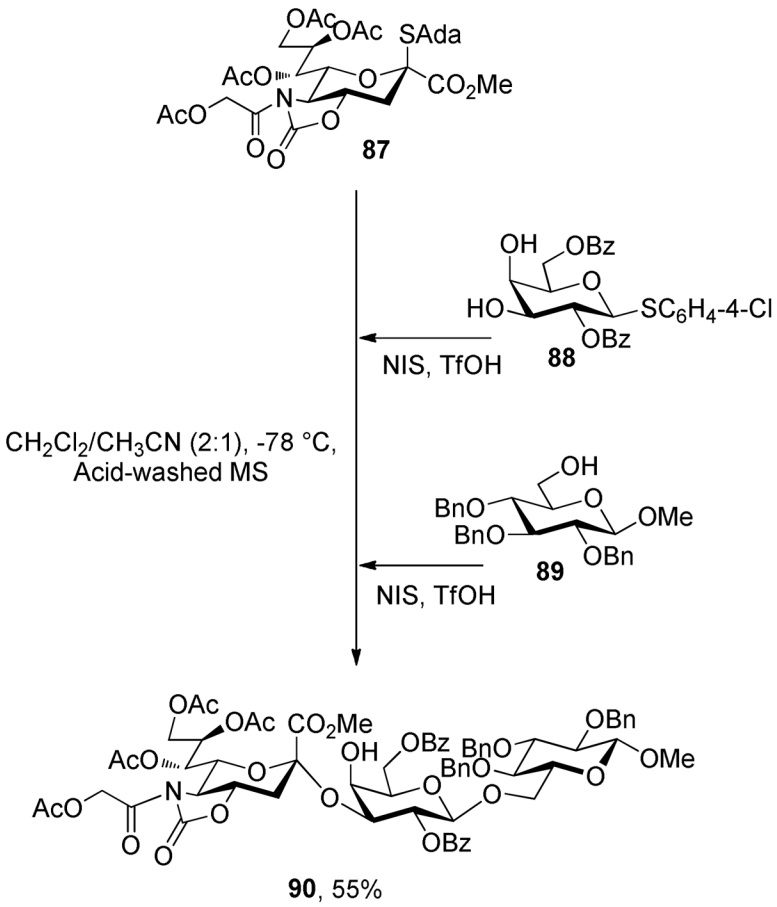
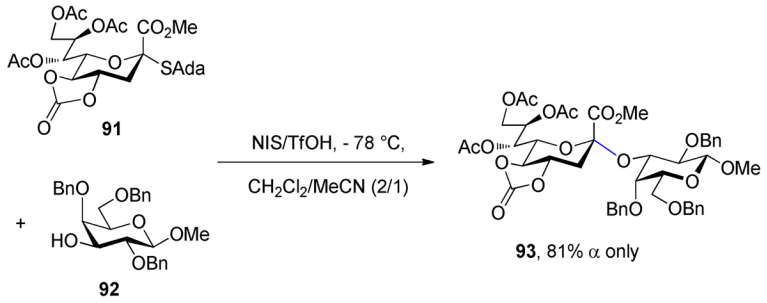


Scheme 22.
One pot trisaccharide synthesis initiated with an adamantanyl thiosialoside



Scheme 23.
4,5-*O*-Carbonate-directed formation of an α-KDN glycoside

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