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Cation Clock Reactions for the Determination of Relative Reaction Kinetics in Glycosylation Reactions: Applications to Gluco- and Mannopyranosyl Sulfoxide and Trichloroacetimidate Type Donors

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Abstract

The development of a cation clock method based on the intramolecular Sakurai reaction for probing the concentration dependence of the nucleophile in glycosylation reactions is described. The method is developed for the sulfoxide and trichloroacetimidate glycosylation protocols. The method reveals that *O*-glycosylation reactions have stronger concentration dependencies than *C*-glycosylation reactions consistent with a more associative, S_N2-like character. For the 4,6-*O*-benzylidene-directed mannosylation reaction a significant difference in concentration dependence is found for the formation of the β- and α-anomers suggesting a difference in mechanism and a rationale for the optimization of selectivity regardless of the type of donor employed. In the mannose series the cyclization reaction employed as clock results in the formation of *cis* and *trans*-fused oxabicyclo[4,4,0]decanes as products with the latter being strongly indicative of the involvement of a conformationally mobile transient glycosyl oxocarbenium ion. With identical protecting group arrays cyclization in the glucopyranose series is more rapid than in the mannopyranose manifold. The potential application of related clock reactions in other carbenium ion-based branches of organic synthesis is considered.

Introduction

In the realm of glycoscience the formation of glycosidic bonds reigns over all other covalent bond forming processes, being central to the preparation of homogeneous glycoconjugates and (oligo)saccharides of all shades. Dating back more than one hundred and thirty years to the Michael synthesis of aryl glycosides,[1] the Fischer glycosidation,[2] and the Koenigs-Knorr

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Supporting Information Available. Full experimental details and ^1H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publication website.

reactions,[3] the chemical synthesis of glycosidic bonds has been extensively researched through the investigation of innumerable combinations of glycosyl donors, glycosyl acceptors, promoters, solvents, temperature and additives. Indeed, if the year 1994 is taken as representative of the annual level of activity in the last several decades,[4] it could be suggested that the entire history of glycosidic bond forming reactions can be classified as a century-long, world-wide exercise in the combinatorial exploration of reaction conditions. This situation arises in part because of the enormous variety of glycosidic linkages possible, both natural and artificial, but also because of uncertainty in the location of any one particular reaction on the S_N1-S_N2 continuum of mechanisms for nucleophilic substitution reactions. It follows that any given glycosylation reaction might be more rationally optimized if its mechanism could be pinpointed, or at least localized, without undue expenditure of effort.

According to Ingold and Hughes,[5] the mechanism of a substitution reaction is characterized by its stereochemistry and its kinetics, yet the enormous majority of glycosylation reactions reported in the literature are discussed only in terms of their stereoselectivity. There is no doubt that this situation pertains because of the preparative significance of the selectivity, but it is also to some extent due to the difficulty in conducting kinetic studies on many glycosylation reactions. The role of ion pairs in nucleophilic substitution reactions in general has been appreciated[6–7] since Winstein's seminal contribution,[8] and in glycosylation in particular since the work of the Vernon,[9] Schuerch,[10] and Lemieux groups,[11] yet the glycosylation literature is replete with depictions of naked glycosyl oxocarbenium ions lacking their essential counterions, a fact which is even more surprising when the sparse physical evidence for existence of such glycosyl oxocarbenium ions is taken into account.[12–20] Even admitting the transient existence of glycosyl oxocarbenium ions, the widespread (and disputed[21–22]) application of basic stereoelectronic principles[23–24] to the rationalization of their face selectivity is of a relatively recent vintage.[25–26]

In our laboratory, driven by the desire to rationalize the benzylidene-directed β-mannopyranosylation,[27–28] and conscious of the major contribution of kinetic isotope effect (KIE) measurements to the understanding of the mechanisms of chemical and enzymatic glycosidic bond hydrolysis and transfer,[29–33] we have introduced[34–35] variants on the Singleton NMR method[36] for the determination of kinetic isotope effects in glycosylation reactions. Nevertheless, however informative these experiments, they are highly instrument intensive and consequently not routinely applicable. Therefore, we sought simple alternative methods for the determination of the relative kinetics and molecularity of glycosylation reactions such as might be applied in synthetic glycochemistry laboratories and so inform the rational optimization of glycosylation reactions. To this end we turned to the development of competition experiments for assessing the relative kinetics of two reactions, a concept that is deeply ingrained in the field of organic (and inorganic) chemistry.[37–54]

In carbohydrate chemistry the Jencks azide clock reaction played an important role in estimating the lifetimes of transient glycosyl oxocarbenium ions in aqueous media,[49–50] but it is not adaptable to the study of glycosylation reactions in organic solution at low temperature. Seeking an operational simple method we focused on cyclization reactions as unimolecular clocks for the investigation of intermolecular glycosylation reactions. In this

Article we report in full on our initial design[55] of such glycosylation clock reactions, present further examples, discuss the evidence for the transient formation of certain glycosyl oxocarbenium ion intermediates, and apply the results to rationalize the variation of glycosylation stereoselectivity according to conditions, most notably the passage from solution to solid phase. Although this Article focuses on glycosylation and oxocarbenium ions, we note that the concept of cyclization reactions as simple cation clocks for estimating the molecularity of nucleophilic attack on transient carbenium ions should, with suitable adaptation, find application in cognate fields.

Results and Discussion

Design

Our design of cyclization reactions for use of intramolecular glycosylation clocks was informed by the general concept of intramolecular aglycone delivery[56–60] and, more particularly, by two instances in our own laboratories of the cyclization of protecting groups at O2 of glycosyl donors onto the anomeric center in the course of previous studies (Scheme 1). Thus it was observed[61] that on warming above 5 °C in CD_2Cl_2 the α-mannosyl triflate **1** underwent decomposition with cyclization onto a benzyl group to give the tricyclic product **2**, which was isolated in 56% yield. On the other hand, the corresponding α-mannosyl triflate derived by in situ activation of the sulfoxide **3** underwent cyclization at −78 °C in CH_2Cl_2 onto the naphthylpropargyl system in competition with reaction with an external alcohol,[62] with yields varying as an inverse function of the reactivity of the external alcohol. In contrast, simple allyl ethers,[63–65] propargyl ethers[66–67] and [3-(4-trifluoromethylphenyl)propargyl] ethers[68–69] may be employed as protecting groups for the O2-postion in mannosylation reactions without complications arising from cyclization. Thus, while the precedent certainly gave rise to the potential for the use of carbon-carbon bond forming cyclization reaction onto O2 protecting groups as an intramolecular clock reaction for glycosylation reactions, it also highlighted the sensitivity of such cyclizations to the structure and reactivity of the nucleophilic function.

Recalling Denmark's use of allylsilanes as nucleophiles in a series of cyclization-based probes designed to interrogate the mechanism of the Lewis acid promoted reaction of allylsilanes with acetals (Scheme 2)[70] and other instances of the intramolecular Sakurai reaction,[71] we designed an initial system **5** (Scheme 3) employing a 2-*O*-(2-trimethylsilylmethyl)allyl group as intramolecular nucleophile. In addition to excluding the formation of an analysis-complicating additional stereogenic center, as observed in the model cyclization of **3** to **4** (Scheme 1), this system takes advantage of the much increased nucleophilicity of allylsilanes over simple alkenes in their reaction with carbocations,[72] thereby increasing the likelihood that cyclization will compete with trapping by an external alcohol nucleophile. Finally, the system envisaged finds precedent in the well-known *C*-glycoside-forming intermolecular reaction of allylsilanes with putative anomeric oxocarbenium ions.[25–26,73–90] The use of more potent tethered nucleophiles, such as alcohols, for the clock cyclization was not explored as it was considered that the high effective molarity of an intramolecular alcohol would lead to an excessively fast cyclization that would outcompete the intermolecular process.

Because of the important role that the 4,6-*O*-benzylidene protected α-mannopyranosyl triflates[91] have played in current debate on glycosylation mechanisms,[12,15–20,27–28,92–98] the initial work was focused on the use of the mannosyl sulfoxides as precursors of the mannosyl triflates. Conscious of the ever-widening range of donor types capable of providing β-mannopyranosides when used in conjunction with the 4,6-*O*-benzylidene or a related acetal,[93–94,99–110] in this study we extend the glycosyl clock method to include the use of the very popular glycosyl trichloroacetimidates.[111] The method is also extended to the 3,4,6-tri-*O*-benzyl mannopyranoside and the 3-*O*-benzyl-4,6-*O*-benzylidene-glucopyranoside series, although it must be recognized that this does not permit direct comparisons of relative glycosylation rates between the differing series owing to structural differences in the clock cyclizations.

Synthesis

The synthesis of the 4,6-*O*-benzylidene mannopyranosyl sulfoxide clock began with phenyl 4,6-*O*-benzylidene-α-D-thiomannopyranoside **7**[112–114] while that of the corresponding trichloroacetimidate followed a parallel path from 2-phenylthioethyl 4,6-*O*-benzylidene-α-D-mannopyranoside **8** (Scheme 4), which was prepared by standard means from pentaacetyl mannopyranose and phenylthioethanol (Supporting Information). Standard[115] regioselective monobenzylation of **7** and **8** with dibutyltin oxide, cesium fluoride and benzyl bromide gave **9**[116] and **10**, respectively, ready for the installation of the allylsilane moiety. In the phenyl thioglycoside series studied initially this was achieved with sodium hydride and commercial 2-(chloromethyl)allyl trimethylsilane in hot THF and gave the anticipated product **11** in 47% yield after 7 days. Subsequently, working with the phenylthioethyl glycosides, we have preferred initial conversion of the chloromethylallysilane to the corresponding iodomethylallylsilane[117] with sodium iodide in acetone followed by reaction with substrate and sodium hydride in THF at 0 °C in the presence of 15-crown-5 when the product **12** was obtained in 81% with greatly reduced reaction times. Controlled oxidation of the thioglycoside **11** with *m*CPBA in dichloromethane at −72 °C gave the sulfoxide **13** as a 16:1 mixture of diastereomers in which the major isomer is assigned the *R* configuration at sulfur consistent with the precedent.[118–120] Treatment of the phenylthioethyl glycoside with lithium naphthenalide[121] in THF at −78 °C gave the mannopyranose **14** in 78% yield, which was converted to the α-trichloroacetimidate **15** in 78% yield on reaction with trichloroacetonitrile in the presence of DBU[122] (Scheme 4).

The synthesis of the corresponding 3,4,6-tri-*O*-benzyl mannopyranosyl sulfoxide clock **18** was achieved analogously from phenyl 3,4,6-tri-*O*-benzyl-α-D-thiomannopyranoside **16**[123] (Scheme 5).

In the 4,6-*O*-benzylidene glucopyranose series (Scheme 6) synthesis of the sulfoxide clock **21** set out from the 3-*O*-benzyl derivative **19**,[124] of which alkylation with sodium hydride and iodomethylallyl trimethylsilane in hot THF gave **20** albeit only in poor yield. Oxidation with *m*CPBA then gave a 3:2 mixture of the two isomers of the sulfoxide **21** in 76% yield (Scheme 6), with the major isomer assigned as the *R* configuration at sulfur consistent with the precedent.[119–120] The two diastereomers of **21** were separable chromatographically but were typically used as mixtures in the kinetic runs that follow. The synthesis of the

trichloroacetimidate clock **27** began with 2-phenylthioethyl 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[125] **22**, itself obtained by standard means from 3-*O*-benzyl-1,2;5,6-di-*O*-isopropylidene-β-D-glucofuranose (Supporting Information). Thus, saponification of **22** gave the triol **23** onto which the benzylidene group was installed in the usual manner to afford 2-phenylthioethyl 3-*O*-benzyl-4,6-*O*-benzilidene-β-D-glucopyranose **24**. Trimethylsilylmethallylation under the improved conditions then gave **25** in 89% yield. Finally, cleavage of the phenylthioethyl group was achieved with lithium naphthenalide to give **26**, and the trichloroacetimidate was installed with the aid of sodium hydride[122] affording the trichloroacetimidate clock **27** (Scheme 6).

Clock Cyclization Reactions

Treatment of the 4,6-*O*-benzylidene-protected mannosyl sulfoxide **13** with triflic anhydride in dichloromethane at −72 °C in the presence of the hindered non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) with quenching at −72 °C after stirring for 2.5 h resulted in the isolation of two tricyclic products **28** and **29** in 45 and 25% isolated yield, respectively (Chart 1, Table 1, entry 1). Attempted activation of the corresponding trichloroacetimidate **15** with catalytic TMSOTf at the same temperature resulted in a very slow reaction. However, raising the temperature to −20 °C enabled a rapid smooth reaction resulting in the isolation of **28** and **29** in 70 and 25 % yields, respectively (Chart 1, Table 1, entry 2). We note that the reported use of 3-*O*-allyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl trichloroacetimidate as a β-selective mannosyl donor was conducted at −50 °C,[99] presumably also for reasons of reduced reactivity in standard dry ice/acetone cooling baths. The 3,4,6-tri-*O*-benzyl protected mannopyranosyl sulfoxide **18** cyclized smoothly on activation with triflic anhydride in the presence of TTBP at −72 °C giving the two bicyclic products **30** and **31** in 52 and 20% isolated yield, respectively (Chart 1, Table 1, entry 3). In the glucopyranose series, however, working with the sulfoxide clock **21** complications arising from sulfenyl transfer to the allylsilane were dominant and resulted in the formation of the anticipated cyclization product **32** in only low yield. Sulfenyl group transfer to substrate-based nucleophiles has been observed previously and can typically be suppressed by working in the presence of a sacrificial alkene.[62,126] However, even working in the presence of multiple equivalents of 1-octene or the highly reactive β-pinene[127–128] we were unable to obtain a satisfactory yield of **32** (Chart 1, Table 1, entry 4). This observation, coupled with the relative paucity of such side reactions in the mannose series (Table 1, entries 1–3), suggests an intramolecular process and caused us to abandon the use of the gluco-configured sulfoxide **21** in clock reactions. Fortunately, the glucosyl trichloroacetimidate **27** behaved in the anticipated manner resulting in a 92% isolated yield of the cyclization product **32** following activation with TMSOTf in the presence of TTBP at −20 °C (Chart 1, Table 1, entry 5).

The structure of the manno-configured *trans*,*trans*-tricyclic system **29**, with the pyranose ring in the $^1S_5$ twist boat conformation and the benzylidene and newly formed rings in chair conformations, was confirmed by X-ray crystallography (CSD refcode YEYDUD[55]). That the overall conformation of **29** does not change on going from the crystal to the solution phase is apparent from the 10.5 Hz coupling of the vicinal trans-pseudo-diaxial hydrogen atoms at the bridgehead positions of the newly formed ring. Crystals of the *trans*-fused

bicyclic analog **31** suitable for X-ray crystallographic analysis could not be obtained, however, the $^{1}S_{5}$ twist boat conformation of the pyranose ring is again revealed by the large coupling constant between the two bridgehead hydrogens. The major *cis*-fused products **28** and **30** in the mannose series were both examined crystallographically (CSD Refcode YEYFAL[55] and CCDC 1403928) and were both found to contain only chair conformers of the various six-membered rings. The single cyclization product **32** formed in the glucopyranose series (Table 1, entries 4 and 5) also adopts the $^{1}S_{5}$ twist boat conformation of the pyranose ring in the crystal (CCDC 878445), while the benzylidene and newly-formed rings take up chair conformations. This conformation is also retained in solution as indicated by the $^{3}J_{1,2}$ and $^{3}J_{2,3}$ (glucose numbering) coupling constants of 3.8 and 5.2 Hz, respectively.

The formation of the *trans*-fused products **29** and **31** as minor isomers from the cyclization of the mannopyranosyl clocks **13**, **15**, and **18** (Table 1, entries 1–3) is instructive and points to the formation of a mannopyranosyl oxocarbenium ion as transient intermediate that populates the $B_{2,5}$ or related conformation. Thus, the mannosyl triflate[91] **33** formed on activation of the donor can be considered to be in equilibrium with the mannosyl oxocarbenium/triflate ion pair **34**, which can adopt several conformations. The $^{4}H_{3}$ and $B_{2,5}$ conformations of **34** are accessible for both the 4,6-*O*-benzylidene and tri-*O*-benzyl systems, while the latter, being less conformationally constrained, also can access the $^{3}H_{4}$ half-chair (Scheme 7). In the $B_{2,5}$ conformation the pendant allylsilane adopts a pseudoequatorial position and is poised to react with either face of the oxocarbenium ion, thereby enabling the formation of the *cis* and *trans*-fused products (Scheme 7). Formation of the *trans*-fused product is also possible from the $^{3}H_{4}$ conformer in the case of the tri-*O*-benzyl protected system. The major *cis*-fused product can be formed from any of the three accessible conformations (Scheme 7).

In the glucopyranose system there are only two conformations, $^{4}H_{3}$ and $B_{2,5}$, of the oxocarbenium ion/triflate ion pair **36** in equilibrium with the initially formed covalent triflate **35**, and both lead to the *cis*-fused product **32** (Scheme 8). The excellent *cis*-selectivity observed in this kinetic ring closure contrasts with the thermodynamic *trans*-selectivity seen on ring closure of 2-*O*-(2-thioethyl)glucopyranosyl cations and related systems to hetero-bicyclo[4.4.0]decane-like systems, which are governed by the steric factors in the product.[129–131] The preference of the tricyclic glucose derivative **32** for the $^{1}S_{5}$ conformation of the pyranose ring as opposed to the $^{4}C_{1}$ chair must arise because of a combination two unfavorable steric interactions in the chair: the 1,3-diaxial interaction between the axial anomeric CC bond and the axial C3-H3 bond and the gauche butane interaction emphasized in red in Scheme 8. This is because simple 4,6-*O*-benzylidene protected α-*C*-glucopyranosides, with an axial substituent at C1 but lacking the third ring, exist predominantly as $^{4}C_{1}$ conformers (vide infra).[80–81]

Schemes 7 and 8 employ triflate as the counterion given that activations were conducted with either triflic anhydride or TMSOTf for the sulfoxide and trichloroacetimidate donors, respectively. This does not restrict the general concept of the cation clock method to the use of triflate-based activating systems and triflates as counterions. The concept is equally valid for glycosylation reactions conducted with other activating systems and leaving groups.

Competition Kinetics

For the sulfoxide donors competition kinetics were conducted at −72 °C in CH_2Cl_2 by addition of triflic anhydride to a mixture of the donor and TTBP followed by addition of incremental amounts of isopropanol or methallyltrimethylsilane as glycosyl acceptor. After stirring for 5 min at −72 °C the reactions were quenched at that temperature, worked up, and the product ratios analyzed by UHPLC giving the data presented in Tables 2 and 4. The crude reaction mixtures from multiple runs were combined and subjected to purification over silica gel yielding pure samples of the glycosides **37** – **41** (Chart 2). For the trichloroacetimidates **15** and **27**, TMSOTf was simply added to preformed mixtures of the donor and acceptors at −20 °C followed by continued stirring at that temperature. After quenching at −20 °C reaction mixtures were again analyzed by UHPLC (Tables 3 and 5), and pooling of crude reaction mixtures afforded sufficient material for the chromatographic purification and full characterization of the glycosides **42**–**44** (Chart 2). The data from Tables 2–5 are presented graphically in the form of plots of glycoside/cyclized product ratios against acceptor concentration in Figures 1a–d.

Comparison of Figures 1a and b reveals that the 4,6-*O*-benzylidene mannosyl donors **13** and **15** display largely parallel behavior toward both isopropanol and methylallyltrimethylsilane in spite of the different reaction temperatures and leaving groups. Thus, with both **13** and **15** the formation of the β-mannoside **37** shows a much stronger concentration dependence than that of the α-anomer **38**, with the latter showing a slightly greater concentration dependence than the formation of the β-*C*-mannoside **39**. Consistent with earlier observations only the β-anomer **39** is formed in the 4,6-*O*-benzylidene-directed C-mannosylation.[80] These observations are most consistent with an S_N2-like associative displacement of an axial leaving group for the formation of the β-*O*-mannoside **37** and of a much more dissociative S_N1-like reaction for the formation of the α-*O*-mannoside **38**, as determined previously using ^{13}C-primary kinetic isotope effect measurements for the case of triflate as leaving group in 4,6-*O*-benzylidene protected mannosyl donors.[35] The very low concentration dependence observed for the formation of the *C*-mannoside **39** is consistent with a highly dissociative mechanism proceeding via an oxocarbenium ion **34** (Scheme 7, R-R = PhCH) that is only loosely associated with the counterion.[132] This in turn is consistent with methallyltrimethylsilane being a much weaker nucleophile than isopropanol and requiring the potent electrophile at the dissociative end of the mechanistic spectrum.[133]

Comparison of Figures 1a and c reveals a very different pattern of behavior between the 4,6-*O*-benzylidene and perbenzyl protected mannosyl donors **13** and **18**. Thus, in contrast to the case of **13**, both the β- and α-perbenzyl mannosides **40** and **41** formed from **18** on coupling to isopropanol display essentially the same concentration dependence. Superposition of Figures 1a and c, as in Figure 1e, reveals the very shallow concentration dependence for the formation of **40** and **41** to approximate that for the formation of the 4,6-*O*-benzylidene protected α-mannoside **38** and strongly suggests that **40** and **41** are formed by dissociative mechanisms that involve the oxocarbenium ion **34** (Scheme 7, R = Bn) only loosely associated with the counterion. This observation is consistent with the strongly disarming nature of the 4,6-*O*-benzylidene acetal,[52,134–136] as compared to two benzyl ethers, which in turn is a function of the imposition of the *trans-gauche* conformation[137] of the C5-C6 bond

in which the electron-withdrawing effect of the C5-O5 bond is maximized.[138–140] A caveat to this argument concerns the use of different clock reactions in Figures 1a and c (vide infra), however, we believe that the comparison is justified here in view of the similarity of the two oxocarbenium ions (Scheme 7, **34**, R = Bn and R-R = PhCH).

Comparison of Figures 1b and d reveals the very different influence of the 4,6-*O*-benzylidene acetal protecting group in the manno- and glucopyranose series. Thus, in contrast to the benzylidene-protected *O*-mannosylation, both anomers **42** and **43** of the benzylidene-protected glucosides are formed with the same concentration dependence. The formation of both *O*-glucosides **42** and **43** shows a much stronger concentration dependence than that of the corresponding *C*-glucoside **44** (Figure 1d), which was formed as a single α-anomer consistent with previous reports.[80–81] If *C*-glucoside formation is interpreted as representative of the concentration dependence of a dissociative S_N1-like mechanism with a weak nucleophile as in the mannose case, these results are again consistent with primary ^{13}C kinetic isotope effect studies on benzylidene-protected *O*-glucosylation with triflate as leaving group which point to both anomers being formed by associative S_N2-like mechanisms from a pair of rapidly equilibrating anomeric glucosyl triflates.[35] The inherent difference in cyclization rates between the mannosyl and glucosyl clocks are most readily appreciated from a direct comparison of *C*-glycoside formation in the two series (Figure 1f). Thus, in order for *C*-glycosylation to compete with the cyclization of **27** to **32** significantly more methallylsilane is required than for *C*-glycosylation to compete with the cyclization of **15** to **28** and **29** under the same reaction conditions. It follows that *C*-glycosylation in the glucose series is less concentration dependent than in the mannose series suggesting that it is closer to a pure S_N1 mechanism.

Conclusions

A cation clock method based on the intramolecular Sakurai reaction has been developed and used to probe the concentration dependence of representative *O*- and *C*-glycosylation reactions. The method is applicable to the use of glycosyl sulfoxides with activation by triflic anhydride and for the use of glycosyl trichloroacetimidates with activation by trimethylsilyl triflate. 4,6-*O*-Benzylidene-directed β-mannosylation is demonstrated to proceed with a strong dependence on the concentration of the acceptor alcohol, whereas the α-anomer is much less concentration dependent. Concentration therefore plays a critical role in the 4,6-*O*-benzylidene-directed β-mannosylation process and can be used to optimize selectivity. The reduced selectivity observed on trapping of 4,6-*O*-benzylidene-protected mannosyl donors by polymer-supported alcohols[141] can be understood in terms of the reduced concentration of the acceptor. Analogous results are observed in 4,6-*O*-benzylidene-directed β-mannosylation conducted by the sulfoxide and trichloroacetimidate methods suggesting a commonality of mechanism if not necessarily of leaving group. In the 3,4,6-tri-*O*-benzyl protected mannopyranosyl and 3-*O*-benzyl-4,6-*O*-benzylidene glucopyranosyl systems the formation of both anomers of the isopropyl glycosides display very similar concentration dependencies which, are nevertheless, greater than that of the formation of *C*-glycosides. The formation of *trans*-fused products from the clock reaction in the mannopyranose series is interpreted in terms of transient glycosyl oxocarbenium ions that

are capable of accessing the $B_{2,5}$ and/or $^{3}H_{4}$ conformers. Further development and application of the method is in progress and will be reported in due course.

Beyond the immediate context of carbohydrate chemistry and the glycosylation reaction, the concept of competition kinetics using a simple cyclization as clock reaction should find broader application in estimating the molecularity of other cation-based processes in organic synthesis. Such reactions might include but are not limited to oxocarbenium-like ions in the nucleophilic ring opening of chiral acetals in simple ether-forming reactions and in Mukaiyama-type aldol reactions, acylium ion-based processes, iminium and *N*-acyl iminium ion chemistry, thiacarbenium ions in Pummerer-type chemistry, and the many reactions of carbenium ions themselves.

Supplementary Material

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Acknowledgments

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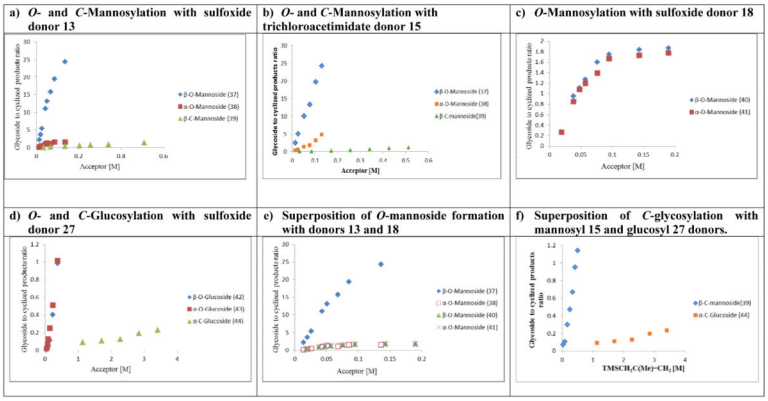
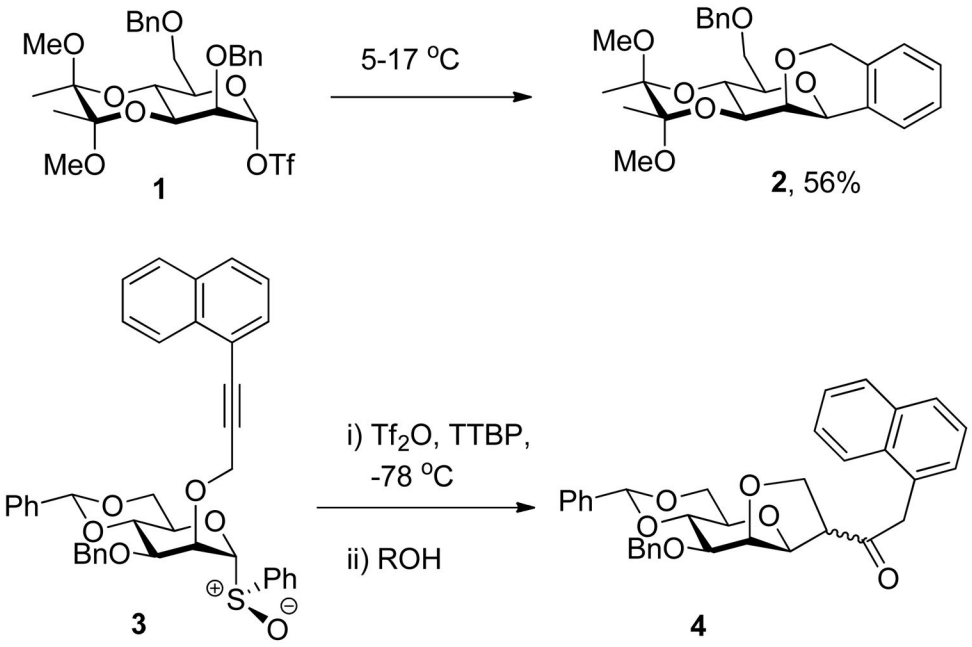
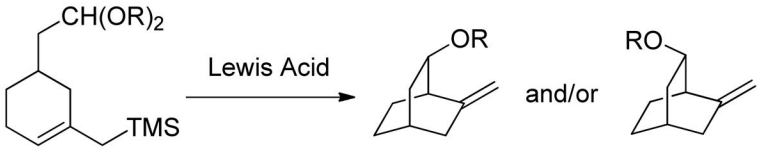


Figure 1.
Graphic Representation of Clock Reactions



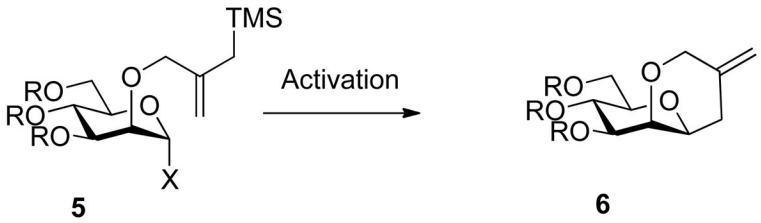
Scheme 1.

Cyclization of Protecting Groups at the 2-Position onto the Anomeric Center.



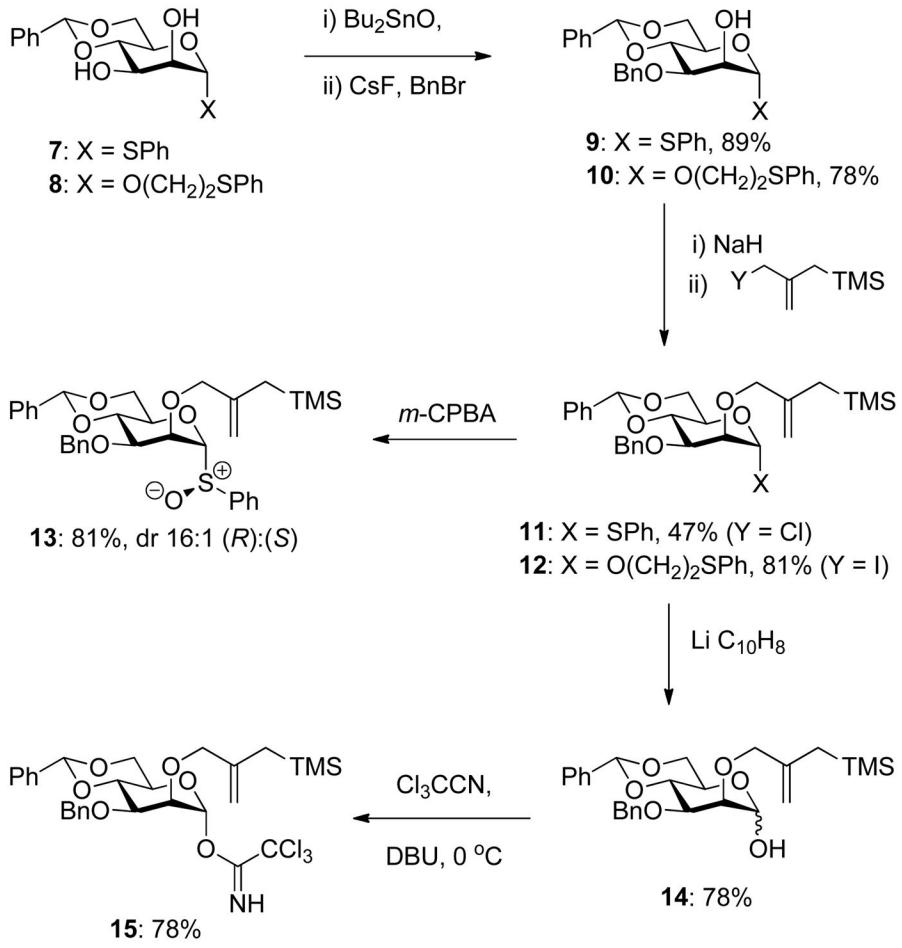
Scheme 2.

Use of an Intramolecular Allylsilane-Acetal Reaction as a Probe of Mechanism.



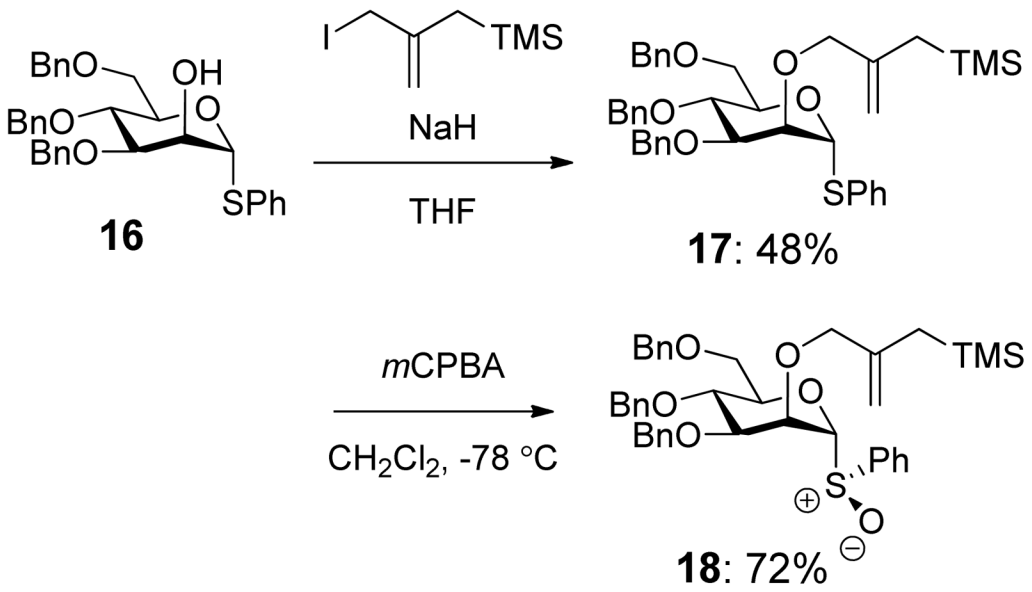
5 **6**

Scheme 3.
Initial Clock Cyclization Design.

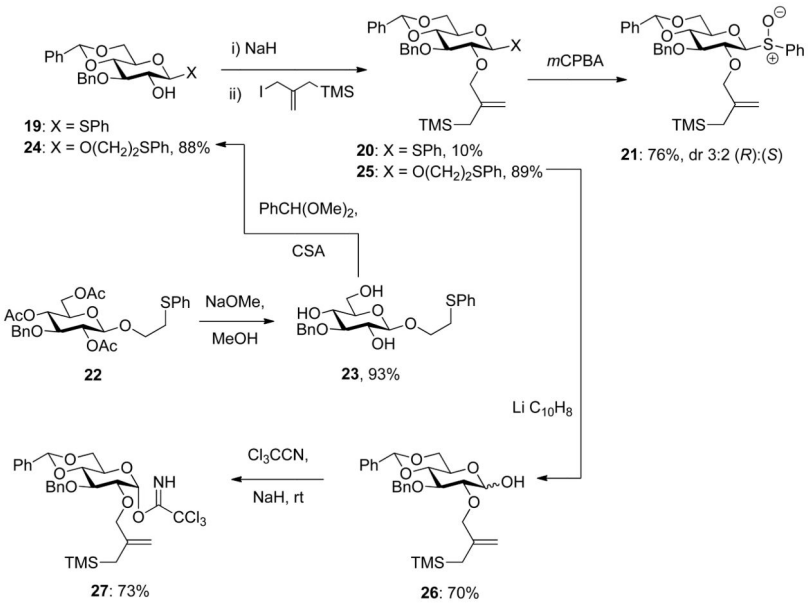


Scheme 4.

Synthesis of the 4,6-*O*-Benzylidene-protected Mannopyranosyl Clocks

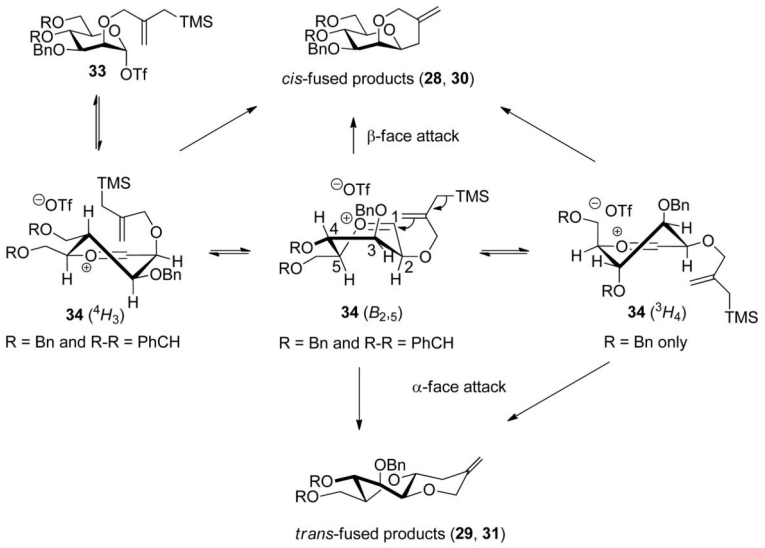


Scheme 5.
Synthesis of the Perbenzyl Mannopyranosyl Clock



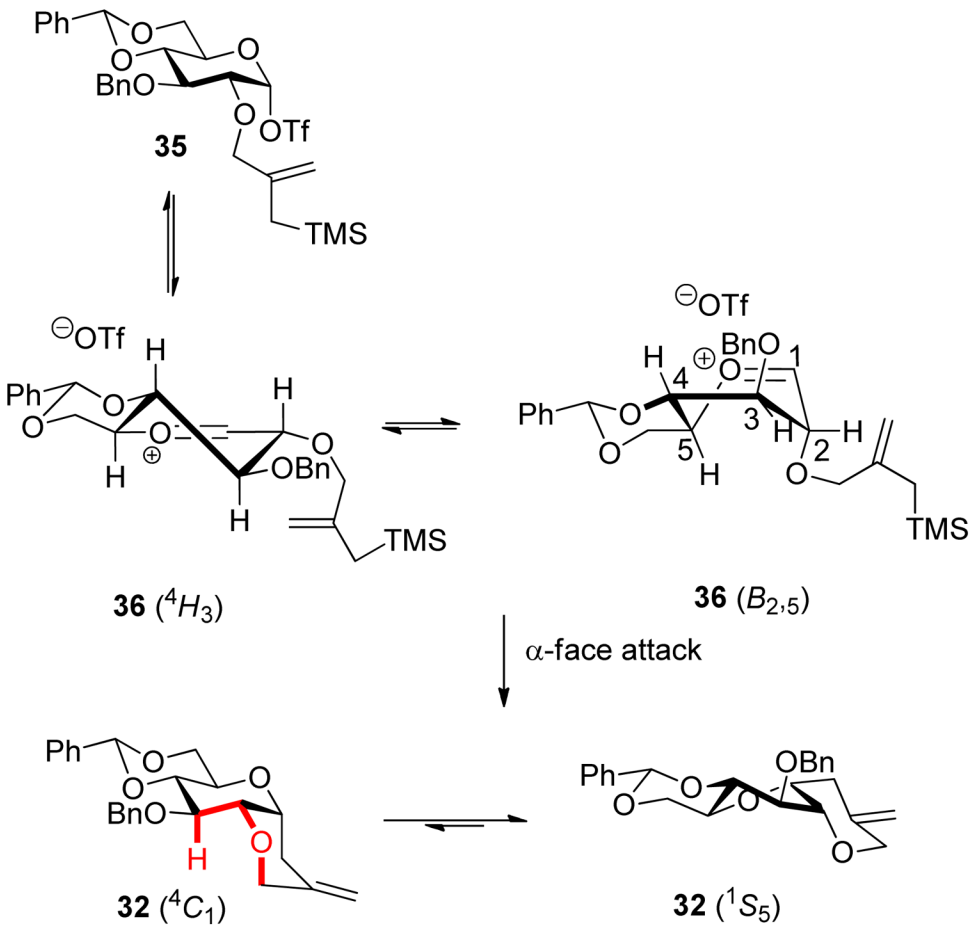
Scheme 6.

Synthesis of the 4,6-*O*-Benzylidene-protected Glucopyranosyl Clocks



Scheme 7.

Conformation and Selectivity of the Mannopyranosyl Oxocarbenium Ion



Scheme 8.

Conformation and Selectivity of the Glucopyranosyl Oxocarbenium Ion

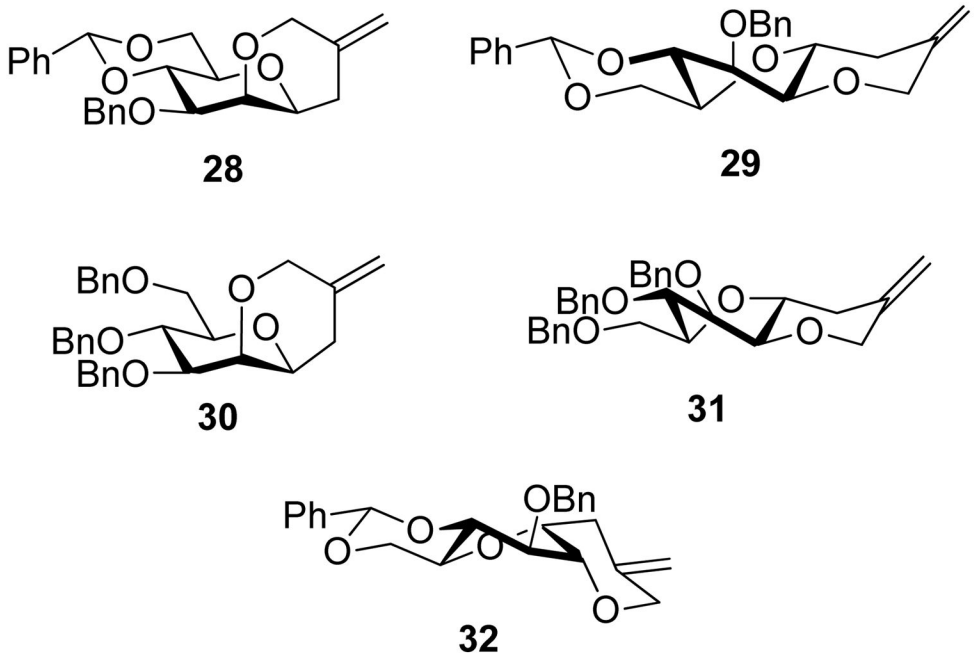


Chart 1.
Clock Cyclization Products

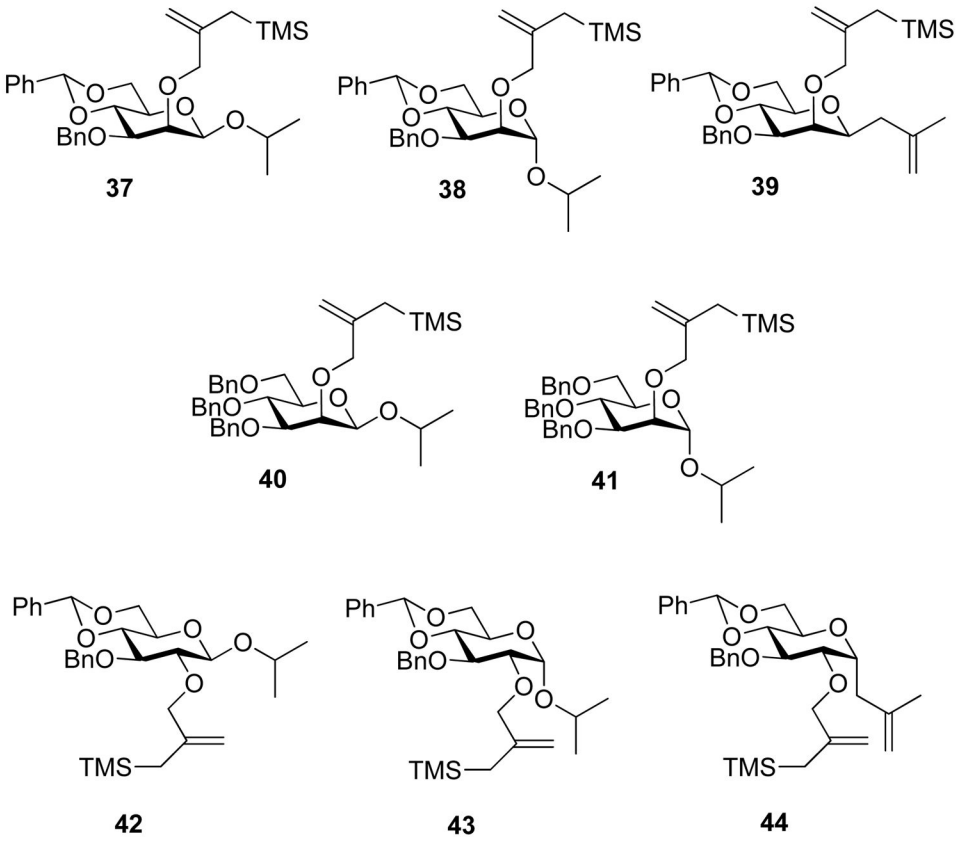


Chart 2.
Glycosides From Competition Kinetic Experiments

Table 1

Cyclization Reactions in the Absence of Added External Nucleophile

Entry	Substrate	Conditions	Products, % yield, (pyranose conformation, method)
1	**13**	Tf_2O, TTBP, −72 °C	**28**, 45% ($^4C_1$, X-ray, NMR) + **29**, 25% ($^1S_5$, X-ray, NMR)
2	**15**	TMSOTf, TTBP, −20 °C	**28**, 70% + **29**, 25%
3	**18**	Tf_2O, TTBP, −72 °C, 1-octene	**30**, 52% ($^4C_1$, X-ray, NMR), + **31**, 20% ($^1S_5$, NMR)
4	**21**	Tf_2O, TTBP, −72 °C, 1-octene or β-pinene	**32**, 20% ($^1S_5$, X-ray, NMR),
5	**27**	TMSOTf, TTBP, −20 °C	**32**, 92%

Table 2

O - and *C*-Mannosylation with Donor **13**.

Entry	Nucleophile	Equiv (M conc)	β-gly/cycl	α-gly/cycl
			37/(**28**+**29**)[c]	**38**/(**28**+**29**)[c]
1[a]	*i*PrOH	0.8 (0.014)	2.17	0.15
2[a]	*i*PrOH	1.2 (0.020)	3.66	0.28
3[a]	*i*PrOH	1.5 (0.026)	5.36	0.44
4[a]	*i*PrOH	2.5 (0.043)	10.99	0.99
5[a]	*i*PrOH	3 (0.051)	13.09	1.28
6[a]	*i*PrOH	4 (0.068)	15.75	1.14
7[a]	*i*PrOH	5 (0.085)	19.38	1.53
8[a]	*i*PrOH	8 (0.136)	24.34	1.60
			39/(**28**+**29**)[c]	-
9[b]	$TMSCH_2C(Me)=CH_2$	2 (0.034)	0.06	-
10[b]	$TMSCH_2C(Me)=CH_2$	4 (0.068)	0.18	-
11[b]	$TMSCH_2C(Me)=CH_2$	8 (0.136)	0.40	-
12[b]	$TMSCH_2C(Me)=CH_2$	12 (0.204)	0.55	-
13[b]	$TMSCH_2C(Me)=CH_2$	15 (0.255)	0.69	-
14[b]	$TMSCH_2C(Me)=CH_2$	20 (0.34)	0.87	-
15[b]	$TMSCH_2C(Me)=CH_2$	30 (0.51)	1.40	-

[a] Experimental conditions: TTBP (4 equiv), 1-octene (10 equiv), molecular sieves 4 Å, Tf_2O (1.2 equiv) at −72 °C;

[b] Experimental conditions: TTBP (4 equiv), molecular sieves 4 Å, Tf_2O (1.2 equiv) at − 72 °C;

[c] Molar ratios were determined by UHPLC/UV/MS

Table 3

O- and *C*-Mannosylation with Donor **15**.

Entry	Nucleophile	Equiv (M conc)	β-gly/cycl	α-gly/cycl
			37/(**28**+**29**)[c]	**38**/(**28**+**29**)[c]
1[a]	*i*PrOH	0.81 (0.013)	2.5702	0.30827
2[a]	*i*PrOH	1.63 (0.026)	5.0541	0.54899
3[a]	*i*PrOH	2.4 (0.052)	10.1031	1.33043
4[a]	*i*PrOH	3.25 (0.078)	13.3632	1.83040
5[a]	*i*PrOH	4.88 (0.104)	19.7443	3.20719
6[a]	*i*PrOH	8.12 (0.130)	24.2748	4.83401
			39/(**28**+**29**)[c]	-
7[b]	$TMSCH_2C(Me)=CH_2$	2.1 (0.032)	0.0729	-
8[b]	$TMSCH_2C(Me)=CH_2$	5.3 (0.085)	0.1046	-
9[b]	$TMSCH_2C(Me)=CH_2$	10.7 (0.171)	0.2996	-
10[b]	$TMSCH_2C(Me)=CH_2$	16.0 (0.256)	0.4712	-
11[b]	$TMSCH_2C(Me)=CH_2$	21.3 (0.341)	0.6673	-
12[b]	$TMSCH_2C(Me)=CH_2$	26.7(0.427)	0.9509	-
13[b]	$TMSCH_2C(Me)=CH_2$	32.0 (0.512)	1.1419	-

[a] Experimental conditions: TTBP (0.3 equiv), TMSOTf (0.3 equiv.) at −20 °C; molecular sieves 4 Å;

[b] Experimental conditions: TTBP (0.3 equiv), TMSOTf(0.3 equiv.) at −20 °C; molecular sieves 4 Å;

[c] Molar ratios were determined by UHPLC/UV/MS

Table 4

O-Mannosylation with Donor **18**.

Entry	Nucleophile	Equiv (M conc)	β-gly/cycl	α-gly/cycl
			40/(30+31)[c]	**41/(30+31)[c]**
1[a]	*i*PrOH	1 (0.019)	0.27	0.27
2[a]	*i*PrOH	2 (0.038)	0.95	0.85
3[a]	*i*PrOH	2.5 (0.048)	1.11	1.08
4[a]	*i*PrOH	3 (0.057)	1.27	1.20
5[a]	*i*PrOH	4 (0.076)	1.60	1.39
6[a]	*i*PrOH	5 (0.095)	1.75	1.67
7[a]	*i*PrOH	7.5 (0.143)	1.84	1.73
8[a]	*i*PrOH	10 (0.190)	1.87	1.78

[a]Experimental conditions: TTBP (10 equiv), β-pinene (30 equiv), molecular sieves 4 Å, Tf_2O (1.2 equiv) at − 60 °C;

[b]Molar ratios were determined by UHPLC/UV/MS

Table 5

O- and *C*-Glucosylation with Donor **27**.

Entry	Nucleophile	Equiv (M conc)	β-gly/cycl	α-gly/cycl
			42/(32)[c]	**43/(32)**[c]
1[a]	*i*PrOH	1 (0.048)	0.0067	0.0227
2[a]	*i*PrOH	1.5 (0.072)	0.0243	0.0708
3[a]	*i*PrOH	2 (0.096)	0.0550	0.1297
4[a]	*i*PrOH	3 (0.144	0.1143	0.2498
5[a]	*i*PrOH	5 (0.239)	0.4043	0.5135
6[a]	*i*PrOH	8 (0.382)	0.9845	1.0176
				44/(**32**)[c]
7[b]	$TMSCH_2C(Me)=CH_2$	23.8 (1.14)	-	0.0899
8[b]	$TMSCH_2C(Me)=CH_2$	35.7 (1.71)	-	0.1078
9[b]	$TMSCH_2C(Me)=CH_2$	47.6 (2.28)	-	0.1273
10[b]	$TMSCH_2C(Me)=CH_2$	59.5 (2.85)	-	0.1957
11[b]	$TMSCH_2C(Me)=CH_2$	71.4 (3.41)	-	0.2331

[a] Experimental conditions: TTBP (0.3 equiv), TMSOTf (0.3 equiv.) at −20 °C; molecular sieves 4 Å;

[b] Experimental conditions: TTBP (0.3 equiv), TMSOTf (0.3 equiv.) at −20 °C; molecular sieves 4 Å;

[c] Molar ratios were determined by UHPLC/UV/MS