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Applying the Bent Bond / Antiperiplanar Hypothesis to the Stereoselective Glycosylation of Bicyclic Furanosides

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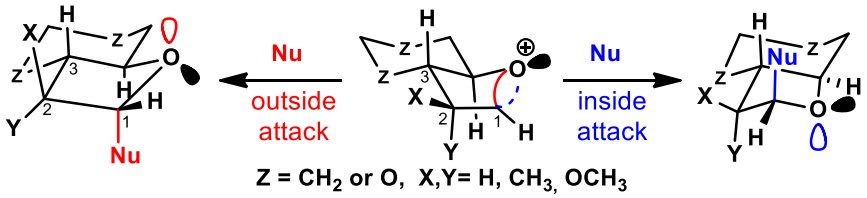
ABSTRACT

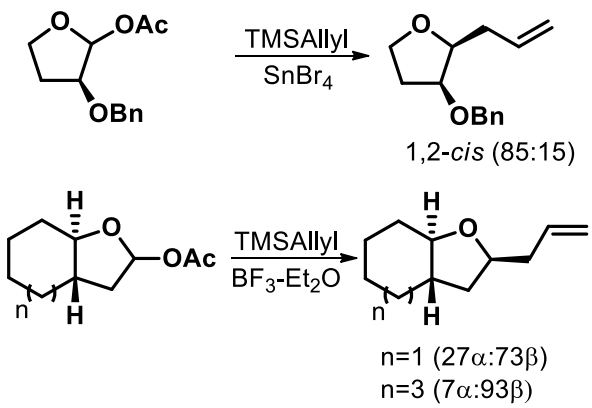


The glycosylation stereoselectivities for a series of bicyclic furanoside models have been carried out in the presence of weak nucleophiles. These results were analyzed through the bent bond / antiperiplanar hypothesis (BBAH) orbital model in order to test its validity. According to the BBAH, incoming nucleophiles displace one of the two bent bonds of bicyclic oxocarbenium ion intermediates in antiperiplanar fashion. The glycosylation stereoselectivity is then governed by displacement of the weaker bent bond as determined by the presence of electron-withdrawing or donating substituents at C_2. Overall, the BBAH analysis expands Woerpel's "inside/outside attack" glycosylation model by considering the stereoelectronic influence of neighbouring electron-withdrawing and donating groups on the nucleophilic addition to oxocarbenium ion intermediates.

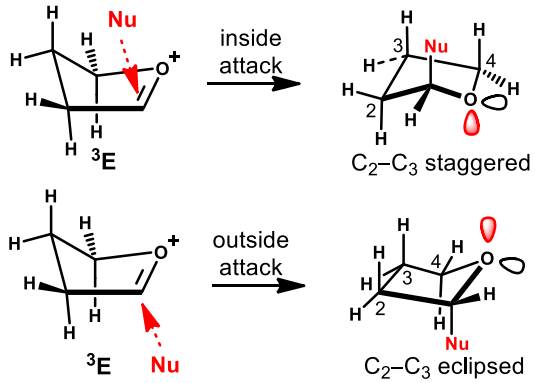
INTRODUCTION

We have previously reported the development and application of the bent bond / antiperiplanar hypothesis (BBAH), a conceptually novel orbital model for rationalizing the reactivity of various types of unsaturated systems.[1,2,3,4,5,6,7] This model was also applied to better understand the parameters that govern the O- and C-glycosylation of pyranosides.[8] We wish to report that the O- and C-glycosylation of furanosides can also be analyzed in a similar fashion using a series of bicyclic furanoside model compounds.

Woerpel and co-workers[9] previously reported the C-glycosylation of several furanosides with allyltrimethylsilane (TMSallyl) in the presence of Lewis acid. For example, a 2-benzyloxyfuranoside acetate gave the 1,2-*cis* product as a major isomer (*cis:trans* 85:15) (Scheme 1).[9e] When the OBn group was replaced by a CH_3 group, the reaction became modestly *trans* selective (*cis-trans* 32:68).[10] Woerpel also reported the allylation of a conformationally rigid bicyclic furanoside, which yielded mainly the β-isomer (27α:73β).[9d,f,g] From these results, Woerpel postulated that the nucleophile preferably undergoes an "inside attack" on the corresponding oxocarbenium ion intermediate in relation to its ^3E conformation. As illustrated in Scheme 2,[9] the inside attack produces a five-membered product in an initial conformation where the substituents at C_2 and C_3 stagger each other. The alternative “outside attack" produces a five-membered product that eclipses the C_2–C_3 bond. The inside attack also eclipses the C_3–C_4 bond, a factor that was used to account for the lower β stereoselectivity for C-allylation of the *trans*-fused cyclohexane model (73%) compared to its more conformationally mobile cyclooctane counterpart (93%) as shown in Scheme 1.



Scheme 1. Allylation of furanosides.

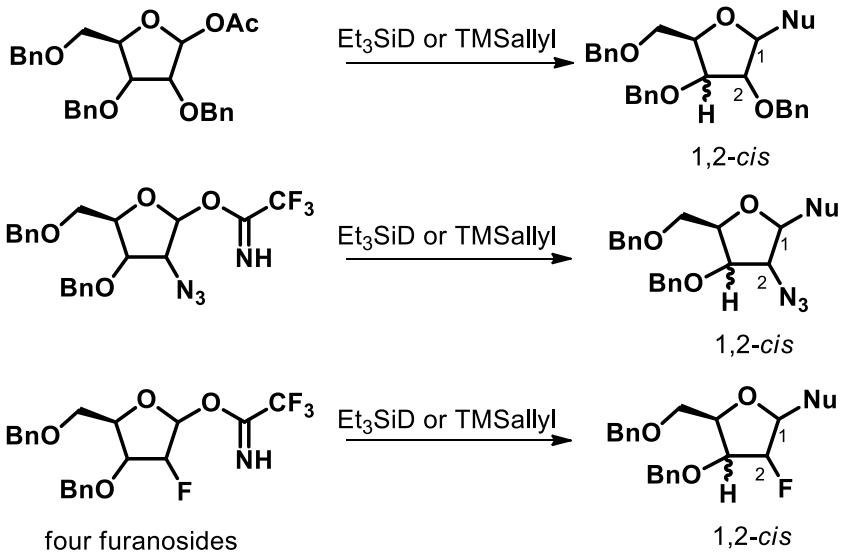


Scheme 2. Inside and outside attack.

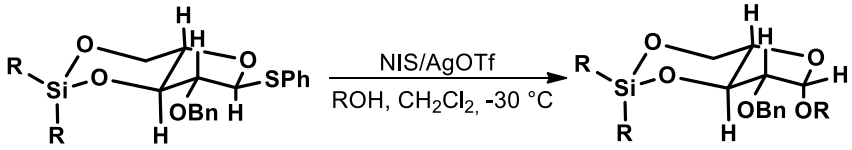
As will be demonstrated herein, a straightforward application of the BBAH orbital model produces the same general outcome as the Woerpel inside/outside attack model but also accounts for the modulation of glycosylation stereoselectivities due to stereoelectronic interactions between the bent bonds of the oxocarbenium ion intermediates and the substituents at C_2.

Codée and colleagues[11a,b] reported the acid-catalyzed additions of deuterium (Et_3SiD) and allyl (TMSallyl) to benzylated pentafuranoside analogues of ribose, arabinose, xylose and lyxose bearing different substituents at C_2 (Scheme 3). The reactions all gave 1,2-*cis* adducts with good (85:15) to excellent (98:2) stereoselectivity. These results were rationalized on the basis of

Woerpel's inside attack model by analyzing the most stable conformation of their respective oxocarbenium ions by *ab initio* calculation. In all cases, the major product had the nucleophile *cis* to the C_2 electron-withdrawing group (EWG). Boons and co-workers[11c] also reported the 1,2-*cis* glycosylation of bicyclic 3,5-O-di-*tert*-butylsilane arabinose furanoside with several carbohydrate nucleophiles (Scheme 4). Once again, the nucleophile added *cis* to the C_2 EWG.



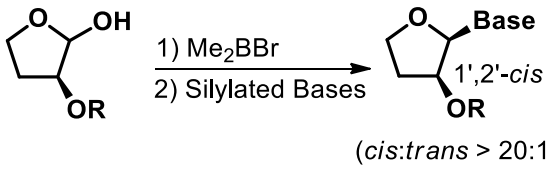
Scheme 3. 1,2-*cis* Deuteration or allylation of pentafuranoside analogues (Nu=D or allyl).



Scheme 4. 1,2-*cis* Glycosylation of arabinose furanoside.

Guindon and co-workers[12] reported a highly diastereoselective route to 1′,2′-*cis* nucleoside analogues in the D-ribo, D-lyxo, D-xylo and D-arabinoside series. These five-membered ring lactols all underwent highly selective N-glycosylation reactions in the presence of dimethylboron bromide and silylated pyrimidine nucleobases (Scheme 5). For example, the five-membered lactol

having a C_2-OR group gave the 1′,2′-*cis* isomer in high yield (*cis*:*trans* ratio >20:1). When the OR group at C_2 was replaced by a CH_3 group, the selectivity was completely lost (*cis*:*trans* ratio 1:1). So, the EWG at C_2 is clearly a dominant factor in the stereoselectivity of furanoside oxocarbenium ion.[9c-d,10b,12,13] These reactions were interpreted through an S_N1 or an "exploded" transition state model.

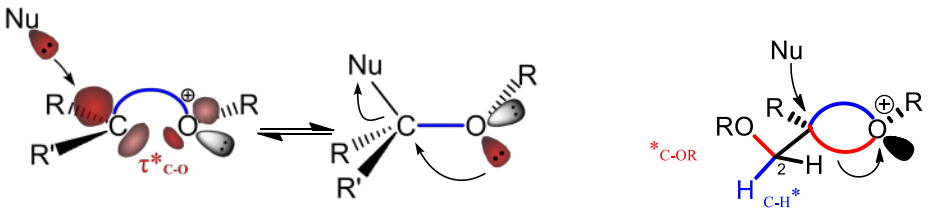


Scheme 5. Highly *cis*-selective N-glycosylation of lactols.

As opposed to the Hückel σ-π model,[14] the bent bond (τ bond) model[15] confers tetrahedral character to the carbon of carbonyl groups and, by extension, to oxocarbenium ions. According to the BBAH, nucleophilic addition to a carbonyl group is viewed as a S_N2-like process in which the nucleophile specifically displaces the *anti* bent bond, and necessarily generates an antiperiplanar oxygen lone pair on the initial product conformation (Scheme 6).[16] The reverse process, corresponding to the elimination of the nucleophile, must occur by assistance of a strictly antiperiplanar oxygen lone pair to reform the bent bonds of the oxocarbenium ion intermediate. In the furanosyl series, nucleophilic displacement of one of the bent bonds on the ^3E conformation of the oxocarbenium ion yields a product conformation in which the new carbon-nucleophile bond has no choice but to be antiperiplanar to the newly produced oxygen lone pair.

During the addition, a filled orbital on the nucleophile overlaps with the large outer lobe of the antibonding τ* C–O orbital (Scheme 6), and release the sp^3 oxygen lone pair in antiperiplanar fashion.[1-8] The electron density of each τ bond can vary independently depending on the stereoelectronic alignment of neighbouring electron-withdrawing or donating groups through

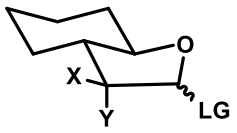
hyperconjugation;[17] the BBAH further states that the nucleophile will preferably displace the weaker (i.e. electron poorer) τ bond. As shown in Scheme 6, one of the oxocarbenium τ bonds is electronically enriched by hyperconjugation with an antiperiplanar C–H bond (a $\sigma_{C\text{-}H} \rightarrow \tau^*$ interaction), while the other τ bond is weakened by the antiperiplanar electron-withdrawing OR group (a $\tau \rightarrow \sigma^*_{C\text{-}OR}$ interaction). As a result, the nucleophile prefers to displace the weaker τ bond and adds *cis* to the OR group. One should note that, in the σ-π model, the two π* lobes correspond to the same orbital and cannot be differentiated in this way. The Cieplak effect[18] and Inomata's *syn* effect[19] can thus be easily rationalized using the τ bond model. Woerpel does mention possible hyperconjugation between axial C_2–H bonds in pseudoequatorial pyranosyl oxocarbenium ions.[20]



Scheme 6. Left: Orbital overlap between incoming Nu and antibonding τ* orbital of *anti* C–O τ bond produces sp^3 oxygen lone pair antiperiplanar to bound Nu. Right: facial selectivity modulated by hyperconjugation between C_2–OR and C_2–H groups antiperiplanar to their respective τ bond of the oxocarbenium ion.

All the previous results presented in Schemes 1-5 are readily rationalized by the BBAH orbital model. To further test this model, we synthesized and studied the glycosylation of a series of conformationally rigid *trans* bicyclic furanosides **1-5** (Scheme 7). Each compound was prepared with either OAc or SPh group at the anomeric position to allow for both C- and O-glycosylation reactions to be analyzed. Four of these bicyclic models have a OCH_3 or a CH_3 group located either in a β-pseudoequatorial or α-pseudoaxial orientation at C_2 and a *trans* bicyclic ring fusion that confines their corresponding 5-membered oxocarbenium ions to basically exist in their ^{3}E

conformation. This conformational restriction can potentially affect glycosylation selectivity. Our model compounds do not perfectly reflect the reactivity of fully oxygenated carbohydrates, our goal being to pinpoint the specific stereoelectronic contribution of the C_2-substituents within the BBAH paradigm. This requires simplified carbohydrate donor surrogates in which the oxocarbenium ion is unaffected by other conformational and stereoelectronic factors. Nevertheless, the term glycosylation can still be applied as the conformational limitations of furanoses and the particular reactivity of the anomeric center are two aspects that are shared in our approach.



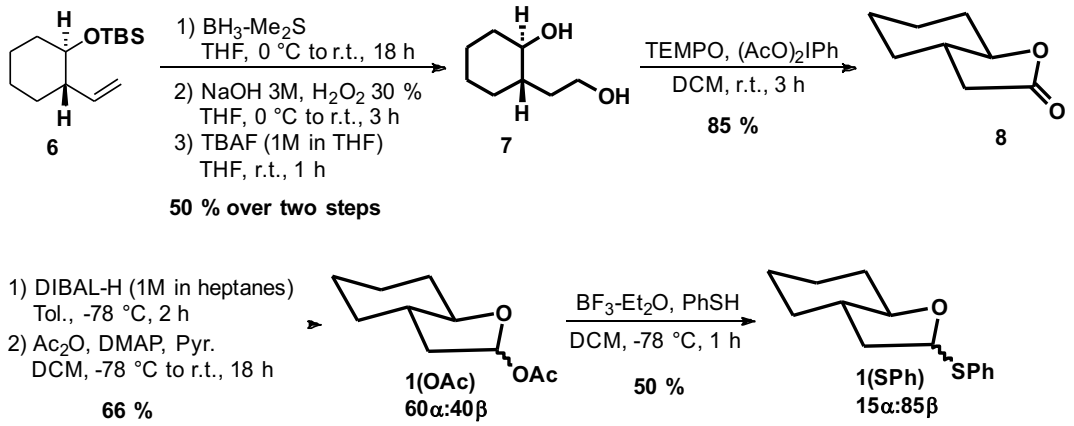
Donor	X	Y
1	H	H
2	OCH_3	H
3	H	OCH_3
4	CH_3	H
5	H	CH_3

Scheme 7. Glycosylation donors. LG=OAc or SPh.

RESULTS AND DISCUSSION

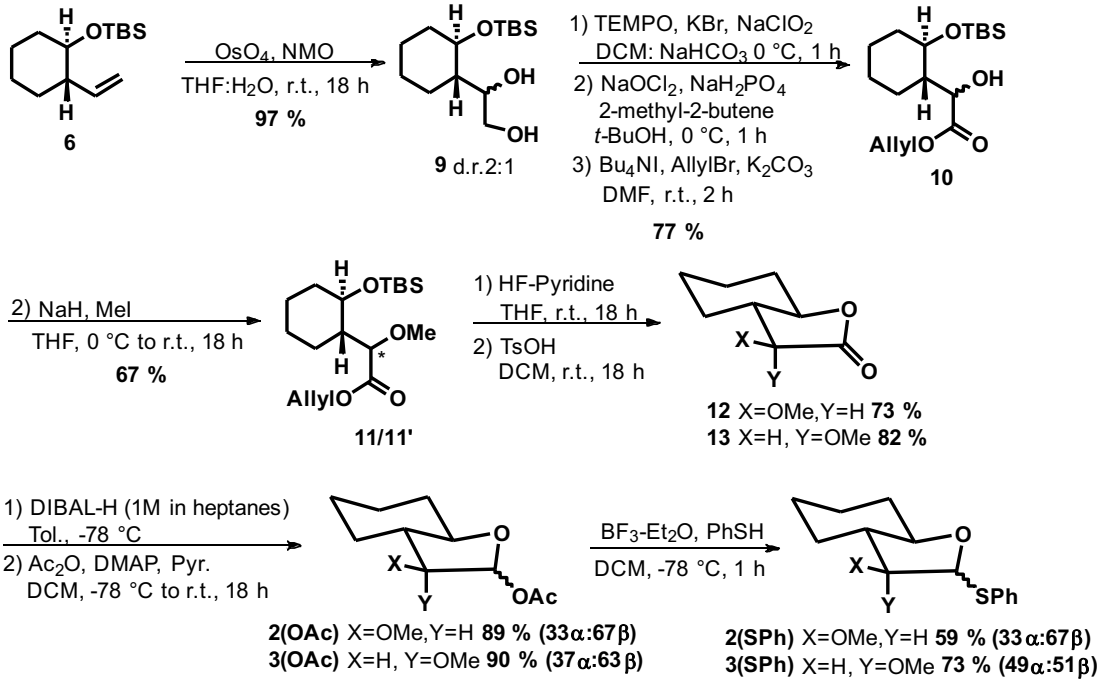
Synthesis of bicyclic models

The starting *trans*-fused bicyclic furanosides were obtained by vinyl anion addition to cyclohexene oxide.[21] The non-substituted donors **1** (Scheme 8) were prepared by hydroboration and deprotection of **6,** which gave diol **7** followed by selective TEMPO oxidation to yield bicyclic lactone **8**.[22] The C-glycosylation donor **1(OAc)** was then prepared from **8** through a one-pot reduction-acetylation procedure.[9d] The O-glycosylation donor **1(SPh)** was obtained from **1(OAc)** using a literature procedure.[23]



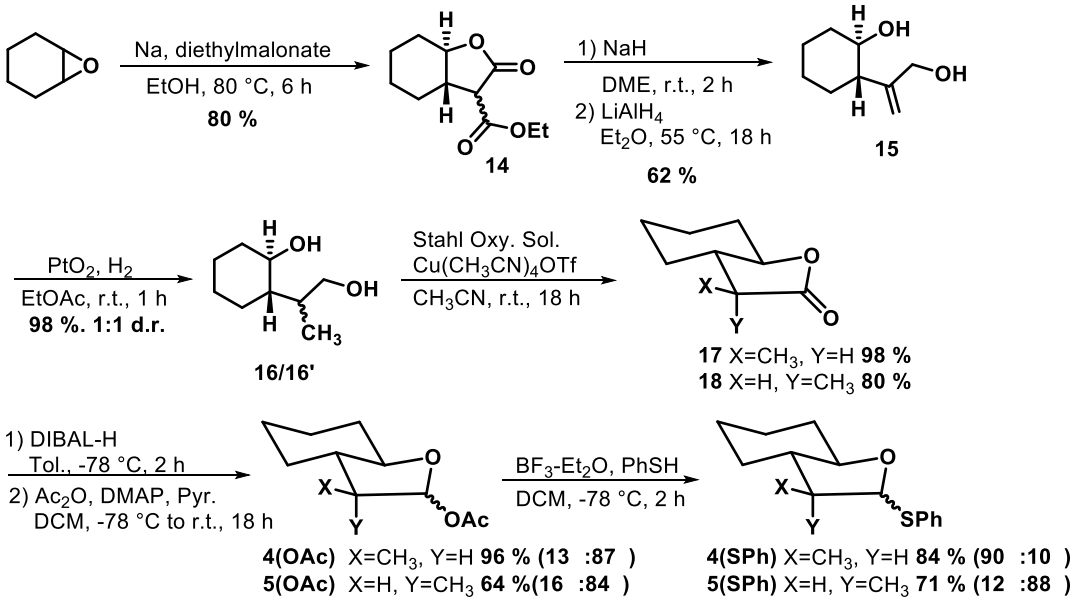
Scheme 8. Synthesis of type **1** donors.

The preparation of C_2–OCH_3 donors **2** and **3** required a more complex synthetic route, similar to that reported for the synthesis of substituted bicyclic pyranosides (Scheme 9).[8] Dihydroxylation of **6** gave a 2:1 mixture of diols **9** in which the primary alcohol was further oxidized to the carboxylic acid using TEMPO followed by a Pinnick oxidation of the aldehyde intermediate.[24] After allyl esterification to yield compound **10**, the remaining secondary alcohol was methylated using standard methodology. The resulting diastereoisomers **11**/**11′** were separated by chromatography and submitted to a deprotection/cyclization sequence to provide lactones **12** and **13**. The donors **2(OAc)**, **3(OAc)**, **2(SPh)** and **3(SPh)** were obtained using the same reaction sequence described above from the corresponding lactone.



Scheme 9. Synthesis of type **2** and **3** donors.

The syntheses of donors **4** and **5** having a methyl group at C_2 began by diethylmalonate anion displacement of cyclohexene oxide, which gave α-carboxyethylbutyrolactone **14** (Scheme 10). Marshall's reduction protocol[25] then yielded the desired allylic alcohol **15**, which was hydrogenated with catalytic platinum(IV) oxide, providing a ~1:1 mixture of diastereoisomeric diols **16**/**16′**. Chromatographic separation followed by Stahl oxidation[26] produced corresponding lactones **17** and **18**. As this reaction is known to use atmospheric oxygen as the external oxidation source, larger scale reactions were speeded-up using pure oxygen gas.[26] These two lactones were obtained in good yields and converted to donors **4** and **5**. To do so, **17** and **18** were reduced with DIBAL-H and acetylated to yield **4(OAc)** (13α:87β) and **5(OAc)** (16α:84β) respectively, providing **4(SPh)** (90α:10β) and **5(SPh)** (12α:88β) with PhSH and $BF_3 \cdot Et_2O$.

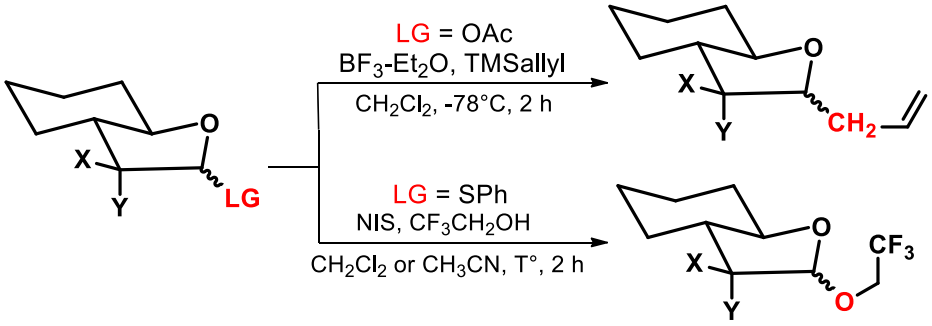


Scheme 10. Synthesis of type **4** and **5** donors.

Glycosylation experiments

Glycosylation experiments were carried out on bicyclic furanosides **1**-**5** (Scheme 11) having OAc or SPh as anomeric leaving groups, allowing for both C- and O-glycosylation to be investigated. For C-glycosylation, the OAc derivatives were reacted with $BF_3 \cdot Et_2O$ and TMSallyl in CH_2Cl_2 for 2 h at low temperature. For O-glycosylation, the SPh derivatives were reacted with NIS and 2,2,2-trifluoroethanol (TFE) in CH_2Cl_2 or CH_3CN for 2 h (Scheme 11). These conditions were based on the work reported by Woerpel.[23] The C-glycosylation conditions do not allow for product epimerization due to the nature of the nucleophile. O-glycosylation reaction conditions can, theoretically, lead to product epimerization. However, we showed that this does not occur under the experimental conditions[8]; isolated products resubmitted to glycosylation conditions with a different donor and nucleophile showed no change from their initial anomeric ratio. Thermodynamic conditions were also performed on an isolated product, showing a change in the anomeric ratio over time. This showed that the thioglycosides activated by NIS provided a clean,

kinetic glycosylation reaction. All the SPh donors allowed for the reactions to be carried out without any Lewis acid or stabilizing triflate source, which often can influence the reaction selectivity (Scheme 11). All product ratios reported in Table 1 were duplicated and determined by ^{1}H NMR and/or ^{19}F NMR using the crude mixture of reaction products. The relative configurations at the anomeric center were established by 1D NOESY experiments. Any variation in the reported isolated yields was attributed to the volatility and stability of the glycosylated adduct on silica gel. Crude ^{1}H NMR showed a complete conversion to the desired compound in almost every case.[27]



Scheme 11. Reaction conditions for C and O-glycosylation described in Table 1.

Table 1. Glycosylation of bicyclic donors **1-5**.

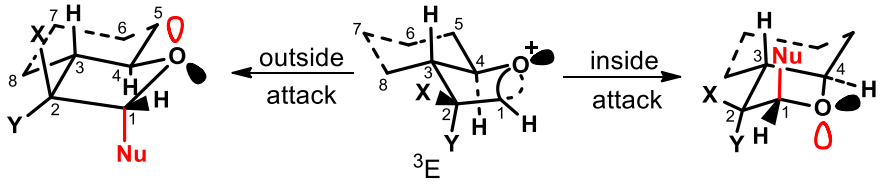
Entry	Donor	LG	Nu	T °C[d]	Solvent	α:β ratio	Yield
1	**1** (X=Y=H)	OAc	TMSallyl	-78	CH_2Cl_2	30:70	N.D.[e]
2	"	SPh (15α:85β)	TFE	-40	"	51:49	37 %
3	"	"	"	-40	CH_3CN	27:73	61 %
4	**2**(X=OMe, Y=H)	OAc	TMSallyl	-78	CH_2Cl_2	34:66	96 %
5[a]	"	SPh (α only)	TFE	-40	"	34:66	67 %
6[b]	"	SPh (β only)	"	-78	"	98:2	N.D.[c]
7	"	SPh (α only)	"	-40	CH_3CN	34:66	86 %
8	"	SPh (69α:31β)	"	-40	"	33:67	74 %
9	**3**(X=H, Y=OMe)	OAc	TMSallyl	-78	CH_2Cl_2	6:94	83 %
10[a]	"	SPh (49α:51β)	TFE	-40	"	18:82	76 %
11[b]	"	"	"	-78	"	13:87	N.D.
12	"	"	"	-40	CH_3CN	22:78	58 %
13	**4**(X=Me, Y=H)	OAc (13α:87β)	TMSallyl	-78	CH_2Cl_2	60:40	98 %
14	"	SPh (90α:10β)	TFE	-40	"	86:14	73 %
15	"	"	"	-40	CH_3CN	92:8	56 %
16	**5**(X=H, Y=Me)	OAc (16α:84β)	TMSallyl	-78	CH_2Cl_2	>3:97	90 %
17	"	SPh (12α:88β)	TFE	-40	"	7:93	73 %
18	"	"	"	-40	CH_3CN	9:91	56 %

[a] The initial temperature was -40 °C and brought to approximately -15 °C. No conversion was observed below -20°C. [b] AgOTf was added as a triflate source and full conversion occurred at -78 °C. [c]No purification performed. Ratio determined using the crude ^{1}H NMR and/or ^{19}F NMR. [d] Initial temperature in CH_2Cl_2 for donor **2** and **3** was -40°C and slowly brought to -20 °C over the 2 h reaction period. [e] N.D.: not determined.

As demonstrated in our previous work[8] and in other studies,[23,28] stereoselectivity at the anomeric carbon is highly affected by the nature of the nucleophile.[29] Stronger nucleophiles generally exhibit a lower stereoselectivity upon addition to oxocarbenium ion intermediates as a result of earlier glycosylation transition state geometries that are less sensitive to steric and electronic asymmetry near the electrophilic center. However, oxocarbenium ion intermediates may not form easily and, as a result, glycosylations may proceed through an exploded S_N2-like transition state,[13] especially in the presence of strong nucleophiles or by forming nitrilium ion intermediates.[30] Glycosylations with weak nucleophiles or stabilized glycosyl donors are expected to be more S_N1-like; the nucleophile addition must then proceed by a later transitions state, and be more heavily influenced by steric hindrance and other factors as the nucleophile approaches the electrophilic center. To tease out the factors guiding glycosylation reactions involving oxocarbenium ion intermediates, only the weaker nucleophiles TMSallyl and TFE were considered for this study. Carbon based nucleophiles are believed to react strictly through an S_N1 mechanism,[29] whereas TFE is generally assumed not to be nucleophilic enough[23] for an S_N2 mechanism. It is thus anticipated that the anomeric configuration of the donor moiety should not influence the glycosylation stereoselectivity under the reaction conditions described in Scheme 11[31] as they are all assumed to involve oxocarbenium ion intermediates. Results presented for donor **2** (entries 7 and 8) support this statement as the initial anomeric orientation of the donor did not influence the selectivity outcome of the reaction.

As shown in Table 1, donors **1**-**3** and **5** preferentially formed β-glycosides with the TMSallyl nucleophile (entries 1, 4, 9 and 16) whereas donor **4** produced the α-glycoside in slight excess (entry 13). With the TFE nucleophile, O-glycosylation in CH_2Cl_2 or CH_3CN showed a similar trend in most cases. Donors **1**-**3** and **5** gave preferentially β-O-glycosides (entries 3; 5, 7-8; 10, 12 and 17-18). As above, donor **4** gave again mainly α-O-glycosides (entries 14-15).

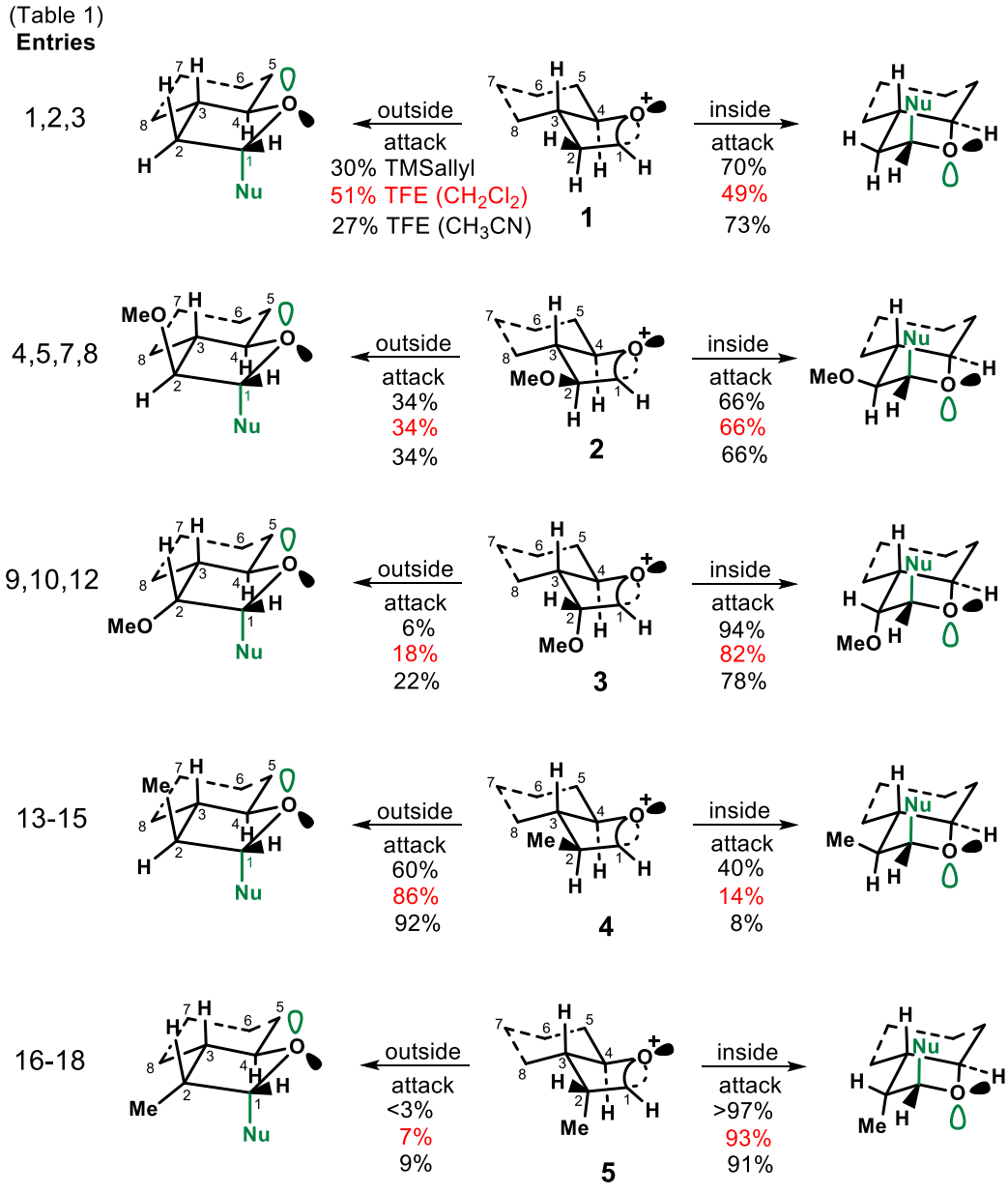
Overall, the BBAH analysis expands Woerpel's "inside/outside attack" glycosylation model by considering the stereoelectronic influence of neighbouring electron-withdrawing and donating groups on the nucleophilic addition to oxocarbenium ion intermediates. As shown in Scheme 12, inside attack on the fixed ^{3}E conformation of the oxocarbenium ion directly furnishes a β-glycoside in a conformation where the C_2 substituents (X/Y) stagger the C_1 and C_3 groups. Conversely, the outside attack produces an α-glycoside in a conformation that eclipses the X and Y substituents at C_2 with the axial H and C_8 methylene at C_3. The BBAH analysis further considers any potential hyperconjugation between τ bonds in the oxocarbenium intermediates and the EWG or electron-donating groups (EDG) at C_2 in the glycosylation reactions.



Scheme 12. Steric and conformational factors to the S_N1 glycosylation reaction of substituted bicyclic furanosides.

The C-glycosylation of donors **1**-**5** with TMSallyl in CH_2Cl_2 is illustrated in Scheme 13. As indicated in entry 1 (Table 1 or Scheme 13) using the carbon-based nucleophile, the bicyclic furanoside **1** with no substituent at C_2 gave a 30:70 ratio of the α- and β-anomers, both under stereoelectronic control. This is in accordance with the results previously reported by Woerpel in

which the β-isomer is favored for conformational reasons as a result of the inside attack.[9c] With TFE in CH_2Cl_2 (entry 2), there is an increase in the α-isomer as the stronger nucleophile predicates an earlier transition state. In CH_3CN (entry 3), the oxocarbenium ion more stabilized so the reaction may involve a somewhat later transition state or contact ion pair.[30] The β selectivity is thus observed as with TMSallyl.



Scheme 13. C-Glycosylation of donors **1-5** with TMSallyl and TFE in CH_2Cl_2 and CH_3CN.

In the case of bicyclic oxocarbenium ion **2** bearing a β-OCH_3 group, the addition of TMSallyl (entry 4) favors the β-anomer (i.e. inside attack) by favorable displacement of the α-bent bond that is weakened by hyperconjugation with the antiperiplanar β-OCH_3 group; conversely, the β-bent bond is instead stabilized as it is antiperiplanar to the donating C_2–H bond.[17,32] Thus, α-attack is disfavored on stereoelectronic grounds. As for the steric effects, α-attack should be favored as *trans* addition avoids repulsion between the β-OCH_3 and the incoming nucleophile but is also disfavored because of eclipsing of the C_2–C_3 bond in the α-addition product.[33] Overall, *cis* addition to donor **2** is slightly favored, and the results with TFE as nucleophile (entries 5, 7-8) are similar to those of TMSallyl (entry 4). The presence of a polar OCH_3 group must produce a more reactive oxocarbenium ion, but TFE is a stronger nucleophile than TMSallyl. As a result, the α:β selectivity remains the same. Interestingly, comparing the reaction of donors **1** and **2** with TFE in CH_2Cl_2 (entries 2 and 5) shows an increase of inside attack with donor **2** (17%). This indicates that the β-OCH_3 hyperconjugation with the α-bent bond is more important than the steric repulsion between the nucleophile and the β-OCH_3 during 1,2-*cis* addition. In the more polar CH_3CN, the inside attack on donor **2** (entries 7-8) is slightly less that on donor **1** (entry 3).

In the case of donor **3** bearing an α-OCH_3 group (entry 9), the β-anomer through the inside attack is stereoelectronically disfavored by a weakening of the β-bent bond (antiperiplanar to α-OCH_3) and concomitant enrichment of the α-bent bond (antiperiplanar to β-C_2–H bond). However, the β-attack is sterically favored as it occurs *trans* to the α-OCH_3 and the inside attack staggers the C_2–C_3 bond; α-attack would eclipse the C_2–C_3 bond including severe repulsion between α-OCH_3 and C_8. On the other hand, formation of the α-isomer is stereoelectronically favored by hyperconjugative effects of the C_2 substituents but is quite sterically disfavored by the outside attack eclipsing the

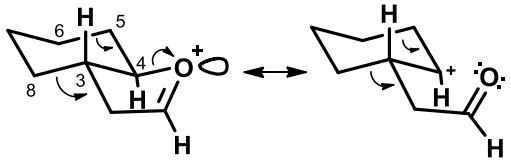
C_2–C_3 bond, and important repulsion between the OCH_3 and the incoming nucleophile. As a result, the α-isomer is produced in only 6% with TMSallyl (entry 9). With TFE in CH_2Cl_2 or CH_3CN (entries 10 and 12), an increase of the α-isomer is observed (~20%) which is probably due to the stronger nucleophile, resulting in a slightly earlier transition state, and lessening the steric selectivity factors.

Donor **4** (entry 13) bears a β-Me group at C_2 and is the only one to produce the α-anomer as major product (60%). In this case, stereoelectronics predict that the β-anomer should be somewhat favored because the β-bent bond is strengthened by hyperconjugation with the antiperiplanar α-C_2–H bond (which is assumed to be somewhat more important than the C_2–CH_3 hyperconjugation) but there is no longer an EWG at C_2 to weaken the antiperiplanar α-bent bond so the stereoelectronic steering is expected to be less than for entries 4,5,7,8.[32] The α-anomer should be sterically favored by adding *trans* to the β-CH_3 group but disfavored by this outside attack that eclipses the C_2–C_3 bond in the α-anomer.[9d] As a result, reaction of donor **4** with the weaker TMSallyl nucleophile (entry 13) should proceed by a later transition state, so the α-isomer prevails (60%) but formation of the BBAH-favored β-isomer is still important despite the strong steric repulsion. With TFE in CH_2Cl_2 (entry 14), the major α-isomer is increased to 86% while in CH_3CN (entry 15), it is raised to 92%. These two results indicate that increasing the nucleophile reactivity leads to an earlier transition state where the steric aspects prevails, yet not fully, over the hyperconjugation. Again, the percentage of the α-isomer increases with a more polar solvent and stabilizing solvent.

In the case of donor **5**, the β-anomer is strongly favored by both the inside attack and the *trans* addition and is only disfavored by the weak C_2–H hyperconjugation. Conversely, the α-anomer is

strongly disfavored by the 1,2-*cis* addition and by outside attack which eclipses the C_2–C_3 bond, including a severe interaction between the α-CH_3 group and the ring CH_2 group at C_8. It is only favored by the C_2–H hyperconjugation. As a result, the β-anomer completely dominates with TMSallyl (entry 16) and is over 90% β-selective with TFE in both solvent (entries 17-18). Again, there is a slight decrease of the β-isomer with the stronger nucleophile TFE**,** as the earlier transition state is less sensitive to the steric environment. Thus, the BBAH can rationalize correctly all these results at the molecular level using classic organic chemistry principles.

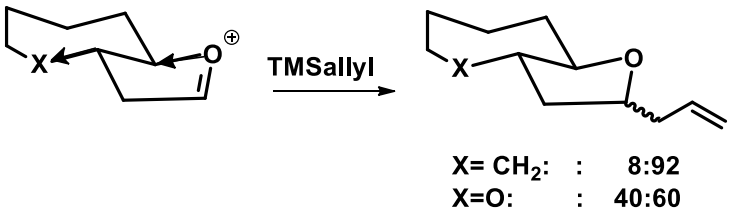
Interestingly, it was also noticed that the electron-donating effect of the CH_3 group can be clearly perceived through the reaction conditions of donors **4** and **5**, where the glycosylation reaction could be kept at -40 °C for the entire transformation without having to increase the temperature, which was required for donors **2** and **3** bearing an OCH_3 EWG group. Consequently, the oxocarbenium ion from donors **4** and **5** would be more stable because of the CH_3 hyperconjugation. This observation led to a realization that the different stereoselectivities observed for donors **2**-**5** and those of sugar-furanosides described in Schemes 1, 3-5 could be explained by the different reactivity of their oxocarbenium ions. In carbohydrates, all the OR groups should destabilize their corresponding oxocarbenium ions through electron-withdrawing inductive effects, rendering them more reactive, and resulting in earlier transition states for nucleophilic addition. Thus, the favored 1,2-*cis* addition described in Schemes 1,3-5 would be the result of an inside attack and the hyperconjugation effect of the OCH_3 group. In bicyclic donor models **1**-**5**, the oxocarbenium ion should be more stable, less reactive, resulting in later transition states for nucleophilic addition. Indeed, for donors **1**-**5**, both the C_5–C_6 and C_3–C_8 bonds are antiperiplanar to the C_4–O bond so the oxocarbenium ion should be more stable and less reactive. This hyperconjugation effect can be expressed by the resonance structures indicated in Scheme 14.[32]



Scheme 14. Resonance structures of a carbobicyclic oxocarbenium ion.

As indicated in entries 2 and 3 (Scheme 13 and Table 1), glycosylation of donor **1** with TFE occurs even at a steady -40°C, which clearly indicates that the oxocarbenium ion intermediate is easily formed and must be relatively stable. This result is further confirmed by the observation that, on treatment of 3,5-O-di-*tert*-butylsilyl arabinose (Scheme 4) with our glycosylation conditions (NIS, CH_3CN, no Lewis acid), no reaction was observed even at 0°C because the oxocarbenium ion is likely not produced. This highly oxygenated donor was synthesized using reported protocols by Crich[13] and Zhu.[34]

Thus, the glycosylation of donors **1**-**5**, compared to that of carbohydrate-derived donors, must occur through later transition states because of their increased oxocarbenium ion stability. Conversely, the glycosylation of carbohydrate pentafuranoside derivatives must occur through earlier transition states because of the inductive effect of several neighbouring oxygens. As a result, the known 1,2-*cis* addition observed in the glycosylation of the 4,6-O-benzylidene derivatives of glucose and mannose must occur through earlier transition states in which the stereoselectivity is essentially controlled by the orientation of the C_2–OR group. Supporting the above analysis, Woerpel and co-workers reported[9f] that, in the postulated 7-membered bicyclic furanoside oxocarbenium intermediates, the α-outside attack is weak (8%) when X=CH_2 and become important (40%) when X=O (Scheme 15).



Scheme 15. Remote oxygen effect on selectivity.

The electron-withdrawing effect of benzylidene groups on oxocarbenium ion reactivity was modeled by DFT calculations. B3LYP/6-31G* calculations were performed on (3a*S*,7a*R*)-1,4,6-trioxahexahydroindene **A** (i.e. model of benzylidene-fused furanosyl oxocarbenium ion) and (3a*S*,7a*R*)-1-oxaoctahydroindene **B** (i.e. cyclohexane-fused furanosyl oxocarbenium ion) from which Merz-Kollman atomic partial charges were derived (Figure 1).[35] Partial charges on the oxocarbenium oxygen were found to be -0.217 for the benzylidene model **A** and -0.285 for the cyclohexane model **B**, supporting the remote electron-withdrawing effect of the benzylidene oxygens on the oxocarbenium oxygen.

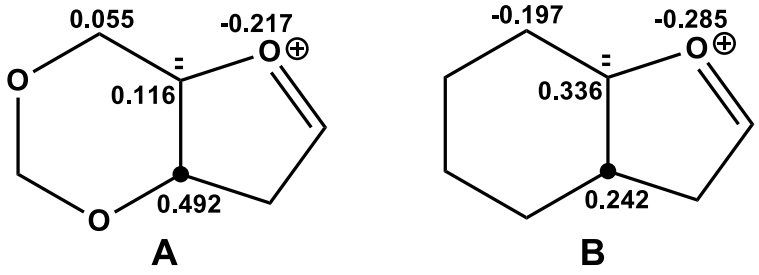
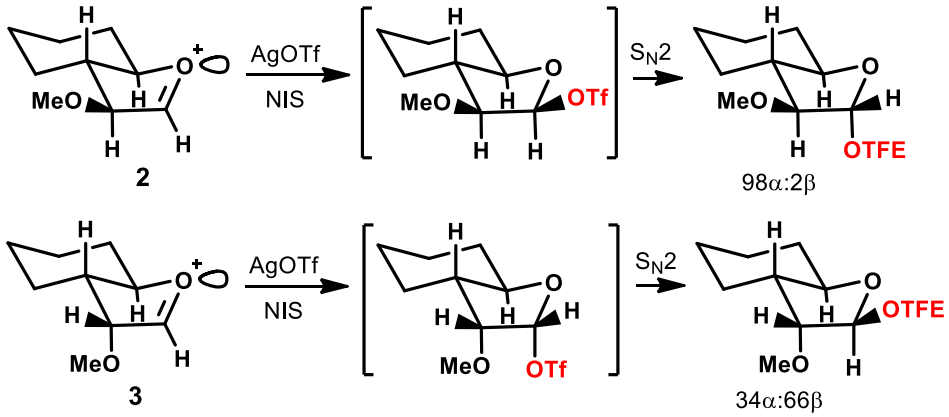


Figure 1. Merz-Kollman charges for oxocarbenium ion models from on B3LYP/6-31-G* calculation.

Finally, entries 6 and 11 of Table 1 describe the glycosylation using conditions reported by Crich[13] in which AgOTf was added in catalytic amount to the standard conditions, under the assumption that catalytic triflate might provide insight into the nature of the reaction intermediate. To our surprise, selectivity was inverted in entry 6 for donor **2** (98α:2β vs 34α:66β initially), whereas

donor **3** produced a greater β-selective glycosylation (entry 11). The transformations occur rapidly even when maintained at -78°C. One can argue that the triflate may preferentially form a α or β covalent bond at the anomeric center depending on the orientation at C_2. Considering the weak nucleophilic nature of TFE, the covalent C_1–OTf bond would have to be highly labile. Thus, formation of a covalent triflate intermediate could follow the bent bond approach by addition to the weaker τ bond followed by S_N2-like displacement with TFE as illustrated in Scheme 16.[36] A contact ion pair can also be considered, which would stabilize the oxocarbenium ion. The presence of a Lewis acid is also known to activate the NIS, which catalyses the reaction. This would explain the high reactivity observed at lower temperature but not the inversion of selectivity.[37]



Scheme 16. Glycosylation in the presence of AgOTf/NIS with TFE.

CONCLUSION

This paper reports the C- and O-glycosylation of bicyclic furanosides **1-5** with allyltrimethylsilane and trifluoroethanol, respectively. These reactions were carried out to test whether the bent bond / antiperiplanar hypothesis (BBAH) orbital model could rationalize the stereoselectivity of glycosylation reactions. The analysis expands Woerpel's "inside/outside attack" reaction model by incorporating the stereoelectronic influence of electron-withdrawing (i.e. OCH_3) and electron-

donating (i.e. H or CH_3) groups at C_2 on the relative nucleophilic displacement of the two τ bonds of the oxocarbenium ion intermediates.

Interestingly, the glycosylation stereoselectivities on bicyclic oxocarbenium glycosyl donors **1**-**5** (Table 1) turned out to be quite different than those reported for five-membered carbohydrates containing multiple OR groups as shown in Schemes 1, 3-5. The glycosylation stereoselectivities for sugar-derived furanosides are rationalized by the Woerpel model with the BBAH-based premise that nucleophilic addition to the oxocarbenium ion intermediates proceeds by early transition states, and that the generally preferred 1,2-*cis* stereoselectivity is due largely to the orientation of the C_2–OR group relative to the τ bonds of the oxocarbenium ion intermediates.

In the case of the bicyclic donors **1**-**5**, the glycosylation outcomes are different because the oxocarbenium ion intermediates are stabilized by opposite hyperconjugative effects involving CH_2 groups at C_5 and C_8. As a result, they form more easily at lower temperatures, whereas their carbohydrate furanoside counterparts were not reactive at the same temperatures under our glycosylation reaction conditions. Thus, nucleophilic addition to the stabilized oxocarbenium ions **1**-**5**, must proceed through later transition states than for their carbohydrate counterparts. Consequently, the conformationally preferred inside attack on donors **1**-**3** and **5** becomes more important, favoring the β-glycosylation. The electron-donating CH_3 group at C_2 plays both a steric and a stereoelectronic role (stabilizing the adjacent antiperiplanar τ bond). Thus, the α-glycosylation in bicyclic model **4** is now favored.

EXPERIMENTAL SECTION

General information

The following section includes the spectroscopic data of newly synthesized compounds. Transformation requiring inert and anhydrous conditions were carried out within an argon atmosphere with dry solvents and oven dried/flame dried glassware. Dry DCM, Et_2O, toluene and THF was obtained from a Vacuum Atmosphere Inc; Solvent Purification System. CH_3CN was distilled over CaH_2. All commercially available reagents were used as received without further purification. Thin-layer chromatography analysis of reaction mixtures were performed using Silicycle's Silica alumina backed TLC plates and analysed using UV light and/or by staining with either potassium permanganate, cerium ammonium molybdate (CAM) or p-anysaldehyde. Flash column chromatography purification was carried out on Silicycle silica gel 60 Å, 230–400 mesh. NMR spectroscopic data for ^1H, ^{13}C, ^{19}F and NOESY 1D were recorded at ambient temperature in neutralized $CDCl_3$ using an Agilent DD2 500, Bruker 300 MHz and Varian Inova 400 spectrometers. High-resolution mass spectra were obtained on a LC/MS–TOF Agilent 6210 using electrospray ionization (ESI). Infrared spectra were obtained using an Aminco Bowmen Adrid Zone infrared spectrometer with a NaCl crystal matrix. Melting point values were determined using a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected.

C-Glycosylation: general procedure A

A solution of an acetate donor in DCM (0.1 M) under argon was brought to −78 °C and allyltrimethylsilane (4 equiv) was added. The mixture was then treated with $BF_3{\cdot}Et_2O$ (1.2 equiv) and brought to ambient temperature over 2 h before quenching with saturated $NaHCO_3$. The organic phase was separated and the aqueous one was washed with DCM (3×), dried over $MgSO_4$ and condensed *in vacuo*. Crude mixtures were analyzed by ^1H NMR spectroscopy and purified as described.

O-Glycosylation: general procedure B

A solution of a thiophenylacetal donor in dry DCM or CH_3CN (0.1 M) and 4Å MS with trifluoroethanol (4 equiv) under argon was brought to −40 °C. The mixture was then treated with NIS (2 equiv) and brought to the required temperature over 1.5 h when needed before quenching with a saturated aqueous solution of $Na_2S_2O_3$. Using CH_3CN as the solvent requires flame dried material and dropwise addition of a NIS/CH_3CN solution in order to maintain an inert atmosphere. NIS was added directly as a powder when DCM is the solvent. The organic phase was separated, and the aqueous phase was washed with DCM (3×). Organic fractions were combined, dried over $MgSO_4$ and condensed *in vacuo*. Special care was is to be taken for the removal of solvent with those compounds as they appeared to be slightly volatile. Crude mixtures were analyzed by ^1H NMR spectroscopy and purified as described. To be noted that the characterization of O-glycosylated products by any HRMS method available to us would often only provide the corresponding oxocarbenium ion after the loss of the trifluoroethyl moiety.

***tert*-Butyldimethyl((2-vinylcyclohexyl)oxy)silane) (6):** To the allyl alcohol (3.5 g, 27.7 mmol) in dry DCM (30 mL) under argon was added imidazole (3.77 g, 55.5 mmol) followed by TBSCl (5.02 g, 33.3 mmol). The mixture was stirred overnight at ambient temperature. Silica was added and the mixture condensed to a powdered blend. The desired compound was recovered by filtration thought a fritted glass funnel filled with 10 cm of silica gel using hexanes to yield after evaporation 6.27 g (94 %) of **6** as colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.6, 10.4, 7.4 Hz, 1H), 5.04 – 4.96 (m, 2H), 3.28 (td, J = 9.6, 4.2 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.85 (m, 1H), 1.78 – 1.70 (m, 2H), 1.67 – 1.61 (m, 1H), 1.37 – 1.13 (m, 4H), 0.88 (s, 8H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.1, 113.9, 74.9, 49.8, 35.8, 30.5, 25.9, 25.0, 24.8,

18.2, -0.02, -4.2, -4.5; HRMS (ESI-TOF) M/Z: $[M+K]^+$ Calcd for $C_{14}H_{28}OSiK$ 279.1546; Found; 279.1532.

2-(2-Hydroxyethyl)cyclohexan-1-ol (7): To a solution of OTBS protected olefin **6** (1.3 g, 5.4 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere was added 2 M BH_3–Me_2S solution in THF (10.81 mmol, 5.41 mL) over 10 min. The reaction was then brought slowly to ambient temperature and stirred for 18 h. The mixture was treated with 3 M NaOH at 0 °C until the pH was basic and excess 30% H_2O_2 was added. The reaction was stirred for 3 h until completion and was diluted with water and DCM. The organic layer was separated, and the aqueous layer washed with DCM (3×). The organic layers were combined, dried over $MgSO_4$ and condensed *in vacuo*. The crude residue was rapidly eluted on a silica gel pad with 50:50 EtOAc/hexanes, condensed *in vaccuo* then diluted in dry THF (5 ml). 1 M TBAF solution in THF (5.4 mL, 5.4 mmol) was then added. The reaction was stirred 1 h at ambient temperature and quenched with saturated $NH_4Cl_{(aq)}$. The reaction was diluted with DCM, the phases separated, and the aqueous portion washed with DCM (3×), dried over $MgSO_4$, filtered and condensed *in vacuo*. The crude mixture was purified by silica gel column chromatography (50% EtOAc/hexanes, TLC stained with *p*-anisaldehyde) to obtain 0.430 g (50 % over two steps) of the diol **7** as a colourless thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 1H), 3.75 (dt, *J* = 10.6, 4.7 Hz, 1H), 3.59 (ddd, *J* = 10.7, 9.5, 3.5 Hz, 1H), 3.19 (td, *J* = 9.8, 4.4 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.77 – 1.64 (m, 3H), 1.64 – 1.56 (m, 1H), 1.51 (dtd, *J* = 14.7, 4.8, 3.6 Hz, 1H), 1.36 – 1.09 (m, 4H), 1.07 – 0.97 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ, 74.9, 61.4, 44.4, 44.37, 38.1, 35.5, 32.7, 25.6, 24.9; HRMS (ESI-TOF) M/Z: $[M+H]^+$Calcd for $C_8H_{17}O_2$ 145.1223; Found 145.1212.

Hexahydrobenzofuran-2(3H)-one (8): To a solution of diol **7** (0.219 g, 1.51 mmol) in dry DCM (3 mL) under argon was added [bis(acetoxy)iodo]benzene (1.46 g, 4.53 mmol) followed by

TEMPO (0.070 g, 0.453 mmol). The reaction was stirred for 3 h at ambient temperature and quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was isolated and washed with DCM (3×). Combined phases were dried over $MgSO_4$, filtered and condensed under reduce pressure. The crude mixture was purified by flash chromatography (20% EtOAc/hexanes, TLC stained with CAM) to yield 0.180 g (85%) of a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (td, *J* = 10.9, 3.8 Hz, 1H), 2.50 (ddd, *J* = 16.1, 6.8, 2.2 Hz, 1H), 2.22 (tt, *J* = 13.1, 4.8 Hz, 2H), 2.02 – 1.86 (m, 3H), 1.82 – 1.76 (m, 1H), 1.53 (qd, *J* = 11.8, 3.4 Hz, 1H), 1.46 – 1.24 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.6, 85.2, 44.8, 35.9, 30.2, 28.3, 25.3, 24.1; IR (NaCl) ν_{max} 2939, 2865, 1781, 1447, 1189, 1030, 931 cm^{-1}; HRMS (ESI-TOF) M/Z: $[M+H]^+$ Calcd for $C_8H_{13}O_2$ 141.0910; Found 141.0905.

Octahydrobenzofuran-2-yl acetate (1(OAc)): To a −78 °C solution of lactone **8** (0.900 g, 6.42 mmol) in dry toluene (20 mL) under an argon atmosphere was added dropwise 1 M DIBAL-H in heptanes (7.70 mL, 7.70 mmol). The reaction was stirred at −78 °C for 2 h. Once the reaction completed by TLC monitoring, pyridine (0.620 mL, 7.70 mmol), was slowly added at −78 °C, followed by DMAP (0.941 g, 7.70 mmol) in 6 mL of dry DCM, stirred for 10 min and Ac_2O (3.03 mL, 32.1 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 h. The mixture was quenched with saturated NH_4Cl and diluted with EtOAc. The extracted organic phase was washed with 1 N $NaHSO_4$ (2×), saturated $NaHCO_3$ (2×), brine (1×), dried over $MgSO_4$ and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes with 2% Et_3N, TLC stained with CAM) to obtain a mixture of two diastereoisomeric acetates **1(OAc)** (0.778 g, 60α:40β, 66 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 6.0, 4.7 Hz, 0.6H), 6.19 (d, *J* = 5.2 Hz, 0.4H), 3.37 (td, *J* = 10.4, 3.8 Hz, 0.6H), 3.19 (td, *J* = 10.7, 3.8 Hz, 0.4H), 2.42 (ddd, *J* = 13.0, 7.1, 6.1 Hz, 0.6H), 2.19 – 2.10 (m, 1H), 2.05 (s,

1.8H), 2.03 (s, 1.2H), 2.00 (dd, *J* = 12.5, 5.4 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.87– 1.80 (m, 1H), 1.79 – 1.66 (m, 2H), 1.57 (ddd, *J* = 12.8, 11.9, 4.7 Hz, 1H), 1.47 – 1.34 (m, 1.4H), 1.33 – 1.02 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 170.4, 98.2, 97.5, 85.4, 82.9, 45.2, 41.9, 37.9, 37.8, 31.5, 30.5, 28.5, 28.4, 25.6, 25.5, 24.2, 24.1, 21.4, 21.3.; IR (NaCl) ν_{max} 2936, 2860, 1749, 1450, 1376, 1234, 1036, 963, 864 cm^{-1}; HRMS (ESI-TOF) M/Z: $[M+Na]^+$ Calcd for $C_{10}H_{16}O_3Na$: 207.0991; Found: 207.0992.

2-(Phenylthio)octahydrobenzofuran (1(SPh)): To a solution of diastereoisomeric acetate **1(OAc)** (0.778. g, 4.22 mmol) in dry DCM (20 mL) under an argon atmosphere was added PhSH (1.72 mL, 16.9 mmol). The mixture was cooled to −78 °C and $BF_3{\cdot}Et_2O$ (0.570 mL, 4.64 mmol) was slowly added. After 1 h of stirring at −78 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, brought to ambient temperature and diluted with DCM. The organic phase was isolated and the aqueous one was washed with DCM (3×). The organic phases were combined, dried over $MgSO_4$ and condensed *in vacuo*. The residue was purified by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give two diastereoisomeric thioacetals **1(SPh)** (0.500 g, 50 %, 15α:85β) as colourless oils; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.35 – 7.16 (m, 3H), 5.63 (t, *J* = 7.2 Hz, 0.85H), 5.50 (dd, *J* = 7.8, 2.7 Hz, 0.15H), 3.39 (td, *J* = 10.2, 3.8 Hz, 0.85H), 3.17 (td, *J* = 10.6, 3.8 Hz, 0.15H), 2.55 (dt, *J* = 12.2, 6.8 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.98 – 1.89 (m, 1H), 1.88 – 1.79 (m, 1H), 1.73 – 1.67 (m, 1H), 1.53 (td, *J* = 11.9, 7.3 Hz, 1H), 1.45 – 1.03 (m, 5H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 131.5, 130.2, 128.7, 126.9, 126.5, 85.6, 84.8, 81.4, 45.1, 44.2, 38.9, 38.5, 31.5, 30.6, 28.7, 25.6, 24.2; HRMS (ESI-TOF) M/Z: $[M+H]^+$ Calcd for $C_{14}H_{19}OS$: 235.1151; Found 235.1148.

1-(2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)ethane-1,2-diol (9): To a solution of **6** (6.27 g, 26.1 mmol) in THF (36 mL) and water (12 mL) at 0 °C was added N-methylmorpholine oxide (6.41 g, 54.6 mmol) followed by catalytic OsO_4 (4% in H_2O, 2 mL). The reaction was stirred for 18 h at ambient temperature. It was then diluted with water and EtOAc. The phases were separated, and the aqueous mixture was washed with EtOAc (5×), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (35% EtOAc/hexanes, TLC stained with CAM) to give two diastereoisomeric diols **9** (6.9 g, 97%) isolated as a thick yellowish oil (ratio ~2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 – 3.53 (m, 4H), 1.98 – 1.87 (m, 1H), 1.80 – 1.51 (m, 5H), 1.40 – 1.10 (m, 5H), 0.91 (s, 5.5H), 0.90 (s, 3.5H), 0.14 (d, J = 8.2 Hz, 3.5H), 0.11 (d, J = 4.1 Hz, 2.5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 78.6, 76.0, 73.6, 73.4, 64.7, 63.9, 47.6, 46.8, 36.4, 36.2, 26.6, 26.2, 25.87, 25.82, 25.78, 25.45, 25.11, 24.7, 24.6, 17.95, 17.87, -3.4, -3.6, -4.69, -4.73; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{14}H_{31}O_3Si$ 275.2037; Found 275.2013.

Allyl 2-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-hydroxyacetate (10): To a solution of diol **9** (4.0 g, 14.6 mmol) in DCM (69 mL) and saturated $NaHCO_{3(aq)}$ (17 mL) was added TEMPO (0.09 g, 0.583 mmol) and KBr (1.91 g, 16.0 mmol). The reaction was stirred rapidly while a 0.435 M solution of NaOCl (36.8 mL, 16.0 mmol) was added at 0 °C. The dark-red reaction was stirred for 1 h until its colour faded to a pale orange. Once completion reached, a $Na_2S_2O_3$ aqueous solution was added and the phases were separated and the aqueous one was washed with DCM (3×). The combine organic phases were dried over $MgSO_4$ and condensed *in vacuo*. The crude aldehyde was directly submitted to the next step. The intermediary aldehyde was put in solution in *t*-BuOH (120 mL) and water (40 mL), NaH_2PO_4 (3.49 g, 29.1 mmol). Once the salt completely dissolved, the reaction was brought to 0 °C and 2-methyl-2-butene 2 M solution in THF (14.6 mL) was added to the mixture followed by solid $NaOCl_2$ pellets (80 % w/w, 3.29 g, 29.1 mmol) The

reaction was stirred at 0 °C for 1 h. Following completion, the mixture was slowly acidified to pH 4 using 1 N HCl. The mixture was extracted using DCM (4×), dried with $MgSO_4$, filtered and condensed under reduced pressure. The crude product was dissolved in minimal amount of DCM and quickly purified through an acid/base workup using 1 N NaOH and 1 N HCl. After reacidification, the desired acid was extracted using DCM (5×), dried over $MgSO_4$ and condensed. The resulting thick yellow oil was put in solution in DMF (25 mL) followed by the addition of K_2CO_3 (3.10 g, 22.49 mmol), tetrabutylammonium iodide (1.66 g, 4.49 mmol) and allyl bromide (1.94 mL, 22.49 mmol) dropwise. The reaction was stirred for 2 h at ambient temperature and then diluted in water and Et_2O. The aqueous phase was washed with Et_2O (3×). The combined organic phases were washed with 1 N HCl (1×) and saturated $NaHCO_3$ (1×). The organic phase was dried over $MgSO_4$ and condensed *in vacuo*. The resulting crude was purified by silica gel column chromatography (5% EtOAc/hexanes, TLC stained with CAM) to yield compound **10** (3.72 g, 77 % over three steps) as a yellowish oily mixture of the two diastereoisomers (2.3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.81 (m, 1H), 5.43 – 5.17 (m, 2H), 4.77 – 4.56 (m, 3H), 4.27 (q, J = 3.4 Hz, 0.77H), 3.68 (ddd, J = 9.7, 3.5 Hz, 0.77H), 3.60 (ddd, J = 9.9, 3.8 Hz, 0.33H), 3.25 (d, J = 4.1 Hz, 0.77H), 2.73 (d, J = 5.5 Hz, 0.33H), 1.97 – 1.80 (m, 2H), 1.78 – 1.59 (m, 3H), 1.35 – 1.00 (m, 4H), 0.88 (s, 3H), 0.86 (s, 6H), 0.08, (s, 1H), 0.07, (s, 1H), 0.05 (s, 4H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 1757, 174.1, 131.7, 131.6, 119.1, 118.8, 69.8, 66.0, 65.9, 49.5, 48.7, 36.2, 36.1, 27.5, 26.0, 25.9, 25.4, 25.2, 24.8, 24.7, 23.8, 18.04, 18.03, -4.00, -4.1, -4.3, -5.0; IR (NaCl) ν_{max} 3529, 2931, 2857, 1733, 1250, 1086 cm^{-1}; HRMS (ESI-TOF) M/Z [M+H]$^+$: Calcd for $C_{17}H_{33}O_4Si$ 329.2142; Found 329.2141.

Allyl 2-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-methoxyacetate (11/11'): To a solution of **10** (3.12 g, 9.48 mmol) in dry THF (11 mL) was added at 0 °C under argon NaH (60 % in

mineral oil, 0.430 g, 10.08 mmol). The mixture was stirred for 15 min after which iodomethane (2.53 mL, 40.6 mmol) was slowly added. Reaction was stirred overnight and quenched with saturated NH_4Cl, diluted with water and Et_2O. The organic phase was isolated, and the aqueous portion extracted with Et_2O (3×). The combined organic phases were dried with $MgSO_4$, filtered and condensed under reduced pressure. The resulting crude was purified by silica gel column chromatography (5% Et_2O/hexanes, TLC stained with CAM) to yield each compound **11** (minor) (0.815 g, 25 %) and **11'** (major) (1.362 g, 42 %) as pale yellowish oils.

Minor 11:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.66 (dddt, *J* = 30.1, 13.3, 5.7, 1.5 Hz, 2H), 4.26 (d, *J* = 2.3 Hz, 1H), 3.61 (ddd, *J* = 10.0, 4.4 Hz, 1H), 3.39 (s, 3H), 1.95 (dt, *J* = 8.6, 3.0 Hz, 1H), 1.75 – 1.58 (m, 2H), 1.45 – 1.18 (m, 4H), 1.17 – 1.02 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07(s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 132.1, 118.3, 79.0, 70.5, 65.1, 58.5, 48.8, 36.1, 26.0, 25.4, 24.7, 24.3, 18.0, -3.6, -4.7; IR (NaCl) ν_{max} 2933, 2857, 1750, 1257, 1086, 835 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+NH_4]^+$: Calcd for $C_{18}H_{38}NO_4Si$ 360.2564; Found 360.2549.

Major 11':

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 – 5.88 (m, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.65 (dt, *J* = 6.0, 1.2 Hz, 2H), 4.13 (d, *J* = 2.9 Hz, 1H), 3.61 (ddd, *J* = 9.9, 9.8, 4.4 Hz, 1H), 3.39 (s, 3H), 1.93 – 1.85 (m, 2H), 1.80 (ddt, *J* = 12.1, 9.7, 3.2 Hz, 1H), 1.71 – 1.58 (m, 2H), 1.30 – 1.22 (m, 1H), 1.19 – 1.13 (m, 2H), 0.95 – 0.90 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 132.1, 119.0, 80.4, 70.6, 65.1, 58.3, 49.2, 36.1, 26.1, 26.0, 25.1, 24.4, 181, -3.9, -4.7; IR (NaCl) ν_{max} 2930, 2857, 1752, 1450, 1090, 836 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{18}H_{35}O_4Si$ 343.2298; Found 343.2296.

3-Methoxyhexahydrobenzofuran-2(3H)-one (12): To a solution of ester **11'** (1.32 g, 3.97 mmol) in a scintillation vial with dry THF (10 mL) at 0 °C under an argon atmosphere was slowly added HF (70 % in pyridine) in excess (1 mL). The reaction was left to reach ambient temperature overnight. A saturated solution of $NaHCO_3$ was then added slowly to the mixture until fizzing would stop and further diluted with water and EtOAc. The organic phase was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were further washed with a small portion of 1 N HCl, then dried over $MgSO_4$, filtered, and condensed under reduced pressure. As only a fraction of the desired cyclisation occurred, the crude mixture was additionally diluted in dry DCM (10 mL) and TsOH (0.068 g, 0.397 mmol) was added. The mixture was stirred overnight and quenched with saturated $NaHCO_{3(aq)}$. The organic layer was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were dried over $MgSO_4$, filtered, and condensed under reduced pressure. The crude was isolated by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield compound **12** (0.494 g, 73%) as a slightly yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (d, J = 11.6 Hz, 1H), 3.73 (ddd, J = 10.9, 3.9 Hz, 1H), 3.61 (s, 3H), 2.19 (dt, J = 10.9, 3.3 Hz, 1H), 2.08 (dt, J = 9.1, 3.2 Hz, 1H), 2.01 – 1.83 (m, 2H), 1.83 – 1.72 (m, 1H), 1.58 – 1.42 (m, 1H), 1.40 – 1.21 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.1, 80.8, 79.1, 58.7, 50.1, 30.3, 27.2, 24.9, 23.8; IR (NaCl) ν_{max} 2940, 1785, 1457, 1197, 1022 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{15}O_3$ 171.1015; Found 171.1018.

3-Methoxyhexahydrobenzofuran-2(3H)-one (13): To a solution of ester **11** (0.815 g, 2.37 mmol) in a scintillation vial with dry THF (10 mL) at 0 °C under an argon atmosphere was slowly added HF (70 % in pyridine) in excess (1 mL). The reaction was left to reach ambient temperature overnight. A saturated solution of $NaHCO_{3(aq)}$ was then added slowly to the mixture until fizzing

would stop and further diluted with water and EtOAc. The organic phase was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were further washed with a small portion of 1 N HCl, then dried over $MgSO_4$, filtered, and condensed under reduced pressure. As only a fraction of the desired cyclisation occurred, the crude mixture was additionally diluted in dry DCM (10 mL) and TsOH (0.040 g, 0.237 mmol) was added. The mixture was stirred overnight and quenched with saturated $NaHCO_{(aq)}$. The organic layer was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were dried over $MgSO_4$, filtered, and condensed under reduced pressure. The crude was isolated by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield compound **13** (0.333 g, 82 %) as a slightly yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (ddd, J = 10.9, 3.9 Hz, 1H), 3.67 (d, J = 4.7 Hz, 1H), 3.49 (s, 3H), 2.26 – 2.20 (m, 1H), 1.91 – 1.68 (m, 4H), 1.61 – 1.22 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.7, 82.5, 78.1, 58.2, 49.5, 30.6, 25.2, 23.8, 22.8; IR (NaCl) ν_{max} 2942, 1785, 1456, 1198, 1026 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{15}O_3$ 171.1015; Found 171.1012.

3-Methoxyoctahydrobenzofuran-2-yl acetate (2(OAc)): Using the same one-pot reduction acetylation reaction as described for compound **1(OAc)**, from lactone **12** (0.333 mg, 1.94 mmol) using 1 M DIBAL-H in heptanes (2.33 mL, 2.33 mmol), pyridine (0.187 mL, 2.33 mmol), DMAP (0.284 g, 2.33 mmol), Ac_2O (1.10 mL, 11.6 mmol) were isolated and separated the two acetylated anomers by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) **α-2(OAc)** (0.125 g, 30 %) and **β-2(OAc)** (0.247 g, 59 %) as colourless oils. Anomers were identified by analogy with **2(SPh)** NMR for which the NOESY shows the more downfield anomeric proton to be the one corresponding to the β-anomer.

Minor α-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.55 (ddd, *J* = 11.1, 11.0, 4.1 Hz, 1H), 3.39 (s, 3H), 2.10 (s, 3H), 2.15 – 2.03 (m, 2H), 1.86 – 1.80 (m, 1H), 1.76 – 1.72 (m, 1H), 1.56 (dt, *J* = 14.3, 9.6 Hz, 1H), 1.42 (ddd, *J* = 11.6, 11.4, 3.9 Hz, 1H), 1.31 – 1.16 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.3, 101.3, 89.6, 81.3, 58.3, 51.3, 30.9, 27.4, 25.3, 23.7, 21.3; IR (NaCl) ν_{max} 2938, 2863, 1748, 1456, 1231 cm^{-1}, HRMS (ESI-TOF) M/Z [M+Na]$^+$: Calcd for $C_{11}H_{18}O_4Na$ 237.1097; Found 237.1097.

Major β-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (d, *J* = 4.5 Hz, 1H), 3.56 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.41 (s, 3H), 3.30 (td, *J* = 11.1, 3.9 Hz, 1H), 2.10 – 2.15 (m, 2H), 2.11 (s, 3H), 1.89 – 1.80 (m, 1H), 1.79 – 1.66 (m, 2H), 1.42 (ddd, *J* = 11.6, 11.4, 3.9 Hz, 1H), 1.31 – 1.08 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 93.3, 84.0, 80.8, 59.0, 46.3, 31.9, 27.1, 25.1, 24.1, 21.4; IR (NaCl) ν_{max} 2938, 2863, 1748, 1237, 1007 cm^{-1}; HRMS (ESI-TOF) M/Z [M+Na]$^+$: Calcd for $C_{11}H_{18}O_4Na$: 237.1097; Found 237.1097.

3-Methoxyoctahydrobenzofuran-2-yl acetate (3(OAc)): Using the same one-pot reduction acetylation reaction as described for compound **1(OAc)**, from lactone **15** (0.494 g, 2.88 mmol) using 1 M DIBAL-H in heptanes (3.45 mL, 3.45 mmol), pyridine (0.278 mL, 3.45 mmol), DMAP (0.421 g, 3.45 mmol), Ac_2O (1.36 mL, 14.4 mmol) were isolated and separated the two acetylated anomers by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield major **β-3(OAc)** (0.348 g, 56 %) and minor **α-3(OAc)** (0.208 g, 34 %) as colourless oils respectively. Anomers were identified by analogy with **3(SPh)** NMR for which the NOESY shows the more downfield anomeric proton to be the one corresponding to the α-anomer. The matching coupling constant $^3J_{H1\text{-}H2}$ of about 4.2 Hz in both cases also confirms the orientation of each anomer.

Major β-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 1H), 3.68 (ddd, *J* = 11.0, 10.9, 3.9 Hz, 1H), 3.61 (d, *J* = 4.0 Hz, 1H), 3.44 (s, 3H), 2.24 – 2.17 (m, 1H), 2.06 (s, 3H), 1.91 – 1.73 (m, 3H), 1.58 – 1.47 (m, 1H), 1.48 – 1.29 (m, 2H), 1.28 – 1.17 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.9, 99.1, 85.5, 82.4, 57.9, 46.6, 32.1, 25.6, 24.0, 23.5, 21.3; IR (NaCl) ν_{max} 2938, 1748, 1373, 1234, 1011 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+Na]^+$: Calcd for $C_{11}H_{18}O_4Na$: 237.1097; Found 237.1093.

Minor α-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, *J* = 4.2 Hz, 1H), 3.87 (dd, *J* = 4.3, 5.0 Hz, 1H), 3.71 (ddd, *J* = 10.4, 10.4, 4.0 Hz, 1H), 3.40 (s, 3H), 2.15 (s, 1H), 2.13 (s, 3H), 1.91 – 1.73 (m, 3H), 1.54 – 1.37 (m, 2H), 1.35 – 1.14 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 99.2, 81.4, 80.9, 60.3, 49.8, 31.1, 25.3, 23.8, 23.6, 21.1; IR (NaCl) ν_{max} 2937, 1733, 1375, 1253, 1026 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+Na]^+$: Calcd for $C_{11}H_{18}O_4Na$ 237.1097; Found 237.1094.

3-Methoxy-2-(phenylthio)octahydrobenzofuran (2(SPh)): Using the same procedure as described for **1(SPh)** from **2(OAc)** (0.300 g, 1.40 mmol) using PhSH (0.571 mL, 5.60 mmol) and BF_3-Et_2O (0.190 mL, 1.54 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield the major **α-2(SPh)** (0.151 g, 40 %) and **β-2(SPh)** (0.066 g. 19 %) as a colourless oil and a white solid (mp: 48.7-55.0 °C) respectively. NOESY experiments showed a coupling between H1 and H4 of the minor isomer, thus confirming the β-SPh orientation.

Major α-2(SPh):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.14 (m, 3H), 5.45 (d, *J* = 4.5 Hz, 1H), 3.67 – 3.52 (m, 2H), 3.51 (s, 3H), 2.21 – 2.06 (m, 2H), 1.94 – 1.80 (m, 1H), 1.79 (d, *J* = 4.4

Hz, 1H), 1.52 (dddd, *J* = 26.7, 23.3, 11.5, 3.5 Hz, 2H), 1.39 – 1.18 (m, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 135.7, 130.4, 128.9, 126.8, 90.5, 90.4, 79.5, 58.8, 51.4, 31.0, 27.7, 25.4, 23.9; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{15}H_{21}O_2S$ 265.1256; Found 265.1261.

Minor β-2(SPh):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.0 Hz, 1H), 7.40 – 7.17 (m, 3H), 5.65 (d, *J* = 6.5 Hz, 1H), 3.87 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.53 (s, 3H), 3.29 (td, *J* = 11.0, 3.9 Hz, 1H), 2.14 (td, *J* = 10.2, 8.9, 4.1 Hz, 2H), 1.91 – 1.66 (m, 1H), 1.52 (ddd, *J* = 11.6, 3.7 Hz, 1H), 1.34 – 1.09 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 13C NMR (75 MHz, $CDCl_3$) δ 135.4, 131.3, 128.8, 126.7, 88.6, 85.6, 81.0, 59.1, 49.7, 32.0, 27.7, 25.3, 24.2; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{15}H_{21}O_2S$ 265.1256; Found 265.1265.

3-Methoxy-2-(phenylthio)octahydrobenzofuran (3(SPh)): Using the same procedure as described for **1(SPh)** from **3(OAc)** (0.134 g, 0.625 mmol) using PhSH (0.255 mL, 2.5 mmol) and BF_3-Et_2O (0.092 mL, 0.75 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give the mixture of thioacetals **3(SPh)** (49α:51β, 0.090 g, 54 %). NOESY experiments showed a coupling between the more downfield H1 and H2 and not H4, thus confirming that the downfield signal belongs to the α-SPh. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 1H), 7.34 – 7.23 (m, 2.5H), 7.21 – 7.16 (m, 0.5H), 5.79 (d, *J* = 4.7 Hz, 0.5H), 5.28 (s, 0.5H), 3.95 (t, *J* = 4.6 Hz, 0.5H), 3.77 (d, *J* = 4.1 Hz, 0.5H), 3.73 (td, *J* = 10.3, 4.2 Hz, 0.5H), 3.57 (td, *J* = 10.8, 4.1 Hz, 0.5H), 3.53 (s, 1.5H), 3.31 (s, 1.5H), 2.24 – 2.13 (m, 1H), 1.93 – 1.71 (m, 4H), 1.56 – 1.08 (m, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 132.1, 130.4, 129.0, 128.8, 127.4, 126.3, 92.1, 89.2, 87.9, 84.0, 82.5, 79.3, 60.9, 57.6, 50.6, 48.7, 32.1, 31.4, 25.6, 25.52, 24.0, 23.99, 23.91; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{15}H_{21}O_2S$ 265.1256; Found 265.1261.

Ethyl-2-oxooctahydrobenzofuran-3-carboxylate (14): In a flame dried bicol, solid sodium chunks (0.561 g, 24.4 mmol) were added to 30 mL of dry ethanol at 0 °C under argon. Once the sodium dissolved, diethylmalonate (3.73 mL, 24.4 mmol) was slowly added and the reaction stirred at ambient temperature for 0.5 h followed by cyclohexene oxide (2.47 mL, 20.4 mmol). The reaction was refluxed overnight, and a white precipitate was formed, indicative of reaction completion. The mixture was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was isolated, and the aqueous phase washed with EtOAc (3×). Combined organic phases were washed with brine, dried with $MgSO_4$, filtered and condensed under reduced pressure. The crude residue was purified by flash chromatography (8% EtOAc/hexanes, TLC stained with $KMnO_4$) to yield **14** (3.61 g, 80%) of colourless viscous oil containing the two diastereoisomers (88eq: 12ax) of the ethyl ester and characterized as such; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 – 4.18 (m, 2H), 3.81 (ddd, *J* = 11.5, 10.7, 3.9 Hz, 1H), 3.48 (d, *J* = 8.4 Hz, 0.12H), 3.24 (d, *J* = 12.9 Hz, 0.88H), 2.39 – 2.20 (m, 2H), 2.00 – 1.88 (m, 3H), 1.86 – 1.76 (m, 1H), 1.58 (qd, *J* = 11.7, 3.9 Hz, 1H), 1.44 – 1.23 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 167.5, 166.7, 83.2, 83.0, 61.9, 61.8, 53.0, 51.5, 48.1, 47.7, 30.4, 30.0, 27.4, 25.4, 25.2, 25.0, 24.0, 23.85, 23.8, 14.2, 14.1; IR (NaCl) ν_{max} 2942, 2867, 1786, 1734, 1165, 1019 cm^{-1}; HRMS (ESI-TOF) M/Z [M+H]$^+$: Calcd for $C_{11}H_{17}O_4$ 214.1155; Found 214.1152.

2-(3-Hydroxyprop-1-en-2-yl)cyclohexan-1-ol (15): To 20 mL of dimethoxymethane in a flame dried bicol under argon was added NaH (0.795 g, 19.9 mmol, 60% dispersed in mineral oil). A 20 mL solution of **14** (2 g, 9.03 mmol) in dimethoxymethane was slowly added and stirred for 2 h at ambient temperature upon which the mixture turned to a white slurry. Solid $LiAlH_4$ (0.939 g, 24.8 mmol) was put in solution with 30 mL of dried Et_2O and added to the reaction mixture. The reaction was refluxed overnight and quenched slowly with aqueous saturated Rochelle's salt. After

2 h of stirring, organic layer was isolated, and the aqueous layer washed with EtOAc (3×). The organic phases were combined, washed with brine, dried with $MgSO_4$ and condensed under reduced pressure. Crude mixture was purified by flash chromatography (45% EtOAc/hexanes, TLC stained with CAM) to yield **15** (0.870 g 62 %) of the desired diol as a white solid (mp: 63.2-66.0 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.05 (s, 1H), 4.15, 4.09 (ABq, J_{AB} = 12.9 Hz, 2H), 3.51 (td, J = 10.1, 4.2 Hz, 1H), 2.46 (s, br, 1H), 2.07 – 2.03 (m, 1H), 2.00 (td, J = 11.4, 10.3, 3.4 Hz, 1H), 1.82 – 1.67 (m, 3H), 1.39 – 1.16 (m, 4H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.9, 112.6, 73.6, 65.7, 50.5, 34.9, 31.8, 25.8, 24.9; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{17}O_2$ 157.1223; Found 157.1201.

2-(1-Hydroxypropan-2-yl)cyclohexan-1-ol (16/16'): To a solution of allylic alcohol (0.125 g, 0.768 mmol) in EtOAc (8 mL) was added PtO_2 (0.0174 g, 10 mol%). The reaction was stirred 1 h under H_2 atmosphere using a rubber balloon and filtered on celite upon completion. The solvent was evaporated and the diastereoisomers isolated by flash chromatography as a thick oil for the least polar **16** (0.05 g, 48.0 %) and a white solid (0.061 g, 50%, mp: 78.3-81.3) for the most polar isomer **16'**.

Diol 16:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (br s, 1H), 3.64, 3.57 (d of ABq, J_d = 5.4 Hz J_{AB}= 10.7, 2H), 3.40 (td, J = 9.9, 4.4 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.80 (m, 1H), 2.75 – 1.68 (m, 1H), 1.67 – 1.61 (m, 1H), 1.61 – 1.53 (m, 1H), 1.44 – 1.34 (m, 1H), 1.30 – 1.10 (m, 4H), 0.95 (d, J = 7.3, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 70.5, 67.0, 49.0, 38.9, 35.9, 30.0, 25.9, 24.9, 11.9; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{19}O_2$ 159.1379; Found 159.1377.

Diol 16':

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58, 3.50 (d of ABq, J_d= 5.5 Hz, J_{AB}= 10.6 Hz, 2H), 3.41 (ddd, *J* = 10.1, 10.1, 4.3 Hz, 1H), 2.38 (br s, 2H), 2.11 – 1.97 (m, 2H), 1.77 – 1.70 (m, 1H), 1.70 – 1.60 (m, 2H), 1.40 (ddt, *J* = 11.9, 10.0, 3.6 Hz, 1H), 1.32 – 1.10 (m, 3H), 0.98 (qd, *J* = 13.2, 3.8 Hz, 1H), 0.87 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 72.0, 66.6, 46.1, 36.5, 35.8, 25.8, 25.7, 25.0, 12.6; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{19}O_2$ 159.1379; Found 159.1375.

3-Methylhexahydrobenzofuran-2(3H)-one (17): To a solution of the most polar diol **16'** (0.433 g, 2.73 mmol) in 13 mL of CH_3CN was added tetrakisacetonitrile copper(I) triflate 0.045 g, 0.121 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.121 mmol, 1.81 mL). The reaction was stirred opened overnight at ambient temperature. As the reaction reached completion, the mixture colour changed from dark brown to blue. Reaction was diluted with H_2O, extracted with 3× DCM, dried with $MgSO_4$, filtered and condensed under reduced pressure. The crude was purified by silica gel flash chromatography (10% EtOAc/hexanes, TLC stained with CAM) to yield 0.420 g (98 %) of the desired lactone **17** as a yellowish oil. Positive NOESY between H4 and H2 and the absence of coupling between H4 and the CH_3 group confirmed the pseudo-equatorial orientation of the CH_3 group; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (td, *J* = 10.8, 3.9 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.96 – 1.87 (m, 2H), 1.86 – 1.74 (m, 1H), 1.56 – 1.22 (m, 5H), 1.19 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.4, 82.8, 51.7, 41.4, 30.1, 27.4, 25.2, 24.1, 12.5; IR (NaCl) ν_{max} 2937, 2865, 1785, 1457, 1178, 1015 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_9H_{15}O_2$ 156.1100; Found 156.1093.

3-Methylhexahydrobenzofuran-2(3H)-one (18): To a solution of the diol **16** (0.733 g, 4.62 mmol) in 27 mL of CH_3CN was added tetrakisacetonitrile copper(I) triflate (0.055 g, 0.136 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.081 mmol, 2.04 mL).

The reaction was stirred opened overnight at ambient temperature. As reaction reached completion, the mixture color changed from dark brown to blue. Reaction was diluted with H_2O, extracted with DCM (3×), dried with $MgSO_4$, filtered and condensed under reduced pressure. The crude was purified by silica gel flash chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield 0.576 g (80 %) of desired lactone **18** as a yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (td, *J* = 11.1, 3.9 Hz, 1H), 2.62 (p, *J* = 7.6 Hz, 1H), 2.24 (dt, *J* = 11.2, 3.4 Hz, 1H), 1.97 (dddd, *J* = 11.8, 10.8, 7.5, 3.3 Hz, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.75 (m, 2H), 1.52 (qd, *J* = 12.0, 11.6, 4.0 Hz, 1H), 1.44 – 1.23 (m, 3H), 1.15 (d, *J* = 7.7 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.1, 81.8, 47.3, 38.8, 30.6, 25.2, 24.6, 24.0, 9.6; IR (NaCl) ν_{max} 2940, 2866, 1779, 1391, 1194, 1017 cm^{-1}; HRMS (ESI-TOF) M/Z [M+H]$^+$: Calcd for $C_9H_{15}O_2$ 156.1100; Found 156.1094.

3-Methyloctahydrobenzofuran-2-yl acetate 4(OAc): From lactone **17** (0.250 g, 1.64 mmol) using the same one-pot reduction acetylation reaction with 1 M DIBAL-H in heptanes (1.97 mL, 1.97 mmol), pyridine (0.157 mL, 1.97 mmol), DMAP (0.241 g, 1.97 mmol), Ac_2O (0.775 mL, 8.2 mmol), the desired compound was isolated by silica gel column chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield a mixture of acetylated compounds **4(OAc)** characterized as such (13α:87β, 0.313 g, 96 %). Positive answer in the 1D NOESY experiment between H4 and the H1 confirmed the β as the major anomer in the mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, *J* = 5.2 Hz, 0.13H), 5.83 (d, *J* = 4.6 Hz, 0.87H), 3.47 (ddd, *J* = 10.8, 9.6, 3.9 Hz, 0.87H), 3.25 (td, *J* = 10.7, 3.8 Hz, 0.13H), 2.13 – 2.06 (m, 1H), 2.05 (s, 2.6H), 2.04 (s, 0.4H), 1.95 – 1.84 (m, 1H), 1.82 (s, 1H), 1.77 – 1.69 (m, 1H), 1.42 – 1.15 (m, 4H), 1.15 – 1.02 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 2.6H), 0.96 (d, *J* = 6.8 Hz, 0.4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 170.5, 104.2, 98.6, 85.1, 83.3, 52.6, 48.1, 45.1, 42.3, 31.7, 30.7, 27.2, 27.0, 25.5, 25.4, 24.3, 24.0, 21.4,

21.3, 14.7, 10.4; IR (NaCl) ν_{max} 2934, 2862, 1745, 1234, 979 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+NH_4]^+$: Calcd for $C_{11}H_{22}O_3N$ 216.1594; Found 216.1591.

3-Methyloctahydrobenzofuran-2-yl acetate (5(OAc)): From lactone **18** (0.253 g, 1.64 mmol) using the same one-pot reduction acetylation reaction with 1 M DIBAL-H in heptanes (1.97 mL, 1.97 mmol), pyridine (0.157 mL, 1.97 mmol), DMAP (0.241 g, 1.97 mmol), Ac_2O (0.775 mL, 8.2 mmol), the desired compound was isolated by silica gel column chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield a mixture of acetylated compounds **5(OAc)** as a colourless oil and characterized as such (16α:84β, 0.200 g, 64 %). The nature of the major anomer was determined by analogy with the **5(SPh)** NOESY experiment; ^1H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 6.0 Hz, 0.15H), 5.84 (s, 0.85H), 3.52 (td, *J* = 10.9, 3.8 Hz, 1H), 2.60 (h, *J* = 7.4 Hz, 0.25H), 2.27 – 2.18 (m, 2H), 2.10 (s, 0.4H), 2.05 (s, 2.6H), 1.87 – 1.70 (m, 4H), 1.41 (dddd, *J* = 11.6, 11.41, 11.41, 3.9 Hz, 1H), 1.31 – 1.15 (m, 3H), 0.98 (d, *J* = 7.5 Hz, 2.6H), 0.89 (d, *J* = 7.5 Hz, 0.4H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.5, 170.5, 103.7, 100.0, 82.2, 79.7, 48.1, 45.2, 41.8, 38.2, 32.2, 31.1, 25.6, 25.5, 25.1, 24.8, 24.2, 24.1, 21.5, 21.2, 10.8, 9.2; IR (NaCl) ν_{max} 2936, 2862, 1740, 1453, 1373, 1239, 973 cm^{-1}; HRMS (ESI-TOF) M/Z $[M+NH_4]^+$: Calcd for $C_{11}H_{22}O_3N$ 216.1594; Found 216.1592.

3-Methyl-2-(phenylthio)octahydrobenzofuran (4(SPh)): With the same procedure as described for **1(SPh)** from **4(OAc)** (0.690 g, 3.48 mmol) using PhSH (1.42 mL, 13.9 mmol) and BF_3-Et_2O (0.471 mL, 3.82 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield a mixture of thiofuranoside **4(SPh)** characterized as such (90α:10β, 0.725 g, 84 %); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.16 (m, 1H), 5.61 (d, *J* = 7.5 Hz, 0.1H), 5.14 (d, *J* = 7.5 Hz, 0.9H), 3.46 (td, *J* = 10.7, 10.3, 3.9 Hz, 0.9H), 3.26 (td, *J* =

10.7, 3.8 Hz, 0.1H), 2.33 – 2.20 (m, 0.1H), 2.18 – 2.10 (m, 1H), 1.97 – 1.72 (m, 4H), 1.48 – 1.14 (m, 4H), 1.18 (d, J = 6.6 Hz, 3H), 1.13 – 0.97 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 136.7, 131.2, 130.2, 128.8, 128.76, 126.5, 126.4, 93.3, 91.6, 84.7, 82.1, 52.4, 50.6, 46.2, 43.4, 31.9, 30.9, 27.5, 27.4, 25.5, 24.4, 24.1, 15.7, 13.6; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{15}H_{21}OS$ 249.1307; Found 249.1310.

3-Methyl-2-(phenylthio)octahydrobenzofuran (5(SPh)): With the same procedure as described for **1(SPh)** from **5(OAc)** (0.454 g, 2.23 mmol) using PhSH (0.910 mL, 8.92 mmol) and BF_3-Et_2O (0.302 mL, 2.45 mmol), the desired compound was isolated by the residue was purified by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield a mixture of thiofuranoside **5(SPh)** characterized as such (ratio 12α:88β, 0.394 g, 71 %). The major β anomer was confirmed be 1D NOESY correlation between H4 and H1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.34 – 7.16 (m, 3H), 5.74 (d, J = 6.4 Hz, 0.13H), 5.01 (d, J = 2.6 Hz, 0.87H), 3.61 (td, J = 10.5, 3.9 Hz, 0.13H), 3.40 (td, J = 10.9, 3.9 Hz, 0.87H), 2.70 (h, J = 7.3 Hz, 0.12H), 2.35 (pd, J = 7.4, 2.6 Hz, 0.83H), 2.19 (dq, J = 11.3, 3.2 Hz, 1H), 1.89 – 1.77 (m, 1H), 1.78 – 1.70 (m, 2H), 1.68 – 1.53 (m, 1H), 1.49 – 1.36 (m, 1H), 1.35 – 1.07 (m, 4H), 1.11(d, J = 7.4, 0.3H) 1.02 (d, J = 7.3 Hz, 2.7H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 136.6, 135.4, 131.2, 130.7, 128.8, 128.8, 128.7, 126.8, 126.3, 92.4, 91.5, 82.2, 79.1, 48.7, 47.4, 42.8, 39.5, 32.1, 31.7, 25.6, 25.4, 25.1, 24.2, 24.1, 11.1; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{15}H_{21}OS$ 249.1307; Found 249.1310.

2-Allyloctahydrobenzofuran (1(allyl)): Similar result and spectral data as reported by Woerpel and co-workers.[9e]

2-Allyl-3-methoxyoctahydrobenzofuran (2(allyl)): From **2(OAc)** (0.04 g, 0.187 mmol) using general procedure A with BF_3-Et_2O (0.028 mL, 0.224 mmol) and allylTMS (0.118 mL and 0.748 mmol) in DCM (1.9 mL), the crude ^{1}H NMR showed a ration of 34α:66β. Compound was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with $KMnO_4$) to yield **2(allyl)** (0.035 g, 96 %) as a colourless oily mixture of anomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.81 (m, 1H), 5.18 – 5.02 (m, 2H), 3.99 (ddd, *J* = 8.5, 7.5, 4.5 Hz, 0.65H), 3.87 (dt, *J* = 6.9, 5.8 Hz, 0.35H), 3.61 (dd, *J* = 8.6, 7.5 Hz, 0.65H), 3.39 (s, 1H), 3.38 (s, 2H), 3.38 – 3.33 (m, 0.35H), 3.27 (td, *J* = 10.9, 4.0 Hz, 0.35H), 3.04 (td, *J* = 10.8, 3.9 Hz, 0.65H), 2.41 – 2.32 (m, 1.3H), 2.31 – 2.21 (m, 0.7H), 2.13 – 2.02 (m, 2H), 1.85 – 1.64 (m, 2H), 1.58 (tdd, *J* = 11.5, 8.9, 3.2 Hz, 0.35H), 1.46 – 1.31 (m, 1.65H), 1.30 – 1.12 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.0, 134.8, 117.1, 116.3, 88.9, 85.7, 81.7, 80.0, 79.7, 79.1, 58.8, 58.3, 51.9, 51.3, 39.3, 35.0, 31.6, 31.5, 28.6, 28.4, 25.7, 25.4, 24.1, 23.9; HRMS (ESI-TOF) M/Z[M+H]$^+$: Calcd for $C_{12}H_{21}O_2$ 197.1536; Found 197.1528.

2-Allyl-3-methoxyoctahydrobenzofuran (3(allyl)): From **3(OAc)** (0.05 g, 0.233 mmol) using general procedure A with BF_3-Et_2O (0.034 mL, 0.279 mmol) and allylTMS (0.148 mL and 0.932 mmol) in DCM (2.3 mL), a mixture of 6α:94β compound was obtained according to the crude ^{1}H NMR. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM) to yield **3(allyl)** as a colourless oil (6α:94β, 0.038 g, 83 %). The major β-anomer was identified by NOESY where the OCH_3 couples with the major anomeric proton, therefore confirming the β-orientation of the substituent; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.06 (td, *J* = 7.2, 4.2 Hz, 0.06H), 3.89 (ddd, *J* = 7.3, 5.7, 1.4 Hz, 0.94H), 3.61 (dt, *J* = 3.8, 1.6 Hz, 0.06H), 3.46 – 3.35 (m, 2H), 3.29 (s, 3H), 2.42 – 2.30 (m, 1H), 2.29 – 2.16 (m, 1H), 2.17 – 2.10 (m, 1H), 1.88 – 1.70 (m, 3H), 1.40 (dddd, *J* = 12.4, 3.5 Hz, 1H), 1.32 – 1.11 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.4, 117.4, 85.5, 83.76, 80.4, 57.4, 49.2, 39.3,

31.8, 25.7, 24.0, 23.96; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{12}H_{21}O_2$ 197.1536; Found 197.1528.

2-Allyl-3-methyloctahydrobenzofuran (4(allyl)): From **4(OAc)** (0.03 g, 0.151 mmol) using general procedure A with BF_3-Et_2O (0.023 mL, 0.181 mmol) and allylTMS (0.096 mL and 0.604 mmol) in DCM (1.5 mL), a mixture of 60α:40β was obtained according to the ^1H NMR. The mixture was characterized as a colourless oil without the need for additional purification **4(allyl)** (0.027 g, 98 %). 1D NOESY showed correlation between the major H1 signal and the CH_3 at the C2 position, confirming the major α-anomer; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 – 5.82 (m, 1H), 5.16 – 5.00 (m, 2H), 4.05 (td, *J* = 8.9, 4.5 Hz, 0.4H), 3.61 (ddd, *J* = 8.3, 6.7, 5.0 Hz, 0.6H), 3.21 (td, *J* = 10.1, 3.8 Hz, 0.6H), 3.07 (td, *J* = 10.5, 3.9 Hz, 0.4H), 2.41 – 2.25 (m, 1H), 2.25 – 2.03 (m, 2H), 1.99 – 1.65 (m, 4H), 1.61 – 1.47 (m, 1H), 1.35 – 1.02 (m, 7H), 0.99 (d, *J* = 6.5 Hz, 1.8H), 0.96 (d, *J* = 7.0 Hz, 1.2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.3, 135.3, 116.7, 116.2, 85.0, 82.5, 82.4, 80.0, 53.2, 51.5, 43.8, 40.7, 39.5, 36.8, 31.7, 31.6, 27.9, 27.5, 25.7, 25.6, 24.4, 24.3, 15.4, 12.7; HRMS (ESI-TOF) M/Z $[M+H]^+$: Calcd for $C_{12}H_{21}O$ 181.1586; Found: 197.1571.

2-Allyl-3-methyloctahydrobenzofuran (5(allyl)): From **5(OAc)** (0.03 g, 0.151 mmol) using general procedure A with BF_3-Et_2O (0.023 mL, 0.181 mmol) and allylTMS (0.096 mL and 0.604 mmol) in DCM (1.5 mL), only pure β-anomer was obtained according to the ^1H NMR and 1D NOESY experiment where and coupling between C_1–H and C_4–H was observed. The desired compound **5(allyl)** was characterized as a colourless oil without the need for additional purification (0.025 g, 90 %); ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddtd, *J* = 17.2, 10.2, 7.0, 1.2 Hz, 1H), 5.12 – 5.02 (m, 2H), 3.53 (dddd, *J* = 6.8, 5.7, 3.4, 1.0 Hz, 1H), 3.21 (td, *J* = 10.5, 3.9 Hz, 1H), 2.36 (dddq, *J* = 13.9, 7.0, 5.8, 1.3 Hz, 1H), 2.26 (dtq, *J* = 14.0, 7.0, 1.2 Hz, 1H), 2.17 – 2.10 (m, 1H), 2.02 – 1.89 (m, 1H), 1.82 – 1.66 (m, 3H), 1.45 – 1.07 (m, 5H), 0.88 (dd, *J* = 7.2, 1.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz,

$CDCl_3$) δ 135.0, 116.9, 86.1, 80.3, 47.6, 40.5, 38.9, 31.8, 25.8, 25.0, 24.2, 15.3; HRMS (ESI-TOF) M/Z $[M+Na]^+$: Calcd for $C_{12}H_{20}ONa$ 203.1406; Found 203.1398.

2-(2,2,2-Trifluoroethoxy)octahydrobenzofuran (1(TFE)): Using general procedure B with NIS (0.096 g, 0.426 mmol) and 2,2,2 trifluroethanol (0.062 mL, 0.852 mmol) in CH_3CN (2.1 mL) from **1(SPh)** (0.05 g, 0.213 mmol, 15α:85β), crude ^1H NMR showed a 22α:78β ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of α/β-**1(TFE)** (0.033 g, 69 %, 21α:79β) was isolated and characterized together as a colourless oil. NOESY experiment showed a coupling between C_1–H and C_4–H as the major anomeric proton was irradiated, meaning that the major anomer is the **β-1(TFE)**; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (dd, *J* = 5.7, 4.3 Hz, 0.79H), 5.14 (d, *J* = 4.7 Hz, 0.21H), 4.06 (dq, *J* = 12.4, 9.1 Hz, 0.79H), 4.05 – 3.95 (m, 0.21H), 3.86 (dq, *J* = 12.3, 8.7 Hz, 0.79H), 3.80 (dt, *J* = 12.2, 8.7 Hz, 0.21H), 3.34 (td, *J* = 10.4, 3.9 Hz, 0.79H), 3.21 (ddd, *J* = 11.1, 9.8, 3.8 Hz, 0.21H), 2.35 (ddd, *J* = 13.2, 7.4, 5.8 Hz, 1H), 2.15 – 2.01 (m, 1H), 1.98 – 1.79 (m, 2H), 1.76 – 1.60 (m, 2H), 1.54 (ddd, *J* = 13.1, 11.7, 4.3 Hz, 1H), 1.43 – 1.01 (m, 4H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 124.0 (q, *J* = 278 Hz), 104.3, 103.3, 85.3, 81.4, 65.0 (q, *J* = 34.2 Hz), 45.6, 42.1, 38.4, 38.3, 31.7, 30.55, 28.5, 28.5, 25.6, 24.3, 24.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.22 (t, *J* = 8.7 Hz, 084F), -74.27 (t, *J* = 8.9 Hz, 2.16F); HRMS (ESI-TOF) M/Z $[M+NH_4]^+$- $[H_2O]$: Calcd for $C_{10}H_{17}F_3ON$ 224.1262; Found 224.1243.

3-Methoxy-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (2(TFE)): Using general procedure B with NIS (0.059 g and 0.264 mmol) and 2,2,2 trifluroethanol (0.038 mL, 0.528 mmol) in CH_3CN (1.3 mL) from **2(SPh)** (0.035 g, 0.132 mmol, 32α:68β), crude ^1H NMR showed a 34α:66β ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), **α-2(TFE)** (0.010 mg, 30 %) and the more polar **β-2(TFE)** (0.019, 56 %) were

obtained and characterized as colourless volatile oils. NOESY experiment on the major **β-2(TFE)** isomer showed a coupling between C_1–H and C_4–H, thus confirming the orientation at the anomeric center.

Minor α-2(TFE):

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.02 (dq, *J* = 12.3, 8.7 Hz, 1H), 3.88 (dq, *J* = 12.6, 8.6 Hz, 1H), 3.55 (d, *J* = 9.1 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.42 (s, 3H), 2.12 – 2.00 (m, 2H), 1.85 – 1.80 (m, 1H), 1.73 (d, *J* = 8.8 Hz, 1H), 1.54 – 1.46 (m, 1H), 1.44 – 1.35 (m, 1H), 1.30 – 1.15 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.25 (t, *J* = 8.7 Hz, 3F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 123.9 (q, *J* = 282.8 Hz), 108.0, 90.3, 80.3, 64.7 (q, *J* = 34.3 Hz) 58.3, 51.6, 30.9, 27.3, 25.3, 23.8; HRMS (ESI-TOF) M/Z $[M+NH4]^+$: Calcd for $C_{11}H_{21}F_3NO_3$ 272.1468; Found 272.1478.

Major β-2(TFE):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 1H), 4.00 (dq, *J* = 20.6, 11.3, 10.8 Hz, 2H), 3.52 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.45 (s, 3H), 3.30 (td, *J* = 12.7, 11.9, 5.4 Hz, 1H), 2.12 – 2.02 (m, 2H), 1.88 – 1.77 (m, 1H), 1.74 (ddt, *J* = 10.6, 8.2, 2.4 Hz, 2H), 1.46 – 1.32 (m, 1H), 1.32 – 1.04 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.92 (t, *J* = 8.9 Hz, 3F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 124.1 (q, *J* =277.8 Hz), 99.6, 84.2, 80.4, 63.8 (q, *J* = 34.3 Hz), 57.9, 46.4, 32.0, 27.1, 25.2, 24.2; HRMS (ESI-TOF) M/Z $[M+NH4]^+$: Calcd for $C_{11}H_{21}F_3NO_3$ 272.1468; Found 272.1451.

3-Methoxy-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (3(TFE)): Using general procedure B with NIS (0.085 g, 0.378 mmol) and 2,2,2 trifluroethanol (0.056 mL, 0.756 mmol) in CH_3CN (1.9 mL) from **3(SPh)** (0.05 g, 0.189 mmol, 50α:50β), crude ^{1}H NMR showed a 22α:78β ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of α/β-**3(TFE)** (0.028 g, 58%, 26α:74β) was isolated and characterized as

a colourless oil. The anomeric ratio was determined by analogy with **3(SPh)** NOESY where the more downfield signal corresponds to the β-oriented anomeric hydrogen; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (d, *J* = 3.9 Hz, 0.22H), 5.02 (s, 0.78H), 4.15 (dq, *J* = 12.7, 9.0 Hz, 0.22H), 4.04 (dq, *J* = 12.3, 9.0 Hz, 0.83H), 3.85 (dq, *J* = 12.3, 8.6 Hz, 0.83H), 3.79 (dd, *J* = 5.4, 3.9 Hz, 0.22H), 3.68 (td, *J* = 11.0, 3.9 Hz, 1H), 3.64 (d, *J* = 4.1 Hz, 0.8H), 3.48 (s, 0.6H), 3.41 (s, 2.4H), 2.20 – 2.11 (m, 1H), 1.89 – 1.73 (m, 3H), 1.58 (dddd, *J* = 12.2, 10.9, 4.1, 3.1 Hz, 1H), 1.51 – 1.14 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.27 (t, *J* = 8.6 Hz, 3F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 125.2, 123.9 (q, *J* = 278.2 Hz), 122.2, 105.2, 104.9, 85.9, 82.2, 81.7, 79.8, 65.3 (q, *J* = 34.3 Hz), 64.1 (q, *J* = 34.4 Hz), 60.1, 57.9, 49.9, 46.7, 32.3, 31.3, 25.6, 25.4, 24.1, 24.1, 23.9, 23.7, 23.6; HRMS (ESI-TOF) M/Z: calcd for $C_{11}H_{21}F_3NO_3$ $[M+NH4]^+$: 272.1468; Found 272.1464.

3-Methyl-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (4(TFE)): Using general procedure B with NIS (0.054 g, 0.242 mmol) and 2,2,2 trifluroethanol (0.035 mL, 0.484 mmol) in CH_3CN (1.2 mL) from **4(SPh)** (0.03 g, 0.121 mmol), crude ^{1}H NMR showed a 91α:9β ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of α/β-**4(TFE)** (0.017 g, 56 %, 91α:9β) was isolated and characterized as a colourless oil. The crude NMR showed a complete conversion to the desired compound. The low yield can be explained by the volatile nature of the compound. Irradiation of the minor isomer C_4–H under NOESY experiment showed a positive coupling with C_1–H whereas the same experiment performed on the major anomer C_4–H did not show the same correlation, which confirms the nature of the minor β-anomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 5.1 Hz, 0.08H), 4.77 (d, *J* = 4.3 Hz, 0.92H), 4.05 (dq, *J* = 12.3, 9.0 Hz, 1H), 3.84 (dq, *J* = 12.4, 8.7 Hz, 1H), 3.45 (ddd, *J* = 10.9, 9.7, 4.0 Hz, 0.92H), 3.26 (td, *J* = 10.5, 3.7 Hz, 0.08H), 2.11 – 2.05 (m, 1H), 1.91 – 1.77 (m, 3H), 1.79 – 1.70 (m, 1H), 1.38 – 0.97 (m, 8H), 1.11 (d, *J* = 6.9 Hz, 2.7H), 1.02 (d, *J* = 6.8 Hz,

0.3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.32 (t, *J* = 8.9 Hz, 0.3F), -74.35 (t, *J* = 8.8 Hz, 2.7F); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 124.0 (q, *J* = 279.8 Hz), 111.2, 105.0, 84.9, 82.1, 65.3 (q *J* = 34.3 Hz), 52.9, 48.0, 45.7, 43.1, 31.9, 30.8, 27.2, 27.1, 25.5, 25.45, 24.4, 24.0, 14.9, 10.2; HRMS (ESI-TOF) M/Z $[M\text{-}CF_3CH_2O]^+$: Calcd for $C_9H_{15}O$ 139.1122; Found 139.1115.

3-Methyl-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (5(TFE)): Using general procedure B with NIS (0.054 g, 0.240 mmol) and 2,2,2 trifluroethanol (0.035 mL, 0.480 mmol) in CH_3CN (1.2 mL) from **5(SPh)** (0.03 g, 0.120 mmol), crude ^{1}H NMR showed a 9α:91β ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of α/β-**5(TFE)** (0.016 g, 55 %, 9α:91β) was isolated and characterized together as a colourless oil. Irradiation of the major isomer C_4–H under NOESY experiment showed a positive coupling with C_1–H, thus confirming the nature of the major β-anomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 5.9 Hz, 0.09H), 4.76 (s, 0.91H), 4.07 (dq, *J* = 12.3, 9.0 Hz, 0.09H), 4.00 (dq, *J* = 12.2, 9.1 Hz, 0.91H), 3.85 (dt, *J* = 12.2, 8.6 Hz, 0.09H), 3.79 (dq, *J* = 12.2, 8.7 Hz, 0.91H), 3.52 (td, *J* = 11.0, 3.9 Hz, 0.91H), 3.45 (td, *J* = 10.5, 4.0 Hz, 0.09H), 2.51 (pd, *J* = 7.6, 5.9 Hz, 0.09H), 2.25 (p, *J* = 7.4 Hz, 0.91H), 2.14 (dq, *J* = 10.1, 3.4 Hz, 1H), 1.84 – 1.72 (m, 4H), 1.36 (qd, *J* = 11.4, 3.9 Hz, 1H), 1.30 – 1.10 (m, 4H), 0.92 (d, *J* = 7.5 Hz, 2.7H), 0.90 (d, *J* = 7.5 Hz, 0.3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.18 (t, *J* = 9.0 Hz, 2.7F), -74.35 (t, *J* = 8.6 Hz, 0.3F); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 124.1 (q, *J* = 278.4 Hz), 109.5, 105.6, 82.1, 63.9 (q, *J* = 34 Hz), 48.5, 45.3, 42.0, 38.8, 32.4, 31.1, 29.7, 25.6, 25.5, 25.0, 24.8, 24.3, 24.2, 10.9, 8.9; HRMS (ESI-TOF) M/Z $[M\text{-}CF_3CH_2O]^+$: Calcd for $C_9H_{15}O$ 139.1122; Found 139.1117.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H, $^{13}C\{^{1}H\}$, ^{19}F, 1D NEOSY NMRs, crude glycosylation NMRs, kinetic control experiments and DFT computational data are available in the SI. (PDF)

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Notes

The authors declare no competing financial interest.

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