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Bent bonds (τ) and the antiperiplanar hypothesis, and the reactivity at the anomeric center in pyranosides†

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The stereoselectivity of nucleophilic addition on oxocarbenium ions derived from the bicyclic pyranoside model with or without a C_2–OR group can be understood through the use of the bent-bond and the antiperiplanar hypothesis in conjunction with the concept of hyperconjugation as an alternative interpretive model of structure and reactivity.

The reaction of an alcohol for instance, ethanol, or a sugar having a free hydroxyl group as a nucleophile (described in the field of carbohydrates as the acceptor) at the anomeric center (C_1) of a glycoside (described as the donor) is the most important chemical transformation in the field of glycochemistry.[1] Numerous experimental studies[2] indicate that this apparently simple *O*-glycosylation step can take place through a large variety of reaction mechanisms which spanned between that of a S_N2-like nucleophilic substitution in which the alcohol displaces the leaving group of an α or a β-glycosyl donor and that of a direct S_N1-like nucleophilic addition of an alcohol on an oxocarbenium ion intermediate. As illustrated in Fig. 1, preactivation of the leaving group of the donor is also necessary and although it can take place by protonation, modern glycosylation procedures which occur at low temperature, avoid such conditions in order to prevent acid equilibration of the final α or β-glycoside product.

In the case of *C*-glycosylation,[3] the reaction is believed to take place by a simple nucleophilic addition to the very reactive oxocarbenium ion because the reagents (allyltrimethylsilane, allyltributylstannane or silyl enol ether,) are poor nucleophiles unable to successfully undergo an S_N2 displacement reaction directly on a glycosyl donor.

Fig. 1 is however an over simplification of the reality since several other factors need to be considered at the glycosylation step. For instance, there is the possibility that a conformational change is taking place because the reaction may occur on a higher energy conformer than that of the ground state of the glycosyl donor (*i.e.* chair $^4C_1$, $^1C_4$ or twist-boat $^1S_3$, $^0S_2$, *etc.*)[4] or

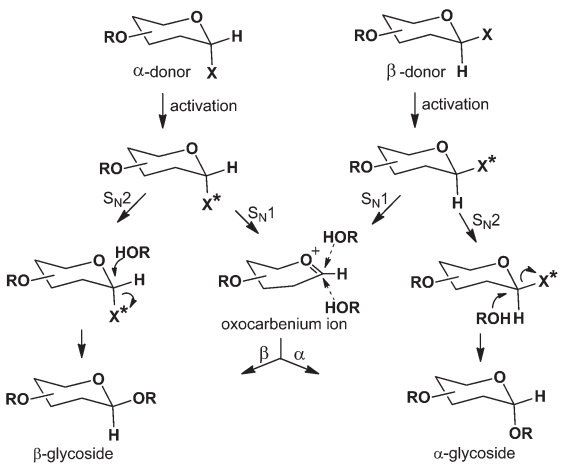

Fig. 1 A general glycosylation machanism.

that of the corresponding oxocarbenium ion (half chair $^4H_3$ or $^3H_4$). In addition, the various inductive effects[3] resulting from the spatial orientation of the equatorial and axial OH or O-protected groups present at C_3, C_4 and C_6 in the glycosyl donor or in the oxocarbenium ion can influence the reactivity of the anomeric center. Also, the non-bonding electron pairs of these oxygen substituents located at various positions of the carbohydrate structure, if appropriately oriented in space, can also electrostatically stabilize the positive charge[5,6] and that may induce a conformational change of the oxocarbenium ion ground state.

In the case of an S_N1-like process and even an S_N2-like process, the angle of attack[7] and the strength of the nucleophile[8] must also be considered and since a given process can take place through an early or a late transition state,[8] this may indicate if steric repulsion between the nucleophile and the neighbouring substituents of the oxocarbenium ion plays a

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discriminating role favoring the formation of an α or a β-glycoside.

Of course, the polarity of the solvent may also induce a S_N1 or a S_N2 process.[8] The glycosylation reaction can be further complicated because the oxocarbenium ion could exist as a transient glycosyl donor intermediate with a very labile leaving group (*e.g.* glycosyl triflate) or a more or less equivalent contact-ion pair (CIP). The oxocarbenium ion could also exist as a solvent-separated ion pair (SSIP) and its stereoselectivity can thus be analyzed while considering the CIP, transient glycosyl donor or SSIP situation.[2e,9] Stereoelectronic effects have also been proposed for the anomeric effect which in combination with steric effects can explain the relative stability of α and β-glycosides; they are also useful to rationalize the reaction mechanism of glycosylation.[10] For instance, stereoelectronic factors like the antiperiplanar[10] *versus* the synperiplanar[11] nucleophilic addition to an oxocarbenium ion can be considered to explain which reaction trajectory will be energetically preferred.

In recent years, FMO based *ab initio* calculations[12] have been used to modulate transition structures of the glycosylation reaction and primary ^{13}C and ^{2}H kinetic isotope effects (KIE)[13] have also been carried out to obtain experimental information on the degree of positive charge at C_1 in the glycosylation step. Finally, it should be pointed out that only the well-established σ–π bonding orbital model of the oxocarbenium ion has been considered so far in carbohydrate chemistry.

In 2011, we reported that using the Slater–Pauling bent bond model (tau-bonds, τ-bonds) in combination with the antiperiplanar hypothesis (BBAH) is a useful conceptual model to understand the conformation and reactivity of organic molecules containing the carbonyl group.[14] Realizing that oxocarbenium ions are the *O*-alkylated derivatives of ketones, we recently became interested to see if the τ bond orbital model could be useful as an alternative to the σ–π model while providing a new approach to the understanding of the key parameters which govern the glycosylation reaction. The bent-bond-antiperiplanar hypothesis as a new interpretive model in conjunction with the concept of hyperconjugation[15,29b] is discussed next.

σ–π *versus* τ bond electronic models

Carbonyl groups can either be expressed by the familiar Hückel σ/π orbital construct[16] or by the Slater–Pauling bent bond model,[17] which is based on two equivalent τ bonds (Fig. 2).[18] There is however a fundamental difference between the σ/π and the τ bond models. In the first model, the π* antibonding lobes above and below the plane of the carbonyl group correspond to the same π* orbital. In the second model, the two antibonding orbitals correspond to two different τ* orbitals, one above and one below the plane of the carbonyl group. As a result, the τ bond model confers a tetrahedral character to the carbonyl group. By considering the antiperiplanar hypothesis, a nucleophile will be added by interacting with a τ* antibonding orbital displacing the corresponding antiperiplanar τ bond in the same manner as a S_N2 reaction displaces a leaving group on a saturated system. We previously explained the nucleophilic addition on cyclohexanone and adamantanone derivatives in this manner.[14] The τ bond model provides a very simple and clear alternative to the Cieplak effect[19] or the Inomata *syn* effect.[20] Consequently, the nucleophilic addition yields a product directly in the more stable conformation **A** (Fig. 2). With the σ–π bonding model, one has to postulate that the nucleophilic addition on an oxocarbenium ion must develop an oxygen lone pair antiperiplanar to the incoming nucleophile to yield the product in the staggered **A** conformation. The alternative synperiplanar nucleophilic addition can be eliminated using both electronic bonding models because the product is formed directly in the higher energy eclipsed conformation **B**. A similar situation[14] is occurring in the E_2 elimination reaction forming an olefin. In the *anti* elimination reaction, the reacting molecule is in the lower energy staggered conformation while the *syn* elimination is normally less favorable because the reacting molecule must be in the higher energy eclipsed conformation. While assuming antiperiplanarity of all reaction groups, the *syn* elimination is believed to occur *via* what is known as a "double inversion pathway" according to Ingold and Sicher[21] in order to avoid the eclipsed conformation. We have also recently shown[22] that product stereoisomers formed in [1,3]-sigmatropic thermal rearrangements can be explained by the preferential formation of staggered over eclipsed conformers of intermediate diradicals.

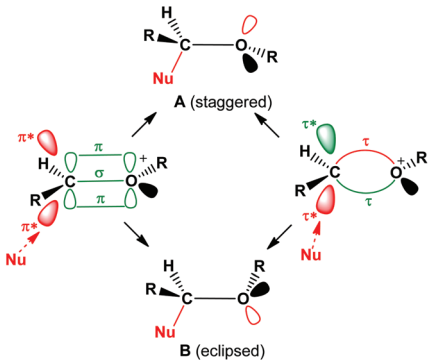


Fig. 2 *anti* and *syn* periplanar addition on σ–π and τ bond models.

A difference between the σ–π and the τ bond models appears when the oxocarbenium ion is in a specific chiral environment opening the possibility of face diastereoselectivity. This situation happens when there is an adjacent chiral center at C_2 bearing an electron withdrawing group (EWG) and an electron donating group (EDG). As indicated in the most stable staggered conformation **C** of an oxocarbenium ion (Fig. 3), the τ bond above the plane is oriented antiperiplanar to the C–X bond which is electron-withdrawing. This τ bond is thus properly aligned to interact with the antibonding orbital of that polar C–X bond; this τ bond will thus be electron poorer because of its donating electronic density through

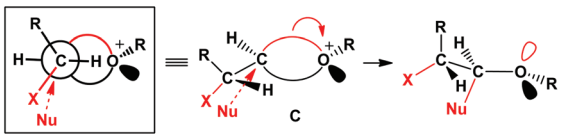


Fig. 3 Stereoelectronically preferred nucleophilic addition.

hyperconjugation.[15] On the other hand, the τ bond below is more electron rich because it is antiperiplanar to the C–R bond of the EDG.[3b] Consequently, the nucleophile will preferably displace the weaker τ bond below the plane as shown. Stereoselective nucleophilic addition on aldehydes or ketones having an α chiral group with an electron withdrawing group was first observed by Cornforth.[23a] A remarkable experimental and theoretical study of stereocontrol in aldol addition reactions of methyl ketone-derived enolates and aldehydes containing an α-alkoxy stereocenter was reported by Evans and his co-workers.[23b,c] The Cornforth–Evans transition model which is proposed to rationalize these results corresponds essentially to transition state model **C**.

A preferential face selectivity can also occur due to a different conformational environment. This is the case for cyclic intermediates like the $^4H_3$ six-membered oxocarbenium ion **D** (Fig. 4). By applying the antiperiplanar hypothesis, the nucleophilic addition below and above the plane leads automatically to the $^4C_1$ chair and the $^1S_3$ twist-boat conformers of the α and β-anomers respectively, the former process being energetically favored for conformational reasons. These two pathways follow a trajectory in which an oxygen lone pair develops antiperiplanar to the attacking nucleophile in the reaction product.[10] Note that we have made the assumption that in the $^4H_3$ oxocarbenium ion **D**, the substituents at C_2 and C_5 are arranged symmetrically relatively to the $C_1{=}O^+$ tau bond. Thus, the two hydrogens at C_2 are each antiperiplanar to a different τ bond contributing equally to the electronic density of the two τ bonds. Also a synperiplanar addition of the nucleophile leads to a half-chair conformation which is energetically higher than the chair or the twist-boat just described. In cyclohexane, the half-chair and the twist-boat are respectively ~10 and ~5–6 kcal mol^{-1} higher in energy than the chair conformation. In addition, the nucleophilic trajectory of the τ bond model[14] follows exactly the Bürgi–Dunitz angle of attack[7] which was deduced from X-ray experimental studies. It is also pertinent to realize that the τ bond model can be used to propose an almost identical geometry for the transition structure of the S_N1 and the S_N2 reaction as illustrated in Fig. 5. In S_N1, the axially oriented leaving group is ejected by an antiperiplanar oxygen lone pair generating the oxocarbenium ion.[14] In the S_N2 reaction, the nucleophile starts to form a bond prior to the complete ejection of the leaving group by the oxygen lone pair.[14] Thus, the C_1–O σ bond and the oxygen lone pair of the anomeric center in α-$^4C_1$ are both involved in the transition structure **E** which can be classified as a loose transition state.[24] Note again that in the S_N2 process, the nucleophilic addition and the leaving group ejection follow the Bürgi–Dunitz angle.[7] With the σ–π model, the nucleophilic reaction has to start by an interaction with the antibonding π* orbital of the oxocarbenium ion, for which knowledge of the spatial orientation comes from *ab initio* calculations.

In order to test the validity of the τ bond model and in order to limit the number of conformations of the pyranose ring, we have first studied the glycosylation reaction of bicyclic pyranoside donors **1–3** which exist in their ground state $^4C_1$ chair conformation, the *trans* junction of the two six-membered rings preventing chair inversion (Fig. 6). In addition, the bicyclic models **1–3** are heavily truncated due to the absence of exocyclic hydroxyl groups or derivatives which are normally present at C_3, C_4, and C_6 in carbohydrates. The choice of these models is thus to eliminate the influence of these oxygen substituents so that the τ bond model can be tested on a $^4C_1$ pyranoside without exocyclic OR groups or only with the presence

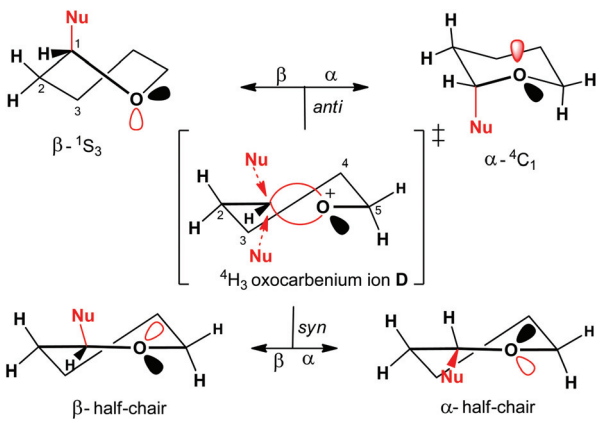


Fig. 4 *anti* and *syn* periplanar addition on the $^4H_3$-oxocarbenium ion.

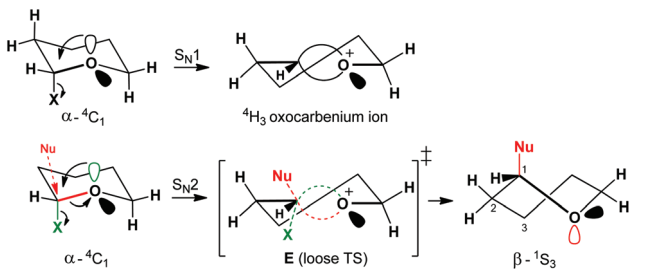


Fig. 5 S_N1 *vs.* S_N2 with τ bonds.

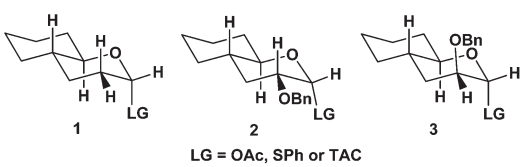


Fig. 6 Bicyclic pyranoside donors **1–3**.

of an equatorial or an axial *O*-benzyl group at C_2 which could influence the glycosylation step through hyperconjugation. We also felt that pyranoside donors **2–3** can be considered 3,4,6-deoxy models of 4,6-*O*-benzylidene[25] (or 4,6-*O*-silylene)[26] of the glucose and mannose donors which on glycosylation are respectively α and β-selective. Results obtained on the glycosylation of **1–3** donors could thus be useful to understand several of the factors which control the α-gluco and β-manno stereoselectivities.

We thus wish to report herein a study on the *C*- and *O*-glycosylation of the three racemic bicyclic pyranoside models **1**, **2**, and **3** having an OAc or a SPh group at the anomeric center. We have also studied pyranosides **2** and **3** having a trichloroacetimidate (TCA) group.

Synthesis of bicyclic pyranoside donors 1–3

The model substrates **1–3** were prepared by starting with cyclohexene oxide which gave direct access to the *trans* substituted and easily derivable 2-allylcyclohexanol intermediate **4** by epoxide opening (Fig. 7).[27a] In order to obtain the desired unsubstituted bicyclic pyranoside **1**, the allylic compound was placed under hydroboration–oxidation conditions to yield 1,5-diol **5**. The *trans* fused six membered bicyclic lactone **6** was obtained by selective δ-oxidative lactonisation of the 1,5 diol using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and (diacetoxyiodo)benzene (BAIB) in 85% yield.[27b] The lactone was further reduced and acetylated in a one-pot reaction using DIBAl-H followed by a standard acetylation procedure to yield acetoxy donor **1(OAc)**, which was used to obtain bicyclic donor **1(SPh)** (α/β = 88 : 12).

The usual α-hydroxylation methods did not provide C_2 substituted intermediates directly from lactone **6**. To access the C_2–OBn derivatives, a different sequence had to be developed. Compound **4** was first protected using TBDMSCl (Fig. 8). The use of this protecting group was helpful for the purification of subsequent reactions, decreasing the polarity of products, and facilitating their isolation. The silylated alcohol **7** was then subjected to dihydroxylation conditions with catalytic OsO_4 to give a high yield of vicinal diol **8** in a 60 : 40 diastereoisomeric ratio. A selective oxidation of the terminal alcohol using TEMPO in the presence of $NaOCl/NaOCl_2$ in a biphasic medium provided efficiently the α-hydroxy carboxylic acid

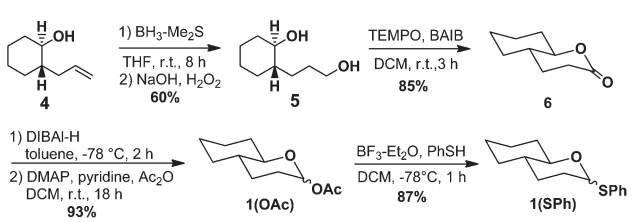


Fig. 7 Synthesis of donors **1**.

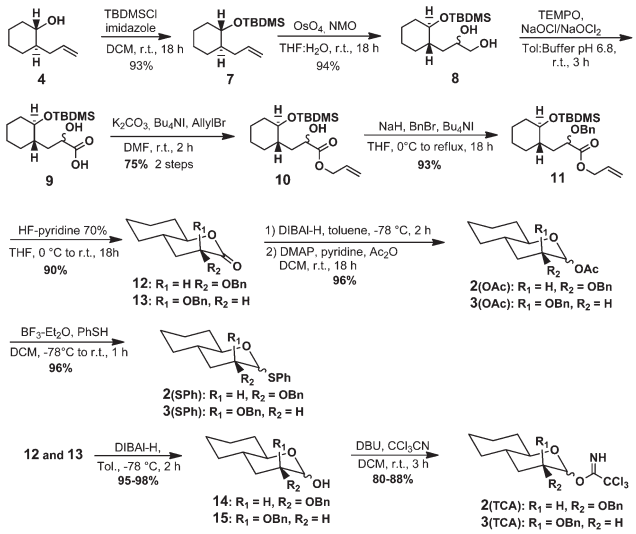


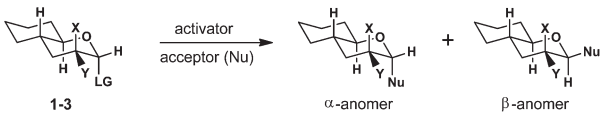
Fig. 8 Synthesis of donors **2** and **3**.

which was converted into allylic ester **10**.[27c] Prior to ring closure, the alcohol was benzylated to compound **11**. Deprotection of the silylated secondary alcohol using excess 70% HF-pyridine carried out for 18 h at room temperature provided directly the two α-benzyloxy **12** and **13** in a 6 : 4 diastereomer ratio which were separated by chromatography. Their stereochemistry was established by ^{1}H NMR spectroscopy. Both isomers **12** and **13** were either reduced and acetylated to yield the bicyclic acetate donors **2(OAc)** and **3(OAc)** or reduced to the corresponding lactols **14** and **15** with DIBAl-H. The **2(OAc)** and **3(OAc)** donors were converted into the corresponding **2(SPh)** and **3(SPh)** donors using the reaction conditions for donors **1(SPh)**. Lactols **14** and **15** were converted further to trichloroacetimidate donors **2(TCA)** and **3(TCA)** efficiently using DBU and trichloroacetonitrile. The synthesis of donor **1(TCA)** was not successful, the final product being unstable under the reaction conditions. In 2-deoxy derivatives, the electron donating ability of the ring oxygen is strong and it can easily eject a good leaving group like TCA. Accordingly, the acid hydrolysis of methyl-2-deoxy-α-D-glucopyranoside is much faster (~2×10^3) than the corresponding glucose derivative.[28]

Glycosylation experiments

Results of the glycosylation of donors **1–3** are shown in Table 1. *C*-Glycosylation was carried out with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C.[3] In *O*-glycosylation, donor **1(SPh)** was reacted with *N*-iodosuccinimide in CH_2Cl_2 at −78 °C[3] and in CH_3CN at −40 °C to −20 °C.[8] Donors **2** and **3(SPh)** were reacted at −40 °C to −20 °C in both CH_2Cl_2 and CH_3CN using the same conditions. Three alcohols with increasing nucleophilicities, CF_3CH_2OH, $ClCH_2CH_2OH$ and CH_3CH_2OH were used as acceptors. Donors

Table 1 Glycosylation of bicyclic donors **1–3**



Entry	Dnr	LG	Nu	*T* °C	S	Y	α : β ratio
1	**1** (X = Y = H)	OAc	TMSAllyl	−78	CH_2Cl_2	88%	α only
2	**1** (X = Y = H)	SPh (77α : 23β)	CF_3CH_2OH	−78	CH_2Cl_2	Qnt	88 : 12
3	**1** (X = Y = H)	SPh (60α : 40β)	CF_3CH_2OH	−40	**CH_3CN**	Qnt	95 : 5
4	**1** (X = Y = H)	SPh (77α : 23β)	$ClCH_2CH_2OH$	−78	CH_2Cl_2	96%	62 : 38
5		SPh (60α : 40β)	$ClCH_2CH_2OH$	−40	**CH_3CN**	82%	90 : 10
6	**1** (X = Y = H)	SPh (77α : 23β)	CH_3CH_2OH	−78	CH_2Cl_2	61%	45 : 55
7	**1** (X = Y = H)	SPh (60α : 40β)	CH_2CH_2OH	−40	**CH_3CN**	81%	72 : 28
8	**2** (X = H, Y = OBn)	OAc	TMSAllyl	−78	CH_2Cl_2	96%	α only
9	**2** (X = H, Y = OBn)	SPh (60α : 40β)	CF_3CH_2OH	−40 to −20	CH_2Cl_2	93%	83 : 17
10	**2** (X = H, Y = OBn)	SPh (α only)	CF_3CH_2OH	−40 to −20	**CH_3CN**	77%	α only
11	**2** (X = H, Y = OBn)	SPh (60α : 40β)	$ClCH_2CH_2OH$	−40 to −20	CH_2Cl_2	93%	63 : 34
12	**2** (X = H, Y = OBn)	SPh (α only)	$ClCH_2CH_2OH$	−40 to −20	**CH_3CN**	87%	60 : 40
13	**2** (X = H, Y = OBn)	SPh (60α : 40β)	CH_3CH_2OH	−40 to −20	CH_2Cl_2	93%	50 : 50
14	**2** (X = H, Y = OBn)	SPh (α only)	CH_3CH_2OH	−40 to −20	**CH_3CN**	97%	35 : 65
15	**2** (X = H, Y = OBn)	TCA (45α : 55β)	CF_3CH_2OH	−78	CH_2Cl_2	78%	80 : 20
16	**2** (X = H, Y = OBn)	TCA (45α : 55β)	CF_3CH_2OH	−78	CH_2Cl_2	91%	45 : 55
17	**3** (X = OBn, Y = H)	OAc (β only)	TMSAllyl	−78	CH_2Cl_2	93%	95 : 5
18	**3** (X = OBn, Y = H)	OAc (α only)	TMSAllyl	−78	CH_2Cl_2	82%	85 : 15
19	**3** (X = OBn, Y = H)	SPh (90α : 10β)	CF_3CH_2OH	−40 to −20	CH_2Cl_2	86%	65 : 35
20	**3** (X = OBn, Y = H)	SPh (β only)	CF_3CH_2OH	−40 to −20	CH_2Cl_2	85%	68 : 32
21	**3** (X = OBn, Y = H)	SPh (β only)	CF_3CH_2OH	−40 to −20	**CH_3CN**	88%	78 : 22
22	**3** (X = OBn, Y = H)	SPh (α only)	CF_3CH_2OH	−40 to −20	**CH_3CN**	88%	82 : 18
23	**3** (X = OBn, Y = H)	SPh (90α : 10β)	$ClCH_2CH_2OH$	−40 to −20	CH_2Cl_2	98%	66 : 34
24	**3** (X = OBn, Y = H)	SPh (β only)	$ClCH_2CH_2OH$	−40 to −20	**CH_3CN**	98%	62 : 38
25	**3** (X = OBn, Y = H)	SPh (90α : 10β)	CH_3CH_2OH	−40 to −20	CH_2Cl_2	93%	50 : 50
26	**3** (X = OBn, Y = H)	SPh (β only)	CH_3CH_2OH	−40 to −20	**CH_3CN**	89%	65 : 35
27	**3** (X = OBn, Y = H)	TCA (91α : 9β)	CF_3CH_2OH	−78	CH_2Cl_2	89%	82 : 18
28	**3** (X = OBn, Y = H)	TCA (91α : 9β)	CH_3CH_2OH	−78	CH_2Cl_2	76%	72 : 28

Dnr: donor; Nu: acceptor; TMSAllyl: allyltrimethylsilane; S: solvent; Y: yield; TCA: trichloroacetimidate ($OCNHCCl_3$); Qnt: quantitative.

2 and **3(TCA)** were reacted with CF_3CH_2OH and CH_3CH_2OH with $BF_3{\cdot}Et_2O$ (1 equiv.) in CH_2Cl_2 at −78 °C.

The method developed by Woerpel[8] was used to confirm that the *O*-glycosylation experiments were conducted under kinetic control. Pure α or β-anomer obtained from donors **1–3** was resubjected to the glycosylation reaction conditions of a different donor and nucleophile. Results showed that there was no anomerization or nucleophile incorporation into the α or β-anomer. Results are described in the ESI.†

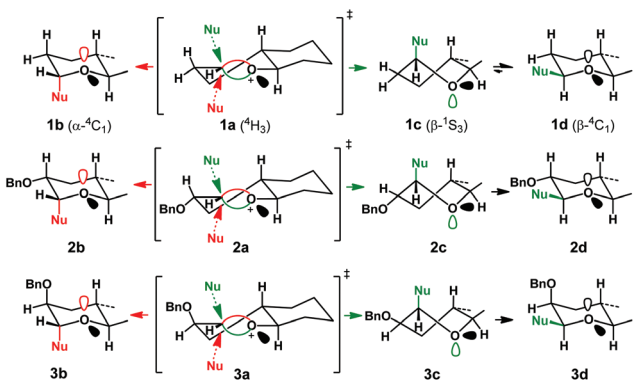


Fig. 9 α/β glycosylation of bicyclic pyranosides.

Rationalization of glycosylation

With the τ bond model, bicyclic pyranoside **1** must form the oxocarbenium ion in the $^4H_3$ half-chair conformation **1a** which will preferably react with the nucleophile on the α-face producing directly the α-anomer **1b** in the α-$^4C_1$ chair conformation (Fig. 9) while the minor β-anomer would be produced in the β-$^1S_3$ twist-boat conformation **1c** which is then converted to the stable $^4C_1$ chair form **1d**.

Bicyclic pyranoside **2** with the equatorial OBn group will generate an oxocarbenium ion in the $^4H_3$ conformation **2a** having the C_2–OBn bond antiperiplanar to the τ bond above the plane of the carbonyl group. As a result, the τ bond above the plane is electron poorer, so, the α nucleophilic addition should take place to an even larger extent due to the presence of the equatorial C_2–OR group producing the α-anomer in the $^4C_1$ chair conformation **2b**. In complete agreement with this analysis, Woerpel and co-workers[3] have previously observed that the *C*-glycosylation of 2-*O*-benzyltetrahydropyran donor **16** gave the 1,2-*cis* product as the major anomer (ratio 83 : 17) *via* a nucleophilic addition on the oxocarbenium ion intermediate

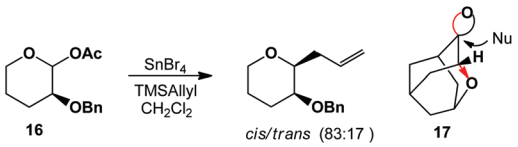


Fig. 10 1,2-*cis* nucleophilic addition on **16** and **17**.

(Fig. 10). This analysis is also supported by the reported[29] reactivity of 6-oxo-2-adamantanone **17** in which all reagents (alkylation or reduction) react exclusively as shown.

Bicyclic pyranoside **3** with the axial OBn group will form an oxocarbenium ion in the $^4H_3$ conformation **3a** having a C_2–OR bond antiperiplanar to the τ bond below the plane of the carbonyl group. The α-isomer is thus favored by the formation of the $^4C_1$ chair conformer but the hyperconjugation of the axial OBn group favors the β-isomer although produced in the less stable $^1S_3$ conformer. These two effects are thus opposing each other.

The glycosylation described in Table 1 can now be examined. The α-anomers are generally obtained as the major isomers with weak nucleophiles TMSAllyl (entries 1, 8, 17 and 18) and CF_3CH_2OH (entries 2, 3, 9, 10, 15 and 19–22) whereas there is almost no stereocontrol with stronger nucleophiles in CH_2Cl_2 (entries 4, 6, 11, 13, 16, 23 and 25) which is not the case in CH_3CN (entries 5, 7, 12, 14, 21, 22, 24 and 26).

C-Glycosylation of donor **1(OAc)** (entry 1) shows that the $^4C_1$ conformer formation is powerful enough that only the α-isomer is observed. When both parameters, *i.e.* $^4C_1$ conformation and hyperconjugation of the OBn group are working in the same direction as in donor **2(OAc)** having an equatorial OBn group (entry 8) only the α-isomer is again observed. However, when both parameters are in opposition as in donor **3(OAc)** (entries 17 and 18), the α-isomer still prevails but the minor formation of the β-isomer indicates that the $^4C_1$ conformation parameter is not completely dominating the hyperconjugation effect of the axial OBn group forming the β-isomer in the $^1S_3$ conformation.

O-Glycosylation can now be examined while taking into account Woerpel's finding[8] that stereoselectivity is greater in CH_3CN than in CH_2Cl_2. Indeed, "Increasing the polarity of the solvent results in stabilization of the cationic intermediate and subsequently reduces the rate of nucleophilic addition. As the rate of nucleophilic addition is decreased from the diffusion limit regime, greater facial selectivity for the stereoelectronically preferred product would be observed".[8] Consequently, the transition state can be considered earlier in CH_2Cl_2 than with CH_3CN to the point that there is a loss of face selectivity in the approach of a nucleophile. It also means that there should be more stereoselectivity with weak than with strong nucleophiles. Indeed, according to Woerpel,[8] the 2-deoxy-3,4,5-OR α-glucosyl donor in CH_3CN gives a 91 : 9 α/β ratio with the weak nucleophile TMSAllyl, a 83 : 17 α/β ratio with CF_3CH_2OH, and a 1 : 1 α/β ratio with EtOH.

O-Glycosylation with CF_3CH_2OH in CH_2Cl_2 and in CH_3CN of the non-substituted donor **1(SPh)** (entries 2 and 3) indicates that the antiperiplanar nucleophilic addition leading to the α-$^4C_1$ conformer is the dominating parameter. The slightly lower α selectivity in CH_2Cl_2 can also indicate that CF_3CH_2OH might be nucleophilic enough to be near the diffusion rate limit which can explain the very minor formation of the β-anomer in this solvent. With the stronger nucleophiles $ClCH_2CH_2OH$ and CH_3CH_2OH, there is a higher α selectivity in CH_3CN (entries 5 and 7) in contrast to CH_2Cl_2 (entries 4 and 6).

With pyranoside donor **2(SPh)**, glycosylation with CF_3CH_2OH in CH_3CN gives only the α-anomer (entry 10) in agreement with the $^4C_1$ conformation and the hyperconjugation of the equatorial OBn group. In CH_2Cl_2, the small quantity (17%) of the β-anomer (entry 9) can be explained in the same manner as that in donor **1(SPh)**. With $ClCH_2CH_2OH$, the reaction is low α selective in CH_3CN and in CH_2Cl_2 (entries 11 and 12). This alcohol being more nucleophilic than CF_3CH_2OH, more β-anomers are observed. With CH_3CH_2OH, there is no selectivity in CH_2Cl_2 and it was surprising to see that the β-anomer was even the major product (entries 13 and 14). CH_3CH_2OH being the strongest nucleophile, it can undergo a S_N2 reaction on the **α-2(SPh)** donor in CH_3CN. This hypothesis is supported by the fact that the α-donor **1(SPh)** by comparison with the α-donor **2(SPh)** is a 2-deoxypyranoside donor which can produce an oxocarbenium ion at a much faster rate.[28] In CH_3CN (and partly in CH_2Cl_2) and specially with CH_3CH_2OH, the S_N2 pathway can be the major process. With donor **2(TAC)**, there are again more β-anomers with CH_3CH_2OH than with CF_3CH_2OH (entries 15 and 16).

O-Glycosylation of donors **3(SPh)** with CF_3CH_2OH in CH_3CN (entries 21 and 22) shows an important quantity (18 to 22%) of the β-anomer which is explained by the hyperconjugation of the axial OBn group despite the fact that it is produced in the less stable $^1S_3$ conformation. Indeed, donor **2** under the same conditions yields only the α-anomer. In CH_2Cl_2 (entries 19 and 20) there is an even larger quantity (32 to 35%) of the β-anomer probably due to the reasons described for donors **1** and **2**. With $ClCH_2CH_2OH$ and CH_3CH_2OH in CH_3CN, donors **3(SPh)** (entries 24 and 26) give an important quantity (35 to 38%) of the β-anomer. In CH_2Cl_2, the minor β-anomer is also very important (34% with $ClCH_2CH_2OH$ and 50% with CH_3CH_2OH) (entries 23 and 25).

The high α- and β-glycosylation of glucose and mannose donors in the presence of nucleophiles remains to be con-

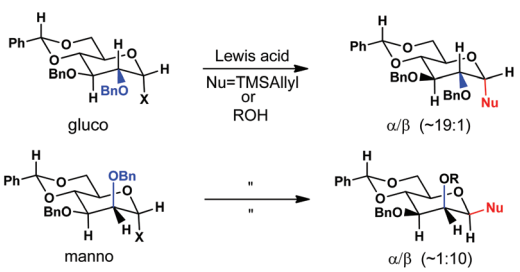


Fig. 11 Glycosidation of 4,6-*O*-gluco and manno pyranosides.

sidered (Fig. 11). The pathways of these reactions have been studied extensively by the groups of Crich,[9,13,30] Bols–Pedersen[26] and theoretically by Kosma.[31] Their work indicates that the reactive conformation of the oxocarbenium ion corresponds to a $^4H_3$ half-chair for glucose and equilibrating $^4H_3$ and $B_{2,5}$ conformations for mannose ($B_{2,5}$ being major). The $B_{2,5}$ conformation in mannose has the C_3–OR group axially oriented and properly located to stabilize the positive charge of the oxocarbenium ion. This conformational electrostatic stabilization has been previously recognized by Woerpel[5b] and us.[6] As a result, the nucleophile would finally preferably react on the β side of $B_{2.5}$ for mannose. The preferred addition on both sugars is in complete agreement with the τ bond model, the nucleophile reacting on the α side of $^4H_3$ for glucose and on the β side of $B_{2,5}$ for mannose (Fig. 12).

It is however important to point out that the polar C_4–O and C_6–O bonds (indicated in green) are perfectly antiperiplanar to the C_5–O bond withdrawing electronic density from the C_5–O^+=C_1– unit by hyperconjugation (Fig. 12). Indeed, the 4,6-*O*-benzylidene group is known to be "disarming"[32] and plays an important role in the stereoselectivity observed. In addition, the polar equatorial C_3–O bond in the glucose oxocarbenium ion is antiperiplanar to the C_2–C_1 bond, also the withdrawing electronic density in the C_2–C_1=O^+– unit. So, clearly, the electron density of the τ bonds of these oxocarbenium ions must be very low due to the hyperconjugation of these oxygen atoms. This means that the glycosylation transition states must be even earlier with these sugars than with the bicyclic models **2** and **3**, without polar C–O bonds at C_3, C_4 and C_6.

This hyperconjugation effect is again strongly supported by the Woerpel study[33] on the *C*-glycosylation of a series of bicyclic furanoside donors. For example, when X = CH_2 in the oxocarbenium ion intermediate **18**, the inside attack is highly favoured (98 : 2) but when X = O, the inside attack preference is lost (60 : 40) (Fig. 13). These experimental results are supported by calculations, which indicates that the inside attack on **18** (X = CH_2) is favoured over the outside attack by 1.6 kcal mol^{-1} whereas the same attack on **18** (X = O) is favoured by only 0.2 kcal mol^{-1}. We interpret these results by the hyperconjugation caused by the polar C–O bond in **18** (X = O) which is antiperiplanar to the C_4–O^+ bond rendering the oxocarbenium ion electron poorer and thus more reactive, causing an early transition state and a loss of selectivity.

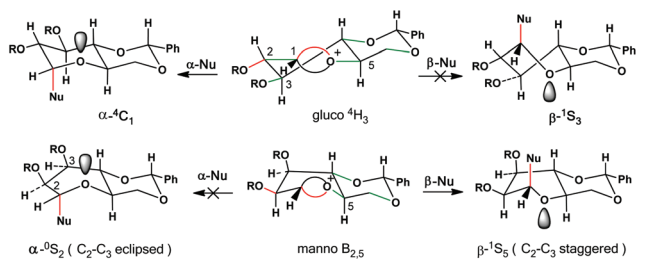


Fig. 12 Glycosylation of the 4,6-*O*-benzylidene of glucose and mannose donors.

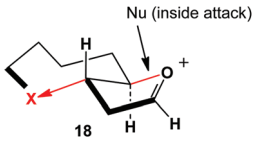


Fig. 13 Nucleophilic addition on bicyclic compound **18** (X = O or CH_2).

It remains to be explained why 4,6-*O*-benzylidene mannose donors are β-selective while bicyclic donors **3** are low α selective with strong nucleophiles and α-selective with weak nucleophiles in CH_2Cl_2. As shown above, glycosylation of glucose and mannose occurs with a transition state considered to be earlier than that of donors **1–3**. It appears unlikely that the stereoselectivity observed in mannose and glucose would be controlled only by the **τ** bond electronic density which depends on the hyperconjugation of the equatorial or axial C_2–OR bond. But if one assumes that, as proposed by Crich[9,13,30] and Bols–Pedersen,[26] the oxocarbenium ions derived from the 4,6-*O*-benzylidenes of glucose and mannose react through their $^4H_3$ and $B_{2,5}$ conformations respectively, it becomes possible to understand their behavior while taking into account the BBA hypothesis.

A nucleophilic displacement of a τ bond is the equivalent of a SN_2 reaction. In glucose, this reaction on the $^4H_3$ conformation of the oxocarbenium ion leads directly to the $^4C_1$ conformation of the α-anomer which is more favourable than a β attack forming the β-anomer in the less stable $^1S_3$ conformation. On the other hand, in the case of mannose, a β nucleophilic attack on the $B_{2,5}$ conformation produces the β-anomer in the $^1S_5$ twist-boat conformation in which the C_2–OBn and C_3–OBn bonds remain staggered. This is a lower energy process than an α attack on $B_{2,5}$, which produces the α-anomer in the $^0S_2$ twist-boat conformation causing the OR groups at C_2 and C_3 to become eclipsed. A similar argument has been used previously by Crich[34] who stated that there is a reduction of the O_2–C_2–C_3–O_3 torsion angle in the $B_{2,5}$ oxocarbenium ion of mannose.[35]

Crich and co-workers have also reported[34,36] the *C*- and *O*-glycosylation of 3-deoxy derivatives of the 4,6-*O*-benzylidene of glucose and mannose donors. The α and β selectivities of the 3-deoxy derivatives were found to be similar in the *C*-glycosylation with those of the natural sugars. However, the *O*-glycosylation differs considerably; it was unselective in 3-deoxy glucose and found to have a low α selectivity with 3-deoxy mannose. Interestingly, donor **3** which is a good 4,6-deoxy model of 3-deoxy mannose is also α selective. Thus, in 3-deoxy mannose, the most stable conformer for the oxocarbenium ion can be the $^4H_3$ conformer and not the $B_{2,5}$ one due to the absence of the electrostatic stabilization of the C_3–OR group. However, further comparison should be made with caution as quite different nucleophiles (1-adamantanol) or bulky sugars (*e.g.*, 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose)

versus ethanol derivatives) were used in these studies. Conformationally restricted donors related to the 4,6-*O*-benzylidene glycopyranose donors having different orientations for the oxygen at C_6 have been recently investigated.[30b,37]

In conclusion, the τ bond model explains why donor **1** is α-selective with weak nucleophiles yielding the product directly in the $^4C_1$ conformation. For the same reason and that of the hyperconjugation effect of the equatorial C_2–OR group and despite the possible steric repulsion of that group with the nucleophile in the transition state, donor **2** remains α-selective. This model also explains that the major formation of the α-anomer with donor **3** is due to the fact that it is produced in the α-$^4C_1$ conformation. It also explains that the presence of the β-anomer as an important minor product is due to the hyperconjugation of the axial C_2–OR group despite the fact that it leads to a product in the β-$^1S_3$ conformation. In addition, there is an important loss of stereocontrol in CH_2Cl_2 which occurs less in CH_3CN.

The τ bond model is also in agreement with the Crich–Bols–Pedersen pathways for the 4,6-*O*-benzylidene derivatives of glucose and mannose. In glucose, the α-anomer is formed preferably through a nucleophile reacting on the $^4H_3$ conformation of the oxocarbenium ion producing the anomer directly in the $^4C_1$ conformation. In the case of mannose, the β-anomer is preferably formed through a nucleophilic reaction on the $B_{2,5}$ conformation of the oxocarbenium ion, producing that anomer in its $^1S_5$ conformation. This process is lower in energy than an α nucleophilic attack on $B_{2,5}$ producing the α-anomer in the less stable $^0S_2$ conformation in which the OR groups at C_2 and C_3 become eclipsed. Finally, the τ bond model can also explain the loss of stereoselectivity in the *O*-glycosylation of the 3-deoxy-4,6-*O*-benzylidene of glucose and mannose donors. It also provides a rationale for the different behavior of glucose and mannose donors and the bicyclic donors **1–3**.[23d]

Finally, the τ bond model combined with the antiperiplanar hypothesis and the concept of hyperconjugation suggests that there are two conformationally different types of resonance structures for a six-membered oxocarbenium ion (Fig. 14). As a consequence, this provides the required information necessary to predict that there are two sterically different stereochemically controlled pathways for the addition of a nucleophile. The pathway having minimal conformational effect is thus expected to be lower in energy. In the example shown (Fig. 14), the nucleophilic addition on the α side of the $^4H_3$ oxocarbenium ion shown should thus prevail and this should be the case even with an early transition state, unless the nucleophile is so strong that it reacts at the diffusion rate.

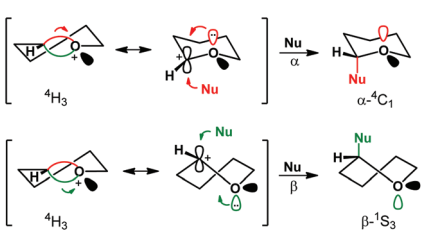


Fig. 14 Resonance structures of τ bonds and stereocontrolled nucleophilic addition on $^4H_3$.

Glycosylation with bicyclic pyranoside models having various EWG and EDG at both C_2 and C_3 is presently being investigated to further confirm the validity of the τ bond model. We are also carrying out an analogous study on the glycosylation of bicyclic furanoside donors similar to the above bicyclic pyranosides. Results will be reported in the near future.

Experimental section

C-Glycosylation: general procedure A

A solution of an acetate donor in DCM (0.1 M) under N_2 was brought to −78 °C and allyltrimethylsilane (4 equiv.) was added. The mixture was then treated with BF_3–Et_2O (1.2 equiv.) and brought to ambient temperature over 2 hours 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 analysed 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) with the nucleophile (4 equiv.) under N_2 was brought to −40 °C. The mixture was then treated with NIS (2 equiv.) and brought to −20 °C over 1.5 hours 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. 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.* Crude mixtures were analysed by ^1H NMR spectroscopy and purified as described.

2-Allylcyclohexanol (4). The compound was obtained following the procedure described by Woerpel *et al.* with comparative yield and similar spectral data;[27a] ^1H NMR (500 MHz, $CDCl_3$) δ 0.90–1.01 (m, 1H), 1.12–1.22 (m, 1H), 1.23–1.29 (m, 1H), 1.33 (dddt, J = 11.7, 9.4, 7.8, 4.0 Hz, 1H), 1.59–1.69 (m, 2H), 1.70–1.83 (m, 2H), 1.93–2.04 (m, 2H), 2.46 (dddt, J = 14.1, 7.1, 4.5, 1.4 Hz, 1H), 3.27 (td, J = 9.8, 4.5 Hz, 1H), 5.00–5.04 (m, 1H), 5.05–5.10 (m, 2H), 5.87 (dddd, J = 17.0, 10.1, 7.6, 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.9, 25.5, 30.4, 35.6, 37.5, 44.9, 74.7, 116.0, 137.5; HRMS (ESI) calculated for $C_9H_{17}O^+$ $(M + H)^+$: 141.1273; Found: 141.1277.

2-(3-Hydroxypropyl)cyclohexanol (5). To a solution of olefin **4** (1.0 g, 7.13 mmol) in dry THF (5 mL) at 0 °C under an nitrogen atmosphere was added 2 M BH_3–Me_2S solution in THF (8.56 mmol, 4.28 mL) over 10 min. The reaction was then brought slowly to ambient temperature and stirred for 8 hours. The mixture was treated with 3 M sodium hydroxide at 0 °C

until the pH was basic and H_2O_2 (14.26 mmol, 1.61 mL) was added. The reaction was stirred for 3 hours until completion and was diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc (3×). The organic layers were combined and washed with brine (1×), dried over $MgSO_4$ and concentrated *in vacuo.* The crude residue was purified by silica gel column chromatography (60% EtOAc/hexanes, R_f = 0.22, TLC stained with *p*-anisaldehyde) to obtain diol **5** (676 mg, 60%) as a colorless thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.99 (m, 1H), 1.09–1.29 (m, 5H), 1.43–1.57 (m, 1H), 1.59 –1.76 (m, 3H), 1.76–1.87 (m, 2H), 1.91–1.99 (m, 1H), 2.17 (s, 2H), 3.22 (td, J = 9.4, 4.5 Hz, 1H), 3.64 (td, J = 6.3, 1.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.6, 28.2, 29.4, 30.4, 35.8, 44.6, 62.9, 74.6; HRMS (ESI) calculated for $C_9H_{19}O_2^+$ $(M + H)^+$: 159.1379; Found: 159.1378.

Octahydro-2*H*-chromen-2-one (6). To a solution of diol **5** (1.13 g, 7.14 mmol) in dry DCM (50 mL) under N_2 were added [bis(acetoxy)iodo]benzene (6.90 g, 21.42 mmol) and TEMPO (0.223 g, 1.43 mmol). The reaction was stirred for 3 hours at ambient temperature and quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was separated and the aqueous one was washed with EtOAc (2×). The combined organic layers were washed sequentially with saturated $NaHCO_3$ (1×), water (1×), dried over $MgSO_4$ and condensed *in vacuo.* The orange residue was purified by silica gel column chromatography (20% EtOAc/hexane, R_f = 0.28, TLC stained with CAM) to obtain lactone **S3** as a yellowish oil (0.940 g, 85%); IR (NaCl) ν 2934, 2861, 1736, 1229, 1179, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.11 (m, 1H), 1.22–1.35 (m, 2H), 1.40–1.57 (m, 3H), 1.68–1.75 (m, 1H), 1.80–1.89 (m, 3H), 2.08–2.14 (m, 1H), 2.5–2.58 (m, 1H), 2.67 (ddd, J = 18.1, 7.4, 3.4 Hz, 1H), 3.88 (ddd, J = 11.0, 10.5, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.1, 25.1, 26.5, 29.9, 31.1, 32.3, 38.8, 83.4, 171.6; HRMS (ESI) calculated for $C_9H_{15}O_2^+$ $(M + H)^+$: 155.1066; Found: 155.1075.

Octahydro-2*H*-chromen-2-yl acetate (1(OAc)). To a −78 °C solution of **6** (0.1 g, 0.648 mmol) in dry toluene (3 mL) under an N_2 atmosphere was added dropwise 1 M DiBAl-H in heptanes (0.778 mL, 0.778 mmol). The reaction was stirred at −78 °C for 2 hours and pyridine (0.061 mL, 0.778 mmol), was slowly added at −78 °C, followed by DMAP (0.095 g, 0.778 mmol) in 1 mL of dry DCM, stirred for 10 minutes and Ac_2O (0.356 mL, 3.89 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 hours. 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, R_f = 0.44, TLC stained with CAM) to obtain a mixture of two diastereoisomeric acetates (0.118 g, 93%, 16α : 84β) **1(OAc)** as a colorless oil; IR (NaCl) ν 2931, 2859, 1748, 1353, 1370, 1225, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 0.90–1.08 (m, 1H), 1.15–1.41 (m, 5H), 1.45–1.61 (m, 1H), 1.62–1.66 (m, 2H), 1.74–1.81 (m, 2H), 1.82–1.84 (m, 1H), 1.91–1.94 (m, 1H), 2.10 (s, 3H), 3.13 (ddd, J = 10.7, 10.2, 4.1 Hz, 0.86H), 3.44 (ddd, J = 10.2, 10.1, 3.9 Hz, 0.18H), 5.67 (dd, J = 10.0, 2.4 Hz, 0.84H), 6.14 (d, J = 2.9 Hz, 0.16H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 21.3, 24.7, 24.8, 25.0, 25.6, 25.7, 29.1, 29.4, 30.7, 31.0, 31.7, 32.1, 32.1, 40.7, 41.2, 75.4, 80.6, 92.5, 94.8, 169.4; HRMS (ESI) calculated for $C_{11}H_{18}O_3K^+$ $(M + K)^+$: 237.0887; Found: 237.0888.

Characteristic peaks for the minor α-isomer: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 3.44 (ddd, J = 10.2, 10.1, 3.9 Hz, 0.18H), 6.14 (d, J = 2.9 Hz, 0.16H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS) δ 21.3, 21.3, 24.8, 25.0, 25.7, 29.4, 31.7, 32.1, 41.2, 75.4, 92.5.

2-(Phenylthio)octahydro-2*H*-chromene (1(SPh)). To a solution of diastereoisomeric acetate **4(OAc)** (0.2 g, 1.08 mmol) in dry DCM (3 mL) under an N_2 atmosphere was added PhSH (0.124 mL, 1.21 mmol). The mixture was cooled to −78 °C and $BF_3{\cdot}Et_2O$ (0.136 mL, 1.11 mmol) was slowly added. After 1 hour of stirring at −78 °C, the reaction was quenched with Et_3N, 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, R_f = 0.44 at 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give two diastereoisomeric thioacetals **1(SPh)** (0.232 g, 87%, 77α : 23β) as white solids which were characterised as mixtures; mp: 45.8–49.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.99 (m, 0.2H), 1.10 (tdd, J = 12.9, 11.3, 3.8 Hz, 0.8H), 1.18–1.48 (m, 5H), 1.48–1.57 (m, 1H), 1.58–1.75 (m, 3H), 1.76–1.85 (m, 2H), 1.92–1.99 (m, 0.5H), 2.03 (dddd, J = 13.9, 4.0, 2.7, 1.1 Hz, 1H), 2.17 (tt, J = 13.5, 5.0 Hz, 1H), 3.05 (ddd, J = 11.0, 9.0, 4.1 Hz, 0.23H), 3.86 (ddd, J = 10.1, 10.0, 3.6 Hz, 0.77H), 4.83 (dd, J = 11.4, 2.2 Hz, 0.23H), 5.63 (d, J = 5.3 Hz, 0.77H), 7.17–7.24 (m, 1H), 7.25–7.32 (m, 3H), 7.46–7.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.1, 25.6, 25.8, 26.7, 31.5, 31.6, 31.9, 32.1, 32.2, 32.4, 40.8, 42.1, 47.5, 73.7, 82.8, 84.8, 85.6, 126.4, 126.6, 128.7, 128.8, 130.5, 130.7, 135.3, 136.2; HRMS (ESI) calculated for $C_{15}H_{21}OS^+$ $(M + H)^+$: 249.1307; Found: 249.1320.

Characteristic peaks for the minor β-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.99 (m, 0.2H), 3.05 (ddd, J = 11.0, 9.0, 4.1 Hz, 0.23H), 4.83 (dd, J = 11.4, 2.2 Hz, 0.23H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.6, 31.5, 32.2, 32.4, 40.8, 82.8, 84.8, 126.6, 128.7, 130.5, 135.3.

2-Allyl-*tert*-butyldimethylsilyloxy cyclohexane (7). To a solution of **4** (2.0 g, 14.26 mmol) in DCM (20 mL) was added imidazole (3.88 g, 57.05 mmol) followed by *tert*-butyldimethylsilylchloride (2.58 g, 17.11 mmol). The solution was stirred for 12 hours and diluted with hexane. The mixture was condensed under reduced pressure and the resulting slurry was filtered with hexane through a large silica pad to remove imidazole. The mixture was then purified by silica gel column chromatography (2% Et_2O/hexanes, R_f = 0.55, TLC stained with $KMnO_4$) to yield **7** as a colorless oil (3.37 g, 93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.81–0.90 (m, 1H), 0.90 (s, 9H), 1.09–1.37 (m, 4H), 1.55–1.63 (m, 1H), 1.68–1.83 (m, 3H), 1.84–1.91 (m, 1H), 2.56 (dddt, J = 13.2, 6.5, 3.3, 1.6 Hz, 1H), 3.23 (td,

J = 9.6, 4.1 Hz, 1H), 4.97–5.03 (m, 2H), 5.77 (dddd, J = 16.7, 10.4, 8.2, 6.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.7, −3.9, 18.1, 25.0, 25.4, 25.9, 29.9, 36.0, 37.0, 45.0, 75.1, 115.5, 137.7; HRMS (ESI) calculated for $C_{15}H_{31}OSi^+$ $(M + H)^+$: 255.2138; Found: 255.2130.

3-(2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)propane-1,2-diol (8). To a solution of **7** (3.0 g, 11.8 mmol) in THF (30 mL) and water (10 mL) was added *N*-methylmorpholine oxide (2.76 g, 23.6 mmol) followed by OsO_4 (4% in H_2O) (5 mol%, 3.8 mL). The reaction was stirred for 18 h with the flask wrapped in aluminum foil. 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, R_f = 0.33, TLC stained with CAM) to give two diastereoisomeric diols **8** (3.18 g, 94%) isolated as a thick colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06–0.11 (m, 6H), 0.86–0.95 (m, 9H), 0.99–1.11 (m, 1H), 1.13–1.34 (m, 4H), 1.35–1.44 (m, 0.5H), 1.44–1.54 (m, 0.5H), 1.57–1.66 (m, 1H), 1.69–1.87 (m, 3H), 1.87–1.94 (m, 1H), 3.18–3.28 (m, 1H), 3.41 (ddd, J = 14.9, 11.1, 7.2 Hz, 1H), 3.61 (ddd, J = 11.0, 4.7, 3.3 Hz, 1H), 3.73 (ddt, J = 10.7, 6.5, 3.1 Hz, 0.5H), 3.86 (dtd, J = 7.7, 6.5, 3.2 Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.2, −4.2, −3.9, 18.1, 24.8, 24.8, 25.5, 25.6, 25.9, 25.9, 32.2, 32.5, 36.0, 37.1, 41.9, 42.4, 66.8, 67.6, 70.7, 70.7, 76.5, 76.9; HRMS (ESI) calculated for $C_{15}H_{33}O_3Si^+$ $(M + H)^+$: 289.2193; Found: 289.2184.

3-(2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-2-hydroxypropanoic acid (9). To a solution of **8** (2.0 g, 6.93 mmol) in toluene (40 mL) and pH 6.8 phosphate buffer (32 mL) was added TEMPO (0.270 g, 1.73 mmol). The reaction was stirred rapidly while a 0.128 M solution of NaOCl (13.53 mL, 1.73 mmol) and a 3.5 M solution of $NaOCl_2$ (7.1 mL, 20.79 mmol) were added simultaneously over 1 minute. The dark red reaction was stirred for 2 hours until its color faded to a pale orange and was then brought to pH 4 by the slow addition of 1 M HCl. The phases were separated and the aqueous one was washed with EtOAc (3×). The combine organic phases were dried over $MgSO_4$ and condensed *in vacuo.* The resulting mixture was rapidly purified with silica gel column chromatography (35% EtOAc/hexanes with 2% AcOH, R_f = 0.35 (strikes), TLC stained with CAM) to yield the two diastereoisomeric acids **9** as a thick yellowish oil which was directly subjected to the next step.

Allyl-3-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-hydroxypropanoate (10). To a solution of **9** (2.0 g, 6.61 mmol) in DMF (14 mL) were added K_2CO_3 (1.37 g, 9.91 mmol), tetrabutylammonium iodide (0.487 g, 1.32 mmol) and allyl bromide (2.28 mL, 36.4 mmol) dropwise. The reaction was stirred for 2 hours 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 mixture was purified with silica gel column chromatography (5% EtOAc/hexanes, R_f = 0.22, TLC stained with CAM) to yield compound **10** (1.45 g, 75% over two steps) as a yellowish oil; IR (NaCl) ν 3485, 2930, 2857, 1736, 1256, 1092, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 0.04–0.08 (m, 6H), 0.88–0.90 (m, 9H), 0.94–1.06 (m, 1H), 1.15–1.37 (m, 4H), 1.40–1.49 (m, 1H), 1.50–1.68 (m, 3H), 1.69–1.77 (m, 1H), 1.88 (ddt, J = 9.7, 4.3, 1.6 Hz, 1H), 1.91–1.99 (m, 1H), 2.04 (ddd, J = 14.2, 11.1, 3.4 Hz, 1H), 2.18 (dt, J = 14.0, 4.8 Hz, 0.25H), 2.92 (d, J = 6.2 Hz, 1H), 3.09 (d, J = 6.2 Hz, 0.2H), 3.22 (td, J = 9.6, 4.0 Hz, 1H), 3.25–3.28 (m, 0.1H), 4.24 (ddd, J = 11.0, 6.1, 3.1 Hz, 1H), 4.33 (q, J = 6.0 Hz, 0.25H), 4.63–4.74 (m, 2H), 5.16–5.39 (m, 2H), 5.92 (ddt, J = 17.2, 10.5, 5.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.6, −4.5, −4.0, −3.9, 0.0, 18.1, 24.7, 25.3, 25.4, 25.9, 25.9, 30.2, 35.8, 37.7, 38.3, 41.4, 42.2, 65.9, 65.9, 68.7, 70.4, 75.8, 118.8, 119.0, 131.6, 175.5; HRMS (ESI) calculated for $C_{18}H_{35}O_4Si^+$ $(M + H)^+$: 343.2291; Found: 343.2293.

Allyl 2-(benzyloxy)-3-(2-(*tert*-butyldimethylsilyl)oxy)cyclohexyl-propanoate (11). To a solution of **10** (1.728 g, 5.04 mmol) in a two-neck flask with dry THF (15 mL) under N_2 were added Bu_4NI (0.186 g, 0.503 mmol) and benzyl bromide (1.2 mL, 10.08 mmol). The mixture was brought to 0 °C and 60% NaH in oil (0.295 g, 6.05 mmol) was slowly added. The reaction was stirred at 0 °C for 1 hour and then brought to reflux and stirred for 16 hours. The mixture was then quenched with saturated NH_4Cl_{aq}, and diluted with water and Et_2O. The organic phase was separated and the aqueous one was washed with Et_2O (3×). The combined organic phase was dried over $MgSO_4$ and condensed *in vacuo.* The residue was purified by silica gel column chromatography (0 to 5% EtOAc/hexanes, R_f = 0.44 at 5% EtOAc/hexanes, TLC stained with CAM) to yield the two diastereoisomers of compound **11** (2.03 g, dr: 3 : 2, 93%) as a colorless thick oil; IR (NaCl) ν 2929, 2856, 1750, 1256, 1091, 835, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03–0.10 (m, 6H), 0.83–0.90 (m, 9H), 0.94–1.40 (m, 3H), 1.41–1.74 (m, 4.5H), 1.78–1.94 (m, 1.5H), 2.15–2.23 (m, 0.45H), 2.29 (ddd, J = 13.6, 10.3, 3.2 Hz, 0.55H), 3.15–3.27 (m, 1H), 4.03 (dd, J = 10.3, 3.6 Hz, 0.56H), 4.11 (dd, J = 7.7, 5.2 Hz, 0.4H), 4.37, 4.73 (ABq, J_{AB} = 11.8 Hz, 1.1H), 4.43, 4.67 (ABq, J_{Ab} = 11.6 Hz, 0.8H), 4.64 (m, 2H), 5.12–5.22 (m, 0.26H), 5.25 (ddt, J = 10.4, 2.0, 1.2 Hz, 0.8H), 5.30–5.38 (m, 0.8H), 5.86–5.98 (m, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.6, −4.0, −4.0, 18.0, 18.1, 24.6, 24.7, 25.0, 25.4, 25.9, 26.0, 29.2, 31.3, 35.6, 35.6, 35.9, 36.3, 40.9, 42.6, 65.2, 65.3, 71.9, 72.3, 75.4, 75.7, 75.8, 78.4, 118.5, 118.7, 127.7, 128.0, 128.1, 128.3, 131.9, 137.7, 172.8, 173.3; HRMS (ESI) calculated for $C_{25}H_{41}O_4Si^+$ $(M + H)^+$: 433.2768; Found: 433.2760.

3α-(Benzyloxy)octahydro-2*H*-chromen-2-one (12 and 13). To a solution of **11** (2.0 g, 4.62 mmol) in dry THF (20 mL) at 0 °C under N_2 was added dropwise excess 70% HF in pyridine (1 mL, 38 mmol). The reaction was brought to room temperature over 1 hour and stirred for an additional 15 hours and was quenched slowly with saturated aqueous $NaHCO_3$. The mixture of the two diastereoisomers was purified for the first time by silica gel flash chromatography at 10% EtOAc to obtain a white solid residue (1.083 g, 90%) and the second time using a Biotage Isolera 1 with a Teledyne Isco 80 g RediSepRf column at 25 mL min^{-1} using a linear gradient of 0 to 10% EtOAc/hexanes to obtain pure fractions of the two

diastereoisomers **12** (R_f = 0.5 at 20% EtOAc/hexanes), **13** (R_f = 0.45 at 20% EtOAc/hexanes) and mixed fractions.

12: white solid; mp: 77.8–81.6 °C; IR (NaCl) ν 2936, 2863, 1739, 1451, 1022, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 1.14 (tdd, J = 12.8, 11.3, 3.1 Hz, 1H), 1.19–1.35 (m, 3H), 1.36–1.46 (m, 1H), 1.54–1.64 (m, 1H), 1.66–1.73 (m, 2H), 1.79–1.88 (m, 2H), 2.12 (ddtd, J = 11.9, 4.2, 3.0, 1.5 Hz, 1H), 2.19 (ddd, J = 13.2, 6.9, 4.5 Hz, 1H), 4.01 (dd, J = 8.7, 6.8 Hz, 1H), 4.06 (ddd, J = 11.3, 11.3, 4.3 Hz, 1H), 4.71, 4.96 (ABq, J_{AB} = 11.9 Hz, 2H), 7.30–7.33 (m, 1H), 7.35–7.40 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.0, 25.0, 31.0, 32.0, 34.8, 38.8, 72.8, 74.1, 83.2, 127.9, 128.0, 128.4, 137.5, 171.3; HRMS (ESI) calculated for $C_{16}H_{21}O_3^+$ $(M + H)^+$: 261.1485; Found 261.1490.

13: white solid; mp: 116.1–120.5 °C; IR (NaCl) ν 2932, 2881, 1729, 1136, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (tdd, J = 12.7, 11.5, 3.5 Hz, 1H), 1.17–1.33 (m, 2H), 1.43 (tdd, J = 12.2, 10.9, 3.7 Hz, 1H), 1.63–1.92 (m, 4H), 2.03 (dt, J = 13.4, 7.8 Hz, 1H), 2.08–2.17 (m, 1H), 3.89 (ddd, J = 10.7, 10.7, 4.4 Hz, 1H), 4.10 (dd, J = 8.6, 7.7 Hz, 1H), 4.61, 4.95(ABq, J_{AB} = 12.0 Hz, 2H) 7.27–7.40 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.9, 24.9, 31.5, 31.9, 33.2, 36.9, 71.5, 72.3, 81.0, 127.9, 128.0, 128.5, 128.5, 137.5, 171.8; HRMS (ESI) calculated for $C_{16}H_{21}O_3^+$ $(M + H)^+$: 261.1485; Found 261.1498.

3-(Benzyloxy)octahydro-2*H*-chromen-2-y-acetate (2(OAc)). From lactone **12** (0.280 g, 1.079 mmol) using the method used for **1(OAc)**, the residue was purified by silica gel column chromatography (20% Et_2O/hexanes, R_f = 0.28, TLC stained with CAM) to yield a diastereoisomeric mixture of **2(OAc)** (14α : 86β, 0.297 g, 90%) as a white solid; mp: 57.4–64.6 °C; IR (NaCl): ν 2930, 2861, 1756, 1453, 1368, 1226, 1041, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98–1.08 (m, 1H), 1.13–1.36 (m, 5H), 1.63–1.68 (m, 2H), 1.75–1.89 (m, 1H), 1.94–1.99 (m, 1H), 2.09–2.13 (m, 1H), 2.12 (s, 2.4H), 2.17 (s, 0.29H), 3.14 (ddd, J = 10.5, 9.0, 4.1 Hz, 085H), 3.38 (ddd, J = 10.6, 4.1 Hz, 0.15H), 3.44 (ddd, J = 10.8, 8.0, 5.1 Hz, 0.84H), 3.62 (ddd, J = 11.8, 4.8, 3.3 Hz, 0.15H), 4.54, 4.62 (ABq, J_{AB} = 12.0 Hz, 0.23H), 4.62, 4.65 (ABq, J_{AB} = 15 Hz, 1.76H), 5.60 (d, J = 8.0 Hz, 0.86H), 6.34 (d, J = 3.4, 0.13H), 7.27–7.37 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 24.5, 24.9, 25.2, 25.3, 30.9, 31.3, 31.5, 31.5, 31.5, 31.6, 36.0, 40.4, 40.6, 70.9, 72.0, 74.1, 74.6, 75.7, 79.9, 90.2, 96.2, 127.5, 127.6, 127.7, 127.7, 128.4, 128.4, 138.4, 169.5; HRMS (ESI) calculated for $C_{18}H_{24}O_4Na^+$ $(M + Na)^+$: 327.1566; Found: 327.1559.

Characteristic peaks of the minor **α-2(OAc)** anomer: ^1H NMR (500 MHz, $CDCl_3$) δ (s, 0.29H), 3.38 (ddd, J = 10.6, 4.1 Hz, 0.15H), 3.62 (ddd, J = 11.8, 4.8, 3.3 Hz, 0.15H), 6.34 (d, J = 3.4, 0.13H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.9, 25.3, 31.3, 31.5, 31.6, 40.6, 70.9, 74.1, 74.6, 79.9, 90.2, 127.7, 127.7, 128.4, 138.0.

3α-(Benzyloxy)octahydro-2*H*-chromen-2-yl-β-acetate (β-3(OAc)). The same one-pot method described for **1(OAc)** starting with lactone **13** (0.1 g, 0.387 mmol) was used. Purification by silica gel column chromatography (10% EtOAc/hexanes, R_f = 0.22, TLC stained with CAM) yields only the β-anomer of **3(OAc)** (0.113 g, 96%) as a colorless oil; IR (NaCl) ν 2931, 2857, 1756, 1451, 1354, 1229, 1043, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (tdd, J = 13.1, 3.9 Hz, 1H), 1.18–1.33 (m, 3H), 1.47 (tdd, J = 12.5, 12.0, 3.7 Hz, 1H), 1.57–1.74 (m, 2H), 1.76–1.82 (m 1H), 1.90–2.00 (m, 2H), 2.10 (s, 2H), 3.17 (ddd, J = 11.0, 9.8, 4.1 Hz, 1H), 3.59–3.61 (m, 1H), 4.65, 4.70 (ABq, J_{AB} = 12.6 Hz, 3H), 5.63 (d, J = 1.4 Hz, 1H), 7.24–7.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 24.6, 25.5, 30.9, 31.7, 34.1, 35.1, 71.9, 72.1, 81.0, 94.8, 127.6, 127.8, 128.2, 138.5, 169.3; HRMS (ESI) calculated for $C_{18}H_{24}O_4Na^+$ $(M + Na)^+$: 327.1566; Found: 327.1555.

3α-(Benzyloxy)octahydro-2*H*-chromen-2-yl-α-acetate (α-3(OAc)). Using the previously described acetylation procedure, acetylation of lactol **15** (0.260 g, 1.00 mmol) provided after silica gel column chromatography (10% EtOAc/hexanes, R_f = 0.34, TLC stained with CAM) the **α-3(OAc)** anomer (0.284 g, 0.933 mmol, 93%) as a colorless oil; IR (NaCl): ν 2930, 2857, 1752, 1451, 1370, 1233, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (qd, J = 12.5, 12.4, 3.7 Hz, 1H), 1.21–1.44 (m, 3H), 1.47–1.69 (m, 3H), 1.70–1.88 (m, 4H), 2.08 (s, 3H), 3.40–3.50 (m, 2H), 4.59, 4.68 (ABq, J_{AB} = 12.3 Hz, 2H), 6.15 (d, J = 1.4 Hz, 1H), 7.25–7.39 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 25.0, 25.6, 30.6, 31.5, 31.8, 35.1, 71.0, 72.3, 75.6, 92.0, 127.6, 127.7, 128.4, 138.2, 169.5; HRMS (ESI) calculated for $C_{18}H_{25}O_4^+$ $(M + H)^+$: 305.1747; Found: 305.1744.

3α-(Benzyloxy)-2-(phenylthio)octahydro-2*H*-chromene (3(SPh)). Using the same protocol as for **1(SPh)**, **3(OAc)** (0.1 g, 0.328 mmol) was converted into **3(SPh)** (0.075 g, 90α : 10β, 0.032 g β-only, 95%) and **2(OAc)** (0.1 g, 0.328 mmol) was converted to **2(SPh)** (0.109 g, 60α : 40β, 94%). Both compounds were purified by silica gel column chromatography (10% Et_2O/hexanes, R_f = α-**3(SPh)**: 0.37; β-**3(SPh)**: 0.3; R_f **2(SPh)**: 0.55 at 10% EtOAc/hexanes, TLC stained with CAM).

2(SPh): mp: 87.0–102.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97–1.08 (m, 0.55H), 1.12–1.43 (m, 5H), 1.49–1.60 (m, 1H), 1.61–1.71 (m, 2H), 1.82 (dddd, J = 13.2, 8.4, 4.7, 1.9 Hz, 1.6H), 1.89 (dddd, J = 12.6, 4.6, 3.5, 1.3 Hz, 0.6H), 1.95–2.03 (m, 0.45H), 2.15–2.22 (m, 0.42H), 3.01 (ddd, J = 10.9, 9.1, 4.1 Hz, 0.4H), 3.40 (ddd, J = 10.4, 9.4, 4.9 Hz, 0.4H), 3.81–3.90 (m, 1.2H), 4.63 (ABq, J = 11.5 Hz, 1.2H), 4.66 (Abq, J = 5.0 Hz, 0.8H), 4.71 (d, J = 9.5 Hz, 0.4H), 7.21–7.42 (m, 8H), 7.52–7.59 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7, 25.0, 25.2, 25.4, 31.2, 31.3, 31.5, 31.9, 33.3, 37.7, 40.5, 40.9, 70.3, 72.0, 73.2, 75.1, 75.7, 82.3, 88.4, 89.2, 126.6, 126.9, 127.7, 127.7, 127.8, 127.9, 128.3, 128.4, 128.7, 128.8, 131.4, 131.4, 134.6, 135.5, 138.0, 138.3; HRMS (ESI) calculated for $C_{22}H_{27}O_2S^+$ $(M + H)^+$: 355.1726; Found: 355.1721.

3(SPh): (90α : 10β); ^1H NMR (500 MHz, $CDCl_3$) δ 1.01–1.12 (m, 1H), 1.22–1.51 (m, 4H), 1.53–1.72 (m, 3H), 1.77–1.91 (m, 4H), 3.08 (ddd, J = 11.1, 9.8, 4.1 Hz, 0.1), 3.77 (ddd, J = 2.8, 1.1 Hz, 0.9H), 3.79–3.80 (m, 0.1), 3.84 (ddd, J = 10.5, 10.4, 3.9 Hz, 0.9H), 4.55, 4.65 (ABq, J_{AB} = 12.2 Hz, 1.8H), 4.61, 4.75 (ABq, J_{AB} = 12.1 Hz, 0.2H), 4.87 (d, J = 1.5 Hz, 0.1H), 5.64 (s, 0.9H), 7.21–7.41 (m, 8H), 7.45–7.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.1, 25.6, 25.7, 31.3, 31.5, 31.7, 31.9, 32.0, 35.9, 70.7, 74.2, 75.2, 82.9, 86.5, 126.6, 126.8, 127.6, 127.6, 128.0, 128.2, 128.4, 128.7, 128.9, 130.3, 130.8, 135.5, 138.2; HRMS

(ESI) calculated for $C_{22}H_{27}O_2S^+$ $(M + H)^+$: 355.1726; Found: 355.1709.

β-3(SPh): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81–0.99 (m, 1H), 1.25 (q, J = 14.7, 12.5 Hz, 4H), 1.47–1.86 (m, 3H), 1.89–2.01 (m, 1H), 2.05 (dt, J = 13.9, 3.3 Hz, 1H), 3.06 (td, J = 10.4, 4.1 Hz, 1H), 3.74–3.81 (m, 1H), 4.60, 4.74 (ABq, J = 12.1, 4.86 Hz) (d, J = 1.6 Hz, 1H), 7.16–7.23 (m, 1H), 7.26 (s, 1H), 7.33–7.39 (m, 2H), 7.44–7.52 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.6, 31.3, 32.0, 34.5, 35.0, 71.5, 75.3, 82.9, 89.0, 126.5, 127.6, 128.0, 128.2, 128.7, 130.3, 136.6, 138.2; HRMS (ESI) calculated for $C_{22}H_{27}O_2S^+$ $(M + H)^+$: 355.1726; Found: 355.1717.

3α-(Benzyloxy)octahydro-2*H*-chromen-2-ol (15). In a solution of **13** (0.1 g, 0.387 mmol) in dry THF under N_2 at −78 °C was added 1 M DiBAl-H in hexanes (0.464 mL, 0.464 mmol). The mixture was stirred for 1.5 hours at −78 °C and quenched at −78 °C with a saturated aqueous solution of sodium potassium tartrate. After 1 hour of stirring at ambient temperature, the organic phase was separated and the aqueous phase was washed with EtOAc (3×). The combined organic phases were dried over $MgSO_4$ and condensed *in vacuo*. The residue was purified by silica gel column chromatography (30% EtOAc/hexanes, R_f = 0.48, TLC stained with CAM) to yield a mixture of **15** (0.091 g, 90%, 80α : 20β) as a white solid; mp: 83.1–89.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–1.06 (m, 1H), 1.17–1.47 (m, 3H), 1.50–1.86 (m, 6.6H), 1.90–1.99 (m, 0.2H), 2.05 (dt, J = 14.3, 3.2 Hz, 0.2H), 3.06 (ddd, J = 11.0, 9.9, 4.2 Hz, 0.2H), 3.35 (d, J = 3.1 Hz, 0.8H), 3.48 (td, J = 2.7, 1.4 Hz, 0.2H), 3.53–3.55 (m, 0.2H), 3.62 (td, J = 10.5, 3.8 Hz, 0.8H), 3.97 (d, J = 12.1 Hz, 0.8H), 4.49, 7.73 (Abq, J_{AB} = 11.9 Hz, 0.4H), 4.56, 4.62 (d, J_{AB} = 12.4 Hz, 1.4H), 4.66 (dd, J = 12.1, 1.8 Hz, 0.2H), 5.18 (dd, J = 3.1, 1.5 Hz, 0.8H), 7.24–7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7, 25.1, 25.6, 25.7, 29.6, 30.9, 31.5, 31.9, 33.0, 34.9, 35.5, 70.8, 71.2, 73.1, 73.6, 74.3, 79.6, 92.6, 94.6, 127.6, 127.6, 127.9, 127.9, 128.3, 128.5, 137.8, 138.4; HRMS (ESI) calculated for $C_{16}H_{22}O_3Na^+$ $(M + Na)^+$:285.1461; Found: 285.1457.

3β-(Benzyloxy)octahydro-2*H*-chromen-2-ol (14). Using the same protocol as for **15** on lactone **12** (0.1 g, 0.387 mmol) and purified by silica gel column chromatography (30% EtOAc/hexanes, R_f = 0.48, TLC stained with CAM), a mixture of **14** (0.98 g, 97%, 35α : 65β) was isolated as a white solid; mp: 76.6–83.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–1.42 (m, 6H), 1.46–1.70 (m, 2.5H), 1.72–1.90 (m, 2H), 1.90–1.97 (m, 0.65H), 2.00–2.08 (m, 0.65H), 3.03 (ddd, J = 10.7, 9.1, 4.1 Hz, 0.6H), 3.14 (br s, 0.35H), 3.24 (ddd, J = 10.7, 7.4, 4.9 Hz, 0.6H), 3.51–3.60 (m, 0.8H), 3.67 (br s, 0.5H), 4.57, 4.62 (ABq, J_{AB} = 12.0 Hz, 0.8H), 4.65 (m, 0.65H), 4.67, 4.76 (ABq, J_{AB} = 12.0 Hz, 1.2H), 5.20–5.47 (m, 0.35H), 7.25–7.37 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.6, 24.9, 25.3, 25.4, 30.5, 30.9, 31.4, 31.6, 31.7, 35.9, 40.5, 40.6, 70.4, 72.0, 72.2, 75.1, 76.7, 77.0, 77.4, 78.1, 79.2, 91.2, 99.0, 127.6, 127.7, 127.8, 127.8, 128.4, 128.5, 138.0, 138.6; HRMS (ESI) calculated for $C_{16}H_{22}O_3Na^+$ $(M + Na)^+$:285.1461; Found: 285.1457.

3β-(Benzyloxy)octahydro-2*H*-chromen-2-yl-2,2,2-trichloroacetimidate (2(TAC)). In a solution of **14** (0.1 g, 0.385 mmol) in dry DCM (3.5 mL) under N_2 were added trichloroacetonitrile (0.156 mL, 1.54 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.077 mmol, 0.015 mL). The reaction was stirred for 3 hours at ambient temperature. After completion, the mixture was condensed and purified by silica gel column chromatography (10% EtOAc/hexanes, 3% Et_3N, R_f = 0.40, TLC stained with CAM) to yield **2(TAC)** (0.138 g, 88%, 45α : 55β) as a colorless oil; IR (NaCl): ν 3341, 2932, 2861, 1669, 1295, 1057, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.43 (m, 6H), 1.61–1.75 (m, 3H), 1.76–1.84 (m, 1H), 1.84–1.94 (m, 1H), 1.96–2.03 (m, 0.5H), 2.11 (dd, J = 9.3, 5.1 Hz, 0.5H), 3.13–3.24 (m, 0.55H), 3.50 (td, J = 10.4, 4.0 Hz, 0.45H), 3.55–3.62 (m, 0.55H), 3.72 (ddd, J = 11.8, 4.8, 3.2 Hz, 0.45H), 4.58, 4.66 (ABq, J_{AB} = 11.9 Hz, 1.1H), 4.67, 4.78 (d, J = 11.9 Hz, 0.9H), 5.75 (d, J = 7.9 Hz, 0.55H), 6.47 (d, J = 3.1 Hz, 0.45H), 7.25–7.38 (m, 5H), 8.52 (s, 0.45H), 8.63 (s, 0.55H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.5, 24.9, 25.2, 25.3, 30.9, 31.3, 31.5, 31.5, 31.5, 36.3, 40.2, 40.5, 70.6, 72.4, 74.5, 75.1, 75.6, 80.0, 94.6, 100.7, 127.5, 127.6, 127.7, 128.3, 128.4, 138.2, 138.4, 161.5, 161.6; HRMS (ESI) calculated for $C_{18}H_{23}Cl_3NO_3^+$ $(M + H)^+$: 406.0738; Found: 406.0729.

3α-(Benzyloxy)octahydro-2*H*-chromen-2-yl-2,2,2-trichloroacetimidate (3(TAC)). In a solution of **14** (0.08 g, 0.308 mmol) in dry DCM (3 mL) under N_2 were added trichloroacetonitrile (0.123 mL, 1.23 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.061 mmol, 0.012 mL). The reaction was stirred for 3 hours at ambient temperature. After completion, the mixture was condensed and purified by silica gel column chromatography (10% EtOAc/hexanes, 3% Et_3N, R_f = 0.38, TLC stained with CAM) to yield **3(TAC)** (0.100 g, 80%, 91α : 9β) as a colorless oil; IR (NaCl): ν 3341, 2931, 2858, 1285, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–1.09 (m, 1H), 1.21–1.47 (m, 3H), 1.56–1.72 (m, 3H), 1.75–1.94 (m, 4H), 3.40 (td, J = 10.6, 4.0 Hz, 0.08H), 3.57 (td, J = 10.5, 4.1 Hz, 0.92H), 3.65 (td, J = 2.7, 1.6 Hz, 1H), 4.63, 4.71 (ABq, J_{AB} = 12.2 Hz, 2H), 5.60 (s, 0.08H), 6.29 (s, 0.92H), 7.27 –7.41 (m, 5H), 8.50 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 25.0, 25.4, 25.6, 30.1, 30.7, 31.3, 31.5, 31.6, 31.7, 34.9, 35.1, 71.1, 71.3, 72.0, 72.4, 75.9, 76.0, 96.1, 96.9, 127.6, 127.6, 127.7, 127.9, 128.4, 128.5, 137.7, 138.2, 159.5, 160.7; HRMS (ESI) calculated for $C_{18}H_{23}Cl_3NO_3^+$ $(M + H)^+$: 406.0738; Found: 406.0745.

Glycosylation of donors 1

2-Allyloctahydro-2*H*-chromene (1(allyl)). From **1(OAc)** (0.055 g, 0.277 mmol) using general procedure A, only pure **α-1(allyl)** (0.044 g, 86%) was obtained without purification. The lower yield can be explained by the compound volatility; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 0.99 (qd, J = 12.8, 11.7, 3.5 Hz, 1H), 1.14–1.40 (m, 5H), 1.47–1.53 (m, 1H), 1.54–1.68 (m, 3H), 1.72–1.80 (m, 2H), 1.86 (tdd, J = 13.5, 5.8, 4.4 Hz, 1H), 2.26–2.34 (m, 1H), 2.60 (dddt, J = 14.3, 8.0, 6.6, 1.4 Hz, 1H), 3.17 (ddd, J = 10.1, 3.7 Hz, 1H), 3.98 (ddt, J = 7.0 Hz, 1H), 5.04 (dt, J = 2.2, 1.2 Hz, 0.5H), 5.05–5.08 (m, 1H), 5.10 (dt, J = 2.1, 1.5 Hz, 0.5H), 5.81 (dddd, J = 16.9, 10.2, 7.4, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS) δ 25.2, 25.6, 25.9, 28.0, 31.8, 32.8, 35.0, 42.3, 72.8, 73.6, 116.4, 135.7; HRMS (ESI) calculated for $C_{12}H_{21}O^+$ $(M + H)^+$: 181.1586; Found: 181.1593.

2-(2,2,2-Trifluoroethoxy)octahydro-2*H*-chromene (1(TFE)). From **4(SPh)** (0.032 g, 0.128 mmol) using general procedure B

in DCM, only α-**1(TFE)** (0.011 g, 36%) could be obtained by flash column chromatography (2% EtOAc/pentanes, 2% Et_3N, R_f = 0.4 at 5% EtOAc/hexanes, TLC stained with CAM) as a colorless oil. The low yield can be attributed to the compound's low stability towards silica gel and its volatility. Crude ^{1}H NMR showed a 90α : 10β ratio and the complete conversion of the starting material to the desired product; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.01 (qd, J = 12.6, 12.37, 3.3 Hz, 1H), 1.16–1.37 (m, 4H), 1.42–1.54 (m, 2H), 1.54–1.71 (m, 1H), 1.71–1.93 (m, 5H), 3.33 (ddd, J = 10.3, 10.3, 3.6 Hz, 1H), 3.80–4.01 (m, 2H), 4.90 (d, J = 2.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 25.0, 25.7, 29.9, 31.6, 32.1, 41.3, 63.1, 63.5, 63.8, 64.2, 73.5, 97.8, 122.8, 125.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.18 (t, J = 9.0 Hz); HRMS: because of the compound's low stability towards any kind of ionisation source available, the only molecular ion that could be observed was $(M–TFE)^+$ calculated for 139.1100; Found 139.1116.

2-(2-Chloroethoxy)octahydro-2*H*-chromene (1(ClEtOH)). From **1(SPh)** (0.02 g, 0.0805 mmol) using general procedure B in DCM, crude ^{1}H NMR showed a 60α : 40β ratio of **1(ClEtO)** which was purified by flash column chromatography (10% Et_2O/hexanes, 2% Et_3N, R_f = 0.37 at 10% Et_2O/hexanes, TLC stained with CAM) to yield a mixture of α : β-**1(ClEtO)** as a colorless oil (0.017 g, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–1.09 (m, 1H), 1.09–1.40 (m, 4H), 1.41–1.68 (m, 4H), 1.69–1.93 (m, 4H), 2.97 (ddd, J = 11.0, 9.1, 4.1 Hz, 0.35H), 3.39 (td, J = 10.1, 3.6 Hz, 0.65H), 3.62–3.78 (m, 3H), 3.84–3.96 (m, 0.65H), 4.10 (ddd, J = 11.0, 6.0, 5.2 Hz, 0.35H), 4.46 (dd, J = 9.7, 2.3 Hz, 0.35H), 4.86 (dd, J = 3.3, 1.6 Hz, 0.65H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 25.1, 25.1, 25.6, 25.8, 29.5, 30.3, 31.1, 31.7, 32.2, 32.2, 40.9, 41.5, 42.9, 43.2, 67.1, 68.8, 73.1, 79.6, 97.6, 102.5; HRMS (ESI) calculated for $C_{11}H_{19}ClO_2Na$ $(M + Na)^+$: 241.0965; Found: 241.0976.

2-Ethoxyoctahydro-2*H*-chromene (1(EtO)). From **1**(SPh) (0.06 g, 0.241 mmol) using general procedure B in DCM, crude ^{1}H NMR showed a 45α : 55β ratio of **1(EtOH)** which was purified by silica gel column chromatography (5% EtOAc/hexanes, 3% Et_3N, R_f = 0.4 at 15% EtOAc/hexanes, TLC stained with CAM) to yield a pure mixture (70α : 30β) of **1(EtOH)** as a colorless oil (0.027 g, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–1.06 (m, 1H), 1.12–1.31 (m, 7H), 1.32–1.57 (m, 2H), 1.57–1.66 (m, 1H), 1.67–1.84 (m, 3H), 1.87 (ddt, J = 11.2, 3.8, 2.1 Hz, 1H), 2.95 (ddd, J = 11.0, 9.0, 4.1 Hz, 0.7H), 3.35 (td, J = 10.1, 3.7 Hz, 0.3H), 3.39–3.55 (m, 1H), 3.71 (dq, J = 9.8, 7.1 Hz, 0.3H), 3.94 (dq, J = 9.5, 7.1 Hz, 0.7H), 4.40 (dd, J = 9.7, 2.2 Hz, 0.7H), 4.81 (dd, J = 2.4 Hz, 0.3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.2, 15.2, 24.8, 25.2, 25.3, 25.7, 25.8, 29.7, 30.6, 31.2, 31.7, 32.0, 32.2, 32.2, 41.0, 41.7, 62.1, 64.0, 72.6, 79.4, 96.9, 101.9; HRMS (ESI) calculated for $C_{11}H_{21}O_2^+$ $(M + H)^+$: 185.1536; Found: 185.1532.

Glycosylation reactions on C_2-substituted donors

2-Allyl-3β-(benzyloxy)octahydro-2*H*-chromene (2(allyl)). Using general procedure A from **2(OAc)** (0.030, 00 985 mmol, 14α : 86β), pure α-**2(allyl)** was obtained without purification as a colorless oil (0.027 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.14 (m, 1H), 1.14–1.41 (m, 5H), 1.58–1.68 (m, 2H), 1.76–1.83 (m, 2H), 1.86 (dt, J = 12.3, 4.0 Hz, 1H), 2.36 (dddt, J = 15.1, 5.1, 3.7, 1.3 Hz, 1H), 2.58–2.66 (m, 1H), 3.10 (td, J = 10.2, 3.9 Hz, 1H), 3.77 (dddd, J = 11.4, 5.5, 4.6, 0.8 Hz, 1H), 4.14 (dt, J = 10.5, 4.5 Hz, 1H), 4.53, 4.57 (ABq, J_{AB} = 15 Hz, 2H), 5.07–5.16 (m, 2H), 5.79–6.02 (m, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.1, 25.5, 28.9, 31.5, 31.9, 32.1, 41.5, 70.6, 72.4, 74.6, 75.6, 116.4, 127.5, 127.6, 128.4, 135.6, 138.6; HRMS (ESI) calculated for $C_{19}H_{26}O_2^+$ $(M + H)^+$: 287.2005; Found: 287.1991.

3β-(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromene (2(TFE)). Using general procedure B in DCM from **2(SPh)** (0.05 g, 0.141 mmol, 60α : 40β) gave after column chromatography (5% EtOAc/hexanes R_f = 0.51(α) and 0.57(β) at 10% EtOAc/hexanes, stained with CAM) pure α (38 mg) and β (7.0 mg) isomers of **2(TFE)** (0.045 g, 93%) isolated and characterised separately. The ^{1}H NMR study on the crude product before purification showed a 83α : 17β ratio of isomers.

α-**2(TFE)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.37 (m, 5H), 1.56–1.70 (m, 3H), 1.74–1.87 (m, 3H), 3.30 (td, J = 10.4, 3.9 Hz, 1H), 3.57 (ddd, J = 11.9, 4.8, 3.4 Hz, 1H), 3.86–4.06 (m, 2H), 4.57, 4.62 (ABq, J_{AB} = 12.1 Hz, 2H), 4.91 (d, J = 3.3 Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 25.3, 30.8, 31.2, 31.4, 40.8, 63.6, 64.0, 64.3, 64.7, 70.6, 72.9, 75.0, 97.5, 122.7, 125.4, 127.7, 127.7, 128.4, 138.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.66 (t, J = 8.9 Hz); HRMS (ESI): calculated for $C_{18}H_{23}F_3O_3Na^+$ $(M + Na)^+$: 367.1491; Found: 367.1476.

β-**2(TFE)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91–1.05 (m, 1H), 1.11–1.40 (m, 4H), 1.59–1.69 (m, 2H), 1.76–1.84 (m, 1H), 1.87–1.96 (m, 1H), 1.98–2.04 (m, 1H), 2.96 (td, J = 9.5, 4.0 Hz, 1H), 3.31 (ddd, J = 11.0, 7.5, 5.3 Hz, 1H), 3.97 (dq, J = 12.3, 8.6 Hz, 1H), 4.21 (dq, J = 12.3, 8.8 Hz, 1H), 4.44 (d, J = 7.5 Hz, 1H), 4.63, 4.82 (ABq, J_{AB} = 11.7 Hz, 2H), 7.25–7.37 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6, 25.2, 30.8, 31.5, 36.4, 40.5, 65.3, 65.6, 65.8, 66.1, 72.8, 76.1, 79.2, 105.7, 127.5, 127.9, 128.3, 138.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 74.17 (t, J = 8.9 Hz); HRMS (ESI): calculated for $C_{18}H_{23}F_3O_3Na^+$ $(M + Na)^+$: 367.1491; Found: 367.1471.

3β-(Benzyloxy)-2-(2-chloroethoxy)octahydro-2*H*-chromene (2(ClEtO)). Using general procedure B in DCM from **2(SPh)** (0.02 g, 0.0564 mmol, 60α : 40β), crude ^{1}H NMR showed a 63α : 34β ratio of anomers. After column chromatography (10% Et_2O/hexanes R_f = 0.18(α) and 0.30(β) at 10% EtOAc/hexanes), a mixture of α/β-**2(ClEtO)** (0.017 g, 93%, 65α : 35β) was isolated and characterised together as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94–1.39 (m, 6H), 1.60–1.70 (m, 2.1H), 1.75–1.86 (m, 2.1H), 1.90–1.96 (m, 0.4H), 2.01 (dd, J = 9.4, 5.1 Hz, 0.4H), 2.96 (ddd, J = 10.7, 8.9, 4.1 Hz, 0.4H), 3.28–3.34 (m, 0.4H), 3.39 (td, J = 10.8, 3.9 Hz, 0.6H), 3.55 (ddd, J = 11.9, 4.7, 3.4 Hz, 0.6H), 3.69–3.74 (m, 2H), 3.75–3.86 (m, 1H), 3.92 (dt, J = 10.9, 6.2 Hz, 0.6H), 4.16 (dt, J = 10.9, 5.5 Hz, 0.4H), 4.40 (d, J = 7.5 Hz, 0.35H), 4.58, 4.65 (ABq, J_{AB} = 12.3 Hz, 1.2H), 4.68, 4.88 (ABq, J_{AB} = 11.9 Hz, 0.8H), 4.86 (s, 0.65H), 7.24–7.40 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6, 25.0, 25.3, 25.4, 30.9, 31.1, 31.3, 31.5, 31.6, 36.6, 40.6, 41.0, 42.8, 42.9, 67.8, 69.4, 70.6, 72.5, 72.8, 75.3, 76.4, 79.0, 97.4, 105.9, 127.4, 127.7,

127.8, 127.8, 128.3, 128.4, 138.5, 138.9; HRMS (ESI): calculated for $C_{18}H_{25}O_3ClNa^+$ $(M + Na)^+$: 347.1384; Found: 347.1387.

3β-(Benzyloxy)-2-ethoxyoctahydro-2*H*-chromene (2(EtO)). Using general procedure B in DCM from **2(SPh)** (0.02 g, 0.0564 mmol, 60α : 40β), crude ^{1}H NMR showed a 50α : 50β ratio of anomers. After column chromatography (10% Et_2O/hexanes, R_f = 0.23, TLC stained with CAM), a mixture of α/β-**2(EtO)** (0.015 g, 93%, 45α : 55β) was isolated as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93–1.15 (m, 1.5H), 1.15–1.41 (m, 7H), 1.60–1.69 (m, 2H), 1.74–1.85 (m, 1.5H), 1.90–1.96 (m, 0.5H), 1.96–2.02 (m, 0.5H), 2.95 (ddd, J = 10.8, 9.0, 4.0 Hz, 0.55H), 3.26–3.36 (m, 0.88H), 3.51–3.59 (m, 0.7H), 3.62 (dq, J = 9.5, 7.1 Hz, 0.55H), 3.77 (dq, J = 10.0, 7.1 Hz, 0.45H), 4.00 (dq, J = 9.4, 7.1 Hz, 0.55H), 4.36 (d, J = 7.5 Hz, 0.55H), 4.57, 4.64 (ABq, J_{AB} = 12.4 Hz, 0.7H), 4.67, 4.84 (ABq, J_{Ab} = 12.0 Hz, 1.3H), 4.84 (d, J = 0.6 Hz, 1H), 4.85 (s, 0.45H), 7.25–7.38 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2, 15.4, 24.7, 25.0, 25.3, 25.5, 31.0, 31.1, 31.3, 31.6, 31.7, 36.7, 40.7, 41.1, 62.8, 65.0, 70.5, 72.0, 72.7, 75.3, 76.7, 78.8, 96.6, 105.5, 127.4, 127.6, 127.7, 127.7, 128.3, 128.3, 138.6, 139.1; HRMS (ESI): calculated for $C_{18}H_{26}O_3Na^+$ $(M + Na)^+$: 313.1774; Found: 313.1770.

2-Allyl-3α-(benzyloxy)octahydro-2*H*-chromene (3(allyl)). From pure β-**3(OAc)** (0.056 g, 0.184 mmol) using general procedure A, crude ^{1}H NMR showed a 95α : 5β ratio of anomers. After purification by silica gel column chromatography (10% Et_2O/hexanes, R_f = 0.35, TLC stained with CAM), compounds were isolated as colorless oils (0.049 g, 93%). From α-**3(OAc)**, there was 82% yield on a similar scale.

α-**3(Allyl)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (ddd, J = 12.6, 12.5, 3.8 Hz, 1H), 1.19–1.46 (m, 4H), 1.53–1.86 (m, 6H), 2.17–2.28 (m, 1H), 2.52 (dddt, J = 14.3, 7.9, 6.4, 1.5 Hz, 1H), 3.18 (ddd, J = 10.1, 3.7 Hz, 1H), 3.37 (td, J = 2.9, 1.1 Hz, 1H), 4.03 (tt, J = 7.7, 1.3 Hz, 1H), 4.54 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 5.01–5.09 (m, 2H), 5.77 (dddd, J = 16.8, 10.2, 7.5, 6.4 Hz, 1H), 7.24–7.29 (m, 1H), 7.30–7.39 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.2, 25.8, 30.7, 31.6, 32.4, 34.6, 36.0, 70.2, 73.8, 75.2, 116.8, 127.4, 127.6, 128.3, 134.8, 134.8, 138.8; HRMS (ESI) calculated for $C_{19}H_{27}O_2^+$ $(M + H)^+$: 287.2005; Found: 287.1997.

β-**3(Allyl)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–1.00 (m, 1H), 1.15 (ddd, J = 13.8, 12.2, 2.6 Hz, 1H), 1.20–1.35 (m, 3H), 1.42 (dddd, J = 14.6, 12.1, 9.5, 3.9 Hz, 1H), 1.54–1.70 (m, 2H), 1.77–1.92 (m, 2H), 2.05 (dt, J = 13.9, 3.2 Hz, 1H), 2.32–2.50 (m, 2H), 2.97 (ddd, J = 11.0, 9.5, 4.1 Hz, 1H), 3.35–3.42 (m, 2H), 4.43, 4.68 (ABq, J_{AB} = 12.1 Hz, 2H), 4.97–5.06 (m, 2H), 5.73 (dddd, J = 16.8, 10.1, 7.8, 6.4 Hz, 1H), 7.28–7.41 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.1, 25.8, 31.5, 32.2, 33.8, 35.8, 36.2, 70.6, 72.6, 79.7, 82.3, 116.7, 127.5, 128.0, 128.2, 135.2, 138.7; HRMS (ESI) calculated for $C_{19}H_{27}O_2^+$ $(M + H)^+$: 287.2005; Found: 287.2002.

3α-(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromene (3(TFE)). Using general procedure B in DCM from **3(SPh)** (0.06 g, 0.169 mmol, 90α : 10β) gave after column chromatography (10% EtOAc/hexanes R_f = 0.38) a 70α : 30β ratio of **3(TFE)** (0.05 g, 86%) isolated and characterised as a mixture. The ^{1}H NMR study on the crude product before purification showed a 65α : 35β ratio of anomers. A similar result was obtained from pure β-**3(SPh)**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82–1.06 (m, 1H), 1.16–1.45 (m, 3H), 1.46–1.96 (m, 8H), 3.02 (ddd, J = 11.1, 9.8, 4.1 Hz, 0.3H), 3.33 (td, J = 10.6, 3.8 Hz, 0.7H), 3.52 (td, J = 2.7, 1.4 Hz, 0.7H), 3.62 (td, J = 2.8, 1.5 Hz, 0.3H), 3.82–4.05 (m, 1.7H), 4.16–4.31 (m, 0.3H), 4.53 (s, 0.3H), 4.57, 4.61 (ABq, J = 12.3 Hz, 1.4H), 4.71, 7.76 (d, J = 12.9 Hz, 0.6H), 4.85 (s, 0.7H), 7.24–7.43 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7, 25.0, 25.5, 25.6, 30.1, 30.9, 31.4, 31.6, 31.7, 34.9, 35.2, 35.3, 63.5, 64.8, 65.1, 65.4, 65.8, 71.0, 72.4, 72.5, 73.0, 73.8, 80.4, 98.2, 102.5, 122.6, 125.4, 127.4, 127.6, 127.7, 127.8, 128.2, 128.4, 138.2, 138.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.32 (t, J = 8.9 Hz), −74.21 (t, J = 8.8 Hz); HRMS (ESI): calculated for $C_{18}H_{23}F_3O_3Na^+$ $(M + Na)^+$: 367.1491; Found: 367.1479.

3α-(Benzyloxy)-2-(2-chloroethoxy)octahydro-2*H*-chromene (3(ClEtO)). From **3(SPh)** (0.02 g, 0.056 mmol) using general procedure B in DCM, the crude ^{1}H NMR showed a ratio of isomers of 6α : 34β. Purification by silica gel column chromatography (10% Et_2O/hexanes, R_f = 0.23, TLC stained with CAM) yielded **3(ClEtO)** as a colorless oil (0.018 g, 98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–1.03 (m, 1H), 1.15–1.44 (m, 3H), 1.48–1.74 (m, 4H), 1.74–1.83 (m, 2.2H), 1.86–1.93 (m, 0.66H), 3.01 (ddd, J = 11.2, 9.8, 4.1 Hz, 0.33H), 3.40 (td, J = 11.2, 10.8, 3.8 Hz, 0.66H), 3.49 (td, J = 2.8, 1.4 Hz, 0.66H), 3.60 (td, J = 3.0, 1.1 Hz, 0.33H), 3.64–3.68 (m, 1.2H), 3.69–3.76 (m, 1.4H), 3.90–3.97 (m, 0.66H), 4.14–4.24 (m, 0.33H), 4.47 (d, J = 1.2 Hz, 0.26H), 4.58, 4.62 (ABq, J_{AB} = 12.4 Hz, 1.3H), 4.75, 4.83 (ABq, J_{AB} = 13.0 Hz, 0.6H), 4.82 (s, 0.66H), 7.24–7.43 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.8, 25.1, 25.6, 25.7, 30.4, 31.0, 31.5, 35.1, 35.4, 35.4, 43.1, 67.2, 69.1, 70.9, 72.4, 72.8, 73.3, 73.5, 80.1, 98.1, 102.9, 127.3, 127.6, 127.6, 127.8, 128.2, 128.4, 138.4, 139.1; HRMS (ESI): calculated for $C_{18}H_{25}O_3ClNa^+$ $(M + Na)^+$: 347.1384; Found: 347.1395.

3α-(Benzyloxy)-2-ethoxyoctahydro-2*H*-chromene (3(EtO)). From **3(SPh)** (0.02 g, 0.056 mmol) using general procedure B in DCM, the crude ^{1}H NMR showed a ratio of anomers of 50α : 50β. Purification by silica gel column chromatography, (5% Et_2O/hexanes, R_f = 0.48 at 10 EtOAc/hexanes, TLC stained with CAM) yielded **3(EtO)** as a colorless oil (0.011 g, 93%, 50α : 50β); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–1.02 (m, 1H), 1.16–1.43 (m, 3H), 1.21 (t, J = 7.1 Hz, 1.5H), 1.27 (t, J = 7.0 Hz, 1.5H), 1.47–1.71 (m, 4H), 1.73–1.84 (m, 2H), 1.85–1.94 (m, 1H), 3.00 (ddd, J = 11.1, 9.7, 4.1 Hz, 0.5H), 3.37 (td, J = 10.4, 3.9 Hz, 0.5H), 3.44 (td, J = 3.0, 1.5 Hz, 0.5H), 3.45–3.53 (m, 1H), 3.55 (td, J = 3.0, 1.0 Hz, 0.5H), 3.76 (dq, J = 9.8, 7.1 Hz, 0.5H), 4.01 (dq, J = 9.4, 7.1 Hz, 0.5H), 4.41 (d, J = 1.1 Hz, 0.5H), 4.59, 4.62 (ABq, J_{AB} = 1.3 Hz, 1H), 4.73, 4.85 (ABq, J_{AB} = 12.9 Hz, 1H), 7.24–7.44 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1, 15.3, 24.8, 25.2, 25.7, 25.7, 30.5, 31.1, 31.5, 31.9, 35.3, 35.5, 35.6, 62.4, 64.5, 70.8, 72.3, 72.9, 73.2, 73.8, 79.9, 97.5, 102.5, 127.2, 127.5, 127.6, 127.7, 128.1, 128.3, 138.6, 139.4; HRMS (ESI): calculated for $C_{18}H_{27}O_3^+$ $(M + H)^+$: 291.1954; Found: 291.1953.

Glycosylation reactions using trichloroacetamidate (TAC)

3β-(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromene (2(TFE)). From **2(TAC)** (0.065 g, 0.160 mmol, 45α : 55β) using

general procedure A, the crude ^{1}H NMR showed a ratio of anomers of 80α : 20β. Purification by silica gel column chromatography, (10% Et_2O/hexanes, TLC stained with CAM) gave a pure mixture of α : β-**2(TFE)** as a colorless oil (0.043 g, 78%, 65α : 35β). Spectral data are similar to the ones obtained from **2(SPh)**.

3β-(Benzyloxy)-2-ethoxyoctahydro-2*H*-chromene (2(EtO)). From **2(TAC)** (0.03 g, 0.074 mmol, 45α : 55β) using general procedure A, the crude ^{1}H NMR showed a ratio of anomers of 45α : 55β. Purification by silica gel column chromatography, (10% Et_2O/hexanes, TLC stained with CAM) gave a pure mixture of α/β-**2(EtO)** as a colorless oil (0.020 g, 91%, 60α : 40β). Spectral data are similar to the ones obtained from **2(SPh)**.

3α-(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromene (3(TFE)). From **3(TAC)** (0.04 g, 0.04 mmol, 91α : 9β) using general procedure A, the crude ^{1}H NMR showed a ratio of anomers of 82α : 18β. Purification by silica gel column chromatography, (10% Et_2O/hexanes, TLC stained with CAM) gave a pure mixture of α/β-**3(TFE)** as a colorless oil (0.022 g, 76%, 85α : 15β). Spectral data are similar to the ones obtained from **3(SPh)**.

3α-(Benzyloxy)-2-ethoxyoctahydro-2*H*-chromene (3(EtO)). From **3(TAC)** (0.04 g, 0.04 mmol, 91α : 9β) using general procedure A, the crude ^{1}H NMR showed a ratio of anomers of 72α : 28β. Purification by silica gel column chromatography, (10% Et_2O/hexanes, TLC stained with CAM) gave a pure mixture of α/β-**3(EtO)** as a colorless oil (0.022 g, 76%, 72α : 28β). Spectral data are similar to the ones obtained from **3(SPh)**.

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