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Computational Study of the Formation of α and β *O*-Unsaturated Glycosides via Ferrier Rearrangement

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ABSTRACT

We studied the formation of new 2,3-unsaturated *O*-glycosides via Ferrier rearrangement using electronic structure calculations at the B3LYP/6-31g level. Using the Gibbs free energy variation, it was possible to indicate the formation of an intermediate stabilized by the anchimeric assistance at C3, which explains the preferred formation of the α-anomer. The calculations show that there is also the possibility of the formation of an anchimeric assistance intermediate at C4, which also favors the formation of the intermediate at C3. We analyzed the hypothesis of the repulsion of the aglycone with the acetoxy group at C6, and the results showed that there is less repulsion from the top of the oxonium ion, which corroborates the thermodynamic data. We propose a transition state starting from the C3 intermediate that explains the formation of the alpha anomer. The effect of the hyperconjugation present in the anomeric effect was studied using the NBO model, and according to the calculations compared to the literature, this factor did not prove to play a fundamental role in explaining the preferential formation of the α-anomer. Thus, the main factor favoring the preferential formation of the α-anomer is the spontaneous formation of the intermediate at C3, which prevents the formation of the β-anomer.

1 | Introduction

Carbohydrates are the most abundant class of molecules on planet Earth [1], can be produced through natural processes [2], and are linked to the energetic and structural functions of various living beings, as well as being obtained through synthetic processes [3]. Among these molecules are glycals [4], which are used dideoxy-hex-2-enopyranoside as the main precursor in the synthesis of *O*-glycosides, which are also called 2,3-did eoxy-hex-2-enopyranosides [5], and can have alkyl, aryl imidiazolic, oxadiazolic, and terpenic groups as aglycones. This category of compounds has a characteristic structure made up of two units: a pyranosidic ring and a part called the aglycone, which is linked to the ring by a specific glycosidic bond. Unsaturated *O*-glycosides-2,3- belong to a class of synthetically valuable compounds due to the presence of the double bond between carbons 2 and 3 of the sugar, which can undergo common addition reactions. There is a range of studies in the literature that propose different ways of synthesizing 2,3-unsaturated *O*-glycosides. However, this work focuses on studying the use of the Ferrier rearrangement methodology [6, 7]. Ferrier rearrangement is a reaction between a glycal and a nucleophile (usually an alcohol) and a Lewis acid. During the reaction, an oxonium intermediate is formed by allylic rearrangement, in which the double bond migrates to carbon 2 and 3, also known as Ferrier rearrangement. This intermediate can be attacked by the nucleophile from the top and bottom and form two isomers: α-anomer and β-anomer. There are works in the literature reporting some factors that may favor the preferential formation of the α-anomer instead of the β-anomer [6, 8–13]; these are catalysts, anchimeric assistance, anomeric effect, steric effects of the nucleophile, the repulsion of the acetoxy group on carbon 6, and solvents. To our knowledge, no computational studies have systematically analyzed the determinants of α-anomer selectivity, particularly the role of anchimeric assistance intermediates. The aim of this work is to study computationally this factor that may favor the majority formation of new α-anomers of 2,3-unsaturated *O*-glycosides with terpenes as the aglycone unit, based on molecules that have already been synthesized using quantum chemistry calculations.

2 | Molecular Models

We built molecular models of the α and β anomers of 2,3-unsaturated *O*-glycosides already synthesized and reported in other works [11] using the Gauss View 6.0.16 program (Figure 1).

We analyzed the formation of these anomers according to the Ferrier rearrangement methodology using tri-*O*-acetyl-D-glucal as the starting reagent (Figure 2). Based on this preliminary study with these synthesized molecules, we propose the formation of new 2,3-unsaturated *O*-glycosides with terpenes as the aglycone unit (Figure 3). We thermodynamically approached the Ferrier rearrangement methodology using Gibbs free energy, based on the most currently accepted proposed mechanism, represented in Figure 2. During the reaction, there is the possibility of the presence of intermediates with anchimeric assistance (Figure 4).

We analyzed the reaction with the presence of these intermediates in an attempt to explain the preferential formation of the α-anomer and propose which intermediate is most likely to be formed using the variation in Gibbs free energy.

2.1 | Reactants, Intermediaries, Aglicone, and Products

The geometries of the tri-*O*-acetyl-D-glucal, aglycones, anchimeric assistance intermediates, and α and β anomers were

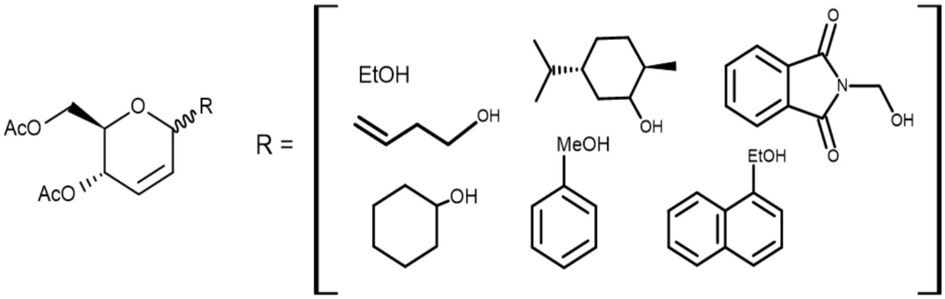

FIGURE 1 | Structures of the synthesized 2,3-unsaturated *O*-glycosides and their aglycone units.

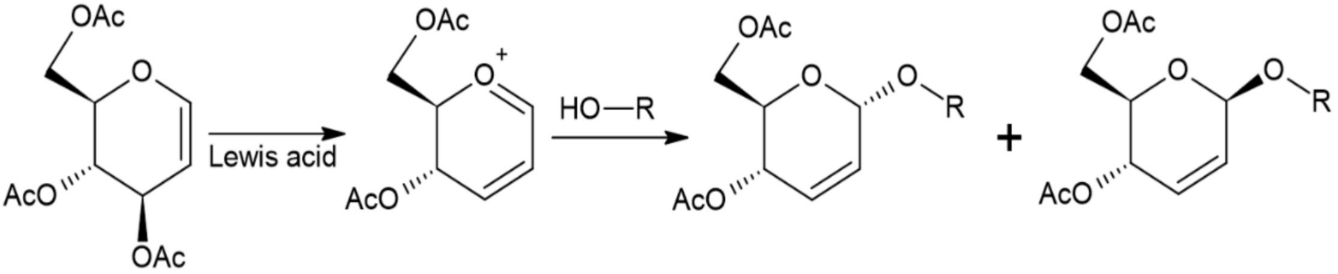

FIGURE 2 | Formation of 2,3-unsaturated *O*-glycosides via Ferrier rearrangement.

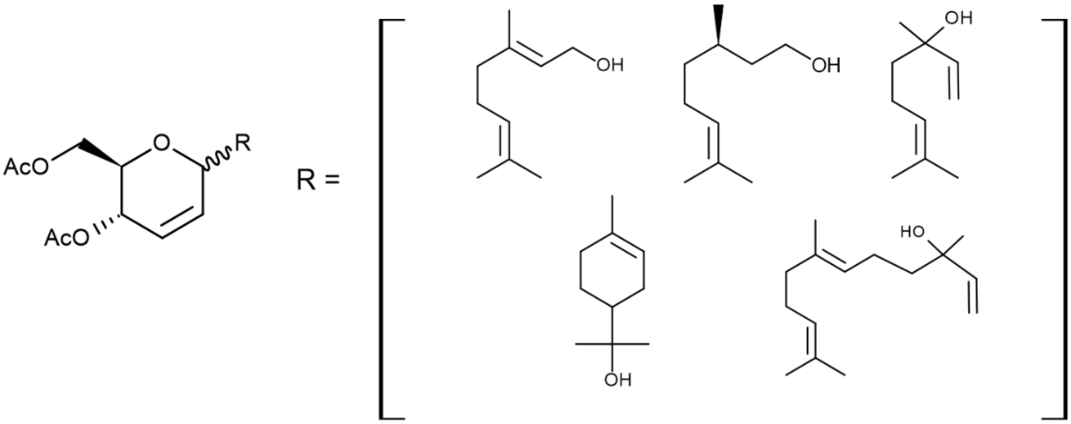

FIGURE 3 | New 2,3-unsaturated *O*-glycosides with terpenes as the aglycone unit.

previously optimized at the AM1 semi-empirical level using the Gaussian 09 program. The $^4H_5$ and $^5H_4$ half-chair conformations of tri-*O*-acetyl-D-glucal, as well as the ^5H_O and $^OH_5$ conformations of the α and β anomers were also optimized at the AM1 semi-empirical level.

2.2 | Thermodynamics and Natural Bond Orbital (NBO)

We obtained the Gibbs free energy of the structures using density functional theory (DFT) at the B3LYP/6-31g calculation level for molecules in vacuum and with the SMD implicit model with the solvent dichloro-methane. For an electrostatic analysis of atomic charges, we performed calculations with the NBO model.

2.3 | Nucleophile Repulsion

For the hypothesis of repulsion between the nucleophile and the acetoxy group at C6, we approximated the nucleophile by the upper and lower regions of the oxonium intermediate up to a distance of 2 Å.

3 | Results and Discussion

3.1 | Analysis of the Tri-*O*-Acetyl-D-Glucal Structure

In order to understand the mechanism of the Ferrier rearrangement, we need to comprehend the first stage at the start of the reaction, which is the formation of the oxonium intermediate by the removal of the OAc group at C3 by the catalyst caused by the structure of the glycal. The tri-*O*-acetyl-D-glucal has a double bond between carbon 1 and 2, which means that it has two half-chair conformations represented by H. Because of this, the O1, C1, C2, and C3 atoms of the ring are kept in the same plane, while the C4 and C5 atoms can be located above or below this plane, generating two conformations. These two conformations are represented by $^4H_5$ and $^5H_4$, where the subscript and superscript refer to the position of these atoms (Figure 5).

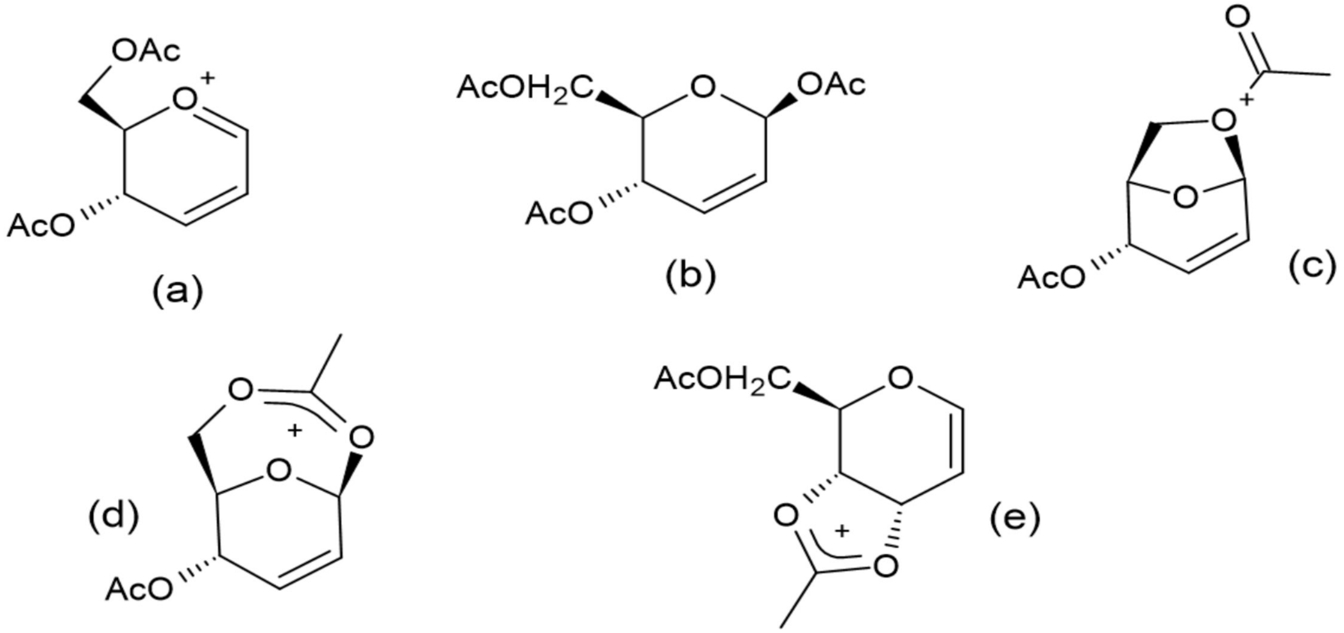

FIGURE 4 | Structure of the intermediates: (a) oxonium, (b) assist. C3, (c) assist. C6–sp^3, (d) assist. C6–sp^2, and (e) assist. C4.

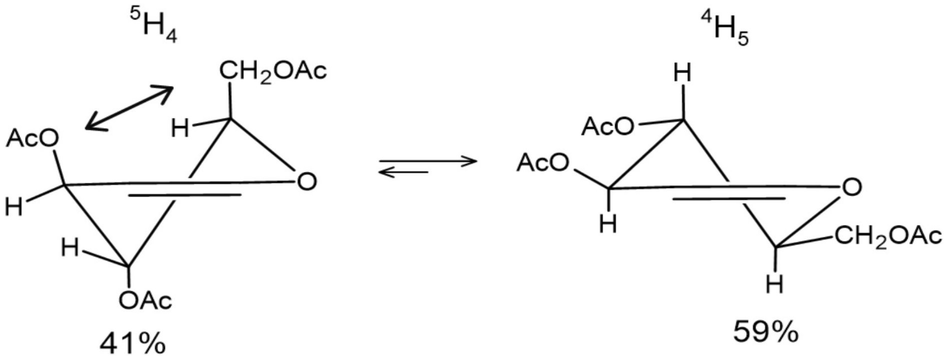

FIGURE 5 | Equilibrium between conformations $^5H_4$ and $^4H_5$ of tri-*O*-acetyl-D-glucal.

These two conformations are in equilibrium and have two factors that favor a certain conformation: the vinyl anomeric effect (VAE) and repulsion between the groups at C3 and C5. The vinyl anomeric effect was originally described by Ferrier and Sankey [10], in which the pseudoaxial orientation of the acetoxy group at C3 is favored due to the hyperconjugation between the oxygen electrons of the pyranoside ring and the antiligand orbital of the C3-O bond $(n \rightarrow \pi \rightarrow \sigma^*)$ (Figure 6).

Another factor that affects conformation is the presence of 1,3-diaxial interactions present in the $^5H_4$ conformation, which destabilizes this conformation, while in the $^4H_5$ conformation, the CH_2OAc group remains in the equatorial orientation without the presence of this 1,3-diaxial interaction. Therefore, these two factors compete with each other, causing the conformational equilibrium of the tri-*O*-acetyl-D-glucal (Figure 5), in which the $^4H_5$ conformation is more favored [14].

3.2 | Analysis of the Structure of 2,3-Unsaturated *O*-Glycosides Formed by Ferrier Rearrangement

The Ferrier rearrangement is known in the literature to be a stereoselective reaction [15]. It is known that in the case of tri-*O*-acetyl-D-glucal, when treated with -OR nucleophiles, the α-anomer is mainly formed. The literature discusses a number of factors that may explain this favoritism: VAE, anchimeric assistance intermediates, the structure of the products formed, and the repulsion of the nucleophile with the acetoxy group at C6.

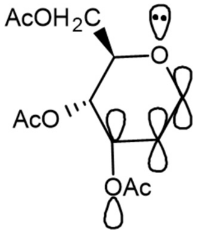

FIGURE 6 | Representation of the vinyl anomeric effect (VAE) in tri-*O*-acetyl-D-glucal.

Initially, we will analyze structural aspects between the α and β anomers, and later, we will analyze the presence of anchimeric assistance intermediates during the reaction.

The 2,3-unsaturated *O*-glycosides have a double bond between C2=C3, which leads the pyranoside ring to adopt the half-chair conformation. Unlike tri-*O*-acetyl-D-glucal, we now have a plane between the C1, C2, C3, and C4 atoms, and the remaining C5 and O1 atoms can be above or below this plane, generating the two conformations ^5H_O and $^OH_5$. Similarly, there are three factors that compete with each other to stabilize these conformations: VAE, anomeric effect, and 1,3-diaxial interactions. In the $^OH_5$ conformation, we have the anomeric effect, which is a stereoelectronic [8] effect in which a heteroatom adjacent to the oxygen of the pyranoside ring prefers the axial position over the equatorial one due to the better alignment of the hyperconjugation between the electronic pairs of the ring oxygen and the antiligand orbital in C1 (red in Figure 7). This effect only appears in the α-anomer of this conformation and in the β-anomer in the ^5H_O conformation. The 1,3-diaxial interactions only appear in the ^5H_O conformation (green in Figure 7) since, in the $^OH_5$ conformation, the group is in the equatorial position. VAE (in blue in Figure 7) occurs in all conformations, but this effect is probably more efficient in the α-anomer in the $^OH_5$ conformation, due to the extension of the hyperconjugation of the anomeric effect from the quasiaxial position of the OR group to the OAc group in C4, whereas in the ^5H_O conformation this same behavior appears in the β-anomer.

3.3 | Thermodynamic Study of the Ferrier Rearrangement and the Probable Reaction Pathway and Anomeric Effect

In order to study the most likely path of how the reaction occurs, we analyzed the reaction with the presence of the anchimeric assistance intermediates. Initially, the OAc group at C3 is removed from the tri-*O*-acetyl-D-glucal by the metal. After this, the oxonium ion (a) is formed, the presence of which in the reaction was a mystery until researchers recently managed to detect its presence using superacids [16]. After this, the nucleophile can attack either the lower or upper regions of the oxonium. If the

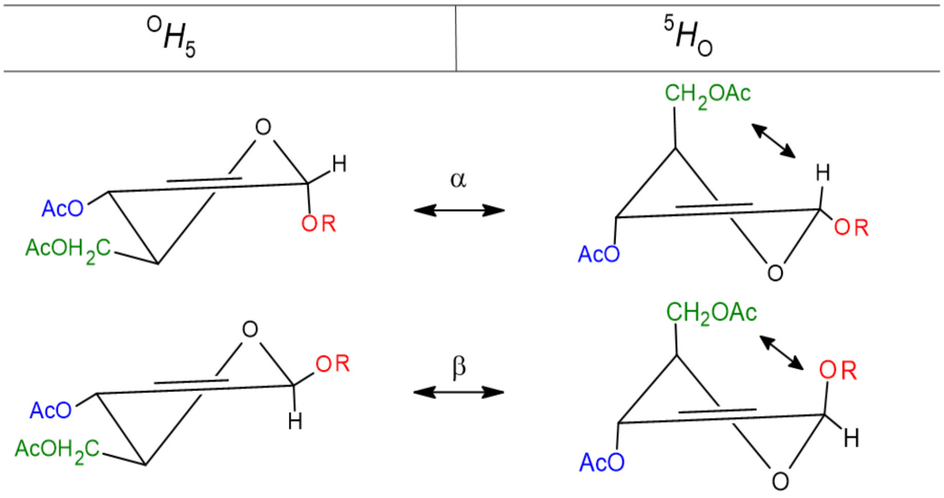

FIGURE 7 | Conformations ^5H_O and $^OH_5$ of α and β anomers.

attack is from the lower region, the α-anomer is formed, and if it is from the upper region, the β-anomer. The structure of the oxonium contains a double bond between carbons C2 and C3, and the positive charge generated on C1 causes the oxygen of the pyranoside ring to change its hybridization to sp^2 and one of its electron pairs to make a bond to stabilize the molecule (Figure 4).

In the literature, there are four possible intermediates for anchimeric assistance. The intermediate at C3 (b) was proposed by Ferrier and Prasad [6], in which the acetoxy group at C3 on the tri-*O*-acetyl-D-glucal migrates to the upper region of the anomeric carbon after the Ferrier rearrangement. The intermediate at C6 (c) was proposed by Boga and Balasubramanian [12], consisting of the formation of a second five-membered ring in the upper region of the sugar after the release of the acetoxy group at C3 by the Ferrier rearrangement. Oliveira and collaborators [13] also proposed a mechanism in which they constructed an intermediate at C6 (d), but the attack would be made by the sp^2 oxygen of the acetoxy group, forming a new seven-membered ring. Due to the presence of the OAc group at C4, an anchimeric assistance intermediate (e) is also proposed to stabilize the positive charge generated by the OAc leaving C3.

Among the intermediates with anchimeric assistance, only structures (b), (c), and (d) have the β position blocked, preventing the nucleophile from approaching from the upper region and causing the attack to take place from the lower region. We calculated the Gibbs free energy variation of the formation of intermediates from oxonium (Table 1).

TABLE 1 | Variation in the Gibbs free energy of the formation of intermediates.

Oxonium → intermediate	ΔG (vacuum)	ΔG (solvent effect)
Assist. C3 ^5H_O	−175.05	−69.73
Assist. C3 $^OH_5$	−216.39	−85.68
Assist. C4	−17.03	−42.03
Assist. C6 (sp^2)	5.24	44.57
Assist. C6 (sp^3)	345.26	294.05

Note: ΔG is given in $kJ\,mol^{-1}$.

According to the data, after oxonium formation, the C3 and C4 assistance intermediates are formed spontaneously ($\Delta G < 0$), while the C6 assistance intermediates are not formed ($\Delta G > 0$). These data corroborate the experimental results because the formation of the intermediate at C3 justifies the majority formation of the α-anomer, since the β-position is blocked. Furthermore, this behavior remains even with calculations using the solvent effect, which lends further credibility to the possibility of the formation of this intermediate. The formation of intermediate (b) is reasonable due to two factors. The OAc ion is relatively smaller than the other nucleophiles (Figure 1). In addition, this nucleophile has a negative charge in resonance between the oxygen atoms, which makes it attracted more efficiently and act as a better nucleophile than other nucleophiles when approaching the electrophile carbon in C1. The C4 intermediate forms a five-membered cycle at the bottom, probably preventing the nucleophile from approaching the lower region. With this in mind, we propose a reaction pathway in which the C4 intermediate is formed and then converted into the C3 assistance intermediate (Figure 8). According to the calculations, the formation of the intermediate in C3 is spontaneous ($\Delta G < 0$) and justifies the preference for the formation of the α-anomer, which is in line with the experimental results.

To corroborate these results, we approximated the -OAc group by the lower and upper regions of the oxonium up to a distance of 2 Å with an angle of $\theta = 110°$ (Figure 9). This angle was chosen because, in the optimization of the structure of the C3 intermediate, the bond angle formed between the O1-C1-O2 bond is $\theta = 110°$.

To find out which side suffers the greatest repulsion, we calculated the total electronic energy, in which the Gaussian program can separate the electron–electron and nucleus-nucleus repulsions and quantify each one (Table 2). According to the calculations, the approach from the upper region experiences less repulsion for both situations, which shows that the -OAc ion should probably suffer less repulsion due to the factors mentioned above. However, if other bulky protective groups [17] are added in the upper region, it is likely that the region on top of the oxonium will become very obstructive to the nucleophile's approach.

Based on these proposals, we calculated a possible transition state by approximating ethanol through the lower region of intermediate (b) in the ^5H_O conformation. The results showed a negative frequency in which the movement simulates the

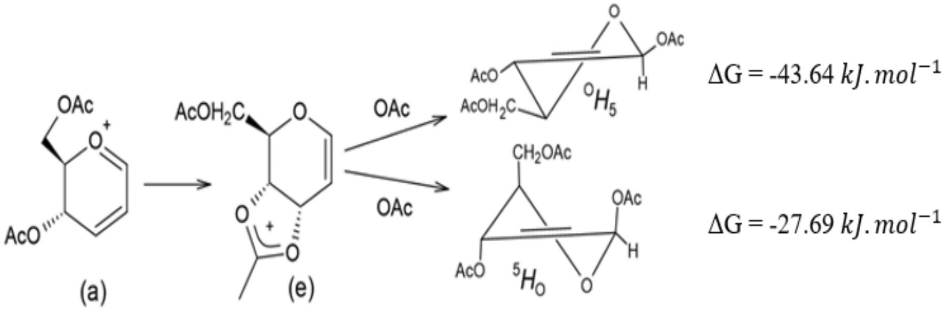

FIGURE 8 | Gibbs free energy variation of the formation of the assist. C3 with the two conformations from the assist. intermediate C4.

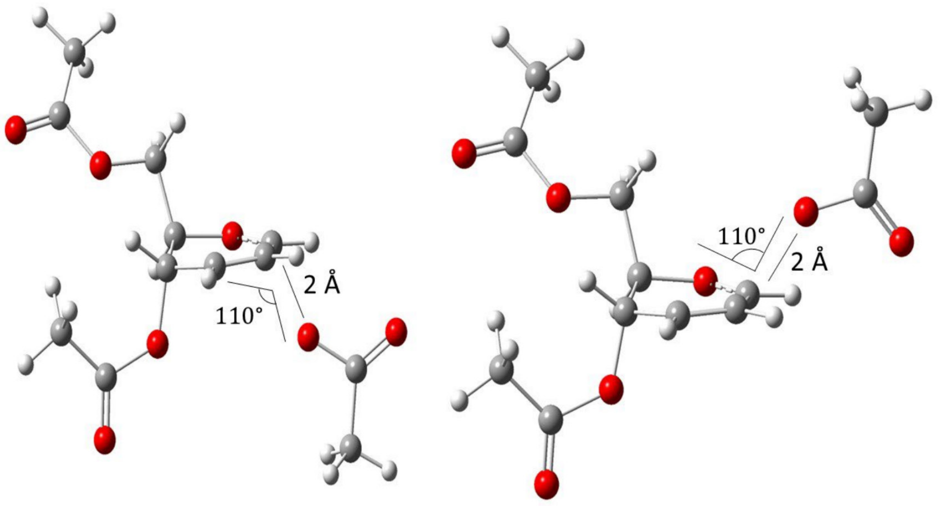

FIGURE 9 | Approach of the -OAc ion below and above the oxonium. The red, gray, and white balls are the O, C, and H atoms, respectively.

TABLE 2 | Nucleus–nucleus and electron–electron repulsion in the upper and lower regions of the -OAc ion given in Hartree.

Approach	Electron–electron	Nucleus–nucleus
Top	1794.99	1452.82
Below	1804.52	1461.89

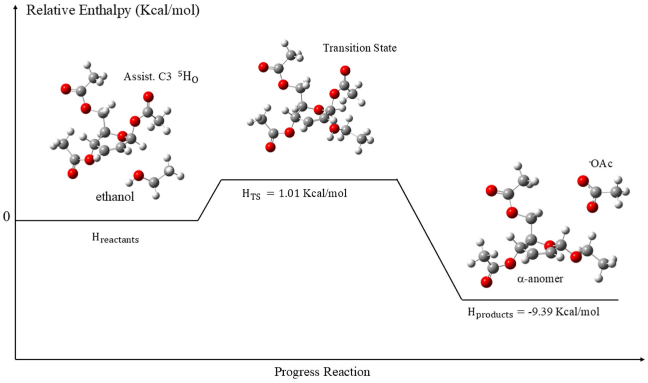

FIGURE 10 | Enthalpies of the transition state formation step.

breaking of the bond with the OAc group and the formation of the bond with the ethanol nucleophile (Figure 10). Our group understands that the reaction is endothermic, and the calculations reinforce this idea. After the bond with the nucleophile is formed, some base present in the solution captures the hydrogen from the nucleophile to stabilize the molecule.

Another factor discussed in the literature for the preferential formation of the α-anomer is the anomeric effect. In an attempt to analyze the presence of this effect in the α and β anomers, we used NBO calculations of the charges present on the anomeric carbon and the nucleophile oxygen. The positive charge on the anomeric carbon is expected to be lower for the α-anomer of the $^OH_5$ conformation and for the β-anomer of the ^5H_O conformation because, in these conformations, there is better overlap of the non-bonding electrons of the oxygen of the pyranoside ring with the anomeric carbon, extending to the oxygen of the aglycone.

TABLE 3 | Charges of the anomeric carbon and oxygen of the aglycone of the ^5H_O and $^OH_5$ conformations.

Aglycone–^5H_O	C1 (α)	C1 (β)	O2 (α)	O2 (β)
Ethanol	0.335	0.318	−0.584	−0.605
But-3-en-1-ol	0.335	0.315	−0.580	−0.601
Cyclohexanol	0.337	0.318	−0.587	−0.605
Phenylmethanol	0.328	0.317	−0.579	−0.601
Menthol	0.326	0.311	−0.580	−0.601
2-Naphthalen-1-ylethanol	0.335	0.316	−0.581	−0.601
N-(Hydroxymethyl) phthalimide	0.328	0.316	−0.577	−0.603
Aglycone–$^OH_5$	**C1 (α)**	**C1 (β)**	**O2 (α)**	**O2 (β)**
Ethanol	0.327	0.341	−0.597	−0.586
But-3-en-1-ol	0.323	0.338	−0.590	−0.587
Cyclohexanol	0.330	0.267	−0.599	−0.543
Phenylmethanol	0.323	0.341	−0.592	−0.580
Menthol	0.321	0.333	−0.594	−0.582
2-Naphthalen-1-ylethanol	0.325	0.342	−0.590	−0.584
N-(Hydroxymethyl) phthalimide	0.317	0.332	−0.593	−0.581

The negative charge of the aglycone oxygen should also be higher for these same conformations due to hyperconjugation. According to the calculations, they follow this pattern satisfactorily for the molecules already synthesized in other works (Table 3). Thus, the hyperconjugation present in both the α-anomer and the β-anomer should provide a balance in the amount of anomers formed.

However, we know that the α-anomer is formed in greater quantities, which leads us to believe that for these compounds, the anomeric effect may not be a decisive factor in explaining the preferential formation of the α-anomer, but rather thermodynamic factors and electronic repulsions.

Even taking this effect into account, there are studies in the literature that show that hyperconjugation does not have a major contribution to the anomeric effect [18–21]. It should also be noted that in these compounds there is the vinyl anomeric effect, which should influence these aspects; however, more analysis is needed, taking into account this effect in glycals with different groups in different positions to understand the extent and magnitude of this effect.

Taking all the factors mentioned above into account, the production of new 2,3-unsaturated *O*-glycosides from tri-*O*-acetyl-D-glucal with terpenes as the aglycone unit should favor the preferential formation of the α-anomer. If the β-anomer is formed in the majority, another factor must be going unnoticed.

4 | Conclusion

We investigated the Ferrier rearrangement reaction considering the possibility of the presence of anomeric assistance intermediates. We were able to demonstrate that the majority of the formation of the α-anomer is caused by the spontaneous formation of the assistance intermediate at C3 predicted without calculations using the solvent effect and also with the SMD solvent effect. This intermediate can be formed from the oxonium ion or from the assistance intermediate at C4. This is probably the main factor why the nucleophile cannot approach from above and produce the β-anomer. The calculations propose a transition state for the nucleophile attack on the intermediate at C3, in which the results predict that the process is endothermic, consistent with the experimental results. The analysis of the repulsion of the nucleophile with the acetoxy group at C6 corroborates the thermodynamic results of the formation of the intermediate at C3. The analysis of hyperconjugation by means of charges with the NBO model of these compounds may favor the formation of the α-anomer, but this should not be a decisive factor in justifying this preference.

Data Availability Statement

Research data are not shared.

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