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Origin of Diastereocontrol in the Oxy-Michael Reactions of δ-Lactol Anions: A Computational and Experimental Study

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Abstract: The diastereoselectivity in the alkylation and Michael addition of "naked" 6-substituted δ-lactolates has been studied by density functional (B3LYP) calculations with ab initio (MP2) energy refinements. The resulting proposed model for the origins of stereocontrol in this reaction has been tested by experiment. The reactions lead to a high *cis* diastereoselectivity across the THP ring due to the preference for both the alkoxide and the 6-substituent to sit equatorial in the alkylation transition structure. In the oxy-Michael addition of these lactolates to β-substituted nitroolefins, we propose that the high diastereoselectivity β- to the nitro group is a result of a combination of steric, stereoelectronic and solvation factors.

Keywords: computational chemistry · diastereoselectivity · lactols · Michael addition · stereochemical models

Introduction

Despite being reported by Loydl[1] as early as 1878 in his synthesis of malic acid, the full synthetic utility of the oxy-Michael reaction was not realised until recent years.[2] These developments have included many examples of stereoselective oxy-Michael additions that compliment the stereoselective aldol reactions in the synthesis of (protected) β-hydroxy carbonyl (or carboxyl) compounds. It is worth mentioning that many examples of oxy-Michael reactions require either the reaction to be intramolecular or the use of oxygen nucleophiles that are more complex than simple alcohols to overcome the thermodynamic preference of the retro-Michael reaction.[2] A highly diastereoselective, intramolecular oxy-Michael reaction under substrate-control has been reported by Evans,[3] whereas Enders reported a range of highly diastereoselective reagent-controlled oxy-Michael additions of *N*-formylnorephedrine to 2-alkyl-1-nitroethenes (however, the stereoselectivity is much reduced when 2-aryl-1-nitroethenes are employed).[4] An alternative diastereoselective approach employing intramolecular delivery of a hemiacetal nucleophile by using a glucose-derived chiral auxillary was reported by Watanabe to give high yields and diastereoselectivities.[5]

More recently, enantioselective catalytic oxy-Michael reactions have been reported that use several modes of catalysis. Jacobsen demonstrated that the addition of aldoximes to α,β-unsaturated imides proceeds with excellent enantiocontrol when catalysed by (salen)aluminium complex Lewis acid catalysts,[6] whereas Maruoka reported a Brønsted acid-catalysed addition of simple alcohols that proceeded with low to moderate stereoselectivity.[7] Other organocatalytic approaches have also been successful, including the secondary amine-catalysed addition of benzaldoxime to α,β-unsaturated aldehydes developed by Jørgensen;[8] and the bifunctional Brønsted acid-base catalytic intramolecular oxy-Michael reactions for boronic hemiesters developed by Falck.[9] Organocatalysed intramolecular oxy-Michael reactions have also been reported by Scheidt[10] and separately by Hintermann[11] in the enantioselective syntheses of flavanones. Many of these reactions have been found to be of use in the synthesis of natural products.[2]

Recently, our group reported that the oxy-Michael addition of the "naked" anion of enantiopure δ-lactol **1** to nitro-

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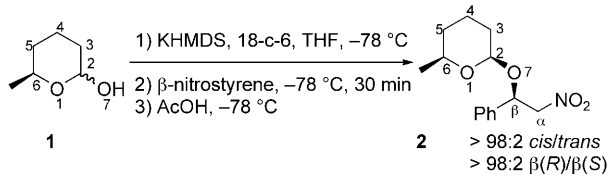
olefins proceeds with excellent diastereoselectivity both across the tetrahydropyranyl (THP) ring and at the newly formed stereocentre β to the nitro group in adduct **2** (Scheme 1).[12] This reaction has been extended to a range of Michael acceptors[13] and has found use in the syntheses of biologically active β-amino alcohols.[14]



Scheme 1. Diastereoselective oxy-Michael reactions of δ-lactols. KHMDS: potassium hexamethyldisilazide.

The high C6–C2 stereocontrol has also been observed in the reactions of the corresponding potassium salts with alkyl and acyl halides and with acetic anhydride.[15] The reaction of the anomeric hydroxyl of protected glucosides with alkyl halides[16] or trichloroacetonitrile[17] in the presence of sodium hydride in polar, aprotic solvents also occurs with high kinetic preference for the formation of the β-anomer. It is reasonable to suggest that the origin of the *cis*-selectivity in all these lactolate reactions is similar but, to date, no computational study of these systems in solution has been reported. Herein, we report our work leading to a model to explain the stereochemical outcome of these reactions.

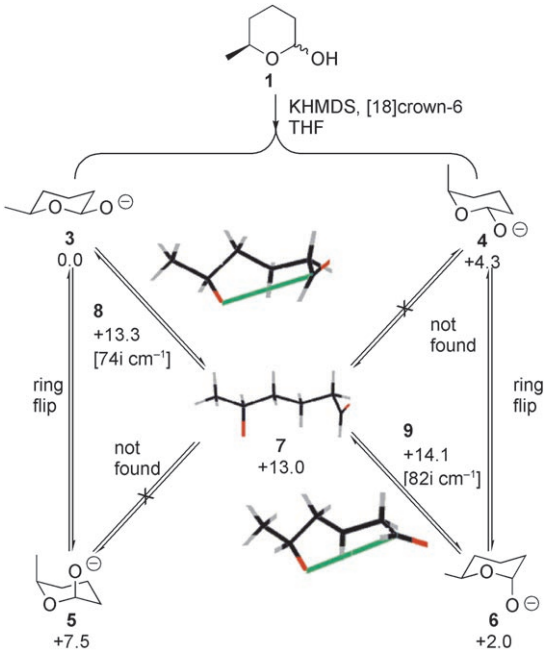
Computational Methods

All calculations were performed by using Jaguar.[18] Energy minimizations and transition-state searches were performed by using a continuum solvent model for THF at the B3LYP/6-31+G(d) level[19] previously used by Salpin to study the gas phase acidity of D-glucose.[20] Energies were refined at the MP2/6-31++G(d,p) level. Transition states were found to have exactly one imaginary frequency that was followed by Goodman's Quick Reaction Coordinate.[21] Frequencies were determined at the B3LYP/6-31+G(d) level and scaled by 0.98.[22] Energies are quoted as free energies at 195 K (−78 °C) at the MP2/6-31++G(d,p)(THF)//B3LYP/6-31+G(d)(THF) level[23] with ZPE and thermochemical corrections determined by vibrational analysis for the species in THF solution. Solvation effects were modelled by using the Jaguar Poisson-Boltzmann/SCRF continuum approach with a variable cavity.[24] Tight SCF and geometry convergence criteria were applied throughout.

Results and Discussion

Locating the transition states for the oxy-Michael reaction of lactol **1** with any nitroolefin proved very computationally demanding. Owing to this, it was decided to initially investigate the *cis* selectivity across the THP ring in the reaction between the anion derived from (*R*)-6-methyl-δ-lactol **1** with chloromethane as a simple model system. As stated earlier, the selectivity in such alkylation reactions is high.[15] The use of a crown ether in the Michael addition reaction means that the "naked" anion assumption is valid.[25]

Deprotonation of an anomeric mixture of lactol **1** with potassium hexamethyldisilazide and addition of crown ether[12] sets up an equilibrium of "naked" anions **3**–**6** and their open-chain forms that can then be reacted with an electrophile (Scheme 2). Assuming that the alkylation is irreversible and, therefore, under kinetic control, a full analysis of the stereoselectivity requires determination of the equilibrium ratios of anions **3**–**6**,[26] the activation energy for their interconversion and the activation energy for the reactions of lactolates **3**–**6** with an electrophile. The calculated relative energies of anions **3**–**6** and the lowest-energy open-chain form **7** (found by a molecular mechanics conformation search[27] followed by DFT re-optimisation and single-point calculation on the ten lowest energy conformers) are shown in Scheme 2.



Scheme 2. The anionic equilibrium. Energies are quoted as Gibbs free energies in kcal mol^{-1} above anion **3**. Numbers in square brackets are imaginary frequencies.

Diequatorial anion **3** dominates the equilibrium, whereas species **6** with the axial alkoxide is more prevalent than the other conformer of the *trans* isomer **4** with the axial methyl group. The concentrations of diaxial anion **5** and open-chain forms are low. All located twist-boat conformations were over 9 kcal mol^{-1} higher in energy than **3**. The calculated *cis*/*trans* ratio at 195 K is 180:1.

The solvation energies of the equatorial anions **3** and **4** are approximately 5 kcal mol^{-1} greater than those for the

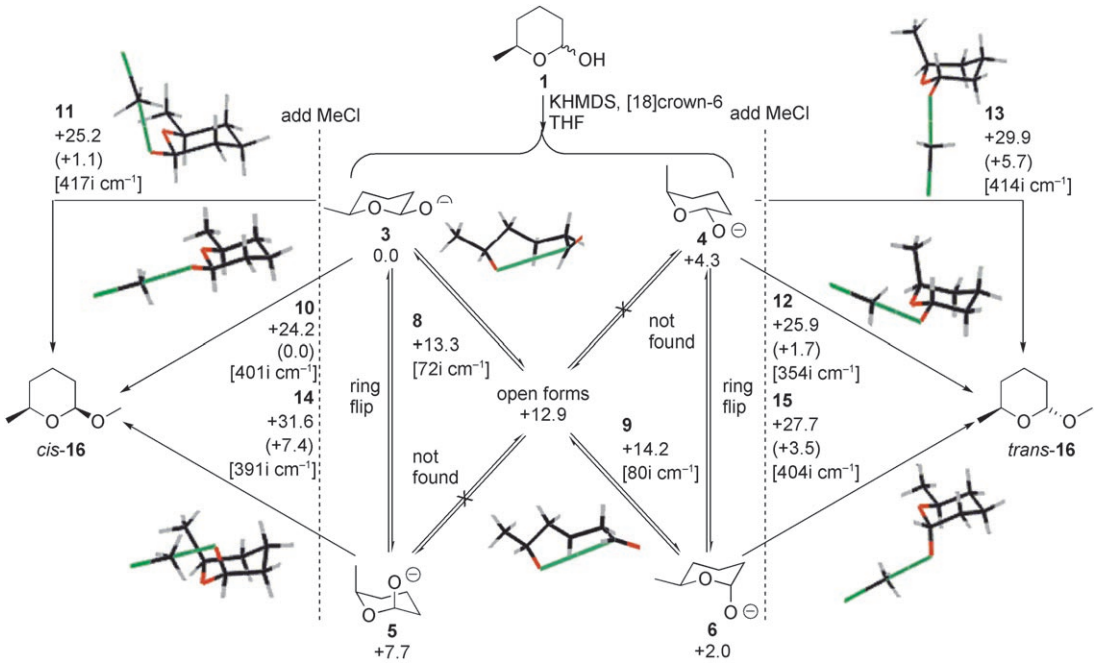
axial anions **5** and **6** showing that the preference for the alkoxide to be equatorial is due to this larger solvation energy that more than cancels out classical anomeric effects observed in previous gas-phase calculations.[20] This greater solvation energy arises from the larger dipole moment of the equatorial anions (11.8 for equatorial alkoxide **3** compared with 8.7 D for the equivalent axial alkoxide **6**),[28] which leads to it being stabilised by the polar solvent. This is consistent with the effect reported by Wiberg for the conformational preference of *trans*-1,2-difluorocyclohexane in the gas and solution phase.[29]

Anion **3** has a long O1–C2 bond (1.501 compared to 1.429 Å in the protonated form minimised under the same conditions and 1.418 Å found in a crystal structure of the oxy-Michael adduct of **1** with β-methyl-β-nitrostyrene[2b]) and a short O7–C2 bond (1.321 Å), and the geometry at C2 is distorted considerably from tetrahedral (bond angles: φ(O1-C2-H) = 102.9, φ(O7-C2-C3) = 115.1°), which is consistent with donation of the alkoxide electron density to the C2–O1 σ*. The energy difference between anions **3** and **4** (4.3 kcal mol^{-1}) is much greater than the A value of a methyl group on a THP ring (2.3 kcal mol^{-1}).[30] This was unexpected because the elongated O1–C2 bond is expected to decrease the 1,3-diaxial interactions. However, on closer inspection of anion **3**, the geometrical distortion at C2 pushes the axial proton closer to that on C6 than it is in lactol **1** (H–H distances: 2.286 and 2.384 Å, respectively) leading to increased steric compression. This distortion is also observed in the anion **4** with the axial methyl group and this is believed to be the cause of the increased A value calculated here. No such distortion is seen in axial alkoxides **5** and **6**.

The interconversion pathways of anions **3–6** were studied by driving the O1–C2 bond length (allowing minimisation of all other variables) and re-optimisation at the saddle point. Whilst pathways could be found connecting anions **3** and **6** with equatorial methyl groups to open forms via transition-states **8** and **9**, respectively, no transition state connecting anions **4** and **5** with the open chain could be found. However, it is reasonable to assume that rapid ring-flipping pathways[31] allow equilibration of **3**⇄**5** and **4**⇄**6**, hence, that the activation barrier to anion equilibration is 14.1 kcal mol^{-1} (Scheme 2).

When studying the reaction of anions **3–6** with chloromethane, two pathways were found for the reaction of the equatorial anions **3–4** with the electrophile approaching such that the dihedral (for anion **3**) ψ(C3-C2-O7-C(H3)) = −178.7 (**10**) or 58.3° (**11**—disfavoured by a steric clash with the axial proton on C3). Only one of these pathways could be found for the reaction of axial alkoxides (for anion **6** ψ(C3-C2-O7-C(H3)) = −155.9°, **15**). The other approach would place the electrophile over the THP ring resulting in substantial steric compression with the axial groups on C4 and C6 (Scheme 3). No pathways were found in which the electrophile approaches antiperiplanar to the C2–O1 bond, which is consistent with this pathway being deactivated by donation of alkoxide electron density in this region to the C2–O1 σ* (Scheme 3).

The activation energy for alkylation (24.2 kcal mol^{-1}) is much greater than that for anion equilibration (14.1 kcal mol^{-1}). The consequence of this is a Curtin–Hammett system in which the diastereoselectivity across the THP ring in the alkylation is determined only by the relative energies



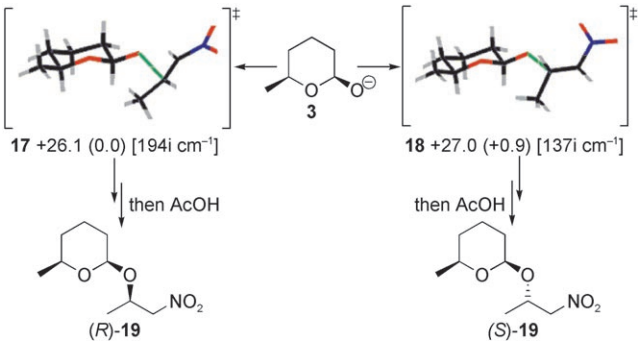
Scheme 3. Alkylation of lactolate anions by chloromethane. Energies are quoted as Gibbs free energies in kcal mol^{-1} above anion **3** (+MeCl). Numbers in parentheses are free energies relative to transition-state **10**. Numbers in square brackets are imaginary frequencies.

of transition-states **10**–**15**. The energies in Scheme 3 predict a kinetic *cis*/*trans* ratio (i.e., of products *cis*-**16**/*trans*-**16**) at 195 K of 70:1. In previous experimental studies, the *trans* isomer is hardly ever observed in these reactions by ^{1}H NMR spectroscopic analysis,[12,15] consistent with the reaction producing this high diastereoselectivity. The difference in solvation energies between transition-states **10** and **15** accounts for the majority of the calculated energy difference between them (3.1 of the 3.6 kcal mol^{-1}). The energy difference between transition-states **10** and **12** (1.6 kcal mol^{-1}) is much closer to the A value of a methyl group on a cyclohexane ring (1.7 kcal mol^{-1})[30] than it was in the anions **3** and **4**. The geometry at C2 in transition-state **10** is closer to tetrahedral than that in anion **3**, making the distance between the axial protons on C2 and C6 larger (2.328 Å) and reducing the steric 1,3-diaxial compression discussed earlier.

Our calculations suggest that the *cis* diastereoselectivity in the alkylation of the anion of lactol **1** is a result of the preference for both the C6 substituent and the alkoxide to occupy equatorial positions in the transition state for steric and solvation reasons, respectively. With these structures located, attention was turned to the reaction with nitroolefins. The high diastereoselectivity at the β-centre in adduct **2** is consistent across a wide range of alkyl and aryl-substituted nitroethenes,[12] so the reaction between 1-nitropropene and the anion of lactol **1** was studied to reduce computational demand. Despite this, location of the oxy-Michael transition states proved difficult. A full study would require at least 12 such transition states to be located (corresponding to the six transition-states **10**–**15** with approaches leading to both the *R* and *S* configurations at Cβ). The reaction is, however, highly *cis* selective so the major transition state must correspond to one of the *cis* structures **10**, **11** and **14** shown in Scheme 3. Additionally, the diequatorial structures **3**, **10** and **11** are always much lower in energy than the corresponding diaxial species **5** and **14**, so it is reasonable to assume that the reaction proceeds through the addition of diequatorial anion **3** to the electrophile. Taking this into account, the stereoselectivity in the oxy-Michael reaction can be investigated by studying the reaction of nitropropene with anion **3** alone.

Transition-state searches on the reaction between nitropropene and lactolate **3** identified only transition-state **17** leading to (*R*)-**19** and transition-state **18** leading to (*S*)-**19** (Scheme 4).

Both these transition states involve the approach of the electrophile approximately antiperiplanar to the endocyclic C2−C3 bond. Extensive dihedral driving about the exocyclic C2−O7 bond and the newly forming O7−Cβ bond and researching (see the Supporting Information for details) did locate species **20**, but vibrational analysis identified this as a second-order saddle point (Figure 1). Following the second imaginary frequency in either direction by QRC led back to the previously located transition-state **17** without passing through any local minima. No corresponding saddle point of any order could be located that would lead to (*S*)-**19**. Species **20** is 4.4 kcal mol^{-1} higher in energy than **17** and is destabilised by a steric interaction with the axial proton on C3. This suggests that the reaction proceeds in such a way that the electrophile approaches antiperiplanar to the C2−C3 bond. The dihedral driving studies also show that there is a strong preference for the nitropropene to approach with the C=C double bond antiperiplanar to the exocyclic C2−O7 bond—a result of electrostatic repulsion between the residual negative charge on the lactolate oxygen atoms and the developing nitronate anion.



Scheme 4. Oxy-Michael addition transition states. Energies are quoted as Gibbs free energies in kcal mol^{-1} above anion **3**+nitropropene. Numbers in parentheses are free energies relative to transition-state **17**. Numbers in square brackets are imaginary frequencies.

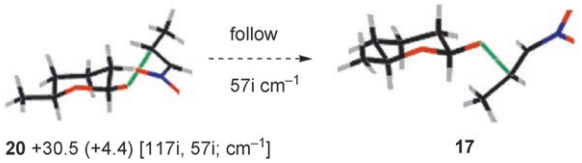


Figure 1. Second-order saddle point located with electrophile APP to C2H. Energies are quoted as Gibbs free energies in kcal mol^{-1} above anion **3**+nitropropene. Numbers in parentheses are free energies relative to transition-state **17**. Numbers in square brackets are imaginary frequencies.

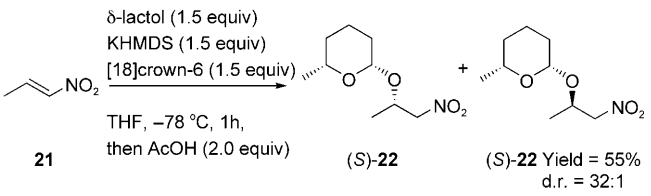
The calculated energy difference between transition-states **17** and **18** suggests a kinetic diastereoselectivity at Cβ of 10:1 in favour of (*R*)-**19**—much lower than the experimental results for all nitroalkenes, but the computation does predict the correct facial selectivity. Attempts to extend this computational study to any of the electrophiles that have been previously used experimentally[12] led to geometry convergence failure. The distance between the methyl group on Cβ and the axial proton on C2 in major transition-state **17** (3.025 Å) is longer than that in the minor transition-state **18** (2.843 Å), which suggests that the stereoselectivity may increase as this methyl group is changed to a larger function.

During optimisation of the reaction, it was noticed that the use of sodium bis(trimethylsilyl)amide and [15]crown-5 in place of the optimal potassium bis(trimethylsilyl)amide and [18]crown-6 did lead to a reduced stereoselectivity at Cβ,[1] which showed that the counter-ion–crown ether complex can still influence the course of the reaction. For the factors discussed here, the conclusions drawn from these cal-

culations on the oxy-Michael reaction are more tentative than those drawn from the alkylation reaction above.

The solvation energy of major transition-state **17** is 5.4 kcal mol^{-1} greater than that for the minor transition-state **18** and this more than accounts for the energy difference between them. This suggests that the stereocontrol in this reaction is controlled once again by preferential solvation of the transition state leading to the *R* diastereomer of adduct **19**—a result of the greater dipole moment on **17** (14.3 compared to 13.1 D). The methyl group on C6 is distant to the Cβ substituent (4.765 Å in major transition-state **17** and 5.048 Å in minor transition-state **18**). This suggests that the role of this substituent is solely to control the conformation of the THP ring and it does not interact with the electrophile.

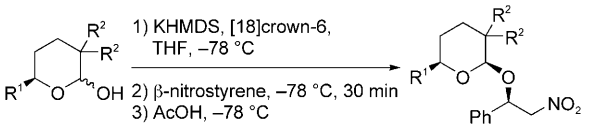
In the original work,[1] nitropropene was not tested as an electrophile. In light of the differences in the predicted diastereomeric ratio from the current calculations (10:1) and that obtained with the larger electrophiles used in the previous work (for example, β-nitrostyrene giving 99:1), we revisited the reaction with nitropropene **21** with the 6*R* enantiomer of lactol **1** (in the computational studies, the 6*S* enantiomer was used in keeping with previous experimental work[12]). The reaction was much less clean than that with other electrophiles (probably due to reaction pathways involving deprotonation of the γ-carbon atom), but we observed a 32:1 ratio of diastereomers in favour of (β*S*)-**22** (Scheme 5). This corresponds to a difference in transition-state energies of 1.3 kcal mol^{-1} compared to the calculated 0.9 kcal mol^{-1}. The discrepancy between these activation energies is within the expected error of the techniques used here.



Scheme 5. Stereoselective oxy-Michael reaction with nitropropene. d.r. = diastereomeric ratio.

Further experimental studies into this stereochemical model were also undertaken by modifying lactol **1** (Table 1). The use of lactols **1** and **23b** shows that increasing the size of the C6 substituent from methyl to hexyl leads to no measurable change in the stereoselectivity at Cβ, which is consistent with this group serving only as a conformational lock. However, when a *tert*-butyl group was placed here (as in lactol **23c**) the selectivity was diminished, which is consistent with the fact that this group lies closer to the substituent on Cβ on the major transition-state **17** than it does in the minor one, **18**. The installation of geminal dimethyl groups on C3 in lactol **23a** has no measurable effect on the stereoselectivity of the reaction, which is consistent with the

Table 1. Lactol modification and stereoselectivity.



Lactol	R^1	R^2	Product	Yield [%]	d.r. at Cβ[a]
1	Me	H	**2**	99	>98:2
23a	Me	Me	**24a**	60	>98:2
23b	*n*-Hex	H	**24b**	55	>98:2
23c	*t*Bu	H	**24c**	62	6:1

[a] Determined by ^{1}H NMR spectroscopic analysis on the crude reaction product. The *cis*/*trans* ratio across the THP ring was >98:2 in all cases.

calculated transition states in which the electrophile approached antiperiplanar to the C2–C3 bond, distant from these groups.

The stereochemical outcome is an indirect result of the preference for the nitro group to be as far from the endocyclic oxygen atom as possible in the transition state. When the reaction is performed in the absence of crown ether, the Lewis acidic counterion would be expected to give rise to a cyclic transition state.[25,32] This would lead to a change in stereoselectivity, as observed experimentally, but a full computational study of this would be far too demanding on current computational resources.

Conclusion

The stereoselectivity in the oxy-Michael reaction of δ-lactol anions can be explained as follows. The reaction proceeds through a *cis* diequatorial transition state due to the preference for the methyl group on C6 and the reacting anomeric alkoxide to be equatorial for steric and solvation reasons. The nitroolefin approaches the lactolate antiperiplanar to the C2–C3 bond to minimise steric compression and with the C=C double bond antiperiplanar to the exocyclic C2–O7 bond to minimise electrostatic repulsions. Finally, with the (*S*)-lactol **1** the reaction proceeds with *R* selectivity owing to preferential solvation of transition-state **17**. The *cis* selectivity across that THP ring is predicted accurately by the computational study, and the predicted selectivity in the oxy-Michael reaction also agrees with experiment when the reaction is conducted with nitropropene. Further predictions of this model about the effects of the lactol structure on the stereoselectivity of this reaction have all been realised experimentally.

Previous explanations for the increased reactivity of equatorial alkoxides invoke lone-pair interactions present in the β-anomer of the anions of glucosides making equatorial alkoxides more reactive.[17] Whilst there is evidence for the equatorial alkoxides being more reactive (alkylation transition-state **15** lies 25.7 kcal mol^{-1} above axial anion **6**, whereas the corresponding transition-state **10** lies 24.1 kcal mol^{-1} above equatorial anion **3**), the reaction is a Curtin–Hammett

system in which the relative energies of the alkylation transition state alone decided the stereochemical outcome of the reaction, so it is the differences observed there that must be the origin of stereocontrol in this reaction.

Acknowledgements

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