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Total Facial Discrimination of 1,3-Dipolar Cycloadditions in a D-Erythrose 1,3-Dioxane Template: Computational Studies of a Concerted Mechanism

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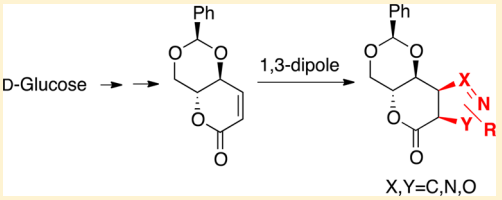
Supporting Information

ABSTRACT: A new D-erythrose 1,3-dioxane derivative was synthesized from D-glucose and found to be a highly stereoselective template as a dipolarophile. Different 1,3-dipoles of allenyl-type were employed, giving different regioselectivities, depending on its nature; the regioselectivity is complete with alkyl azides and phenyldiazomethane, but is inexistence with nitrile oxides. Computational studies were performed to understand the mechanisms of cycloadditions. All the studied cycloadditions were found to be concerted involving small free activation energies and are all exoenergonic. The stereoselectivity is due to a combined result of the steric effect H-8a and the hyperconjugative effect of the *C−O to the incoming 1,3-dipole. The regioselectivity observed in alkyl azides and phenyldiazomethane is mostly dependent on the distortion effect during the cycloaddition process. This distortion effect is however higher in the alkyl azide compounds than in phenyldiazomethane.



1. INTRODUCTION

The synthesis of a multiple stereogenic center molecules can be efficiently made by adding up small chiral synthons to build larger structures.[1] Tetroses are in this context interesting versatile fragments, useful in the synthesis of iminosugars of several types.[2] 2,4-*O*-Ethylidene/benzylidene-D-erythroses are tetroses easily accessed in large scale from cheap D-glucose in two steps. In particular, the synthesis of benzylidene-D-erythrose[3,4] is a quite accessible starting material. Wittig elongation of the aldehyde function would generate α,β-unsaturated carbonyl compounds to which many applications in syntheses can be ascribed.[5] In fact, the compounds are scarcely known in the literature. This is probably due to poor facial selectivity of the olefinic portion in reactions, connected to its high degree of freedom. Elongation of 2,4-*O*-ethylidene D-erythrose with simultaneous functionalization of the olefinic portion was attempted before by reaction with sulfur ylides, but a 3:2 mixture of diastereomeric epoxides was obtained.[6] Reasoning that the lock of the double bond into a six-membered ring would improve the stereoselectivity of the reactions, a δ-lactone was obtained from the *Z*-stereoisomer. Besides, the α,β-unsaturated lactone bearing a well exposed electronic π cloud would enable better reactivity than the open-chain precursor. This compound can be envisaged as a good 1,4-Michael acceptor and as an electron-poor dipolarophile/dienophile.

In the present work the lactone was synthesized and reacted with alkyl azides, phenyldiazomethane, and nitrile oxides by [3π + 2π] cycloaddition to afford the respective adducts. The concept of "cycloaddition" gives a formal description of the overall reaction but not a mechanistic interpretation. Unlike the Diels−Alder reaction, in the case of [3 + 2] cycloadditions the principal question is whether the new σ-bonds that are generated during the fusion of the 1,3-dipole with the dipolarophile, and from which results a five-membered ring, occur in a concerted or stepwise way. In addition, the cycloaddition can follow different routes depending on the nature of the 1,3-dipole molecule. It can exhibit polar character, when the reactant displays electro- or nucleophilic activity,[7] a biradical character,[8] or even nonpolar character.[9]

In order to understand the mechanism of the [3 + 2] cycloadditions, the free energy profile of these reactions was studied by theoretical and computational means.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Lactone 1. As far as we know lactone **1** is a new compound with nonstudied reactivity and selectivity. It was obtained from D-erythrose derivative **2** by Wittig olefination with methyl (triphenylphosphoranylidene)acetate. First a 2.3:1 ratio of *Z* and *E* isomers **3** was obtained. The isomeric mixture was heated in dry toluene in the presence of silica in a rotary evaporator for several hours. After consumption of the *Z* isomer, the crude was chromatographed

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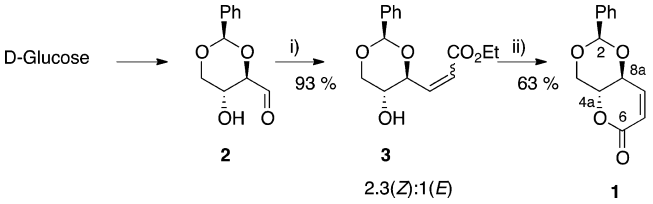
to give lactone **1** in 63% overall yield, from D-erythrose derivative **2** (Scheme 1).

Scheme 1. Synthesis of Lactone 1[a]



[a](i) Methyl (triphenylphosphoranylidene)acetate, TsOH (cat), dry THF, 23 h, rt; (ii) silica, dry toluene, 75 °C, vacuum.

2.2. 1,3-Cycloadditions of Lactone 1 with 1,3-Dipoles.

Lactone **1** was reacted with three types of 1,3-dipoles: alkyl azides (**4**), nitrile oxides (**5**), and a diazo compound (**6**). According to the nature of the 1,3-dipole, reactions took place within a large range of temperatures, from rt to 102 °C. In the cases of alkyl azides and the diazo compound, products are isolated as single isomers, within the detection limit of ^{1}HNMR spectroscopy. With nitrile oxides the stereoselectivity of reactions continue to be effective, but the regioselectivity is not (Scheme 2).

Intermolecular reactions of alkenes to azides are known but not common and require harsh conditions, due to the poor reactivity of the reactants.[10] On the other hand, intramolecular 1,3-cycloadditions are frequent, although triazoline cycloadducts are rarely isolated, and in most cases the chiral center(s) formed are destroyed in the following rearrangements. Nevertheless, reaction of tri-*O*-acetyl-D-glucal with alkyl azides occurred before at high temperature in trimethyl- or triethylorthoformate, and the respective triazolines were isolated in good yields and with complete stereoselectivity.[11] Inspired by these reactions lactone **1** was combined with three alkyl azides under reflux in trimethylorthoformate. Triazolines were obtained in high yields in two cases (**7a,c**), and in moderate yield in one case (**7b**). Stereo- and regioselectivities are complete in every case. An ORTEP X-ray analysis of the adduct **7a** is consistent with the attack of an alkyl azide on the *re* face of the lactone ring (see Figure 1 in the Supporting Information).

Reaction of lactone **1** with phenyldiazomethane gave a single product in 76% yield. ^{1}H NMR spectrum evidenced that the primary cycloadduct suffered a 1,3-H-shift rearrangement to form compound **8**. The regioselectivity of the reaction was elucidated by an NOE experiment on compound **8**: irradiation of 9a-H induced an increase of 9b-H and H-aromatic signals (Figure 1). These observations are consistent with the regiochemistry of compound **8** in Scheme 2. The NOE experiment also showed that phenyldiazomethane approaches lactone by the *re* face, since 9a-H and 9b-H protons are located on the same side of the molecule.

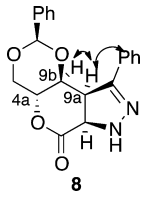
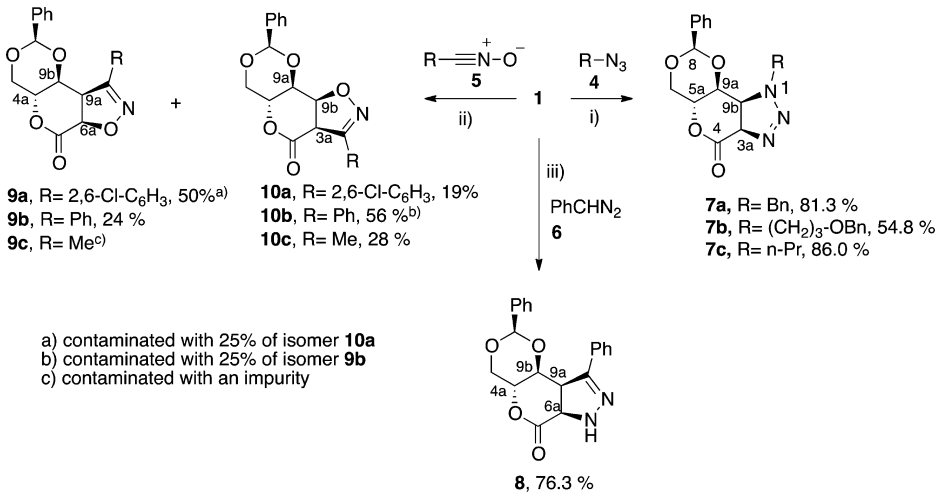


Figure 1. NOE interaction elucidates both the regio- and stereochemistry of the newly formed chiral centers.

Reactions of lactone **1** with nitrile oxides gave a pair of regioisomers **9** and **10**, in an approximately 1:1 ratio. Identification of isomers was conclusive after ^{1}H MNR spectra analysis: the oxygen position in the fused-oxazole **9**/**10** is likely to affect the proton chemical shift attached to its neighbor carbon atom. In fact, isomers **9** showed consistently H-6a at a higher chemical shift (δ_H 5.33−5.10 ppm) than H-9a (δ_H 4.86−3.95 ppm); the opposite trend occurs in isomers **10** where H-9a appears at δ_H 5.37−5.09, higher than H-6a (δ_H 4.98−4.34 ppm). Irradiation of 6a-H's signal in compound **10b** induced a 13.9% increase of the aromatic peak, demonstrating its proximity to the aromatic ring. The facial approach of the

Scheme 2. 1,3-Dipolar Cycloaddition of Lactone 1 to Azides, Nitrile Oxides, and Phenyldiazomethane[a]



[a](i) (a) Benzyl azide (2 equiv), $HC(OMe)_3$, reflux, 65 h; (b) (3-azidopropoxy)methylbenzene (2 equiv), 95 °C, 44 h; (c) *n*-propyl azide, (1 equiv., every 3 h for 30 h); 95 °C; (ii) (a) 2,6-dichloro-*N*-hydroxybenzimidoyl chloride, dry ether, Et_3N, 0°−rt, 15 h; (b) *N*-hydroxybenzimidoyl chloride, dry ether, Et_3N, 0°−rt, 12 h; (c) NCS, acetaldehyde oxime, pyridine then Et_3N in toluene, 0°−rt, 15h; (iii) phenyldiazomethane, toluene, 60−70 °C, 1 h 15 m.

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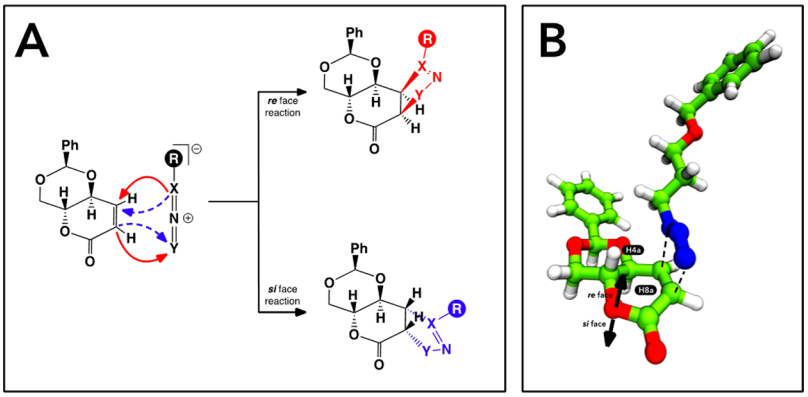

Figure 2. (A) Stereoselectivity of the reactions of the lactone **1** with 1,3-dipole compounds. The red pathway shows the attack in the *re* (top) face of the lactone ring. The blue pathway shows the attack in the *si* (bottom) face of the lactone ring (do not happen). (B) Transition state structure obtained from cycloaddition of an azide compound at the *re* face of the lactone.

nitrile oxide to the lactone **1** was also determined by an NOE experiment: irradiation of H-9b's signals in the pair **9b**/**10b** indicated that H-9a and H-9b are located on the same side in both isomers. As C-9b's configuration refers to the starting material, it is clear that the approach of reagents would have occurred from the *re* face of the lactone. Additionally, H-2 signals also increase by H-9b's irradiation in both isomers.

3. COMPUTATIONAL RESULTS

3.1. Stereospecificity of the Cycloadducts. The high stereoselectivity of the compounds is one of the key features of the studied reactions. In all of the studied cases, the cycloaddition of the 1,3-dipoles was found to occur by the *re* face of the lactone ring, *i.e.*, in the opposite plane where the hydrogen atom covalently bonded to carbon C**8a** is located at (Figure 2A). The transition state structures of these reactions show that the main moiety of the lactone, including the keto group, are perpendicular to the new bonds formed during the 1,3-dipoles' approach in the top face of the lactone (Figure 2B). This process is facilitated by the small size of the 1,3-dipole molecules, allowing them to react in largely occluded areas where other reagents cannot fit due to steric bulk. Hydrogens **8a** in the lactone is very close to the reactive region, and it was found to play an important role in the stereospecificity of the cycloaddition process. Hydrogen **8a** located at the *si* face precludes the correct alignment of the 1,3-dipole to the lactone. This is patent on free energies calculated for the nitrile oxide, R = Ph, that requires an activation energy of 40 kcal/mol, and the reaction is endothermic by 15 kcal/mol. On the other hand the hydrogen **4a** is located further away from the region where the reaction takes place, at the *re* face of the lactone, leading to a more suitable approach of the 1,3-dipole at the *re* face of the lactone. Moreover, the attack at the *re* face is also favored by an hyperconjugative interaction of the σ*C−O to the electron positively charged atom of the 1,3-dipole. So the *re* face is more favored by either steric and electronic effects.[12] In fact, the cycloaddition process at the *re* face requires a free activation energy of 21.3 kcal/mol and a free reaction energy of −17.8 kcal/mol. The same conclusion is applied to the azides, diazo, and nitrile oxide compounds.

3.2. Regiospecificity of the Compounds. The cycloaddition involving an unsymmetrical 1,3-dipole and the lactone **1** can potentially generate two regioisomeric products, depending on the orientation of the 1,3-dipole molecules in relation to the lactone. When the R group of the 1,3-dipole molecule is pointing to the same side of the phenyl group of the lactone, the cycloaddition follows pathway A (Figure 3)).

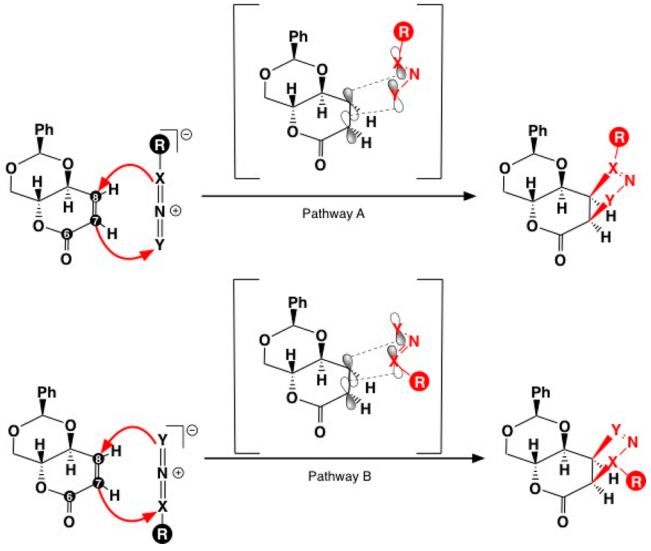

Figure 3. Possible catalytic mechanisms of lactone **1** with 1,3-dipoles. Y, X = N in the case of alkyl azides; X = C, Y = O in the case of nitrile oxides; X = C, Y = NH in the case of phenyldiazomethane.

Otherwise, when the R group is pointing toward the opposite direction of the phenyl group of the lactone, the cycloaddition follows pathway B (Figure 3). In principle a mixture of both regioisomers could be obtained in these types of reactions, as it was observed in the reactions with the nitrile oxides **5**. However, alkyl azides **4** and diazo compound **6** gave a single regioisomer cycloadduct.

The most generally satisfactory interpretation of the regiochemistry of dipolar cycloadditions is based on frontier molecular orbitals (FMO) concepts. As with the Diels−Alder reaction, the most favorable orientation is the one that involves the complementary interaction between the frontier orbitals.

Generally, the 1,3-cycloadditions can be classified in three types based on the relative FMO energies between the dipole and the dipolarophile. In 1,3-cycloadditions type I, the dominant FMO interaction is that of the HOMO dipole with the LUMO's dipolarophile. For 1,3-cycloadditions type II, the similarity of the dipole and dipolarophile FMO energies implies that both HOMO−LUMO interactions are important. In 1,3-

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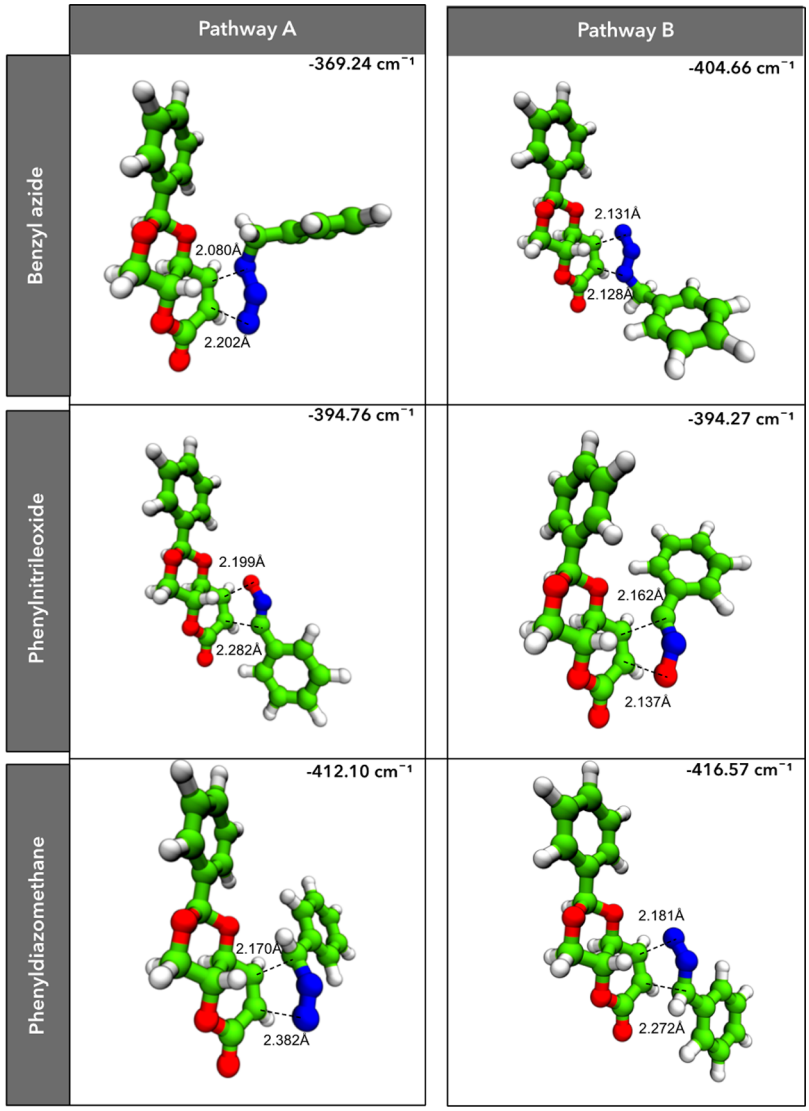

Figure 4. Transition state structures of the cycloaddition process of lactone **1** and benzyl azide (**7a**), phenylnitrileoxide (**9b**/**10b**), and the diazo compound (**8**).

cycloadditions type III the interaction is obtained between the LUMO's dipole and the HOMO's dipolarophile.

The evaluation of the energies of the HOMO and LUMO of all the transition state structures involving the reaction of diazo, azide, and nitrile oxides compounds with the lactone reveals that the diazo compounds follow a mechanism of type I and the azide and nitrile oxides compounds follow a mechanism of type II. The mechanism of type II is characteristic of the reactions involving 1,3-dipole molecules with a high nucleophilic nature, as it is the case of the nitrile oxides and alkyl azides, which causes the energy gap between the HOMO and LUMO of the dipole and dipolarophile to be very close to each other (see Supporting Information for a detailed description of the energy involved in this process).

This interpretation of the results is however not sufficient to explain the origin of the regiospecificity present on the studied reactions. For example, the mechanism of cycloadditions involving either nitrile oxides and alkyl azides is type II; however, the energy gap between the HOMO and LUMO in the transition state cannot be used to explain why nitrile oxides gave two regioisomers and alkyl azides gave only one isomer.

A better explanation to understand the regiospecificity of the studied reactions was obtained analyzing the energetic profiles of the cycloaddition process.

3.2.1. Mechanism of the 1,3-Cycloadditions. The computational results have shown that the 1,3-cycloadditions are controlled by the electronic/stereoelectronic and steric factors that require highly ordered transition states and only moderate free energy requirements.

Independently of the pathway that is followed (pathway A or B), the full process is complete in a unique step involving the concerted formation of two covalent bonds between the 1,3-dipole molecules and the lactone. This is confirmed by all the transition state structures, from all the studied reactions, that present a single imaginary frequency, and in which the 1,3-dipole molecule adopts a partially folded conformation well-aligned and in close contact to the C7 and C8 carbons of the lactone. Examples of the transition state structures involved in the cycloaddition process of lactone **1** and each of the 1,3-dipole molecules are shown in Figure 4.

Independent of the 1,3-dipole molecule that was studied and of the substituents present on these molecules, all the reactions

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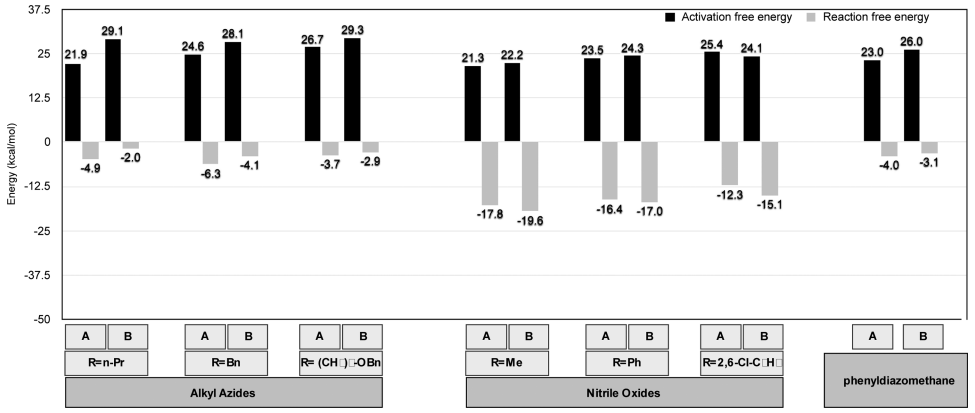

Figure 5. Activation and reaction free energies of the cycloaddition process involving lactone **1** and the alkyl azides, nitrile oxides, and phenyldiazomethane.

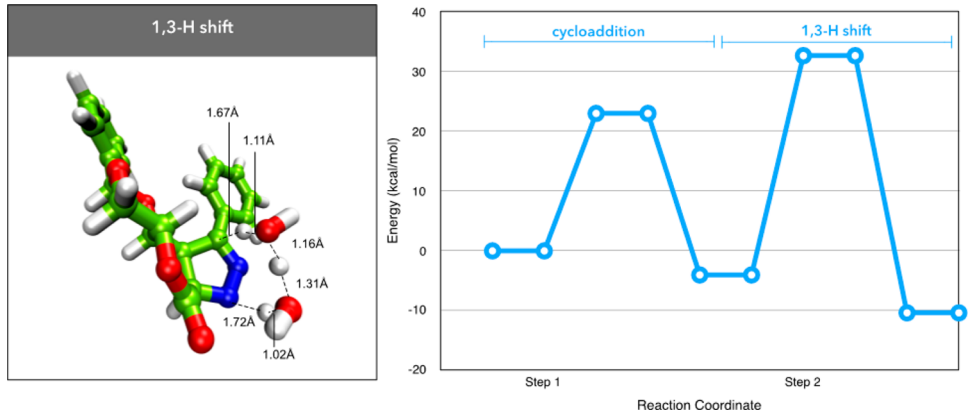

Figure 6. (Left) Transition state structure of the 1,3-H shift mechanism. (Right) Free energetic profile for the formation of compound **8**.

require relatively small free activation energies (below 28 kcal/mol) and are all exoenergonic (Figure 5). Despite these similarities, the free energetic profiles of the studied reactions, whenever pathway A or B is followed, are distinct and allow for understanding the origin of the regiospecificity of the cycloadditions of the studied 1,3-dipole molecules.

The calculated free energies involving the cycloaddition of the 1,3-dipole azides with lactone **1** reveal that pathway A is always favored either from the kinetic or thermodynamic points of views in relation to pathway B. This is more clear in the cycloaddition process involving the 1,3-dipole azides that are substituted with propyl and benzyl groups, in which pathway A is favored kinetically in more than 3.5 kcal/mol and thermodynamically in more than 2.3 kcal/mol. When the 1,3-dipole azides has a $(CH_2)_3$-OBn group, pathway A continues to be kinetically favored in 2.6 kcal/mol but it is only thermodynamically favored in 1 kcal/mol. These results agree to what is observed experimentally, since only one isomer is observed and isolated (Figure 5).

The cycloaddition process of the 1,3-dipole nitrile oxides with lactone **1** produces two isomers instead of a single one, in contrast to what is observed with 1,3-dipole azides. The computational results indicate that the energetic profiles of pathways A and B for these reactions are very similar either from the kinetic (energy differences below 1.2 kcal/mol) and thermodynamic (energy differences below 2.8 kcal/mol) point of view, indicating that both pathways should be competitive. These results are in line with what is observed experimentally, since a mixture of two isomers is obtained (Figure 5). For example in the case of compounds **9b** and **10b**, compound **9b** is obtained in 24% yield, and compound **10b**, in 56%. However, as compound **10b** is contaminated with 25% of compound **9b**, the ratio between the yields is near 1:1, in agreement with the computational results.

The cycloaddition of lactone **1** with the 1,3-dipole phenyldiazomethane was also studied through pathways A and B. However, and contrarily to what was found with nitrile oxides and the alkyl azides, the formation of compound **8** requires two steps instead of one. First, the cycloaddition process occurs. Afterward, the 1,3-H shift takes place.

The calculated free energy profiles for pathway A (E_a = 23.0 kcal/mol and E_r = −4.0 kcal/mol) and pathway B (E_a = 26.0 kcal/mol and E_r = −3.1 kcal/mol) indicate that pathway A is from the kinetic and thermodynamic points of view favored in relation to pathway B (Figure 5). These results are in line with the experimental observations in which only one isomer is isolated from this reaction.

The second step of the reaction involves the 1,3-H shift. Since pathway A was the most favored, this reaction was only studied for the product of this reaction. The 1,3-H shift requires the participation of two water molecules that form a hydrogen bond network allowing the proton exchange between the carbon and nitrogen atoms from the cycloaddition product obtained in pathway A. The transition state of this reaction is characterized by an imaginary frequency at −944.57 cm^{-1}, and the full process requires a free activation energy of 38.14 kcal/mol and is exoenergonic (−8.03 kcal/mol).

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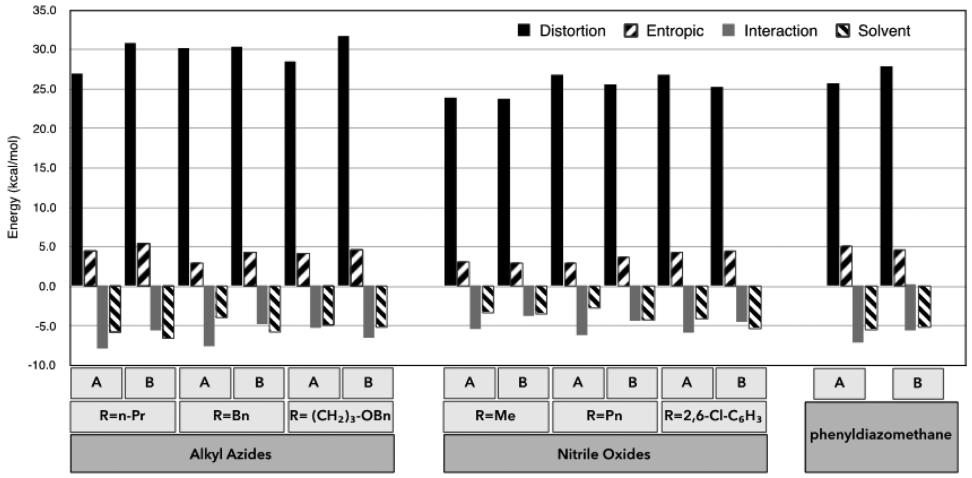

1,3-Dipole Molecule		Pathway	Decomposition of the activation energies (kcal/mol)			
			Distortion	Entropic	Interaction	Solvent
Alkyl Azide	R=n-Pr	A	26.8	4.4	-8.0	-5.8
		B	30.7	5.3	-5.6	-6.6
	R= Bn	A	30.1	3.0	-7.6	-3.9
		B	30.3	4.3	-4.9	-5.9
	R= $(CH_2)_3$-OBn	A	28.5	4.2	-5.3	-4.9
		B	31.7	4.7	-6.5	-5.2
Nitrile Oxides	R=Me	A	23.9	3.1	-5.4	-3.3
		B	23.7	2.9	-3.7	-3.5
	R=Ph	A	26.8	2.9	-6.2	-2.8
		B	25.6	3.7	-4.4	-4.2
	R=2,6-Cl-C_6H_3	A	26.7	4.3	-5.9	-4.0
		B	25.2	4.4	-4.5	-5.4
Phenyldiazomethane		A	25.6	5.1	-7.1	-5.5
		B	27.9	4.6	-5.8	-5.2

Figure 7. Decomposition of the activation energies of the cycloaddition process involving lactone **1** and the alkyl azides, nitrile oxides, and the diazo compound.

The full energetic profile obtained for the formation of compound **8** is depicted in Figure 6. The computational results reveal that the 1,3-H shift mechanism is the rate limiting step in the formation of compound **8**.

3.2.2. Origin of the Regiospecificity of the Cycloadditions. In order to evaluate the origin of the regiospecificity of the alkyl azides and phenyldiazomethane in relation to the nitrile oxide compounds we have decomposed the free activation energies in different energetic terms: the distortion energy, interaction energy, entropic contribution, and solvent effects.

The distortion energy was calculated summing up the energy difference between the geometry of lactone and 1,3-dipole *per se* and for each reagent in the transition state. The interaction energy was calculated based on the energy difference between the energies of the 1,3-dipole and the lactone molecules together and alone in the transition state and reactants of all the studied reactions. The entropic contributions and the solvent effect on each reaction were obtained directly from the calculations. The results from these analyses are displayed on Figure 7.

The results indicate that the main contributor for all the calculated activation energies is the distortion energy, i.e. the energy that is required to move the 1,3-dipole molecules and the lactone in a proper way to endorse the concerted cycloaddition process. From these two molecules, the 1,3-dipoles are the ones that suffer the highest distortion effect. The calculations also reveal that the distortion of these molecules accounts for an average 70% of the total distortion energy (see Supporting Information). The other negative contributor for the activation energies of all the studied reactions is the entropy. This is expected since the cyclization process is from the entropic point of view unfavorable. However, its contribution is very small (below 5 kcal/mol) when compared to the distortion energy. The calculated interaction energy and solvent effects have a positive contribution to the calculated activation energies; they decrease the activation energies in −5.9 kcal/mol and −4.2 kcal/mol, respectively. The interaction energy is the one that makes the cycloaddition process possible. The solvent effect was introduced in the calculations with the inclusion of a dielectric constant. This was found to be important for the stabilization of zwitterionic species particularly during the distortion of these molecules nearby the transition state.

From all the studied reactions, the cycloadditions of alkyl azides with lactone **1** are the ones that require higher activation energies. The results show that this is proportional to the higher distortion effect that is observed in the 1,3-dipole molecules. These results also show that the distortion effect of alkyl azides in pathway B is higher than that in pathway A and justifies why these reactions are regioselective (pathway A).

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In the case of nitrile oxides, a similar contribution of the energetic terms that were calculated is observed on pathways A and B, justifying why in this case two isomers are obtained.

The energy decomposition of the cycloaddition of phenyldiazomethane with lactone **1** reveal that the energetic profile is similar to the one observed with nitrile oxides. However, in this case the distortion energy is smaller in pathway A than in pathway B causing this reaction to be regioselective for pathway A, similarly to what happens in the mechanism of alkyl azides.

3.3. Effect on the Substituents of the 1,3-Dipoles on the Calculated Free Energies. The cycloaddition of the lactone with the 1,3-dipoles, nitrile oxides and alkyl azides, having different substituents, were also carried out in order to understand the effect of such substituents on the free energies of the reactions and so in the obtained yields (Figure 5). With the alkyl azides bearing propyl, and benzyl groups pathway A is favored either from the kinetic and thermodynamic points of view relatively to pathway B. The computational results with (propoxymethyl)benzene showed to be less favorable than in the other two cycloadditions, which go in line with the experimental results; compound **7b** was obtained with a lower yield (55%) than the others. The computational results indicate that the energetic profile of pathway A is less favored because of the volume of the (propoxymethyl)benzene that creates a steric hindrance either with the Ph group of the lactone in pathway A and with the carbonyl group in pathway B.

The cycloaddition of the nitrile oxides was also investigated with the methyl, phenyl and dichorophenyl groups. The computational results reveal that in all of the three reactions, pathway A and pathway B present similar energetic profiles. For each compound the activation free energies for each pathway differ by only 1 kcal/mol, and the reaction free energies are below 3 kcal/mol. This indicates that the cycloadditions of the nitrile oxides with the two different orientations are competitive and therefore a mixture of both isomers should be obtained in the end. This is in accordance with the experimental results where both isomers were obtained in similar amounts in the three reactions.

4. CONCLUSION

A new D-erythrose 1,3-dioxane derivative, lactone **1**, has been synthesized and found to be a highly selective template in 1,3-dipolar cycloadditions. Alkyl azides, nitrile oxides, and diazoalkanes were reacted as models. The computational results showed the stereoselectivity is due to the steric effect of the hydrogen atom (H8a). The activation and reaction free energies calculated for the cycloadditions allow for an explaination of the origin of the regioselectivity observed with alkyl azides and diazo compounds in relation to the nitrile oxides.

The cycloaddition processes can occur with two different orientations of the 1,3-dipole molecule in relation to the lactone (pathway A and B). In the nitrile oxides cases, pathways A and B are competitive and both isomers are obtained. However, in the cases of the alkyl azides and diazo compounds only one isomer is favored from kinetic and thermodynamic points of view. The detailed analysis of the energies involved in the cycloaddition process indicate that pathway A is favored because it requires a lower distortion of the 1,3-dipole molecules during the reaction.

5. EXPERIMENTAL SECTION

5.1. General. Solvents were used as purchased except: dichloromethane and methanol, dried under CaH_2 and Mg/I_2, respectively; tetrahydrofuran, and ether, dried under Na-benzophenone, and DMF and toluene distilled with elimination of the head distillation fractions. Petroleum ether 40−60 °C used in chromatography was submitted to distillation. D-Erythrose benzylidene acetal was obtained according to literature.[3,4] Alkylazides were obtained from the respective alkyl bromides, by reaction with sodium azide under standard conditions.[13] Benzyloxypropyl azide was prepared from 3-bromopropanol by reaction with sodium azide followed by protection of the hydroxyl group with benzyl bromide.[14] Nitrile oxides were obtained *in situ* from α-chlorobenzaldoximes in the presence of triethylamine.[15] Phenyldiazomethane was obtained from the aldehyde and tosylhydrazone according to literature.[16]

All other reagents were purchased and used without further purification. Glassware was dried prior to use. Compounds were purified by dry flash chromatography using silica 60, <0.063 mm, and water pump vacuum or by flash-chromatography using silica 60 Å 230−400 mesh as stationary phases. TLC plates (silica gel 60 F_{254}) were visualized either with a UV lamp or in a I_2 chamber.

5.2. Synthesis of Lactone 1. *5.2.1. Synthesis of Methyl 3-((2′R,4′S,5′R)-5′-Hydroxy-2′-phenyl-1′,3′-dioxan-4′-yl)acrylate.* To a solution of aldehyde **2** (1.0 g, 4.8 mmol) in dry THF (20 mL), stirred under nitrogen in the presence of a catalytic amount of *p*-toluene sulfonic acid (5 mg), was added a solution of methyl (triphenylphosphoranylidene)acetate (1.6 g, 4.8 mmol) in dry THF (10 mL). The solvent was evaporated until dryness after 23 h, and the crude was subjected to column chromatography (ethyl acetate/petroleum ether 1:1). A mixture of *Z*/*E* isomers was obtained in a 2.3:1 ratio (1.18 g, 4.5 mmol, 92.8%). The mixture was submitted to the next step without further purification. Some ^{1}H NMR peaks of the *Z* isomer in the spectrum of the crude product are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, OMe), 5.21 (td, *J* = 9.0, 1.2 Hz, 1H, 4′-*H*), 5.57 (s, 1H, 2′-*H*), 6.19 (dd, *J* = 11.8, 1.4 Hz, 1H, 2-*H*), 6.36 (dd, *J* = 11.8, 7.7 Hz, 1H, 3-*H*).

5.2.2. Synthesis of (2R,4aR,8aS)-2-Phenyl-4,4a-dihydropyrano-[3,2-d][1,3]dioxin-6(8aH)-one (1). To a solution of the crude material obtained in (i) (0.80 g, 3.03 mmol) in ethyl acetate (70 mL) was added silica (*ca.* 40 g). The mixture was heated at 75 °C for 10 h in a rotary evaporator under a water pump vacuum. Successive portions of dry toluene (5 × 100 mL) were added to the flask to avoid dryness. The residue was purified by column chromatography (ethyl acetate/petroleum ether 1:1), giving a white solid (0.03 g, 1.29 mmol, 63.0%), identified as lactone **1**. Mp: 135.9−136.8 °C; $[\alpha]_D^{25}$ = +17.6 (conc. 0.5%, DCM); IR (nujol mull): ν_{max}/cm^{-1} 3070, 3054, 1753 (s, C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (t, *J* = 10.0 Hz, 1H, 4-*H*), 4.40 (dd, *J* = 10.4, 4.8 Hz, 1H, 4a-*H*), 4.69 (dd, *J* = 10.4, 4.8 Hz, 1H, 4-*H*), 4.89 (ddd, *J* = 10.0, 2.4, 1.6 Hz, 1H, 8a-*H*), 5.65 (s, 1H, 2-*H*), 6.04 (dd, *J* = 10.0, 2.8 Hz, 1H, 7-*H*), 7.03 (dm, *J* = 10.0 Hz, 1H, 8-*H*), 7.42−7.40 (m, 3H, 3′-*H* + 4′-*H*), 7.51−7.50 (m, 2H, 2′-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 68.2 (4-C), 72.7 (4a-C), 73.9 (8a-C), 102.4 (2-C), 120.7 (7-C), 126.1 (CH), 128.5 (CH), 129.6 (CH), 136.3 (Cq), 146.9 (8-C), 161.8 (6-C); HRMS (ESI-TOF) found for $C_{13}H_{12}O_4Na$: 255.0621; calcd: 255.0628.

5.3. Synthesis of 1,3-Dipoles. *5.3.1. Nitrile Oxides 5.* A solution of 2,6-dichlorobenzaldehyde/benzaldehyde oximes (0.104−0.143 g) in dry DMF (10 mL) was preheated at 40−43 °C. A solution of *N*-chlorosuccinimide (NCS) (0.100 g; 0.75 mmol) in dry DMF (5 mL) was added dropwise, under magnetic stirring and a N_2 atmosphere. The reaction mixture was kept for 3 h, followed by another 15−19 h period at rt. The reaction was quenched in ice/water (ca. 30 mL) and extracted with ether (4 × 20 mL). The Etheral solution was washed with sat. aq. sol. NaCl (2 × 10 mL) and water (2 × 10 mL). The organic phases were combined and dried over $MgSO_4$. The solvent was removed in the rotary evaporator to give the respective chloro oximes (η = 77%−89%).

5.3.1.1. 2,6-Dichloro-N-hydroxybenzimidoyl Chloride. 2,6-Dichlorobenzaldehyde oxime (0.143 g; 0.75 mmol); 43 °C; 15 h, rt;

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beige solid (0.130 g; 0.58 mmol; η = 77%); ^{1}H NMR: δ (300 MHz, $CDCl_3$) 7.20−7.40 (3H, m, Ar); 10.11 (1H, sl, OH).

5.3.1.2. N-Hydroxybenzimidoyl Chloride. Benzaldehyde oxime (0.104 g; 0.86 mmol); 40 °C; 19 h, rt; brownish oil (0.123 g; 0.790 mmol; η = 89%); ^{1}H NMR: δ 300 MHz, $CDCl_3$) 7.32−7.41 (3H, m, Ar), 7.80−7.88 (2H, m, Ar); 10.9 (1H, br s, OH).

5.3.1.3. N-Hydroxymethylimidoyl Chloride. *N*-Hydroxymethylimidoyl chloride was generated "*in situ*" by a similar methodology described to the synthesis of previous chloro oximes and used immediately in the 1,3-dipolar cycloaddition.

5.4. 1,3-Dipolar Cycloadditions. *5.4.1. Utilization of Alkyl Azides* ***4***. To a solution of lactone **1** (0.10−0.360 g; 0.431 mmol−1.55 mmol) in methyl orthoformate (20−25 mL) was added the alkyl azide **4** (2−20 equiv). The reaction mixture was heated under a nitrogen atmosphere for 30 to 65 h. The solvent was evaporated, and the resulting solid residue recrystallized from ethanol. The title compound was obtained as a white solid (38.3−86%).

*5.4.1.1. Synthesis of (3aS,5aR,9aS,9bR)-1-Benzyl-8-phenyl-(5a,6,9a,9b)-tetrahydro-1H-[1,3]dioxino(4′,5′:5,6)pyrano[3,4-d]-[1,2,3]triazol-4(3aH)-one (**7a**).* Lactone **1** (0.36 g, 1.55 mmol), methyl orthoformate (25 mL), benzyl azide (2 equiv, 387 μL, 3.10 mmol), reflux, 65 h; obtained product (0.46 g, 1.26 mmol, 81.3%); mp 177.4−178.1 °C; $[\alpha]_D^{25}$ = −438.0° (conc. 2.7%, DCM); UV−vis: 267.1 nm; IR (nujol mull): ν_{max}/cm^{-1} 1753 (s, C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85−3.78 (m, 1H, 6-H), 3.83 (dd, *J* = 13.2, 4.0 Hz, 1H, 9b-*H*), 4.10 (dd, *J* = 9.6, 4.0 Hz, 1H, 9a-*H*), 4.39 (dd, *J* = 10.0, 5.6 Hz, 1H, 5a-*H*), 4.49 (dd, *J* = 10.8, 5.6 Hz, 1H, 6-*H*), 4.69 (d, *J* = 14.8 Hz, 1H, CH_2), 5.31 (d, *J* = 13.2 Hz, 1H, 3a-*H*), 5.43 (d, *J* = 14.8 Hz, 1H, CH_2), 5.60 (s, 1H, 8-*H*), 7.18−7.16 (m, 2H, Ar), 7.53−7.32 (m, 8H, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 52.7 (9b-C), 54.2 (CH_2), 65.8 (5a-C), 67.8 (6-C), 76.1 (9a-C), 80.8 (3a-C), 102.3 (8-C), 128.2 (CH, Ph), 128.5 (CH, Ph), 128.8 (CH, Ph), 128.9 (CH, Ph), 134.8 (Cq, Ph), 136.3 (Cq, Ph), 161.6 (4-C); *Crystallography*: Formula: $C_{20}H_{19}N_3O_4$; Molecular weight: 365.38; Temperature: 100(2) K; *a* (Å) = 5.6268(11); *b* (Å) = 17.614(3); *c* (Å) = 9.1708(17); (deg) = 105.330(2); GoF: 1.064; *R* = 0.0390.

*5.4.1.2. Synthesis of (3aS,5aR,9aS,9bR)-1-(Propyl-3′-benzyloxy)-8-phenyl-(5a,6,9a,9b)-tetrahydro-1H-[1,3]dioxino(4′,5′:5,6)pyrano-[3,4-d][1,2,3]triazol-4(3aH)-one (**7b**).* Lactone **1** (0.10 g, 0.431 mmol); methyl orthoformate (20 mL); (3-azidopropoxy)methyl) benzene (2 equiv, 166 mg, 0.862 mmol; 100 °C; 44 h; obtained product (70 mg, 0.165 mmol, 38.3%); mp 110.3−110.5 °C; $[\alpha]_D^{25}$ = −235.6 (conc. 2.4%, CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 2097 m, 1772 i (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05−2.02 (m, 2H, 2′-*H*), 3.50 (dt, *J* = 6.4, 3.6 Hz, 2H, 3′-*H*), 3.78 (t, *J* = 10.8 Hz, 1H, 6-*H*), 3.82 (t, *J* = 6.4 Hz, 1H, 1′-*H*), 4.07−4.05 (m, 3H, 9b-*H* + 9a-H + 1′-*H*), 4.22 (dt, *J* = 9.6, 5.6 Hz, 1H, 5a-*H*), 4.43 (dd, *J* = 10.8, 5.6 Hz, 1H, 6-*H*), 4.43 (s, 2H, 4′-*H*), 5.25 (d, *J* = 12.8 Hz, 1H, 3a-*H*), 5.56 (s, 1H, 8-*H*), 7.39−7.27 (m, 8H, Ph), 7.47−7.46 (m, 2H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.2 (2′-C), 48.1 (1′-C), 54.7 (9b-C), 65.6 (5a-C), 67.6 (3′-C), 67.8 (6-C), 73.0 (4′-C), 76.0 (9a-C), 80.2 (3a-C), 102.1 (8-C), 125.9 (CH, Ph), 127.6 (CH, Ph), 127.7 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 129.4 (CH, Ph), 136.2 (Cq, Ph), 138.0 (Cq, Ph), 162.0 (4-C); HRMS (ESI-TOF), found for $C_{23}H_{26}N_3O_5$: 424.1860, calcd: 424.1867.

*5.4.1.3. Synthesis of (3aS,5aR,9aS,9bR)-1-Propyl-8-phenyl-(5a,6,9a,9b)-tetrahydro-1H-[1,3]dioxino(4′,5′:5,6)pyrano[3,4-d]-[1,2,3]triazol-4(3aH)-one (**7c**).* Lactone **1** (0.20 g, 0.86 mmol), methyl orthoformate (20 mL), propyl azide (2 equiv, every 3 h), 95 °C; 30 h; obtained product (0.25 g, 0.754 mmol, 86%). Mp 125.4−126.3 °C; $[\alpha]_D^{25}$ = −279.1 (conc. 3.2%, CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 1774 s (C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H, 3′-*H*), 1.78 (m, 1H, 2′-*H*), 3.65 (ddd, *J* = 13.6, 8.0, 5.6 Hz, 1H, 1′-*H*), 3.80 (t, *J* = 10.4 Hz, 1H, 6-*H*), 3.87−3.80 (m, 1H,1′-*H*), 4.13−4.08 (m, 2H, 9b-*H* + 9a-*H*), 4.27 (dt, *J* = 9.4, 5.4 Hz, 1H, 5a-*H*), 4.47 (dd, *J* = 11.0, 5.4 Hz, 1H, 6-*H*), 5.41 (d, *J* = 13.2 Hz, 1H, 3a-*H*), 5.57 (s, 1H, 8-*H*), 7.46−7.27 (m, 5H, H−Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (3′-C), 21.4 (2′-C), 52.1 (1′-C), 54.8 (9b-C), 65.6 (5a-C), 67.9 (6-C), 76.2 (9a-C), 80.1 (3a-C), 102.3 (8-C), 126.0 (CH, Ph), 128.4 (CH, Ph), 129.6 (CH, Ph), 136.3 (Cq, Ph), 162.0 (4-C); HRMS (ESI-TOF), found for $C_{16}H_{20}N_3O_4$: 318.1455; calcd: 318.1448.

*5.4.2. Utilization of Diazomethylbenzene (**6**).* Diazomethylbenzene (**6**)[12] (3 equiv; 0.35 g; 2.99 mmol) recently obtained and contained in a round-bottom flask was added to a solution of lactone **1** (0.212 g; 0.999 mmol) in dry toluene (18 mL). The reaction mixture was kept under nitrogen, with stirring, and submitted to heat in a preheated oil bath at 60−70 °C. After some time a light pink color developed and faded away after 1 h and 25 min. The reaction mixture was refrigerated in an ice/water bath. A solid precipitated out and was removed by filtration, and the mother-liquid was evaporated to a residue. A white solid (0.210 g; 0.598 mmol; η = 76.3%) was recrystallized from ethanol giving compound **8**.

*5.4.2.1. Synthesis of (4aR,6aR,9aR,9bS)-2,9-Diphenyl-6a,7,9a,9b-tetrahydro-4H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-c]pyrazol-6(4aH)-one (**8**).* Mp = 159.5−160.7 (dec.); $[\alpha]_D^{25}$ = −116 (0.7%, CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 3337 (s, NH); 1750 (s, C═O); 1586. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (1H, dd, *J* = 9.0, 15.2 Hz, *H*-9a); 3.98 (1H, dd, *J* = 9.6, 10.4 Hz, *H*-4$_{ax}$); 4.28−4.37 (2H, m, *H*-4a + *H*-9b); 4.59 (1H, dd, *J* = 4.8, 10.4 Hz, *H*-4$_{eq}$); 4.44 (1H, d, *J* = 15.2 Hz, *H*-6a); 5.57 (1H, s, *H*-2); 6.56 (1H, br s, *H*-7); 7.32−7.35 (3H, m, Ph); 7.40−7.42 (5H, m, Ph); 7.50−7.54 (2H, m, Ph); ^{13}C NMR δ 100.6 MHz, $CDCl_3$) 50.1 (C-9a); 68.0 (C-4); 69.5 (C-4a); 73.2 (C-6a); 75.2 (C-9b); 101.1 (C-2); 125.9 (CH, Ph); 128.0 (CH, Ph); 128.2 (CH, Ph); 128.5 (CH, Ph); 128.6 (CH, Ph); 129.2 (CH, Ph); 136.4 (Cq, Ph); 137.8 (Cq, Ph); 140.7 (C-9); 161.0 (C-6). Elem. Anal. Found: C, 68.48%; H, 5.05%; N, 7.72%. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56%; H, 5.18%; N, 8.00%.

5.4.3. Utilization of Nitrile Oxides. Method A. A solution of 2,6-dichloro-*N*-hydroxybenzimidoyl chloride/*N*-hydroxybenzimidoyl chloride (0.11−0.130 g; 0.58−0.70 mmol) in dry ether (3−5 mL) was added to lactone **1** (0.084−0.091 g; 0.40−0.43 mmol) contained in a round-bottom flask kept under nitrogen and in an ice/water bath. To the previous mixture was added dropwise triethylamine (51−55 mL; 0.037−0.040 g; 0.37−0.39 mmol) recently distilled, in dry ether (6 mL) for 30−40 min. The reaction mixture was stirred at rt for 12−15 h. The volatiles were removed in the rotary evaporator, and the residue was redissolved in dichloromethane (10 mL) and passed through a pad of Celite. The filtrate was evaporated to give solids, as mixtures of isomers **9a**,**b** and **10a**,**b**.

*5.4.3.1. Synthesis of (2R,4aR,6aR,9aR,9bS)-9-(2,6-Dichlorophenyl)-2-phenyl-4,4a,9a,9b-tetrahydro-[1,3]dioxino[4′,5′:5,6]-pyrano[4,3-d]isoxazol-6(6aH)-one (**9a**) and (5aR,8R,9aR,9bR)-3-(2,6-Dichlorophenyl)-8-phenyl-5a,6,9a,9b-tetrahydro-[1,3]dioxino-[4′,5′:5,6]pyrano[3,4-d]isoxazol-4(3aH)-one (**10a**).* 2,6-Dichloro-*N*-hydroxybenzimidoyl chloride (0.130 g; 0.58 mmol), ether (5 mL), lactone **1** (0.084 g; 0.40 mmol), triethylamine (55 mL; 0.040 g; 0.39 mmol), rt; 15 h; white-greenish solid (0.172 g; 0.409 mmol; η = quant.) recrystallized from ethanol, giving two fractions (the ^{1}H NMR spectrum showed a 1.25 (**9a**):1(**10a**) mixture of isomers): the first fraction contained isomer **10a** as a white solid (0.031 g; 0.074 mmol; 19%); the second fraction contained a 3 (**9a**):1(**10a**) mixture of isomers (0.083 g; 0.198 mmol; 50%).

*Isomer **9a** (Contaminated with 25% of Isomer **10a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (1H, dd, *J* = 10.4, 10.8 Hz, *H*-4$_{ax}$); 4.07 (1H, dd, *J* = 7.2, 9.6 Hz, *H*-9b); 4.54 (1H, dd, *J* = 5.6, 10.8 Hz, *H*-4$_{eq}$); 4.83 (1H, dt, *J* = 5.6, 10.0 Hz, *H*-4a); 4.86 (1H, dd, *J* = 7.2, 10.8 Hz, *H*-9a); 5.33 (1H, d, *J* = 10.4 Hz, *H*-6a); 5.41 (1H, s, *H*-2); 6.94−6.98 (2H, m, Ar) 7.15−7.46 (6H, m, Ar); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 51.5 (C-9a); 66.6 (C-4a); 67.9 (C-4); 74.8 (C-9b); 80.4 (C-6a); 101.5 (C-2); 125.6 (CH, Ar); 127.8 (CH, Ar); 128.9 (CH, Ar); 130.7 (Cq, Ar); 135.7 (Cq, Ar); 153.4 (C-9); 163.1 (C-6).

*Isomer **10a**.* Mp = 209.5−211.0 (dec,); $[\alpha]_D^{25}$ = +86.7 (0.3%, CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 1749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (1H, t, *J* = 10.4 Hz, H-4$_{ax}$); 4.17 (1H, dd, *J* = 3.6, 10.0 Hz, H-9b); 4.58 (1H, dd, *J* = 5.2, 10.8 Hz, H-4$_{eq}$); 4.90 (1H, m, H-4a); 4.91 (1H, d, *J* = 10.8 Hz, H-6a); 5.37 (1H, dd, *J* = 3.2, 11.2 Hz, H-9a); 5.68 (1H, s, H-2); 7.34−7.45 (6H, m, H−Ar); 7.55−7.59 (2H, m, H−Ar); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 56.6 (C-6a); 65.2 (C-4a); 68.0 (C-4); 75.1 (C-9b); 77.9 (C-9a); 102.6 (C-2); 125.5 (CH, Ar); 126.4

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(CH, Ar); 128.2 (CH, Ar); 128.4 (CH, Ar); 129.6 (CH, Ar); 132.0 (Cq, Ar); 135.1 (Cq, Ar); 136.1 (Cq, Ar); 149.6 (C-9); 161.4 (C-6). HRMS (ESI-TOF), found for $C_{20}H_{15}Cl_2NO_5$: 420.0397; calcd 420.0400.

*5.4.3.2. Synthesis of (2R,4aR,6aR,9aR,9bS)-2,9-Diphenyl-4,4a,9a,9b-tetrahydro[1,3]dioxino[4′,5′:5,6]pyrano[4,3-d]isoxazol-6(6aH)-one (**9b**) and (3aR,5aR,8R,9aR,9bS)-3,8-Diphenyl-5a,6,9a,9b-tetrahydro[1,3]dioxino[4′,5′:5,6]pyrano[3,4-d]isoxazol-4(3aH)-one (**10b**).* *N*-Hydroxybenzimidoyl chloride (0.11 g; 0.70 mmol), dry ether (3 mL), lactone **1** (0.091 g; 0.43 mmol), triethylamine (51 mL; 0.037 g; 0.37 mmol), 12 h; white solid (0.132 g; 0.38 mmol; μ = 87.6%) constituted by a mixture of 1 (**9b**):1.25 (**10b**). Isomer **9b** was obtained from dichloromethane (0.036 g; 0.102 mmol; 24%). Isomer **10b** recrystallized from dichloromethane (0.085 g; 0.24 mmol; 56%), contaminated with 25% of isomer **9b**.

*Isomer **9b**.* Mp = 296.0−298.0 °C (dec.); $[\alpha]_D^{25}$ = −93.6 (0.25%; CH_3CN); IR (nujol mull): ν_{max}/cm^{-1} 1758; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (1H, dd, J = 10.2, 10.8 Hz, H-4_{ax}); 4.18 (1H, dd, J = 7.4, 9.8 Hz, H-9b); 4.46 (1H, dd, J = 5.2, 10.2 Hz, H-4_{eq}); 4.58 (1H, dt, J = 5.6, 10 Hz, H-4a), 4.60 (1H, dd, J = 7.2, 9.2 Hz, H-9a); 5.20 (1H, d, J = 9.6 Hz, H-6a); 5.46 (1H, s, H-2); 6.71−6.76 (2H, m, Ph); 7.07−7.13 (2H, m, Ph); 7.20−7.26 (1H, m, Ph); 7.36−7.49 (3H, m, Ph); 7.75−7.80 (2H, m, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.7 (C-9a); 66.6 (C-4a); 67.9 (C-4); 74.9 (C-9b); 80.8 (C-6a); 101.6 (C-2); 125.8 (CH, Ph); 128.0 (CH, Ph); 128.1 (CH, Ph); 128.5 (CH, Ph); 128.9 (CH, Ph); 129.1 (CH, Ph); 130.4 (Cq, Ph); 135.7 (Cq, Ph); 157.3 (C-9); 163.7 (C-6). Elem. Anal. Found: C, 67.32; H, 4.79; N, 4.09. Calcd for $C_{20}H_{17}NO_5 \cdot 1/3H_2O$: C, 67.22; H, 4.98; N, 3.92.

*Isomer **10b**.* Mp = 220.7−222.5 °C (dec.); $[\alpha]_D^{25}$ = +184 (0.3%; CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (1H, t, J = 10.4 Hz, H-4_{ax}); 4.12 (1H, dd, J = 3.2, 9.6 Hz, H-9b); 4.50 (1H, dd, J = 5.4, 11.0 Hz, H-4_{eq}); 4.72 (1H, dt, J = 5.6, 10.0 Hz, H-4a); 4.98 (1H, d, J = 10.8 Hz, H-6a); 5.32 (1H, dd, J = 3.2, 10.8 Hz, H-9a); 5.65 (1H, s, H-2); 7.38−7.48 (6H, m, Ph); 7.53−7.58 (2H, m, Ph); 7.89−7.93 (2H, m, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 55.0 (C-6a); 65.3 (C-4a); 68.0 (C-4); 75.5 (C-9b); 78.5 (C-9a); 102.5 (C-2); 126.4 (CH, Ph); 126.7 (CH, Ph); 127.7 (CH, Ph); 128.4 (CH, Ph); 128.8 (CH, Ph); 129.6 (CH, Ph); 131.0 (Cq, Ph); 136.2 (Cq, Ph); 152.4 (C-7); 162.5 (C-6). Elem. Anal. Found: C, 67.32; H, 4.79; N 4.09. Calcd for $C_{20}H_{17}NO_5 \cdot 1/3H_2O$: C, 67.22; H, 4.98; N 3.92.

Method B. To a suspension of *N*-chlorosuccinimide (0.227 g; 1.70 mmol) in dichloromethane (3 mL) was added a solution of acetaldehyde oxime (0.127 g; 2.14 mmol) and pyridine (0.05 mL) in dichloromethane (2 mL). The mixture was stirred until complete NCS dissolution. To this mixture was added lactone **1**.

*5.4.3.3. Synthesis of (2R,4aR,6aR,9aR,9bS)-9-Methyl-2-phenyl-4,4a,9a,9b-tetrahydro[1,3]dioxino[4′,5′:5,6]pyrano[4,3-d]isoxazol-6(6aH)-one (**9c**) and (3aR,5aR,8R,9aR,9bR)-3-Methyl-8-phenyl-5a,6,9a,9b-tetrahydro[1,3]dioxino[4′,5′:5,6]pyrano[3,4-d]isoxazol-4(3aH)-ona (**10c**).* A solution of lactone **1** (0.10 g; 0.431 mmol) in dry toluene (18 mL) was added to the acetaldehyde oxime generated "*in situ*" followed by dropwise addition of triethylamine (0.5 mL; 3.16 mmol) in dry toluene (5 mL), for 2 h. The reaction mixture was stirred at rt for 15 h. The solvents were removed in rotary evaporator, and the residue was redissolved in dichloromethane and passed through a pad of Celite. The filtrate was evaporated to give a solid consisting of a 1.2 (**9c**):1 (**10c**) mixture of adducts. The crude product was recrystallized from ethanol to give two fractions: the first fraction contained a pure isomer (**10c**) as a white solid (0.035 g; 0.12 mmol; 28%); the second fraction contained the other isomer **9c** which was not possible to purify from impurities (0.075g).

*Isomer **9c**.* ^1H NMR (400 MHz, $CDCl_3$) (some peaks of isomer **9c**, taken from a spectrum containing both isomers **9c** and **10c**) δ 2.15 (3H, d, J = 0.8 Hz, CH_3); 3.85−3.77 (m, 1H); 3,90 (1 H, dd, J = 7.6, 9.80 Hz, H-4a); 4.12 (1H, dd, J = 7.3, 9.6 Hz, H-9b); 4.46−4.53 (m, 1H); 5.01 (1H, d, J = 10.8 Hz, H-6a); 5.54 (1H, s, H-2); 7.31−7.35 (3H, m, Ph); 7.37−7.42 (2H, m, Ph).

*Isomer **10c**.* Mp = 229.7−231.5 (dec.); $[\alpha]_D^{25}$ = +33.6 (0.75%; CH_2Cl_2); IR (nujol mull): ν_{max}/cm^{-1} 1744 cm^{-1} (s, C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (3H, d, J = 0.8 Hz, CH_3); 3.82 (1H, t, J = 10.6 Hz, H-4_{ax}); 4.06 (1H, dd, J = 3.4, 10.0 Hz, H-9b); 4.34 (1H, dd, J = 0.8, 10.0 Hz, H-3a); 4.51 (1H, dd, J = 5.6, 10.8 Hz, H-4_{eq}); 4.62 (1H, dt; J = 5.2, 10.0 Hz, H-4a); 5.09 (1H, dd, J = 3.2, 10.8 Hz, H-9a); 5.62 (1H, s, H-2); 7.37−7.42 (3H, m, Ph); 7.50−7.54 (2H, m, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.6 (CH_3); 58.2 (C-6a); 65.3 (C-4a); 67.9 (C-4); 75.2 (C-9b); 76.7 (C-9a); 102.5 (C-2); 126.3 (CH, Ph); 128.4 (CH, Ph); 129.6 (CH, Ph); 136.1 (Cq, Ph); 150.8 (C-3); 162.2 (C-4). Elem. Anal. Found: C, 61.36; H, 5.54; N 4.89. Calcd for $C_{15}H_{15}NO_5 \cdot 1/3H_2O$: C, 61.01; H, 5.35; N, 4.74.

5.5. Computational Methodology. All geometry optimizations were performed with Gaussian 09,[17] by applying density functional theory,[18] with the B3LYP functional[19] together with the 6-31G(d) basis set.[20] The geometry optimizations were conducted with a conductor-like polarizable continuum model using the integral equation formalism variant (IEF-PCM).[21]

In all geometry optimizations, we first searched for the transition state starting from a structure similar to the reactant model. This was generally obtained with undimensional scans along the particular reaction coordinate in which we were interested. Once a putative transition structure was located, it was fully optimized. The reactants and products associated with it were determined after intrinsic reaction coordinate (IRC) calculations. In all cases, the geometry optimizations and the stationary points were obtained with standard Gaussian convergence criteria. The transition state structures were all verified by vibrational frequency calculations, having exactly one imaginary frequency with the correct transition vector, even using frozen atoms, which shows that the frozen atoms were almost free from steric strain. The ZPE and thermal and entropic energy corrections were calculated using the same method and basis set (T = 310.15 K, P = 1 bar).

The final electronic energies were calculated using the all-electron 6-311++G(3df,2pd) basis set and the functional M06-2X.[22,23] A conductor-like polarizable continuum model using the integral equation formalism variant (IEF-PCM), as implemented in Gaussian 09, with a dielectric constant of 2.4, 4.0, 33.0 was used to simulate the toluene, diethyl ether, and methanol solvent, respectively.[21]

All the activation and reaction energies provided in the text and figures refer to free energy differences calculated at the M06-2x/6-311++(3df,2pd) level detailed above, while the atomic charge distributions were calculated at the B3LYP level by employing a Mulliken population analysis, using the basis set 6-31G(d).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02518.

NMR spectra and X-ray data for **7a** (PDF)

All the structures of reactants, transition states and products of the studied reactions (ZIP)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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