Combined experimental and computational studies devoted to the synthesis of 1,4-lactones

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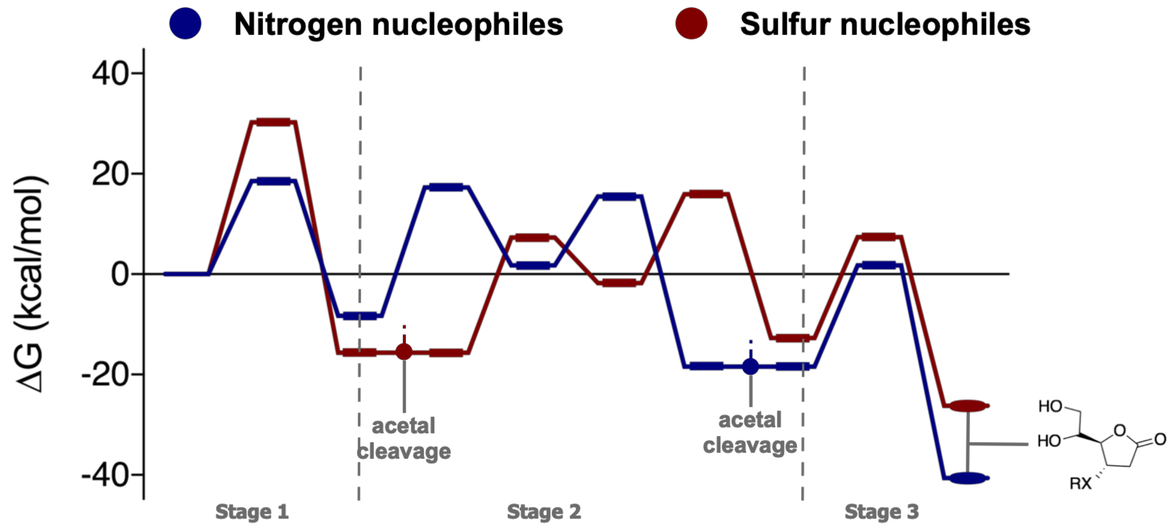
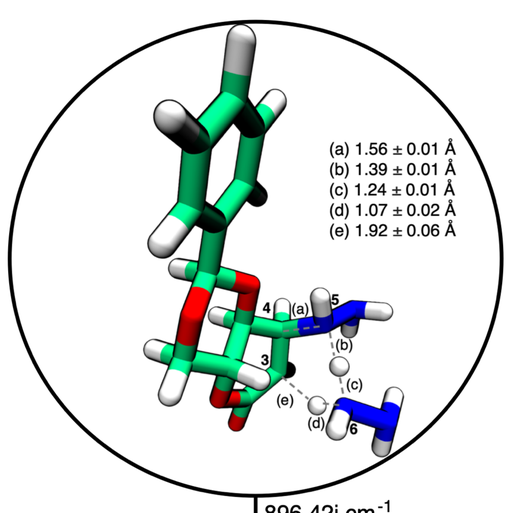
INTRODUCTION

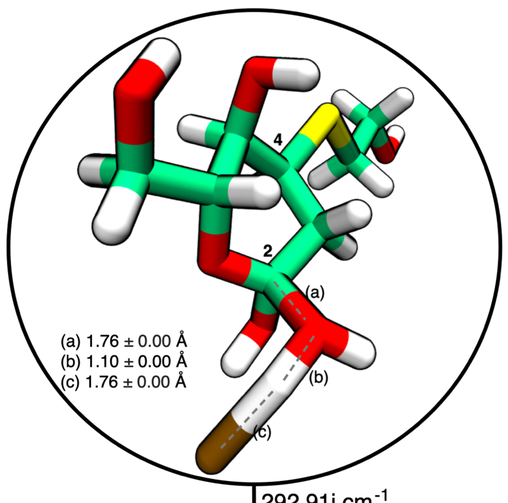
Lactones are important biological molecules that offer a new molecular scaffold to develop new and more selective inhibitors targeting glycosidases. The chemical routes that can speed up their synthesis in a *stereo*- and *regio*-selective way have become a major demand. A new derivative of 2,4-O-alkylidene-D-erythrose, enclosing a C=C moiety into a 1,5-lactone ring, was found to induce a complete facial selectivity in 1,3-dipolar cycloadditions. This new D-erythrosyl 1,5-lactone was studied as a Michael acceptor with sulfur and nitrogen nucleophiles and from which a complete facial selectivity was demonstrated in all reactions. Sulfides attack exclusively at C-4, but primary amines and hydrazine attack both at C-2 and C-4. The sulfur adducts formed are 1 (D-erythrose derivative):1 (nucleophile), and the nitrogen adducts are 1:2. The theoretical and computational results clearly explain the origin of the *stereo*-selectivity, and the energetic course of the reactions, starting with nitrogen and sulfide nucleophiles. Considering that the 1,4-lactones obtained in this work offer a new molecular scaffold for organic synthesis, these new results provide a solid theoretical platform that can be used to speed up synthesis of other derivatives
in a *stereo*- and *regio*-selective way.

RESULTS

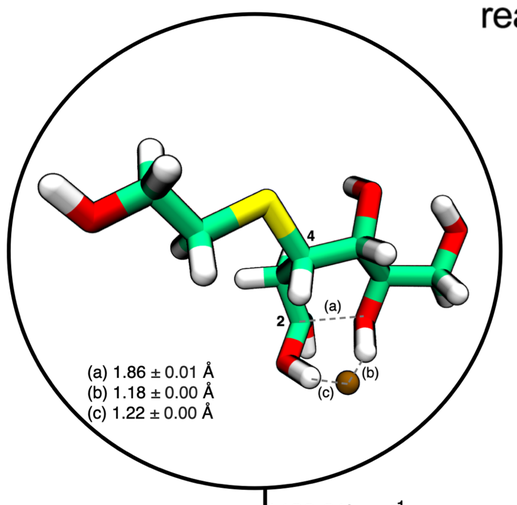




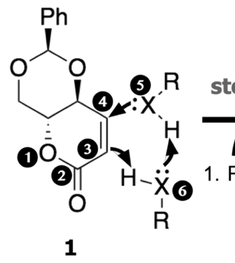
896.42i cm^{-1}



292.91i cm^{-1}



1428.61i cm^{-1}



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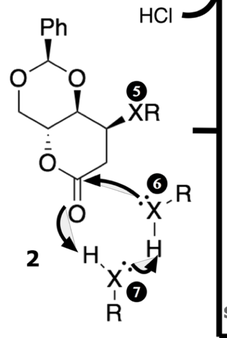
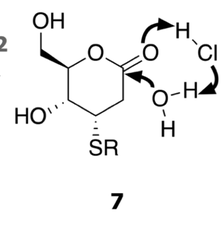


2

2a X = S R = CH_2CH_2OH
2b X = S R = Bn

Acetal cleavage
HCl



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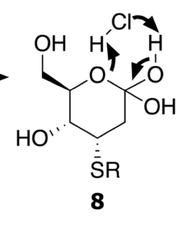

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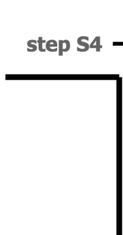
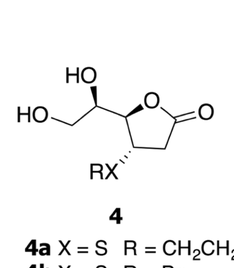


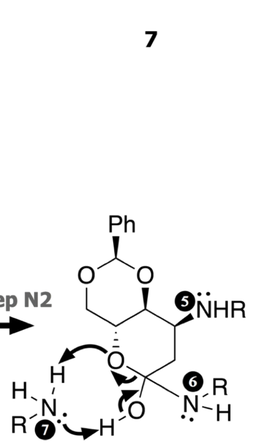
5

5a X = S R = CH_2CH_2OH Y = OH
5b X = S R = Bn Y = OH
5c X = NH R = CH_2CH_2OH Y = XR
5d X = NH R = Bn Y = XR
5e X = NH R = Pr Y = XR



4

4a X = S R = CH_2CH_2OH
4b X = S R = Bn
4c X = NH R = CH_2CH_2OH
4d X = NH R = Bn
4e X = NH R = Pr



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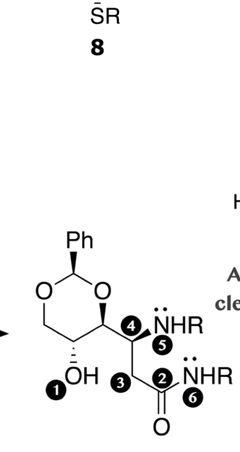
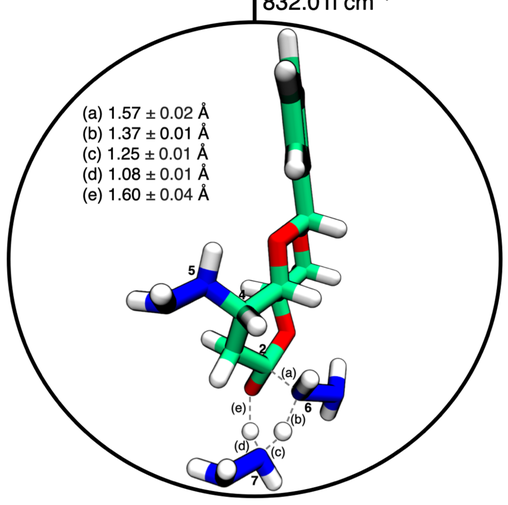
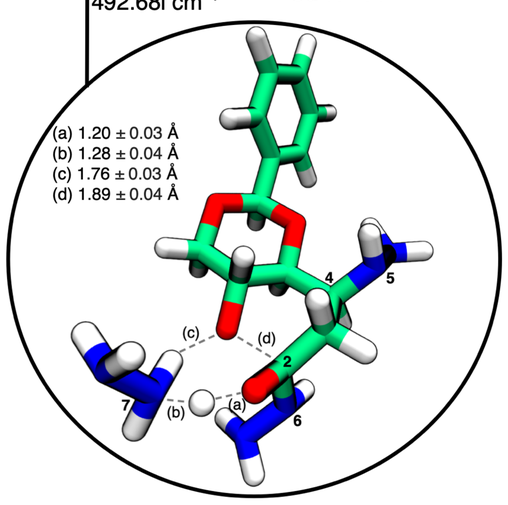


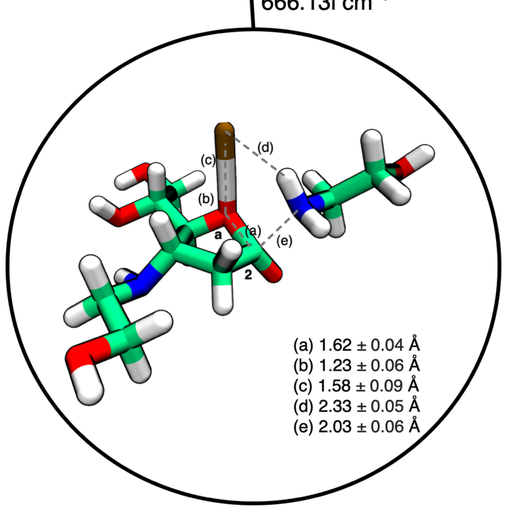
3

3a R = NH_2
3b R = CH_2CH_2OH
3c R = Bn
3d R = Pr

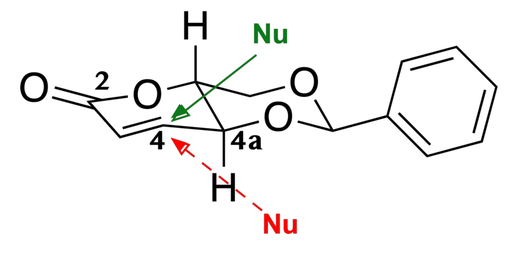
Acetal cleavage
step N4
HCl







The origin of the stereoselectivity observed in these reactions can be justified by the position occupied by hydrogen H-4a from the lactone that precludes the nucleophile molecule to attack the lactone at the bottom face.



METHODS

All geometry optimizations were performed with Gaussian 09, applying density functional theory. Becke's three-parameter exchange functional together with the 6-31G(d) basis set was used for all atoms.The final electronic energies were calculated using the all-electron 6-311++G(3df,2pd) basis set and the functional B3LYP for all atoms. A conductor-like polarizable continuum model using the integral equation formalism variant (IEF-PCM), as implemented in Gaussian 09, was used to simulate the water solvent with different dielectric constant.

CONCLUSION

- Reaction of lactone with the nitrogen nucleophiles is from kinetic and thermodynamic points of view more favored than the one with sulfur nucleophiles.

- The lower reactivity of the sulfur nucleophiles in relation to the nitrogen nucleophiles can be attributed to the larger size of the sulfur atoms that during the nucleophilic attack generates some steric hindrance near the carbon of the lactone, which does not favor the chemical reaction.

- The studied reactions bring a great advantage to organic chemistry since they are *stereo*- and *regio*specific.

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