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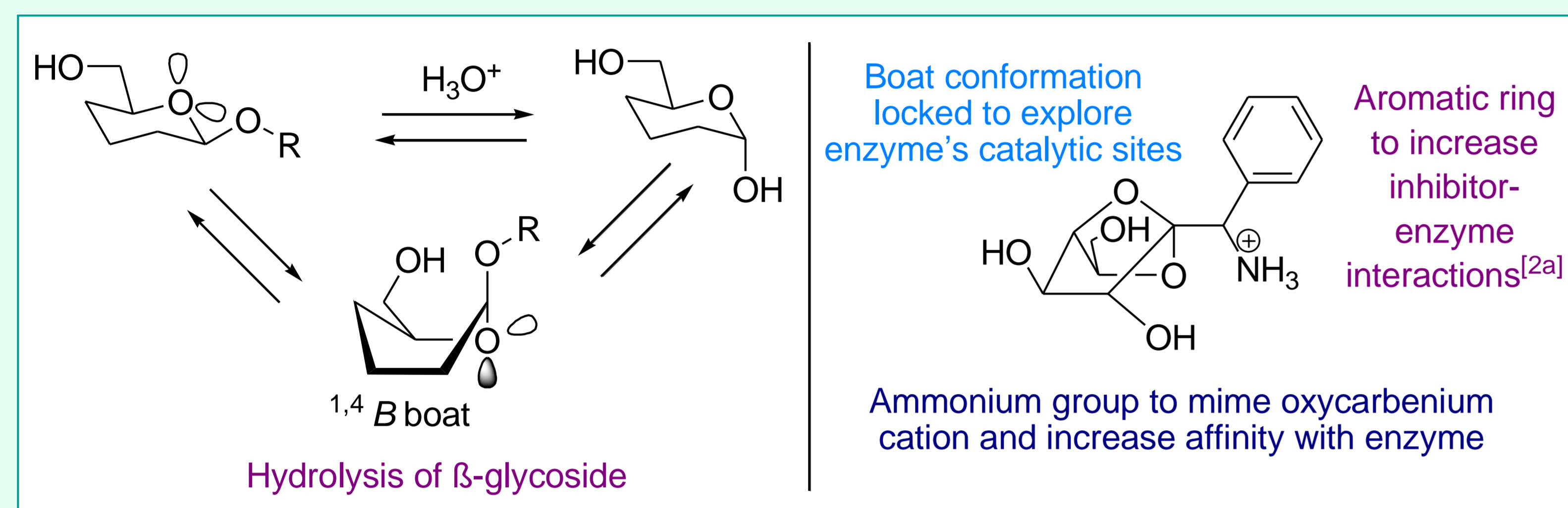
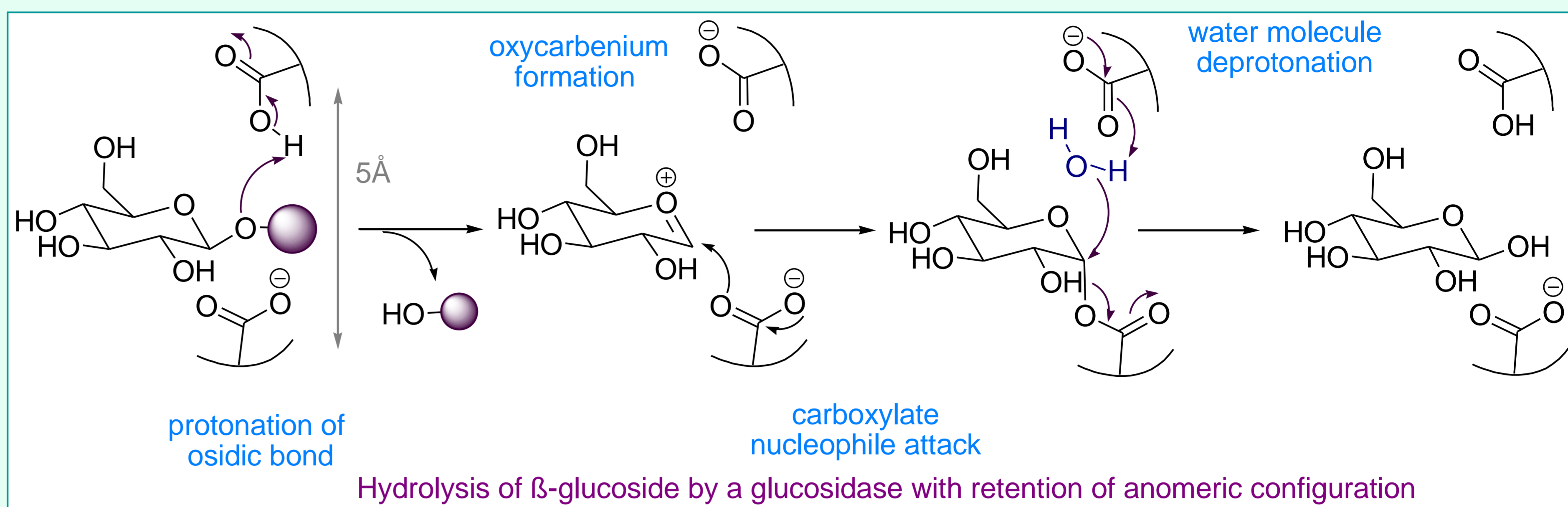
SYNTHESIS OF BOAT LOCKED GALACTOSIDES AS ENZYME INHIBITORS AND CONFORMATIONAL PROBES

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RATIONAL DESIGN OF GLYCOSIDASES INHIBITORS

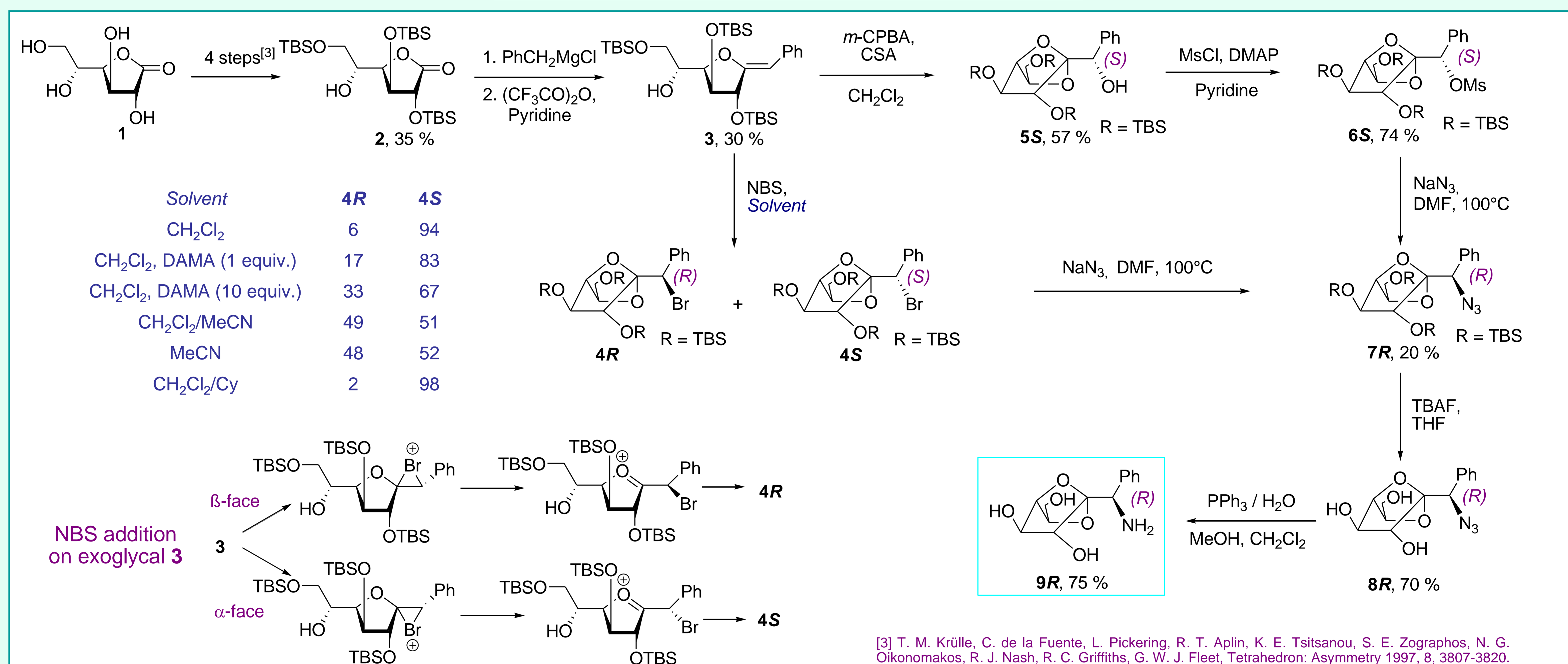
Glycoside hydrolases or glycosidases are the enzymes catalysing the hydrolysis of glycosidic bonds. Their structures have been extensively studied and, for some of them, have been determined at the molecular level. Their mechanism are being probed by means of specific design and synthesis of mono- and oligosaccharide mimics as well as glycoconjugates.[1] Despite the large number of known glycosidases, their catalytic mechanisms are similar. They typically operate by means of acid/base catalysis with inversion or retention of the anomeric configuration. For the latter class, a nucleophilic catalysis involves a covalent intermediate between the enzyme and its substrate. During the past decade, there has been increasing evidence that several glycosidases are adapted to recognize and stabilize high-energy conformations of carbohydrate units before or during the hydrolytic process. Particularly, pyranoses may adopt a distorted boat or skewboat conformation instead of the relaxed ⁴C₁ chair conformation.[2]



In order to study the mechanism of a key enzyme involved in the bacterial cell wall biosynthesis of important pathogens, we developed an efficient method for the synthesis of galactose derivatives locked in a ^{1,4}B boat conformation.[3] We present here the synthesis of constrained galactosides, designed to mimic the putative transition state or the conformation of high-energy intermediates of the enzymatic glycoside hydrolysis.

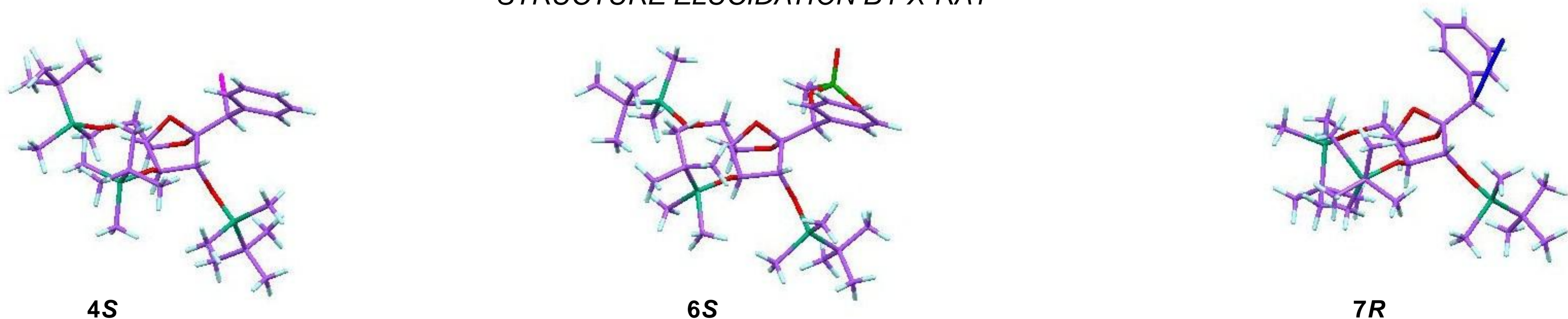
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STRUCTURE ELUCIDATION BY X-RAY



CONCLUSION AND PERSPECTIVES

The target molecule has been synthesized in 12 steps. The intermediate compounds stereochemistry has been determined by DRX analysis. As we could confirm the mesylate substitution by azide follows a S_N2 mechanism. Phosphonate galactosides locked in ^{1,4}B boat conformation have been synthesized according to this strategy. Stereochemical effects have been observed and are actually examined. These compounds series will be tested as glycosidases inhibitors.

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