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# Synthesis of 3,5-diazabicyclo [5.1.0] octenes. A new platform to mimic glycosidase transition states

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ABSTRACT

All-*cis* 1-hydroxymethyl 2,3 bis-aminomethyl cyclopropane was used to construct the first 3,5-diazabicyclo [5.1.0]-3-octenes. This system has the interesting ability to exist in a conformation that resembles a snapshot of a glycoside hydrolysis reaction with respect to charge and geometric analogy to an oxocarbenium ion, and the positioning of the departing aglycon. The *cis*-configured cyclopropane core was synthesized by Cu-catalyzed intramolecular cyclopropanation of benzyl protected *cis*-2-butene-1,4-diol diazoacetate ester. Serial functionalization to bis-aminomethyl cyclopropanes and subsequent cyclization to amidines lead to the target bicyclic compounds in good overall yields. Several glycosidases were surveyed for the inhibitory potential of these transition state analogs, and amongst them, selective competitive inhibitors with micromolar $K_i$ values were identified.



## 1. Introduction

As an enzyme guides reacting substrate ensembles over the reaction coordinate, it provides a dynamic complementarity to afford low energy pathways leading to products.[1,2] A significant component to the rate acceleration has been ascribed to transition state complementarity,[3] whereby favorable binding interactions between enzyme and the fleeting transition state provide a decrease in the activation barrier. As this concept evolved further, the observed tight binding of stable chemical compounds that were analogs of the transition state was rationalized on the basis of the favorable complementarity between the transition state analog and the enzyme.[4] A number of potent inhibitors has been identified that presumably operate in this way.[5–7] This is never a simple matter; an implicit design problem is that stable ground state molecules only approximate the electronic and geometric configuration of a transition state. For example, consider $S_N2$-like (e.g., $A_ND_N$ type)[8] reactions, there is a degree of pentavalent character at the electrophilic carbon that depends on nucleophile and leaving group bond orders, and the timing, or symmetry of bond breaking and formation. Likewise, in a dissassociative $S_N1$-like e.g., $[D_N+A_N]$[8] reaction that generates carbocationic transition states or intermediates, (or the corresponding capture of these species by nucleophile in the reverse reaction) the leaving group departs in a trajectory nearly orthogonal to the plane defining the carbocation atoms (Fig. 1).

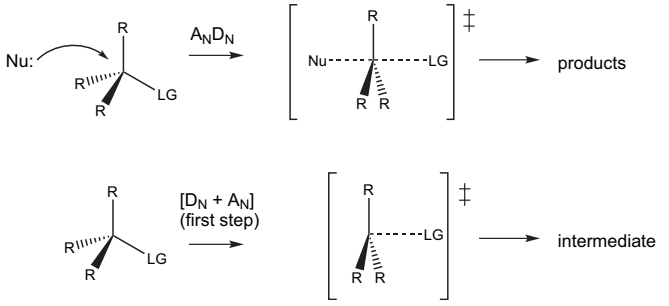


**Figure 1.** Transition structures for hypothetical associative and disassociative reactions. Note the non-standard geometries at the central carbon atom.

In both of these reaction types, the bonding between the leaving group, nucleophile, and central carbon atom have non-ground state angular geometries and partial bonds having lengths greater than found for stable ground state molecules. Mimicry of these structures using direct connectivity with first or second row elements is difficult, if not impossible. We sought to develop an approach to circumvent the geometric limitations imposed by direct connectivity. Our initial focus is on glycosidase and

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glycosyltransferase enzymes, responsible for creation of carbohydrate structures of incredible diversity and complexity.[9] The creation and hydrolysis of the glycosidic bond are central to the extremely broad biological functions found for carbohydrates,[10] making glycosyl transfer enzymes important targets for inhibition.[11] The reaction mechanisms for glycosidases vary in detail with respect to acid/base chemistry, and the nature of nucleophilic participation.[12,13] However, with few exceptions[14] a common mechanistic element is that as the glycosidic bond is being cleaved, the sugar glycon develops oxocarbenium ion character. This places the departing aglycon in a Burgi/Dunitz like trajectory[15,16] over the glycon ring, which is flattened and positively charged.[17,18] Figure 2 shows a conceptual model for inhibitor design whereby the transition state is simulated with a rigid bicyclic ring system used to position an aglycon analog over the plane of a positively charged ring, analogous to the flattened oxocarbenium ion like transition state of typical glycohydrolase enzymes.

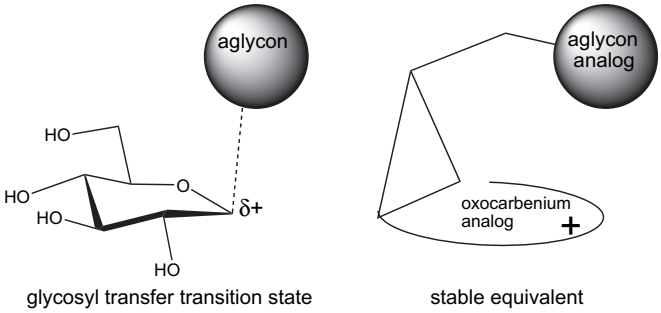


**Figure 2.** A mimic (right) for disassociative glycosyl transfer transition states (left).

With the exploration of this design strategy, we expand the well-known ability of sugar analogs with basic nitrogen atoms to inhibit glycosidases.[7,19,20] Further, inclusion of the aglycon or a nucleophile into the inhibitor structure with transition state geometric constraint affords opportunities to increase binding affinity and direct specificity. In the present study, we describe synthesis of parent molecules that could serve to validate this concept and provide the basis for synthesis of more elaborate compounds. Figure 3 presents our targets, substituted 3,5-diazabicyclo-[5.1.0] octanes, which to the best of our knowledge have not been reported. They are both geometric and charged analogs of glycosidase transition states. The amidinium portion of the ring mimics the charge and shape of a glycosyl oxocarbenium ion,[21] because it is flattened, positively charged, and has delocalization of charge. The all-*cis* cyclopropyl ring system creates an oriented tether with

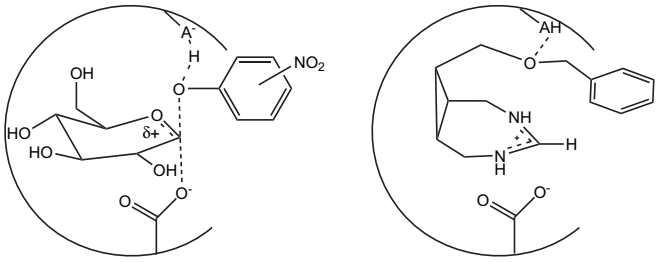


**Figure 3.** Archetypical glycosidase transition state and bicyclic amidinium analog. On the left is a model for an enzyme bound glycosidase transition state featuring oxocarbenium ion character and the leaving group orthogonal to the π-system of the oxocarbenium ion. The bicyclic amidine on the right places an analog of a phenolic leaving group aglycon above the amidine plane that mimics the electronics and flat geometry of an oxocarbenium ion.

which to attach an analog of a leaving group aglycon. Earlier work has explored geometric and electronic aspects of this design.[22,23] The compounds we report here are an interesting counterpoint to the calystegines, which are glycosidase inhibitors with a bridged bicyclic nortropane skeleton.[24] Presumably the bicyclic framework of the calystegines serves to rigidify the ring and hydroxyl group positions, whereas, the design presented in this work utilizes a bicyclic diaza-framework to position the aglycon and provide delocalized charge mimicry.

## 2. Results and discussion

### 2.1. Synthesis of bicyclic amidines

We envisioned arriving at our target [5.1.0] diaza bicyclooctenes by cyclization of bis-amino all-*cis* cyclopropanes. Scheme 1 presents the route for synthesis of the key intermediate bis-aminomethyl cyclopropane **8**.

*cis*-2-Butene-1,4-diol **1** was converted to the monobenzylated derivative **2** using standard methods.[25] Subsequent reaction of the free hydroxyl group with diketene gave the unsaturated β-keto ester **3** in 86% yield.[26] Reaction of **3** with *p*-ABSA (*p*-acetamido benzenesulfonyl azide) in $Et_3N$ gave the desired *cis*-diazoacetic ester **4**.[26] A key step in this synthetic design was the intramolecular cyclopropanation of **4** to give an all-*cis* trisubstituted cyclic system. With intramolecular cycloaddition, only one fused bicyclic ring is formed due to geometric constraints.[27] Hence, starting from a *cis*-alkene, the resulting fused cyclopropyl lactone **5**[26] will have all substituents in an all-*cis* relative configuration. Several cyclopropanation catalyst systems were explored, leading to identification of copper triflate and Evan's bis-oxazoline valinol ligand[28] as being optimal, producing (+)-**5** in 60% yield. The ee obtained for **5** was only 22%,[26] but was fully acceptable for this work given that our target and intermediates were *meso* compounds. The lactone ring of **5** was reductively opened with $LiAlH_4$ to give the *meso* diol **6** in 74% yield. Conversion to the bis-azide **7** was smoothly effected by mesylation of **6** and displacement with azide in DMF at 60 °C. The diazide **7** was used without further purification for synthesis of diamine **8** in (95% yield, two steps) by triphenylphosphine mediated reduction. All-*cis* cyclopropanes related to compound **8** have recently been discussed as potential tripodal ligands for Pd-based catalysts, so compounds like **8** may be of further interest for creation of new Pd ligands.[29]

Scheme 2 presents the conversion of **8** into different bicyclic amidines **9**–**13**. Initial attempts to synthesize compound **9** using neat trimethyl orthoformate/HCl instead lead to bis-formamide **14** based on MS and 500 MHz NMR analyses. While cyclization with 1 equiv of trimethyl orthoformate proved to afford **9** in 46% yield, we sought an alternate method to give improved yields. Reaction