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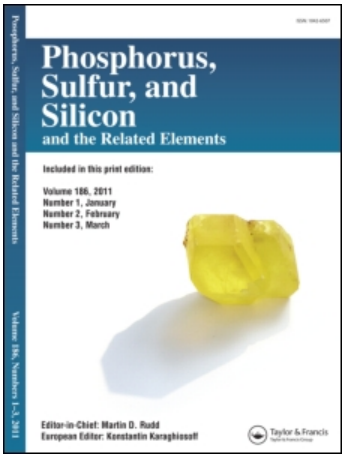

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Atropisomeric Transition State Analogs

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Atropisomerism is shown to be a useful design element for transition state analogs. A hydride transfer reaction between dihydroquinolines and ketones was mimicked using 1-substituted 2-naphthoamide derivatives.

Keywords: atropisomerism; transition state analogs; catalytic antibodies; alcohol dehydrogenase; 2-naphthoic acid derivatives

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INTRODUCTION

Transition state mimicry represents one of the most successful paradigms in enzyme inhibitor design. One of its remarkable applications has been the development catalytic antibodies, whereby stable transition state analogs (TSA) of chemical reactions are used to create new catalytic activities by immunization.[1] Covalent constraints such as carbocycles are frequently used in TSA to enforce a conformation resembling that of a transition state. Herein we report the design and synthesis of TSA using atropisomerism as key element of conformational control. Atropisomerism relates to the existence of stereoisomers in structurally constrained molecules due to a frozen rotation around a carbon-carbon bond, for example in binaphthol.[2]

RESULTS

In our effort to create an alcohol dehydrogenase catalytic antibody,[3] we faced the necessity to design a conformationally stable transition state analog for hydride transfer between a dihydropyridine and a carbonyl compound. Based on calculated transition state structures[4] and on evidence that N-oxide and phosphonates are suitable mimics for polarized carbonyl groups to induce antibodies catalyzing ketone reductions with $NaBH_3CN$,[5] we designed phosphonate **1** and N-oxide **2** to serve as mimics for a hydride transfer from a secondary alcohol to give 1,4-dihydroquinolines **3** and a methyl ketone.

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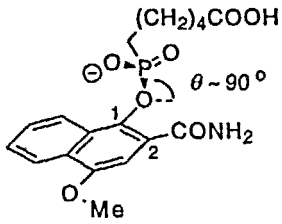

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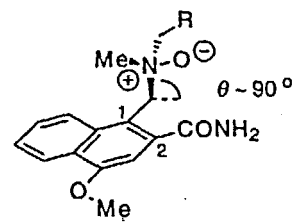
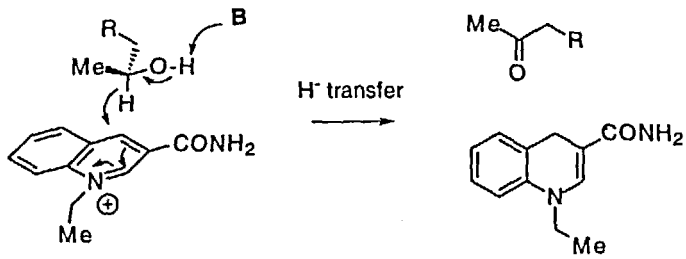


2a (R = $(CH_2)_5COOH$)
2b (R = CH_3)



3

Molecular modeling shows that TSA **1** and **2** display atropisomerism due to a frozen rotation of their $C^{(1)}$ substituent, with the

dihedral angles θ ($C^{(2)}$-$C^{(1)}$-O-P) and θ ($C^{(2)}$-$C^{(1)}$-C-N) being fixed at approximately 90°. The phosphonate in **1** and N-oxide in **2** are positioned above the naphthalene ring and mimic the polarized C-O bond during hydride transfer. A general base (B) induced by these groups during immunization would be placed suitably to assist alcohol oxidation by deprotonation. Both analogs show excellent spatial and electrostatic overlap with a transition state model of the reaction.

Phosphonylation of naphthol **4** with phosphonyl dichloride **5** under a variety of conditions gave only cyclized product **6**. By contrast compound **2a** and its dimethyl analog **2b** were readily prepared by sequential aminolysis of bromide **7** with $MeNH(CH_2)_6COOEt$ or Me_2NH (20 °C → CH_2Br) and ammonia (100 °C → CO_2Me), followed by N-oxidation with *m*-CPBA.

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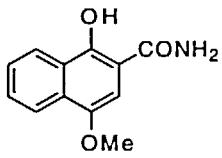

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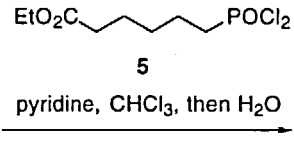

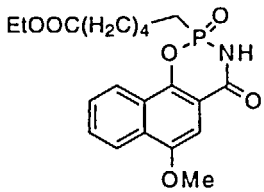

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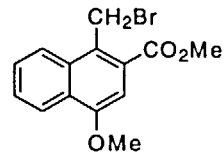

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Variable temperature ^{1}H- and ^{13}C-NMR spectra of compound **2b** show signal coalescence for the benzylic methylene group (T_c = 40 °C, k_{coal} = 100 s^{-1}) and the methyl substituents of the N-oxide (T_c = 30 °C,

k_{coal} = 184 s^{-1}), corresponding to an activation energy of ΔG = 62 $kJmol^{-1}$ for hindered rotation around the benzylic bond. Similar numbers are obtained by molecular modeling. Although this rotation barrier is insufficient to allow isolation of atropisomers, it is well sufficient to ensure that only the desired conformers are significantly populated in solution.

CONCLUSION

Atropisomerism, more generally the existence of preferred conformers in flexible molecules, can be used to design accurate transition state analogs. A relatively low rotational barrier is sufficient to ensure that a particular conformer is populated by > 95 %. This TSA design principle illustrated here for a hydride transfer reaction may be applicable to many couplings involving carbon-carbon double bonds such as aldol and aromatic substitution reactions.

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