

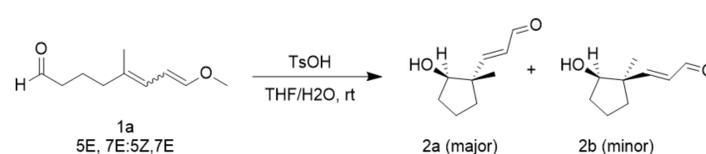
Generation of All-Carbon Quaternary Stereocenters Using a Novel, Acid-Initiated Vinylogous Aldol Reaction (VAR)

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Abstract

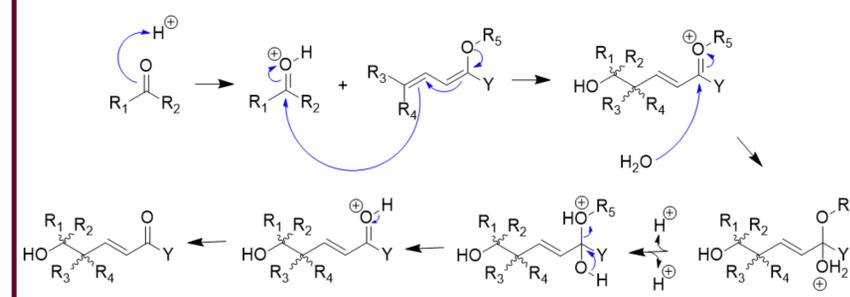
Tetrahedral all-carbon stereocenters are of much interest in synthetic chemistry due to their prevalence in biological molecules and pharmaceuticals.¹ However, molecules featuring these moieties are difficult to prepare due to the steric and torsional strain that occurs during their construction. The desire for stereoselective product formation further complicates synthesis techniques. During an unrelated project, we discovered that dienol ethers tethered to aldehyde electrophiles condense to form cyclic products containing an all-carbon quaternary stereocenter with high yield and stereoselectivity. We present here the initial results of a methodology study to explore the scope and limitations of this approach to stereoselectively prepare all-carbon quaternary stereocenters. Thus far, we have observed the operation of the reaction with three different tether types connecting the reacting functional groups: four-carbon, five-carbon, and methyl-substituted five-carbon. Illustrated are the outcomes regarding performance of the three tether types examined and insights about the sensitivity of the reaction with three different dienol ethers.

Original VAR and Data³

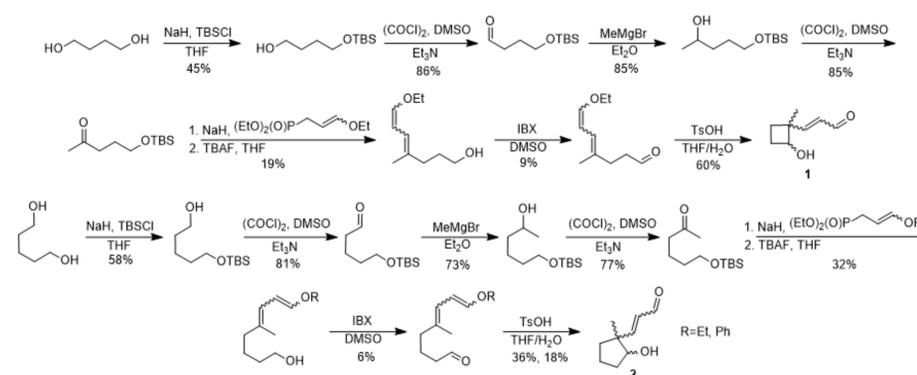


eq. TsOH	Yield	Time (h)	d.r.
1	93%	1	10:1
0.01	Quan.	4	10:1

Key Step Mechanism



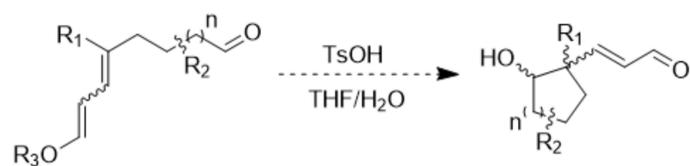
Complete Synthetic Scheme and Data



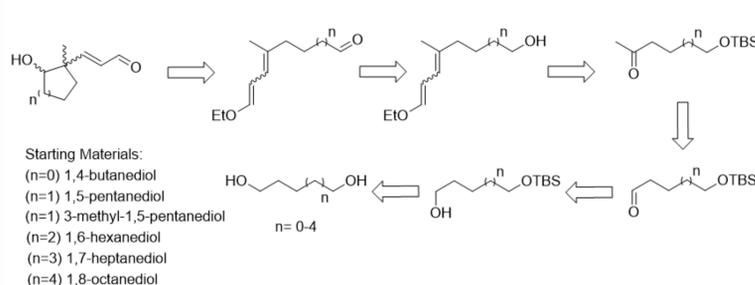
Title compound	eq. TsOH	Time (h)	d.r.
1 R=Et	0.01	12	2:1
2 R=Et	0.01	12	3:1
2 R=Ph (50°C)	0.01	48	1:1
3 R=Et	0.01	12	1:1
2* R=Me	0.01	4	10:1
2* R=Me	1	1	10:1

*original cyclic aldol

Proposed Methodology Study



Retrosynthetic Plan



Conclusions and Future Directions

We have confirmed and reproduced the performance of our novel aldol reaction in forming an all-carbon quaternary stereocenter within different size ring structures, using both an ethyl and phenyl variation of the phosphonate reagent. We now hope to separate stereoisomers and obtain spectral data from the successful cyclic aldol products of carbon tether lengths four, five, and five with a 3-methyl substitution. We are also in the process of testing tether lengths of three, six, seven, and eight. Once we have established which ring sizes can be formed, we will strive to enhance the diastereoselectivity of the reaction using isomerically pure dienol ethers. We will also explore the impact of chiral, non-racemic acid catalysts on the enantioselectivity of this novel reaction. Further comparison tests will be conducted to explore the performance of the reaction with different alkyl substituents at position R₃ in our proposed methodology study.

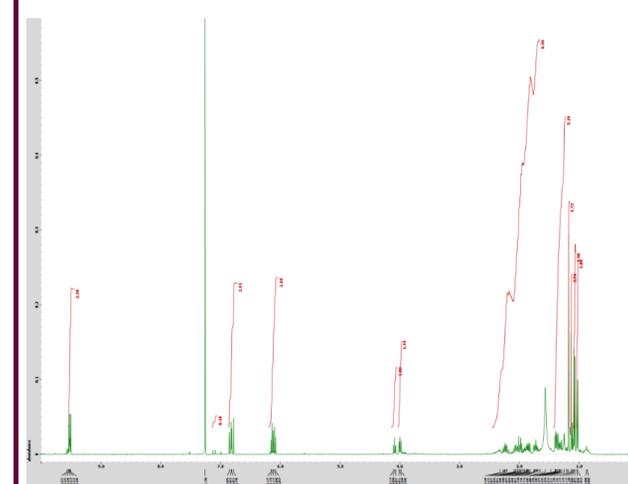
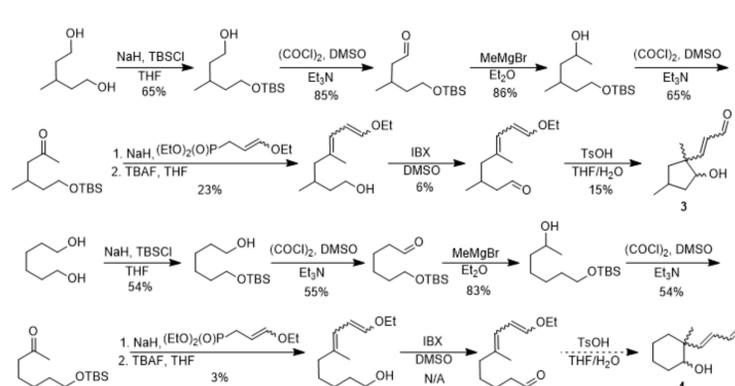
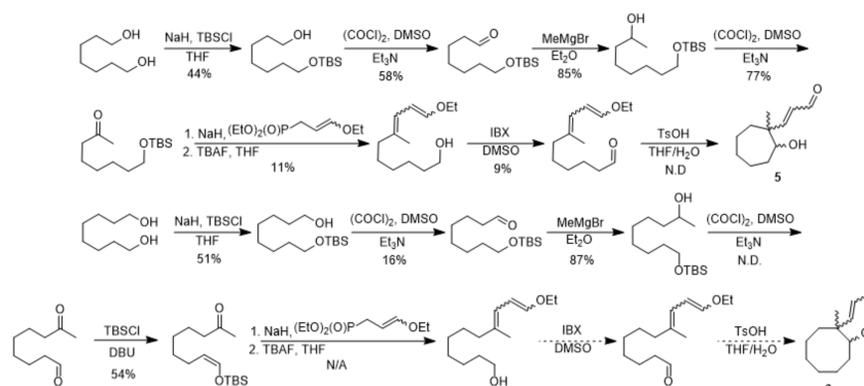


Figure 1. ¹H NMR spectrum for cyclic aldol 3 illustrating two major diastereomers



References

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