Exploring the Potential of an Acid-Initiated Vinylogous Aldol Reaction to form All-Carbon Quaternary Stereocenters

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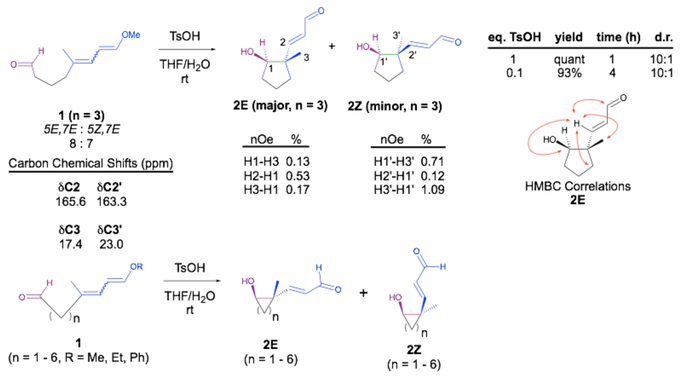
Abstract[1]

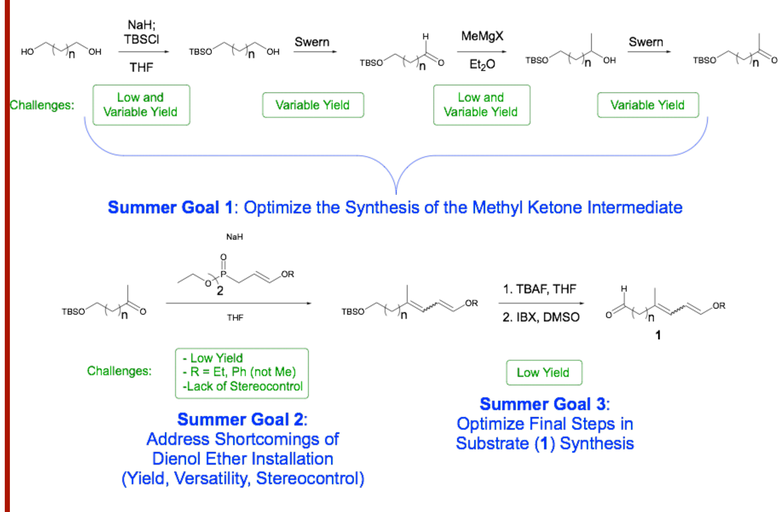
There is great interest in methods to prepare all-carbon quaternary stereocenters (ACQS) due to their presence in important biological molecules and pharmaceuticals. However, ACQS synthesis presents a challenge due to steric compression that inevitably results in the transition states of reactions leading to their assembly. Further, achieving stereoselective ACQS assembly is an important challenge in synthetic organic chemistry. Previous research in the Hofferberth Lab has included the discovery of a vinylogous aldol ring closure that stereoselectively produces functionalized carbocycles which contain the ACQS. To study this process in more detail, a robust synthetic route to the aldol substrate, a dienol ether tethered to an aldehyde, is needed. Our goal this summer was to optimize the seven-step synthesis of the aldol substrate or devise a superior synthetic approach. To that end, we examined the first five steps of the established synthesis and significantly improved the yield, reduced the time required, and decreased material waste of the first four steps. Examination and optimization of the fifth step, the introduction of the dienol ether, was underway at the conclusion of the summer.

Preliminary Results[2]



n	R	Ring Closure (Yield)	E : Z
1		In Progress	
2	Et	Yes (trace)	More Data Needed
3	Me	Yes (quant)	10 : 1
3	Et	Yes (36%)	3 : 1
3	Ph	Yes (18%)	1 : 1
3 (with 3-Me)	Et	Yes (15%)	1 : 1
4	Et	Yes (45%)	2 : 1
5		In Progress	
6		In Progress	

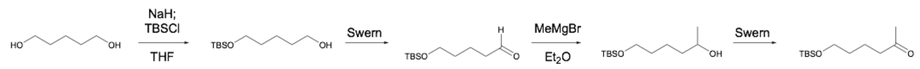
Established Synthesis and Challenges[3,4]



Challenges: Synthesis of ring closure substrate is low yielding, inconsistent, and non versatile, making study of the ring closure step difficult.

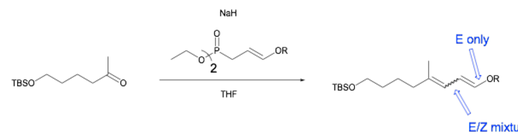
Primary goal: Find a consistent and high yielding preparation for ring closure substrates that is versatile enough to allow different tether lengths (n=1-8) and different alkyl groups (R= Me, Et, Ph) to be studied.

Goal 1: Optimize Methyl Ketone Synthesis

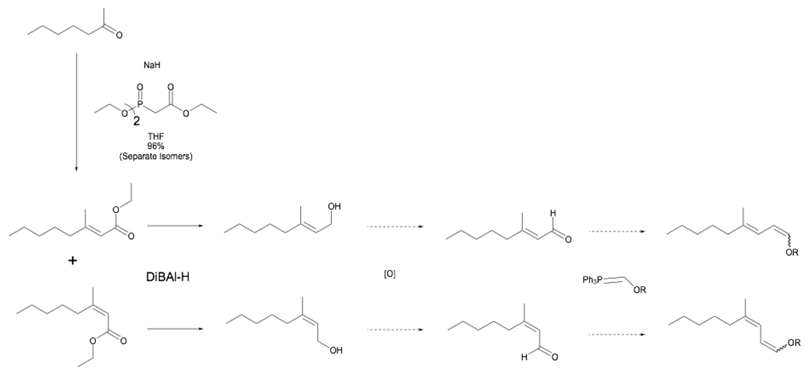


	Protection	First Swern	Grignard/ Second Swern
Initial Status	Low and variable yield	Variable yield	Low yield
Observations	1. With ~1 eq of NaH variable mixtures of mono & diprotected 2. Gas evolution during Aq. quench 3. Even with long times, NaH is not fully reaction and is doing so heterogeneously	1. TLC of reaction consistently good 2. Product decomposes during SiO_2 gel chromatography	1. TLC of reaction looks good 2. TBS group labile during column chromatography
Optimization	Use sonication to assure complete deprotonation prior to TBSCl addition	Purify by Kugelrohr distillation	Purify by Kugelrohr distillation
Optimized Status	Consistently high (85-91%) yields of desired product	Consistently high yields (76-85%) of desired product	Consistently high yields (Grignard ~75%, Swern 85-94%)

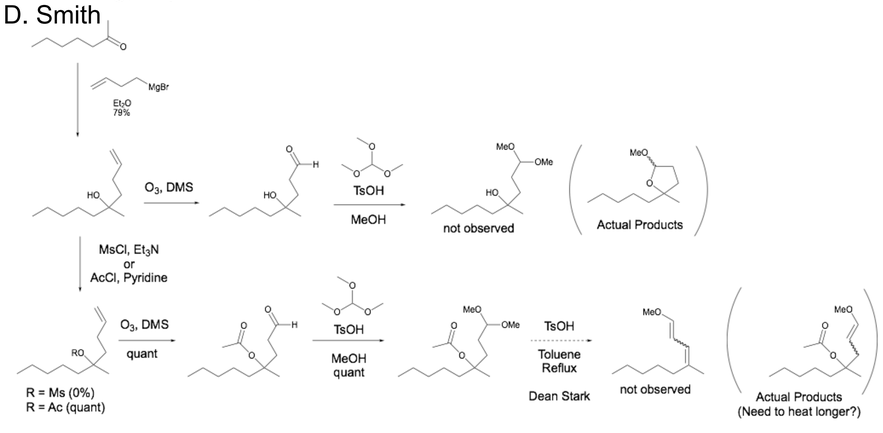
Goal 2: Optimize Conversion of Methyl Ketone to Dienol Ether



Three ideas for improvement of dienol ether installation (above), shown in below schemes with 2-heptanone as a model substrate.

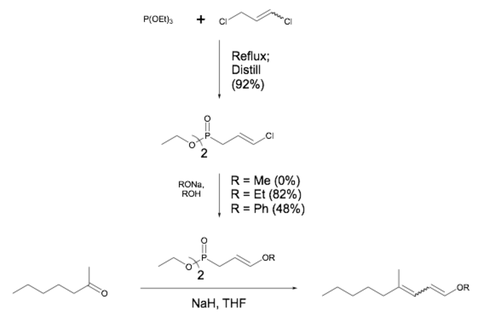


Idea 1. Strengths: reliable with commercially available reagents, possible separation of stereoisomers, potentially high yields. Weaknesses: long, time consuming, expensive, and atom inefficient.Lauri Vares; Atanas V. Koulov; Bradley D. Smith



Idea 2. Strengths: short, atom-efficient, inexpensive. Weaknesses: Yield and stereochemistry unknown

Goal 2 cont.[5]



Idea 3. Improvement of existing 1-step Horner-Emmons Wittig reaction

Bubbles during quench suggest incomplete deprotonation, sonication may help. Distillation, to avoid losses on column, resulted in impure product mixture. Synthesis of R=Me phosphonate generally gives very complex product mixture. A low temp synthesis & careful fractional distillation of reagent seems promising. A reasonably pure sample of this product is in hand and awaiting further testing.

Conclusions and Future Directions

We have optimized the first four steps in the synthesis of the vinylogous aldol substrate. The discovery that sonication during the protection of linear terminal diols reliably gives high yields of only monoprotected products represents a significant improvement to the previously inconsistent, slow, and low-yielding process that occurs with standard stirring. The observation that all of the intermediates in the first-four reaction steps can be purified to homogeneity using Kugelrohr distillation was significant for several reasons: (1) the aldehyde products tend to decompose during silica gel chromatography, (2) Kugelrohr distillation is rapid and can be easily scaled to large batches, and (3) distillation results little waste in the form of spent silica gel or organic eluents. The scrutiny of three approaches to convert the methyl ketone to the requisite dienol ether are underway. Future research will include applying the optimized synthesis to the production of the aldol precursor allowing sufficient quantities of the precursor for detailed examination of the reaction characteristics.

References

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Acknowledgements

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