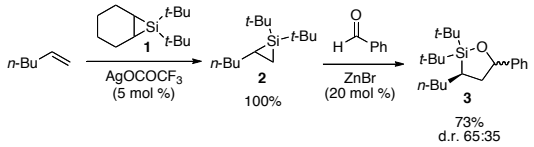
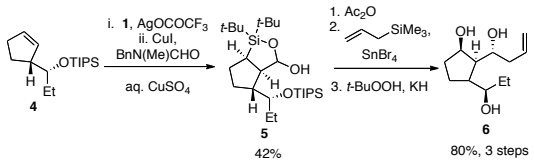
Research Summary of Brett E. Howard

University of California, Irvine

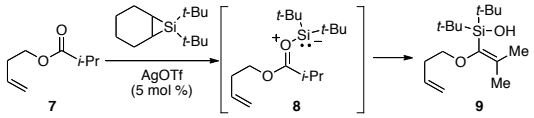
Silylene Mediated Synthesis of α-Hydroxy Acids

The Woerpel Laboratory has developed a method for the diastereoselective formation of 1,3 diols via silylene transfer to olefins. The resulting silacyclopropanes undergo carbonyl insertion to provide oxasilacyclopentanes, often with high regioselectivity. Oxidation of the resulting silicon–carbon bonds under Tamao conditions affords synthetically useful 1,3 diols as single diastereomers.[1]

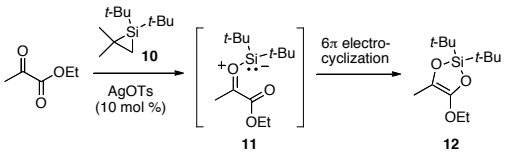




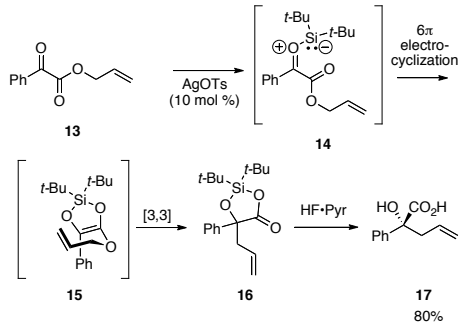
The silylene transfer methodology tolerates many functional groups; during initial investigations, however, unexpected product **9** was formed when ester **7** was subjected to transfer conditions. The vinyl-silanol **9** was hypothesized to form via a silacarbonyl ylide intermediate.



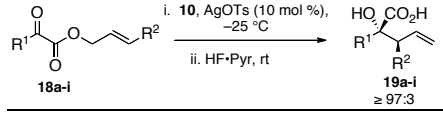
My initial investigations into this area revealed that ester substrates undergo 6π electrocyclic reactions under silylene transfer conditions. Treating ethyl pyruvate with 2,2 dimethyl-di-*tert*-butyl silacyclopropane (**10**) and 10 mol % AgOTs provided dioxasilacyclopentene **12**.



Utilizing α-keto esters with pendant allylic groups allows the substrates to undergo tandem Ireland-Claisen rearrangements, affording disubstituted α-hydroxy acid products in a one-flask, two-step procedure.

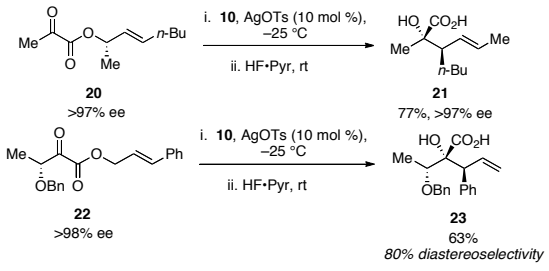


A large range of substrates with varying substitution patterns are tolerated by the reaction, allowing for the generation of two new stereocenters in one step. In all cases, the products were formed in diastereomeric ratios of greater than 97:3.

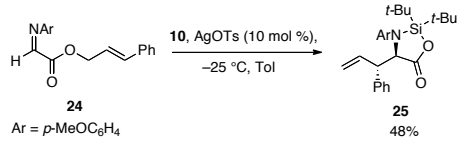


entry	R^1	R^2	yield (%)[a]
1	Me	Ph	70
2	Et	Ph	84
3	*i*-Pr	Ph	54
4	*t*-Bu	Ph	47
5	Ph	Ph	71
6	Ph	Me	62
7	Ph	*n*-Bu	72
8	Ph	$CH_2OTBDMS$	71
9	Et	$(CH_2)_2OBn$	75

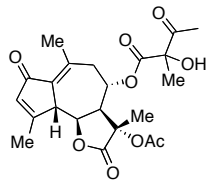
The silylene-mediated synthesis of α-hydroxy acids can be applied to the preparation of enantiomerically enriched products. Reactions of chiral substrates led to complete or partial transfer of stereochemistry, depending on the substitution pattern of the α-keto ester.



Preliminary experiments demonstrate that this method can be extended to the synthesis of α-amino acid derivatives from α-imino esters.[2]

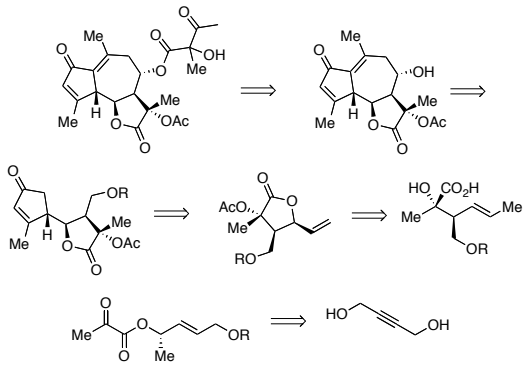


Efforts Towards the Total Synthesis of Ferupennin F

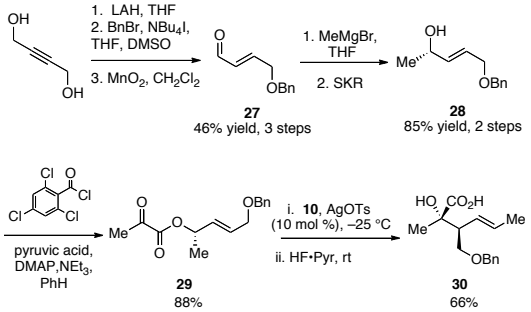


26

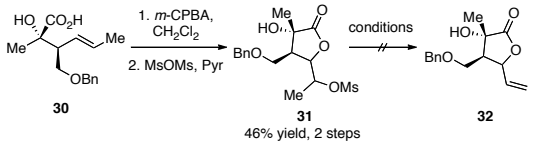
Isolated in 2002 from *Ferula penninervis*, ferupennin F has been shown to inhibit cytokine production. The silylene transfer methodology developed to synthesize α-hydroxy acids provides a potential route to the functionalized lactone ring. The remaining two rings are envisioned to come from a Pauson-Khand reaction and subsequent condensation reaction.



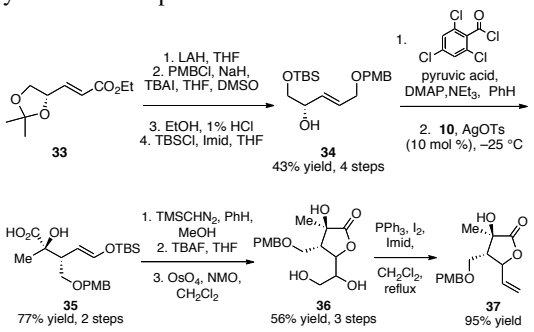
Synthesis of the α-keto ester fragment began with 1,4-butynediol. Reduction of the alkyne, followed by mono-benzylation and oxidation led to aldehyde **27** in 46% yield over three steps. Methylation and subsequent resolution provided allylic alcohol **28** in 85% yield. Pyruvic acid was then coupled to the alcohol using Yamaguchi conditions affording α-keto ester **29** in 88% yield. Silylene transfer was completed on an 11 mmol scale in 66% yield to afford the desired α-hydroxy acid **30**.



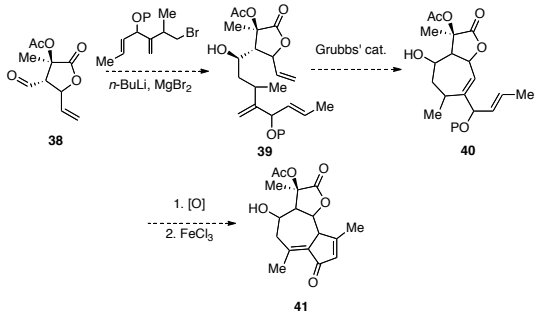
Lactone formation was accomplished with *m*-CPBA and the product was subsequently mesylated using methanesulfonic anhydride in pyridine. Unfortunately, no conditions were found that led to the E2 elimination product. Further exploration of tosylate and triflate derivatives were also unsuccessful.



With the difficulties encountered during the E2 elimination attempts in mind, the route was redesigned whereby a reductive elimination procedure would be followed to provide the desired olefin. Model studies began with ester **33** which is accessible from commercially available material in one step, albeit with the incorrect stereochemistry. Ester **33** was reduced to the alcohol using LAH which was then protected as a PMB ether. Removal of the acetonide followed by selective TBS protection of the primary alcohol provided **34** in 43% yield over 4 steps. **34** was then coupled to pyruvic acid and then treated with silylene transfer conditions to provide α-hydroxy acid **35** in 77% yield over 2 steps.



Methylation of the carboxylic acid followed by deprotection of the TBS group allowed the lactonization step to proceed smoothly, providing lactone **36** in 56% yield over 3 steps. Exposure of the diol to triphenylphosphine, imidazole and iodine in refluxing methylene chloride provided the proper reductive elimination product, **37**, in 95% yield. Unforunately, **37** did not react with any alkynes to form Pauson-Khand products. Future efforts will be focused on additions to Aldehyde **38** and subsequent RCM and Nazarov cyclization.



1. Ćiraković, J.; Driver, T. G.; Woerpel, K. A. *J. Org. Chem.* **2004**, *69*, 4007-4012.
2. Howard, B. E.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 4651-4653.