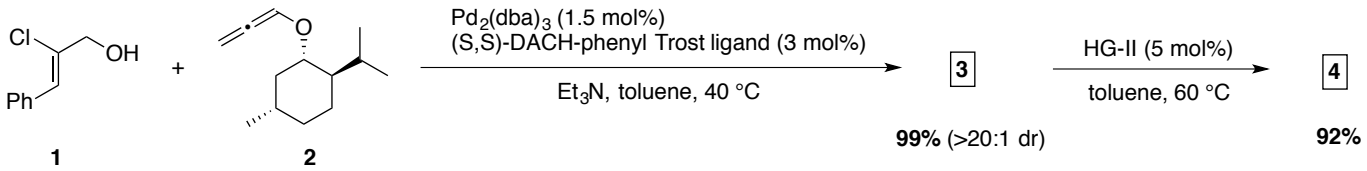
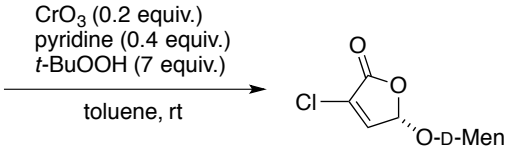
Submitted by Sam

A Short Enantioslective Synthesis of Cheloviolene A

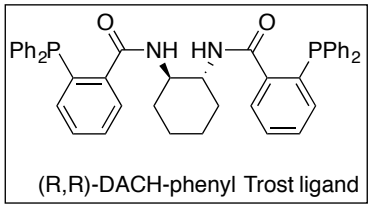
Q1: Provide the missing intermediates in the synthesis of the first key fragment (**5**) and give the mechanism for the formation of **3** from alcohol **1** and allene **2**. Can you give a rational for the selectivity of the first step? (Think about the intermediate that is formed)



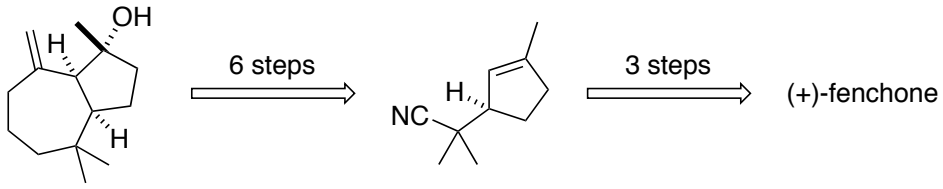
1 **2** **99%** (>20:1 dr) **92%**



5
32%



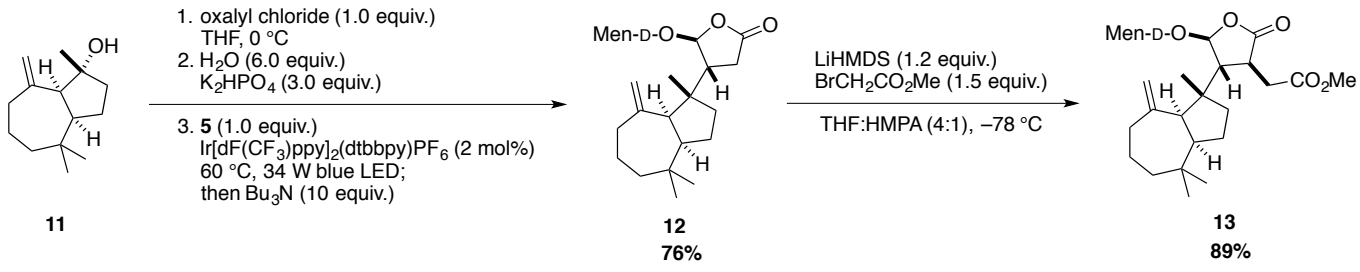
Q2: **2.1**) The second key fragment (**11**) was prepared from enantiopure cyclopentene **6** in 6 synthetic steps. Can you provide a plausible retrosynthesis?



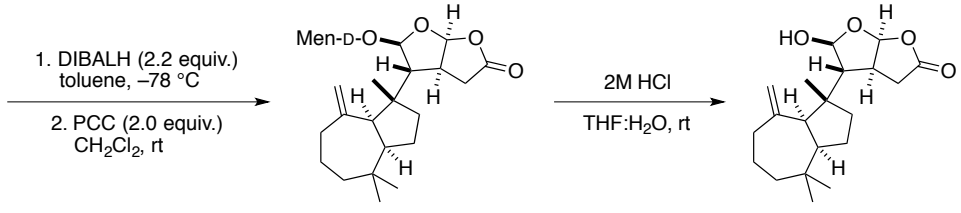
11 **6**

2.2) Starting from the commercially available (+)-fenchone, cyclopentene was prepared in three steps. However, in one step the product is obtained as a 1:1 mixture of stereoisomers. What are these isomers and how would you separate them (1 step)?

Q3: In the pivotal step, the two fragments **11** and **5** are linked together using Ir(III)-mediated photocatalysis. Provide a mechanism for this transformation. (Hint: Irradiation is continued after the addition of Bu_3N)



11 **12** **76%** **13** **89%**

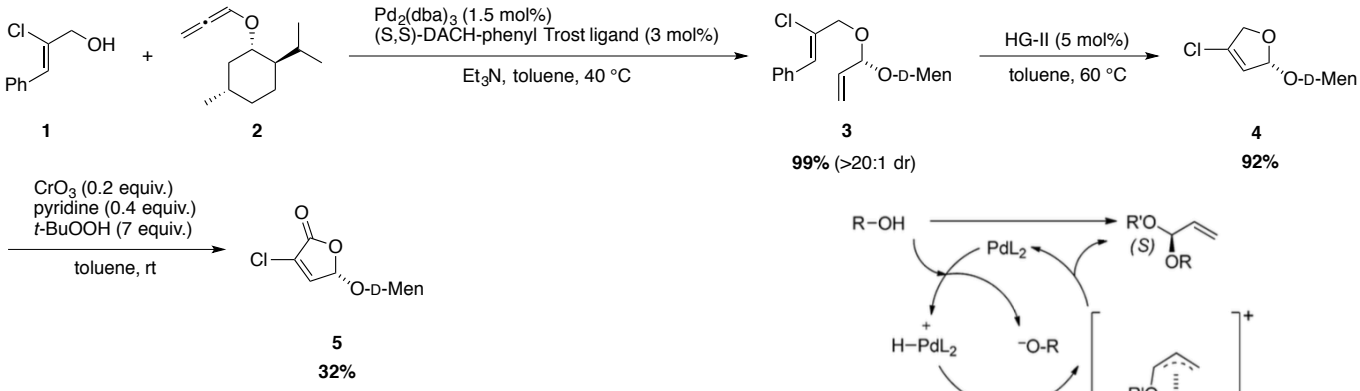


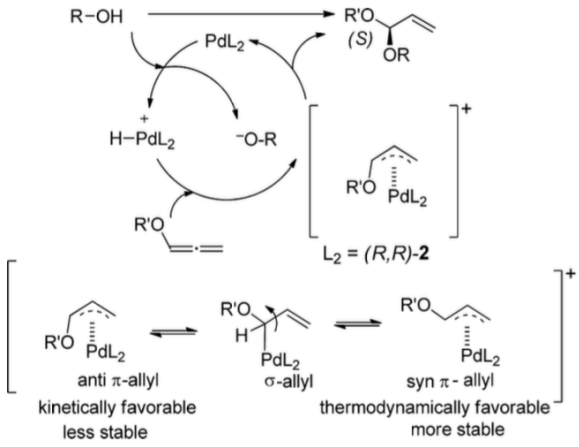
15 **86%** (two steps) **16** cheloviolene A (**92%**)

Solution:

Y. Slutskyy, C. R. Jamison, P. Zhao, J. Lee, Y. H. Rhee, L. E. Overman, *J. Am. Chem. Soc.* **2017**, jacs.7b04265.

A1:

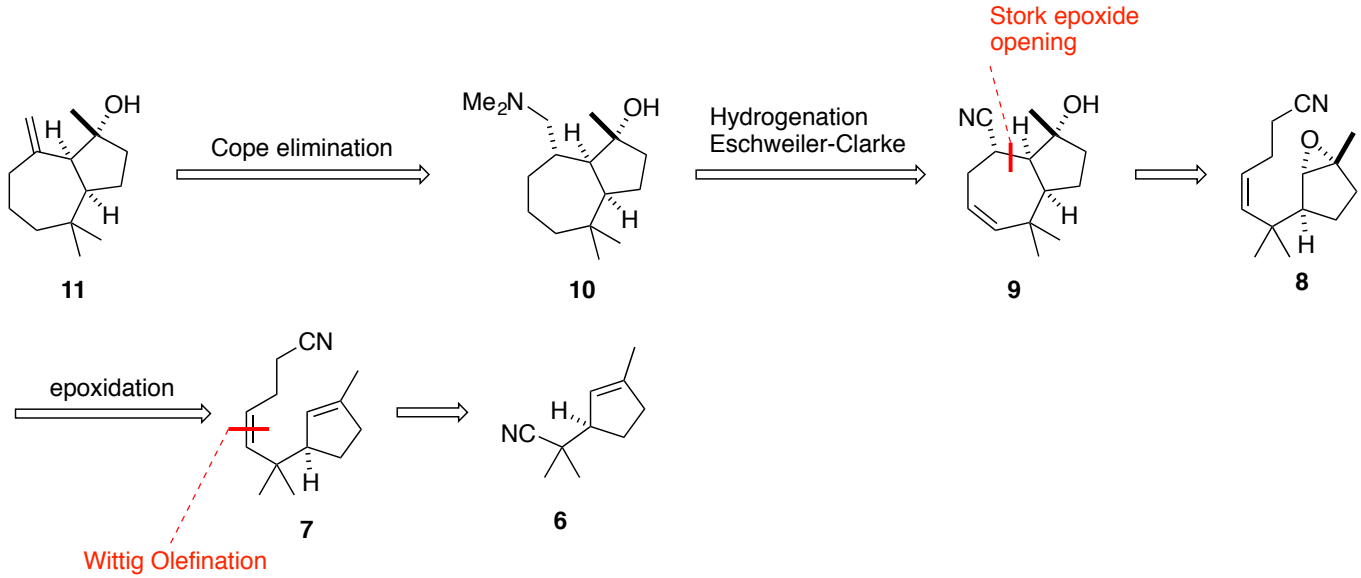




Stability of the intermediate π-allyl complex, kinetic vs thermodynamic. The selectivity can be explained by fast outer-sphere addition of the alkoxide to the kinetically favored anti-π-allyl complex relative to the π_{anti}-σ-π_{syn} equilibration process. Thus, non-polar solvents thighten the bond between the Pd and the alkoxide anion, thus leading to a faster attack of the anion. Although a bulkier group on the counter anion (alkoxide) should shift the equilibrium to the thermodynamically favoured syn π-allyl complex, higher yields and selectivites are observed for these systems. This can be rationalized with the sterical congestion of the syn π-allyl complex relative to the anti π-allyl complex.

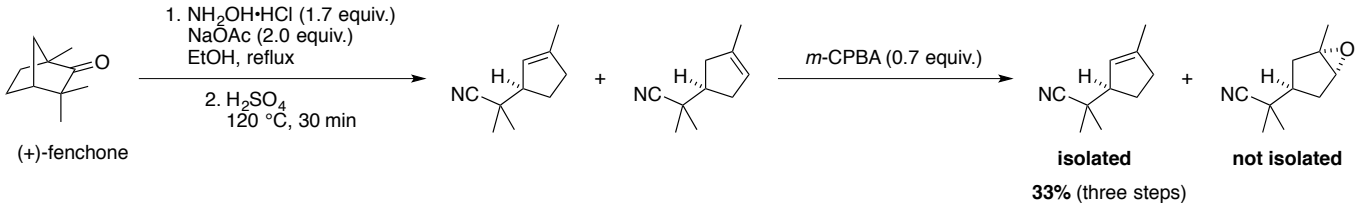
W. Lim, J. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2014**, *136*, 13618–13621

A2:



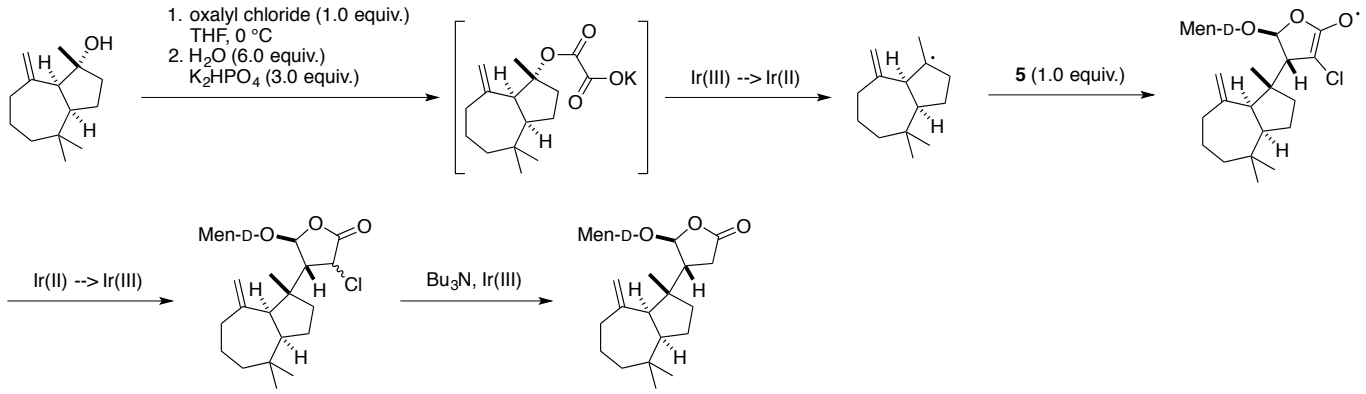
The selective epoxidation of the trisubstituted olefin in favor of the disubstituted comes from the difference in electron density. The Wittig olefination was performed with a non-stabilized ylid, resulting in the *Z*-olefin. The stereospecific Stork epoxide opening is used to fix the bicyclic core in a *cis*-fashion after attack from the top-face.

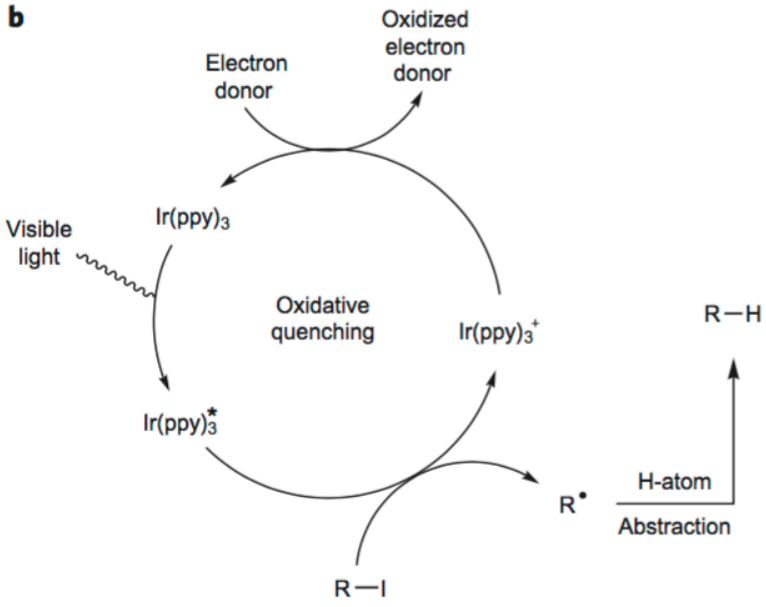
Submitted by Sam



The starting compound **6** was prepared by formation of the oxime of (+)-fenchone upon reaction with hydroxylamine. Subsequent protonation of the intermediate lead to ring-opening and formation of two stereoisomers. These two isomers were not separated, however oxidation with a substoichiometric amount m-CPBA lead to formation of only one epoxide (approach of peracid sterically less hindered) which could then be removed from the desired compound by FC.

A3:





The initially formed oxalyl chloride species is hydrolyzed with water and subsequently deprotonated with K_2HPO_4 to furnish the intermediate potassium oxalate. This is then oxidized in the photocatalyzed Ir(III) reaction to result in the 3° alkyl radical after extrusion of 2 equiv. of CO_2. This radical adds then diastereoselectively to the enone resulting in the enol radical which is reduced to the enolate by Ir(II). This step concludes the catalytic cycle. In a second step, the Bu3N acts as an electron donor for the Ir(III) assisted removal of the α-carbonyl chloride. The resulting α-carbonyl radical is quenched by HAT from the solvent, most probably THF.

J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854–859.