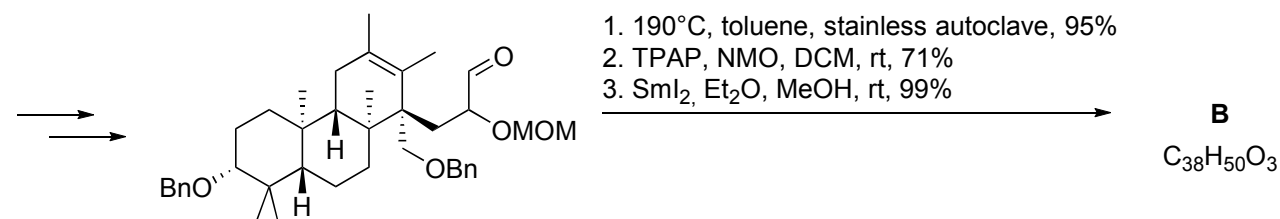
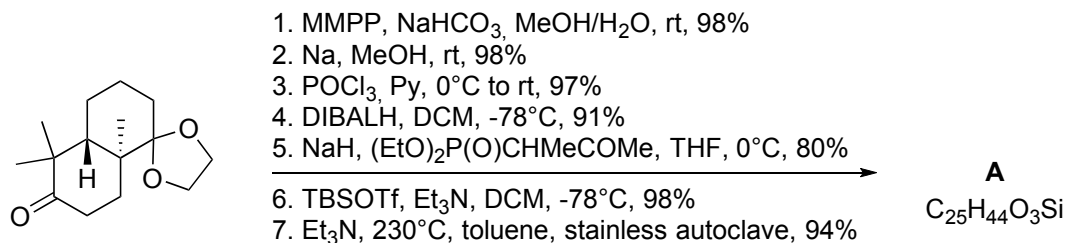


Problem session (1)

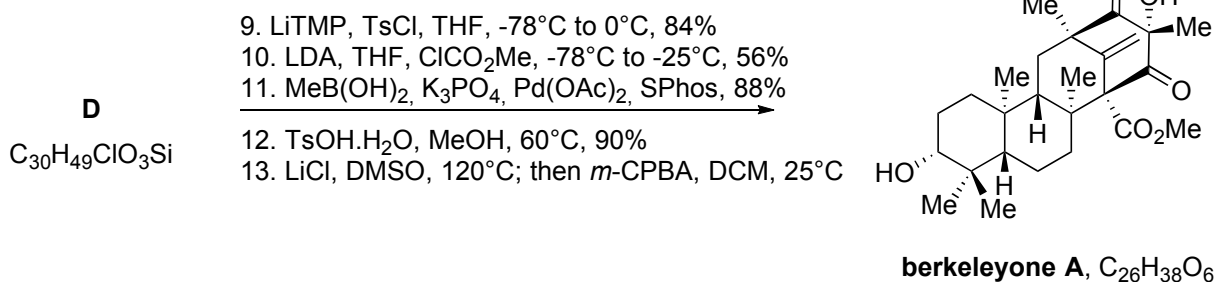
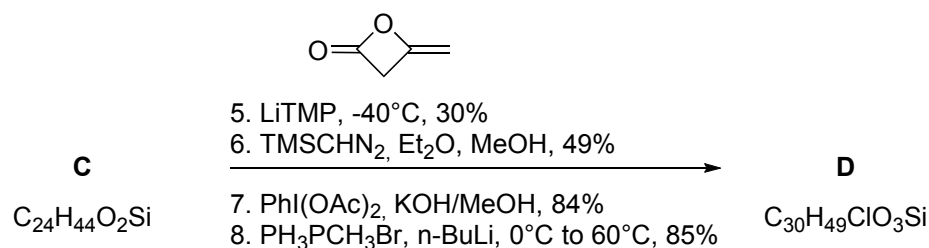
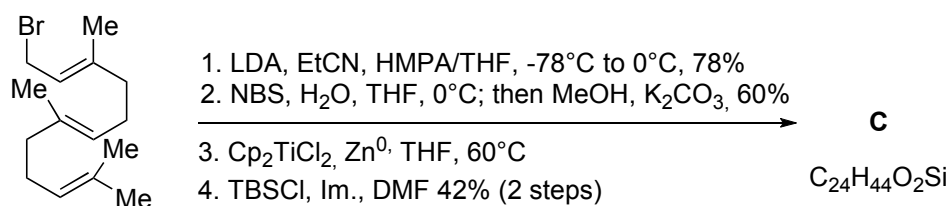
Benjamin Ovadia
2017.01.07

Please provide structure of compounds **A**, **B**, **C** and **D** and give the mechanism of each step

Problem 1



Problem 2



Problem session (1)-Answers

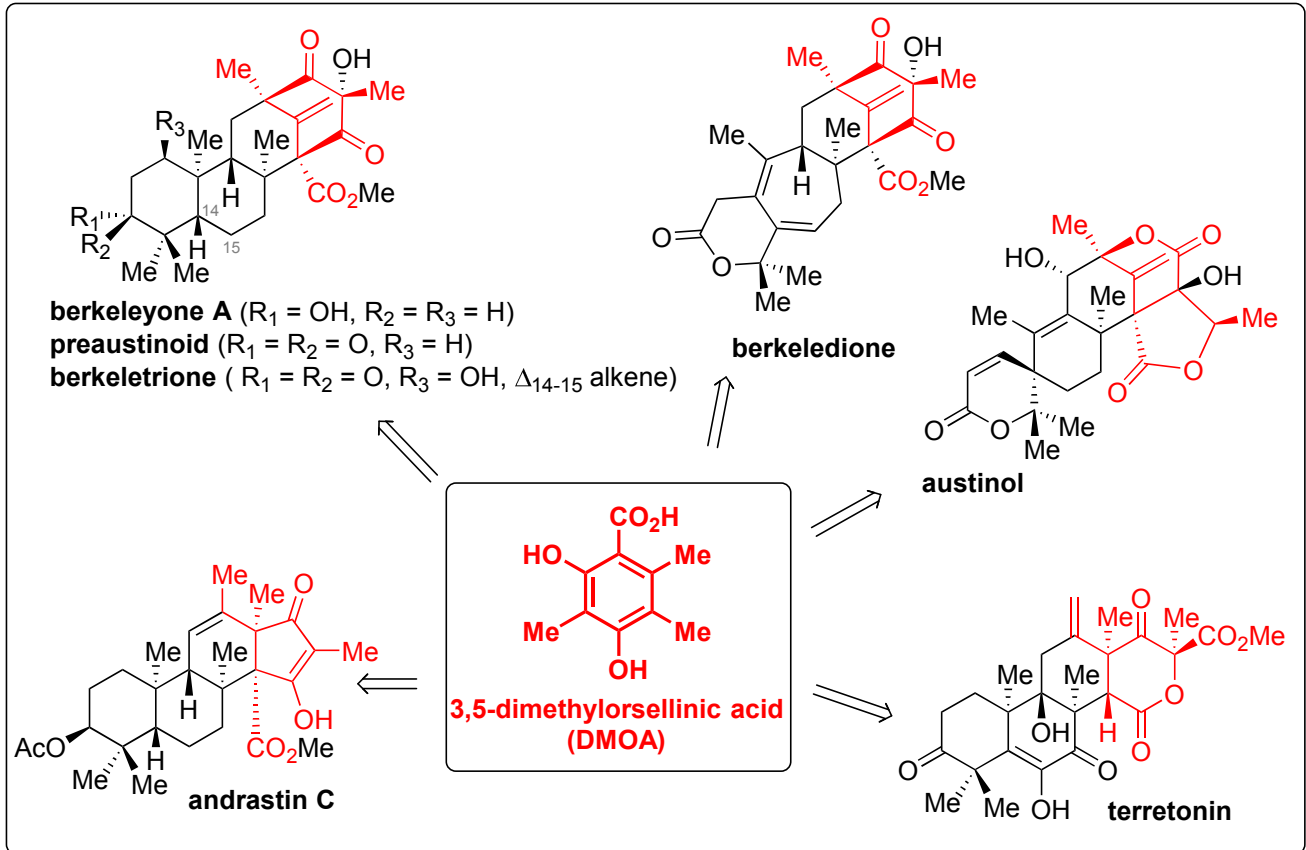
Benjamin Ovadia
2017.01.07

Topic : Synthetic study of complex meroterpenes. Total synthesis of berkeleyone A

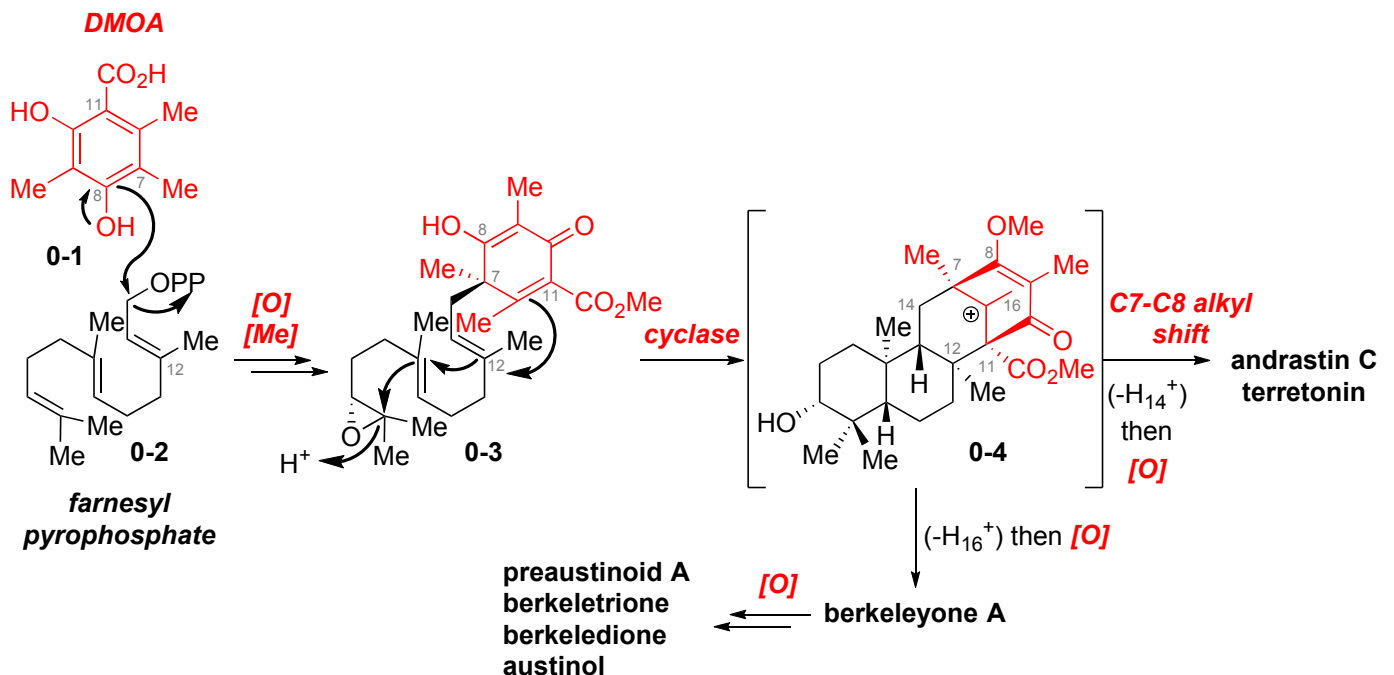
0. Introduction

Meroterpenoids : Hybrid natural products partially derived from terpenoids.

More than 100 meroterpenes derived from the aromatic tetraketide 3,5-dimethylorsellinic acid (DMOA) have been described.



0.1. Biosynthetic pathway leading to meroterpenes derived from DMOA and farnesyl pyrophosphate : Matsuda, Y.; Abe, I. *Nat. Prod. Rep.* **2016**, 33, 26 ; Geris, R.; Simpson, T. J. *Nat. Prod. Rep.* **2009**, 26, 1063



0.2. Introduction to andrastin C

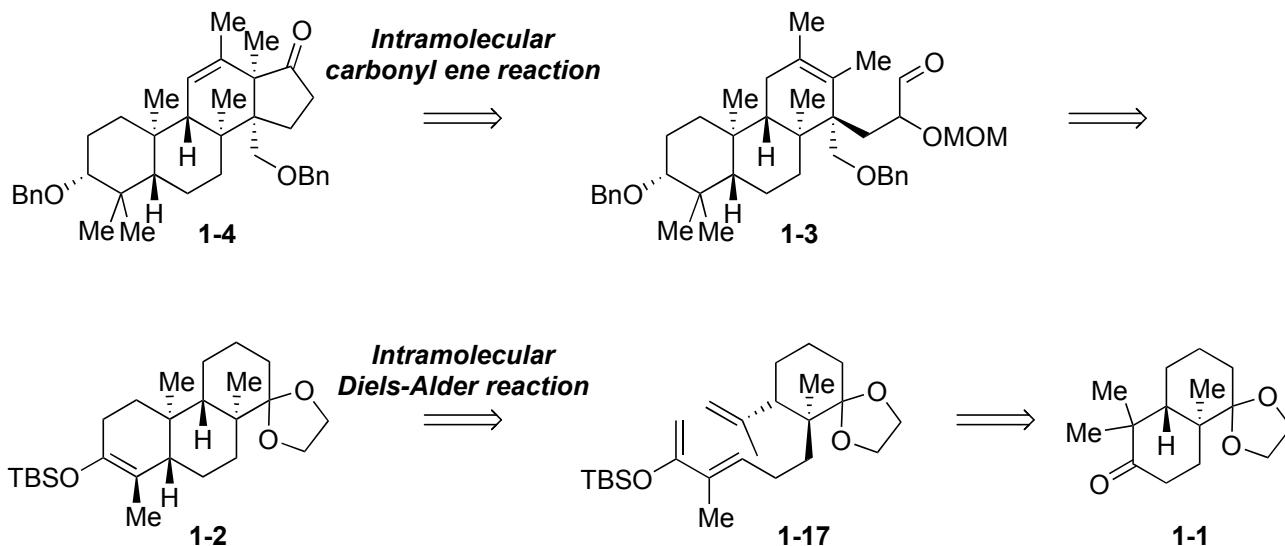
Isolation : from the culture broth of *Penicillium* sp. FO-3929. (Ommura, S. *et al. Tetrahedron Lett.* **1996**, 37, 1265).

Biological activity : inhibitor of protein farnesyltransferase.

Synthetic study : Toyota, M.; Okamoto, R., Ogata, T.; Ihara, M. *Tetrahedron Lett.* **2004**, 45, 9203 ; Okamoto, R.; Takeda, K.; Tokuyama, H.; Ihara, M.; Toyota, M. *J. Org. Chem.* **2013**, 78, 93 (problem 1).

Structural features : Sterically hindered *cis*-hydrindane ring system possessing vicinal quaternary center at the bridgehead positions of the CD ring system.

Retrosynthetic analysis :



0.2. Introduction to the Total synthesis of berkeleyone A

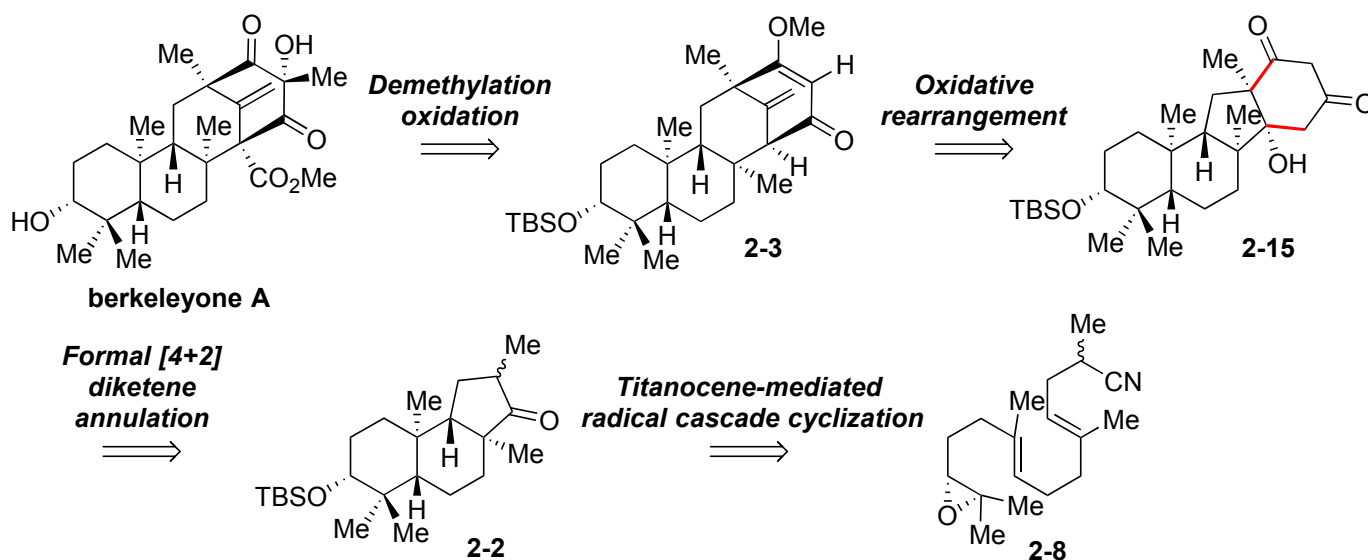
Isolation : from the fungus *Penicillium rubrum*, growing in metal sulfate rich (>500 ppm) and acidic water (pH 2.5) of Berkeley Pit, a former copper mine turned into waste lake. (Stierle, D B. *et al. J. Nat. Prod.* **2011**, 74, 2273 ; *J. Nat. Prod.* **2007**, 70, 1820).

Total synthesis : Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, 138, 14868 (problem 2).

Biological activity : inhibitor of the signaling enzyme caspase -1 and interleukin-1 β production by inflammasomes.

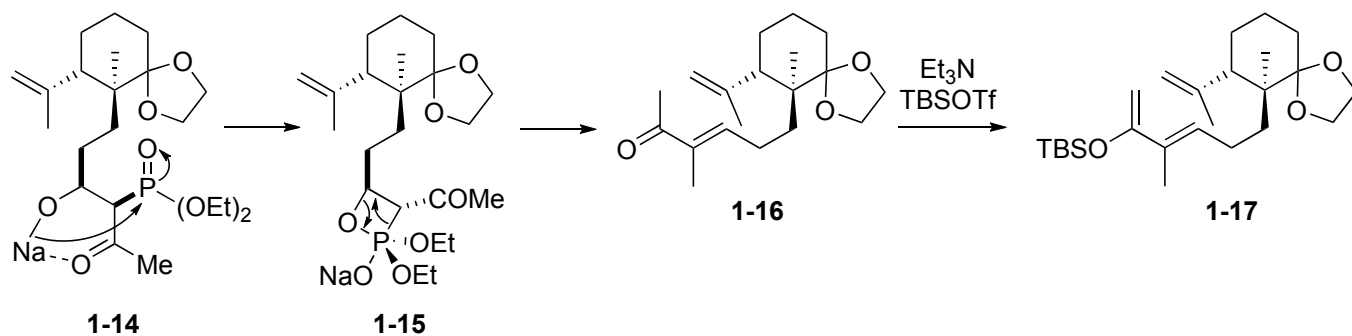
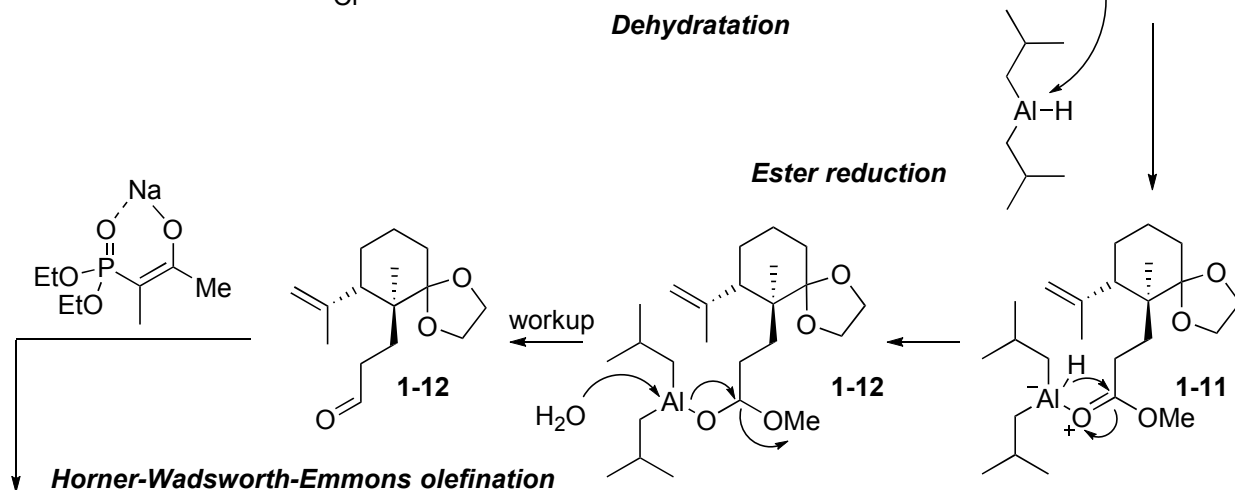
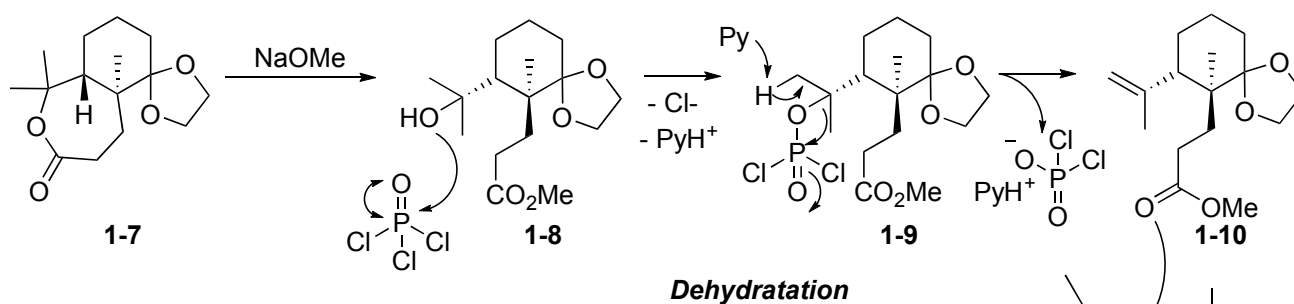
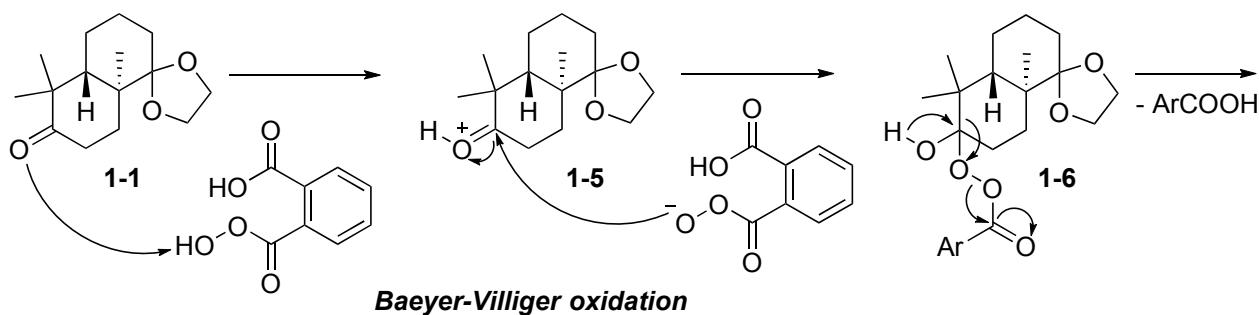
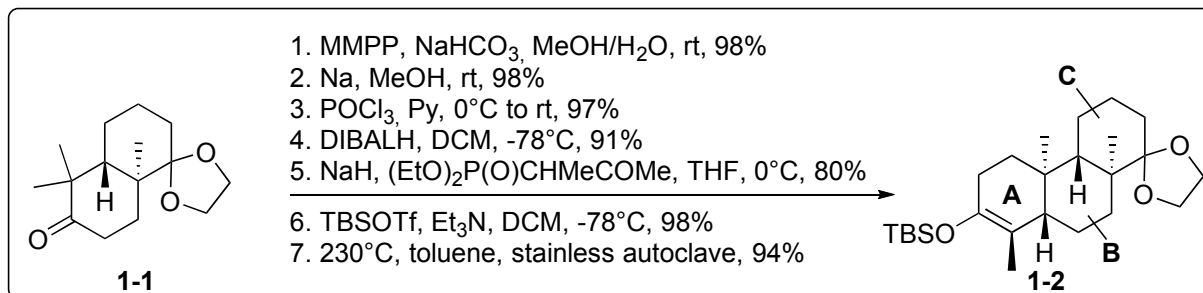
Structural features : Eight stereogenic centers, four are all-carbon quaternary stereocenters, embedded within a dense tetracyclic framework containing a bicyclo[3.3.1]nonane scaffold.

Retrosynthetic analysis :

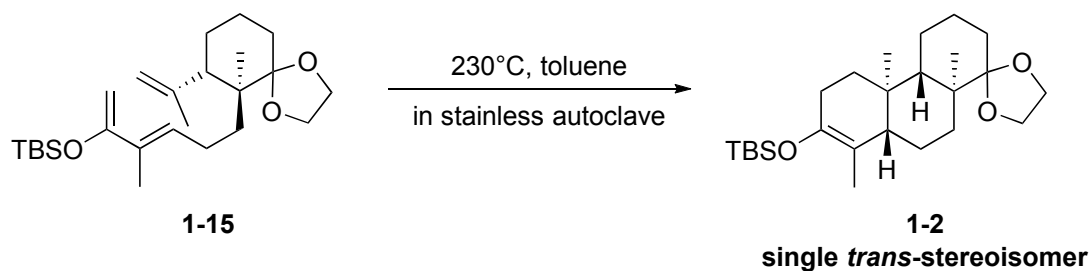


1. Synthetic study of the tetracyclic core of andrastin C

1.1. Construction of ABC-ring system



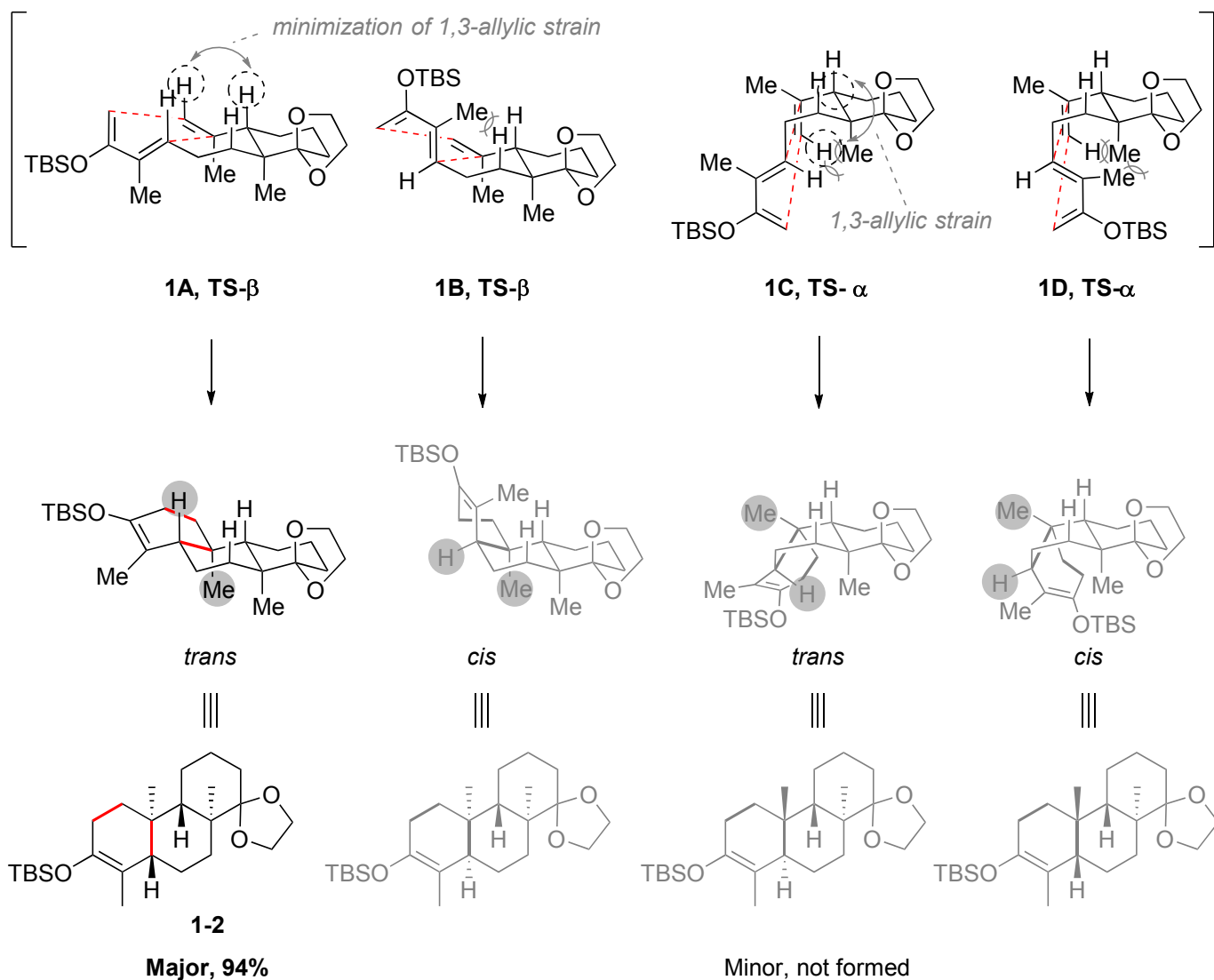
Construction of the ABC ring system : Intramolecular Diels-Alder cyclisation



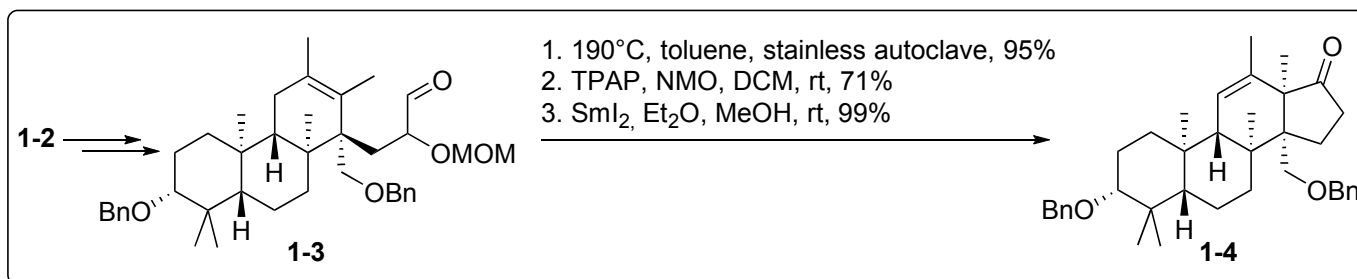
Rationalisation of the stereoselectivity of IMDA

Approach through the β -face of the dienophile. 1,3-allylic strain is minimized in both conformers A and B. But the conformer B suffers from nonbonding interaction between the methyl group on the diene and the axial hydrogen of the methylene.

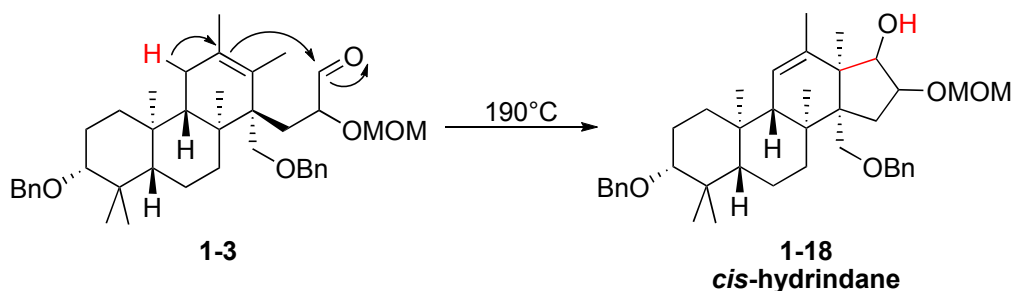
Approach through the α -face of the dienophile. Both conformers C and D suffer from 1,3-allylic strain and severe non bonding interactions between the axial methyl and the methyl or hydrogen of the diene and dienophile



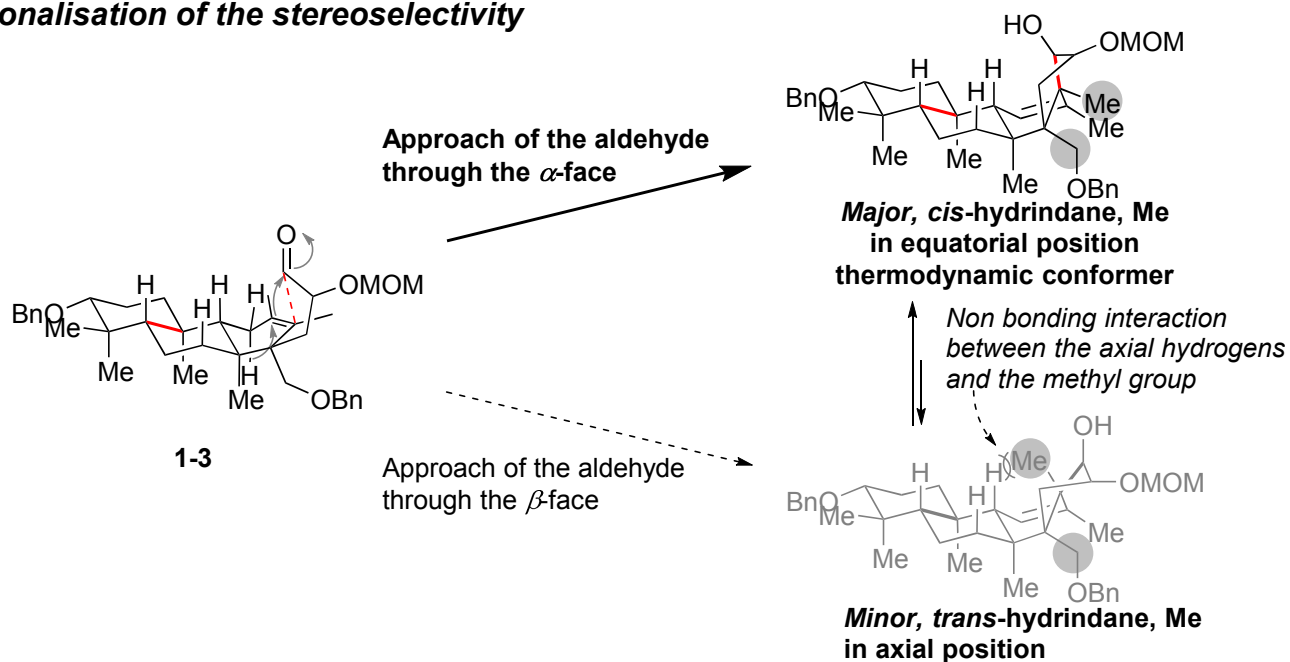
1.2. Construction of CD-ring system



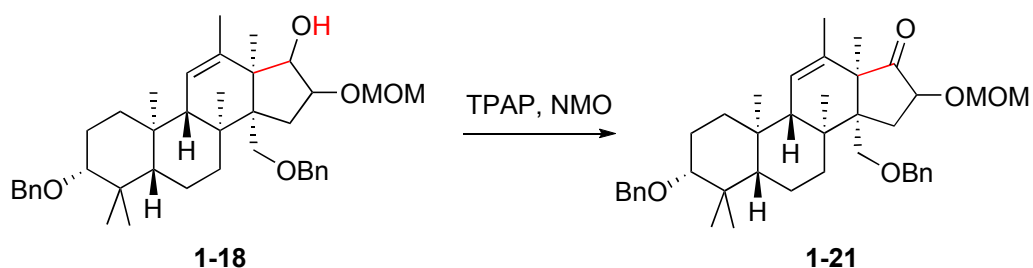
Intramolecular carbonyl-ene reaction



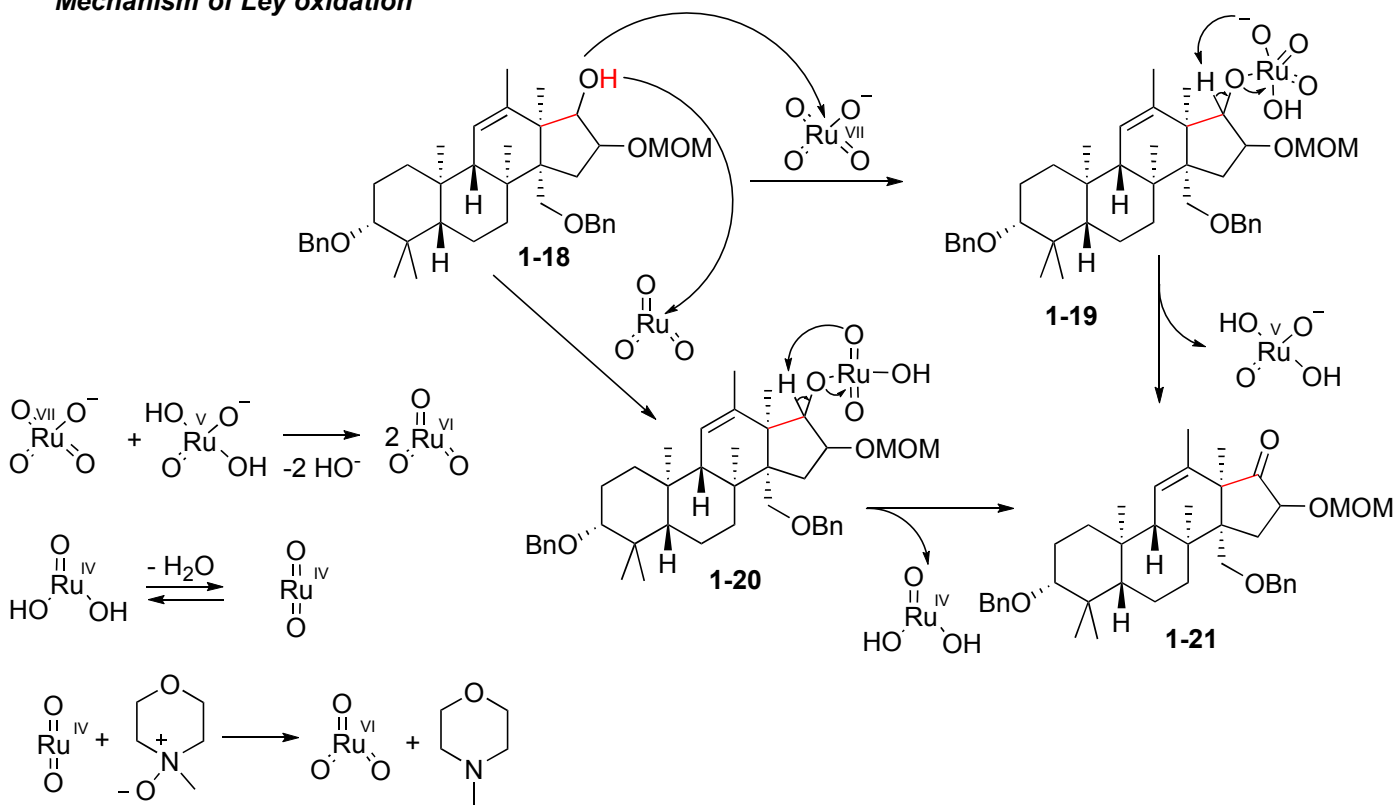
Rationalisation of the stereoselectivity



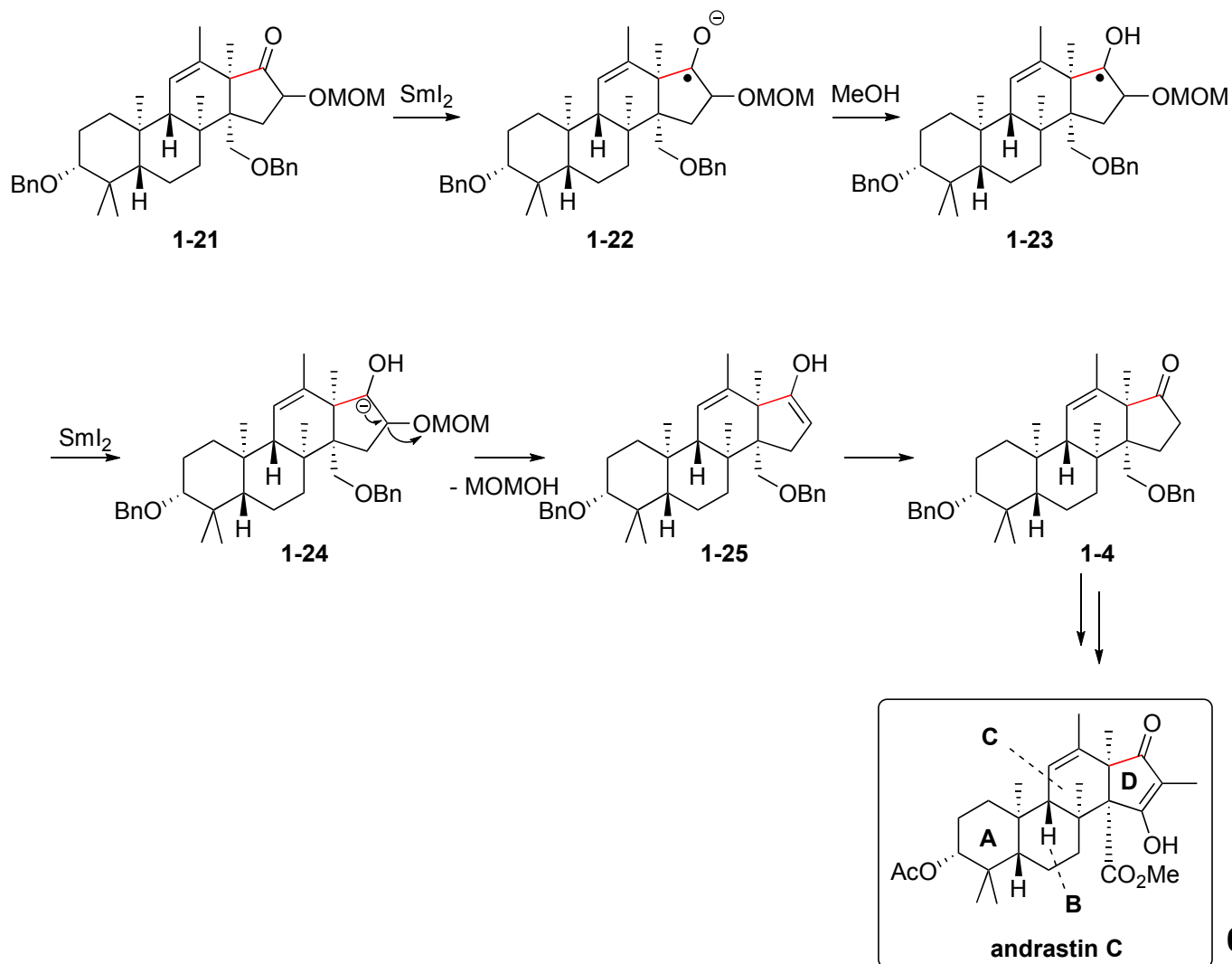
Ley oxidation of alcohol



Mechanism of Ley oxidation

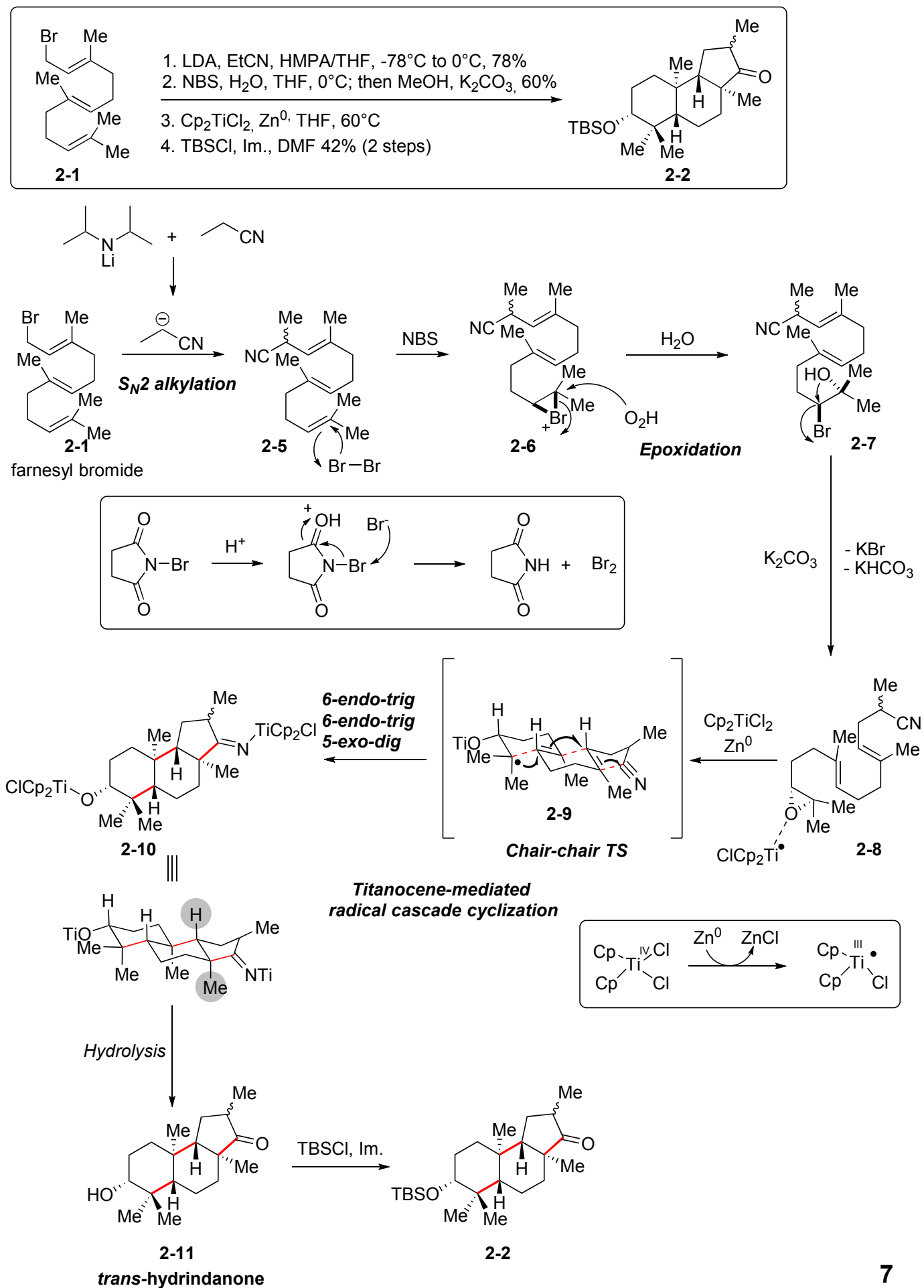


Reduction of α -oxygenated ketone



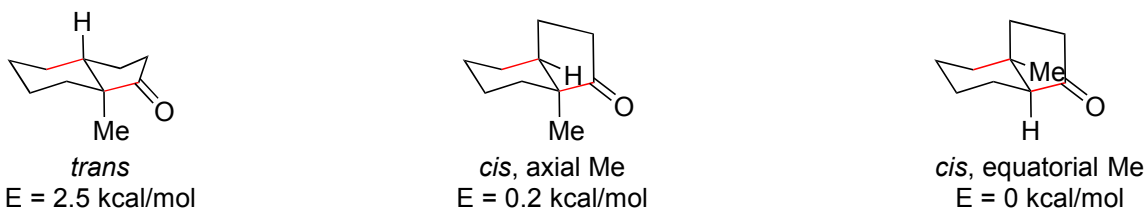
2. Total synthesis of berkeleyone A

2.1. Construction of 6/6/5-fused ring system



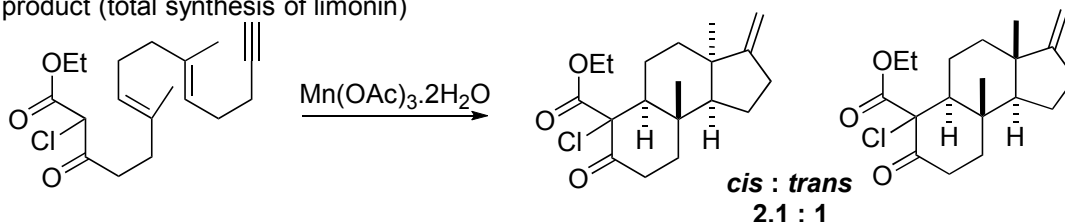
Discussion about the stereoselectivity of the radical cascade cyclization

- In general cases, in 8-methylhydrindanones the *cis* isomer is calculated to be more stable than the *trans*.



Tribber, M. T.; Allinger, N. L. *Tetrahedron*, **1972**, *28*, 1191

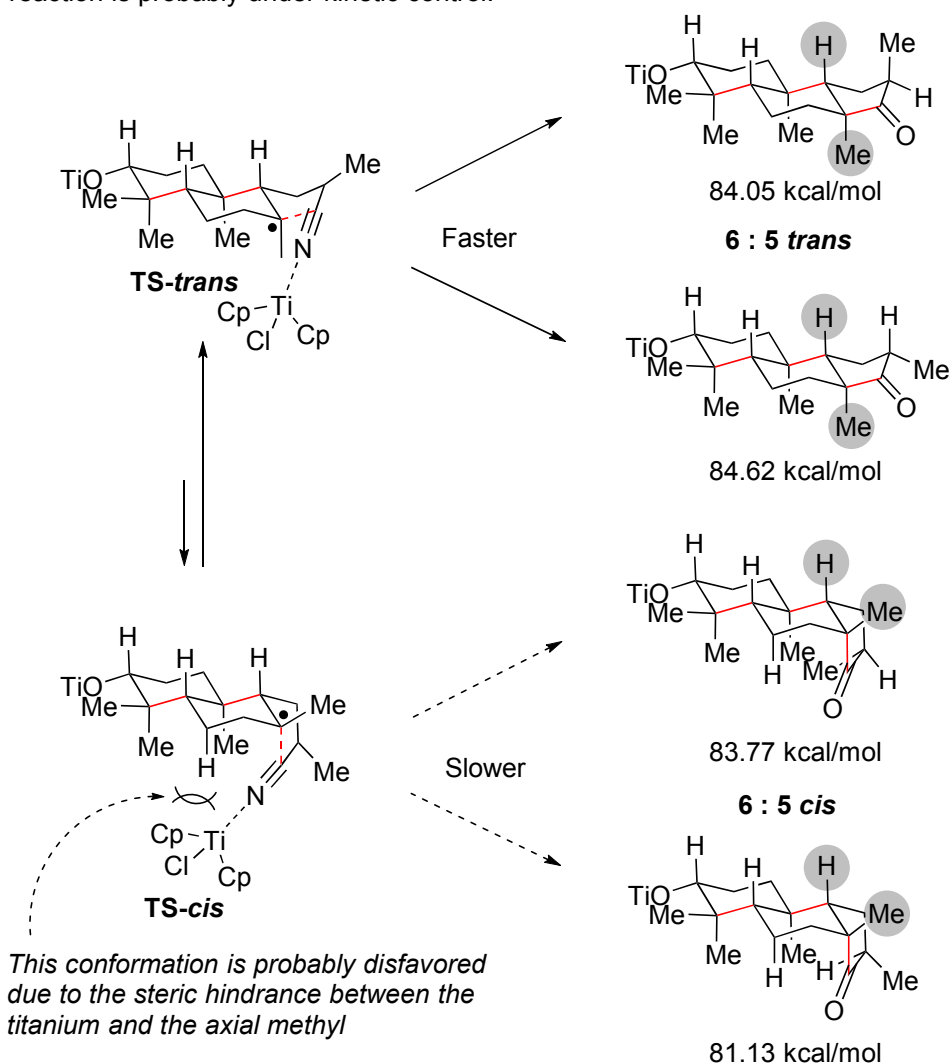
- In a recent example of Mn-mediated radical cascade cyclization onto alkyne, the *cis* isomer is obtained as major product (total synthesis of limonin)



150926_PS_Wang

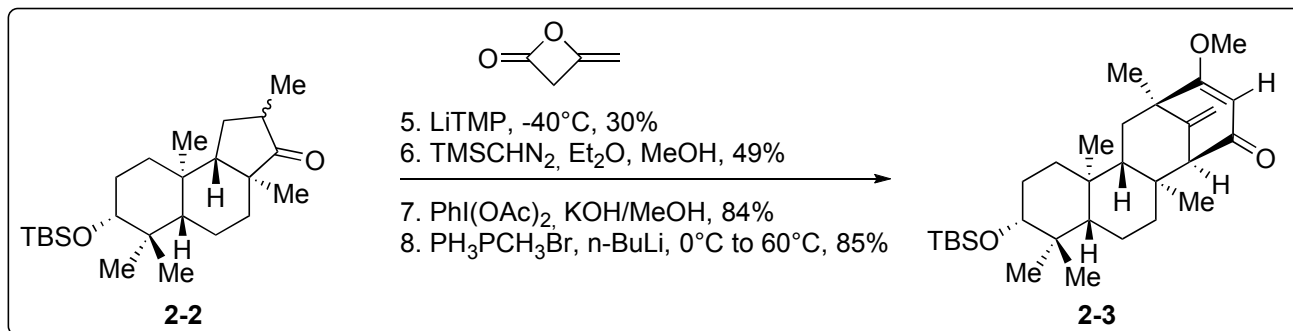
Yamashita, S.; Naruko, A.; Nakazawa, Y.; Zhao, L.; Hayashi, Y.; Hirma, M. *Angew. Chem. Int. Ed.* **2000**, *54*, 8538

- In that cases, energies calculation and previous examples shown that the 6/5-*cis* conformation is the more favorable, but experimentally the *trans* one is obtained as major isomer. This result is not clear but maybe the activation of the cyanide by titanium induce a steric hindrance which favored the *trans*-transition state, the reaction is probably under kinetic control.

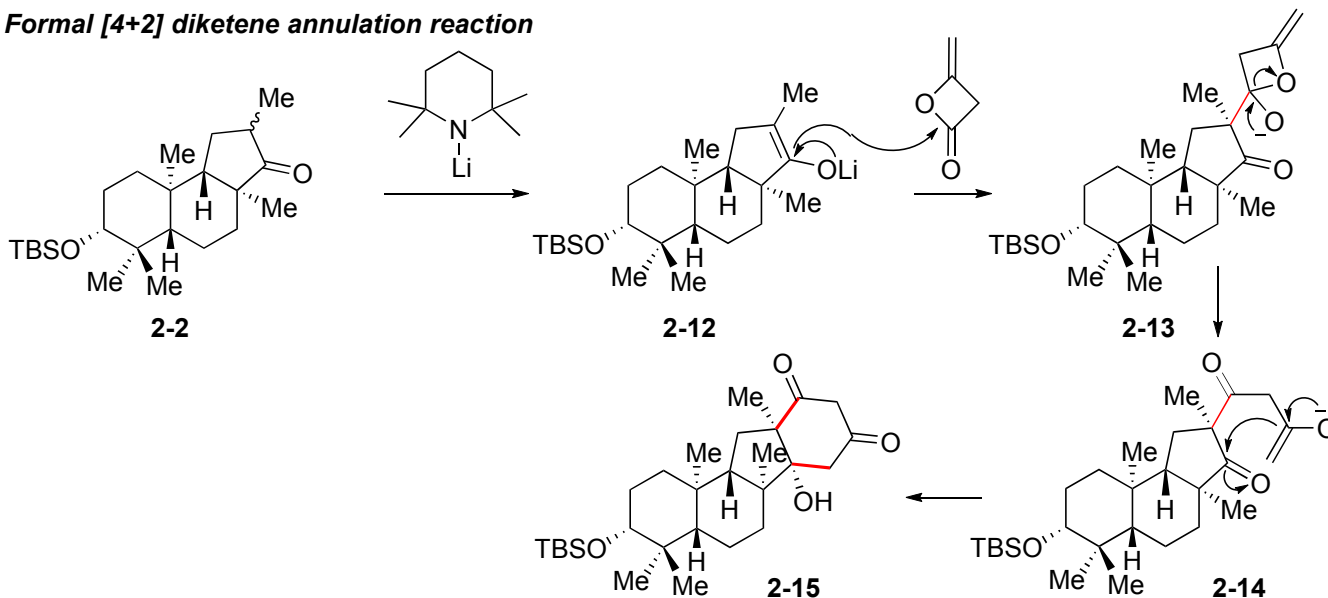


Energies calculated by MacroModel (MMFF/MCMM)

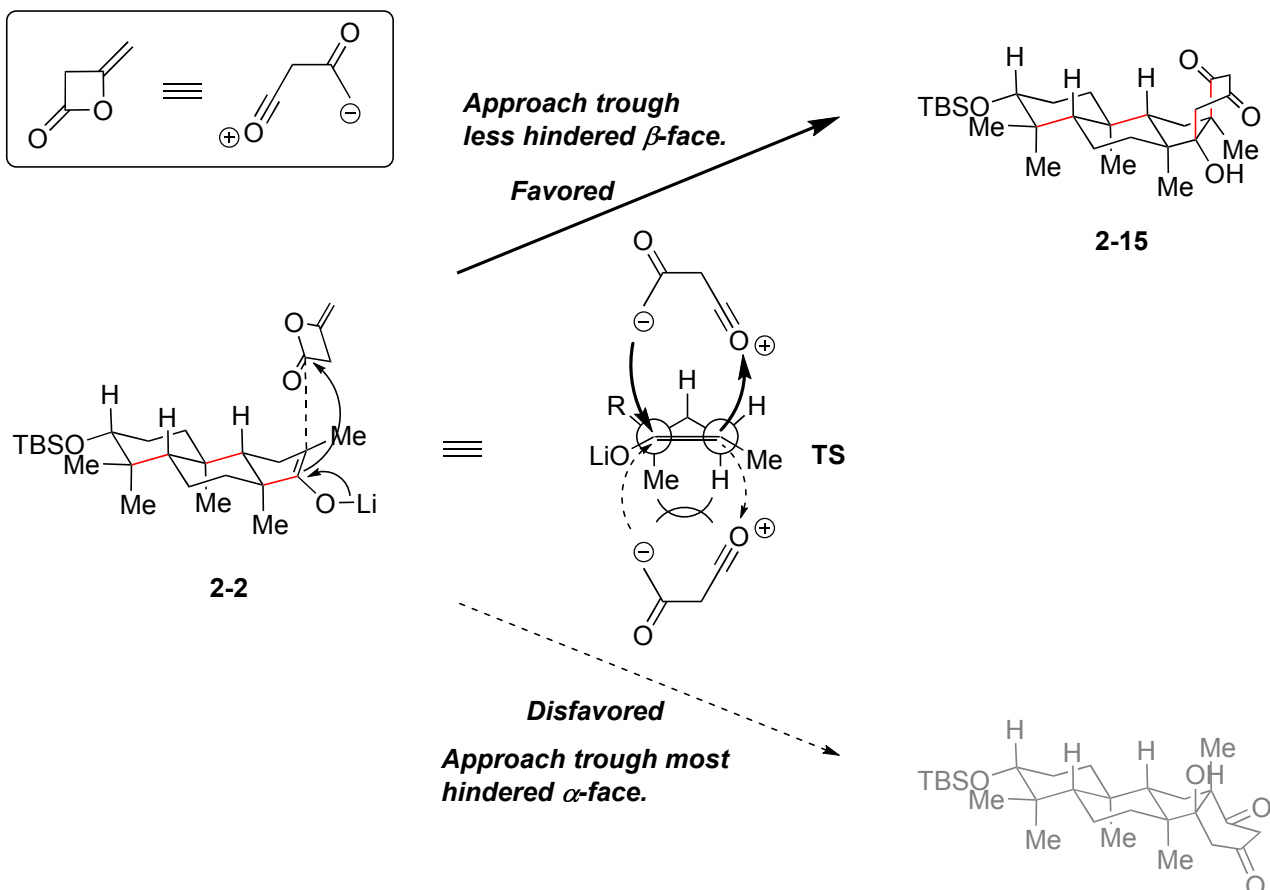
2.2. Construction of the bicyclo[3,3,1]nonane skeleton

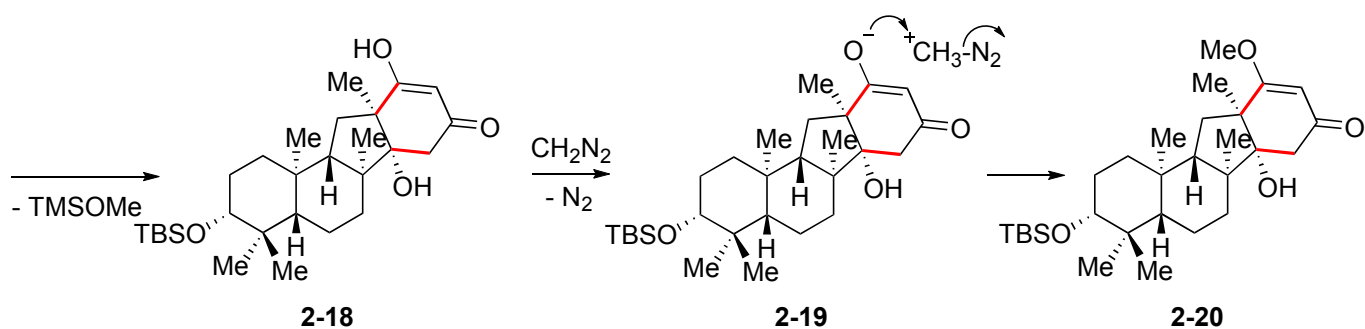
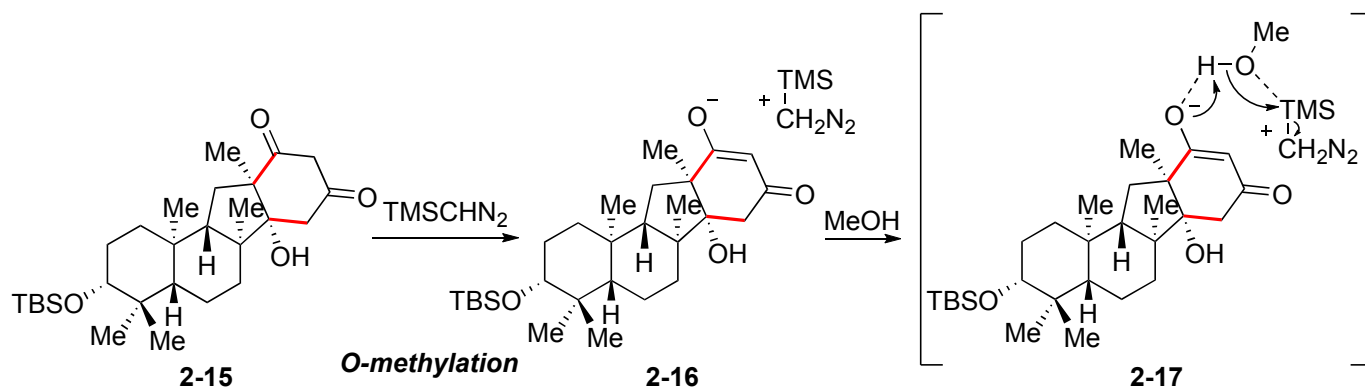


Formal [4+2] diketene annulation reaction

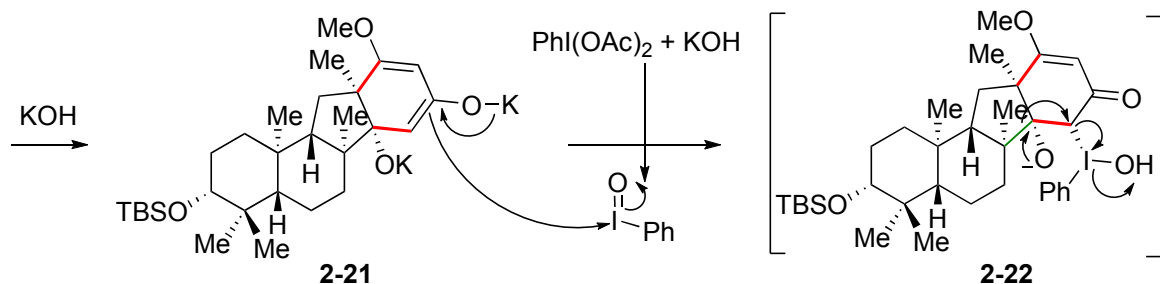


Rationalisation of the stereoselectivity :

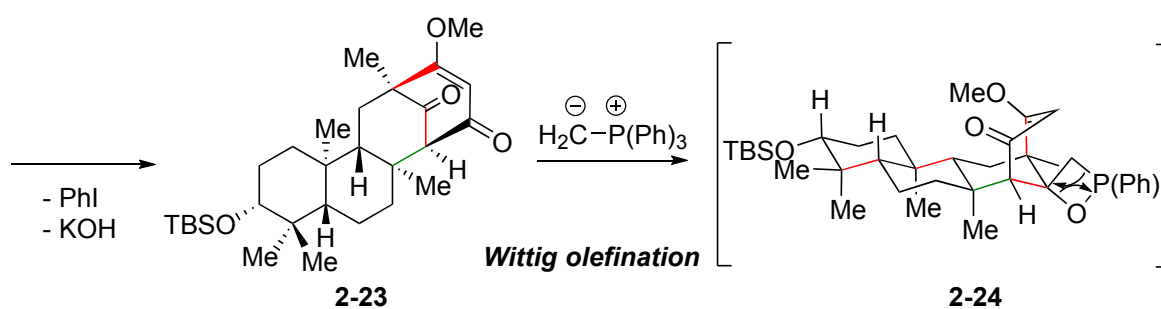




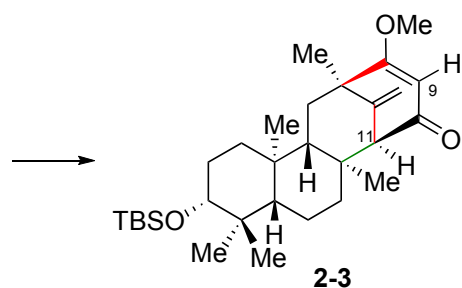
Obtain in mixture with the thermodynamically more stable regioisomer (Me placed away from the all-carbon quaternary center)



oxidative fragmentation
Favorskii-type rearrangement



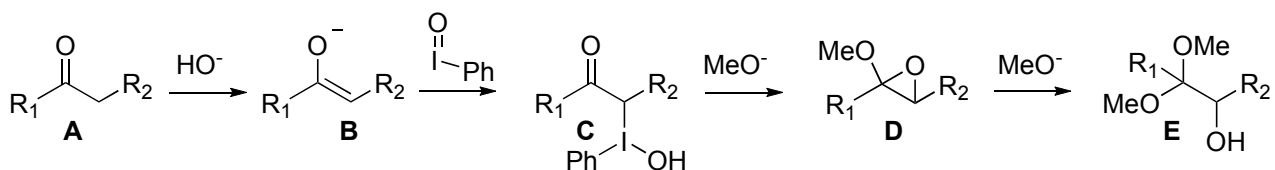
Wittig olefination



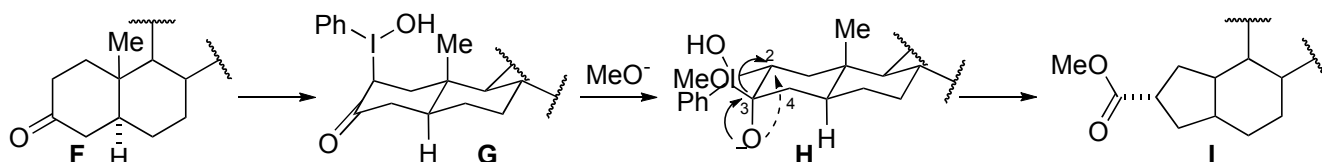
Discussion about the oxidative fragmentation : steric effects

Moriarty, R.M. *et al. tetrahedron lett.* 1984, 51, 5867

- Treatment of unencumbered ketone with $\text{PhI}(\text{OAc})_2/\text{KOH}/\text{MeOH}$: formation of α -hydroxydimethyl acetals

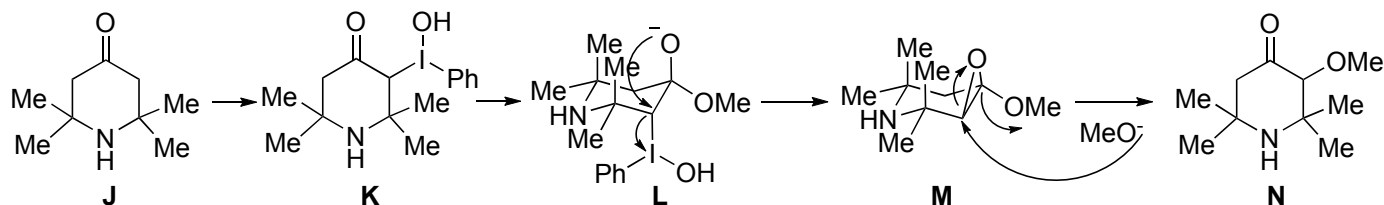


- Treatment of cholestanone with $\text{PhI}(\text{OAc})_2/\text{KOH}/\text{MeOH}$: formation of methyl ester with ring contraction



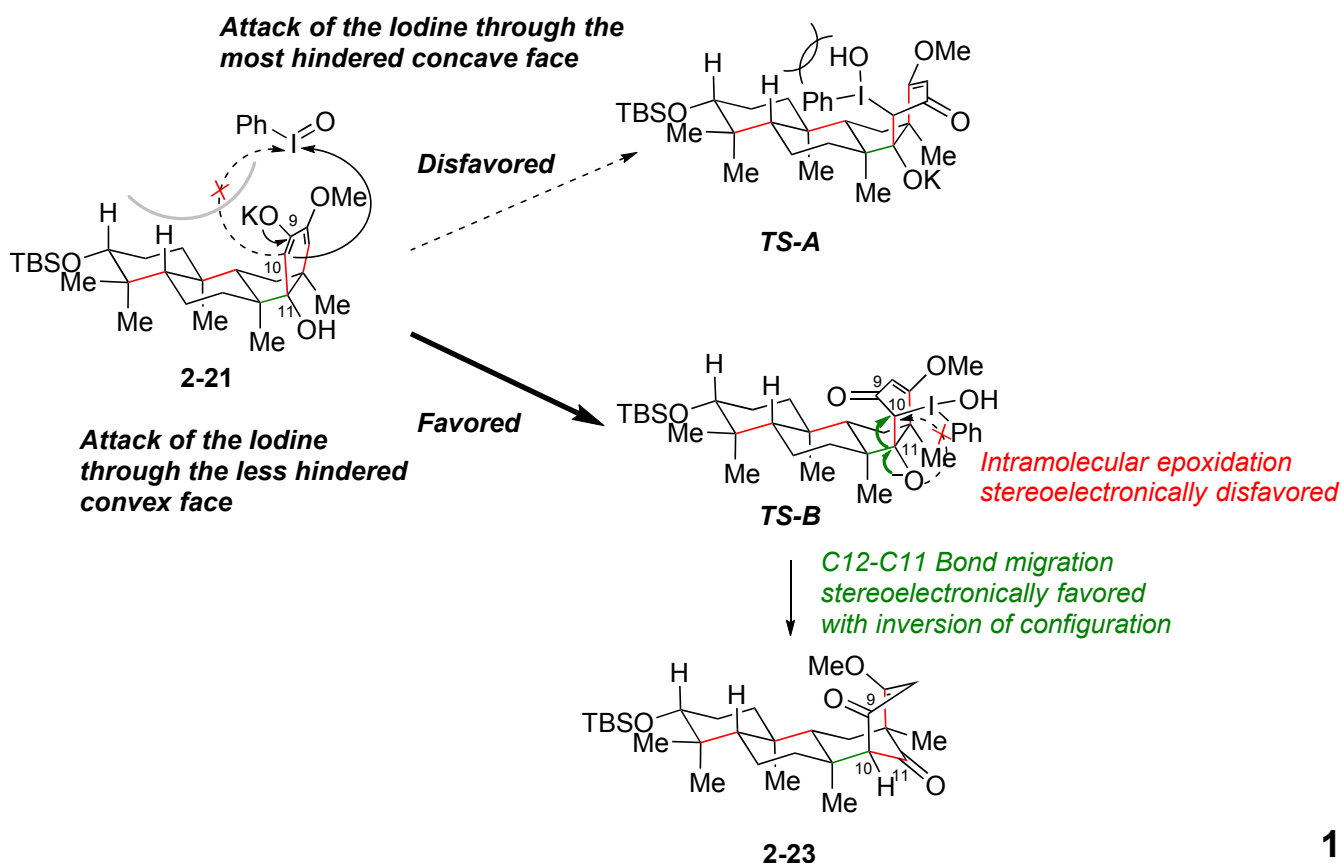
C-1 bond stereoelectronically incorrect for intramolecular epoxidation but correct for migration of the C3-C4 bond with inversion of configuration at C2.

- Treatment of sterically congested ketones with $\text{PhI}(\text{OAc})_2/\text{KOH}/\text{MeOH}$: formation of α -methoxyketone



Due to the steric crowding, attack of the methoxide anion occurs on the less substituted carbon of the epoxide.

- Treatment of **2-21** with $\text{PhI}(\text{OAc})_2/\text{KOH}/\text{MeOH}$: ring expansion



2.3. Completion of the synthesis

