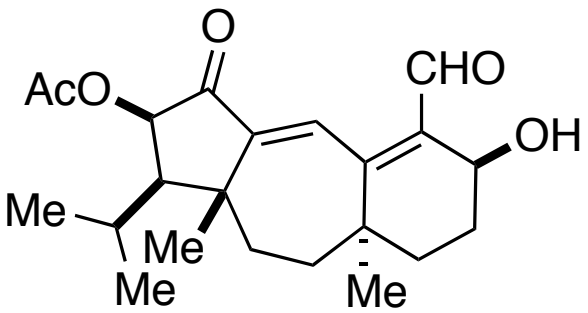
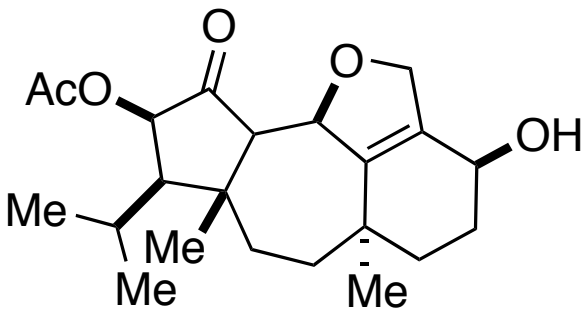
Progress in the Synthesis of Guanacastepenes



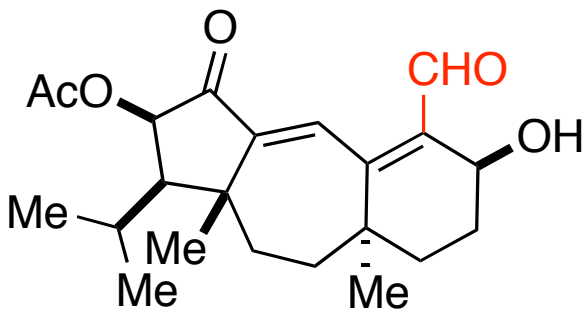
Guanacastepene A



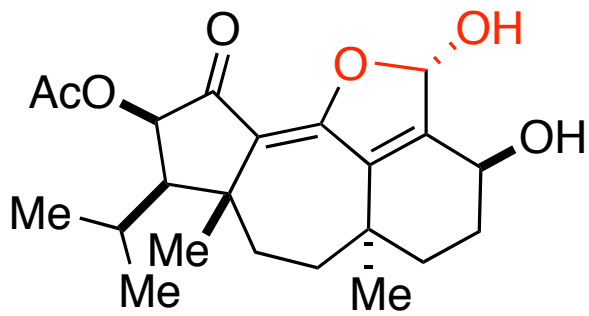
Guanacastepene E

Chris Regens
SED Group Meeting
12/12/2006

Guanacastepenes: Antibacterial Properties



Guanacastepene A



Guanacastepene I

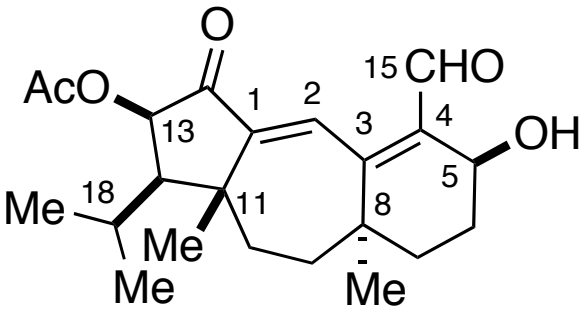
- A member of a family of diterpenes containing 14 other members
- Isolated from the extracts of a previously unknown endophytic fungus discovered in Guanacaste Conservation Area in Costa Rica
- Activity: resistance against Meticillin-resistant *S. aureus*
  Vancomycin-resistant *E. faecalis*
- Structures were determined by a combination of NMR and X ray crystallographic methods

Brady, S.F.; Singh, M.P.; Janso, J.E.; Clady, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116.

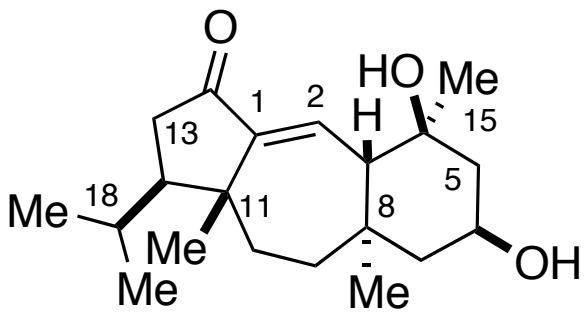
Brady, S.F.; Bondi, S.M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

Singh, M.P.; Janso, J.E.; Luckman, S.W.; Brady, S.F.; Clardy, J.; Greenstein, M.; Maiese, W.M. *J. Antibiot.* **2000**, *53*, 25

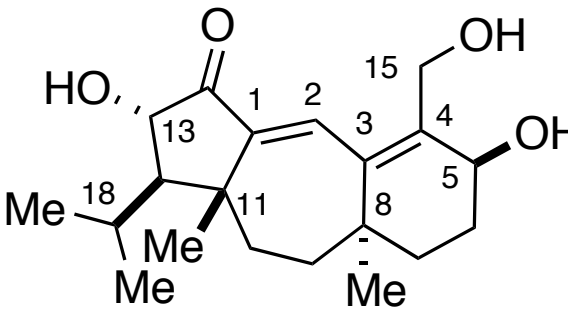
Guanacastepenes: The Five [5-7-6] Diterpene Ring Systems



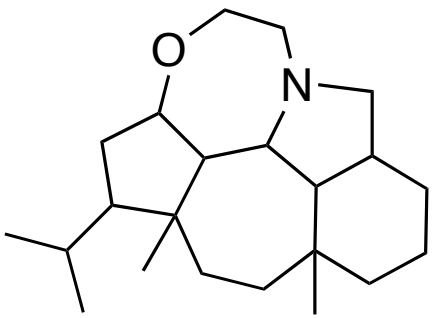
Guanacastepene A

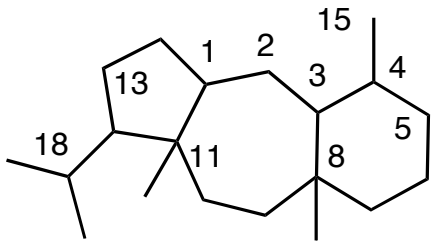


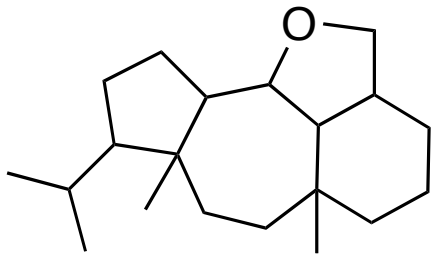
Guanacastepene B

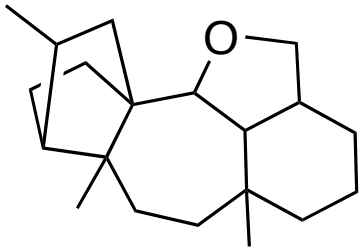


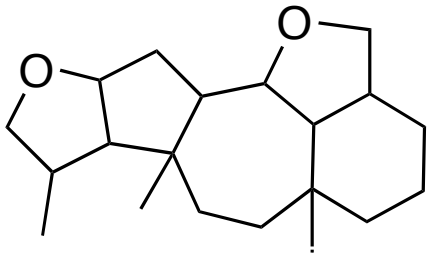
Guanacastepene C



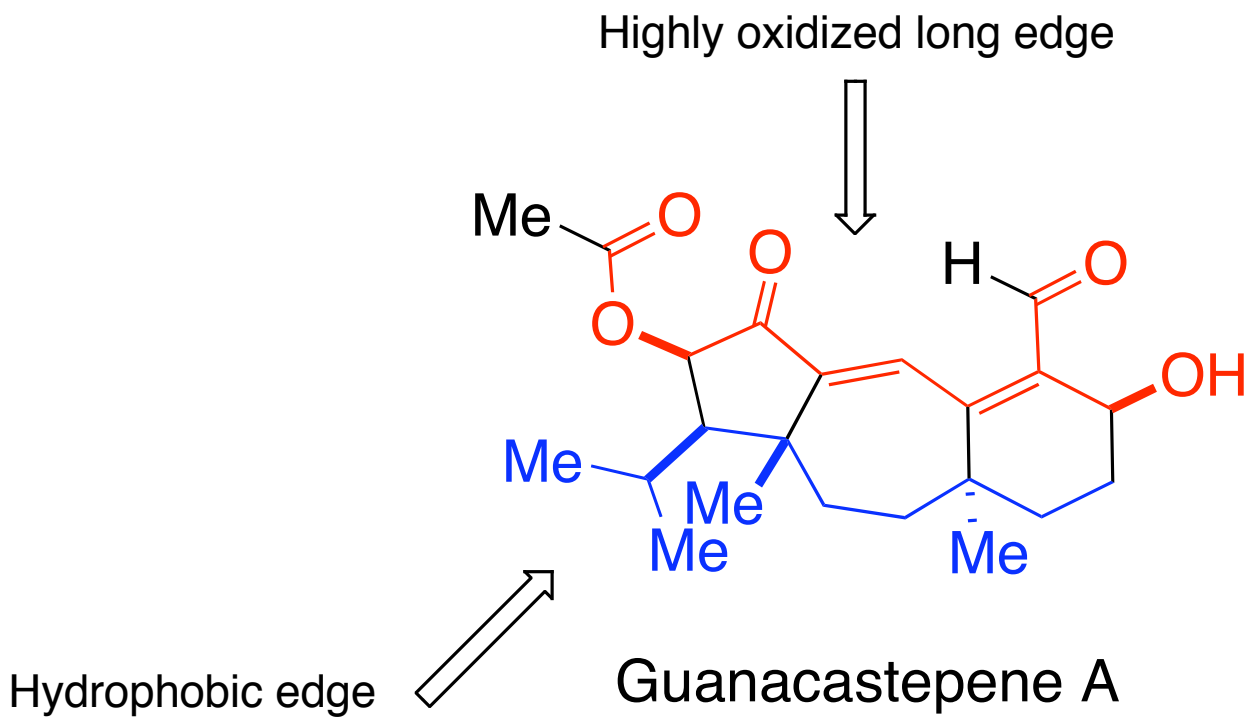






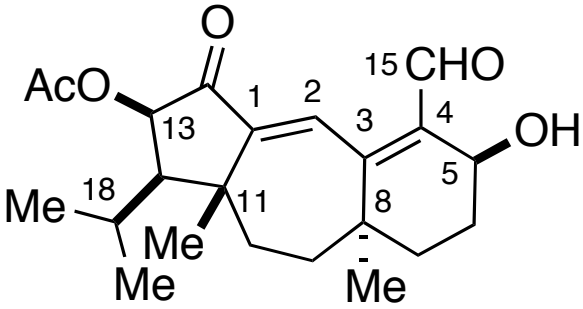


Guanacastepenes: Interesting Diterpene Structure

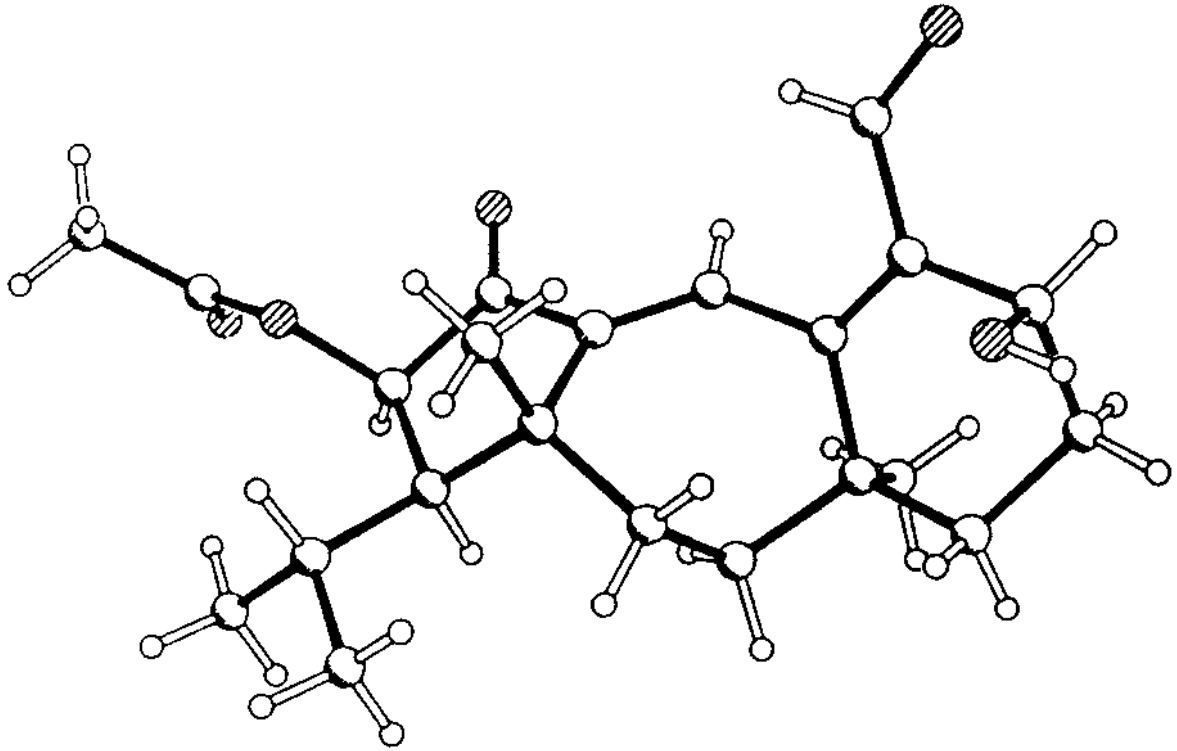


Guanacastepene A

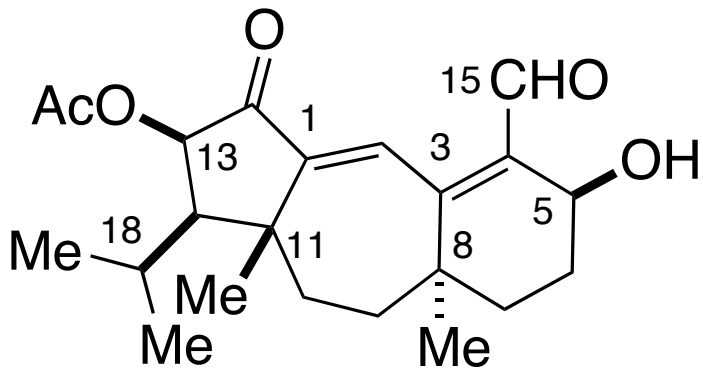
Guanacastepenes: Interesting Diterpene Structure



Guanacastepene A



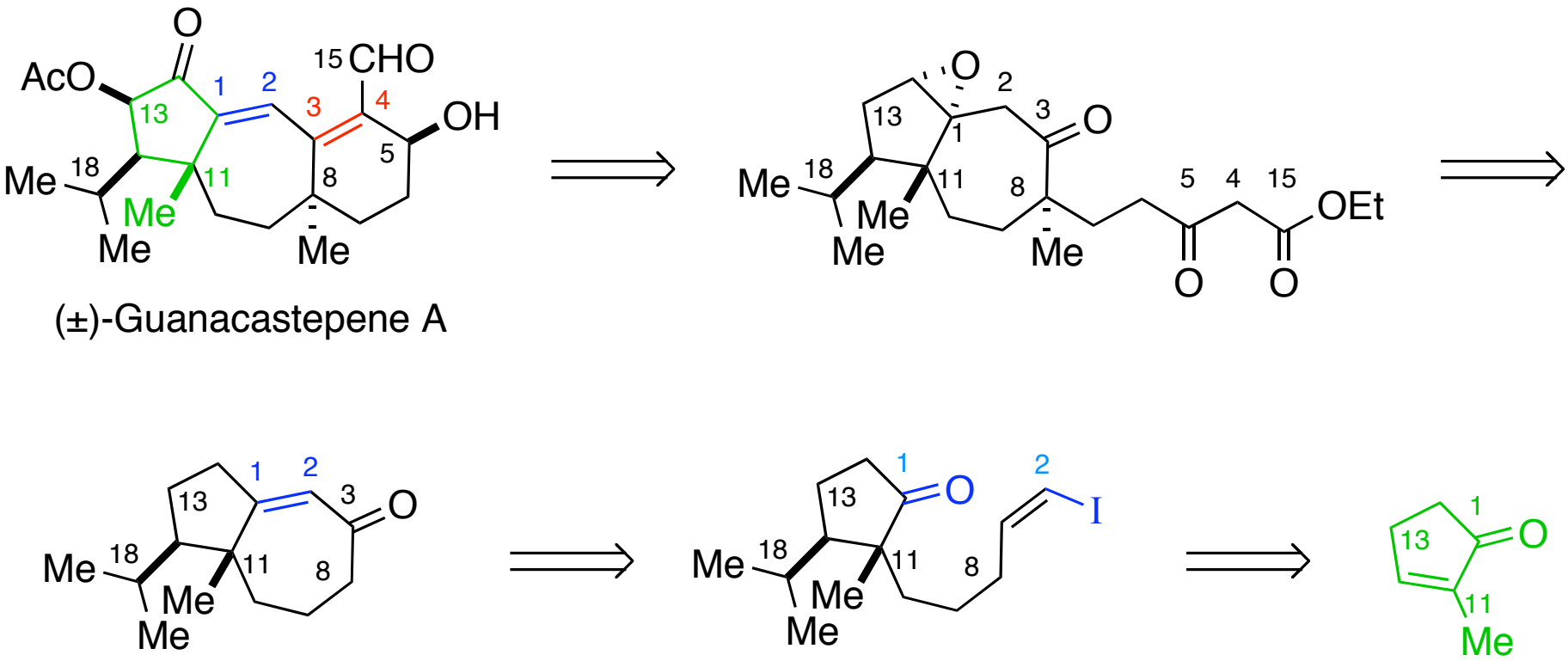
Question: Reterosynthetic Analysis of Guanacastepene A



Guanacastepene A

?

(±)-Guanacastepene A: Danishefsky's Retrosynthetic Analysis



Tan, D.S.; Dudley, G.B.; Danishefsky, S.J. *Awgew. Chem. Int. Ed.* **2002**, *41*, 2185.

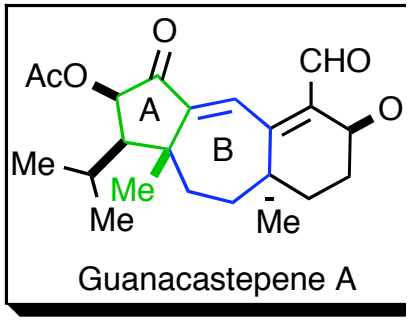
Lin, S.N.; Dudley, G.B.; Tan, D.S.; Danishefsky, S.J. *Awgew. Chem. Int. Ed.* **2002**, *41*, 2188.

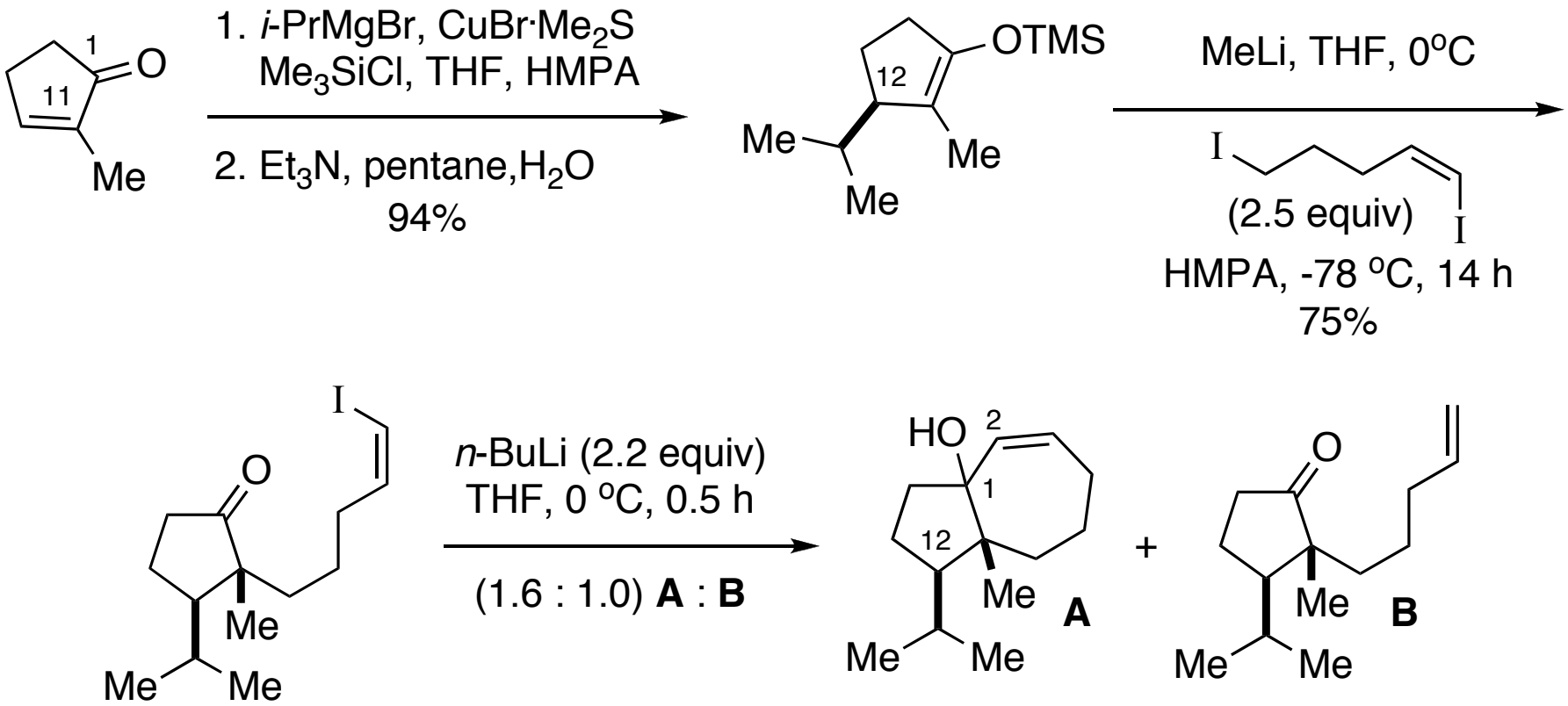
Mandal, M.; Danishefsky, S.J. *Tetrahedron Lett.* **2004**, *45*, 3827.

Mandal, M.; Danishefsky, S.J. *Tetrahedron Lett.* **2004**, *45*, 3831.

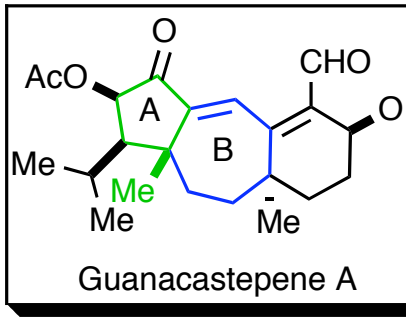
Mandal, M.; Yun, H.D.; Dudley, G.B.; Lin, S.N.; Tan, D.S.; Danishefsky, S.J. *J. Org. Chem.* **2005**, *70*, 10619.

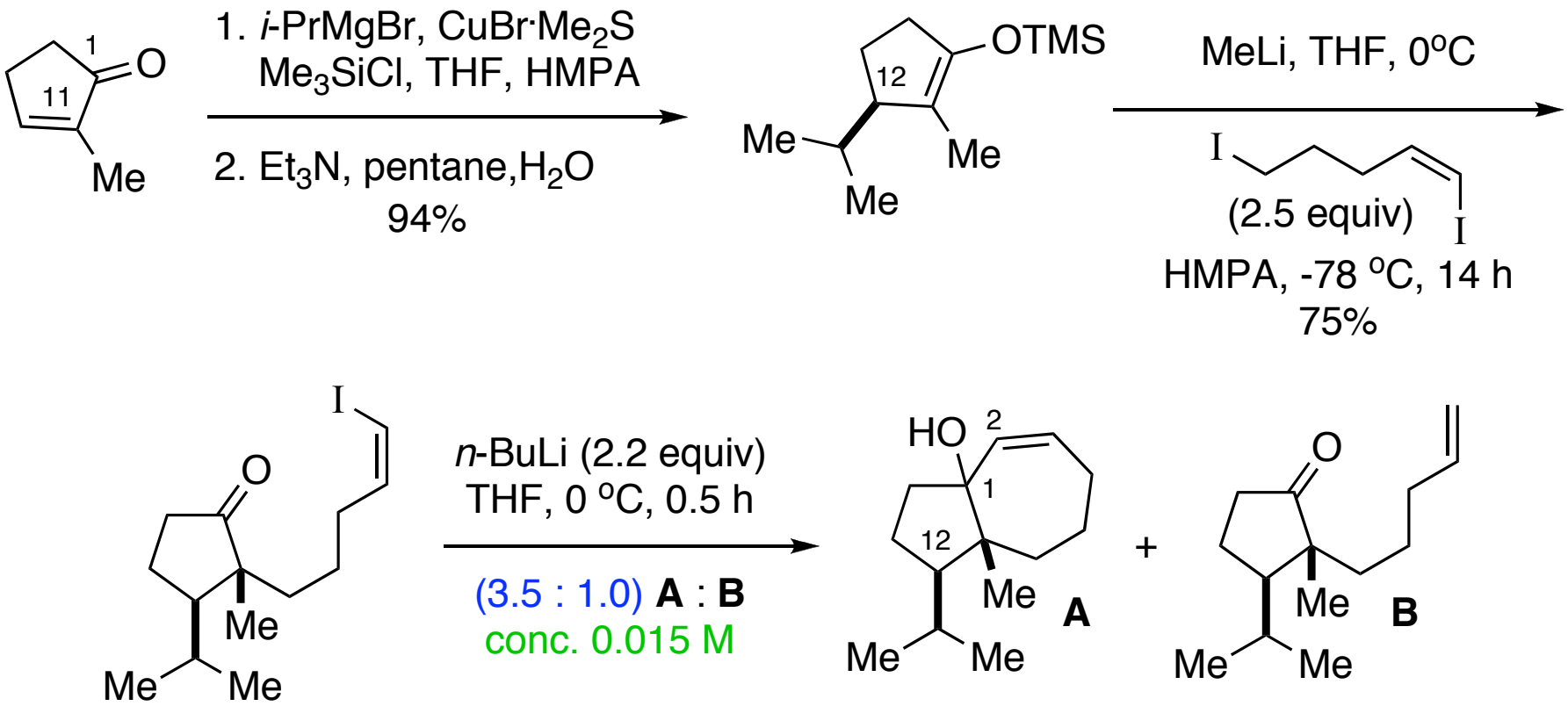
(±)-Guanacastepene A: Danishefsky's Preparation of Ring **A**



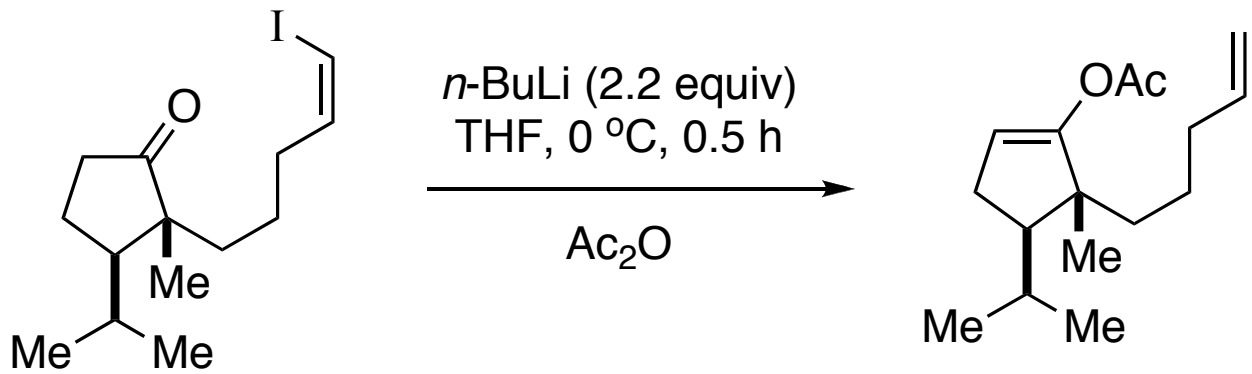


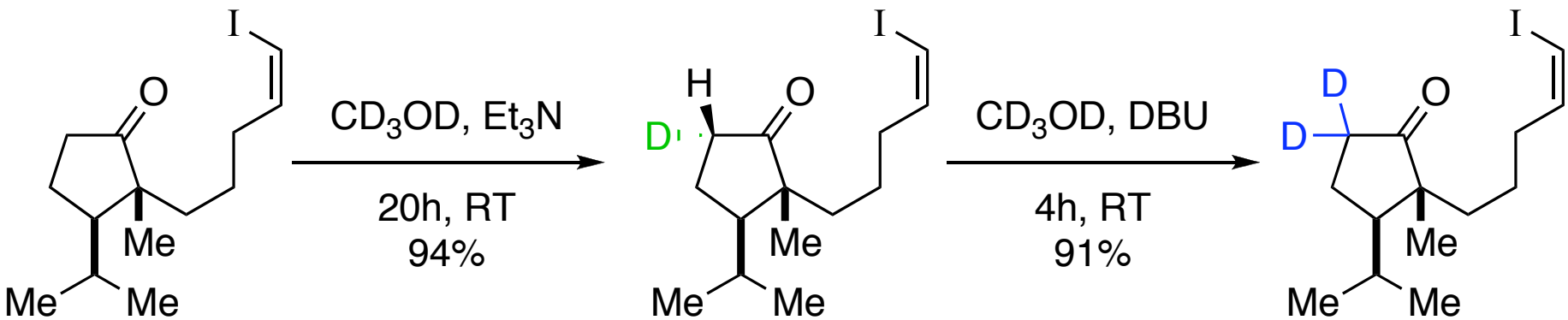
(±)-Guanacastepene A: Danishefsky's Preparation of Ring **A**





(±)-Guanacastepene A: Solving the Proton-Transfer Problem

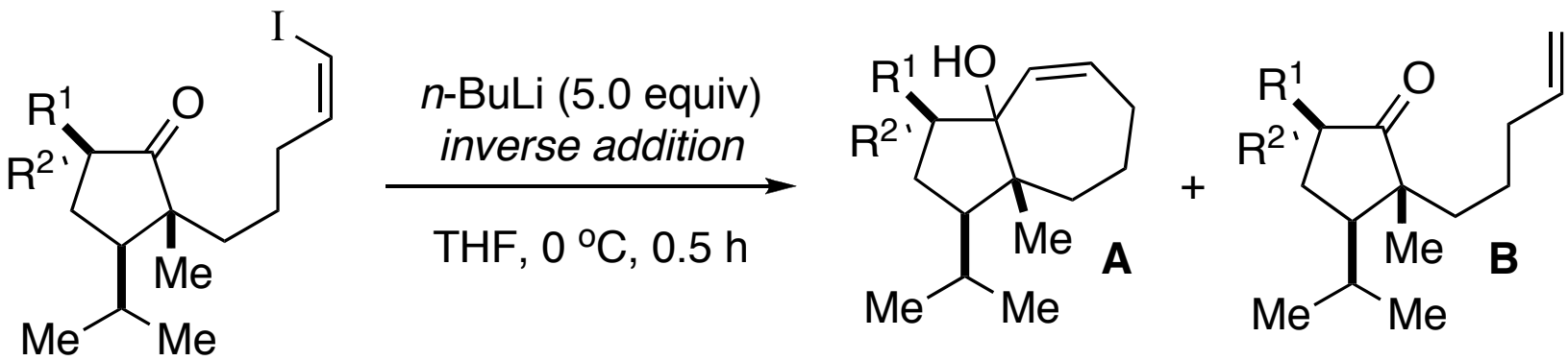




d-0 *d*-1 *d*-2

- Repalcement of the α-protons with the less "kinetically acidic" deuterium atom, should shift the product ratio favoring cyclization

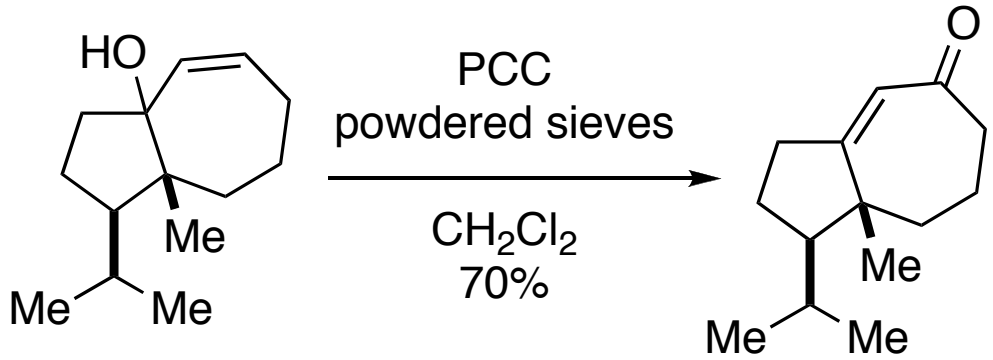
(±)-Guanacastepene A: Deuterium to the Rescue

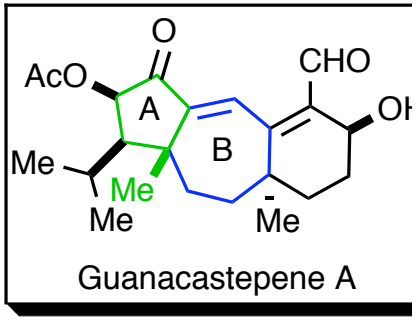


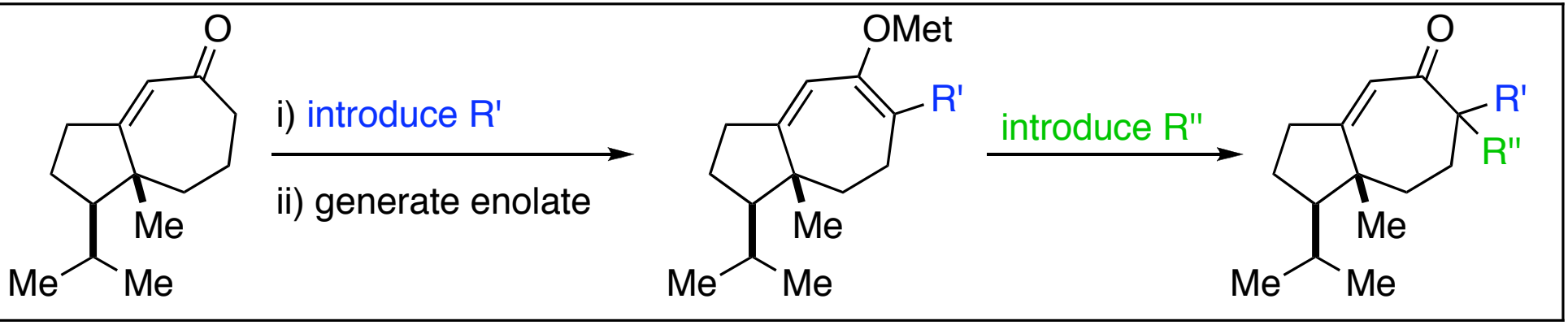
Compound	yield, **A**	yield, **B**	Ratio (**A** : **B**)
d-0 ($R^1 = R^2 = H$)	65%	18%	78 : 22
d-1 ($R^1 = D$, $R^2 = H$)	71%	9.3%	88 : 12
d-2 ($R^1 = R^2 = D$)	84%	8.6%	91 : 9

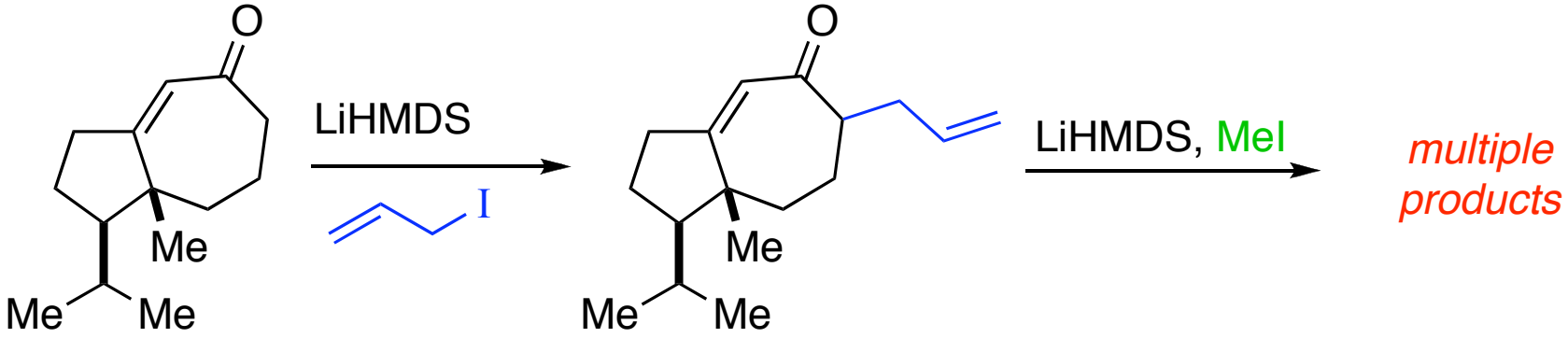
- Replacing the protons with deuterium isotopes significantly suppressed the noncyclization pathwa

(±)-Guanacastepene A: Elaboration of Ring B

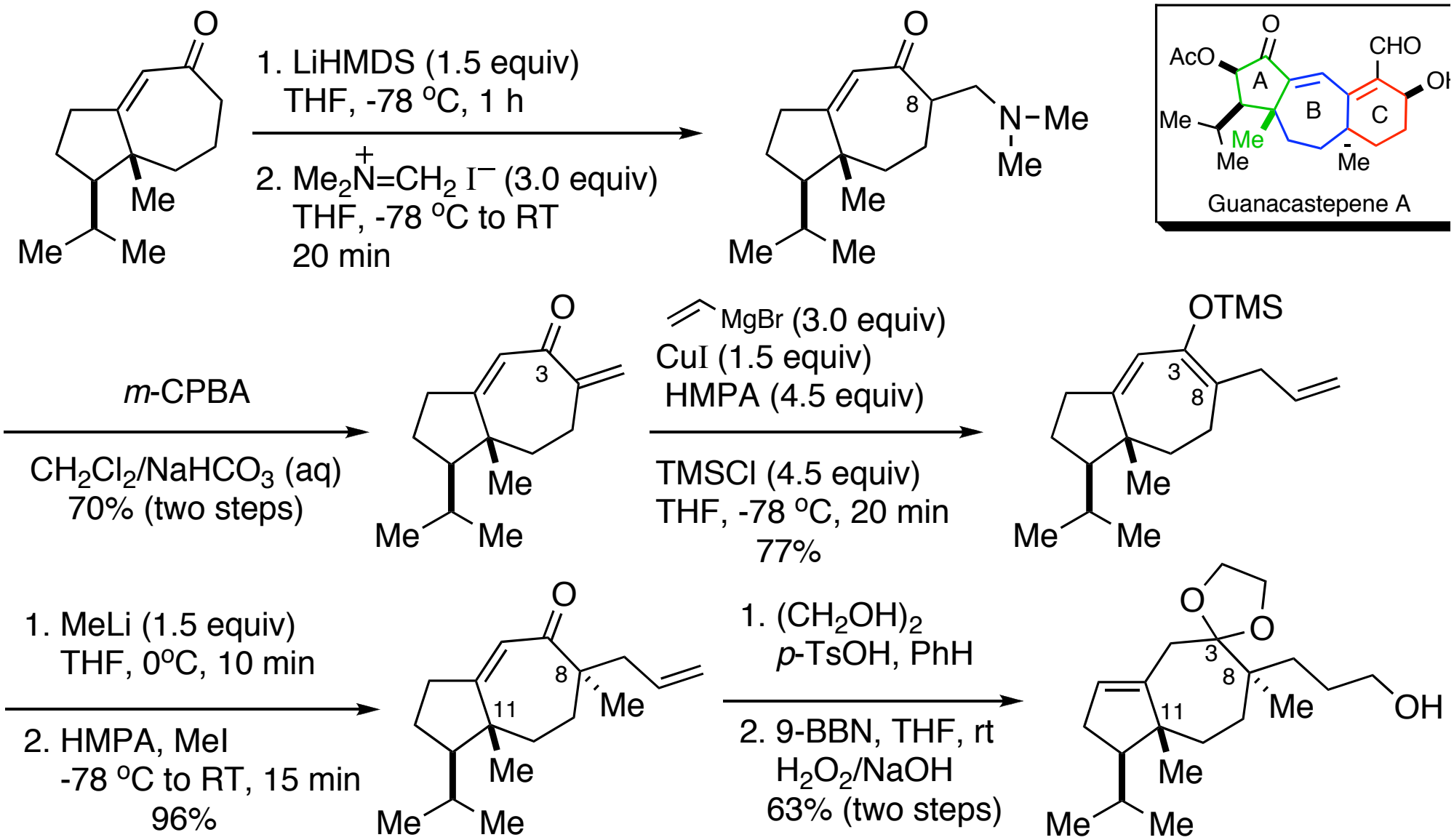




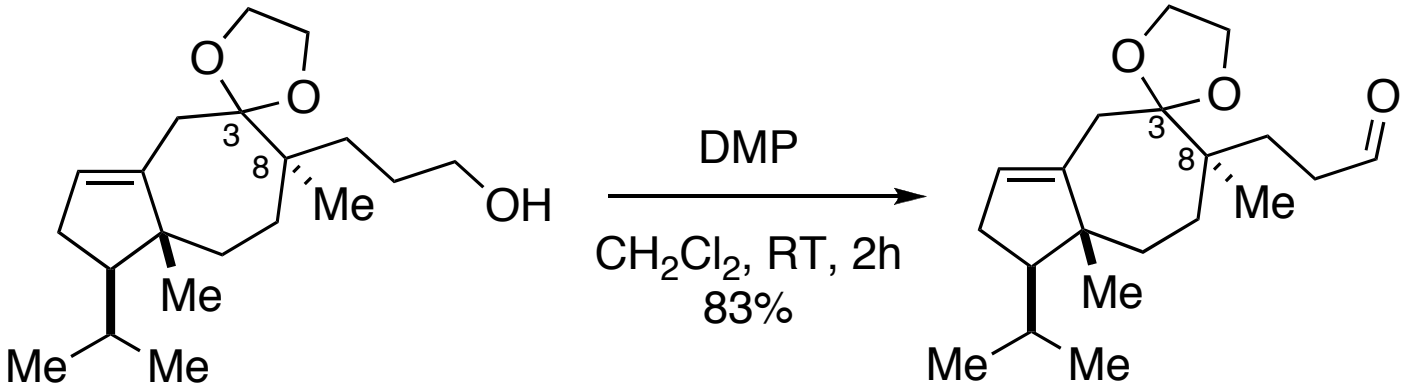


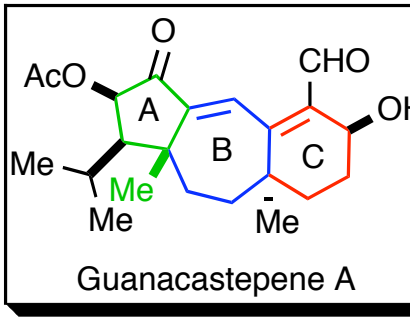


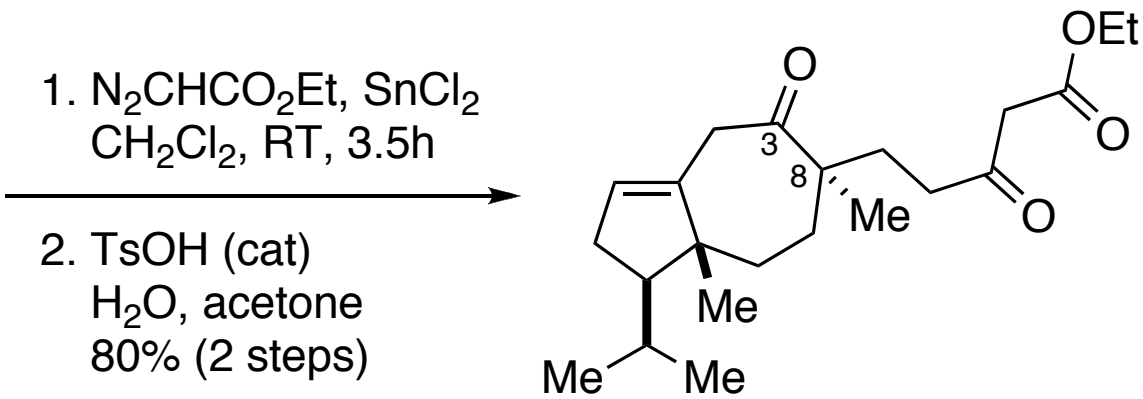
(±)-Guanacastepene A: Building the C-(8) Quaternary Methyl Group



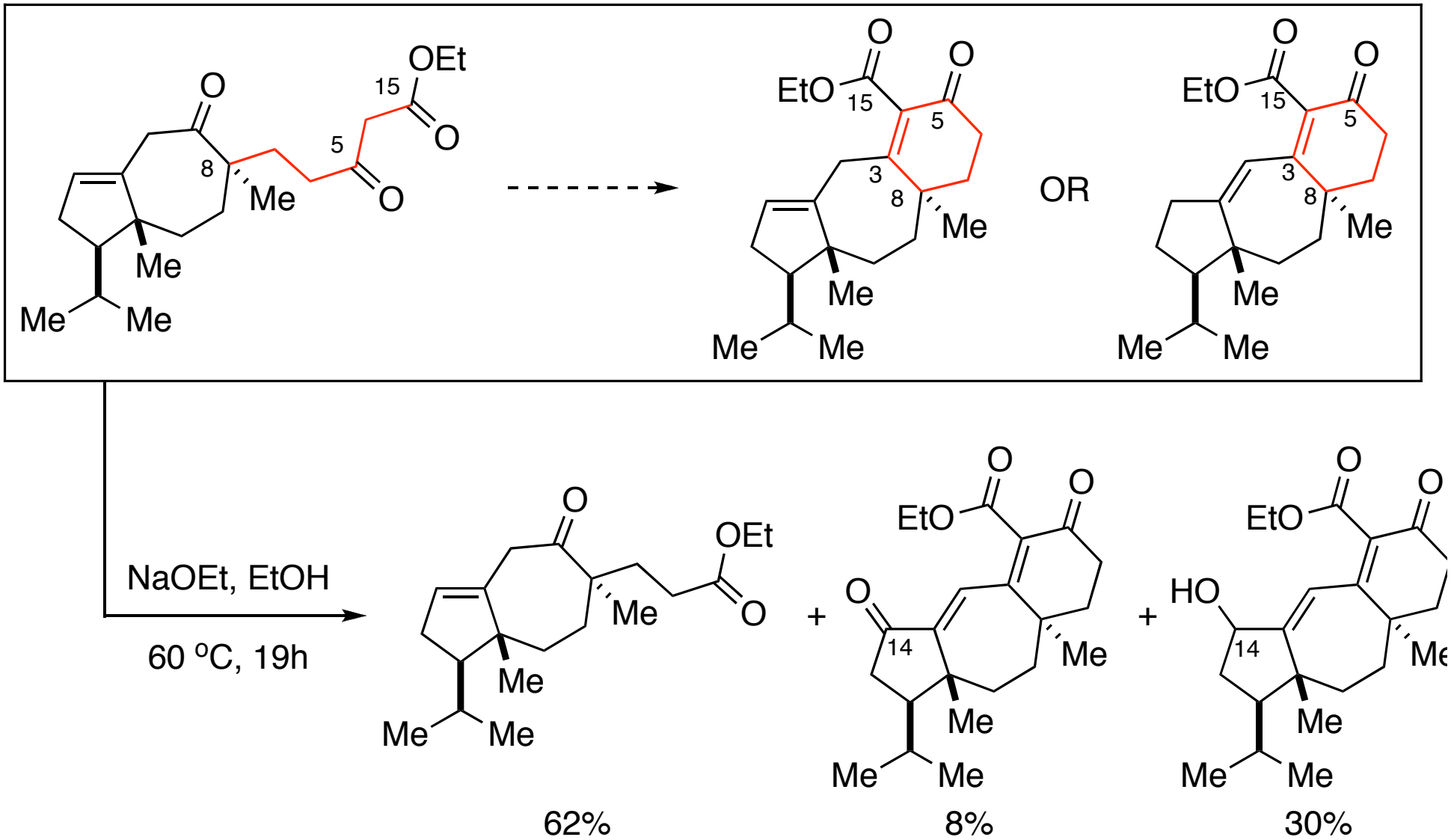
(±)-Guanacastepene A: Setting the Stage for the Formation of Ring C



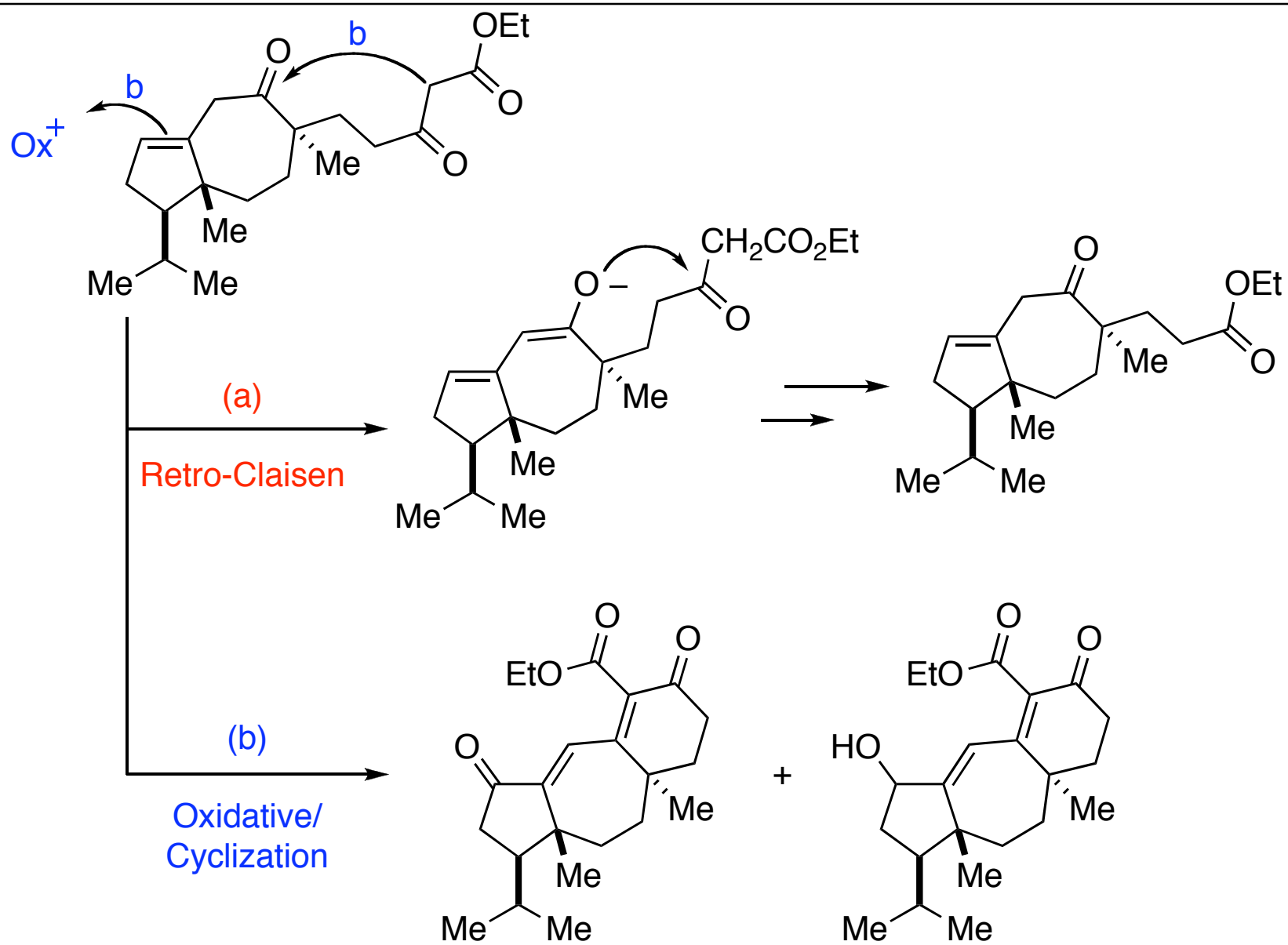




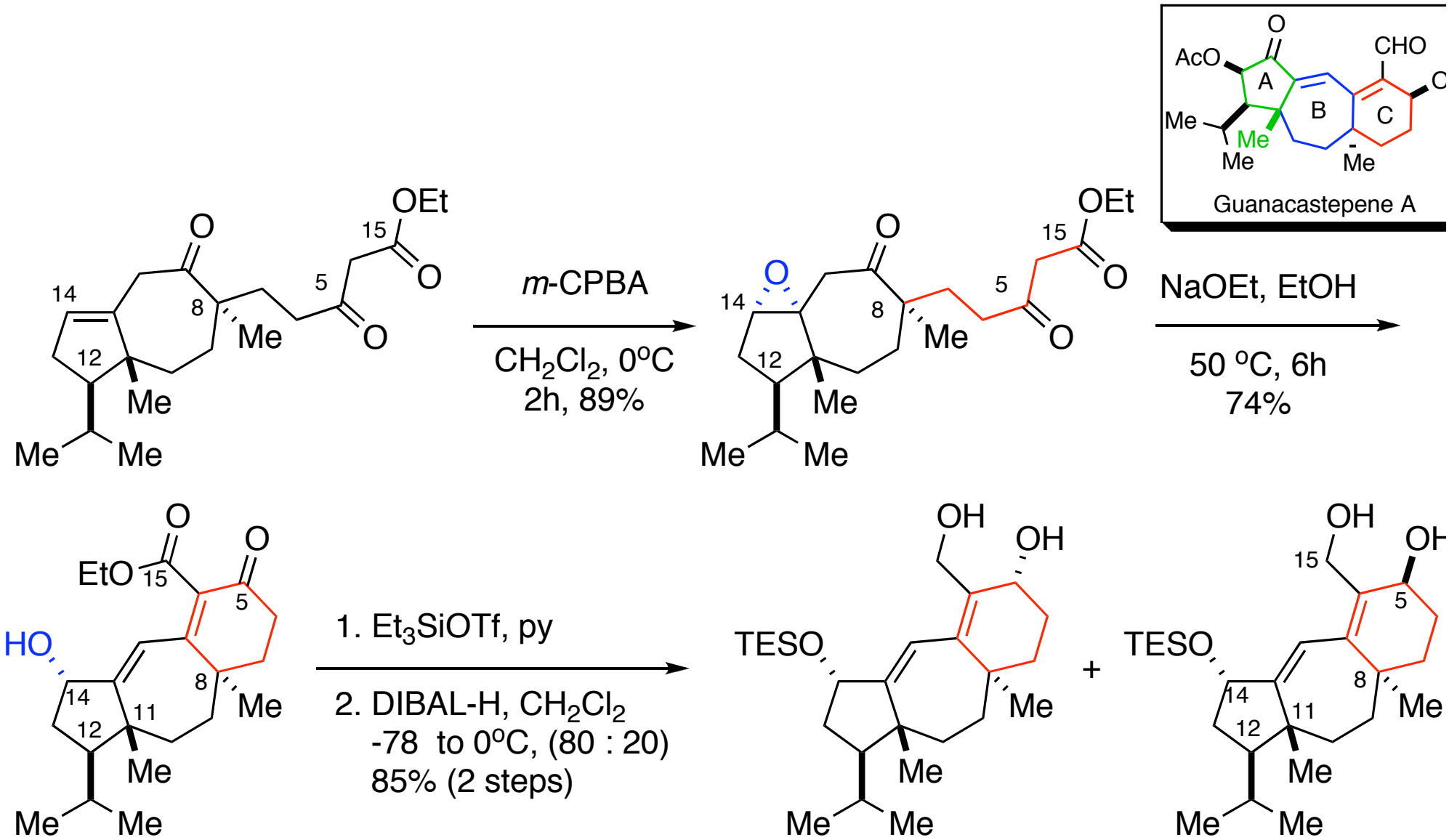
Intamolecular Knoevenagel Condensation in Practice



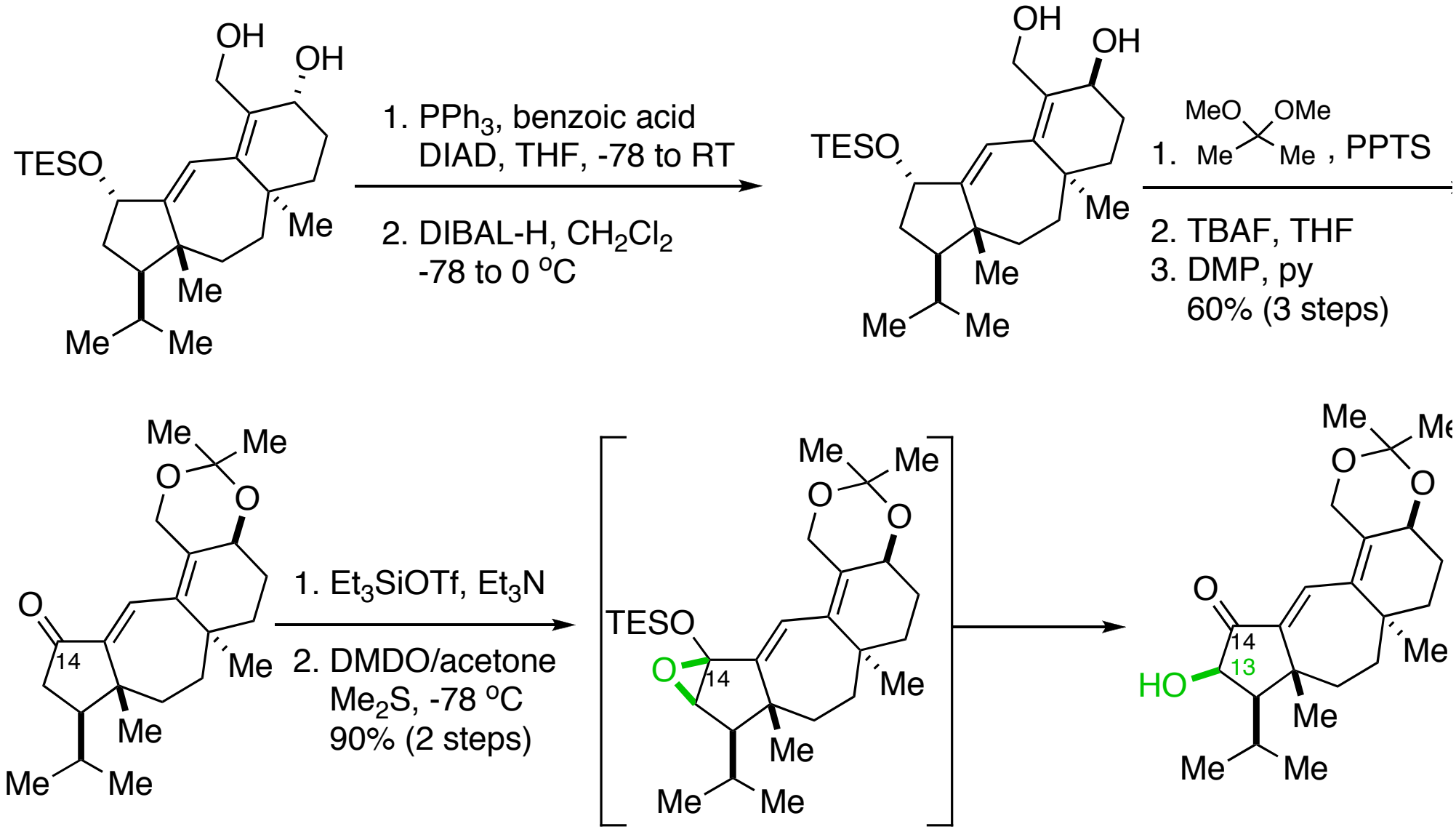
Proposed Pathway for the Formation of Retro-Claisen Product



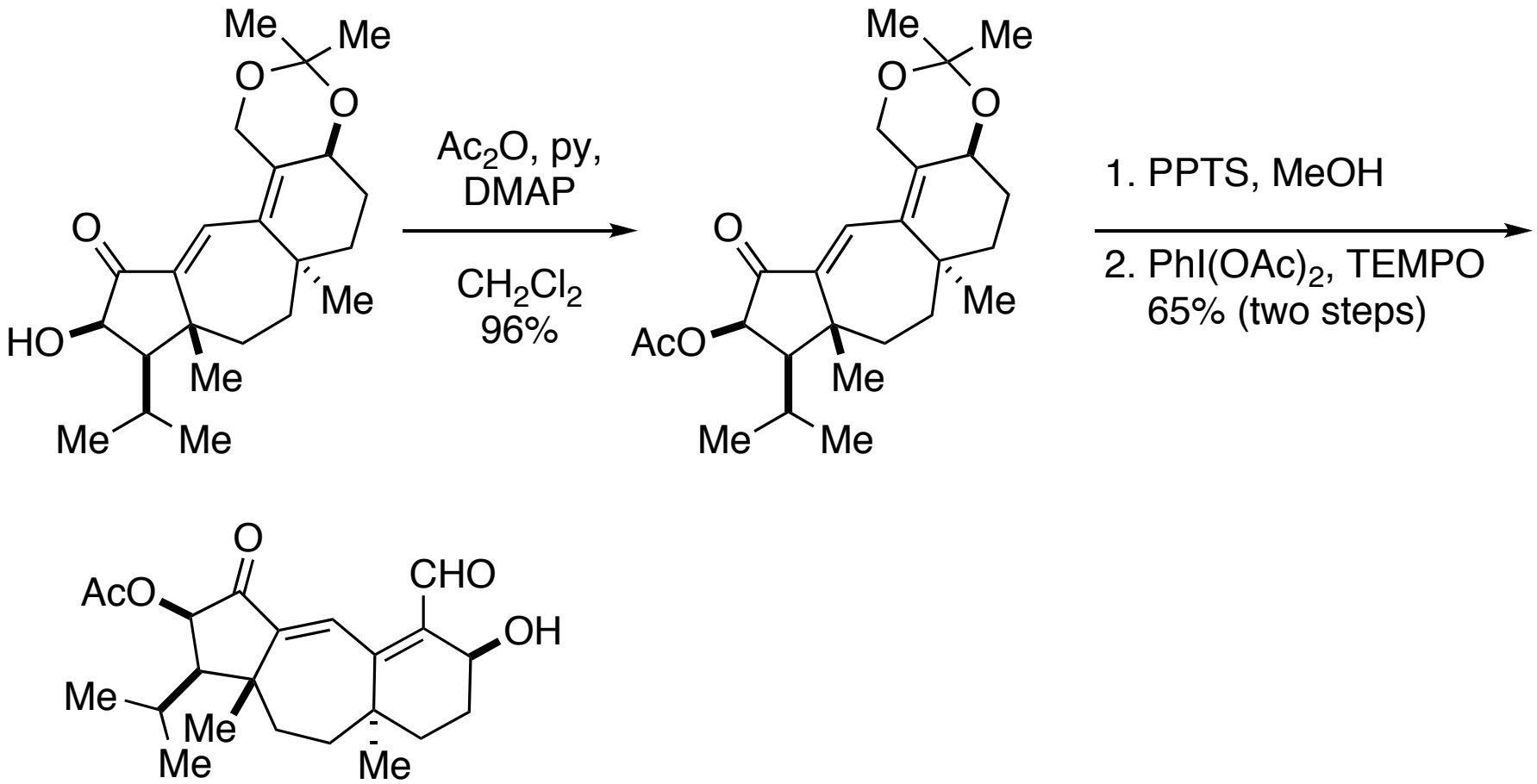
(±)-Guanacastepene A: Reduction Favors The Wrong Epimer



(±)-Guanacastepene A: Installing the C-(13) Hydroxyl Group

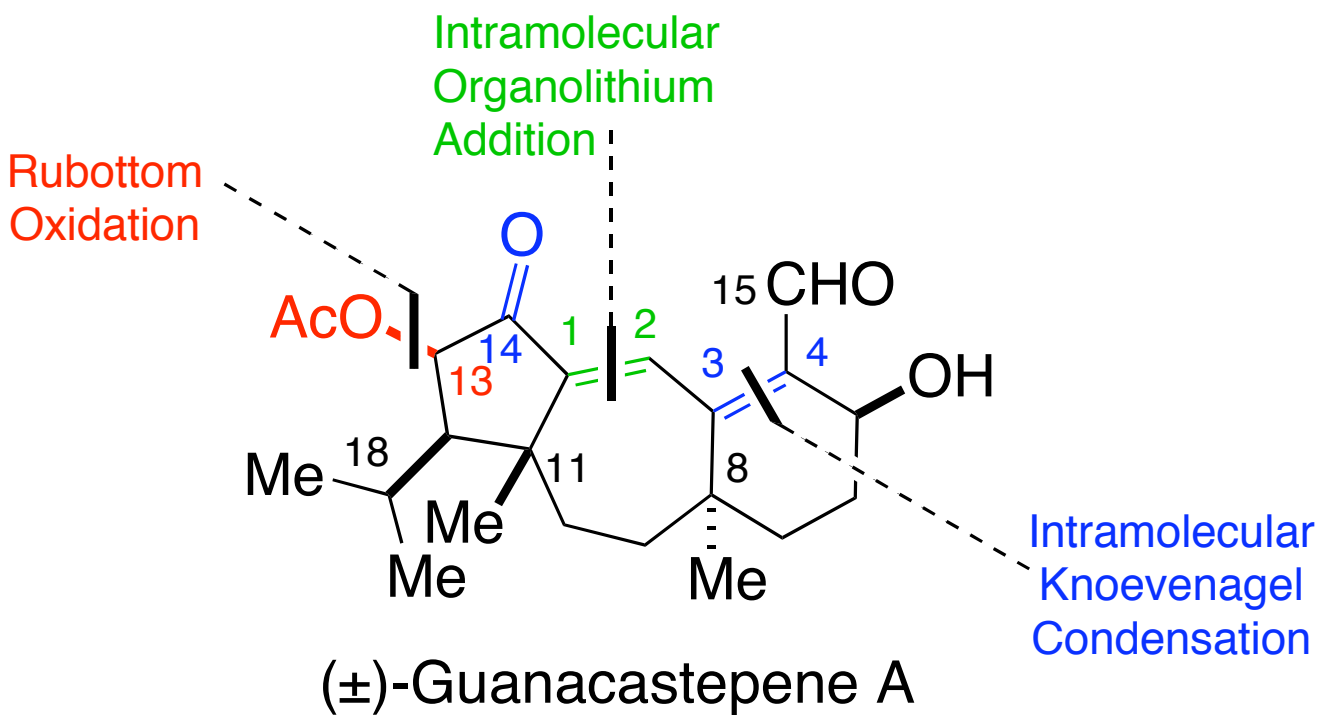


(±)-Guanacastepene A: Completing the Synthesis



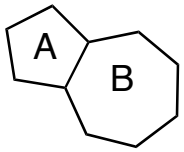
(±)-Guanacastepene A

Summary: Danishefsky's Total Synthesis of (±)-Guanacastepene A

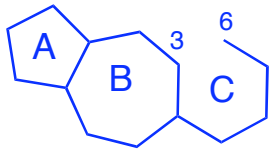


(±)-Guanacastepene A

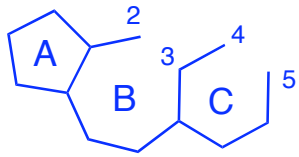
Other Approaches to the Guanacastepenes



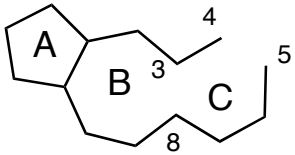
Mangnus (2002) Pyrylium ylide
Tius (2002) RCM
Chiu (2004) Nazarov
Srikrishna (2004) RCM



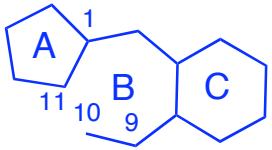
Danishefsky (2002) Knoevenagel condensation
Snider (2002) Intramolecular condensation
Mehta (2005) Knoevenagel condensation



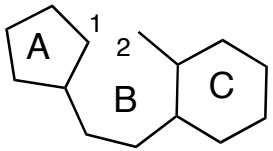
Hanna (2004) Tandem RCM



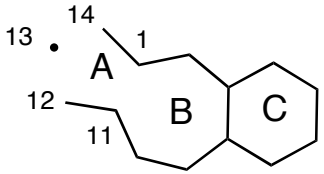
Yang (2005) IMDA of a furan and alkyne



Sorensen (2006) [2 +2] photocycloadditon and fragmentation

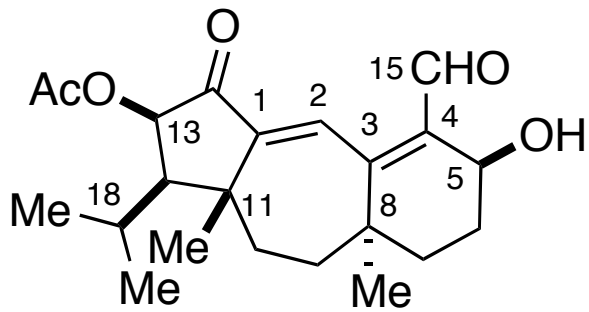


Trauner (2006) Electrochemical oxidation of furans
Kwon (2003) Mukaiyama aldol
Overman (2006) 7-endo-Heck

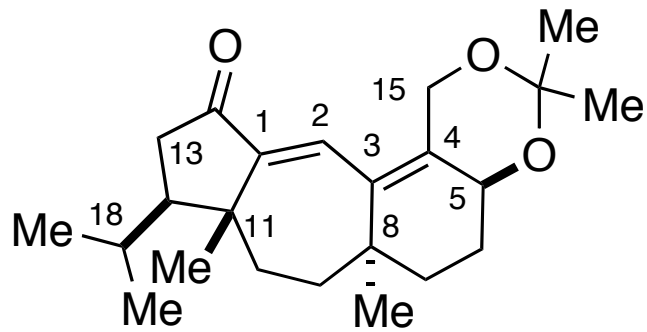


Brummond (2003) Pausen-Khand

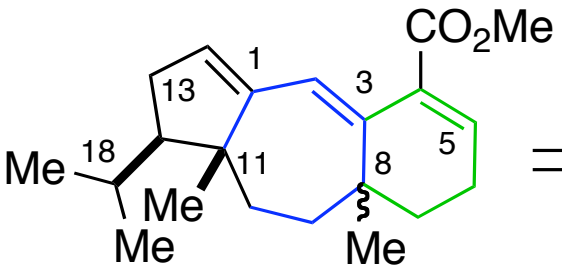
Synthesis of Guanacastepene A: Hanna's Tandem RCM Approach

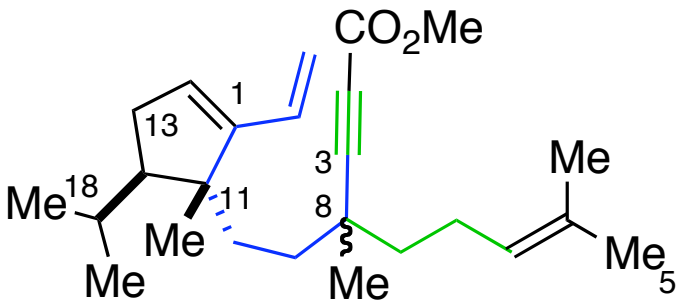


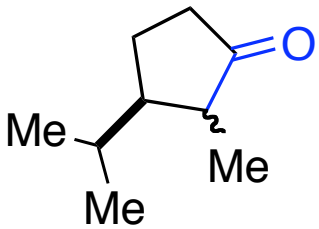
(±)-Guanacastepene A



Danishefsky's intermediate

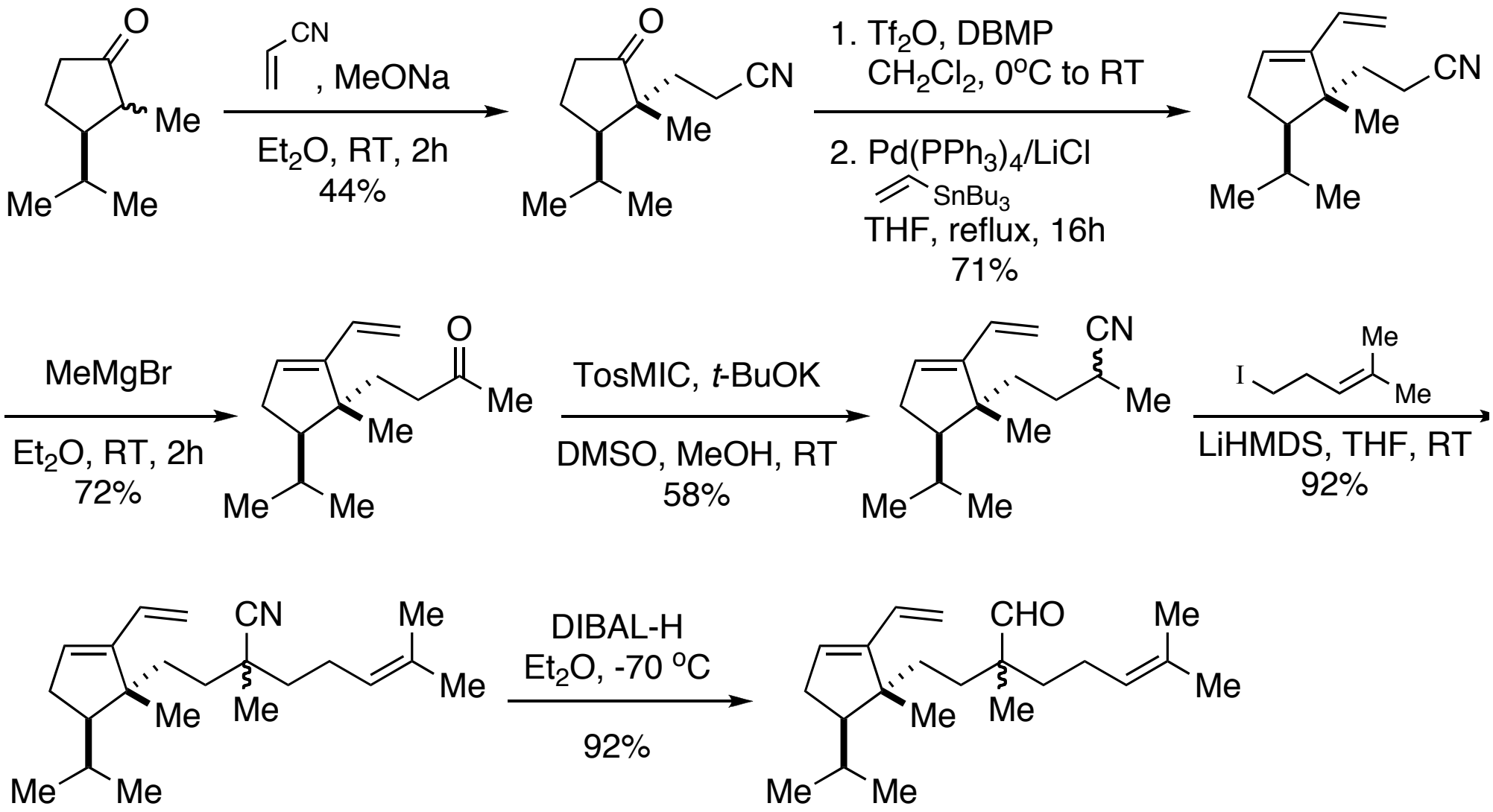




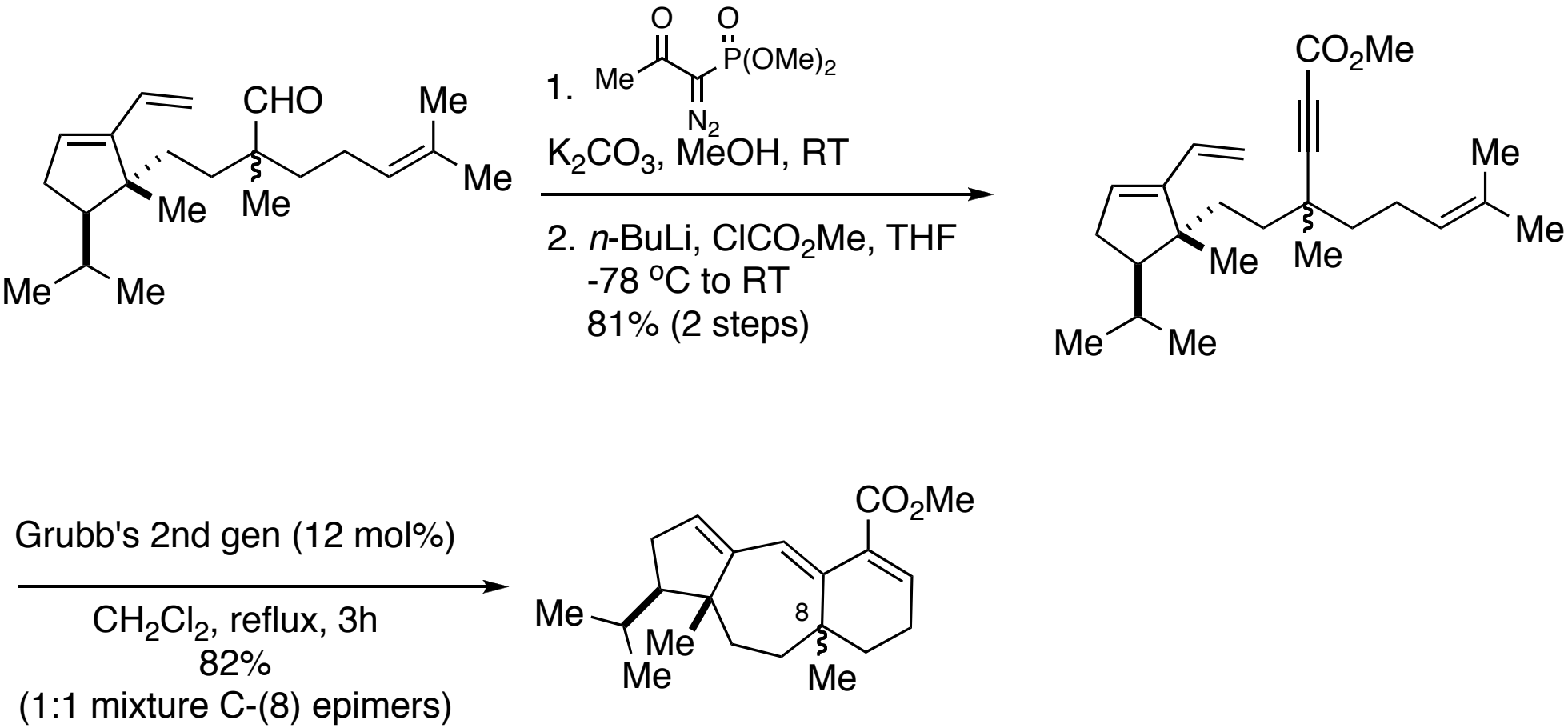


Boyer, F-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817.

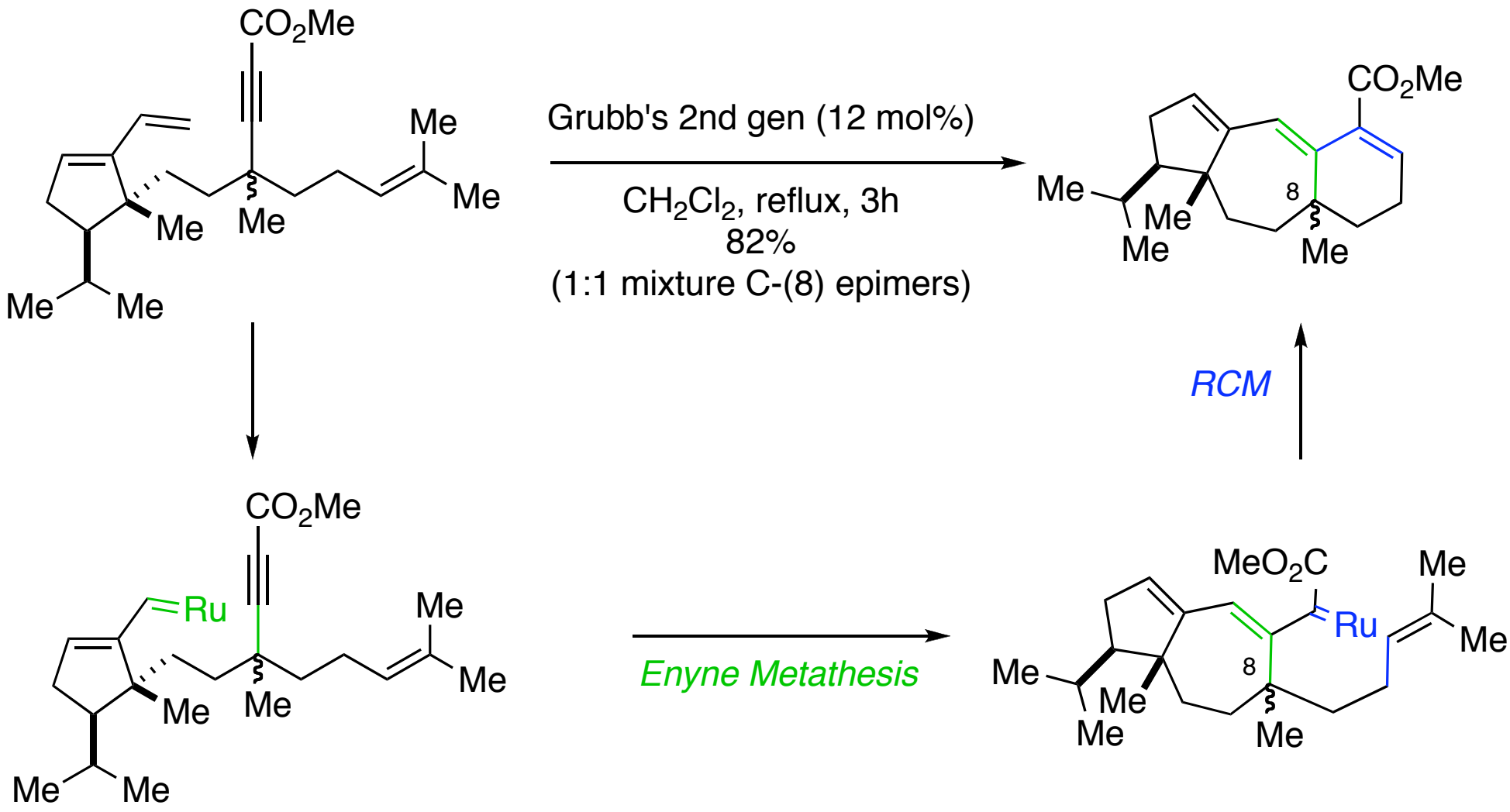
Hanna's Formal Synthesis: Preparation of RCM Precursor



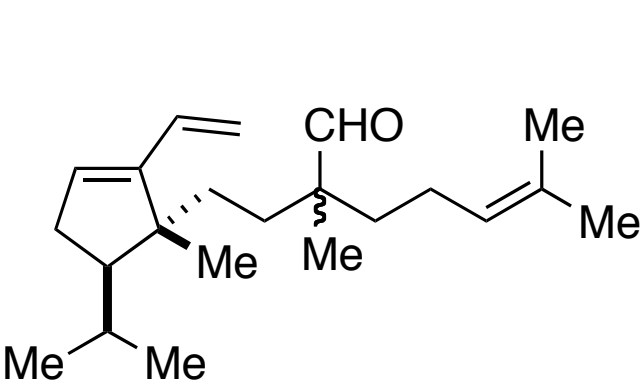
Hanna's Formal Synthesis: Key Tandem Ring-Closing Metathesis

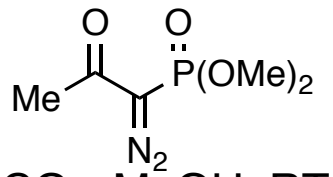


Hanna's Formal Synthesis: Key Tandem Ring-Closing Metathesis



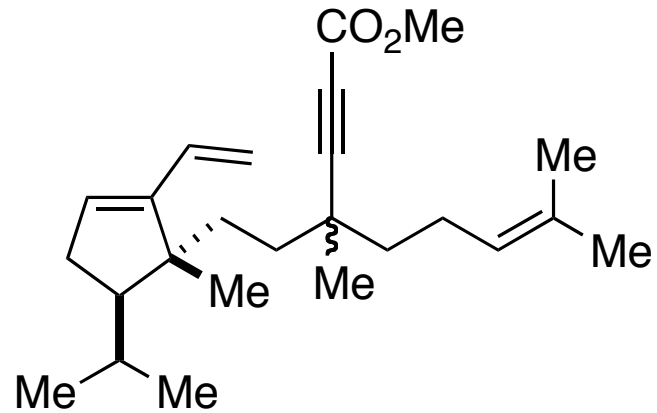
Hanna's Formal Synthesis: Danishefsky's Intermediate



1. 

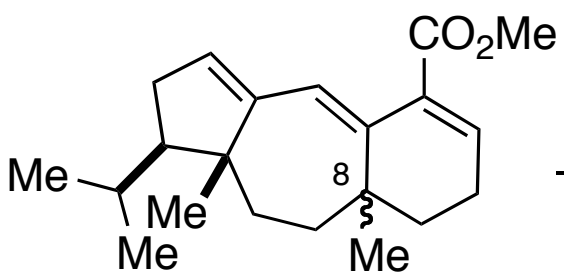
K_2CO_3, MeOH, RT

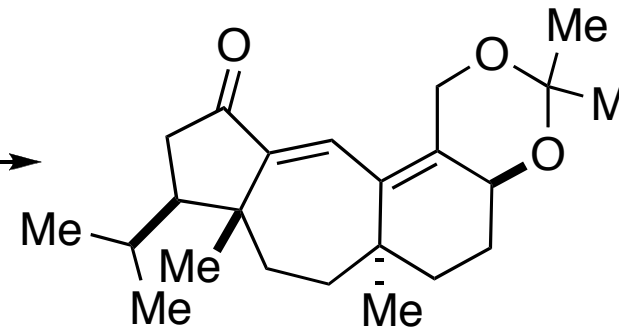
2. *n*-BuLi, $ClCO_2Me$, THF
-78 °C to RT
81% (2 steps)



Grubb's 2nd gen (12 mol%)

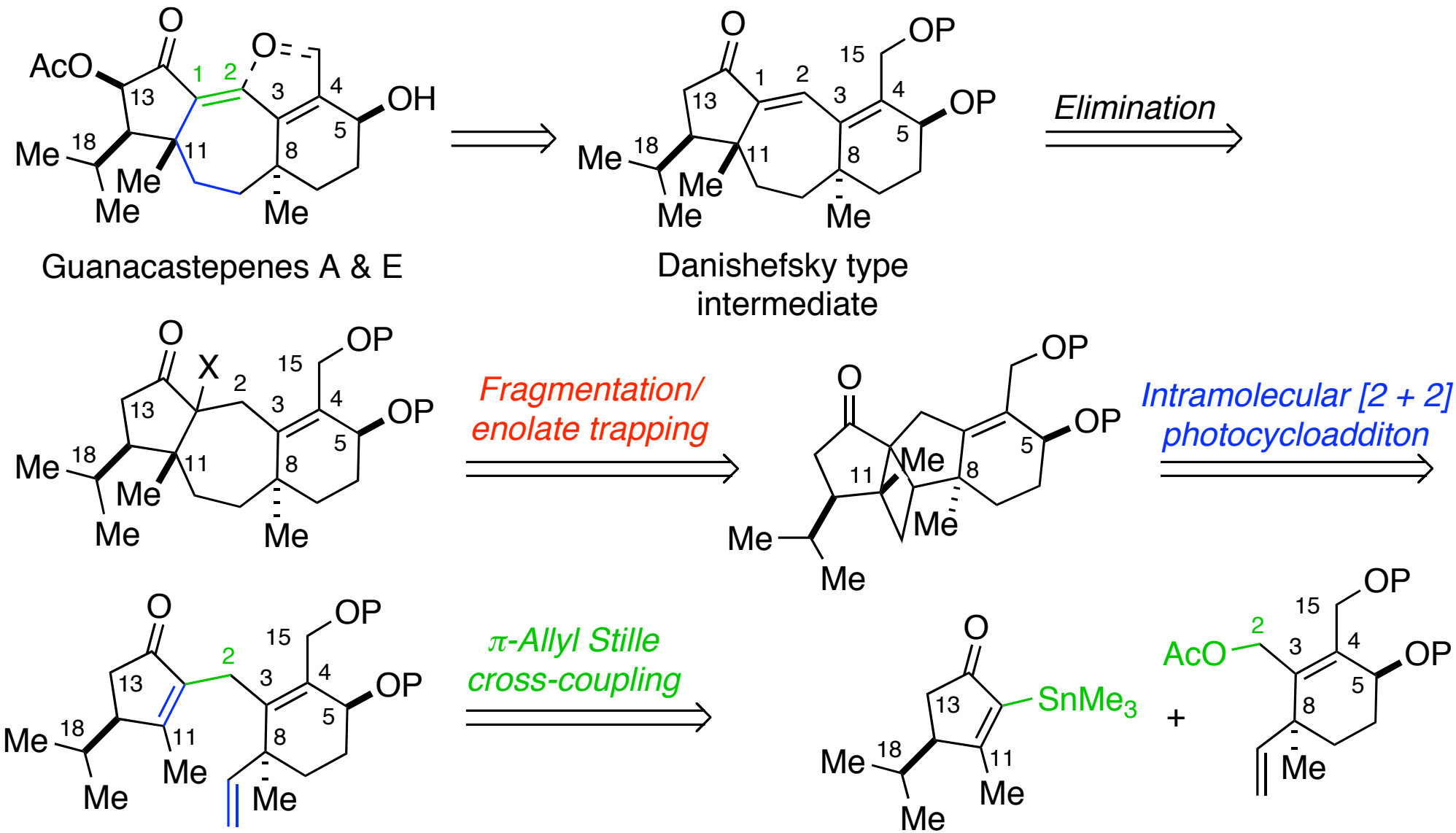
CH_2Cl_2, reflux, 3h
82%
(1:1 mixture C-(8) epimers)



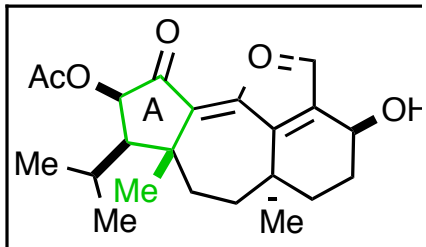


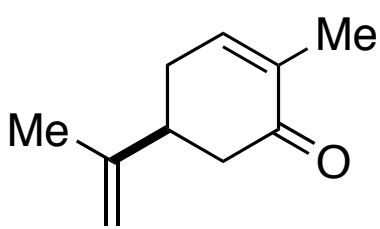
Danishefsky's intermediate

(+)-Guanacastepenes A and E: Sorensen's Approach



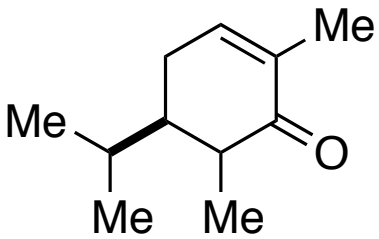
(+)-Guanacastepenes A and E: Building Ring A





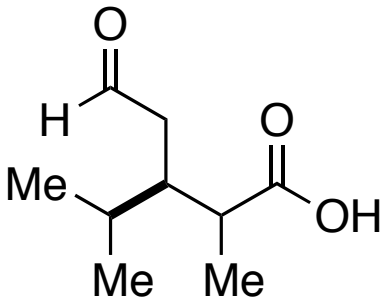
(*S*)-(*+*)-Carvone

1. Pt_2O_2 (0.2 mol%), H_2 RT, 23h
2. LDA, THF, -78 to 0 °C
3. MeI, 0 °C to RT, 17h (5.5 : 1), 96% (2 steps)



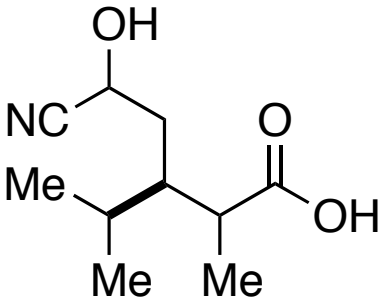
O_3, EtOAc, -78 °C

H_2, Pd/C, RT
54%



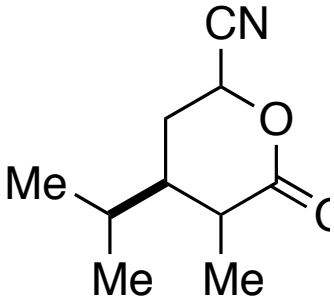
NaCN, TsOH

THF·H_2O, RT
99%



EDCI, 0 °C to RT

CH_2Cl_2, 7h
79%



4 compounds

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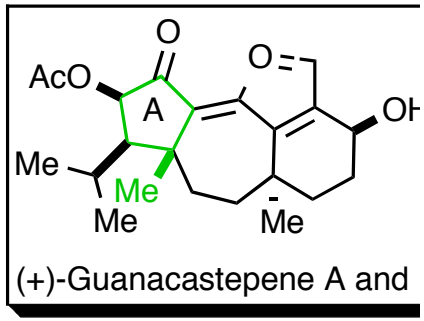
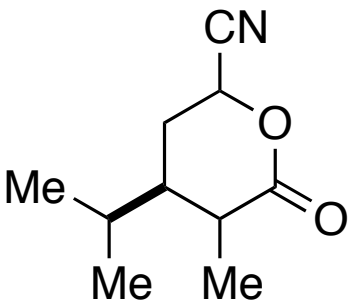
Guanacastepenes A & E: Proposed Ring Contraction



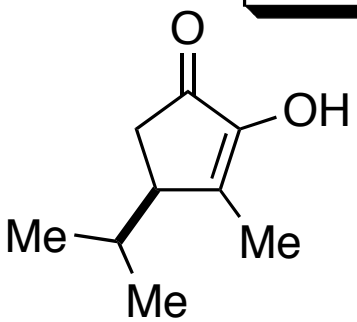


1. LiHMDS (3.0 equiv)

THF, RT, 2h

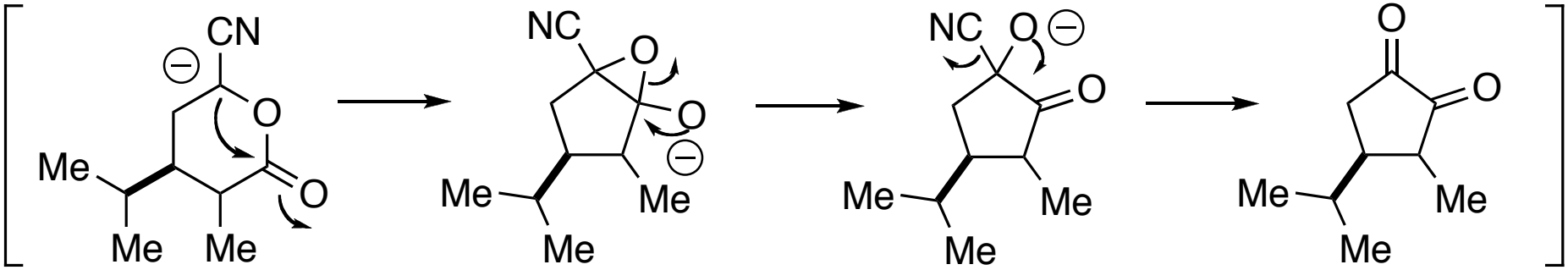
2. 1N HCl

58%

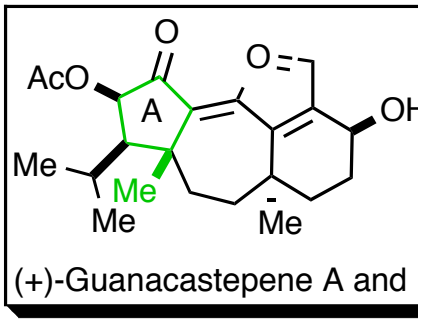


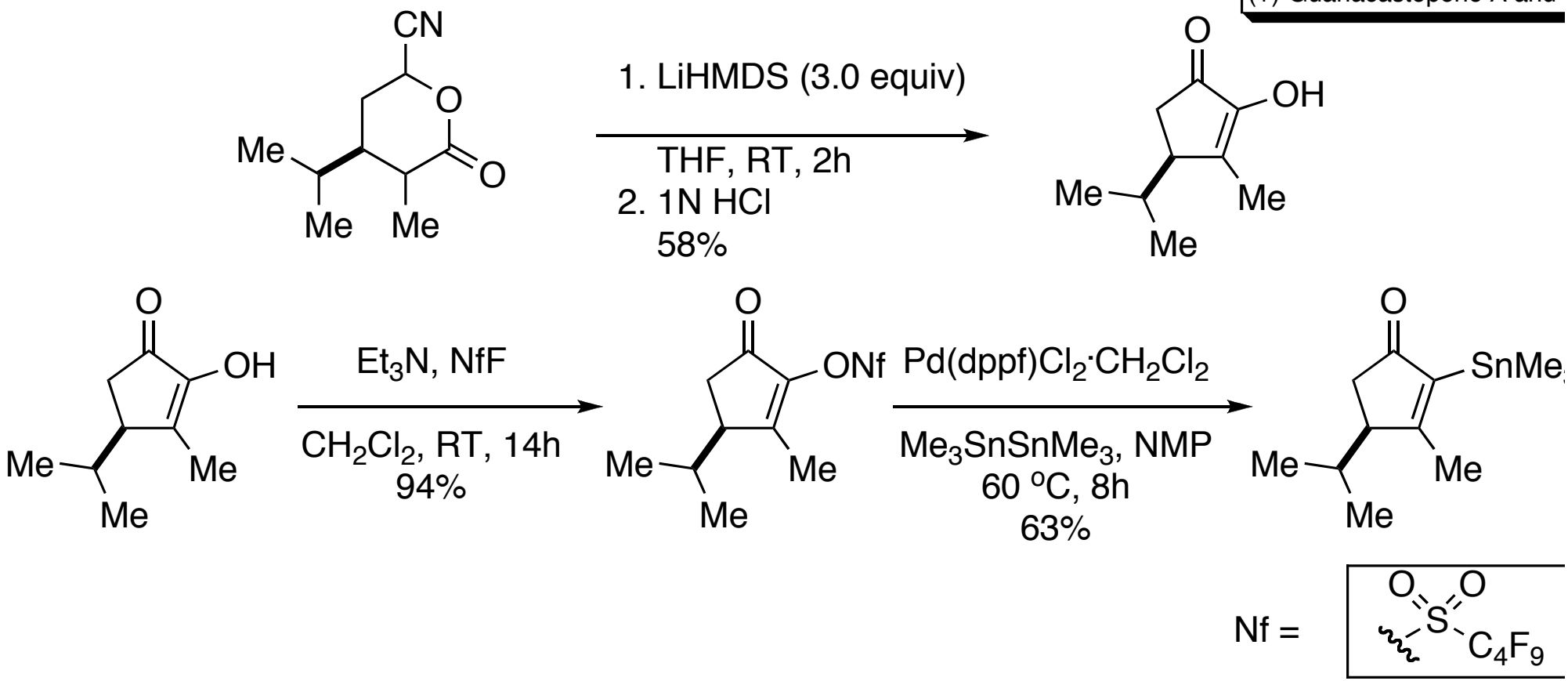
LiHMDS

Tautomerization

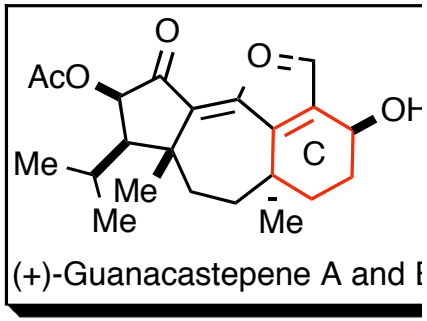


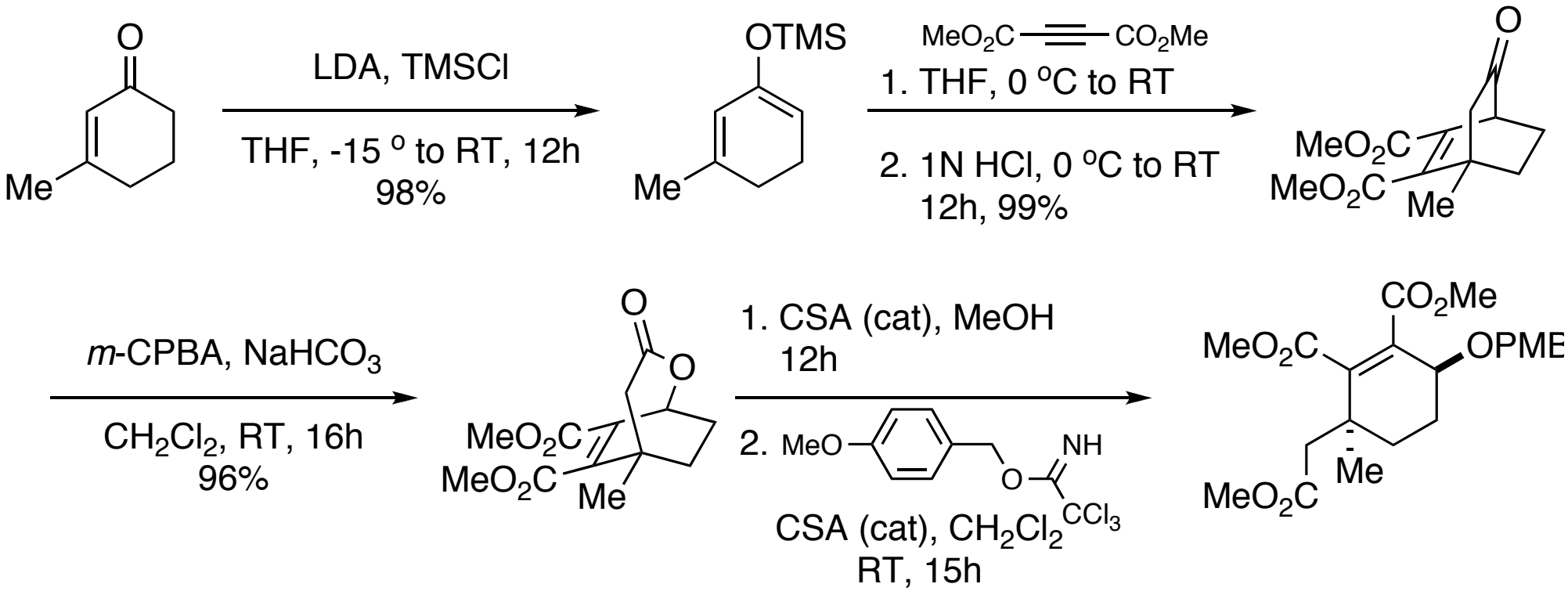
Guanacastepenes A & E: Formation of Cyclopentylstannane





(+)-Guanacastepenes A and E: Building Ring C





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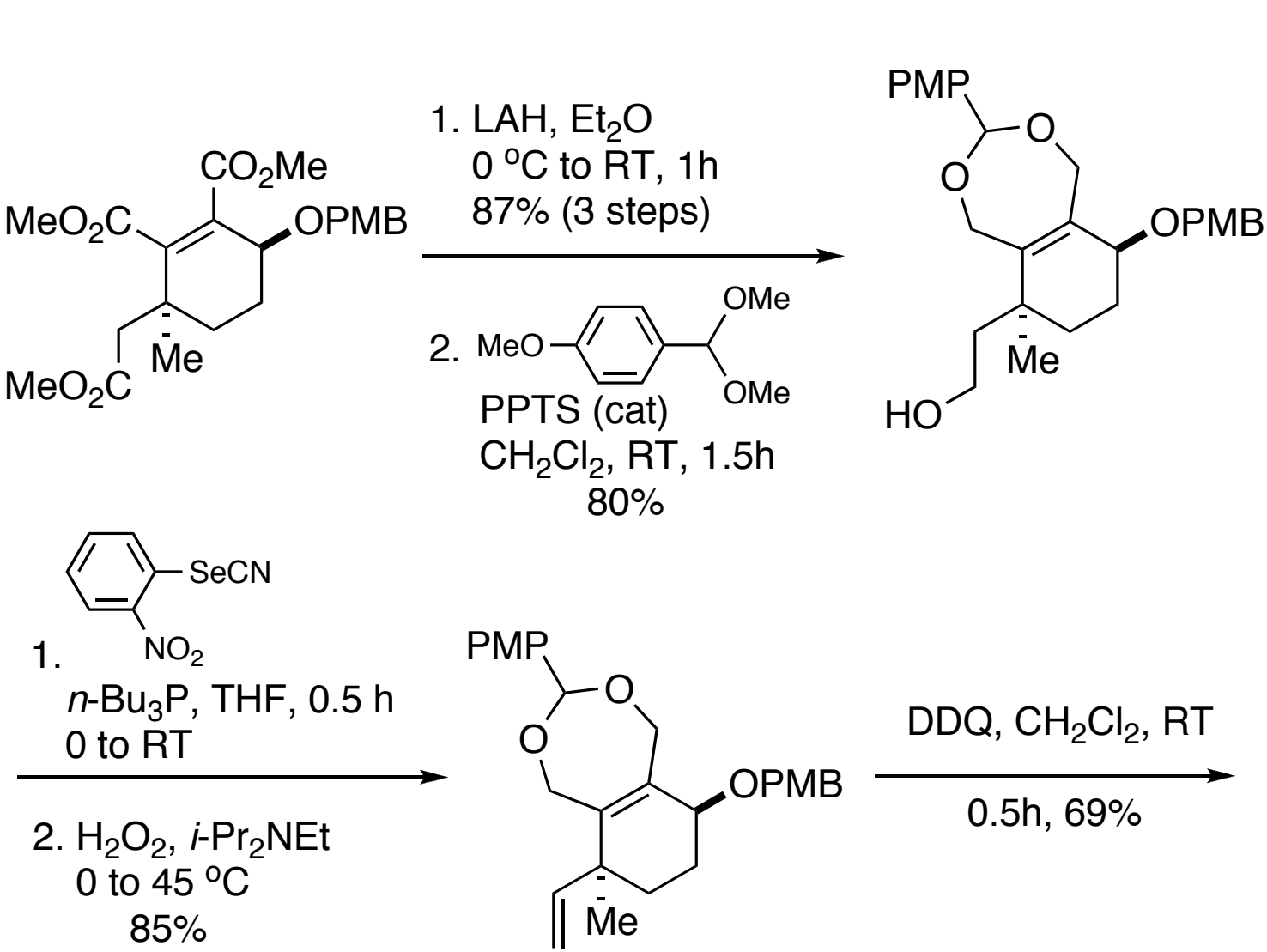
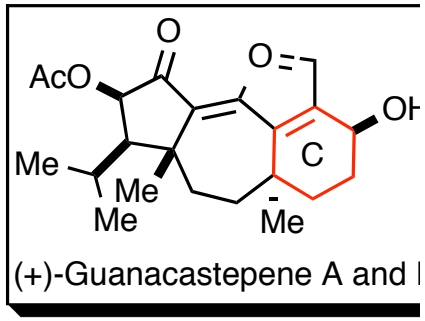
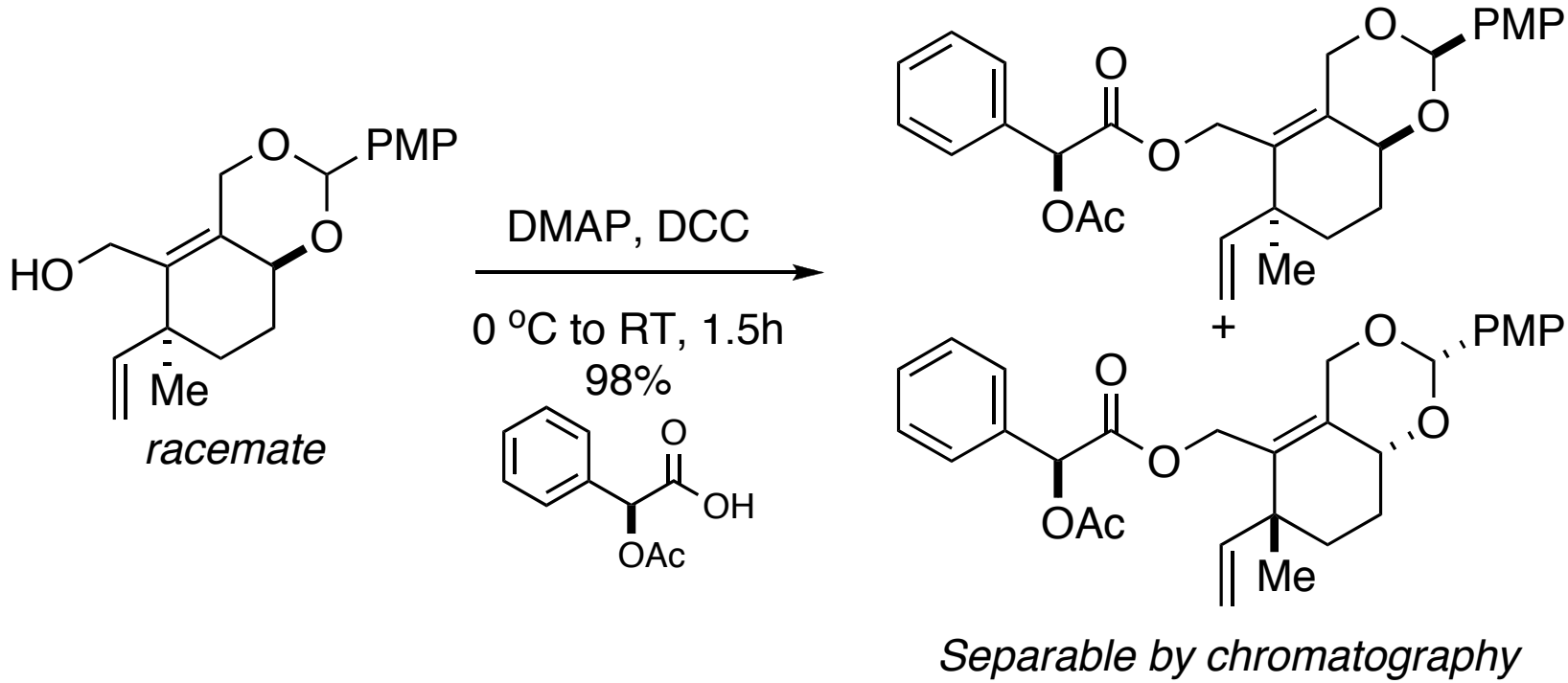
(+)-Guanacastepenes A and E: Building Ring C

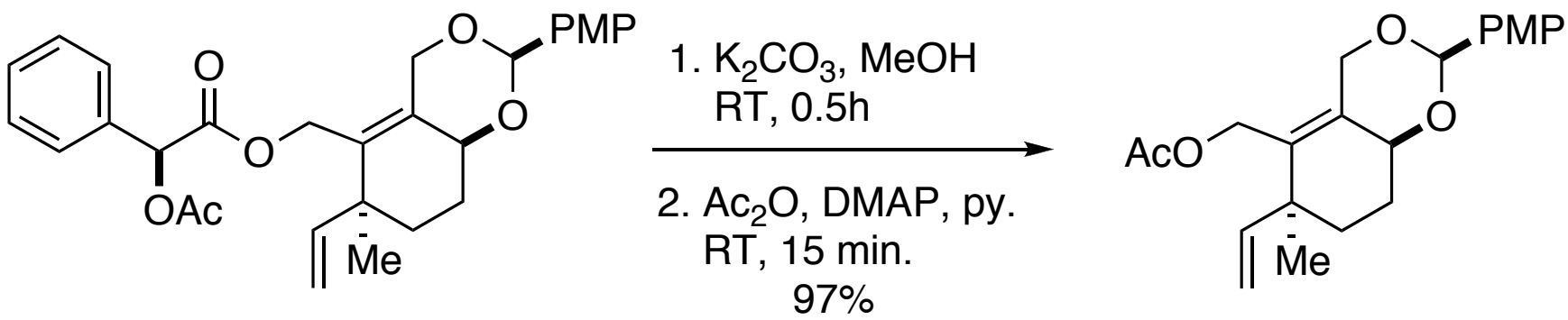




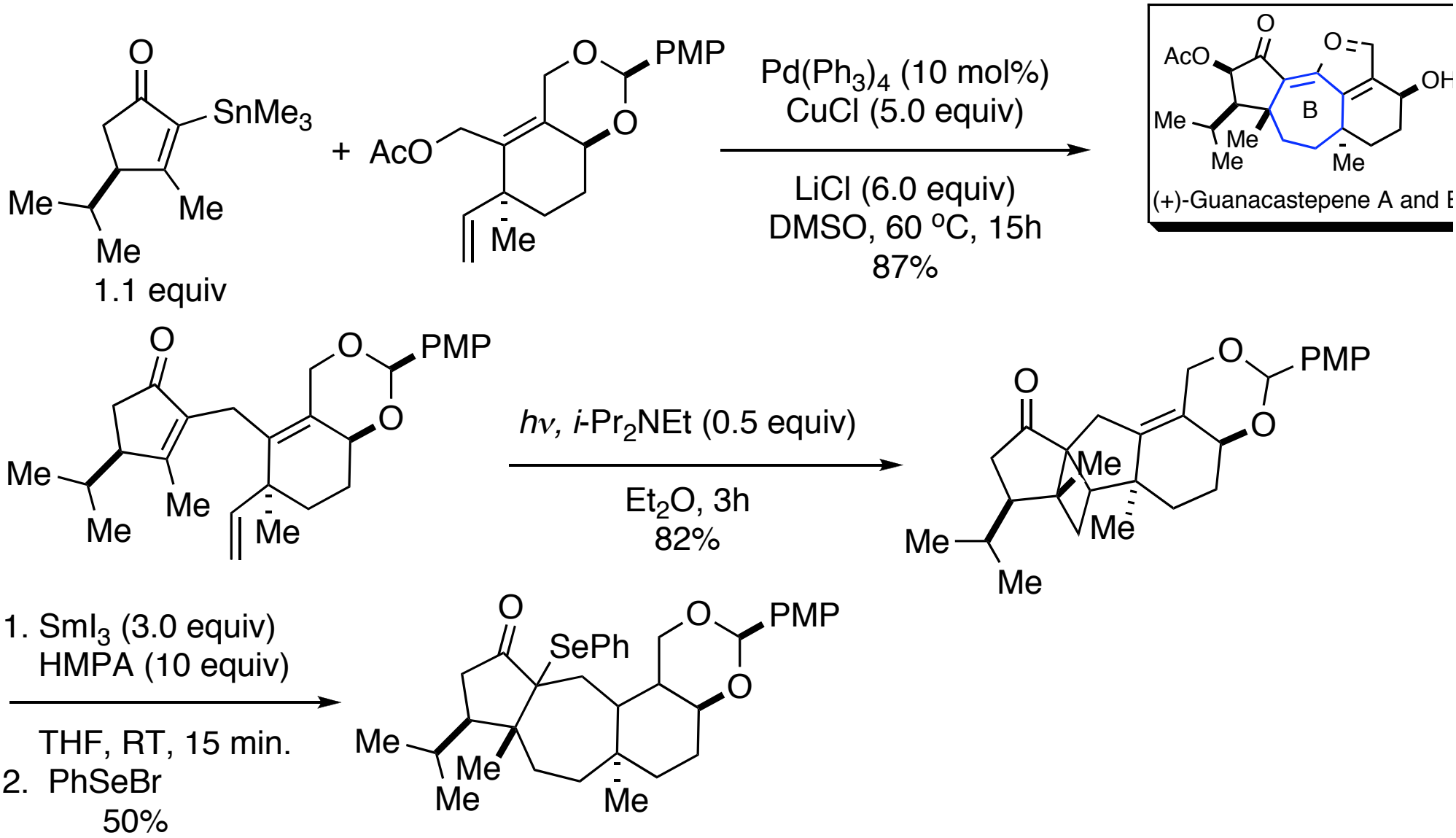
(+)-Guanacastepenes A and E: Resolution of Ring C



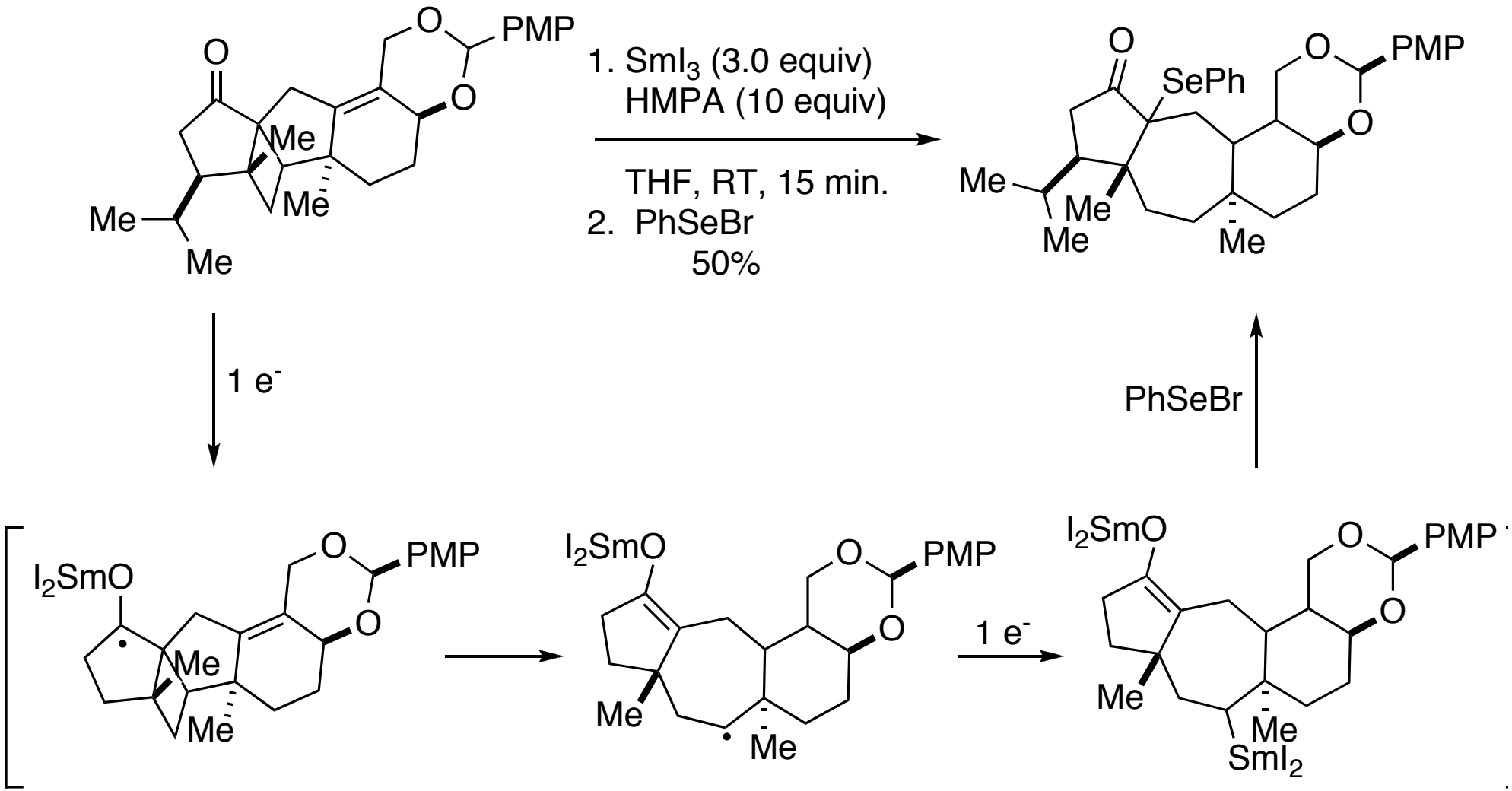
Separable by chromatography



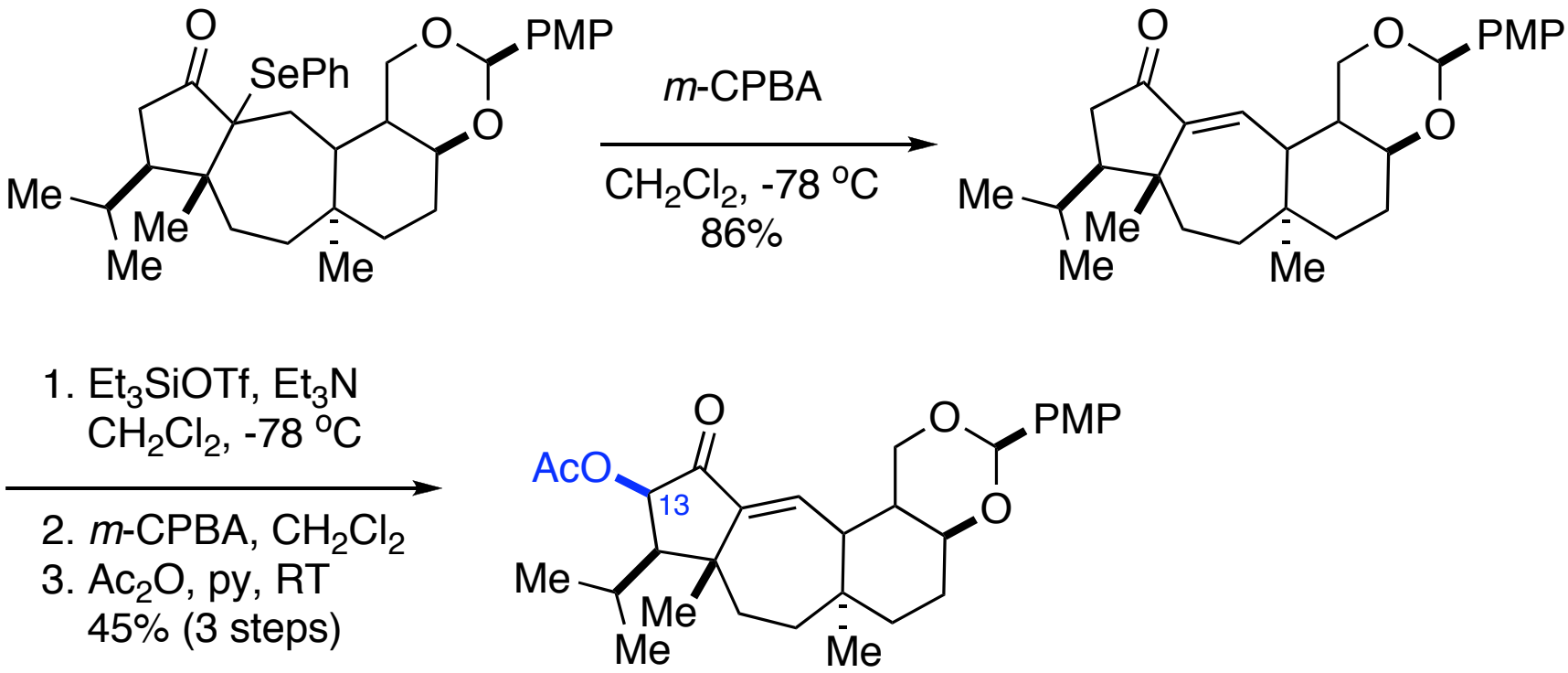
(+)-Guanacastepenes A and E: Build the Tricycle



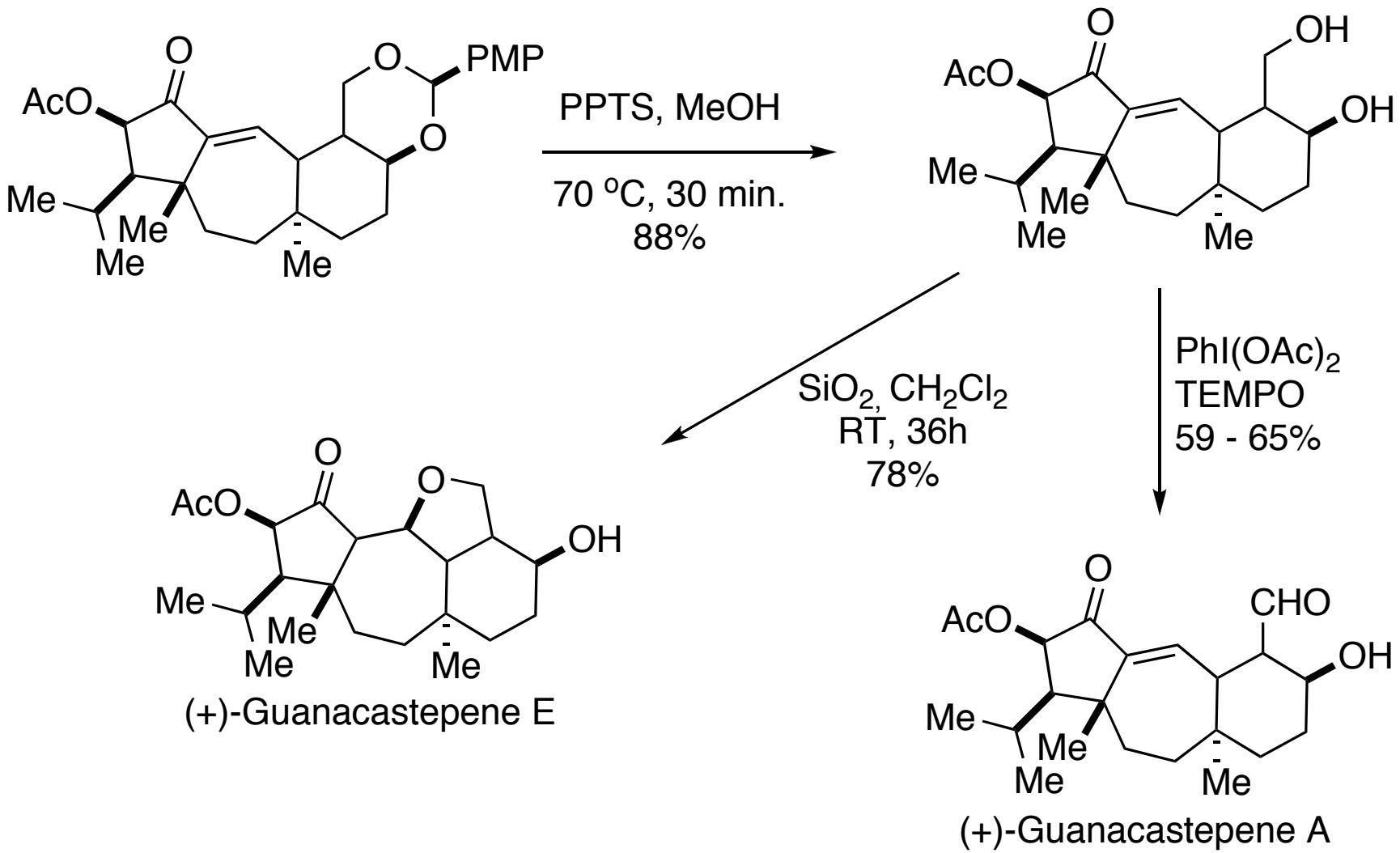
Proposed Pathway for the Radical Fragmentation



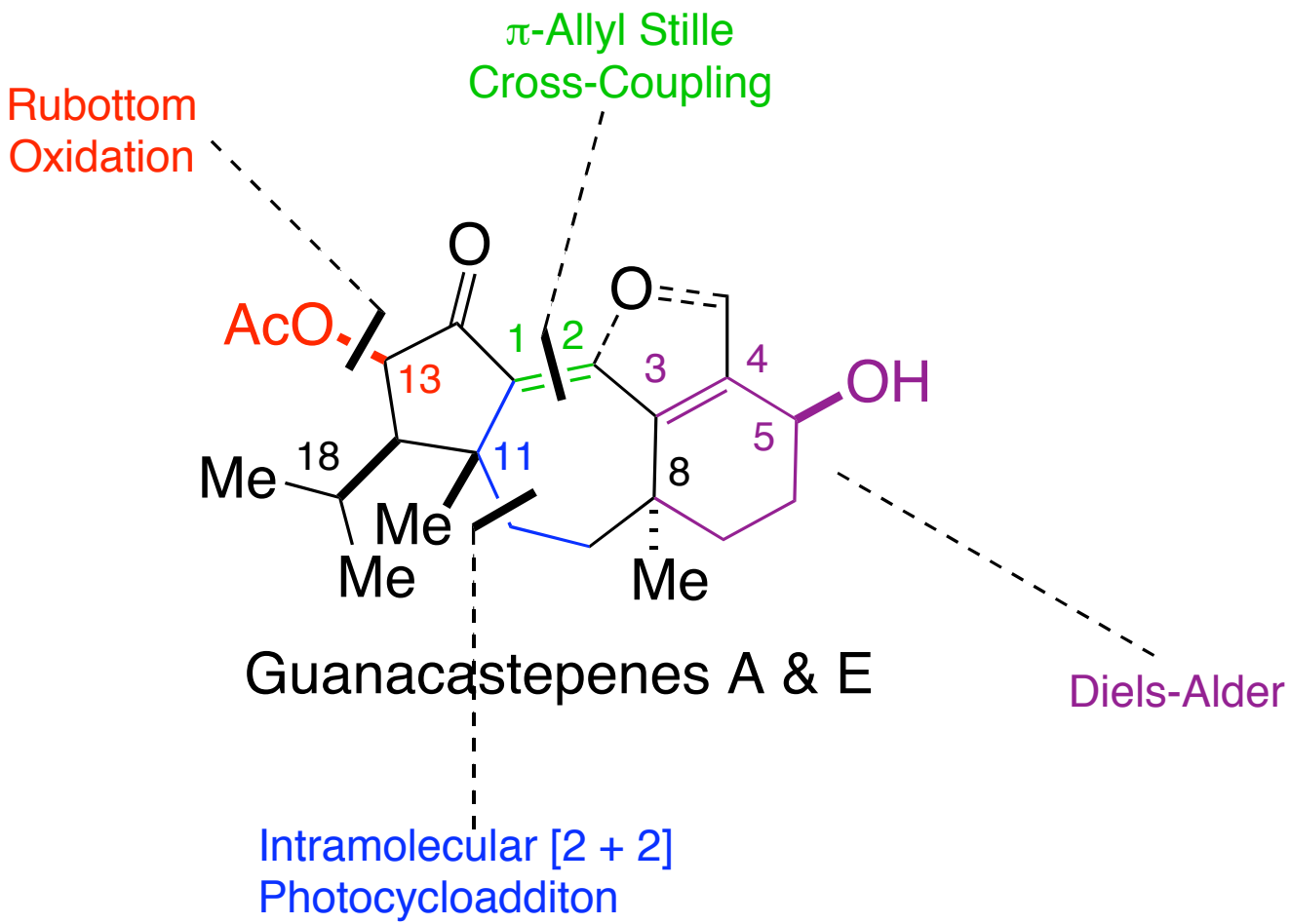
(+)-Guanacastepenes A and E: Elimination and Rubottom Oxidation



(+)-Guanacastepenes A and E: Completing the Synthesis

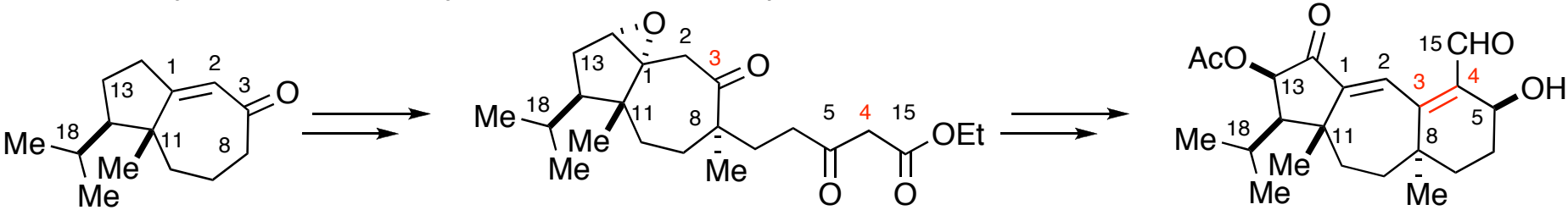


Summary: Sorensens' Total Synthesis of (+)-Guanacastepene A & E



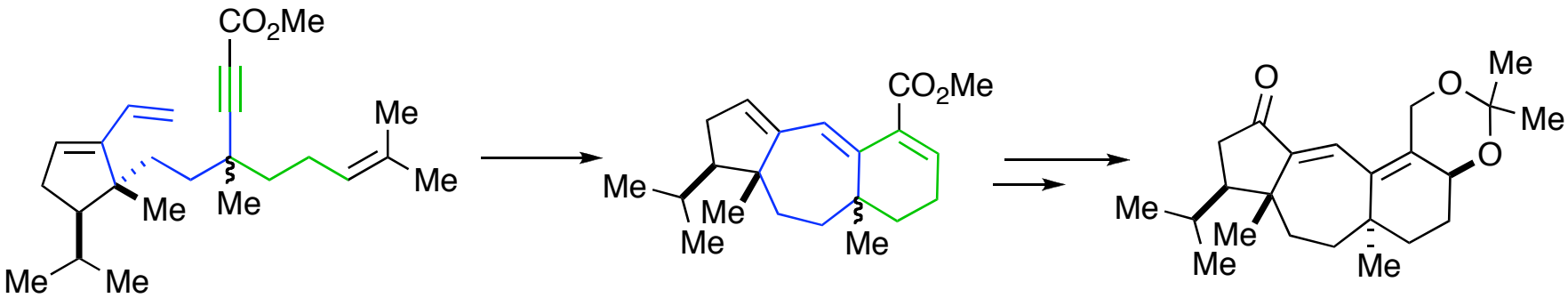
Conclusion

- Danishefsky's Racemic Total Synthesis of Guanacastepene A



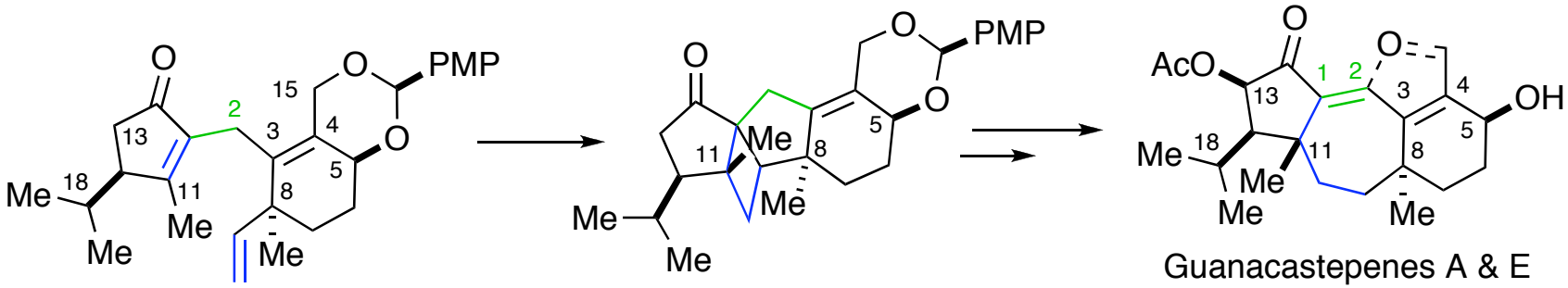
(±)-Guanacastepene A

- Hanna's Formal Synthesis of Guanacastepene A



Danishefsky's intermediate

- Sorensens' Enantioselective Total Synthesis of Guanacastepene A and E



Guanacastepenes A & E

Biblography

Reviews

1. Hiersemann, M. *Nachr. Chem.* **2006**, *54*, 29-33.
2. Hiersemann, M.; Helmboldt, H. *Top. Curr. Chem.* **2005**, *243*, 73-136.
3. Maifeld, S.V.; Lee, D. *Synlett* **2006**, 1623-1644.
3. Mischne, M. *Curr. Org. Synth.***2005**, *2*, 261-279.

Isolation

1. Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256-261.
2. Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116-2117.
3. Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900-9901.

Synthesis

1. Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399-2402.
2. Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789-6791.
3. Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605-5606.
4. Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185-2188.
5. Lin, S. N.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188-2191.
6. Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3827-3829.
7. Mandal, M.; Danishefsky,S. J. *Tetrahedron Lett.* **2004**, *45*, 3831-3833.
8. Yun, H. D.; Meng, Z.Y.; Danishefsky, S. J. *Heterocycles* **2005**, *66*, 711-725.
9. Yun, H. D.; Danishefsky, S. J. *Tetrahedron Lett.* **2005**, *46*, 3879-3882.
10. Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619-10637.
11. Cheong, P. H. Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513-1516.
12. Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569-572.
13. Snider, B. B.;Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123-9126.
14. Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030-1042.
15. Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469-7472.
16. Boyer, F. D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817-1820.
17. Boyer, F. D.; Hanna, I. *J. Org. Chem.* **2005**, *70*, 1077-1080.

Biblography

18. Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063-1066.
19. Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975-6978.
20. Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233-4237.
21. Mehta, G.; Umarye, J. D. *Tetrahedron Lett.* **2003**, *44*, 7285-7289.
22. Mehta, G.; Pallavi, K.; Umarye, J. D. *Chem. Commun.* **2005**, 4456-4458.
23. Shipe,W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063-2066.
24. Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025-7035.
25. Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095-13101.
26. Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V.*Tetrahedron Lett.* **2001**, *42*, 4947-4950.
27. Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605-9609.
28. Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033-4036.
29. Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. S. *Org. Lett.* **2002**, *4*, 3959-3962.
30. Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363-3366.
31. Du, X. H.; Chu, H. F. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923-1926.
32. Du, X. H.; Chu, H. F. V.; Kwon, O. Y. *Tetrahedron Lett.* **2004**, *45*, 8843-8846.
33. Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165-168.
34. Chiu,P.; Li, S. L. *Org. Lett.* **2004**, *6*, 613-616.
35. Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491-3494.
36. Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624-13625.
37. Li, C. C.; Liang, S.; Zhang, X. H.; Xie, Z. X.; Chen, J. H.; Wu, Y. D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709-3712.
38. Li, C. C.; Wang, C. H.; Liang, B.; Zhang, X. H.; Deng, L. J.; Liang, S.; Chen, J. H.; Wu, Y. D.; Yang, Z. *J. Org. Chem.***2006**, *71*, 6892-6897.
39. Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411-414.
40. Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113-4115.
41. Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425-3428.