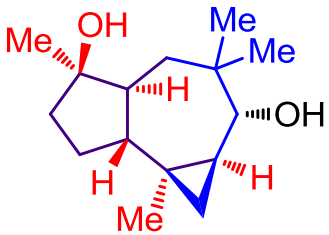
Total Synthesis of (+)-Omphadiol

Liu G.; Romo D. *Angew. Chem. Int. Ed.* **2011**, *50*, 7537 –7540

Yongzhao Yan
Current Lit.
2011.9.3

Isolation

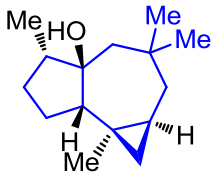


(+)-omphadiol

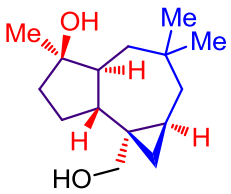
- First isolated from *Omphalotus illudens* extract.[a]
- This mushroom are found thought much of North America, poisonous but not fatal.[a]
- Omphadiol and its analog, pyxidatol C are also found in *Clavicorona pyxidata*, which is a wild mushroom used as a traditional medicine in China.[b]
- Bioactivity of Omphadiol was not tested because of insufficient material.[a]

a) T. C. McMorris, R. Lira, P. K. Gantzel, M. J. Kelner, R. Dawe, *J. Nat. Prod.* **2000**, *63*, 1557;
b) Y.-B. Zheng, C.-H. Lu, Z.-H. Zheng, X.-J. Lin, W.-J. Su, Y.-M. Shen, *Helv. Chim. Acta* **2008**, *91*, 2174.

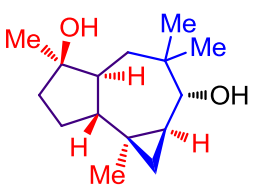
Structurally Similar Terpenoids



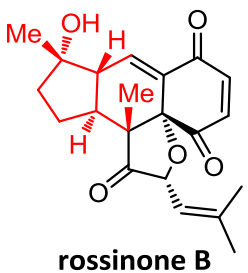
(+)-africanol
1



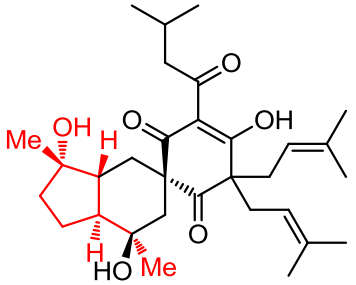
pyxidatol C
2



(+)-omphadiol
3



rossinone B
4



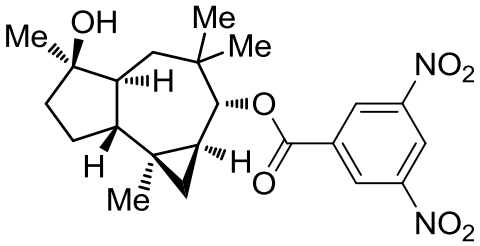
tomoeone F
5

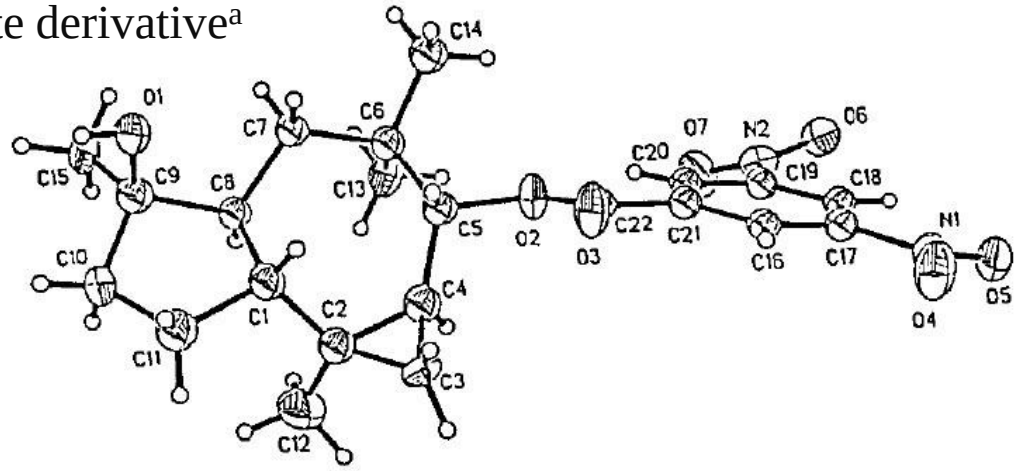
- As a member of the ***Africanane*** family of sesquiterpenes, **1**, **2** and **3** all possess a 5-7-3 tricyclic core and 5~6 contiguous stereogenic center.
- ***Africanol* (1)** had been synthesized for several times.[a]
- A large family of sesquiterpenes and diterpenes share a common tetra-substituted cyclopentane ring.
- ***Rossinone B* (4)** possesses anti-inflammatory, antiviral, and antiproliferative activities and has been synthesized by bio-mimic synthesis.[b,c]
- ***Tomoeone F* (5)** displays significant cytotoxicity against KB cells.[d]

a) W. Fan, J. B. White, *J. Org. Chem.* **1993**, *58*, 3557 – 3562;
b) D. R. Appleton, C. S. Chuen, M. V. Berridge, V. L. Webb, B. R. Copp, *J. Org. Chem*. **2009**, *74*, 9195.
c) Z.-Y. Zhang, J.-H. Chen, Z. Yang, Y.-F. Tang, *Org. Lett*. **2010**, *12*, 5554.
d) M. Nagai, M. Toda, *Chem. Lett.* **1987,** *1337.*

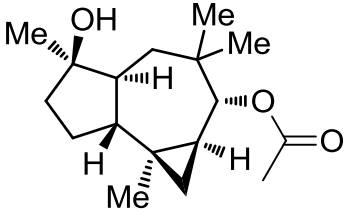
Structure Elucidation

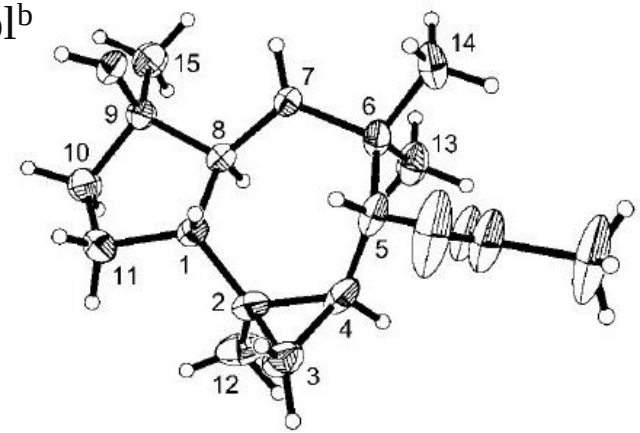
- MS, NMR, and X-ray in 2000[a]
- X-ray of 3,5-dinitrobenzoate derivative[a]





- X-ray of acetate of omphadiol[b]





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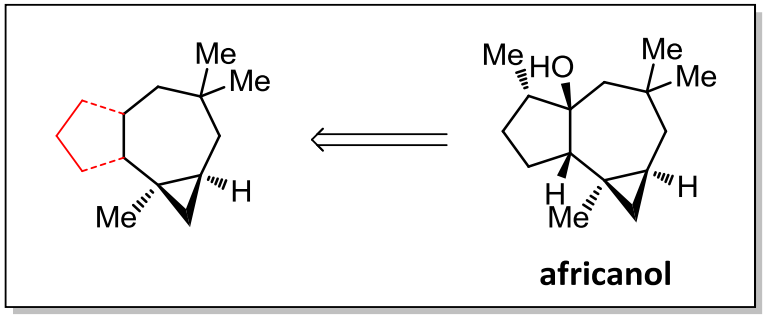
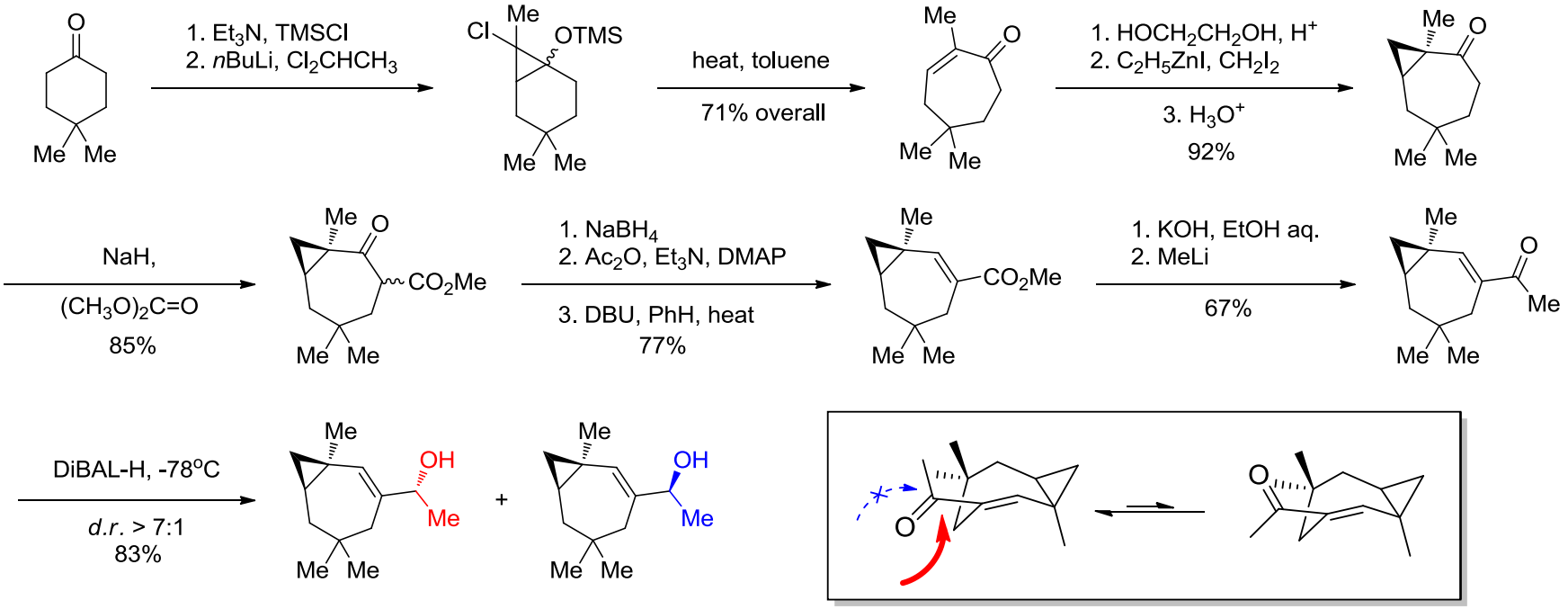
b) J.-B. Zheng, C.-H. Lu, Z.-H. Zheng, X.-J. Lin, W.-J. Su, Y.-M. Shen, *Helv. Chim. Acta* **2008**, *91*, 2174.

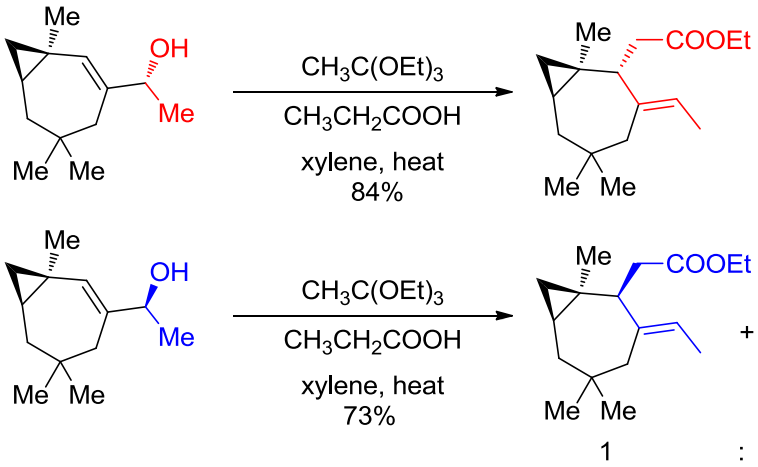
Paquette's Synthesis of Africanol

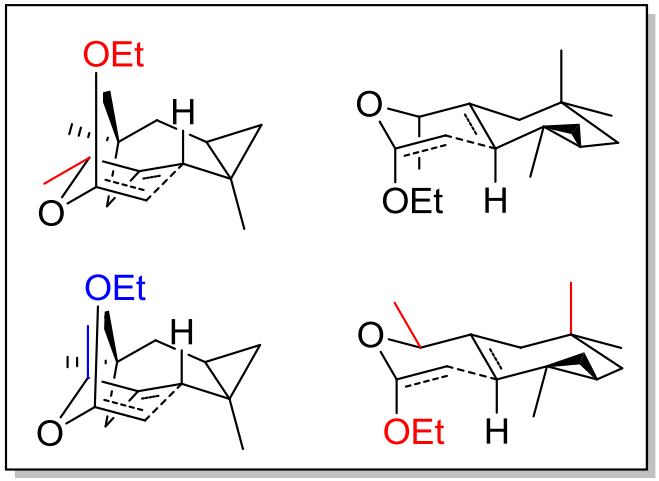


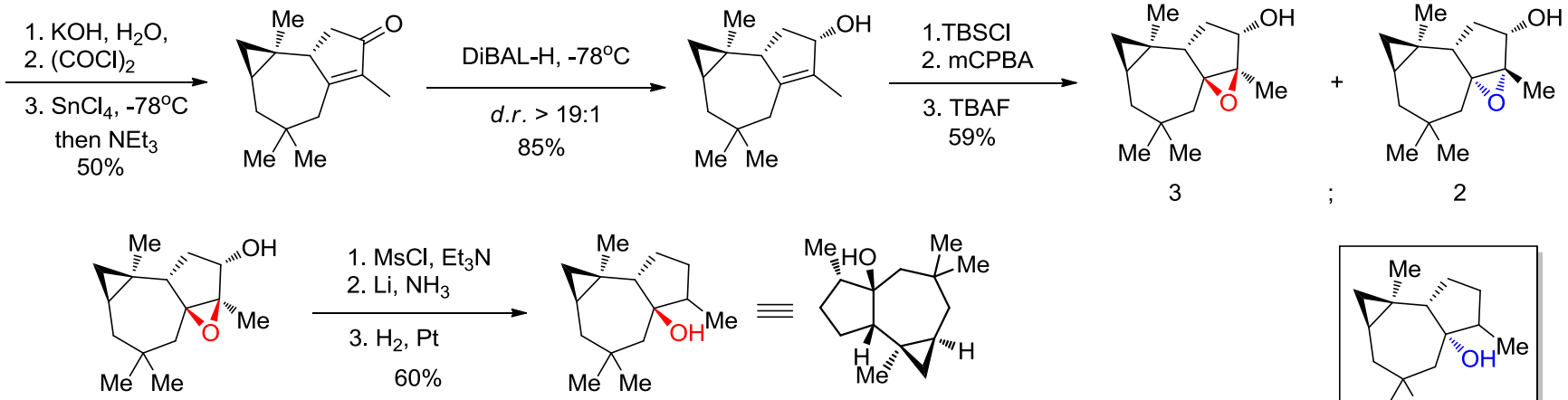


a) L. A. Paquette, W. H. Ham, *J. Am. Chem. Soc.* **1987**, *109*, 3025 – 3036

Paquette's Synthesis of Africanol







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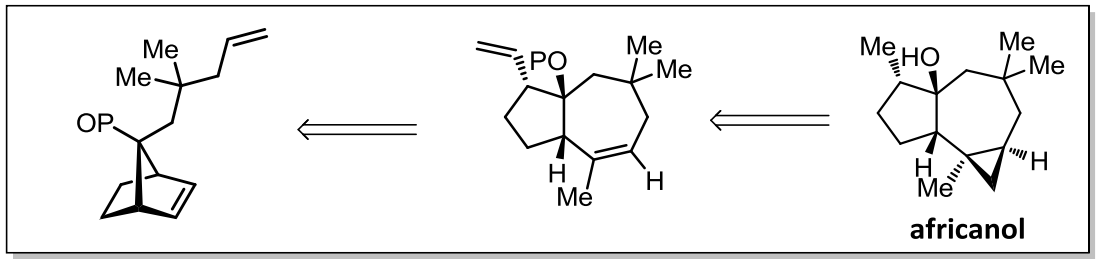
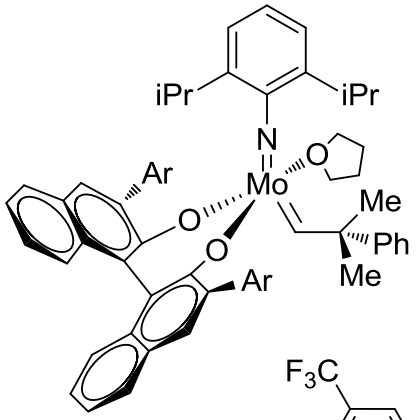
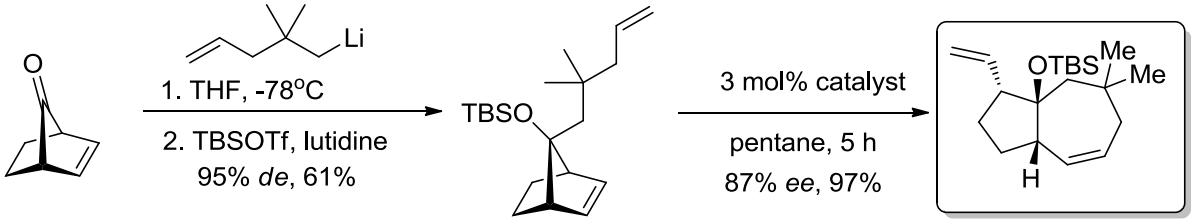
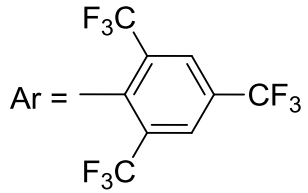
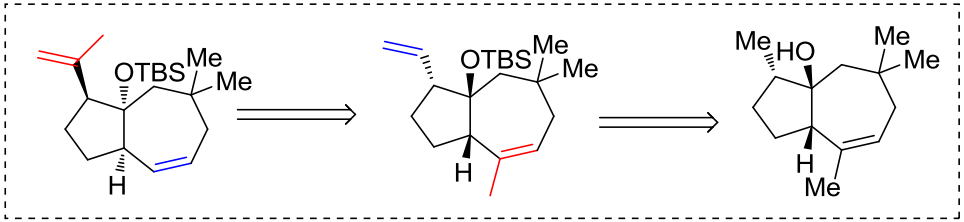
Hoveyda's Synthesis of Africanol





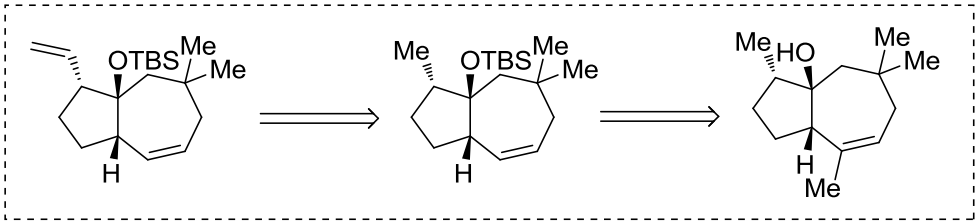


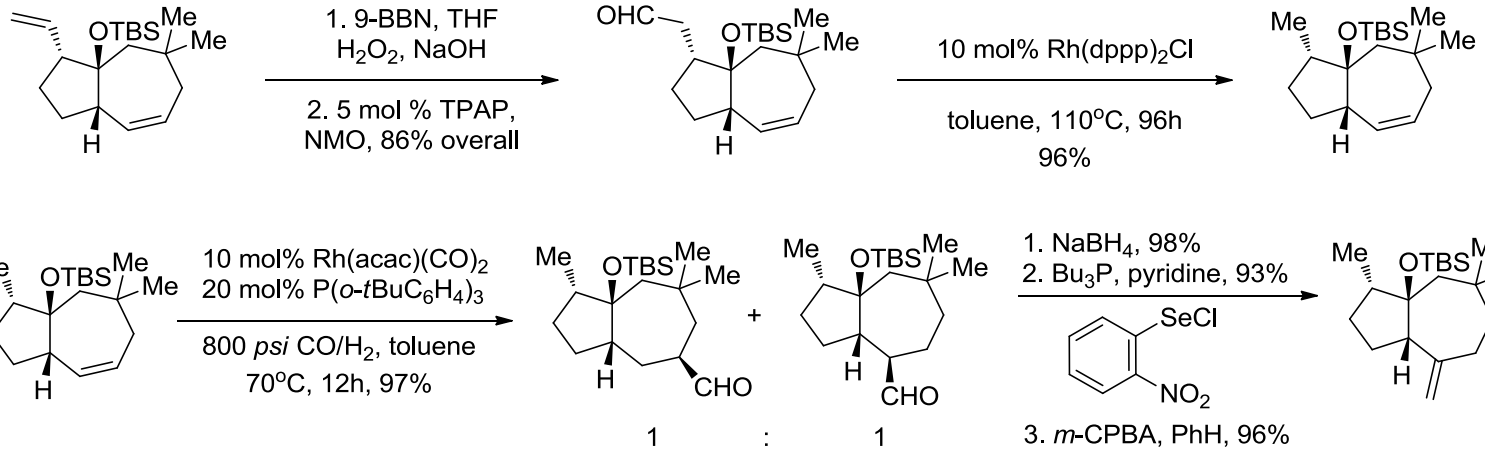




a) G. S. Weatherhead, G. A. Cortez, R. R. Schrock, A. H. Hoveyda, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5805.
b) S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock, A. H. Hoveyda *Nature* **2011**, *471*, 461.
c) A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, A. R. Zhugralin. *Angew. Chem., Int. Ed.* **2010**, *49*, 34.

Hoveyda's Synthesis of Africanol





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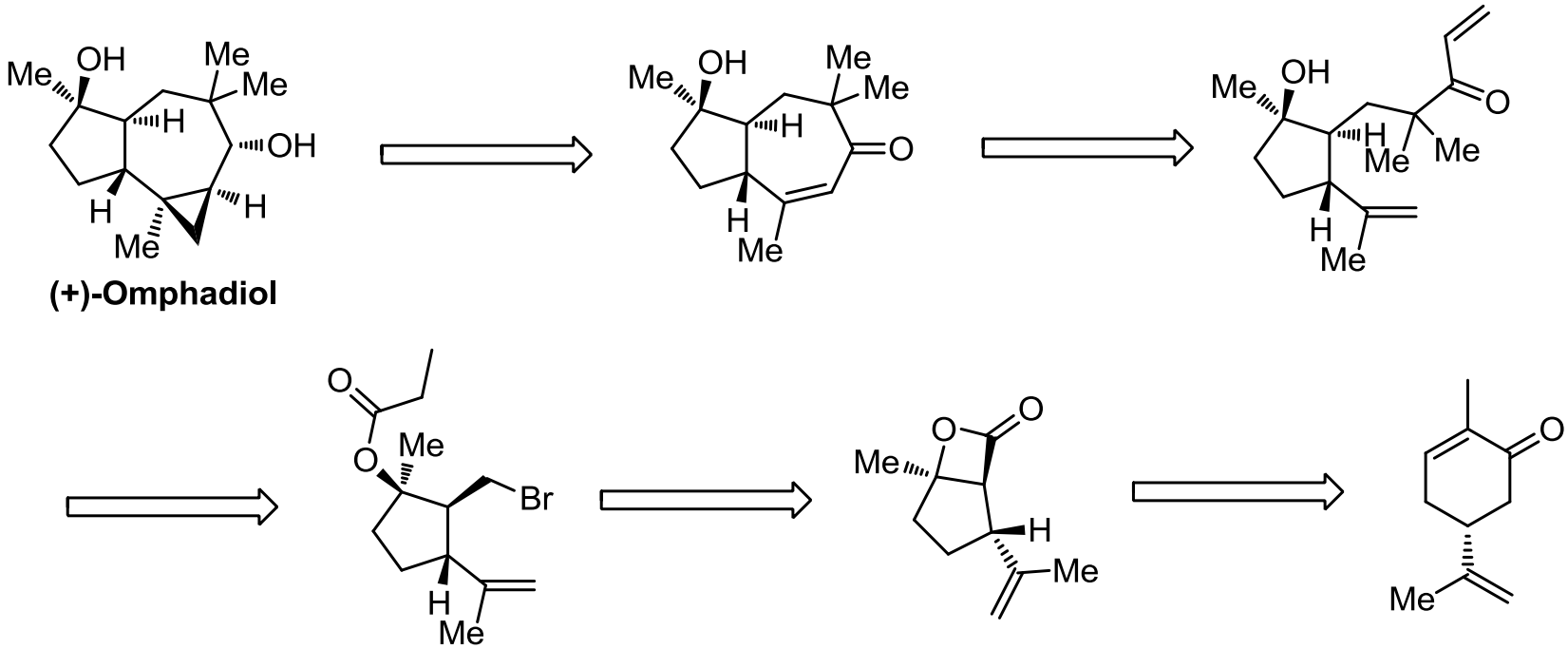
Retrosynthetic Analysis



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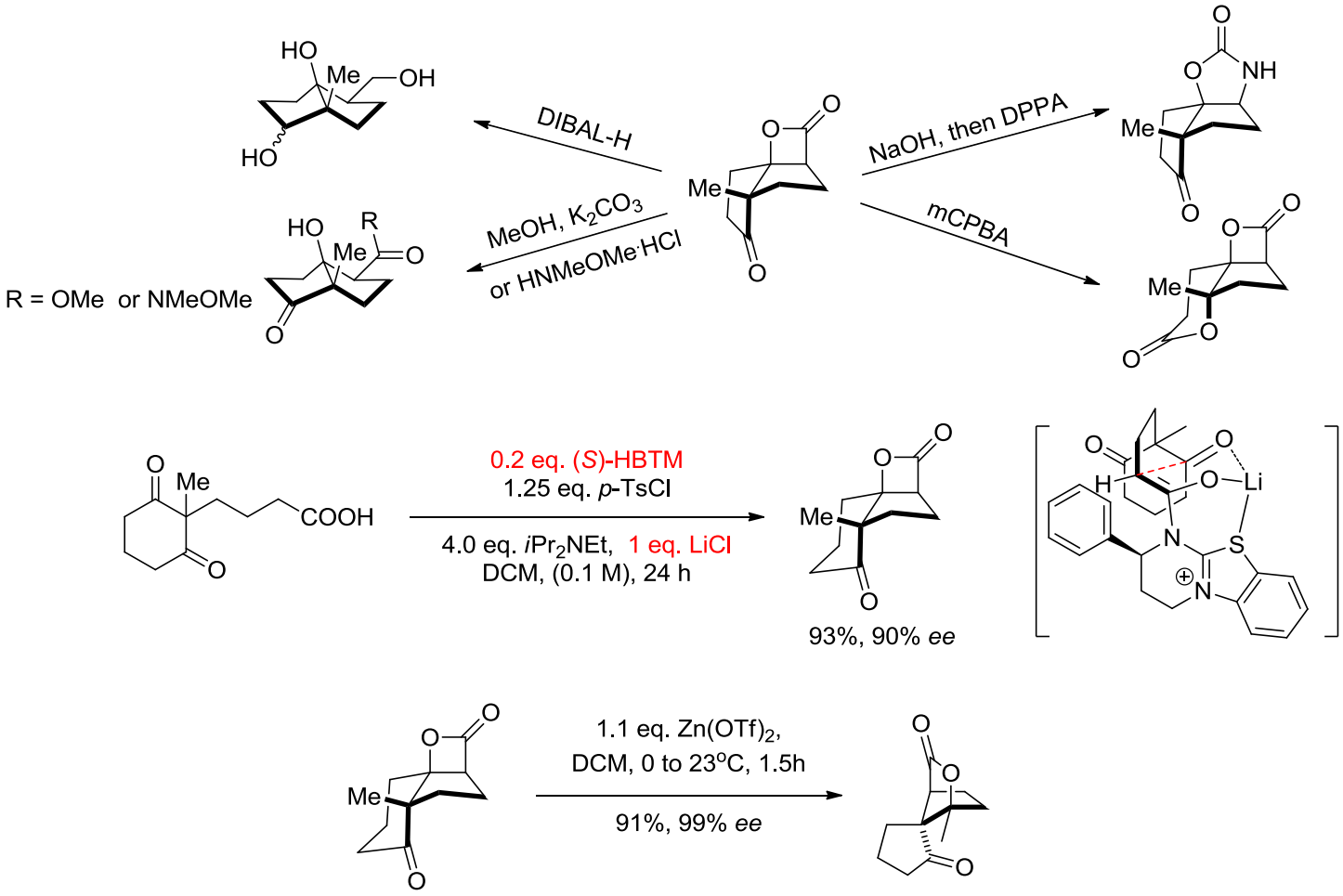
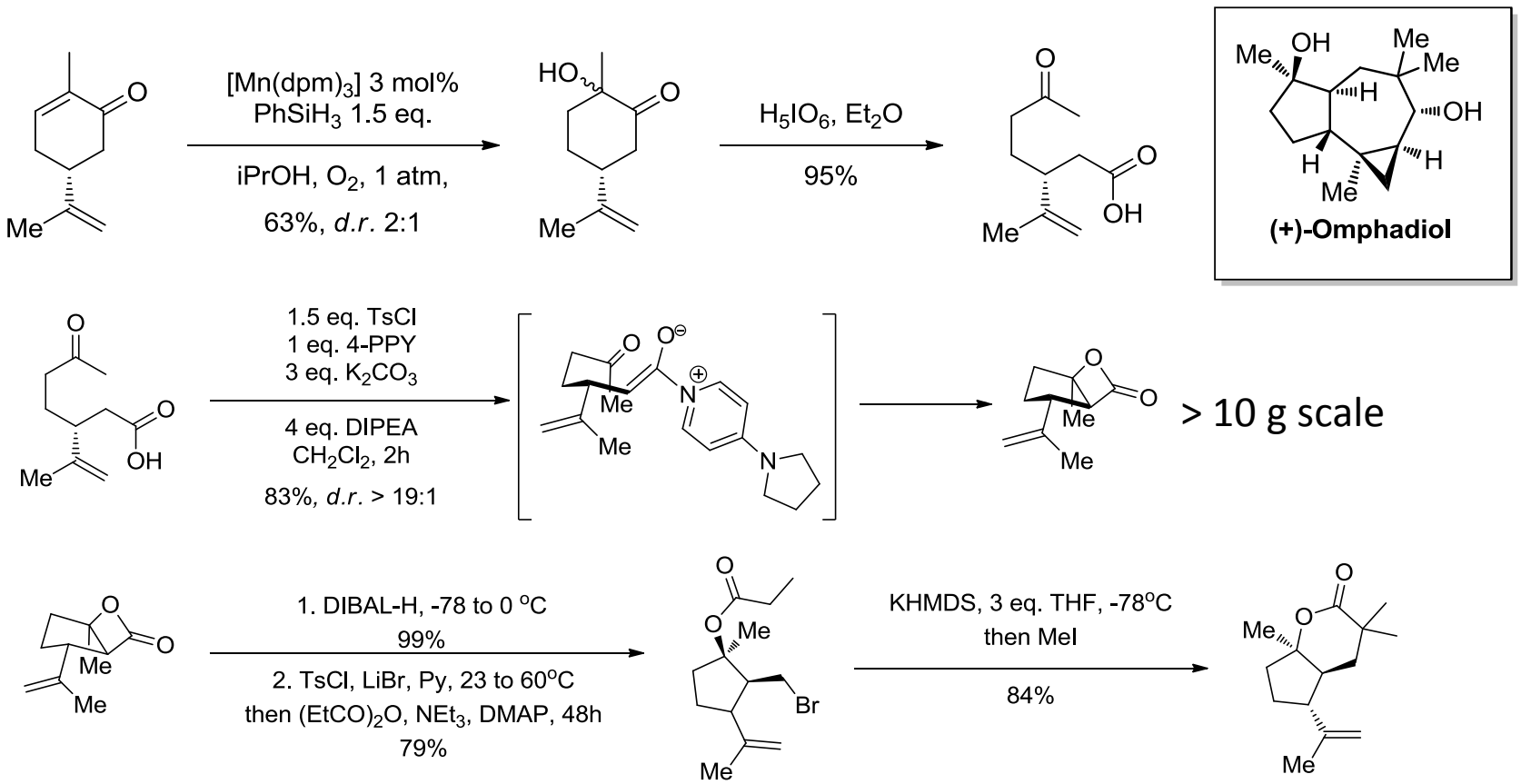
β-Lactone Methodology



a) Leverett, C.A.; Purohit, V.C.; Romo, D. *Angew.Chem. Int. Ed.* **2010**, *49*, 9479-9483.

b) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478-10479.

Total Synthesis of (+)-Omphadiol



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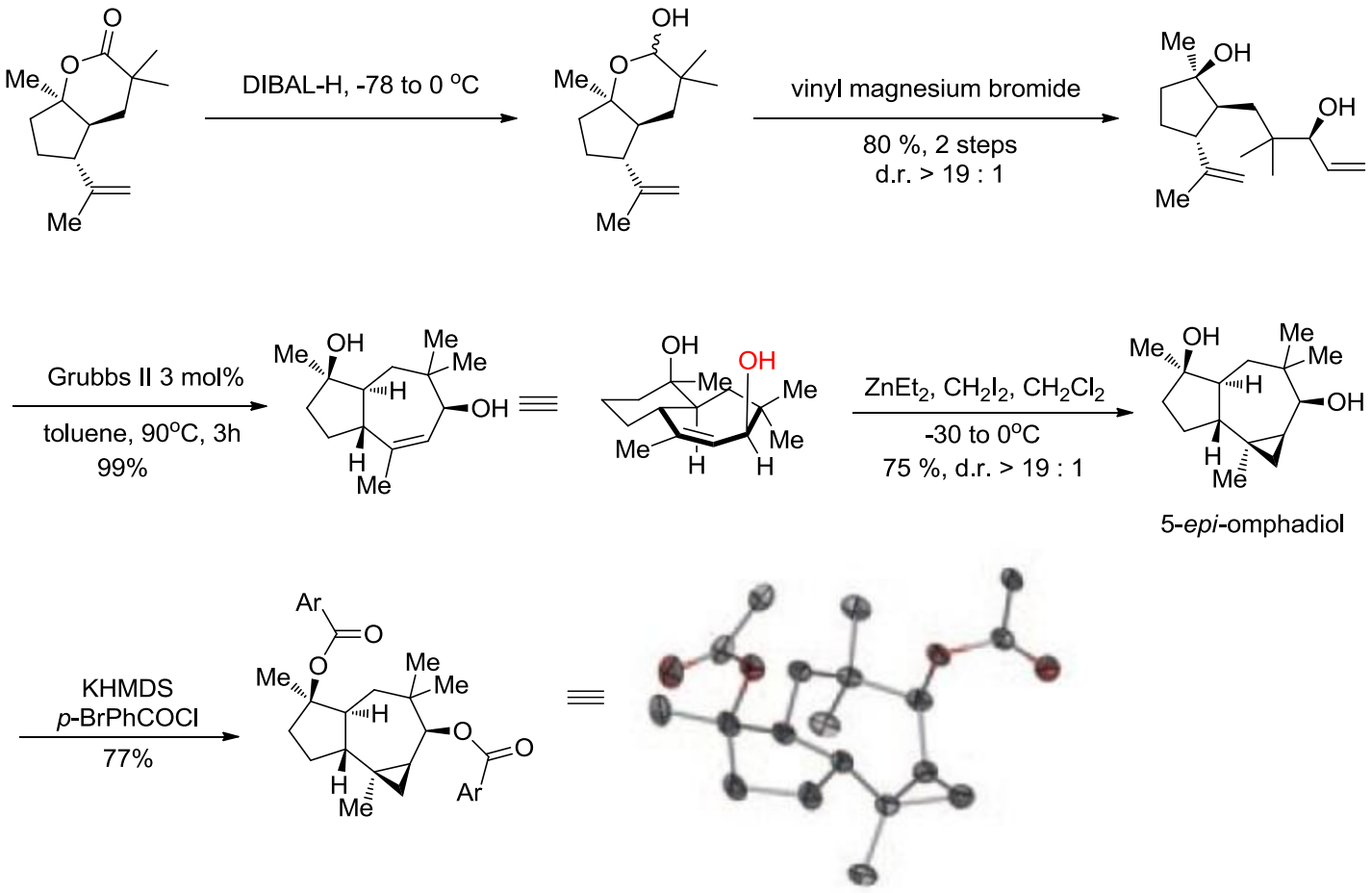

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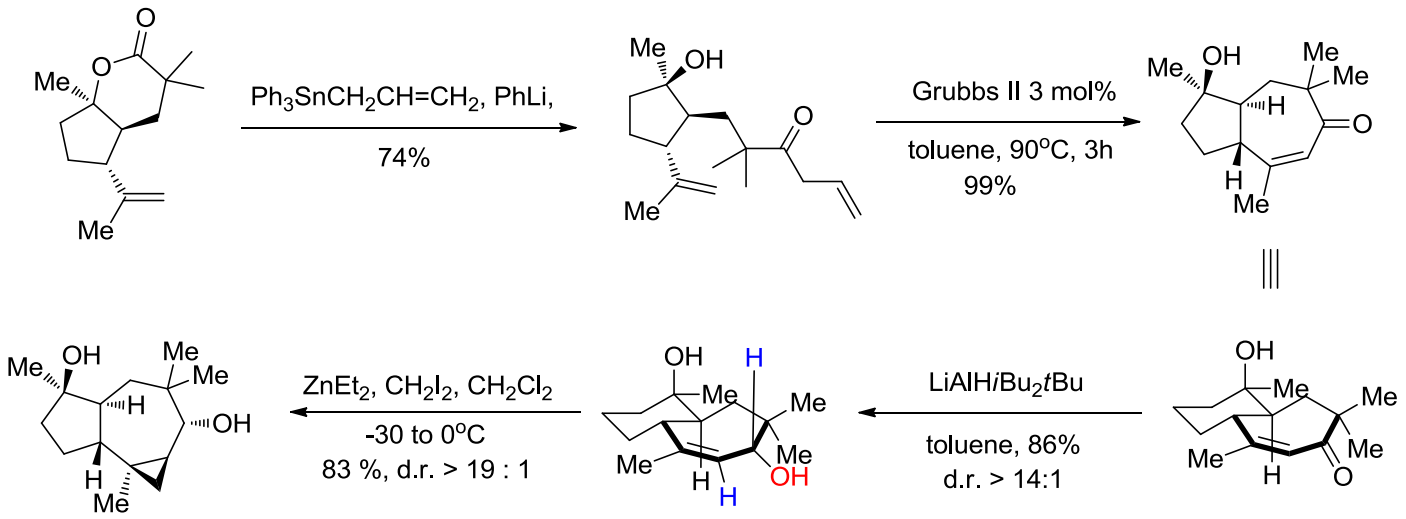

(+)-Omphadiol

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Summary

- First total synthesis of (+)-omphadiol
- 10 steps from (R)-carvone
- 18% overall yield
- highly stereocontrolled introduction of the six contiguous stereogenic centers exclusively by using substrate control from a single stereocenter
- high ratio of CC bond-forming steps (5/10)
- absence of protecting groups.
- further biological studies of omphadiol and its congeners.