Literature Report

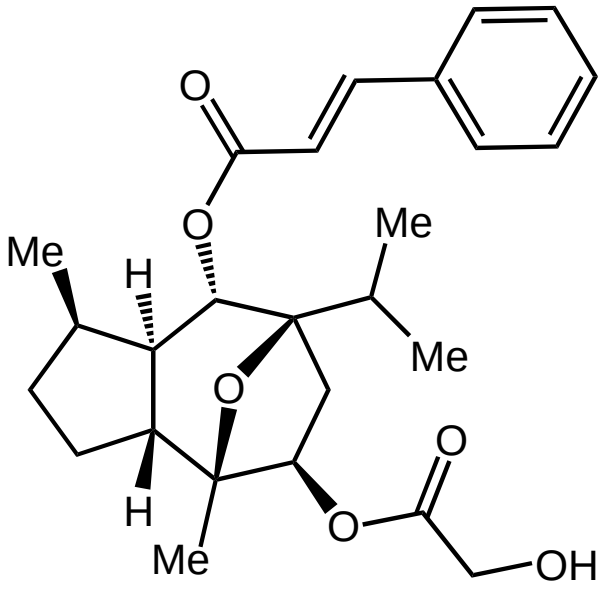
Total Synthesis of Englerin A

[Nicolaou, K. C. *et al J. Am. Chem. Soc.* **2010**, *132*, ASAP.]

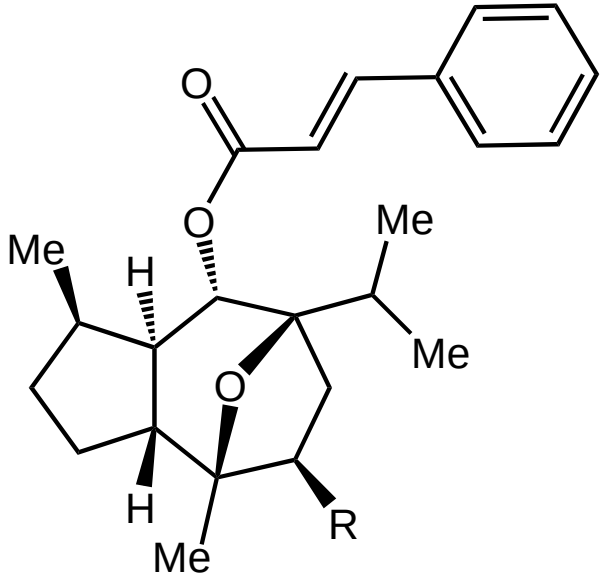
Xiao-Yu Zhou　Checker：Duo-Sheng Wang

22/06/2010

Englerin A and B

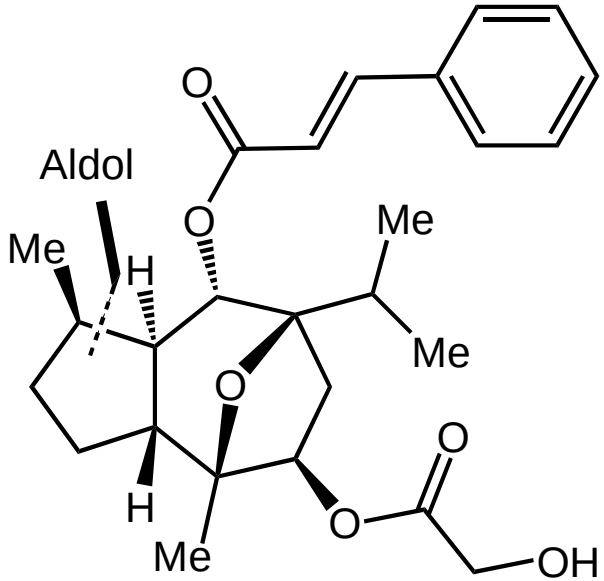


(-)-englerin A [(-)-**1**]

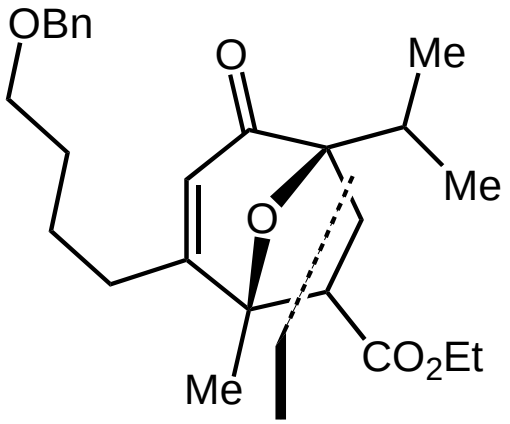


R = OH, (-)-englerin B [(-)-**2**]
R = OAc, (-)-englerin B acetate [(-)-**3**]

Retrosynthetic Disconnection



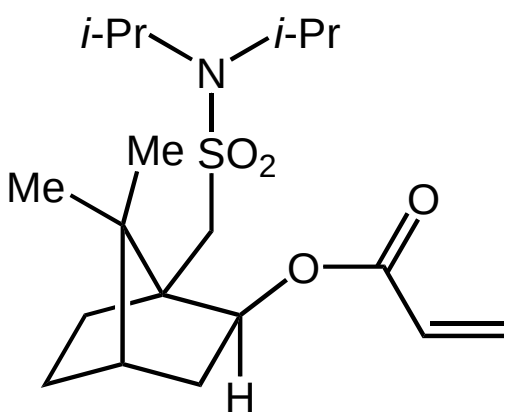
(-)-englerin A [(-)-**1**]



[5+2] Cycloaddition

4

Retrosynthetic Disconnection



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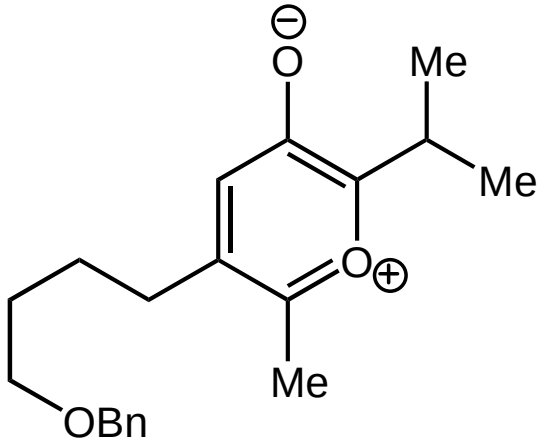

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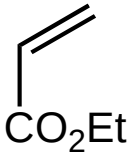
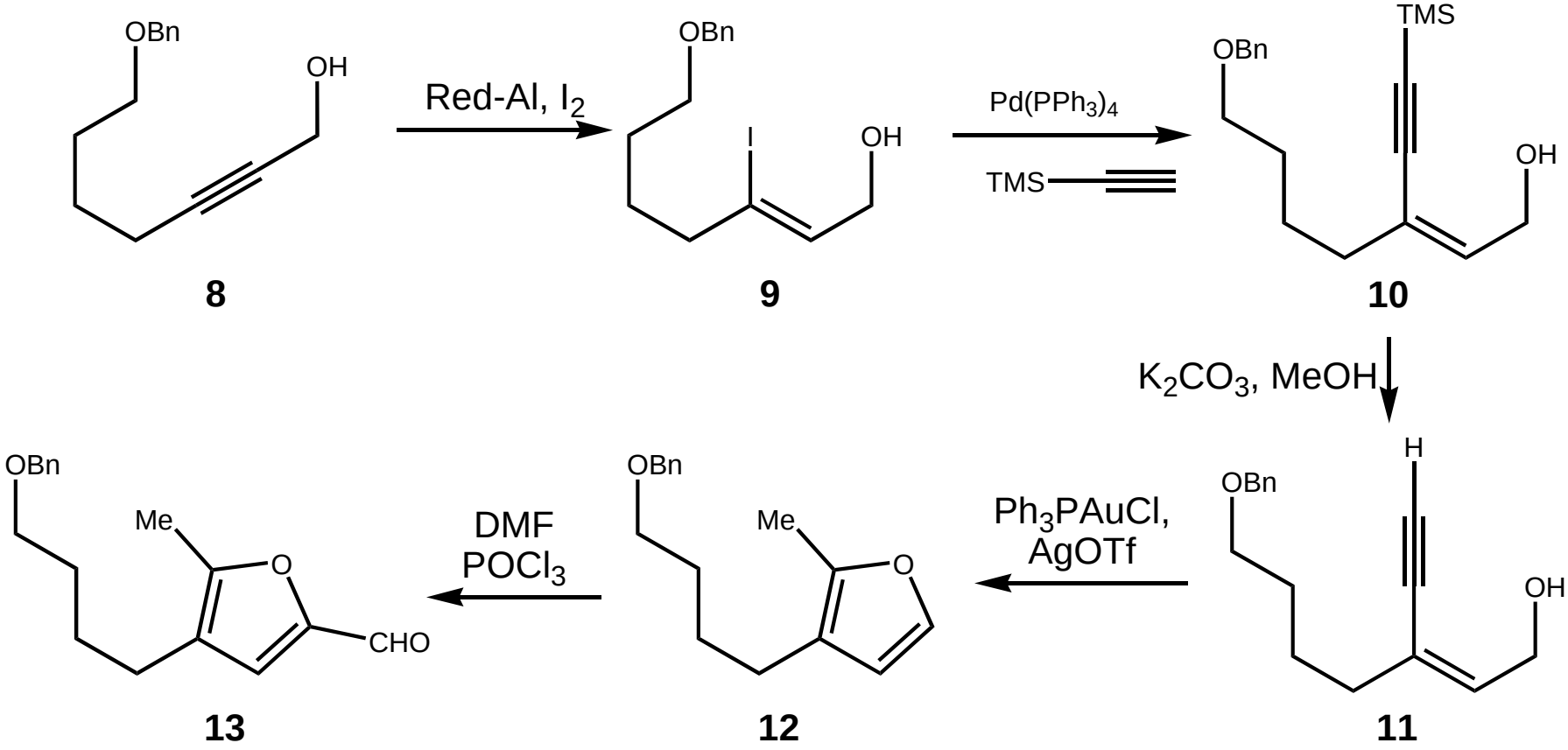
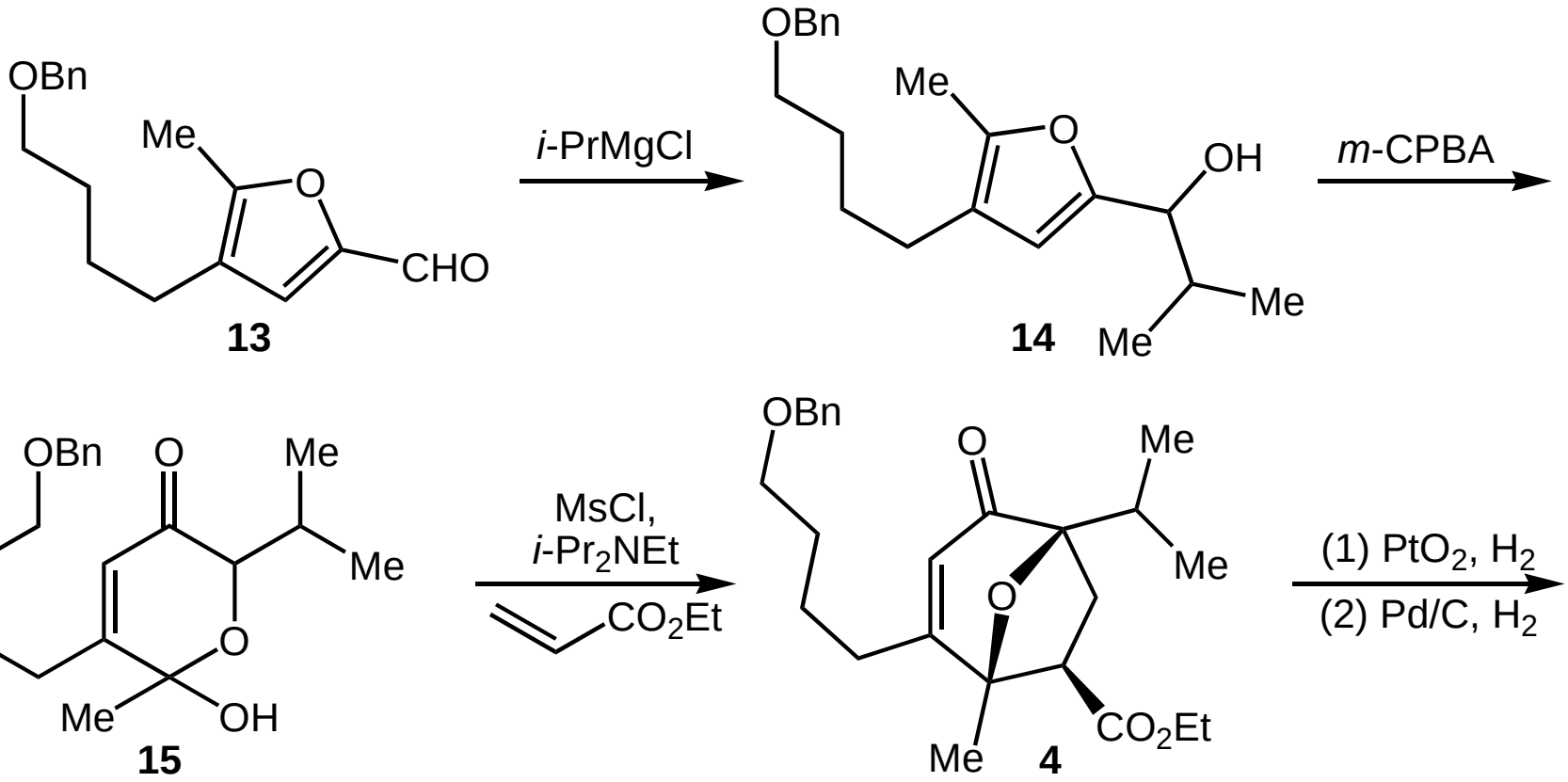


6

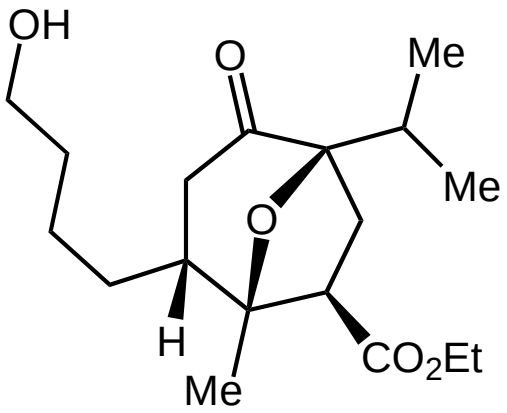
Synthesis of Ketoester 16



Synthesis of Ketoester 16

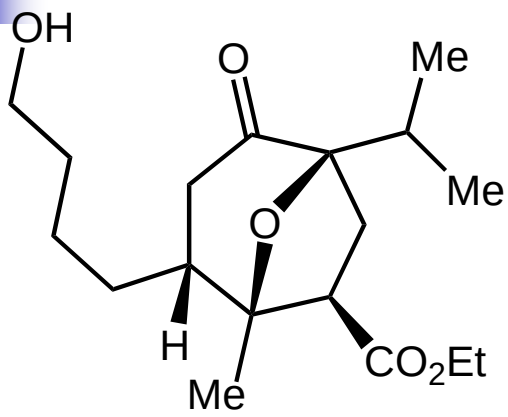


Synthesis of Ketoester 16



16

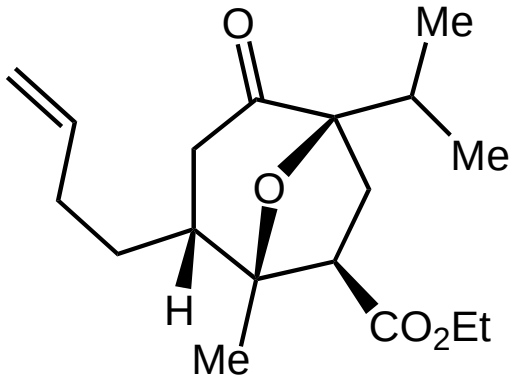
Completion of the Total Synthesis



16

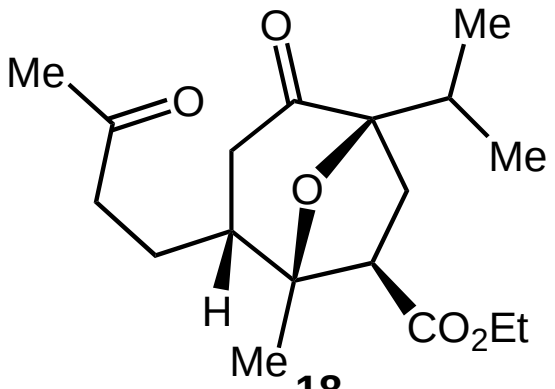
ArSeCN, *n*-Bu_3P

then *m*-CPBA



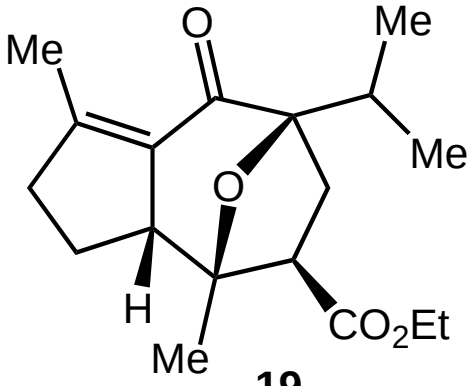
17

Wacker [O]



18

KHMDS



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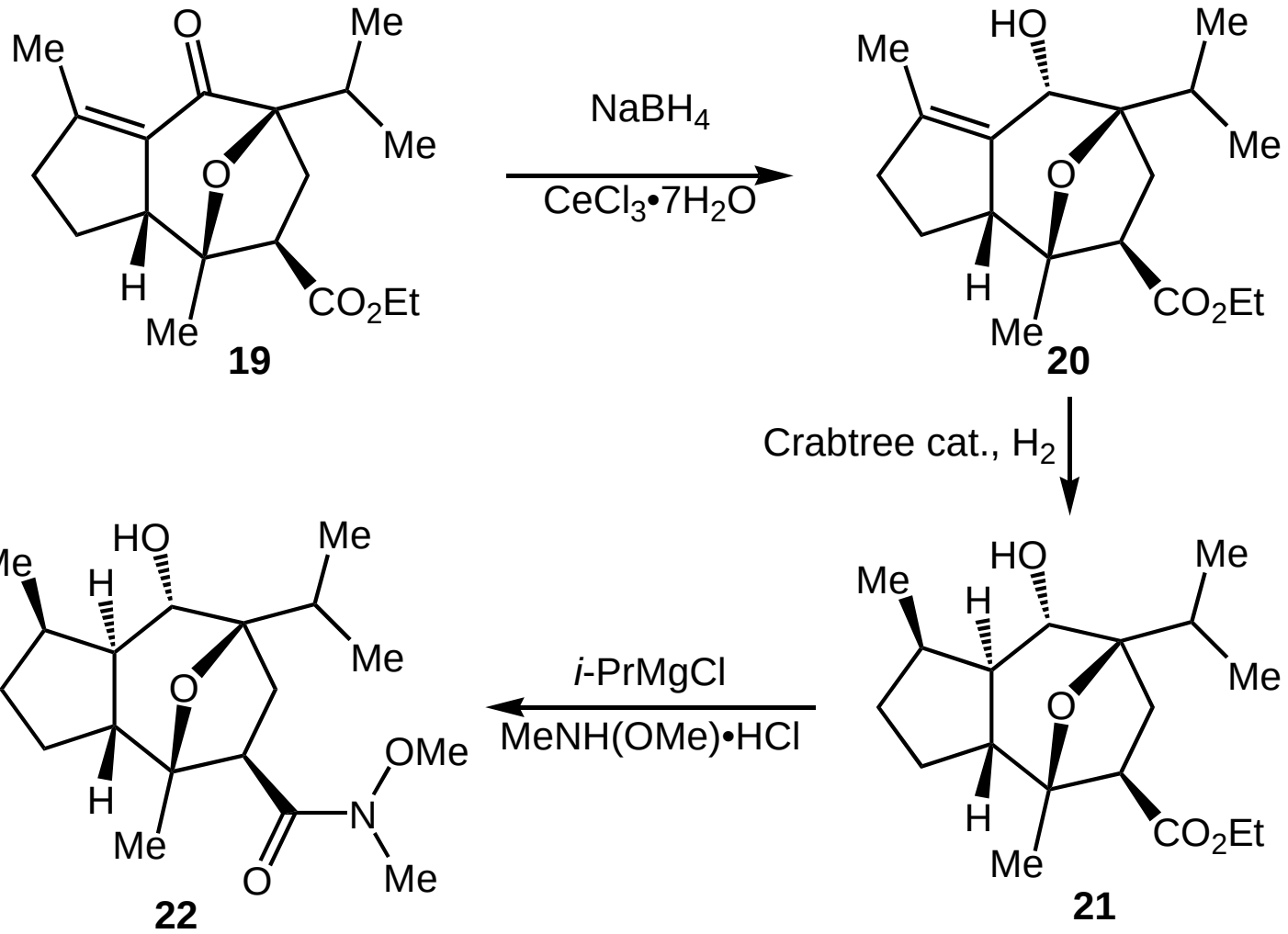
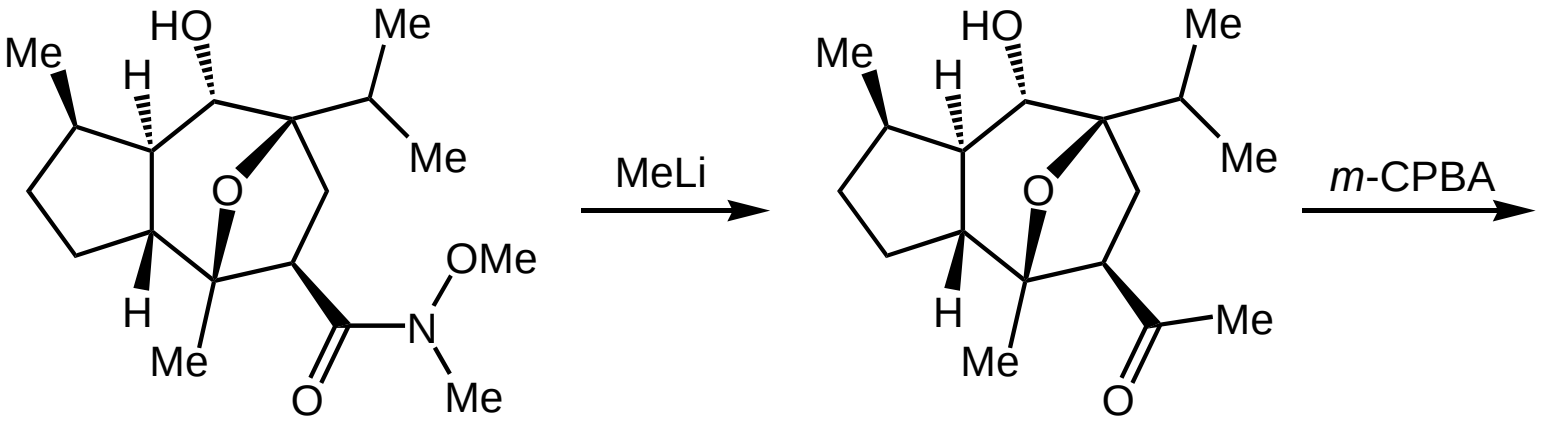
Completion of the Total Synthesis

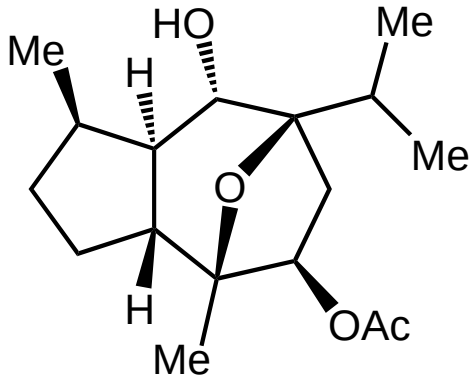


Completion of the Total Synthesis



22 **23**

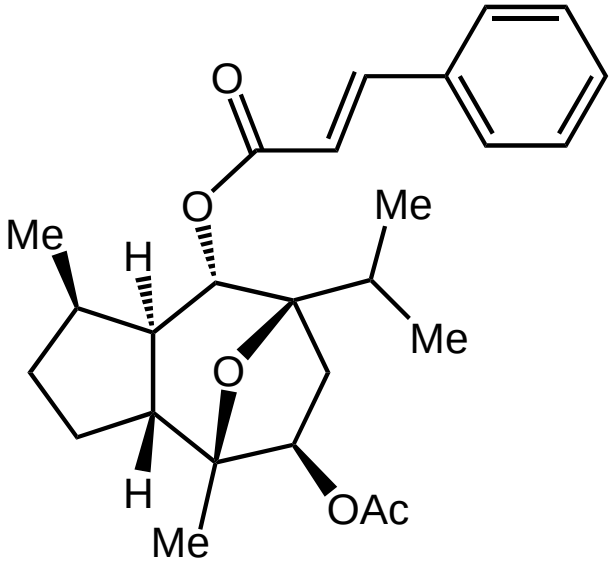
Completion of the Total Synthesis



24

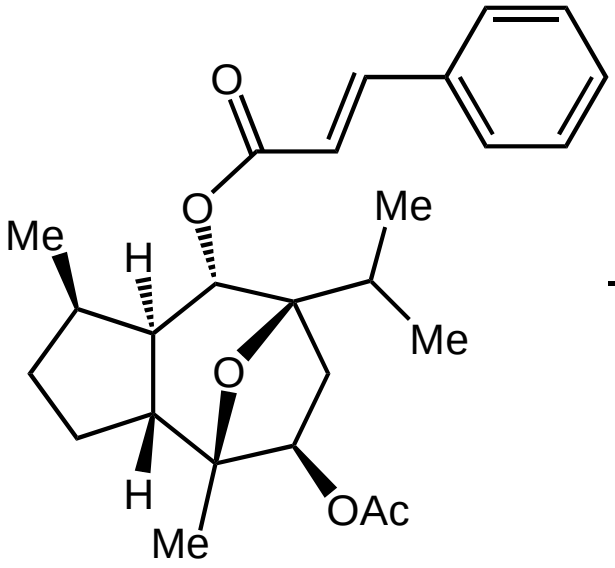
$2,4,6\text{-}Cl_3C_6H_2COCl$

cinnamic acid



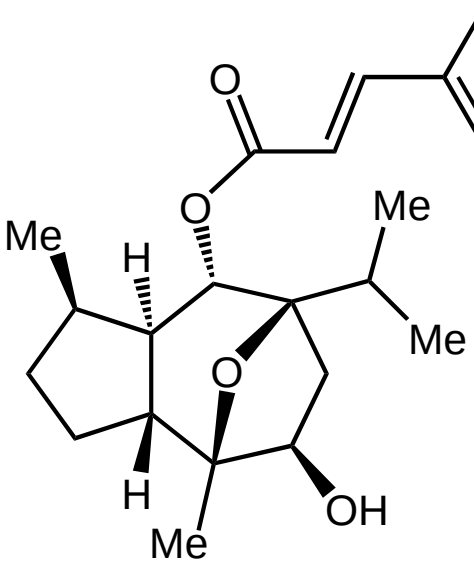
(±)-englerin B [(±)-**3**] acetate

Completion of the Total Synthesis



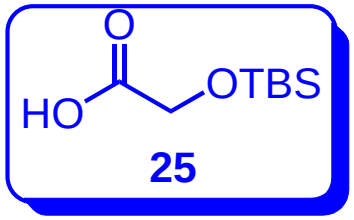
(±)-englerin B [(±)-**3**]
acetate

K_2CO_3

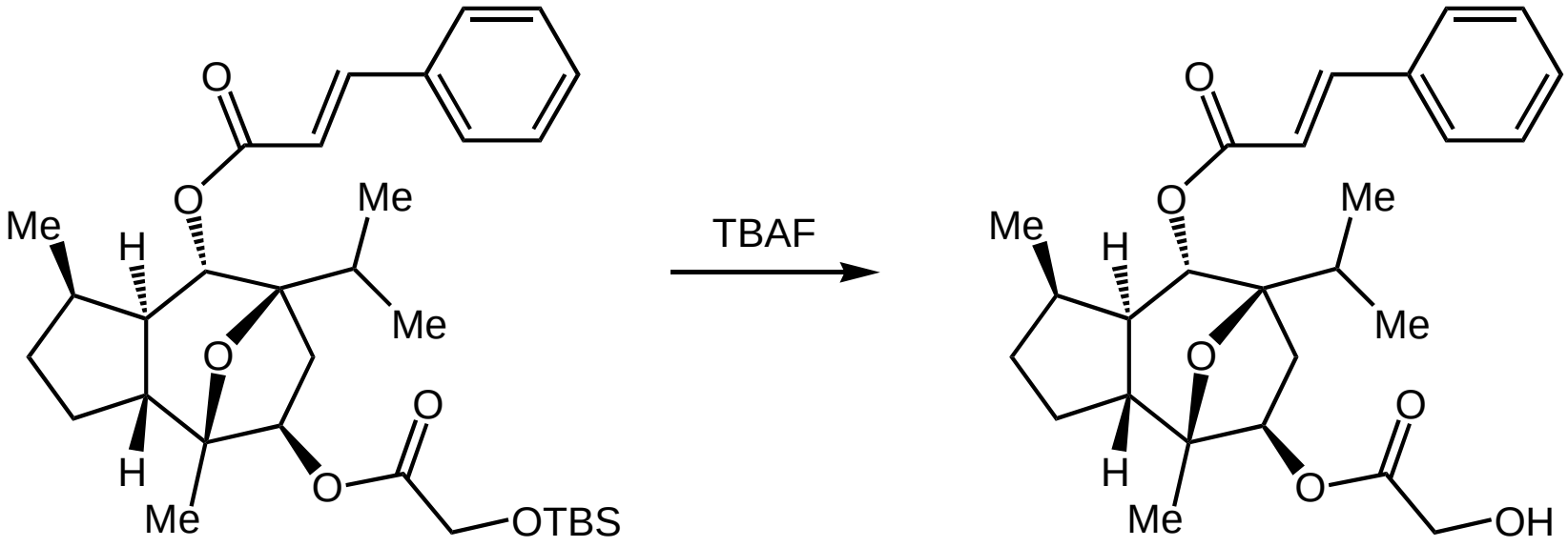


(±)-englerin B [(±)-**2**]

25



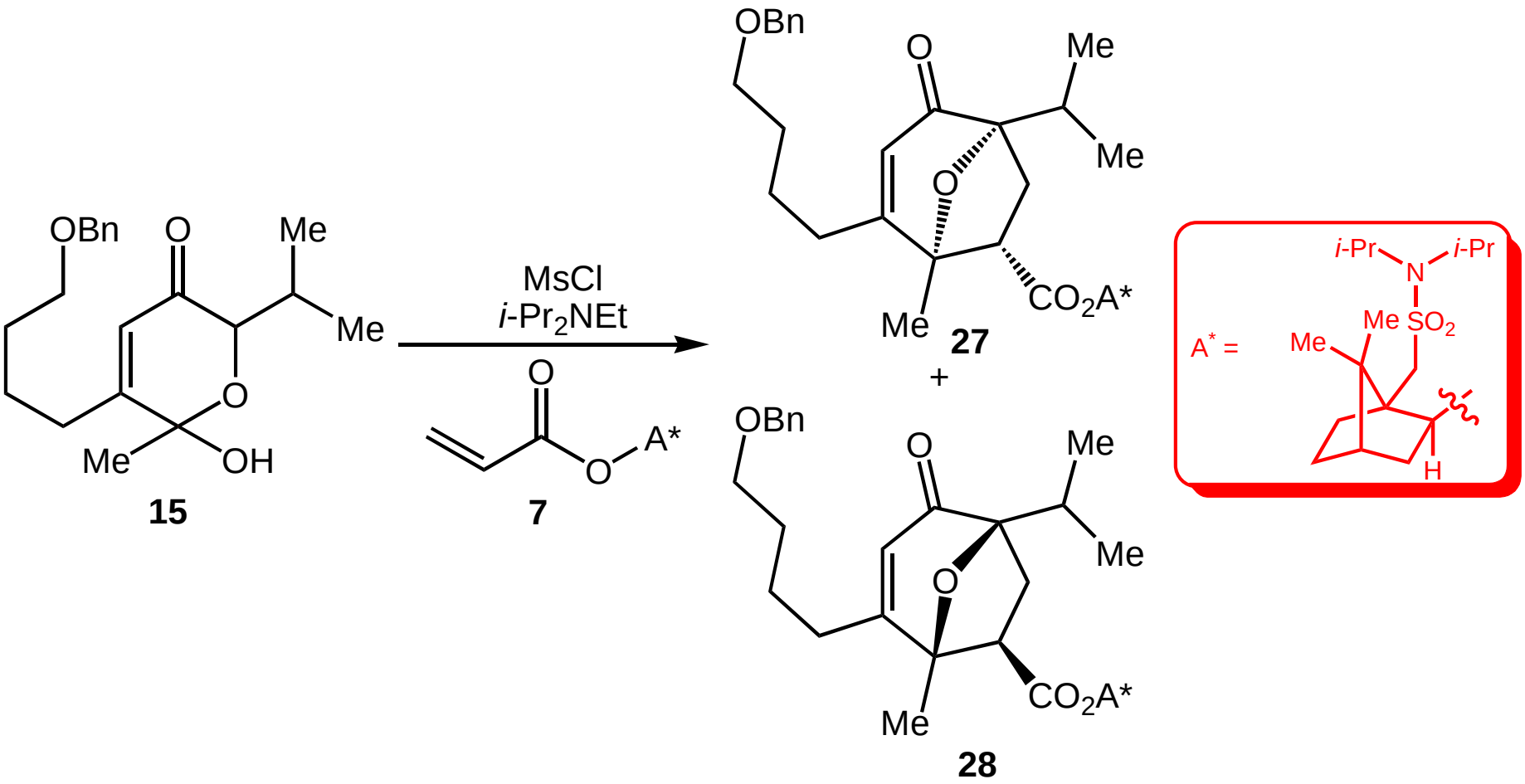
Completion of the Total Synthesis



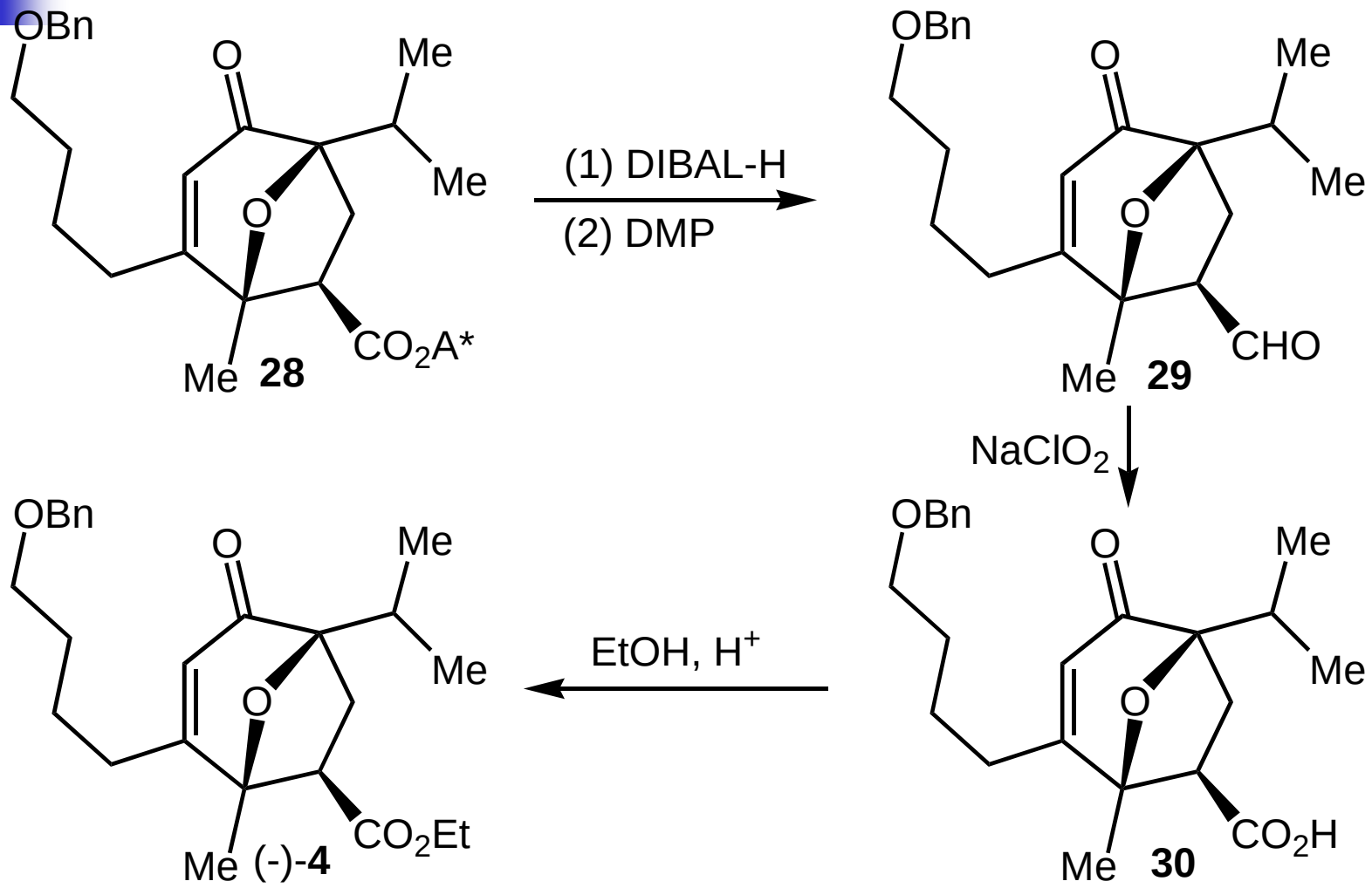
26

(±)-englerin A [(±)-**1**]

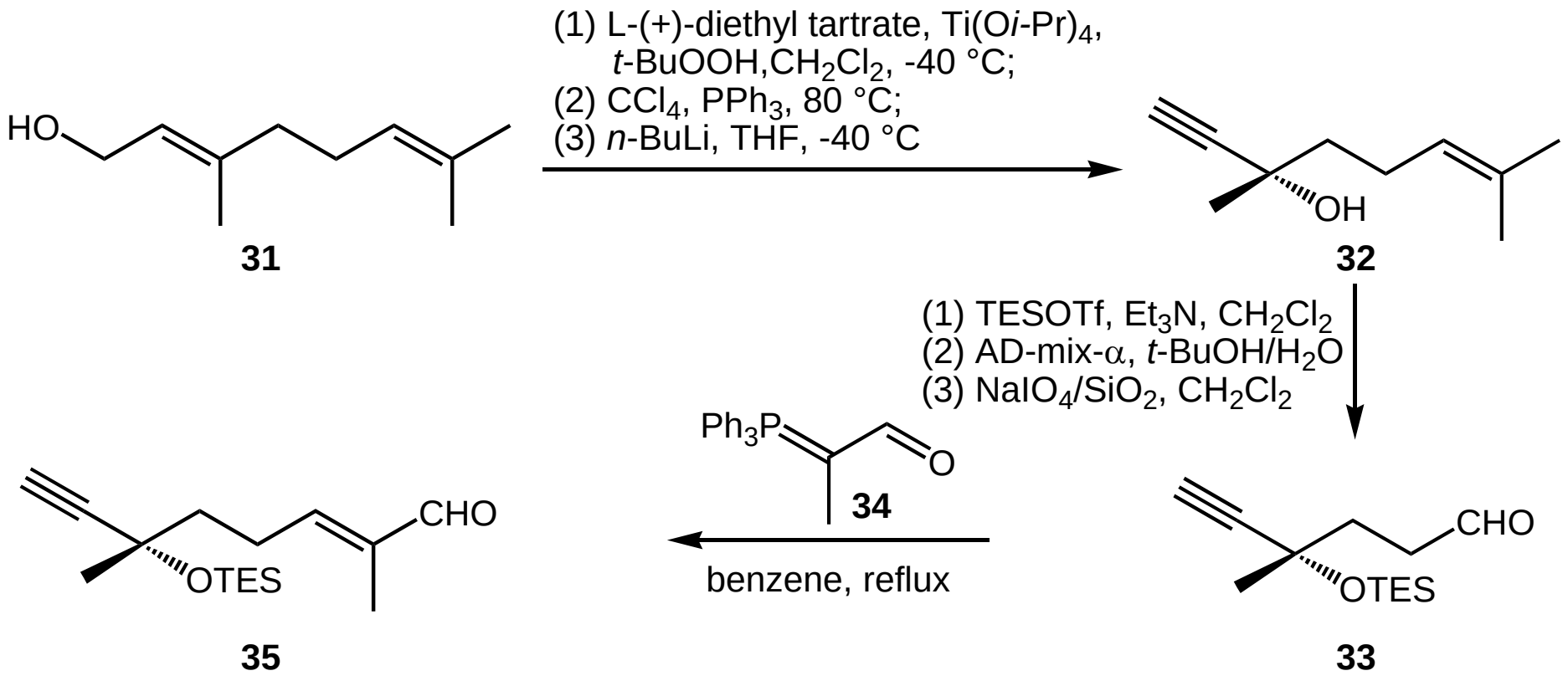
Asymmetric Synthesis of 4



Asymmetric Synthesis of 4

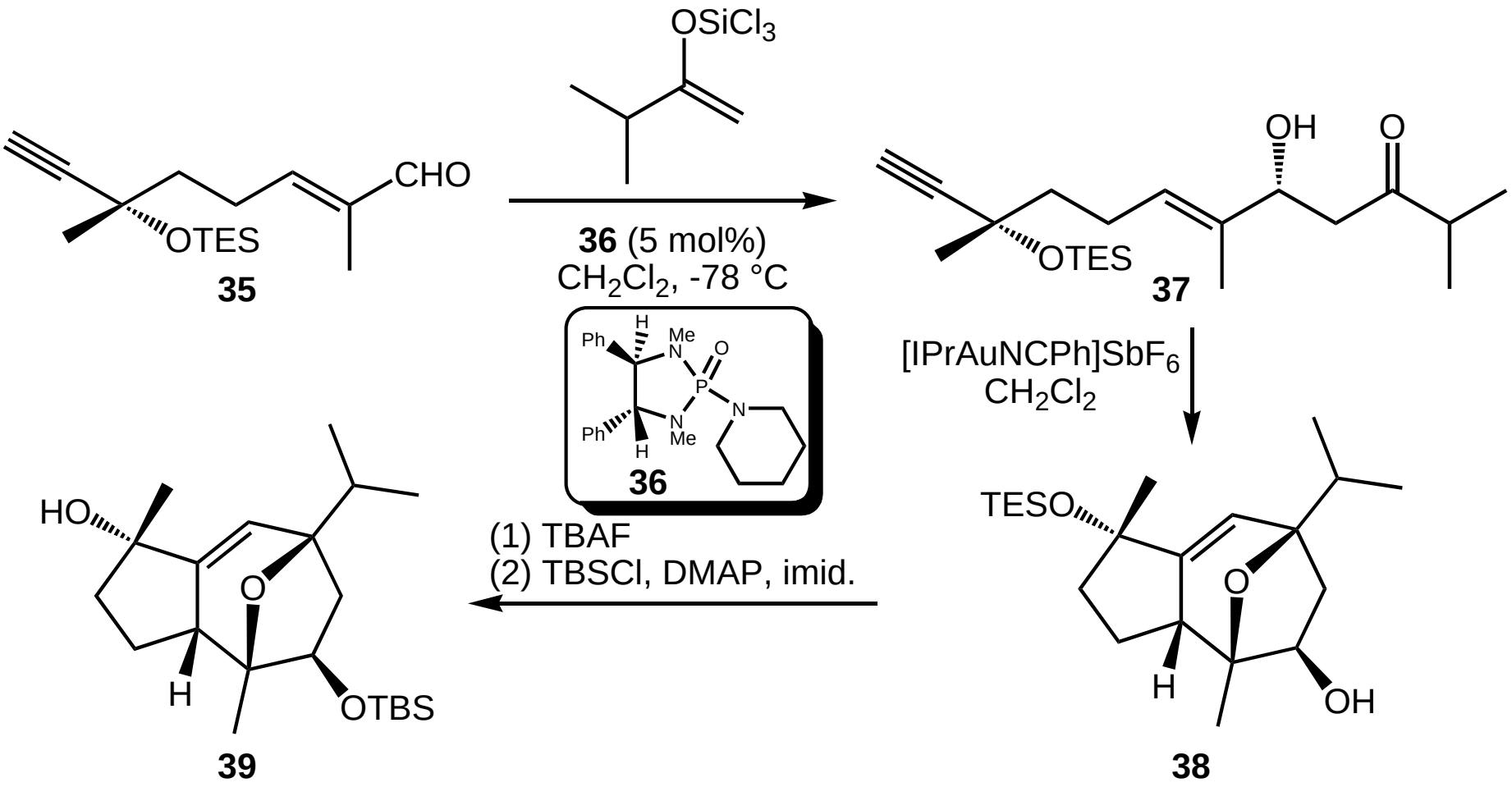


Echavarren's Work

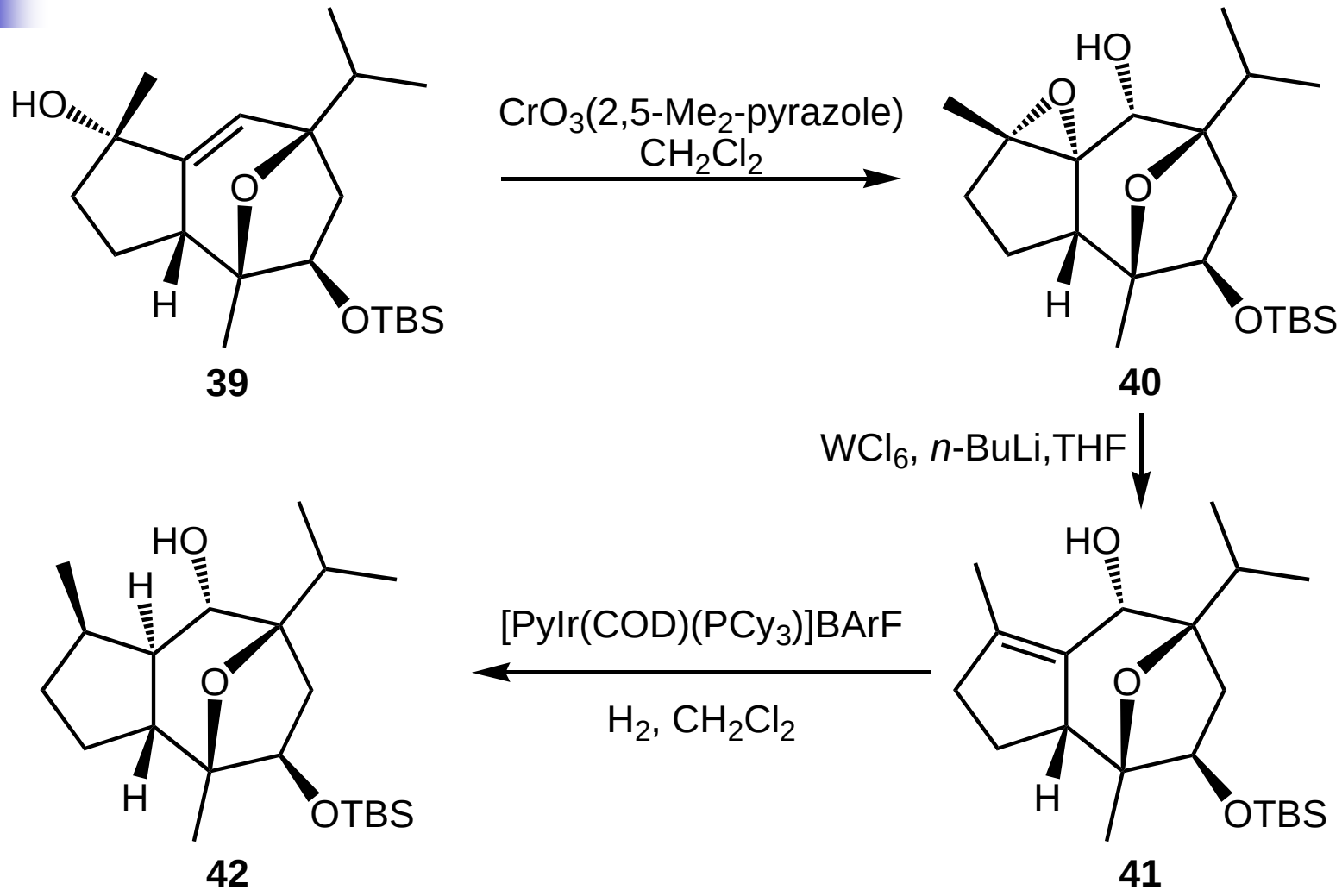


Echavarren, A. M. *et al Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

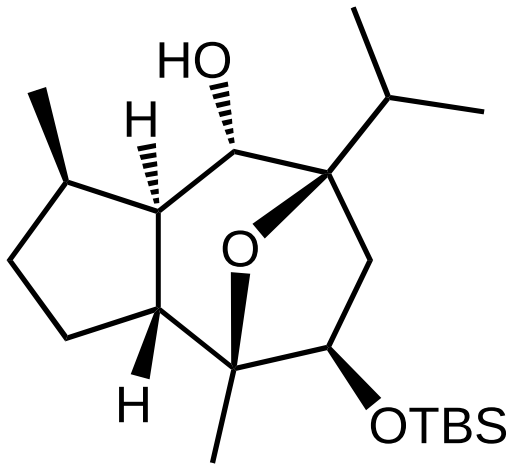
Echavarren's Work



Echavarren's Work

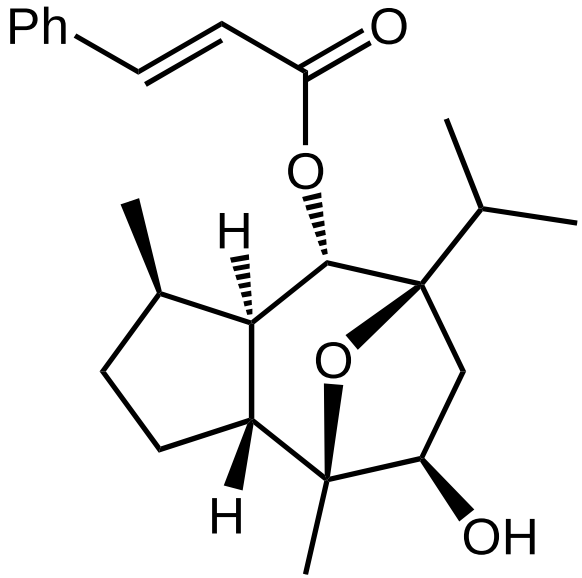


Echavarren's Work



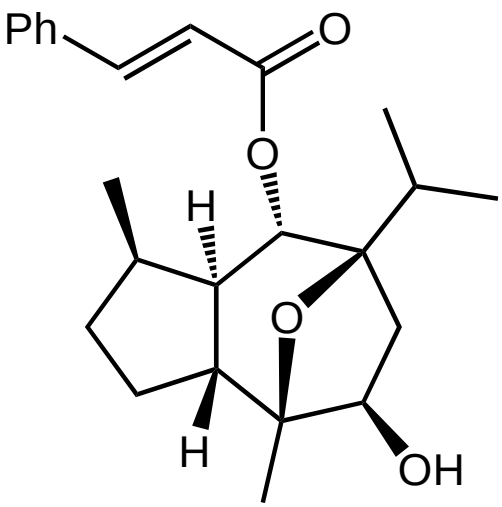
42

(1) cinnamoyl chloride
DMAP, CH_2Cl_2/NEt_3
(2) TBAF, CH_2Cl_2

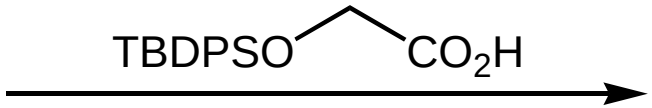


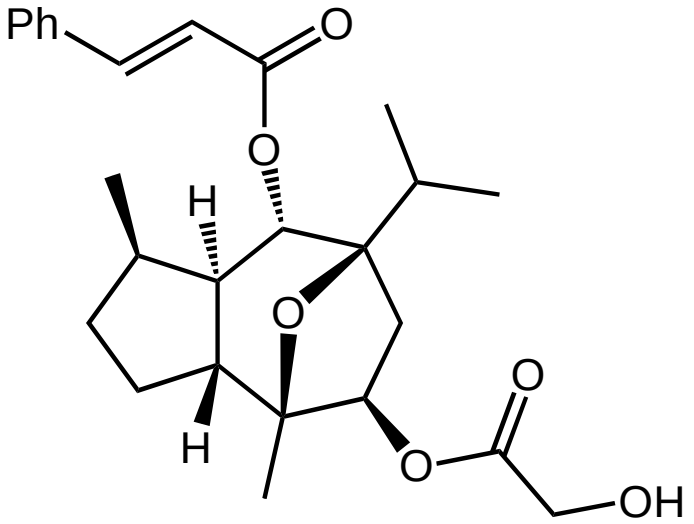
(-)-englerin B [(-)-**2**]

Echavarren's Work



(-)-englerin B [(-)-**2**]

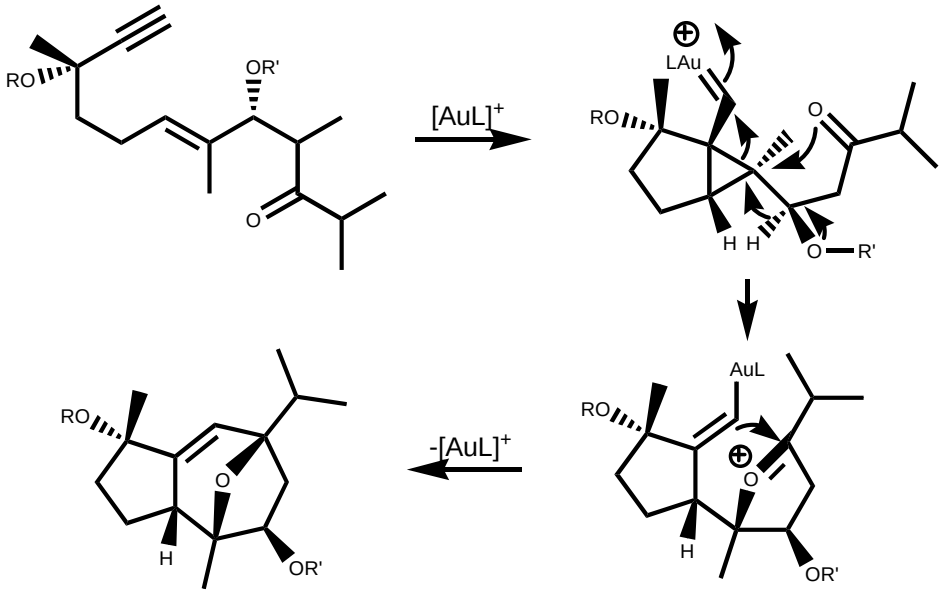


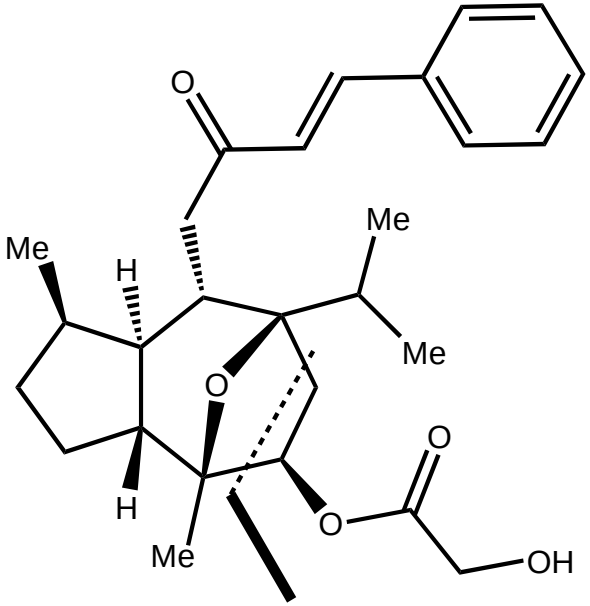


(-)-englerin A [(-)-**1**]

Conclusion

Echavarren's Work:

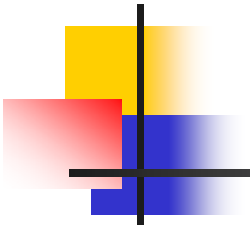




Nicolaou's Work:
[5+2] Cycloaddition

Englerin A (**1**) is a newly discovered guaiane sesquiterpene from the stem bark of *Phyllanthus engleri* collected in Tanzania. Its importance derives from its potent and selective growth inhibitory (GI) activities against renal cancer cells. Its unique structure includes a tricyclic motif carrying two esters, one to a cinnamic acid and the other to a glycolic acid residue. The latter is apparently crucial for its potency and selectivity, since englerin B (**2**) and englerin B acetate (**3**) showed significant loss of potency and selectivity toward renal cancer cells. Intrigued by the structure and biological properties of englerin A (**1**) as a lead compound for drug discovery, we initiated a program directed at its total synthesis. Herein we report the total synthesis of englerin A [(±)-**1**], englerin B [(±)-**2**], and englerin B acetate [(±)-**3**] from simple starting materials. In addition, a formal asymmetric synthesis of these compounds has also been accomplished by reaching a late-stage key intermediate in its optically active form.

The described chemistry provides a ready access to englerins A and B and englerin B acetate (**1**-**3**). A formal asymmetric total synthesis of these compounds has also been demonstrated through the synthesis of optically active advanced key intermediate bicyclic enone **4**. The synthetic strategy employed features a [5 + 2] cycloaddition reaction of an oxopyrilium species **5** with appropriate acrylate esters, stereoselective Luche and Crabtree reductions, and a Baeyer-Villiger oxidation to secure the tricyclic core onto which the two ester side chains were attached through Yamaguchi esterifications. Biological evaluations of selected synthesized compounds provided valuable structure-activity relationships for future investigations toward drug discovery and development in cancer chemotherapy.



THANKS!