C_2-C_{11} Cyclised Cembranoids

Organic LETTERS

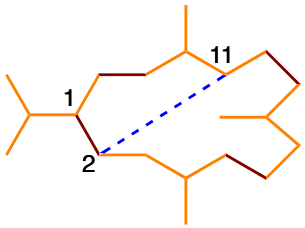
Total Syntheses of (+)-Vigulariol and (–)-Sclerophytin A

Michael T. Crimmins,** Christina S. Stauffer, and Mark C. Mans

(*Org. Lett.* **2011**, *13,* 4890-4893, *DOI: 10.1021/ol201981j*)

C_2-C_{11} Cyclised Cembranoids

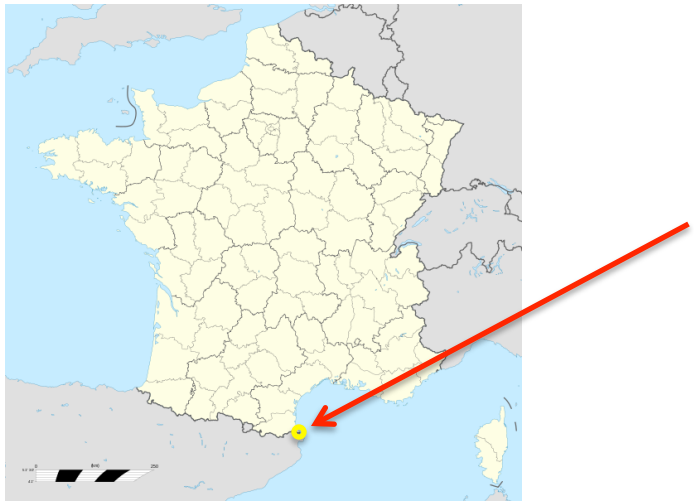
- *Over 100 secondary metabolites isolated from gorgonian corals*



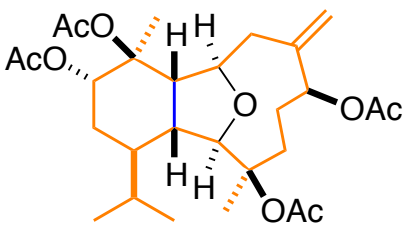
C_2-C_{11} cyclisation → *eunicellins, briarellins, sarcodictyins, asbestinins.*

cembranes

Cyclic **diterpenes: C_{20} , 4 isoprene units**



Eunicellin isolated in **1968**, in **Banyuls-sur-Mer, France.**

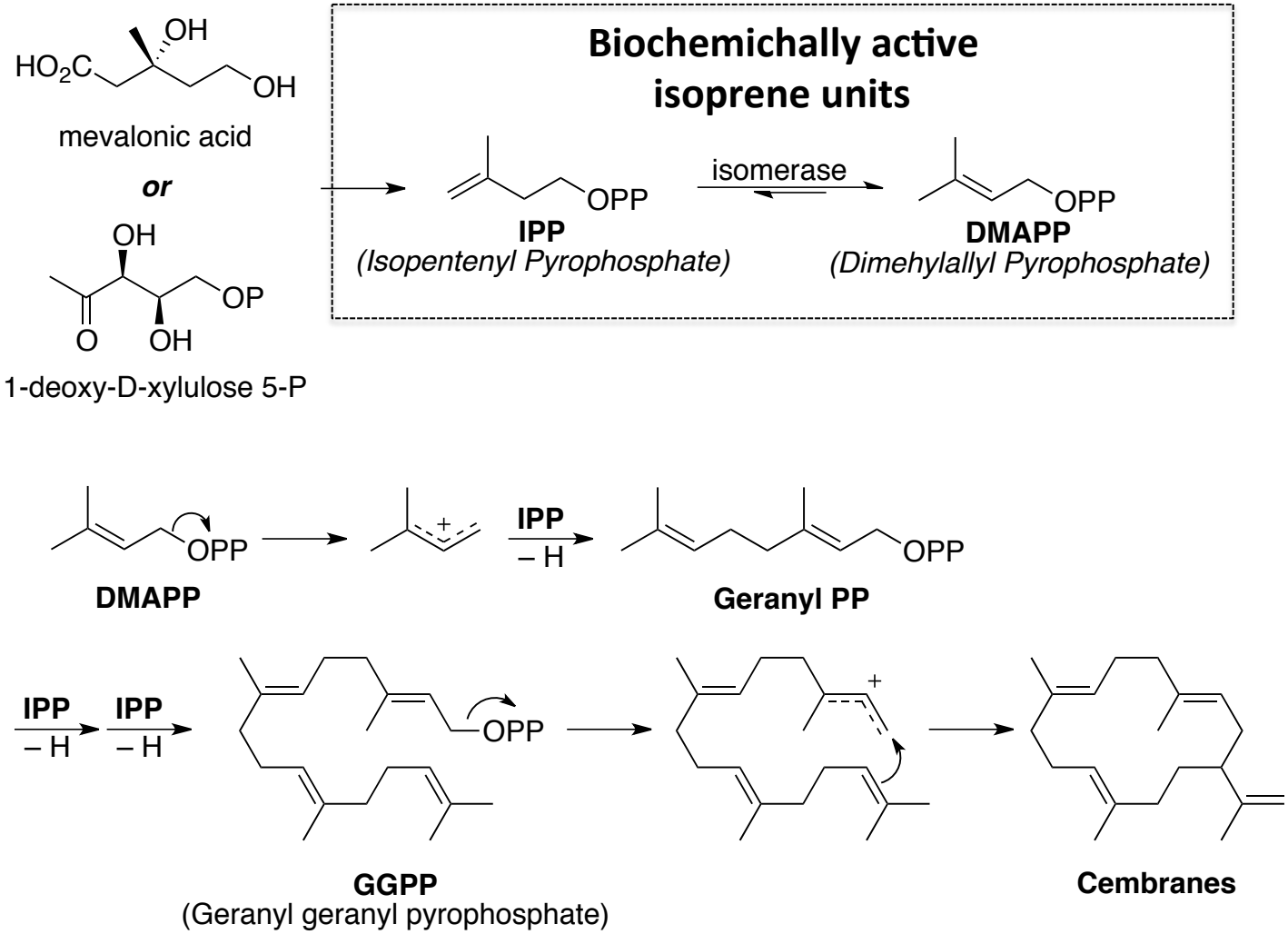


eunicellin

Review : J. M. Ellis, M. Crimmins *Chem. Rev.* **2008**, *108,* 5278-5298.

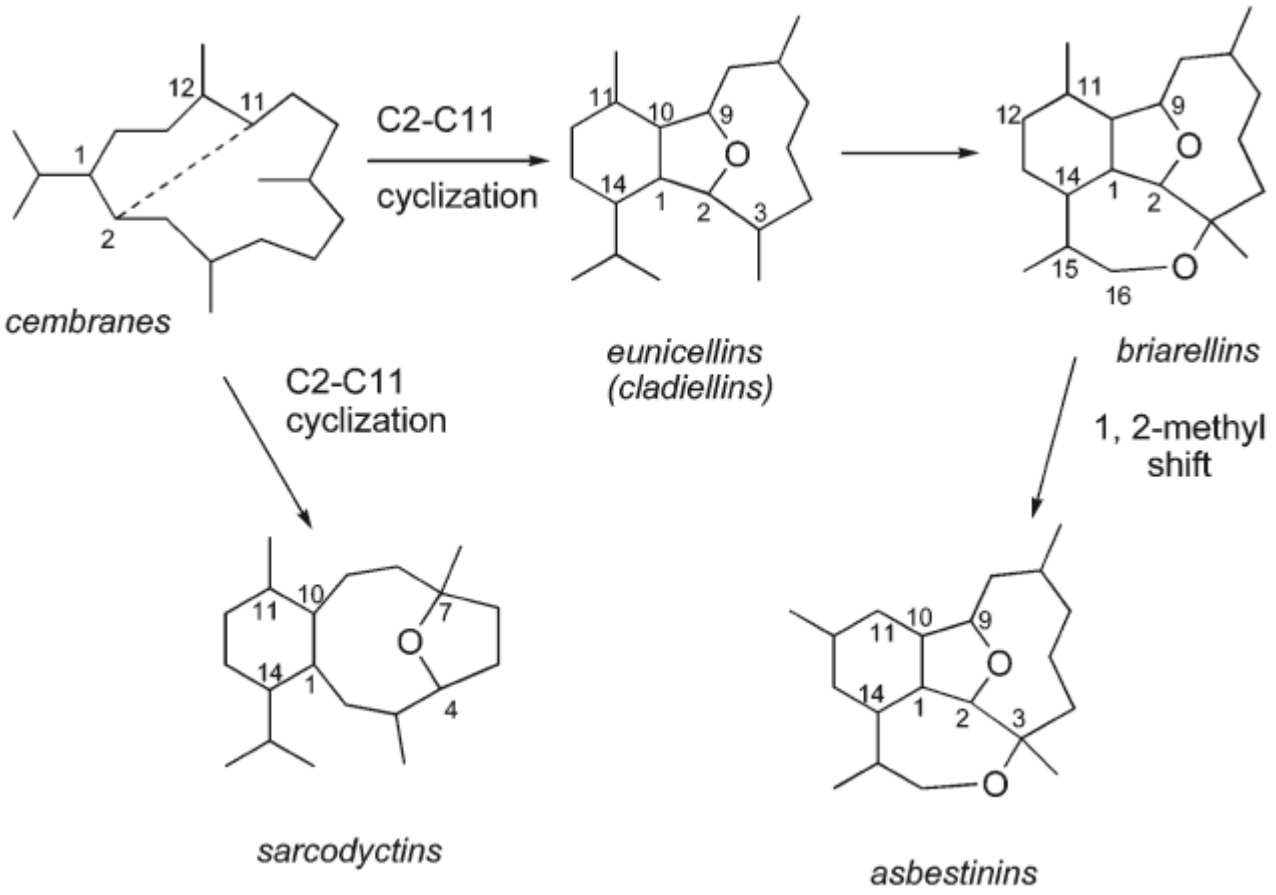
C_2-C_{11} Cyclised Cembranoids

- *Biosynthesis*

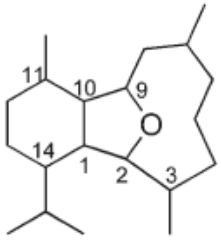


C_2-C_{11} Cyclised Cembranoids

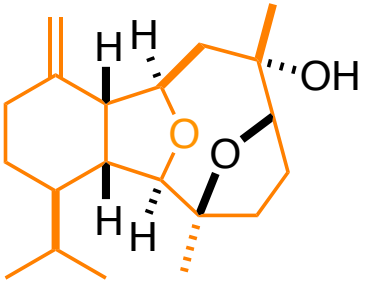
- *Biosynthesis*



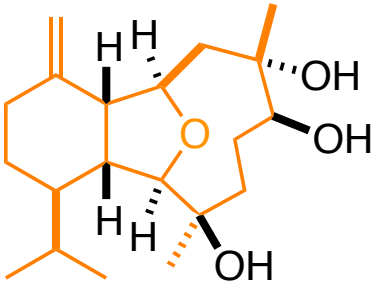
Total Syntheses of (+)-Vigulariol and (–)-Sclerophytin A



eunicellins
(cladiellins)



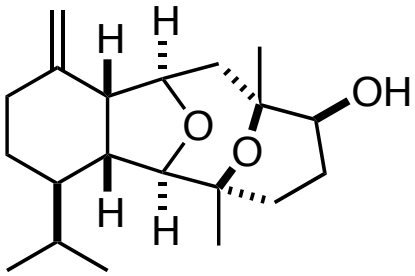
(+)-vigulariol



(–)-sclerophytin A

- J. Stephen Clark
- Dieter Hoppe

- Larry E. Overman
- Leo A. Paquette

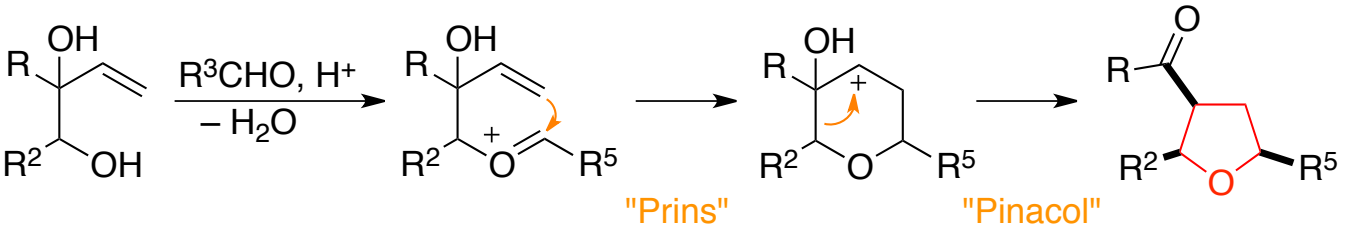


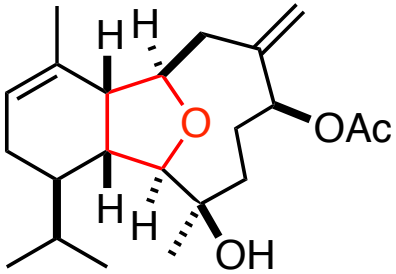
Supposed structure (*up to 2000*) of
sclerophytin A

J. M. Ellis, M. Crimmins *Chem. Rev.* **2008**, *108,* 5278-5298.
M. T. Crimmins *Org. Lett.* **2011**, *13*, 4890-4893.

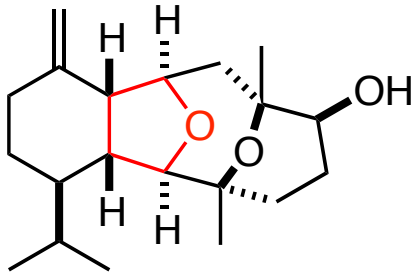
L. E. Overman's approach

- ***Prins-Pinacol Condensation-Rearrangement*** *(1991)*
- *First total synthesis of a C_2-C_{11} cyclised cembranoid:* ***(–)-7-deacetoxyalcyonin*** *(1995)*





(–)-7-Deacetoxyalcyonin



Supposed structure of
sclerophytin A

*J. Am. Chem. Soc.***1991**, *113*, 5354-5365.
*J. Am. Chem. Soc.***1995**, *117*, 10391-10392.

L. E. Overman's approach

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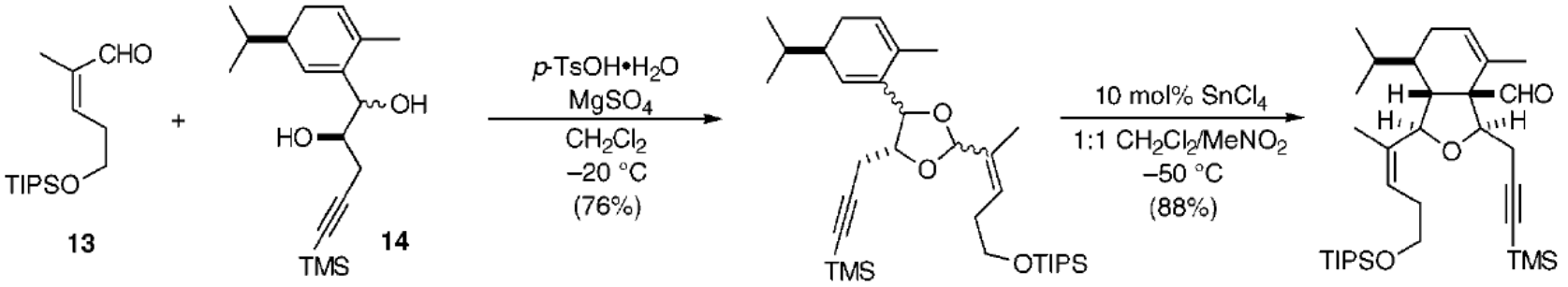
- ***Prins-Pinacol Condensation-Rearrangement: supposed (±)-sclerophytin A***

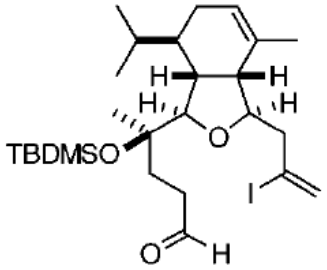


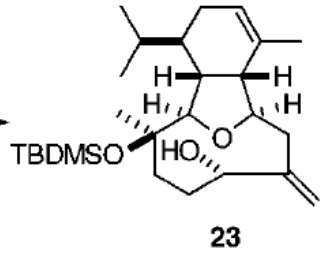
4 steps

6 steps

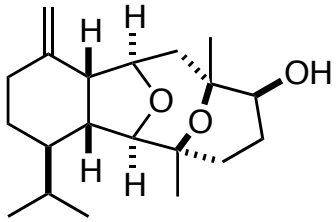
All carbons installed

9 steps





5 steps

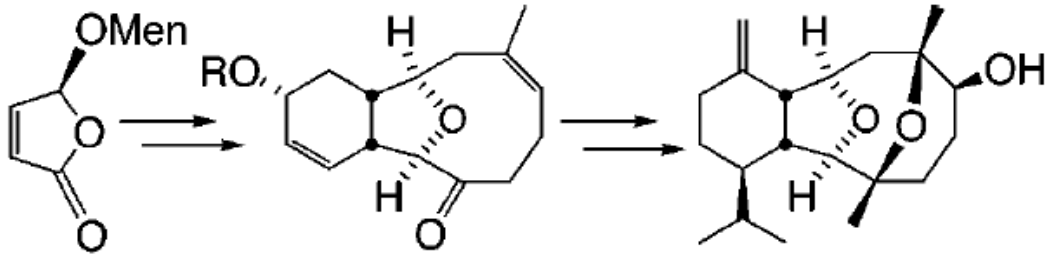


Supposed structure of **sclerophytin A**

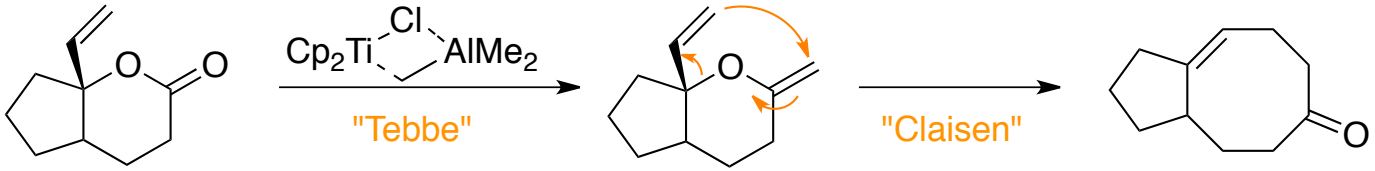
Org. Lett. **2000**, *2*, 2683–2686.

L. A. Paquette's approach

- ***Diels-Alder / Tebbe olefination / Claisen Rearrangement: supposed (±)-sclerophytin A***



Supposed structure of **sclerophytin A**



Org. Lett. **2000**, *2*, 1875–1878.
*J. Am. Chem. Soc.***2001**, *123*, 9021-9032.

L. A. Paquette's approach

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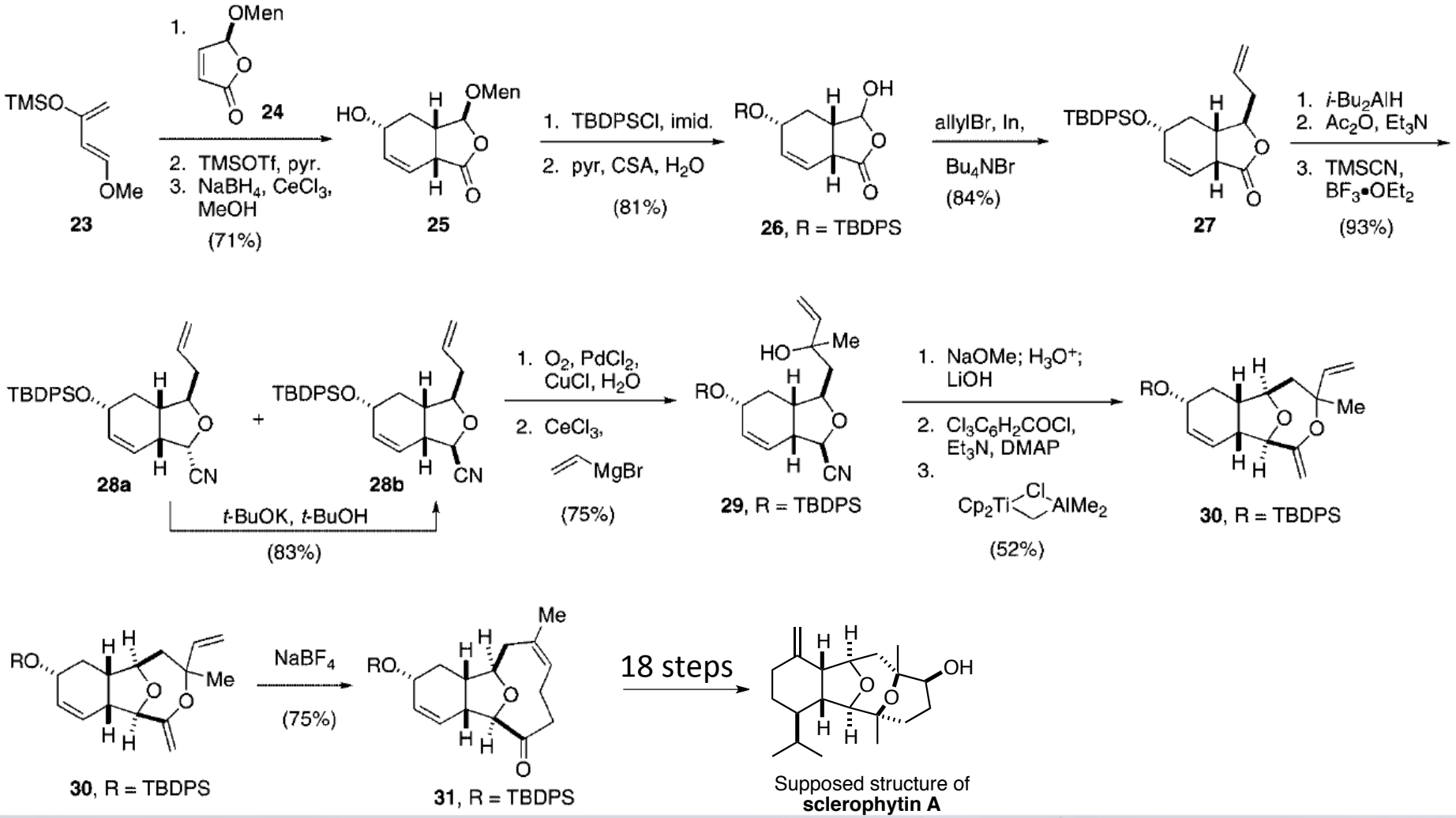
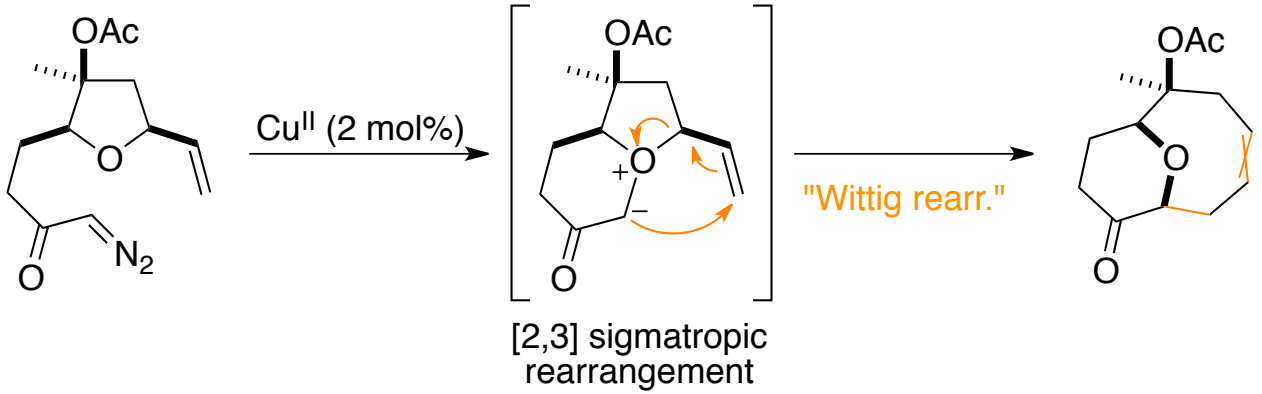
- ***Diels-Alder / Tebbe olefination / Claisen Rearrangement: supposed (±)-sclerophytin A***

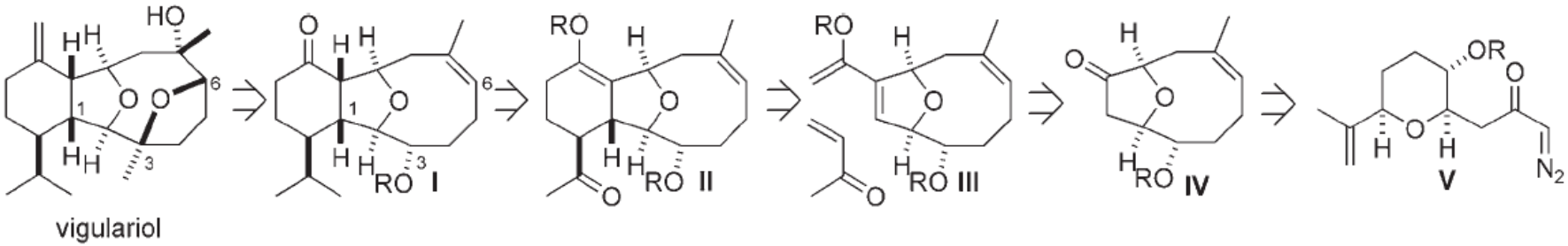


Org. Lett. **2000**, *2*, 1875–1878.
*J. Am. Chem. Soc.***2001**, *123*, 9021-9032.

J. S. Clark's approach

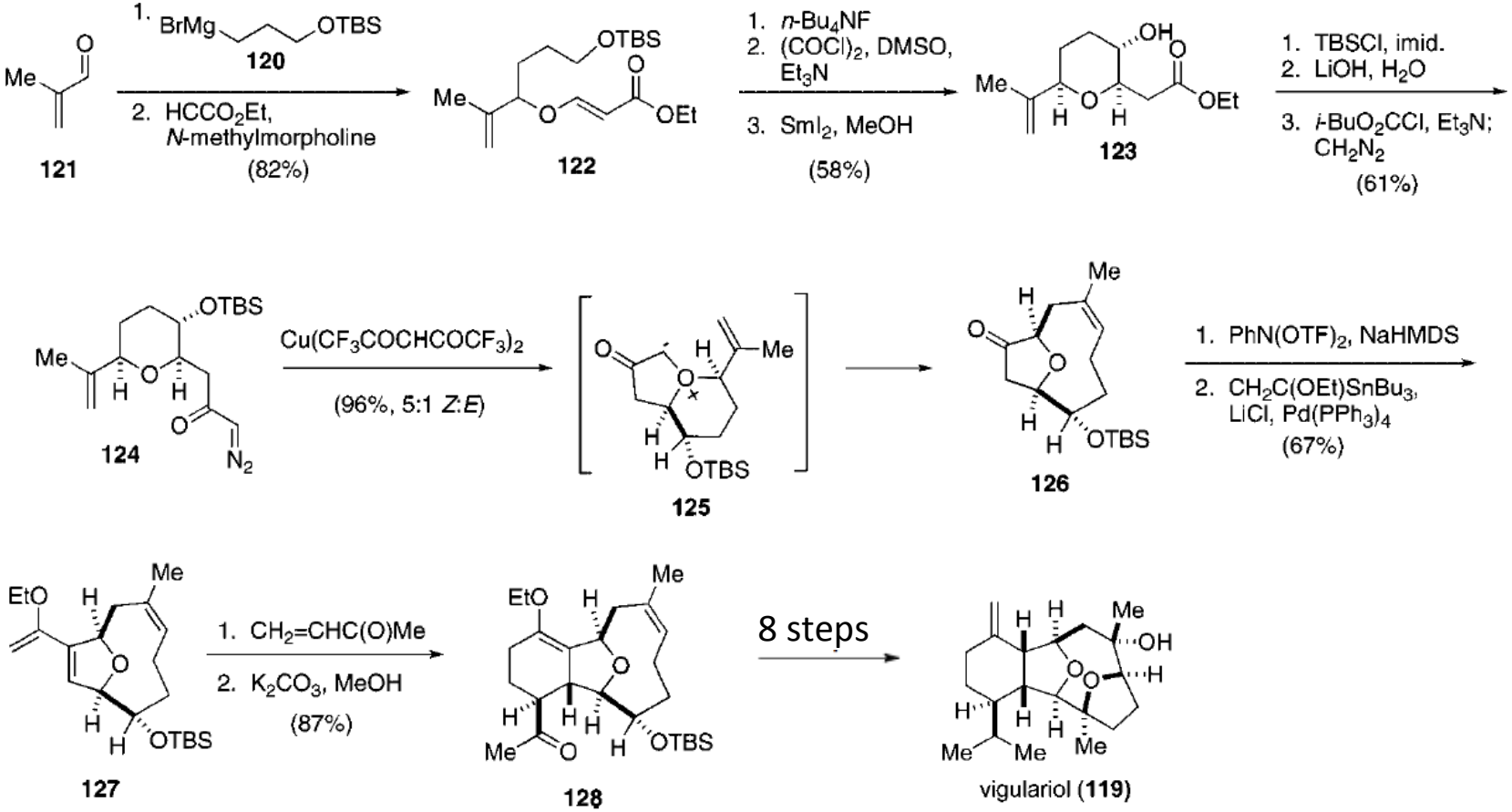
- ***Wittig Rearrangement / Intermolecular Diels-Alder: (±)-Vigulariol***





J. S. Clark's approach

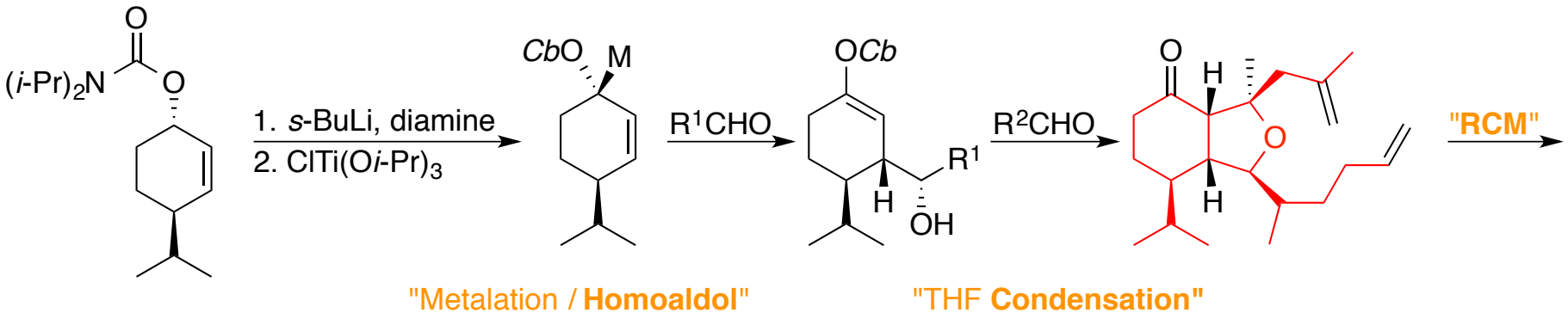
- ***Wittig Rearrangement / Intermolecular Diels-Alder: (±)-Vigulariol***

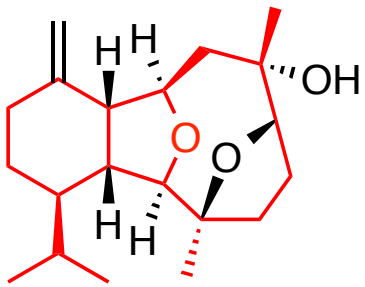


Angew. Chem. Int. Ed. **2007**, *46*, 437–440.
***Enantioselective version**: Angew. Chem. Int. Ed.* **2010**, *49*, 9867–9870.

D. Hoppe's approach

- ***Homoaldol / Cyclocondensation / Ring-Closing Metathesis: (+)-Vigulariol***



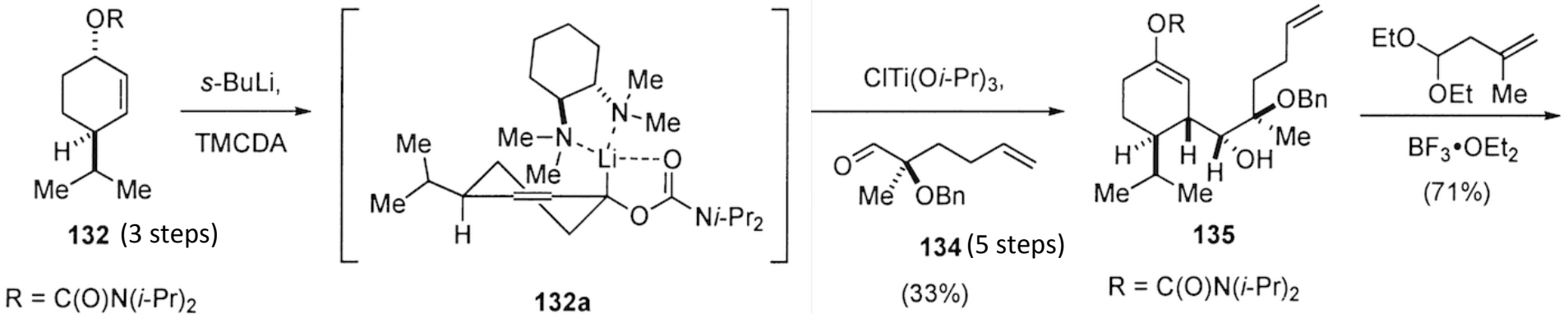


(+)-vigulariol

Angew. Chem. Int. Ed. **2007**, *46,* 1645 –1649.
Eur. J. Org. Chem. **2007**, 3349–3364.

D. Hoppe's approach

- ***Homoaldol / Cyclocondensation / Ring-Closing Metathesis: (+)-Vigulariol***



132 (3 steps)

R = C(O)N(*i*-Pr)$_2$

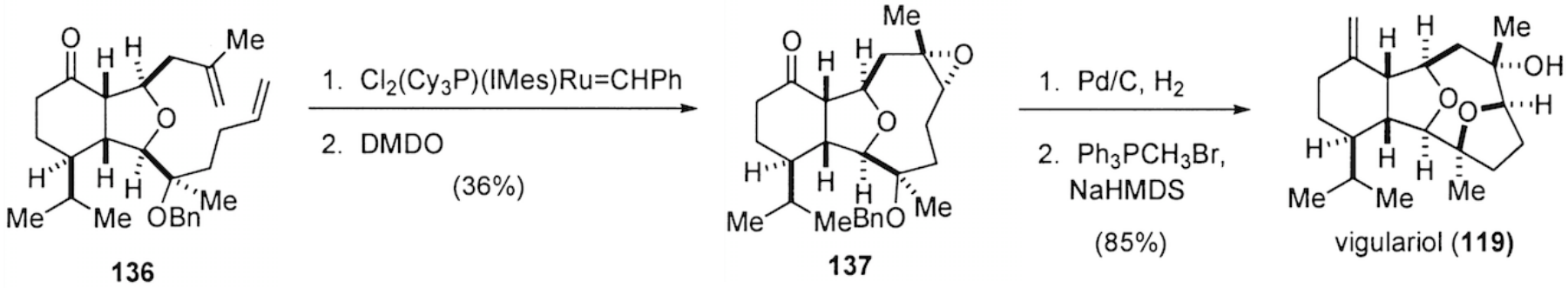
132a

134 (5 steps)

(33%)

135

R = C(O)N(*i*-Pr)$_2$



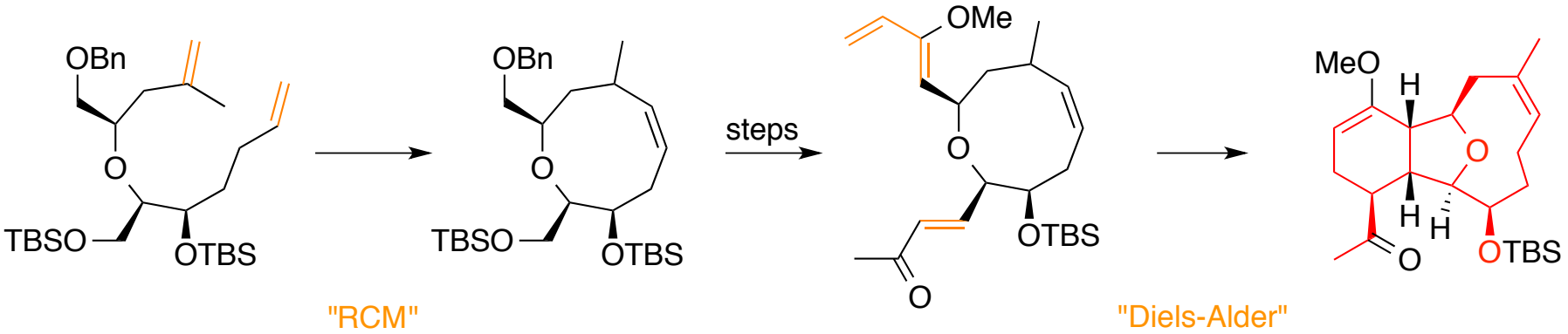
136

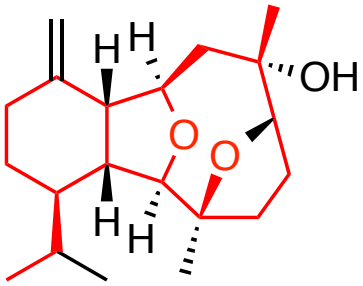
137

vigulariol (**119**)

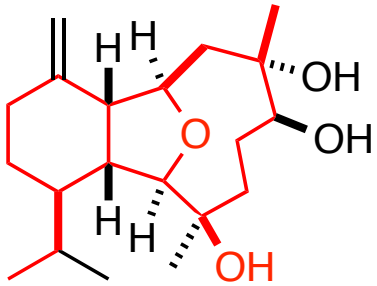
Michael T. Crimmins' approach

- ***Ring-Closing Metathesis / Intramolecular Diels-Alder: (+)-Vigulariol & (–)-Sclerophytin A***





(+)-vigulariol



(–)-sclerophytin A

J. Org. Chem. **1997**, *62*, 7548-7549.
J. Am. Chem. Soc. **2005**, *127*, 17200-17201.

Michael T. Crimmins' approach

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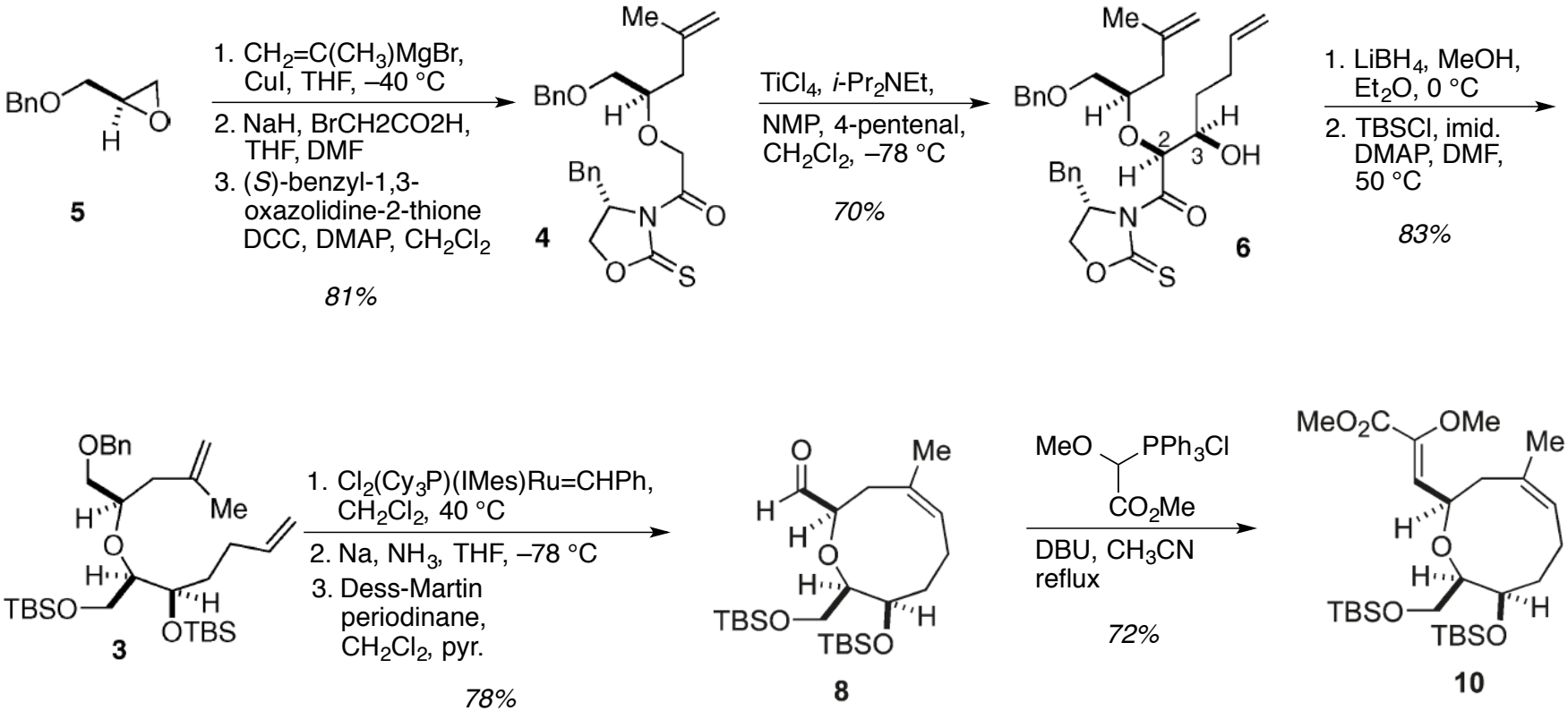
- ***Ring-Closing Metathesis / Intramolecular Diels-Alder: (+)-Vigulariol & (–)-Sclerophytin A***



J. Am. Chem. Soc. **2005**, *127*, 17200-17201.
Org. Lett. **2011**, *13*, 4890-4893.

Michael T. Crimmins' approach

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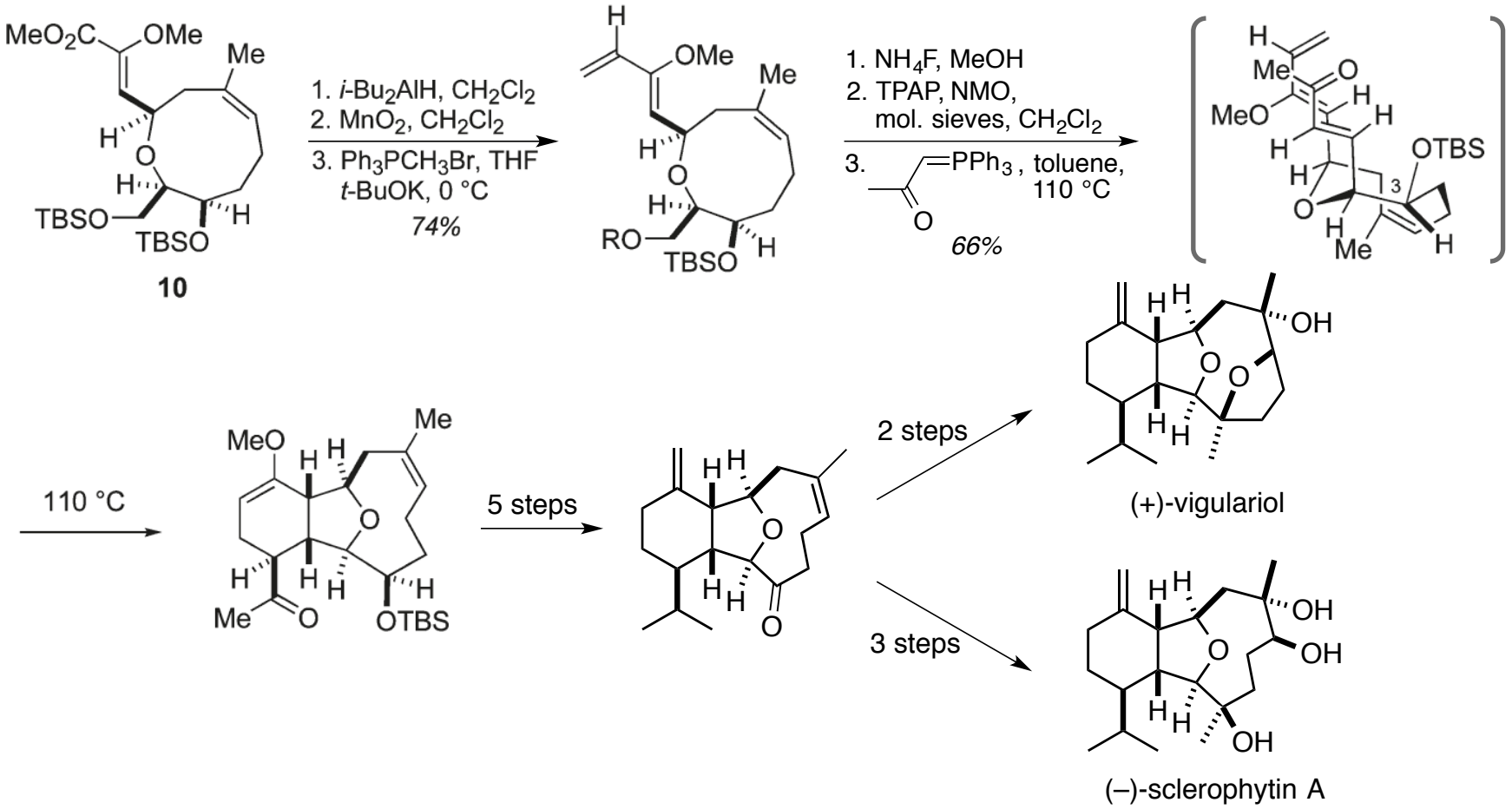
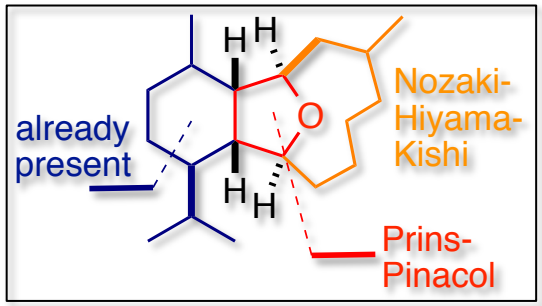
- ***Completion of the syntheses: (+)-Vigulariol & (–)-Sclerophytin A***



Org. Lett. **2011**, *13*, 4890-4893.

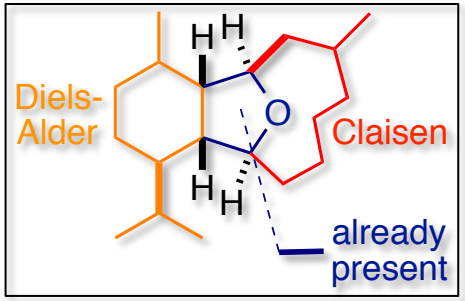
Summary / Conclusion

L. E. Overman



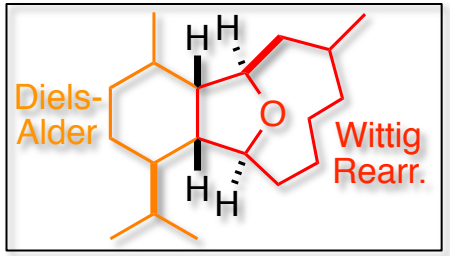
20 steps
± 1% yield

L. A. Paquette



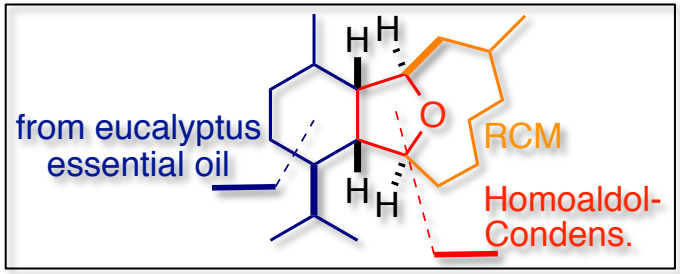
28 steps
± 0.5% yield

J. S. Clark



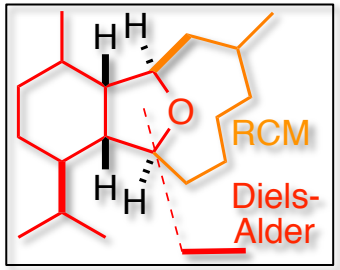
20 steps
± 4% yield

D. Hoppe



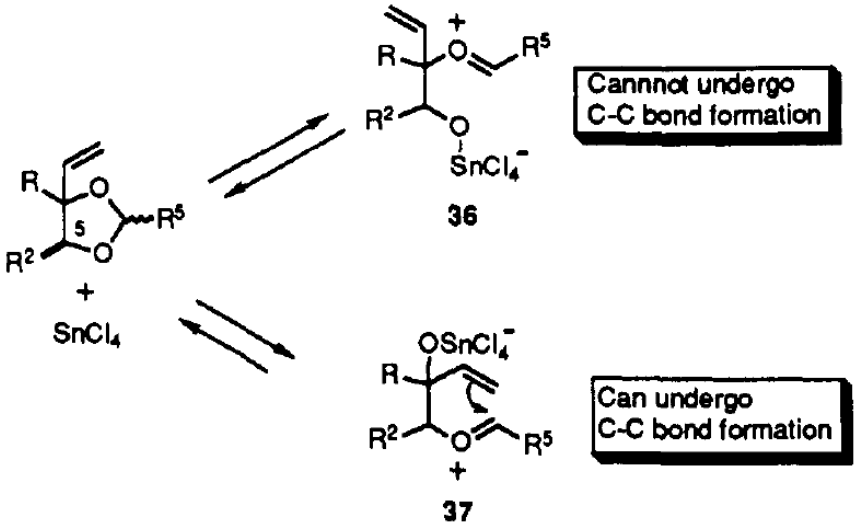
11 steps
± 7% yield

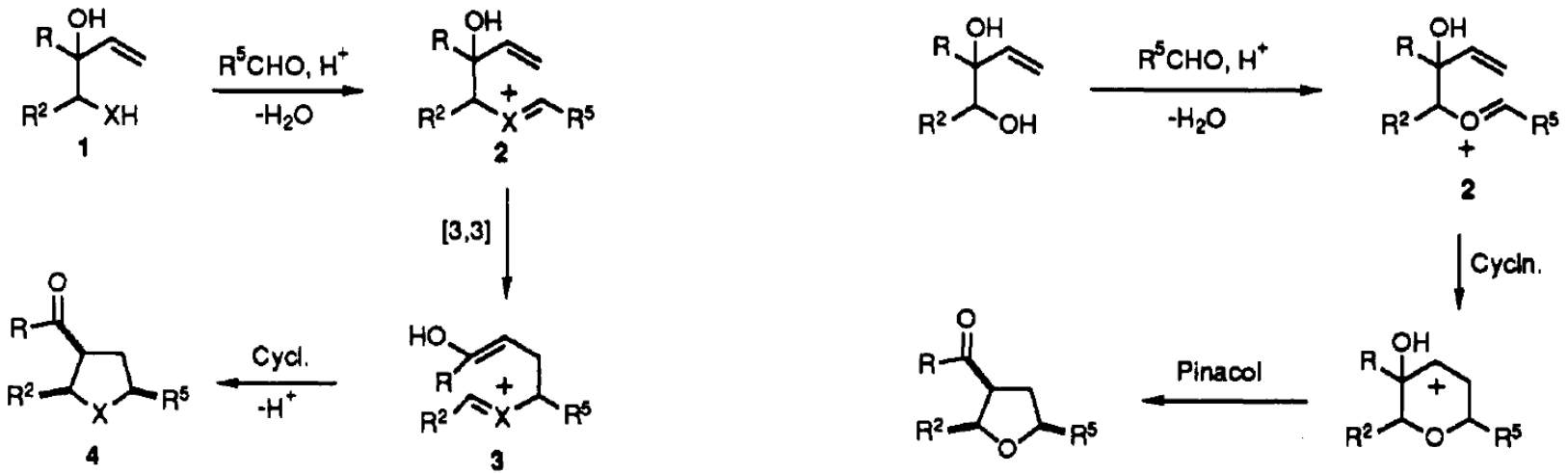
M. T. Crimmins



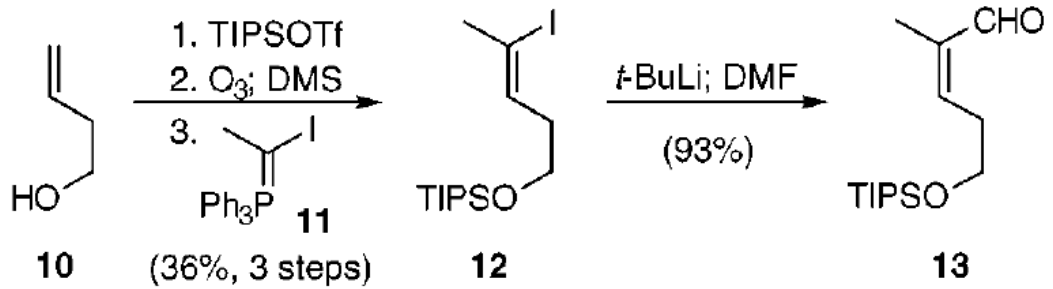
23-24 steps
± 5% yield

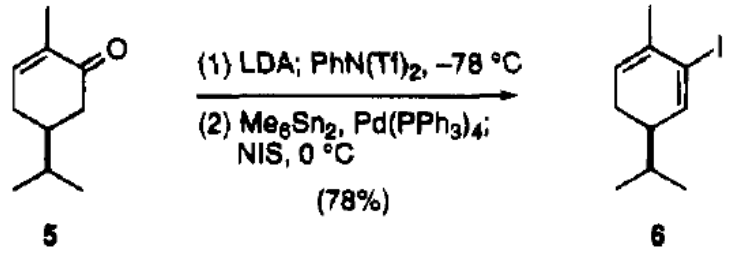
Prins-Pinacol Mechanism

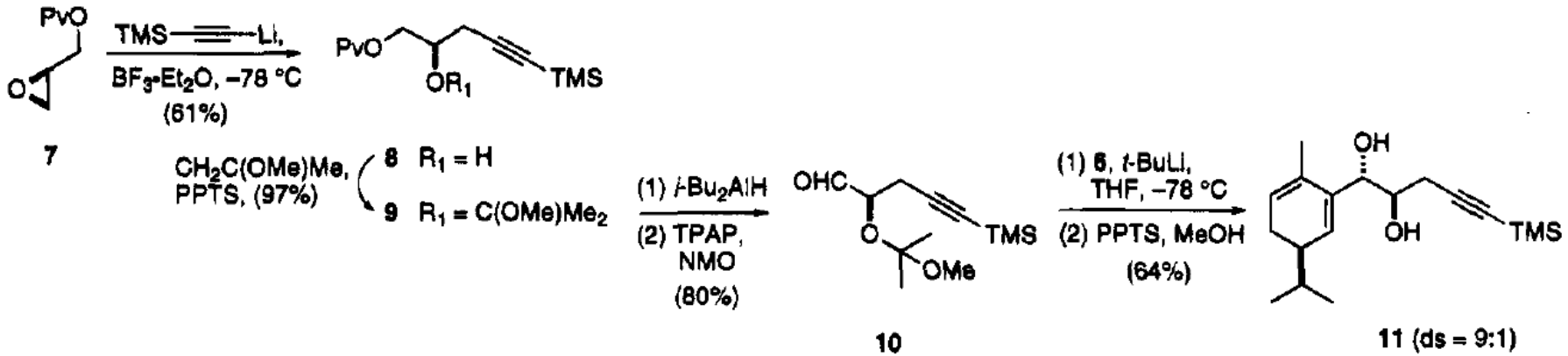




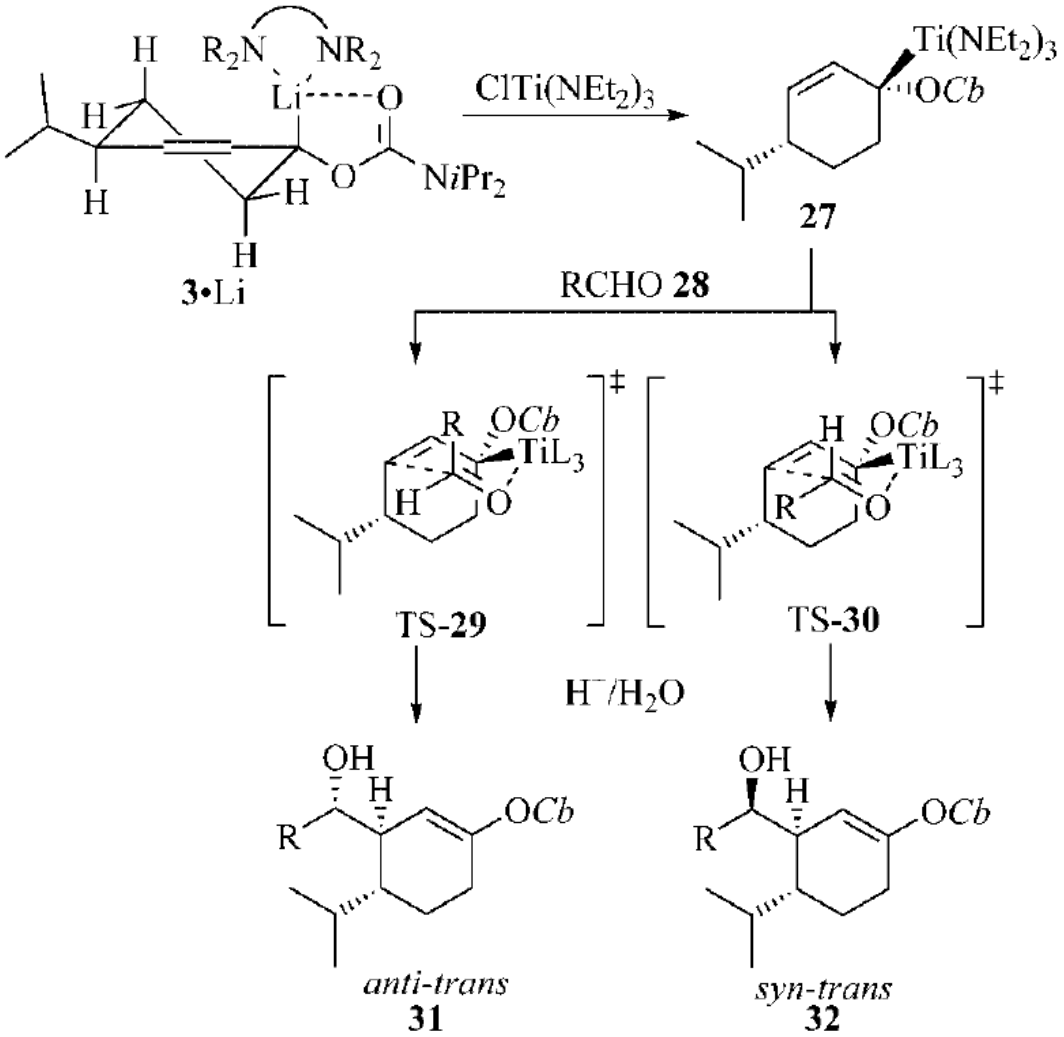
Preparation of the Starting Materials







Homoaldol Reaction



Endgame for L. A. Paquette's approach