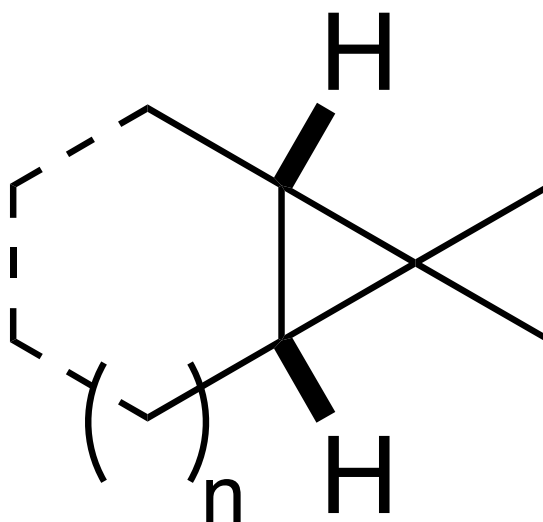
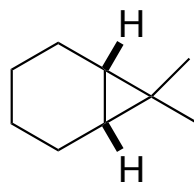


*gem*-dimethylcyclopropane  
containing Natural Products and  
their Total Syntheses



Journal Club  
Nick Tappin  
Renaud Group  
22/10/15

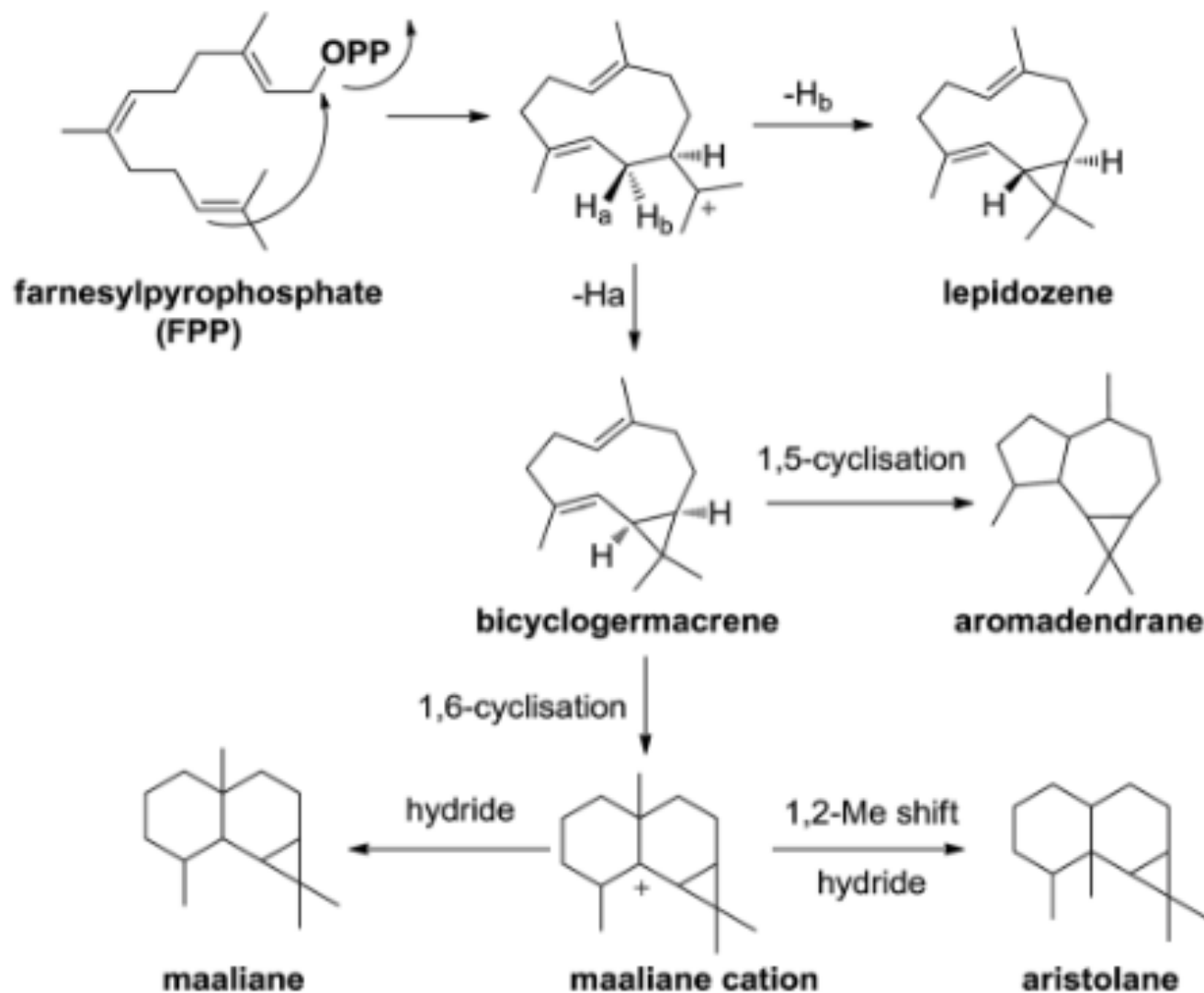
fused cyclohexyl-*gem*-dimethylcyclopropanes



dimethylbicyclo[4.1.0]heptane

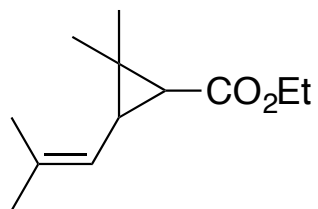
- 115 substance hits for natural product isolations in Reaxys search for this structural motif
- 30 of which have pharmacological data
- 15-20 of which have appreciable synthetic complexity (enough to interest a synthetic chemist!)
- *but*, the cyclohexyl unit is a smaller subclass: many cycloheptane derivatives, and medium sized rings

# Proposed common biosynthetic pathway for sesquiterpenes containing a *gem*-dimethylcyclopropane



Common strategy: to buy in *gem*-dimethylcyclopropane from starting point of synthesis

Ethyl chrysanthemate

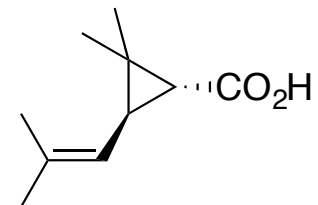


mix of *cis*/*trans*  
£160/kg

problem...

no physical method to  
separate *cis*/*trans*

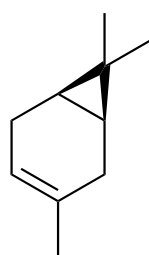
Natural (+)-*trans*-chrysanthemic acid



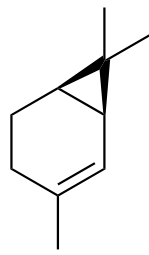
£260/1g

chiral pool not an option  
for diastereoselective synthesis

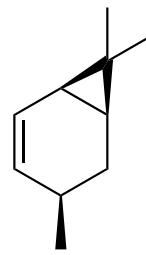
Other *gem*-dimethylcyclopropane chiral pool precursors



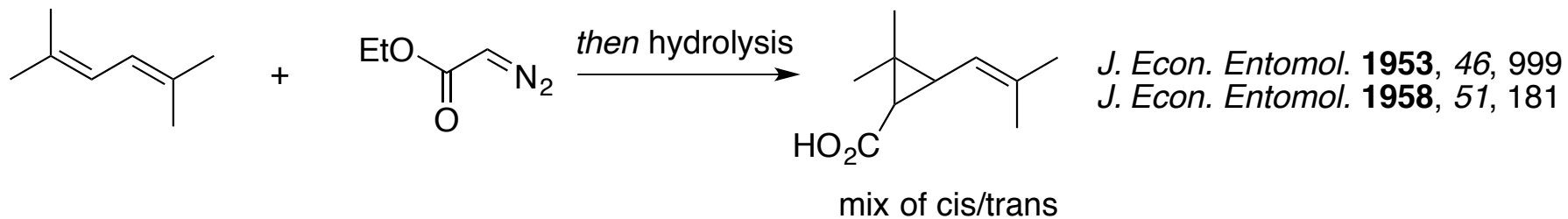
(+)-3-carene



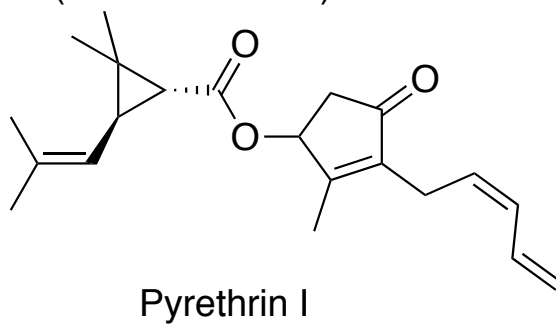
(+)-2-carene



*cis*-4-carene

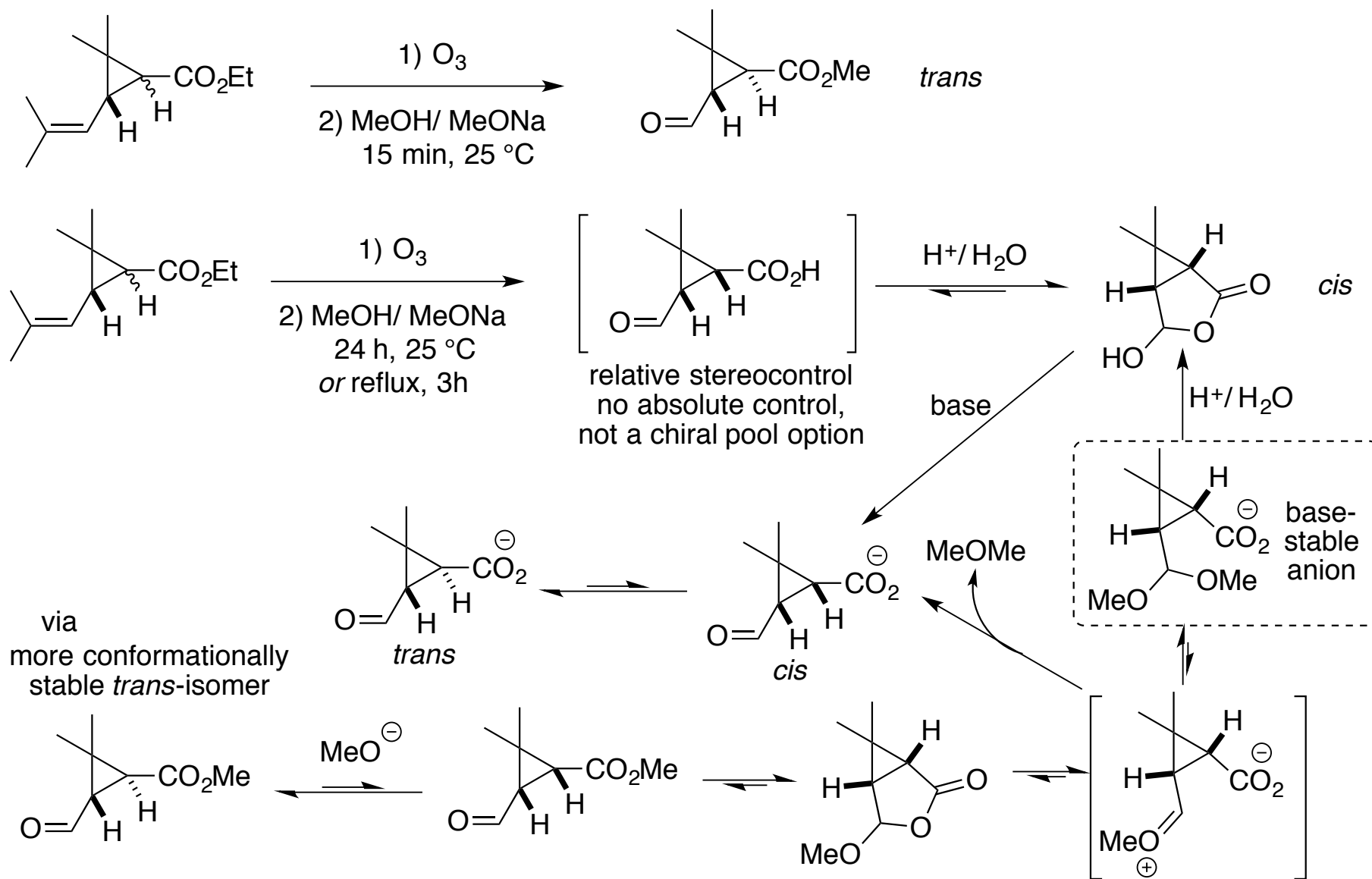


Has received considerable synthetic interest (1970s to 1980s) due to the insecticides pyrethrins which have a very low toxicity to mammals and birds

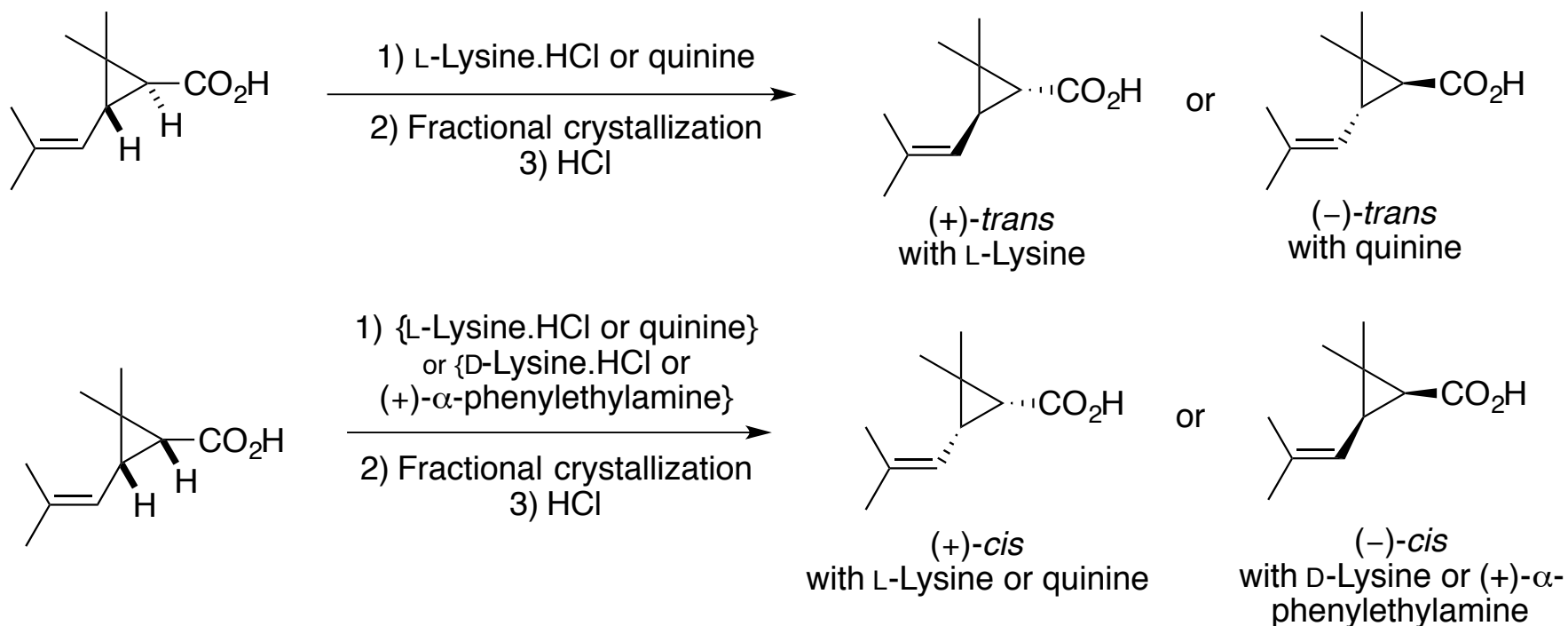


A chemical solution to cis/ trans mix...

For a discussion of exact mechanism see: *J. Org. Chem.*, **1978**, *43*, 4323-4328. For original synthetic work: *Tetrahedron Lett.* **1976**, 3911; *Tetrahedron Lett.* **1976**, 3915; *J. Org. Chem.* **1976**, *41*, 885; *J. Org. Chem.* **1977**, *42*, 2108.



*Agr. Biol. Chem.* **1971**, *35*, 1984-1985



But how to separate *cis*- from *trans*-ethyl chrysanthemate?  
Chemical synthesis via aldehyde and basic transesterification.

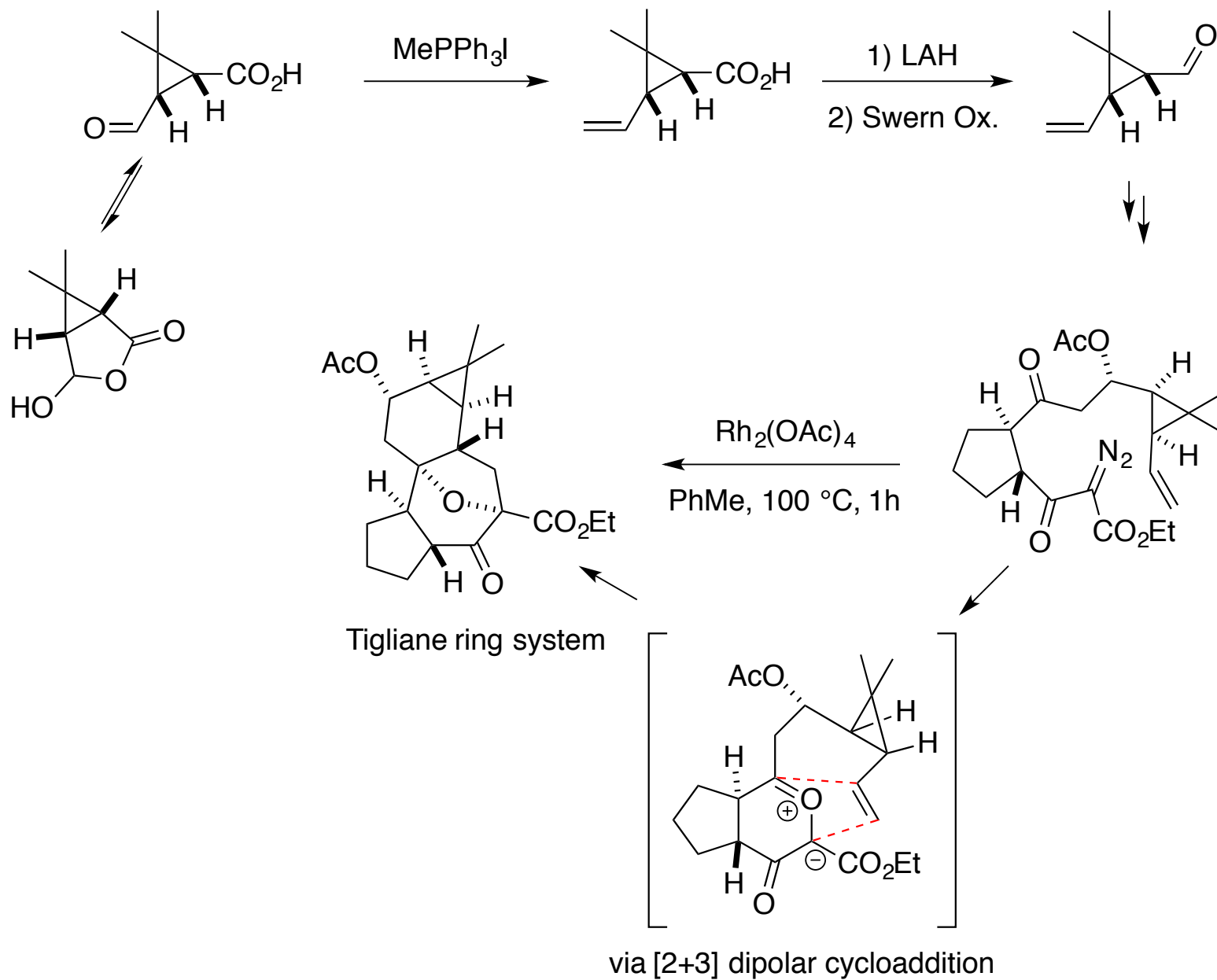
A recent solution for *trans*-isomers...  
*Chem Eur. J.* **2010**, *16*, 9789-9795



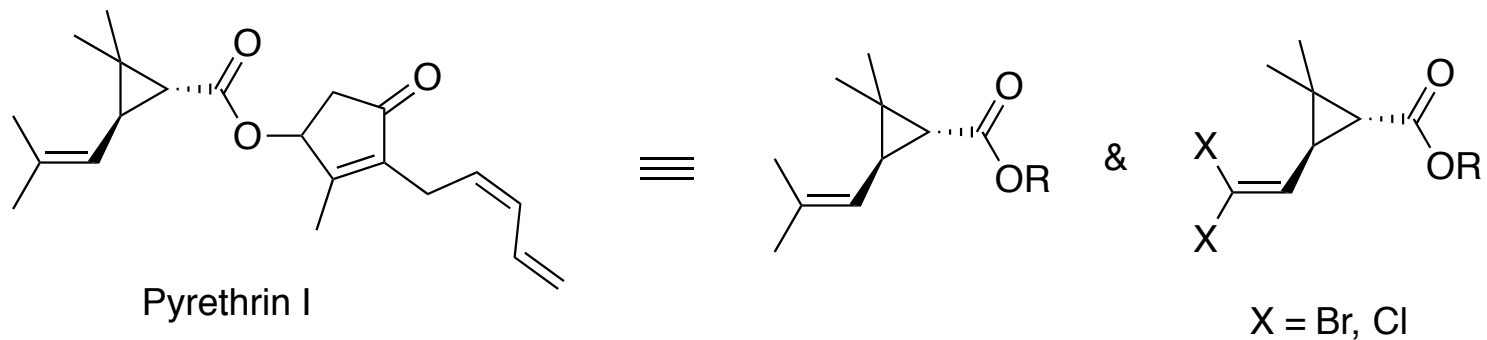
no enantiopure compound available from purely synthetic methods: a resolution with chiral amine is always needed

This method was applied to the total synthesis of the tigliane skeleton

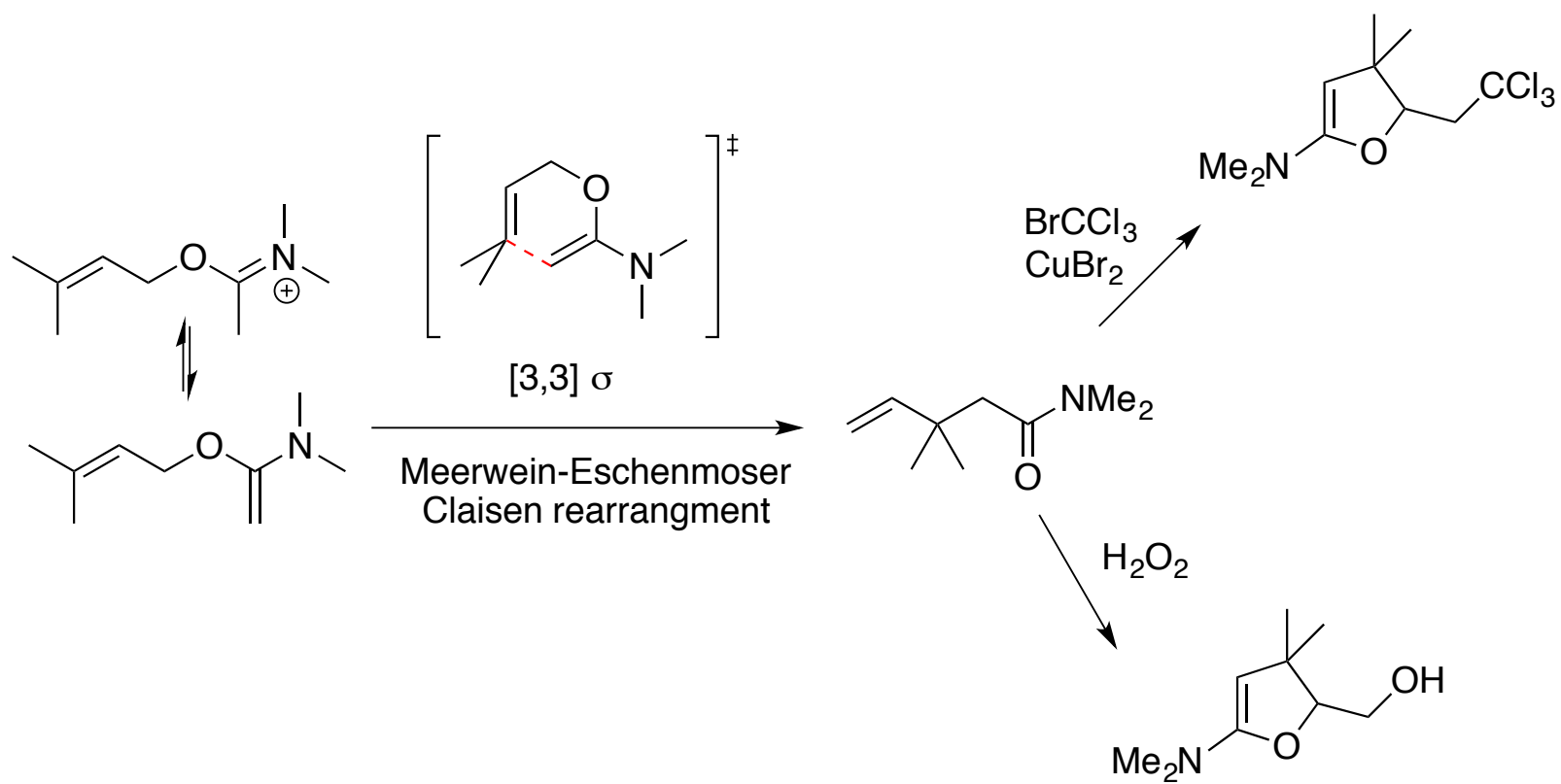
Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.*, **1993**, *53*, 7635-7637.

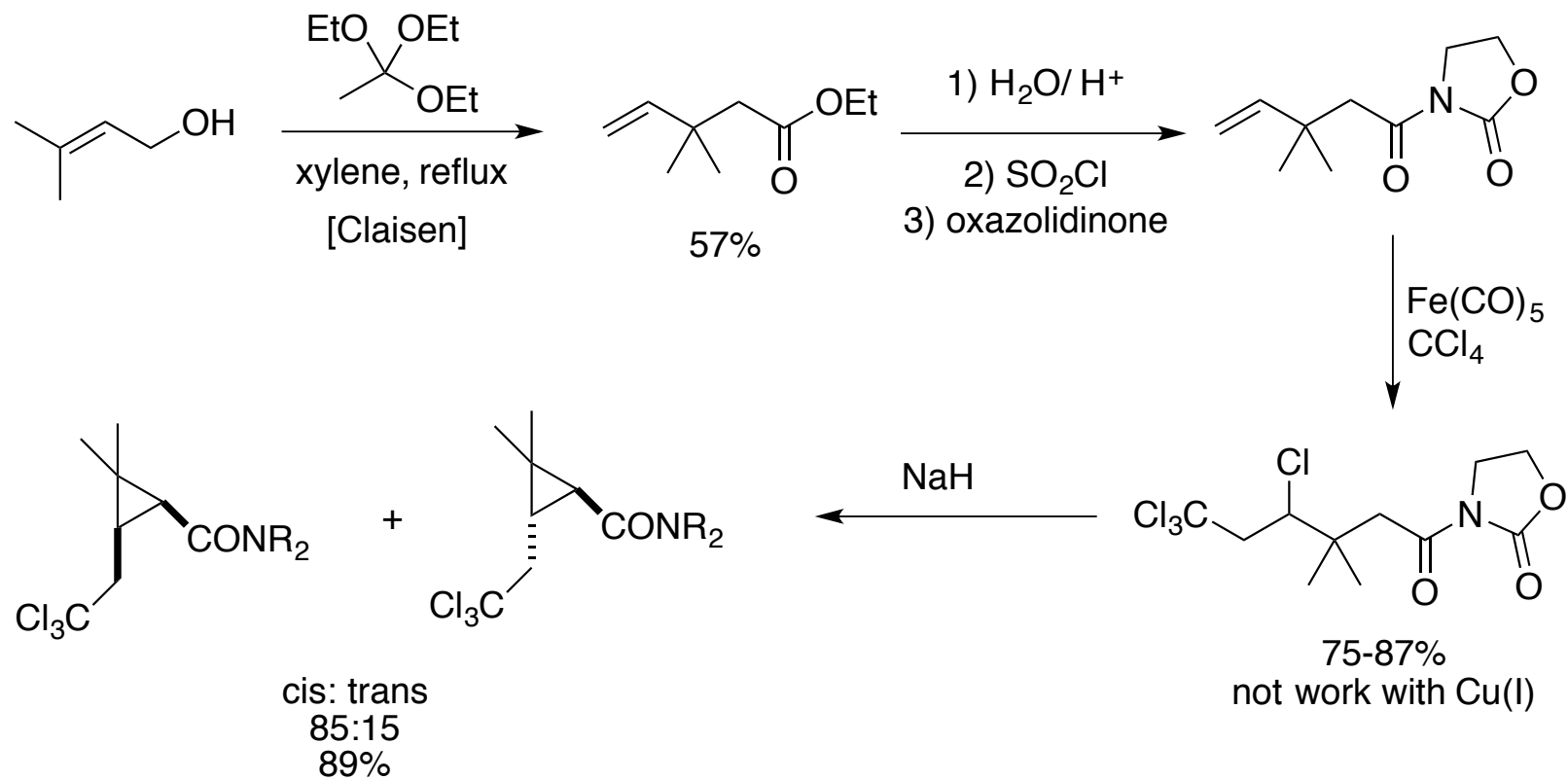




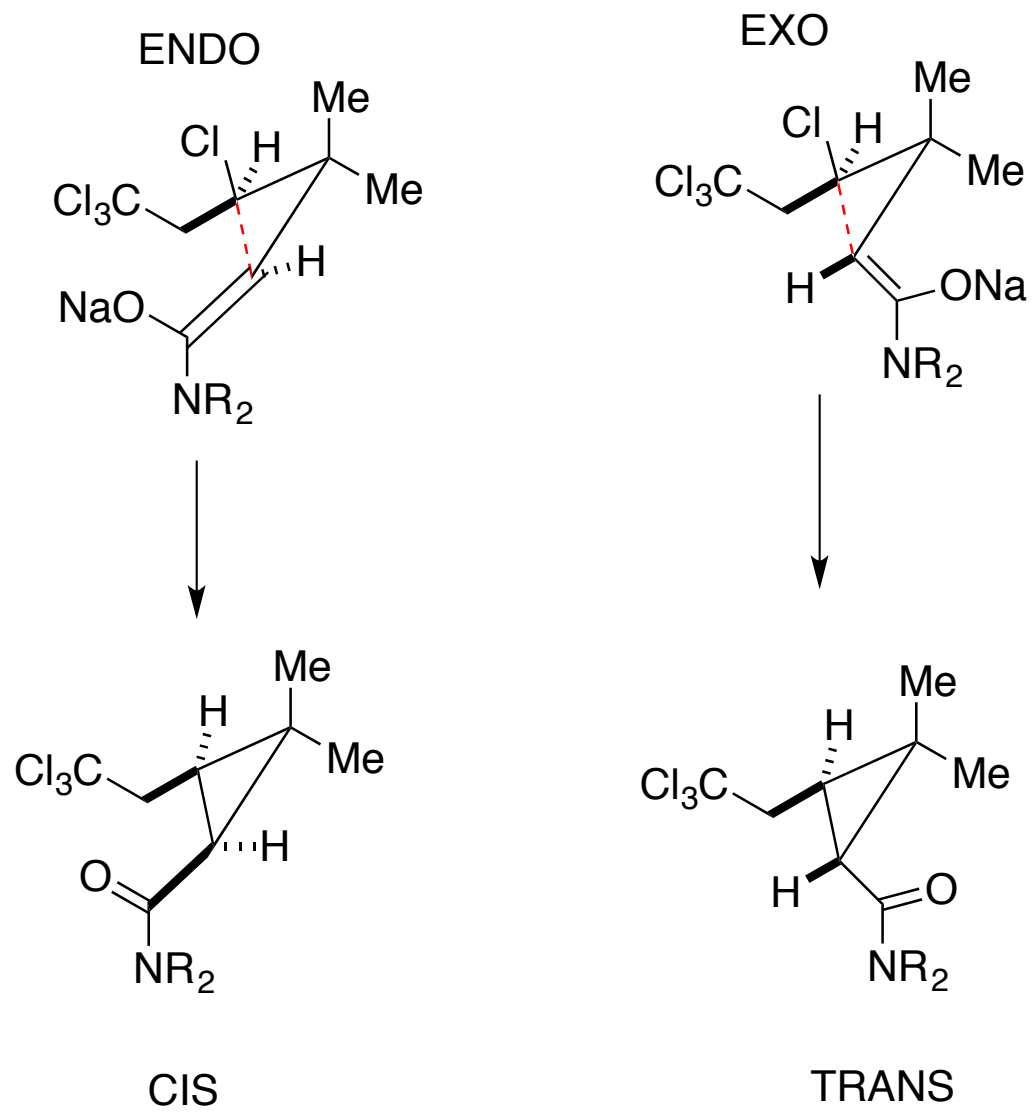


JOC, 1984, 49, 2682-2687  
 JOC, 1986, 51, 5429-5433

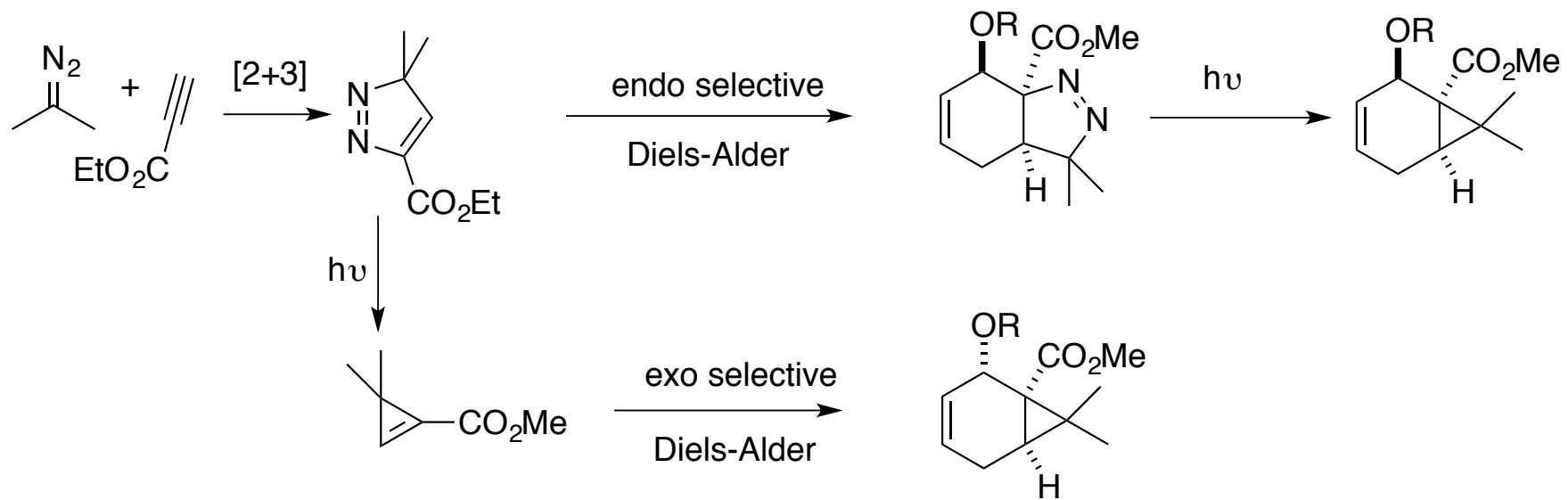




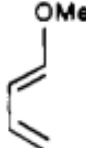
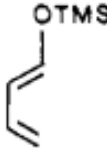
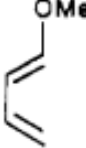

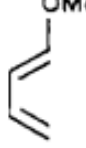
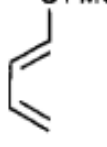
From cis-enolate



JACS, 1989. 111, 4125-4126

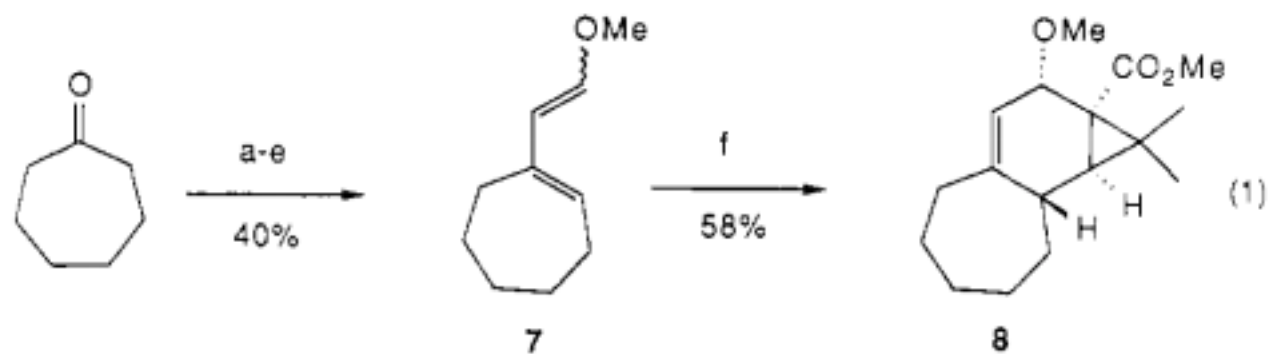


**Table I.** Cycloadditions of Cyclopropane and Pyrazole Addends with Dienes

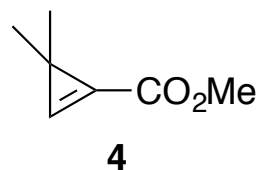
entry	diene	dienophile	pressure (kbar)	exo:endo	% yield of cyclopropane <sup>a</sup>
1		<b>3a</b>	10	1:22	92 <sup>b,c</sup>
2		<b>3a</b>	10	1:5	89 <sup>b,c</sup>
3		<b>3b</b>	10	1:19	98 <sup>b,c</sup>
4		<b>3b</b>	10	1:50	92 <sup>b,c</sup>
5		<b>4</b>	10	50:1	81 <sup>c</sup>
6		<b>4</b>	10	50:1	78 <sup>c</sup>

<sup>a</sup>All new compounds reported herein exhibited satisfactory spectral (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR), analytical, and/or high resolution mass spectral characteristics. <sup>b</sup>Overall yield for cycloaddition and quantitative photochemical nitrogen extrusion. <sup>c</sup>Yield of isolated, purified products.

**Scheme I<sup>a</sup>**



<sup>a</sup>(a) Tf<sub>2</sub>O, (*t*-Bu)<sub>2</sub>MeC<sub>5</sub>H<sub>5</sub>N;<sup>13</sup> (b) CO, MeOH, Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, Ph<sub>3</sub>P;<sup>14</sup> (c) Dibal; (d) Swern oxidation; (e) Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>OMe Cl<sup>-</sup>, *n*-BuLi; (f) 4, 6 kbar.



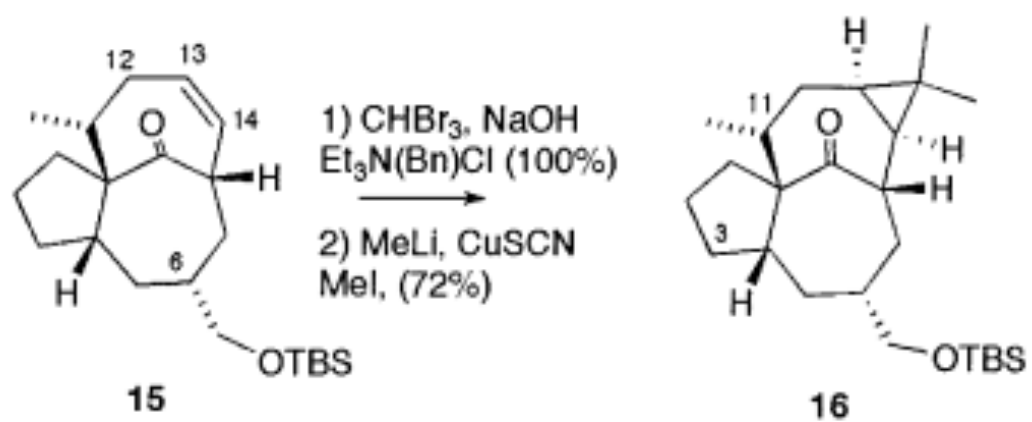
Application of this methodology to the total synthesis of phorbol and further examination of the unique stereochemical features of this chemistry are underway in our laboratory.

JOC, 2013, 78, 3342

**Scheme 1. Chiral Cyclopropenyl Ketones: Highly Reactive Dienophiles in Which the Cyclopropene Directs the Stereochemical Outcome**

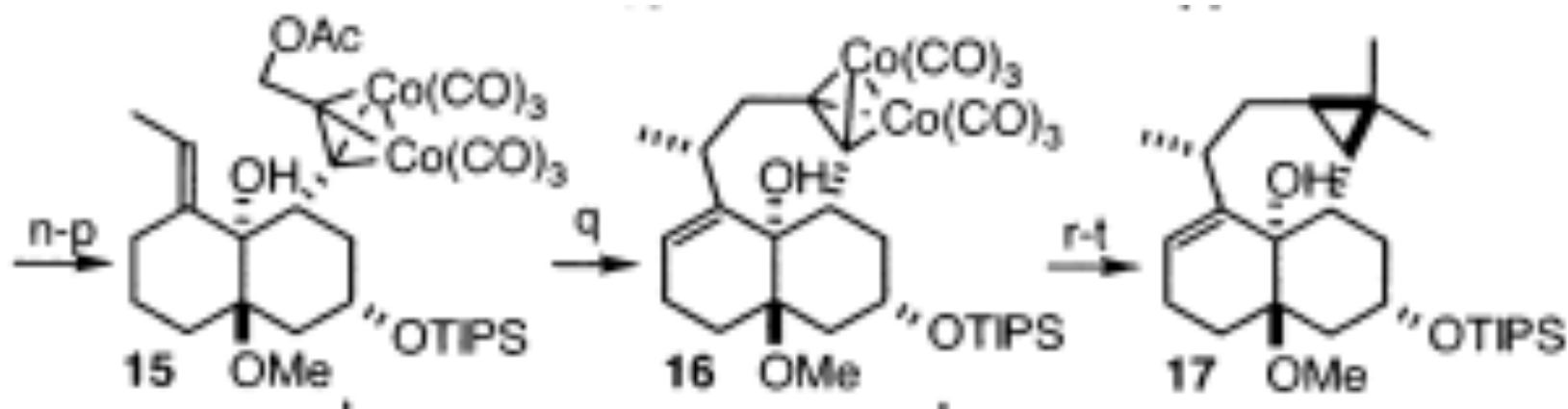


JACS, 2002, 124, 9726-9728,





JOC, 1997, 62, 3032;  
JACS, 2003, 125, 1498



CH<sub>2</sub>Cl<sub>2</sub> (99%); (p) Co<sub>2</sub>(CO)<sub>8</sub>, CH<sub>2</sub>Cl<sub>2</sub> (95%); (q) methylaluminum bis(2,6-dimethyl-4-nitrophenoxide) CH<sub>2</sub>Cl<sub>2</sub>; (r) Li, liq. NH<sub>3</sub> (67% in 2 steps); (s) CHBr<sub>3</sub>, NaOH, BnEt<sub>3</sub>NCl, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O (71%); (t) Me<sub>3</sub>CuLi<sub>2</sub>, ether, then MeI (95%); (u) TBHP, Ti(O<sup>i</sup>Pr)<sub>4</sub>, MS 4A, CH<sub>2</sub>Cl<sub>2</sub>; (v) Me<sub>3</sub>Al, CH<sub>2</sub>Cl<sub>2</sub> (76% in 2 steps).

# Conclusions

- May install gem-dimethylcyclopropane via SM purchase or synthetic method
  - Methods:
    - rely on inherent diastereoselectivity (not enantio)
    - Numerous operations
    - For cyclohexyl, may use an elegant D-A approach
  - Starting material
    - Carene derivatives expensive
    - Chysenthamate derivatives tedious but well described