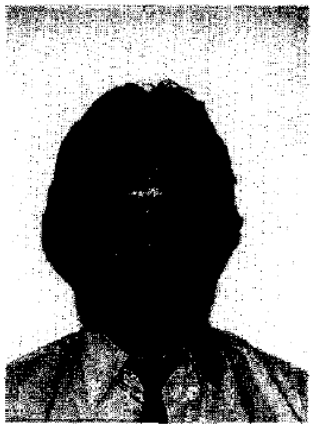
Synthesis of Clavirolide C and Other Dolabellane Diterpenes

Alex Predeus

March 6, 2009

Literature Used

- Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130(39)*, 12904 – 12906;
- Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118(5)*, 1229 – 1230;
- Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127(40)*, 13813 – 13815;
- Rodriguez, A. D.; Gonzalez, E.; Ramirez, C. *Tetrahedron*, **1998**, *54*, 11683 – 11729.



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Eduvigis González

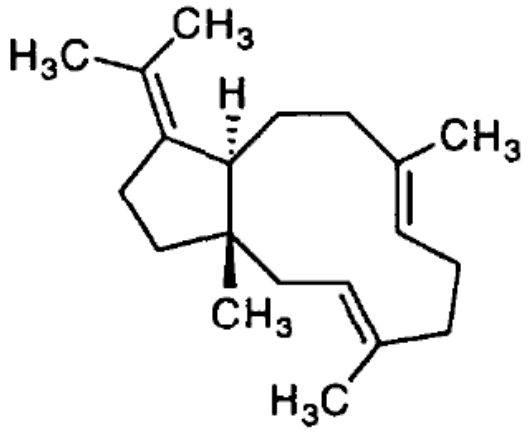
Catherine Ramírez

Have You Seen Us?

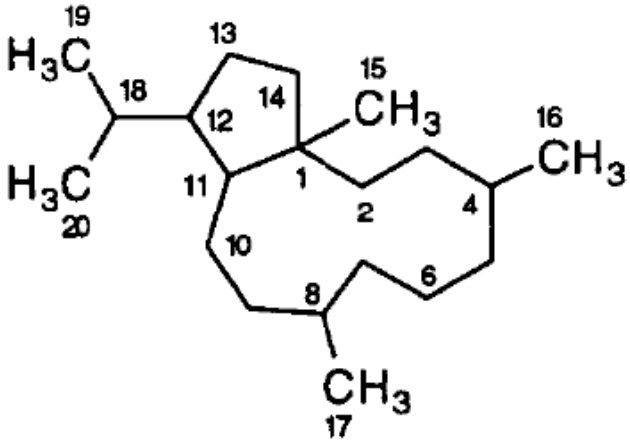
Marine Diterpenoids

- Virtually unknown by 1960
- Over 2000 compounds and 125 unique carbon skeletons by 2000
- Produced by mollusks, soft corals and algae
- Also found in terrestrial mold, moss, and higher plant species
- Possess wide array of biological properties, including cytotoxicity, antifungal, antibacterial, antiviral activities, etc.

Dolabellane Skeleton and Numbering



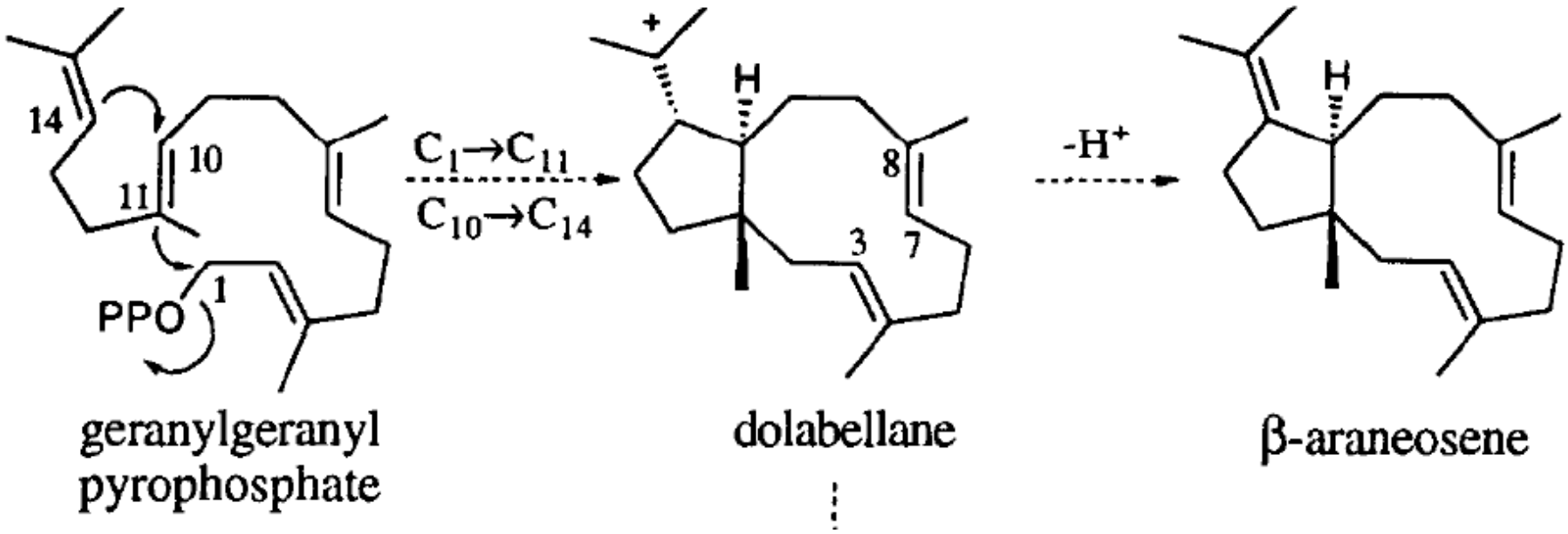
β-araneosene



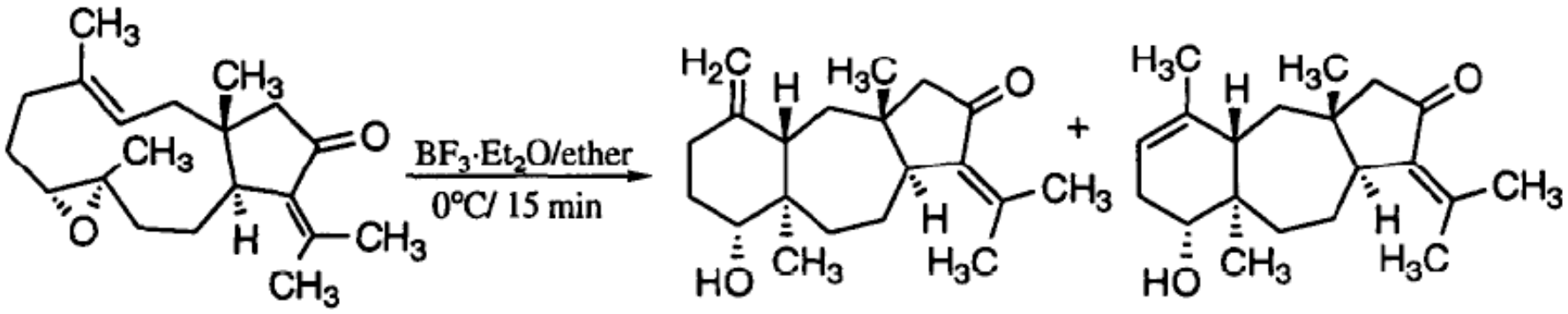
Dolabellane skeleton with numbering system

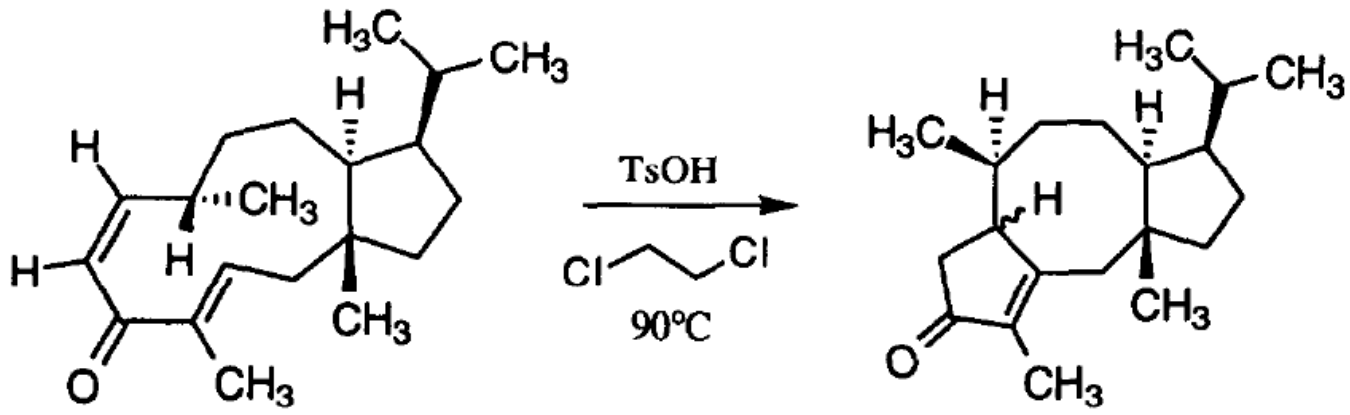
Dolabella Californica (sea hare)

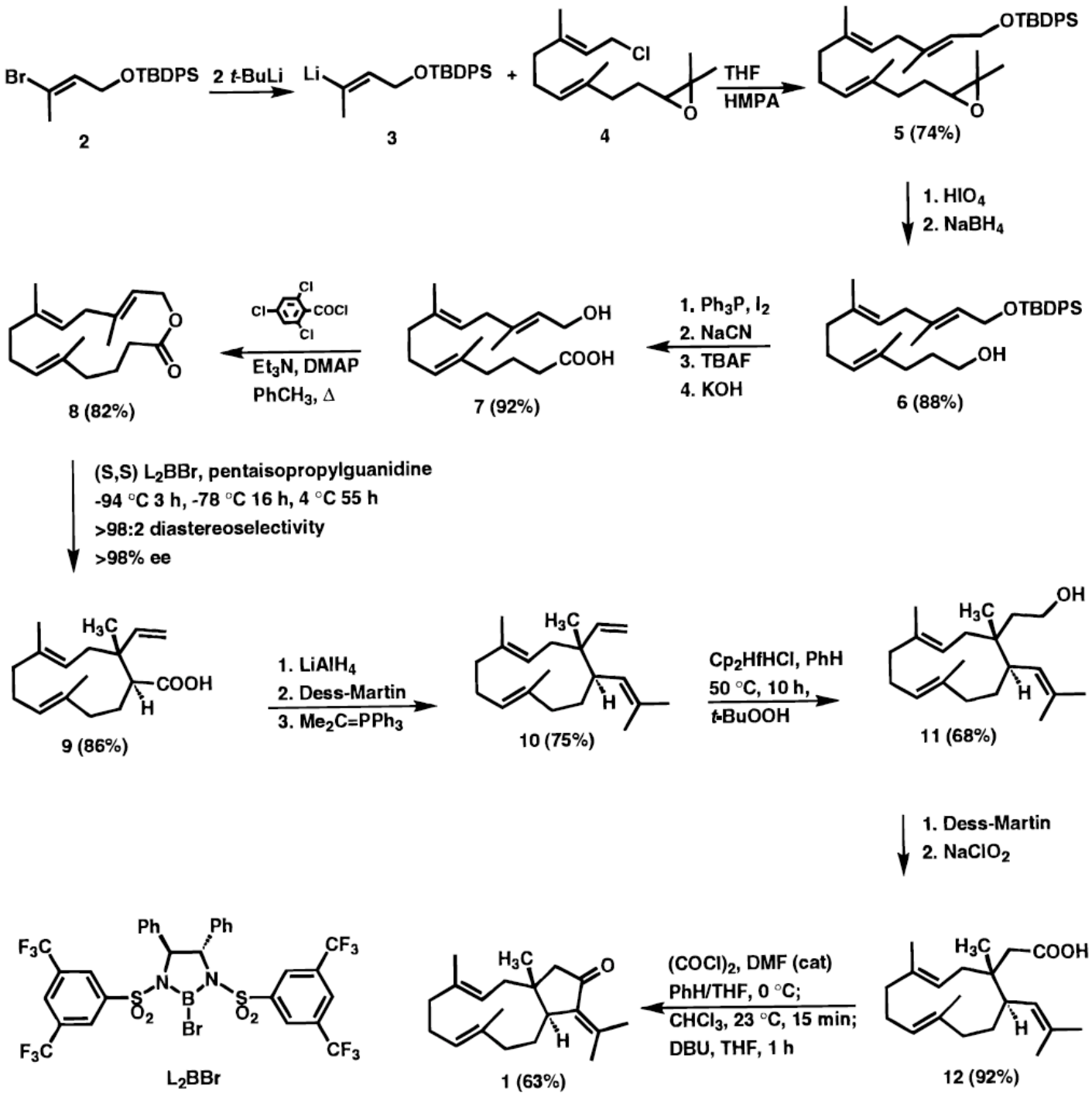
Proposed Dolabellane Biosynthesis



Dolabellane Skeleton: A Strained [9.3.0] System

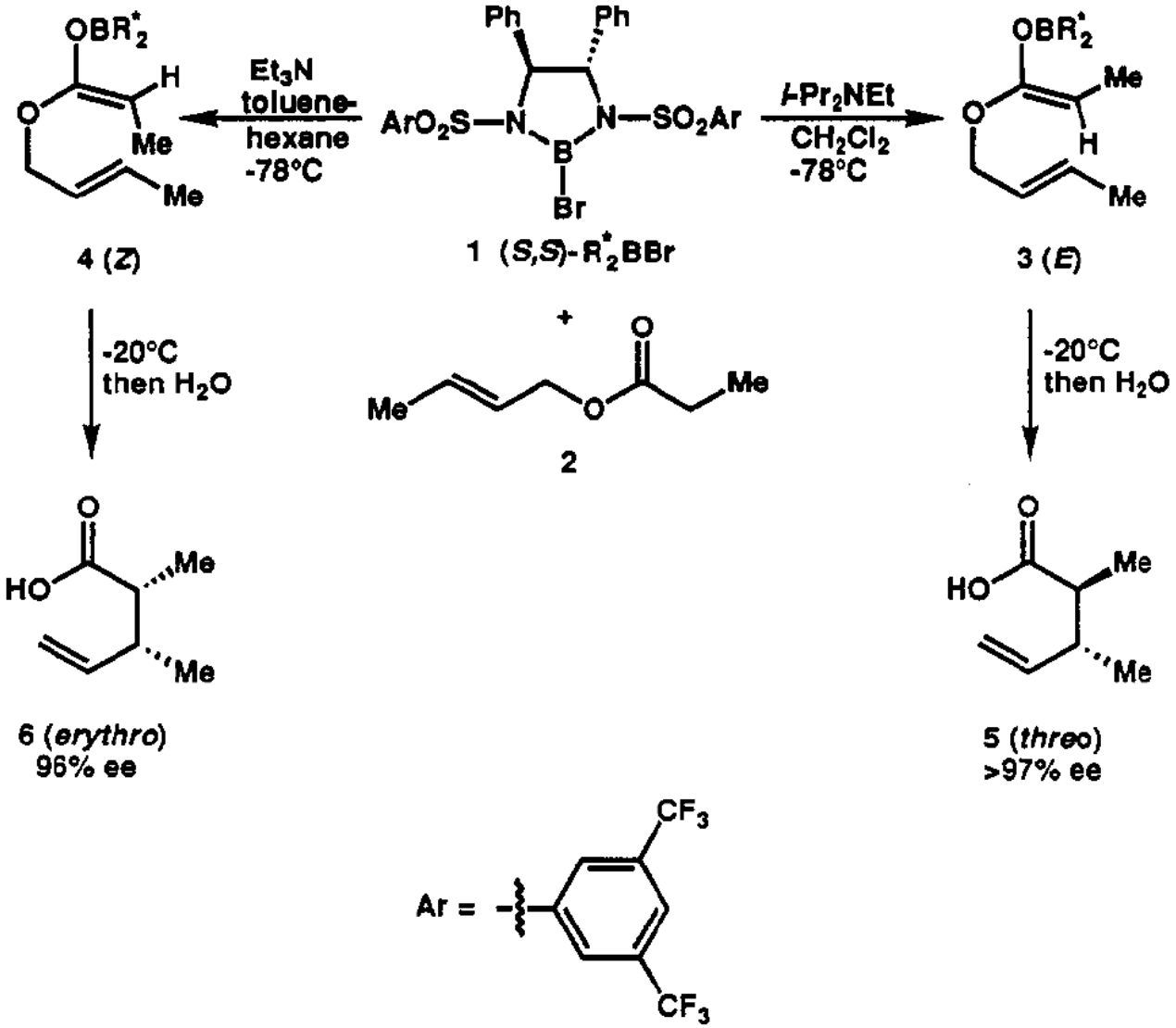




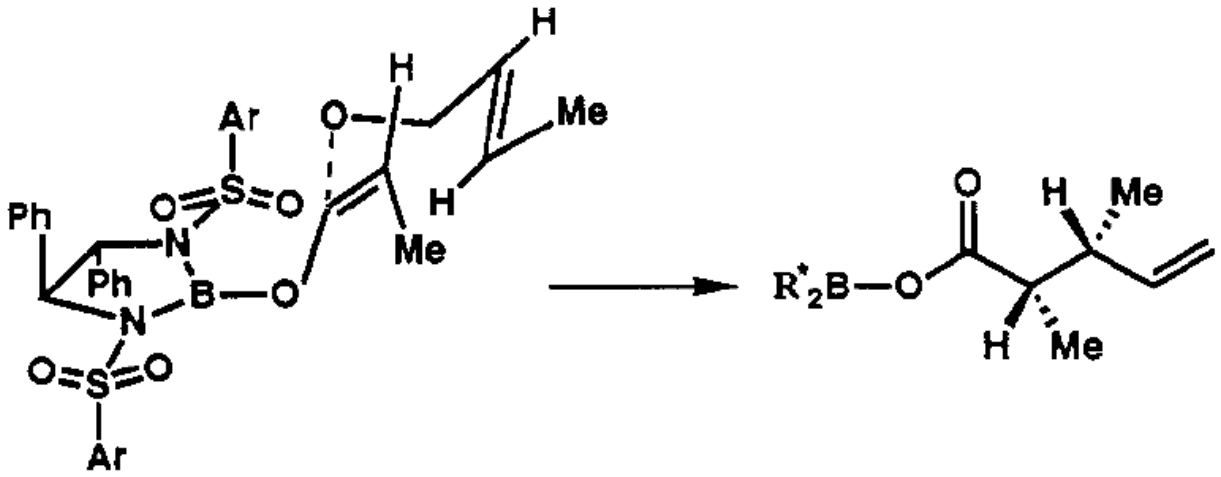


Corey-Kania Synthesis of Dolabella-trienone

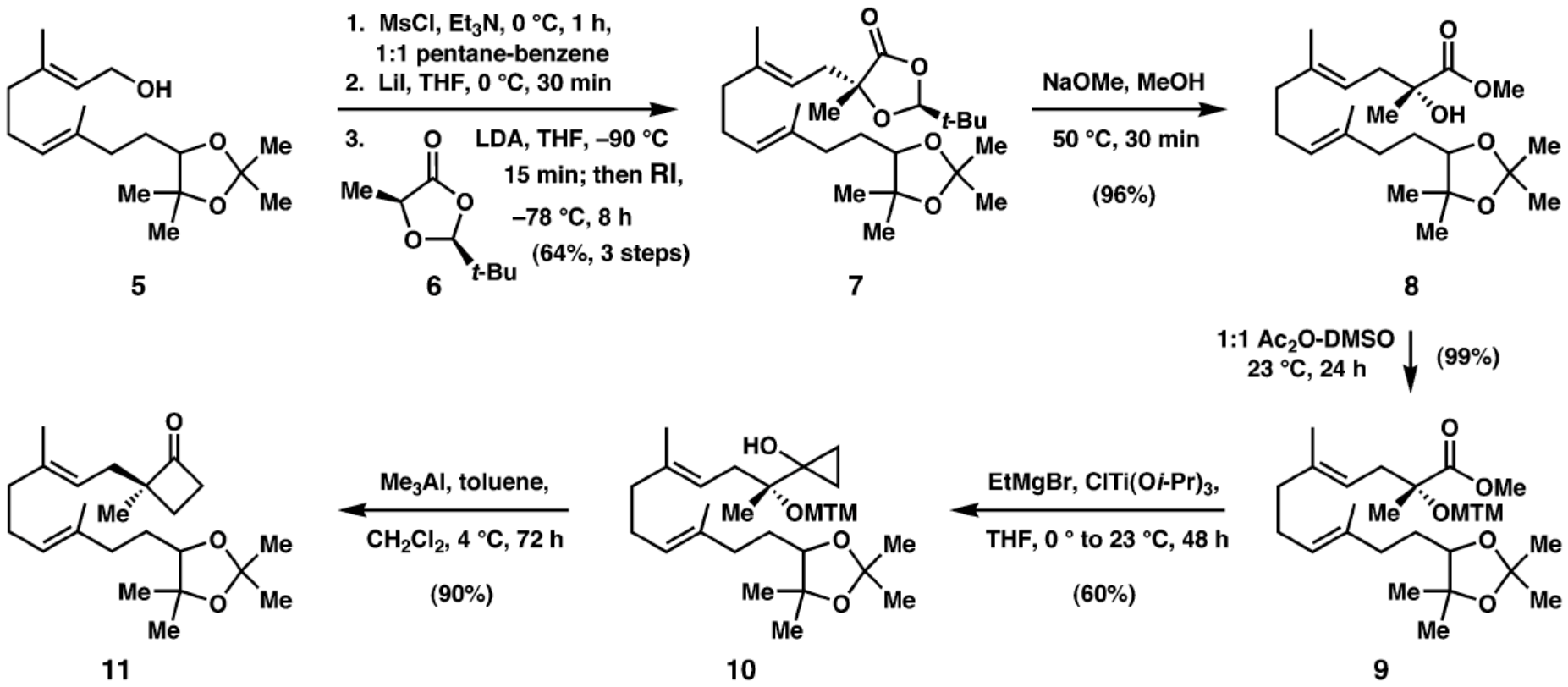
Enantioselective Ireland-Claisen Rearrangement



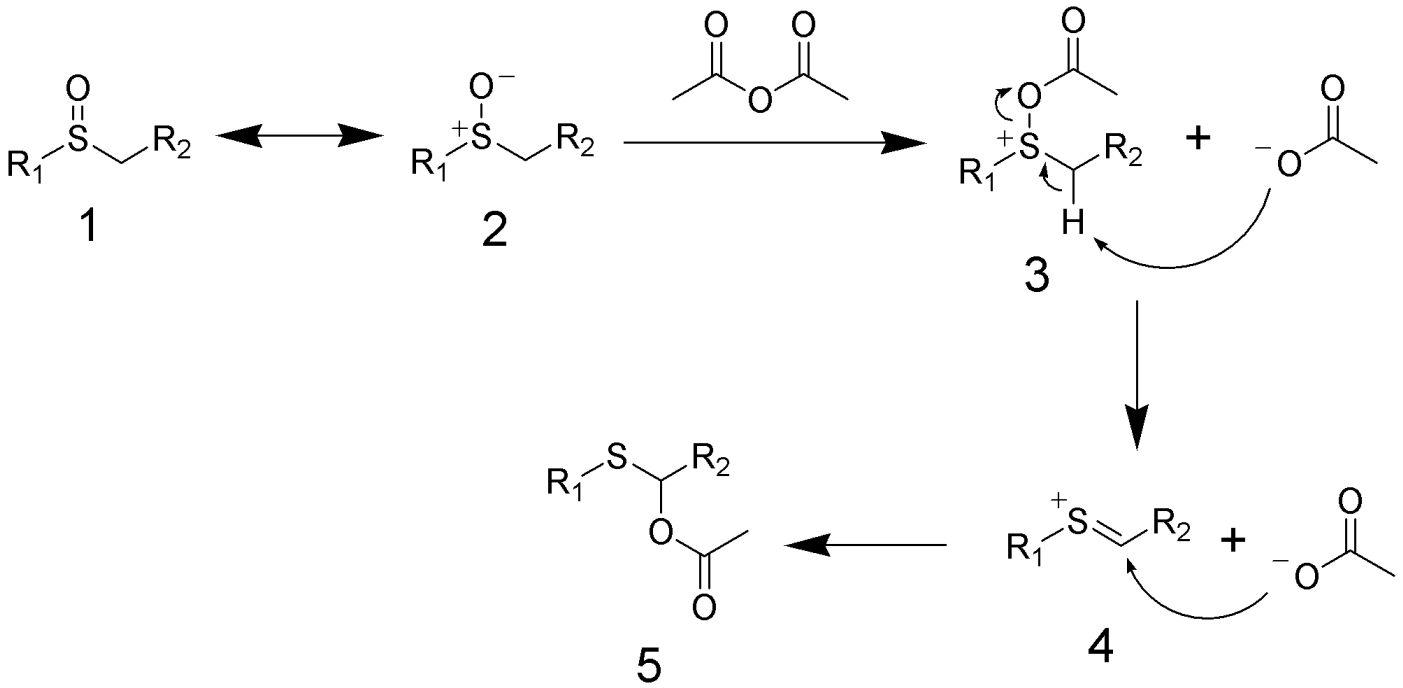
Suggested TS for Ireland-Claisen Rearrangement

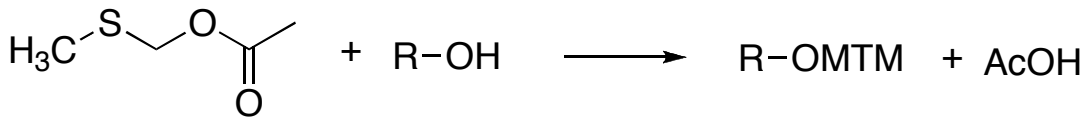


More Corey! The “Unconventional” Approach

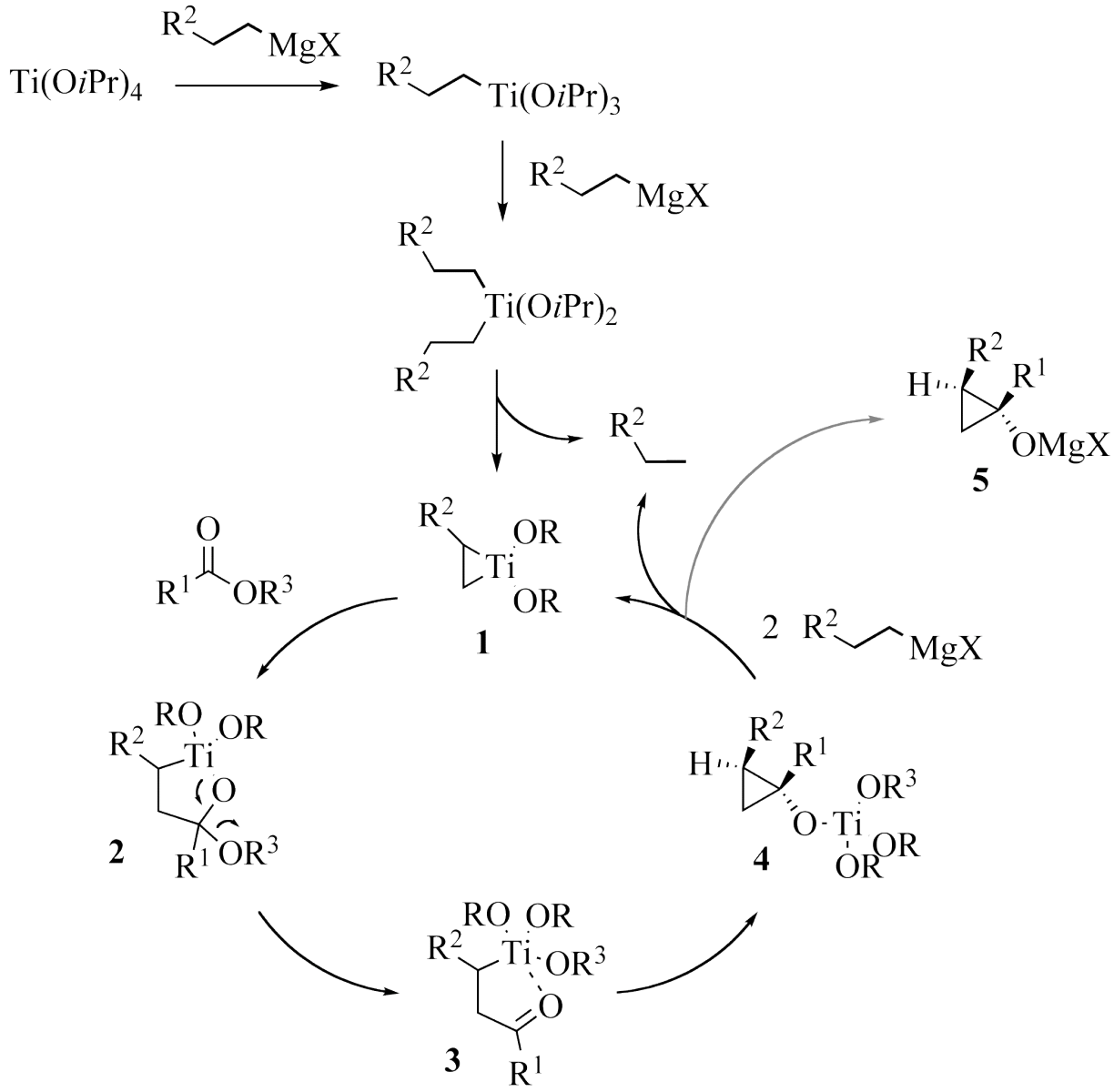


MTM Protection Involving Pummerer Rearrangement

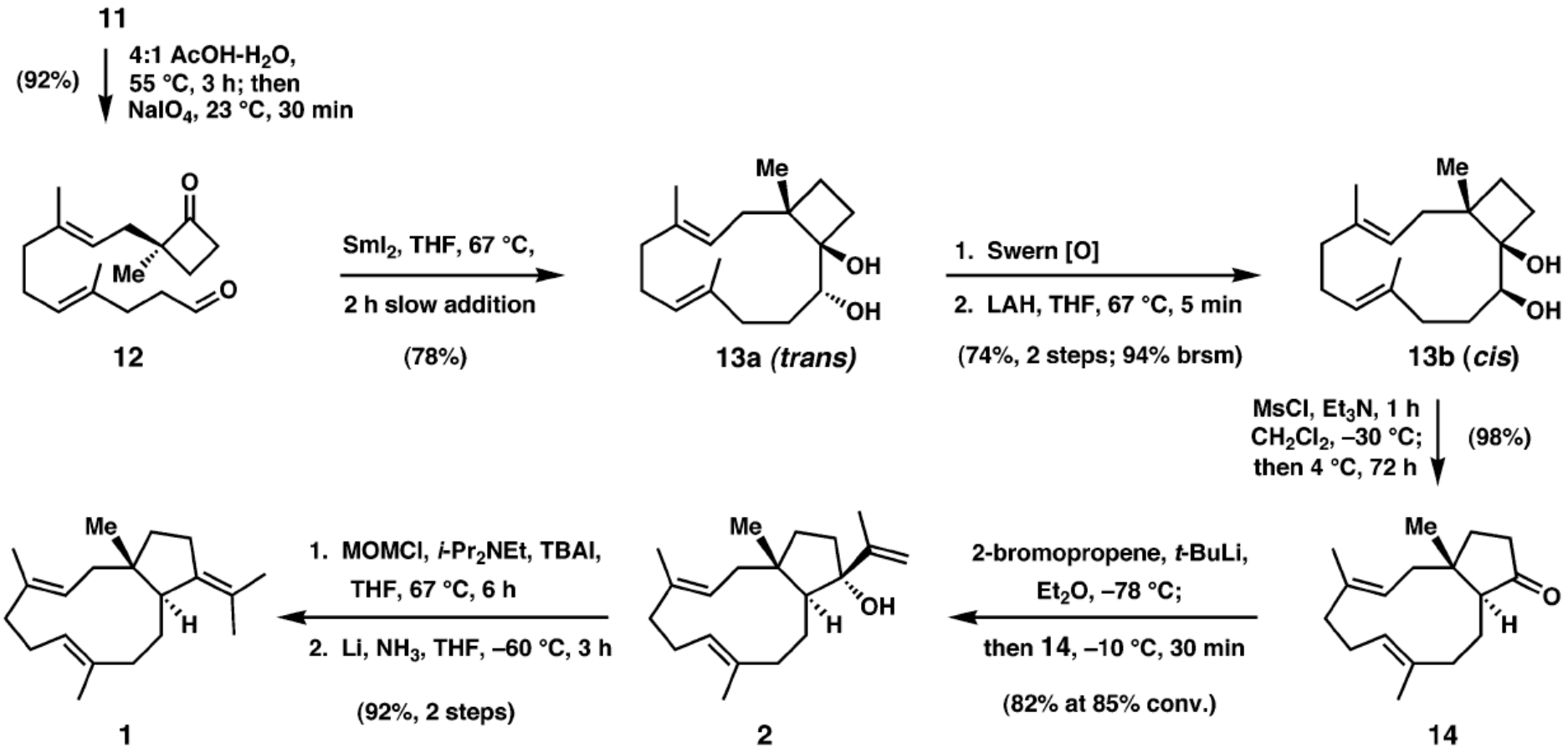




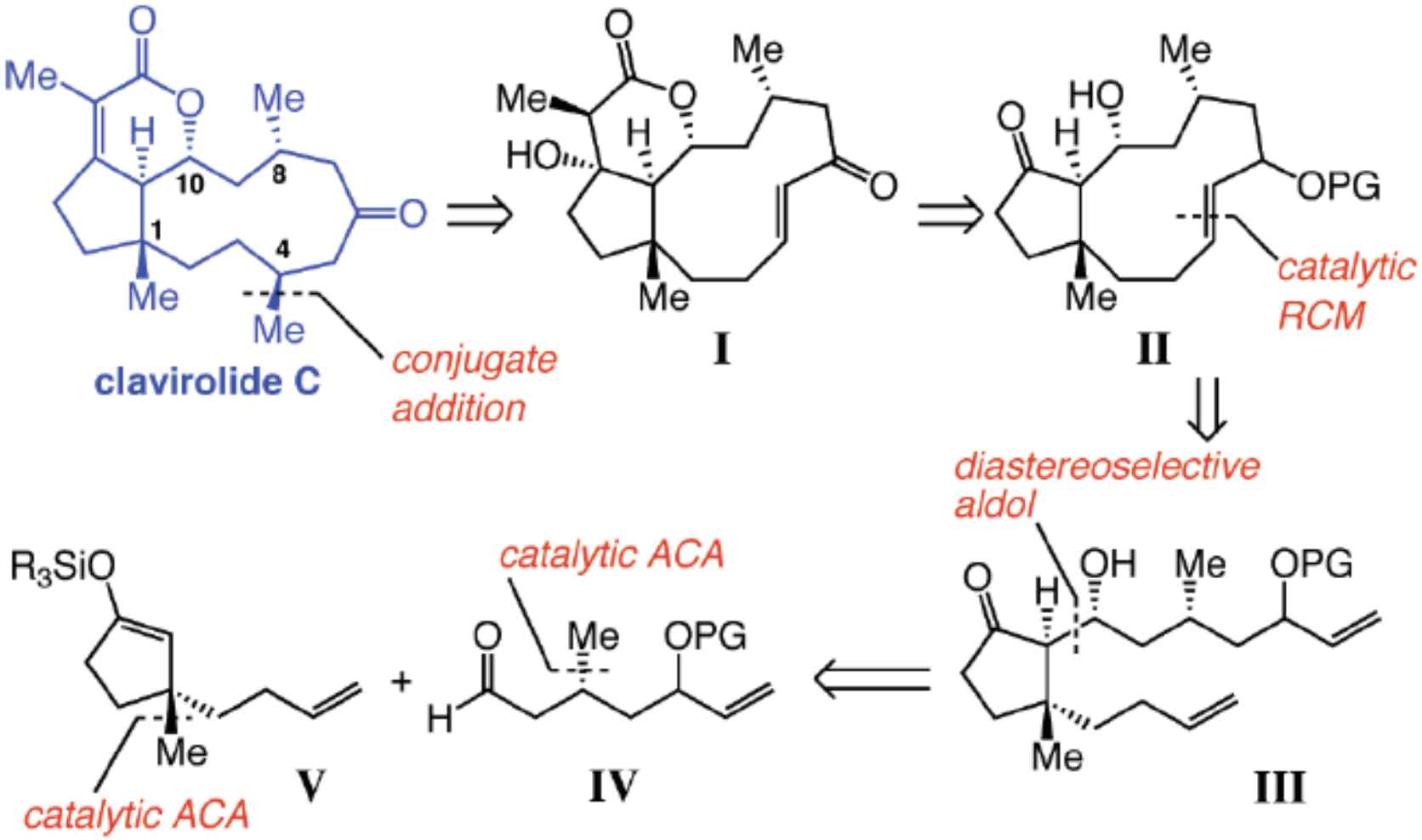
Kulinkovich Reaction



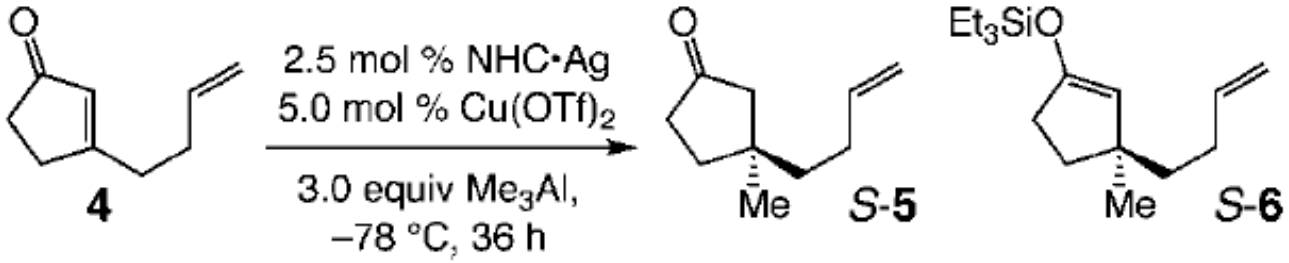
The Endgame: Isoedunol and β-Araneosene



Hoveyda's Synthesis: Retrosynthetic Analysis



Asymmetric Catalytic Addition I

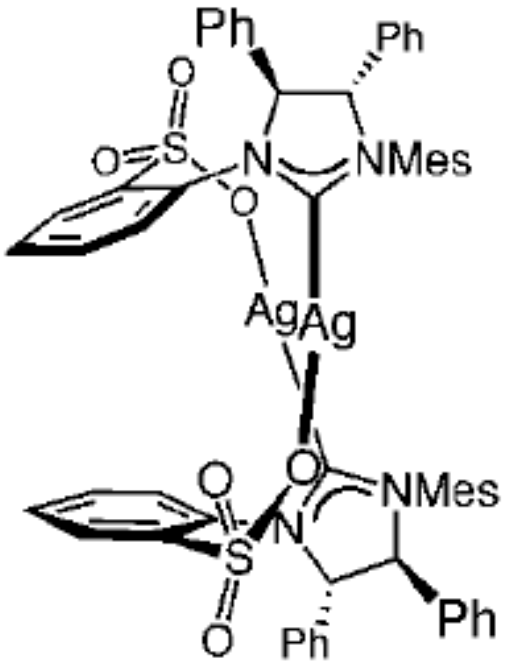


4 S-5 S-6

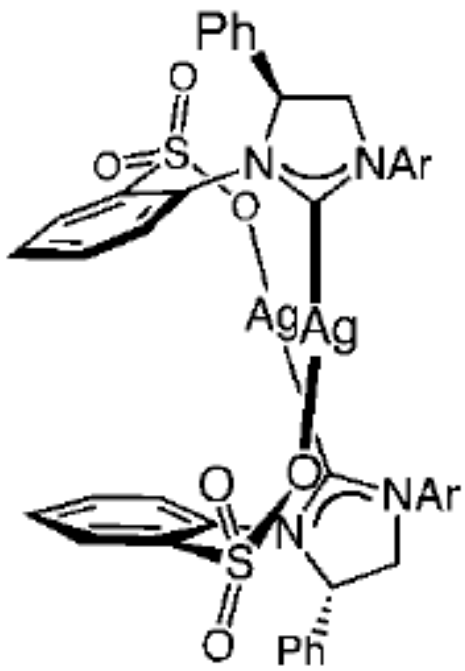
entry	NHC · Ag complex	product	conv (%);[b] yield (%)[c]	er[d]	ee (%)[d]
1	**1**	*S*-**5**	75; nd	73.5:26.5	47
2	**2**	*S*-**5**	97; nd	86:14	72
3	**3**	*S*-**5**	86; 80	93:7	86
4	**3**[e]	*S*-**6**	>98; 72	92:8	84

[a] Reactions performed under N_2 in THF. [b] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures. [c] Yields of purified products. [d] Determined by chiral GLC analysis; see the Supporting Information for details. [e] Reaction was performed with 3.75 mol % **3** and 7.5 mol % $Cu(OTf)_2$; 4.0 equiv of Et_3SiOTf were added after 36 h (−78 °C, 4 h); see the Supporting Information for details. nd = not determined.

ACA I Catalysts



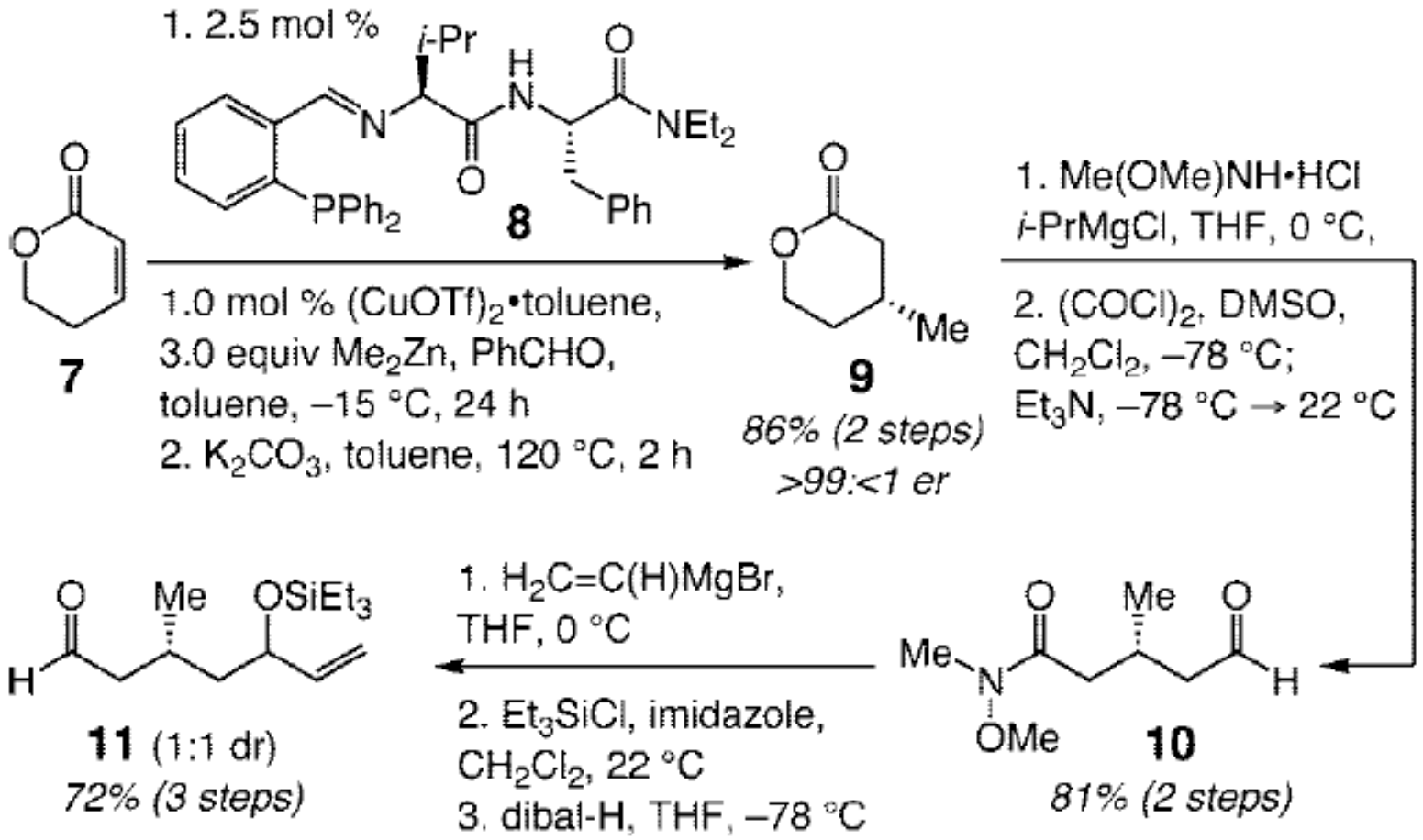
(*S*,*S*)-**1**

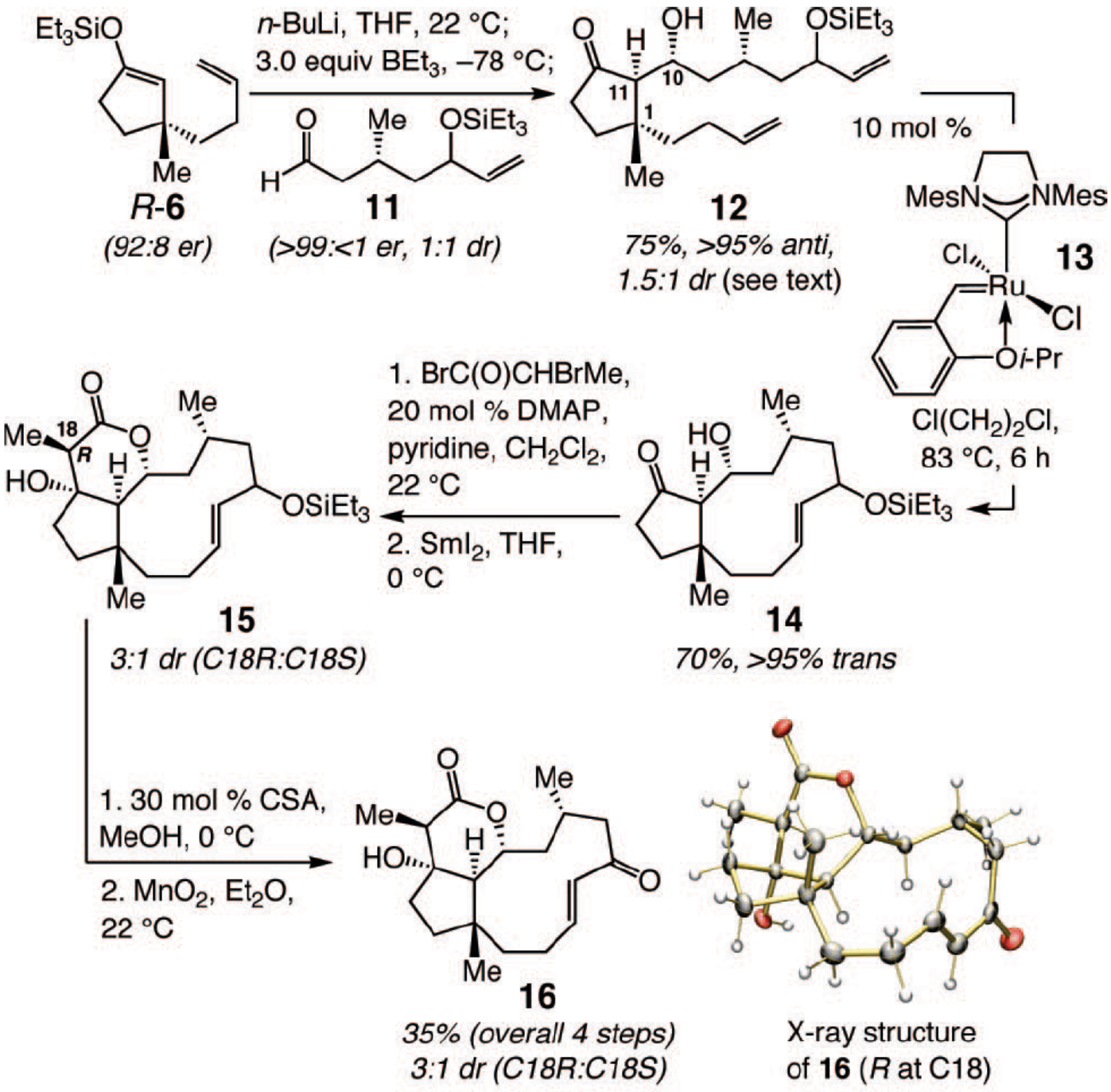


(*S*)-**2** Ar = 2,4,6-$(Me)_3C_6H_2$ (Mes)

(*S*)-**3** Ar = 2,6-$(Et)_2C_6H_3$

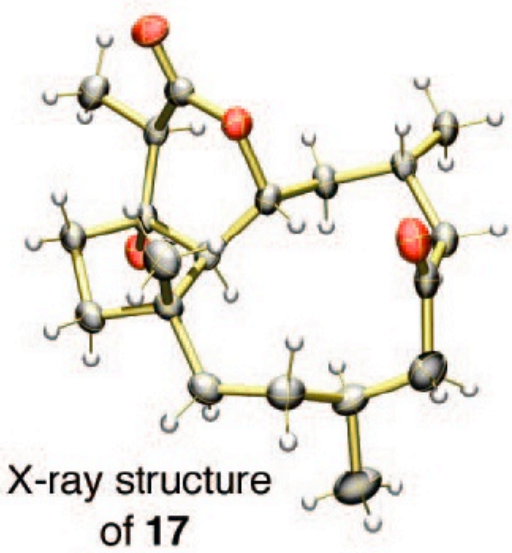
Asymmetric Catalytic Addition II



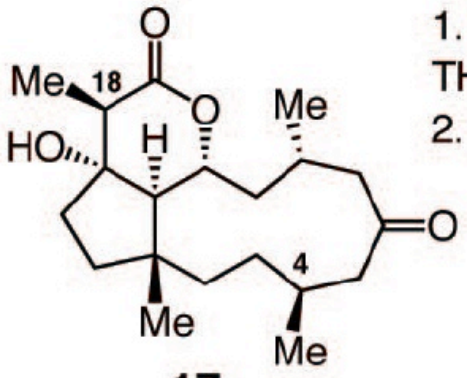


Metathesis, etc.

Hoveyda's Synthesis: Final Steps



X-ray structure of **17**

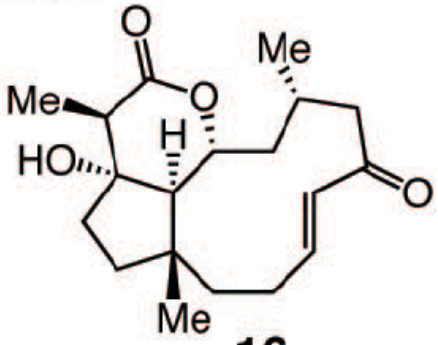


17

9:1 dr at C4

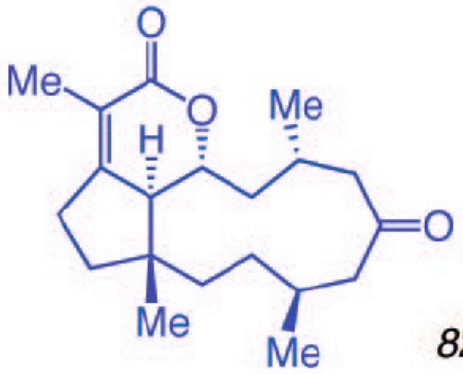
71% (>98% R at C18)

1. Me_2CuLi•LiI, TMSCl, THF, –78 °C
2. HF•pyr, THF, 0 °C



16

1. MsCl, Et_3N, CH_2Cl_2, 22 °C
2. DBU, MeOH, 55 °C



clavirolide C

82% (overall 2 steps)

This is The End…