Literature Report VII

Total Synthesis of Crinipellins

Reporter: Xiao-Yong Zhai
Checker: Huan-Ping Xie
Date: 2018-9-25

Lee, H.-Y. *et al. J. Am. Chem. Soc.* **2014**, *136*, 10274.
Yang, *Z. et al. Angew. Chem. Int. Ed*. **2018**, *57*, 8874.

CV of Prof. Zhen Yang

Zhen Yang

Background:

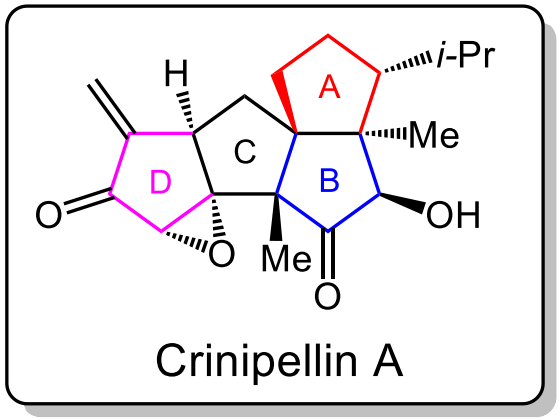
- **1978-1986** B.S. & M.S., Shenyang Pharmaceutical University
- **1989-1992** Ph.D., The Chinese University of Hong Kong
- **1992-1995** Postdoctoral, Scripps Research Institute
- **1995-1998** Assistant Professor, Scripps Research Institute
- **1998-2001** Institute Fellow, Harvard University
- **2001-present** Professor, Peking University

Research:

➢ Developing novel synthetic methodologies and strategies, then applying them to the syntheses of complex natural products.

Contents

Introduction



Crinipellin A

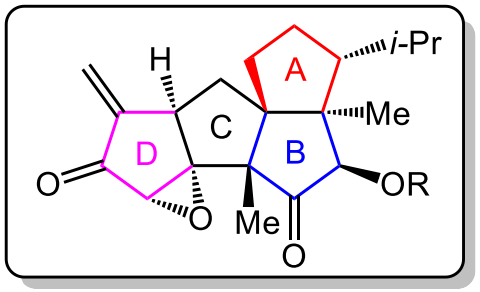
Crinipellis

- Isolated from *Crinipellis stipitaria* in 1979;
- Exhibiting antibiotic activities;
- Inhibiting the syntheses of DNA, RNA, and proteins in Ehrlich carcinoma cells;
- A unique tetraquinane core, eight stereogenic centers, three contiguous quaternary carbon atoms.

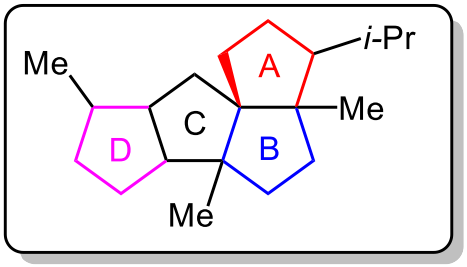
Steglich, W. J. *et al. Antibiot.* **1979**, *32*, 130.

Introduction

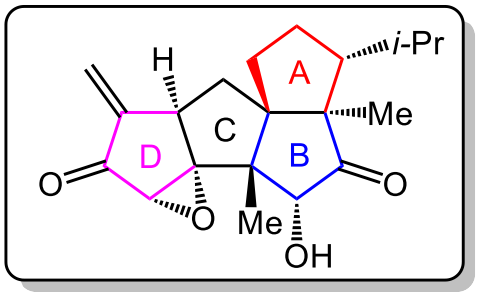
Selected tetraquinane crinipellins



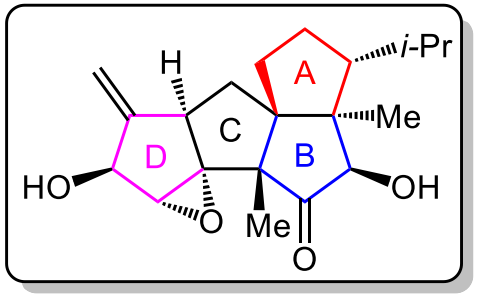
Crinipellin A (R = H)
Crinipellin A acetate (R = Ac)



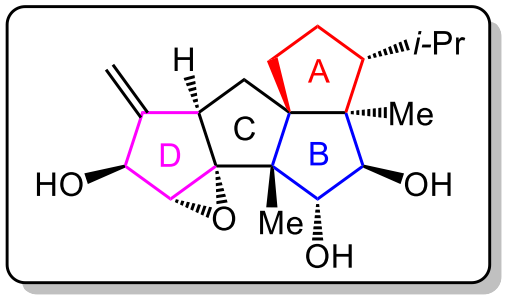
Tetracyclic core of crinipellins



Crinipellin B

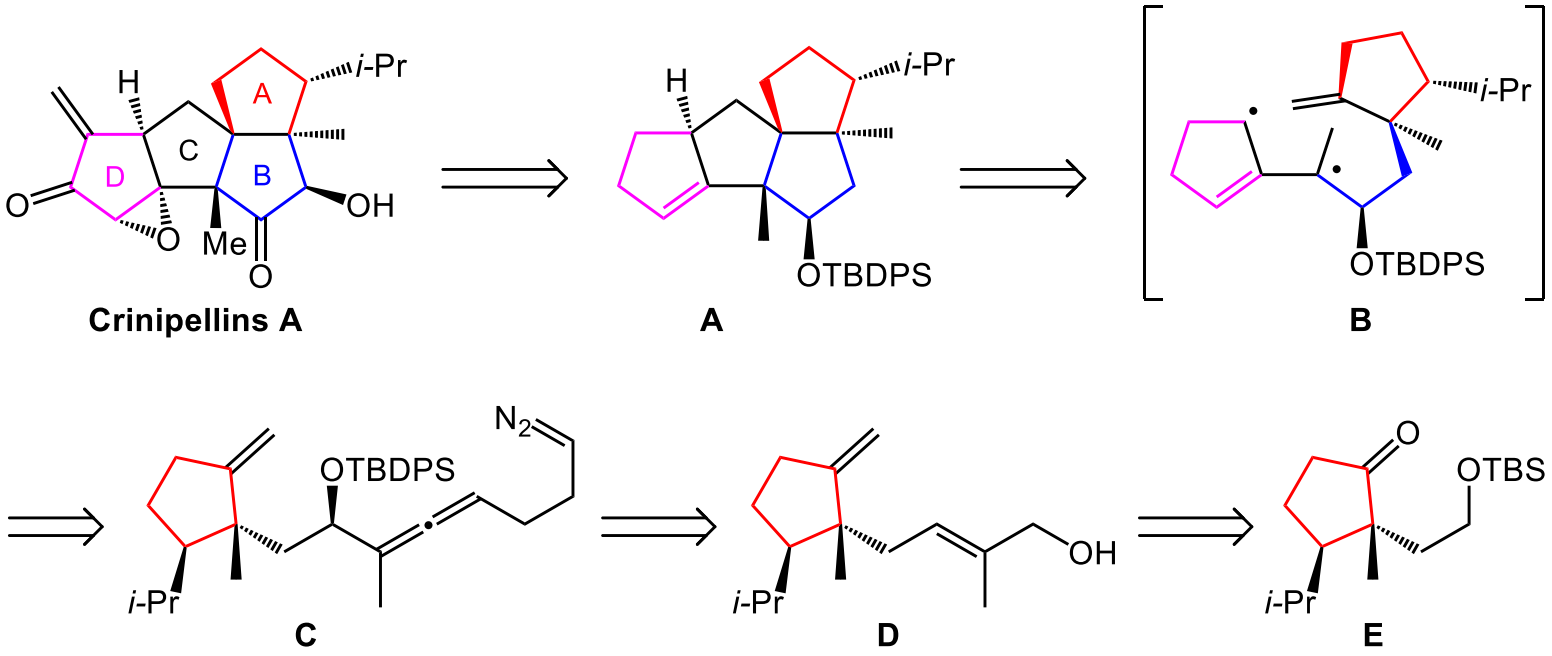


Dihydrorinipellin A



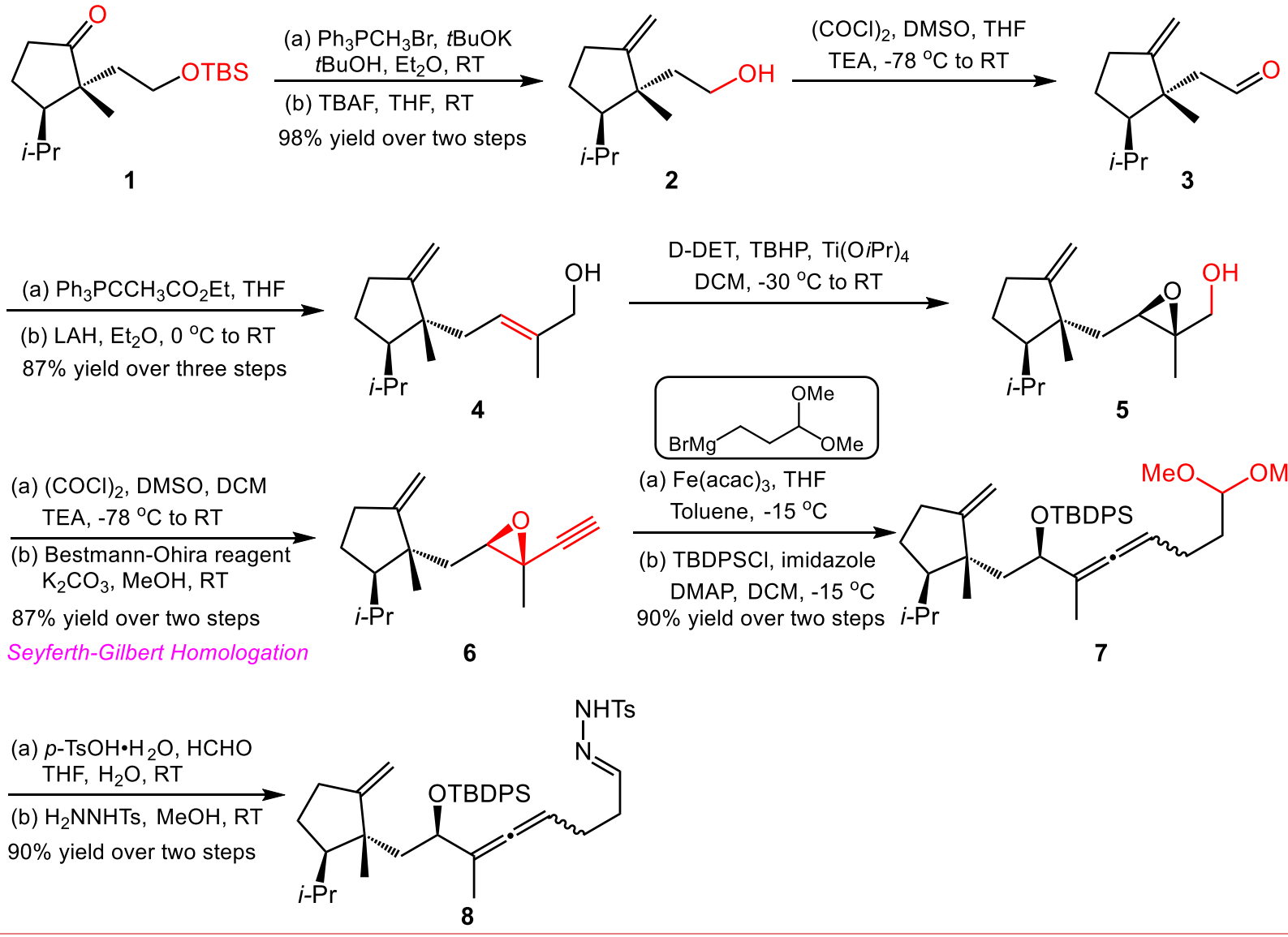
Tetrahydrorinipellin B

Retrosynthetic analysis

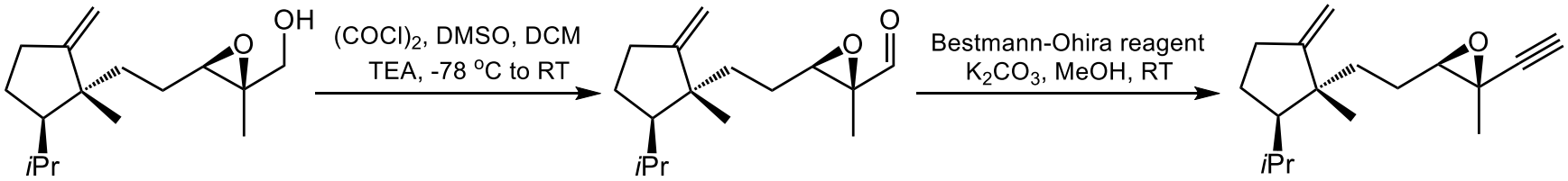


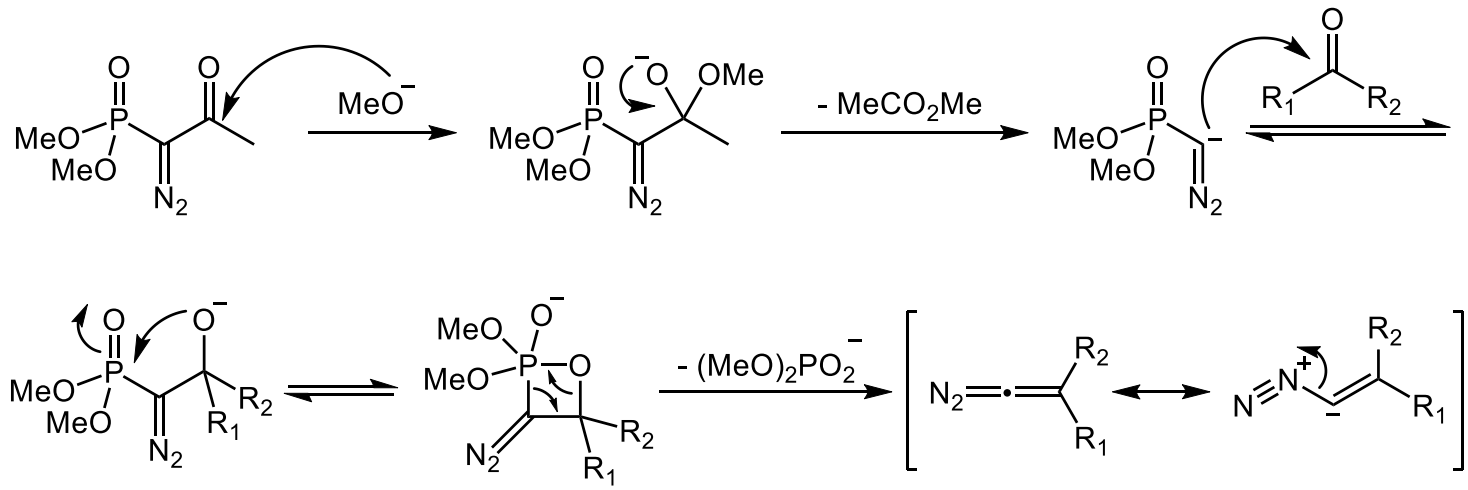
Lee, H.-Y. *et al. J. Am. Chem. Soc.* **2014**, *136*, 10274.

The synthesis of 8

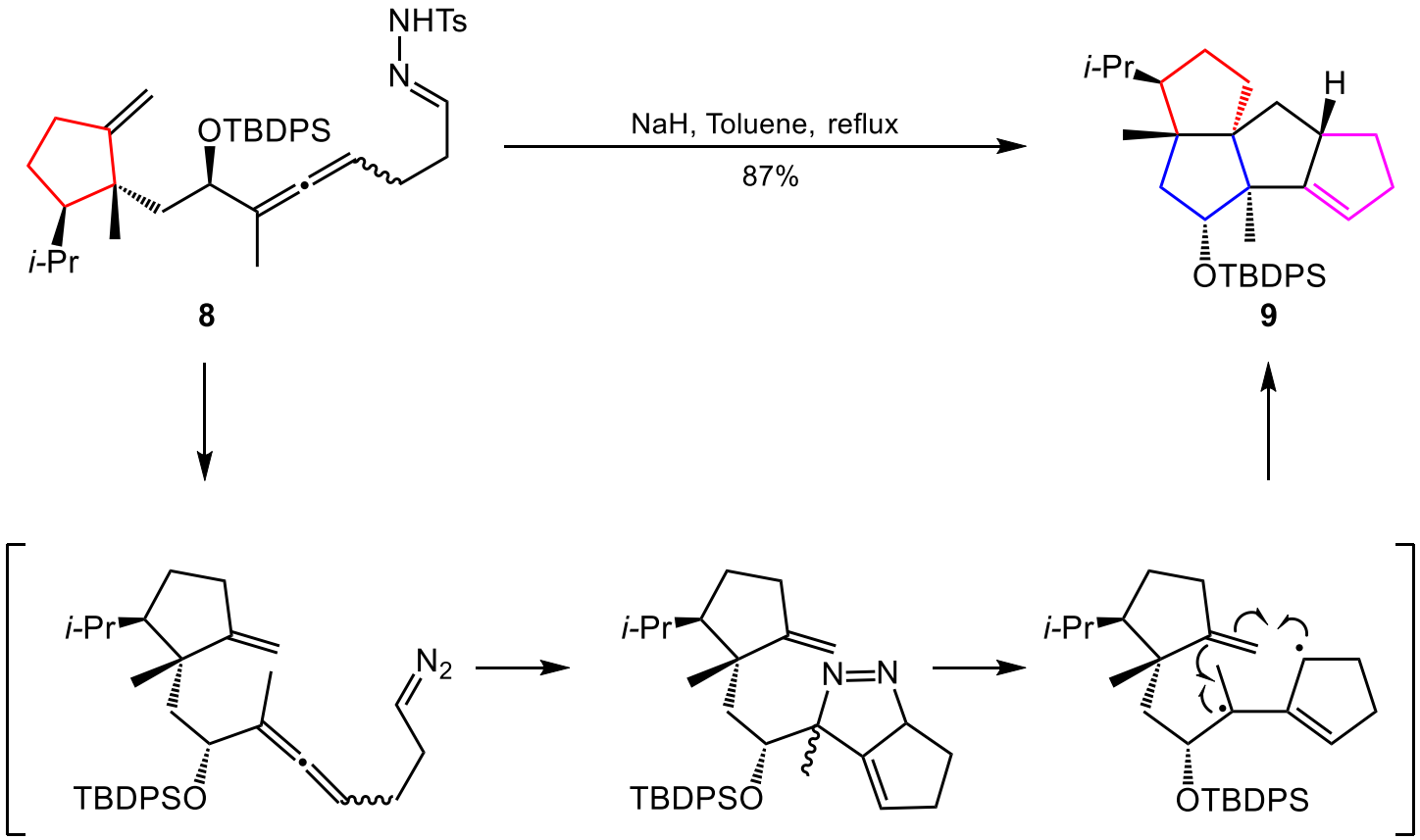


Seyferth-Gilbert Homologation

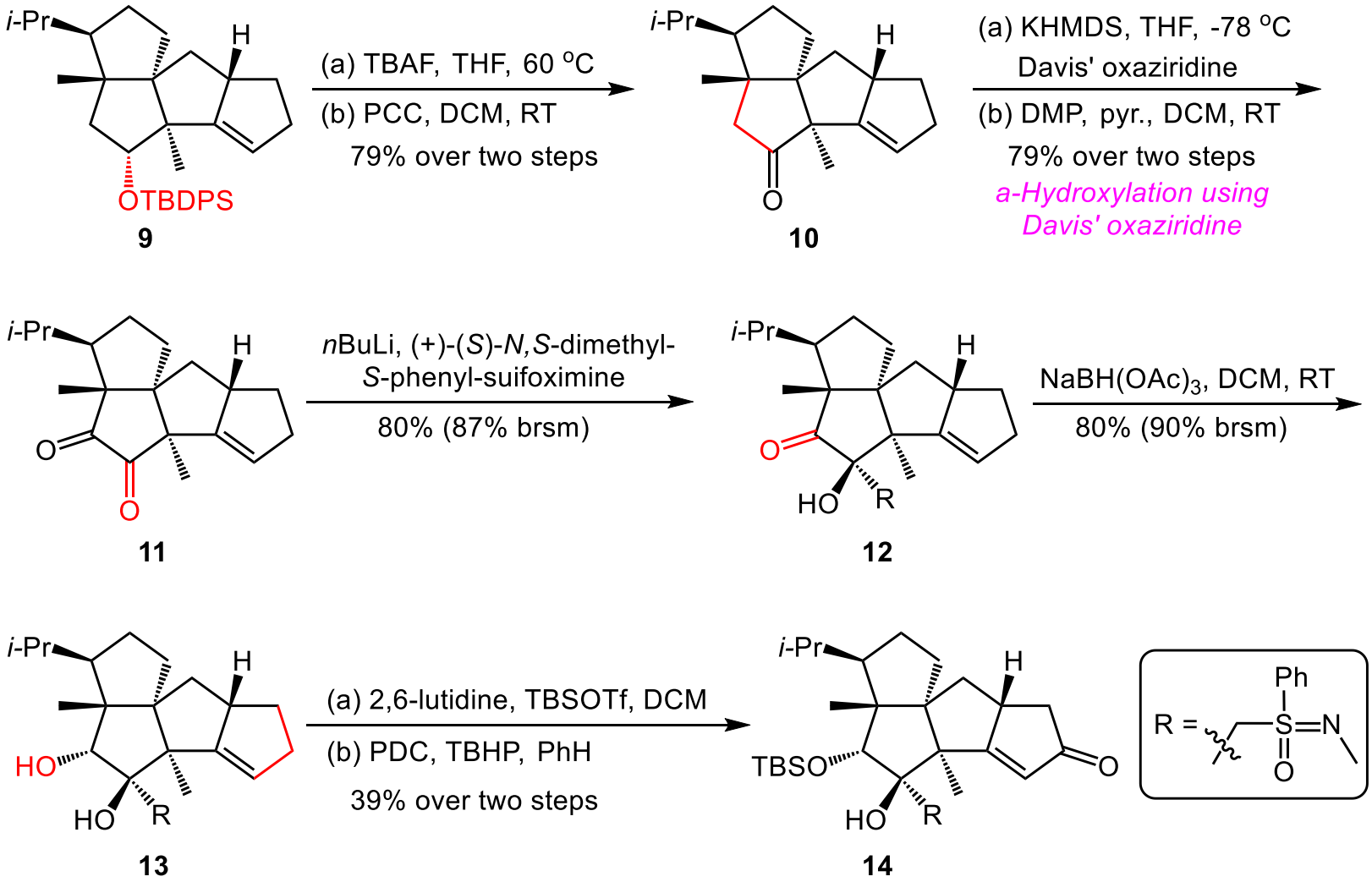




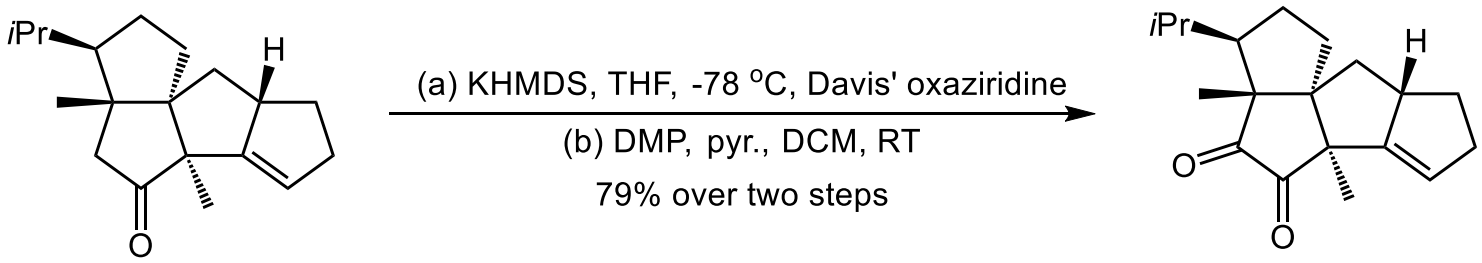
Tandem Cycloaddition Reaction

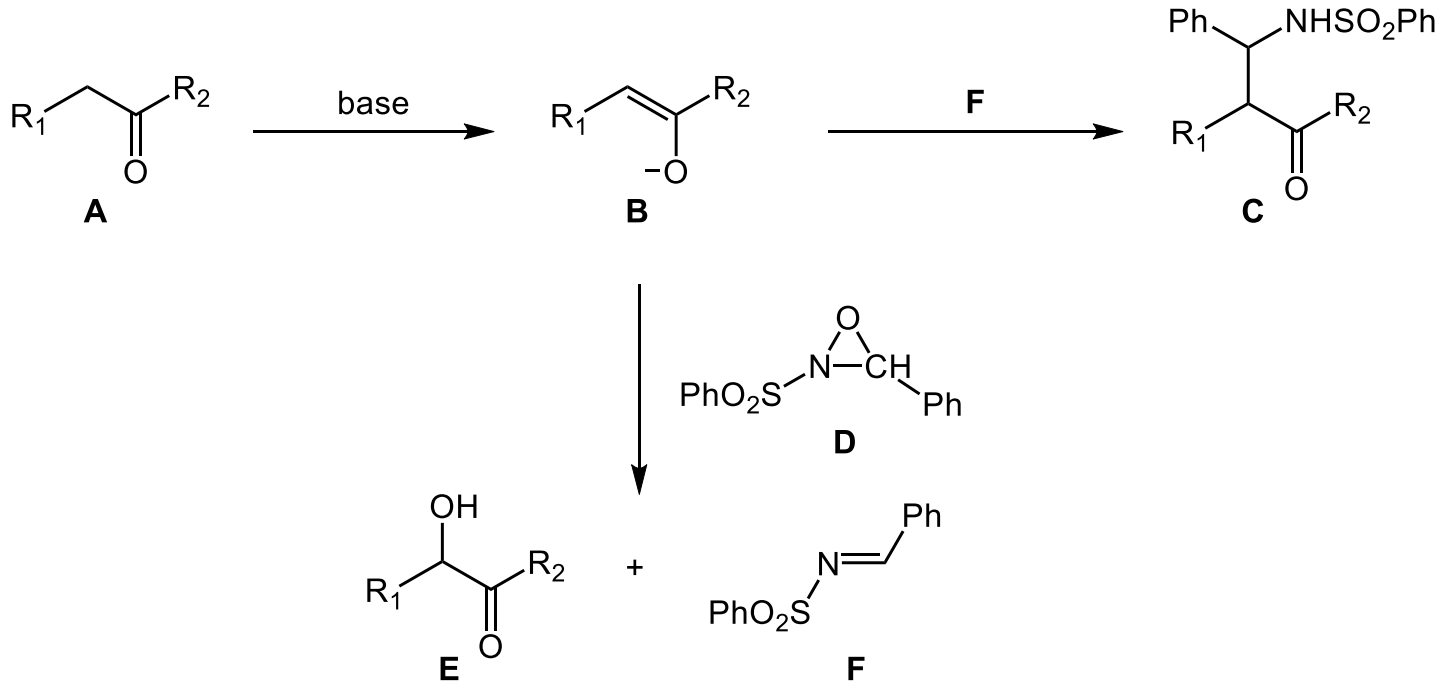


The synthesis of 14

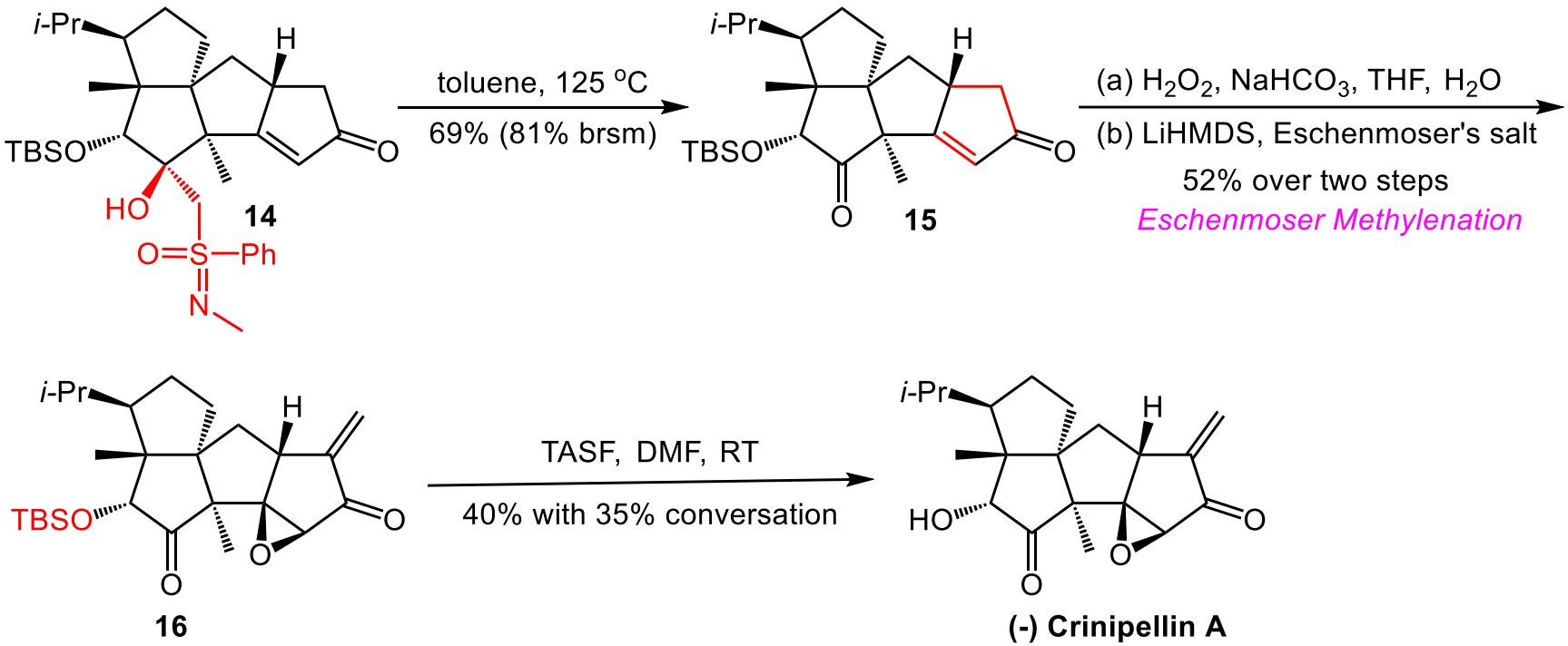


α-Hydroxylation using Davis' oxaziridine

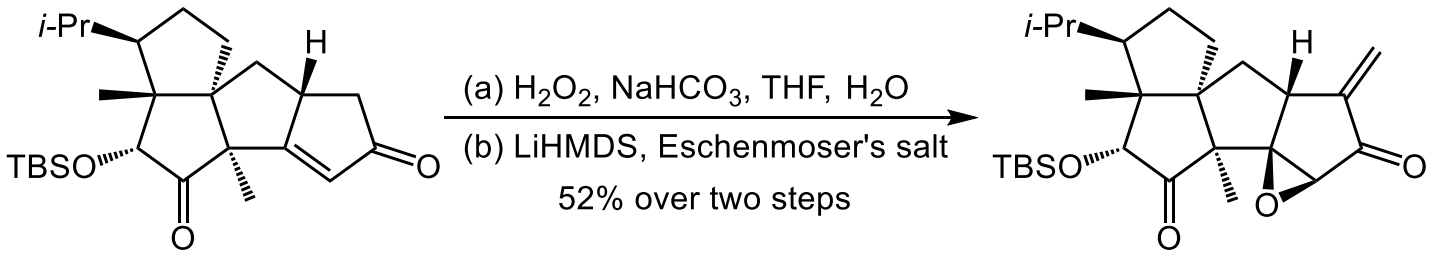


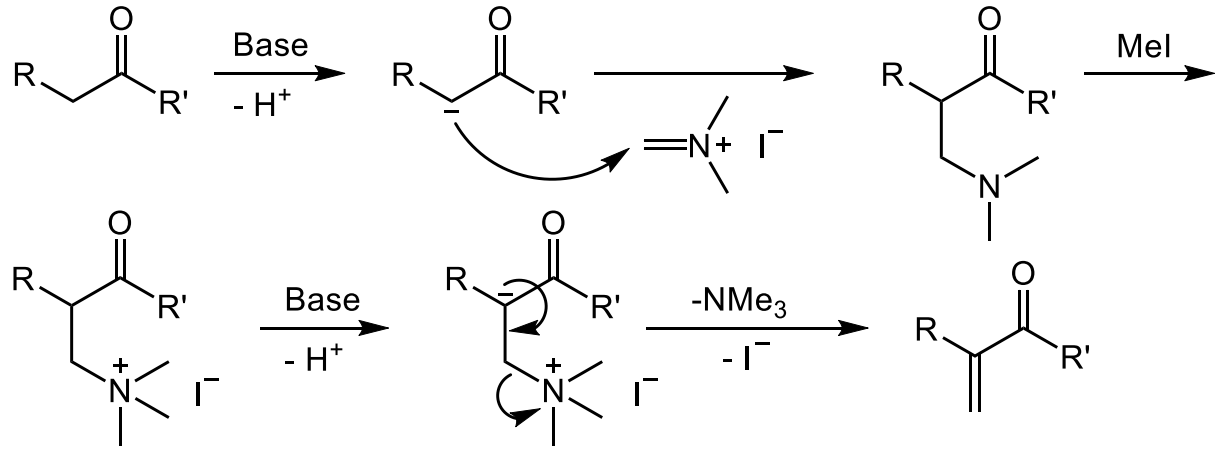


Completion of the Synthesis

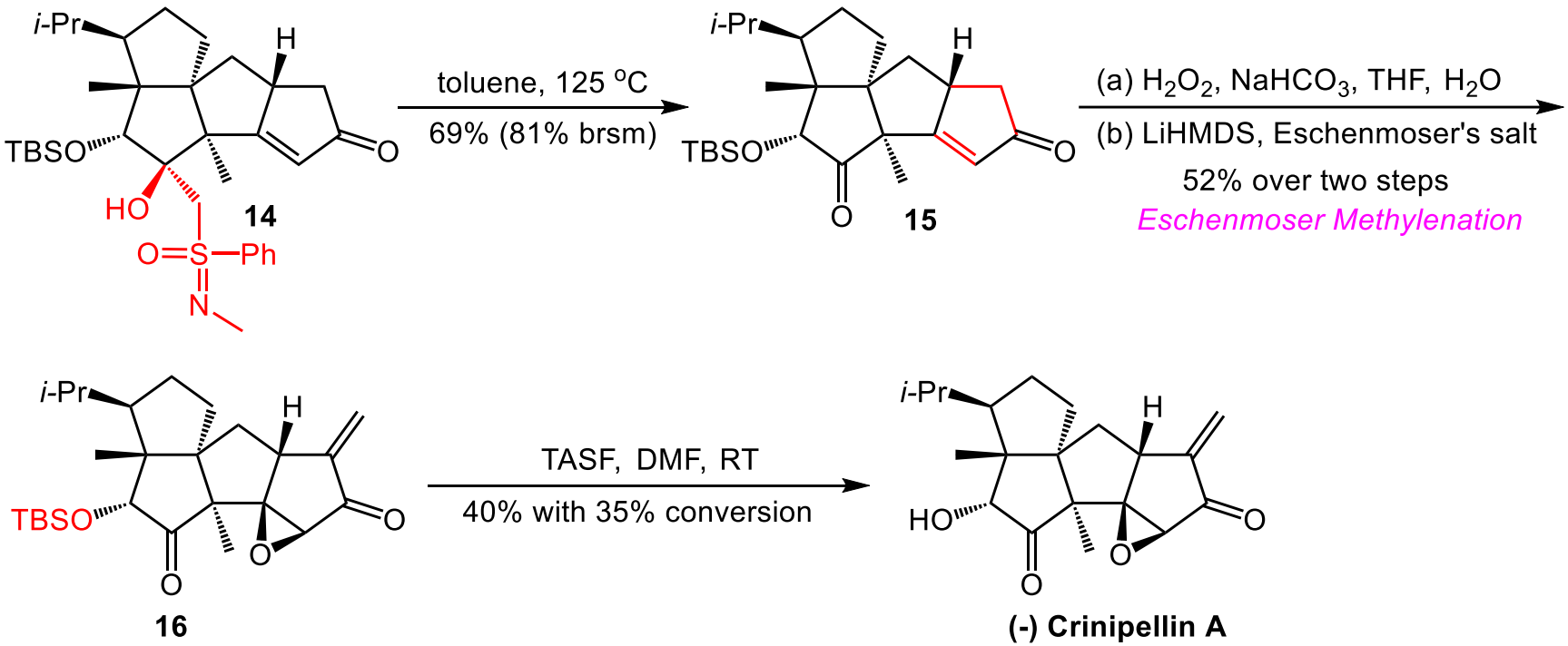


Eschenmoser Methylenation

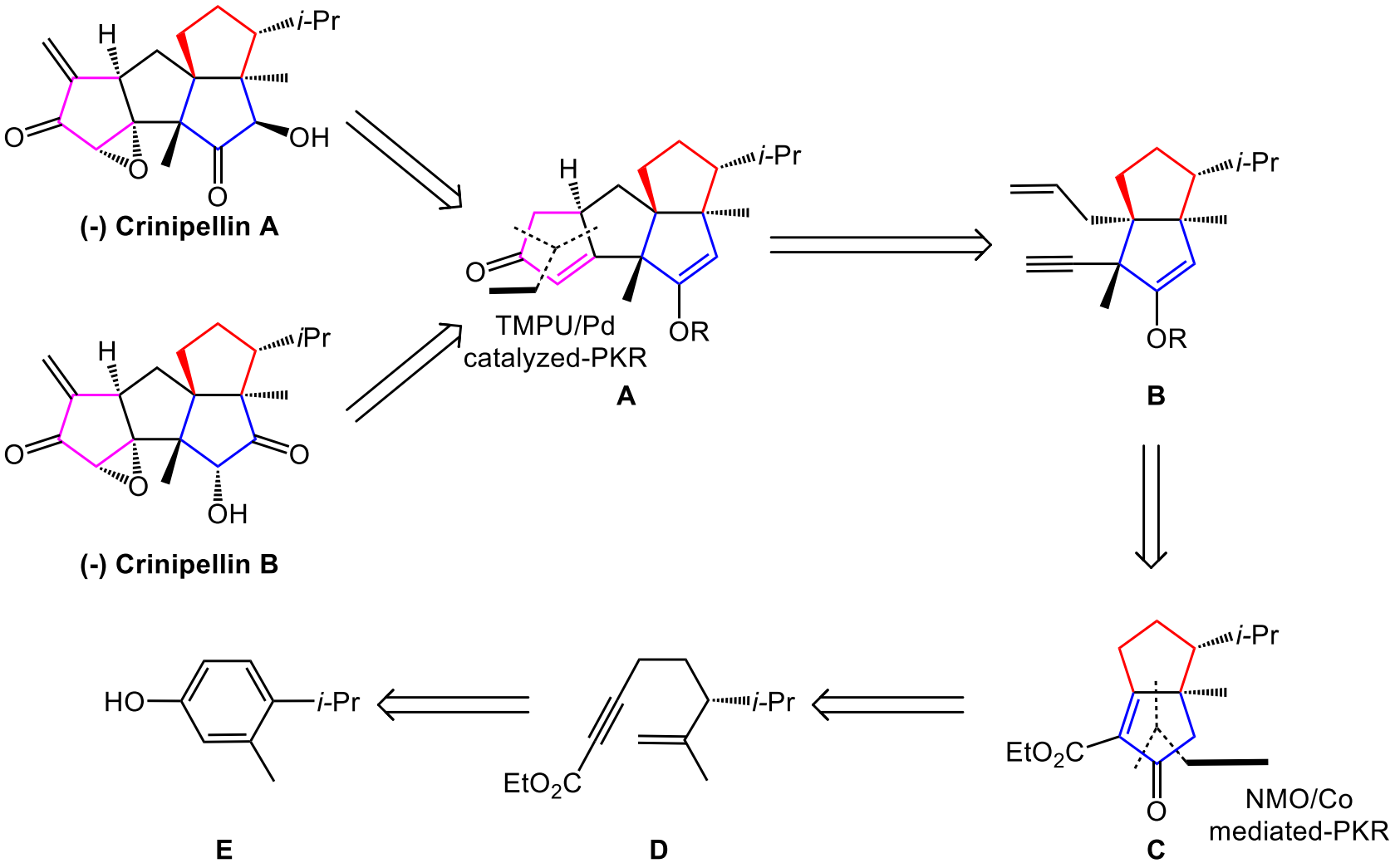




Completion of the Synthesis

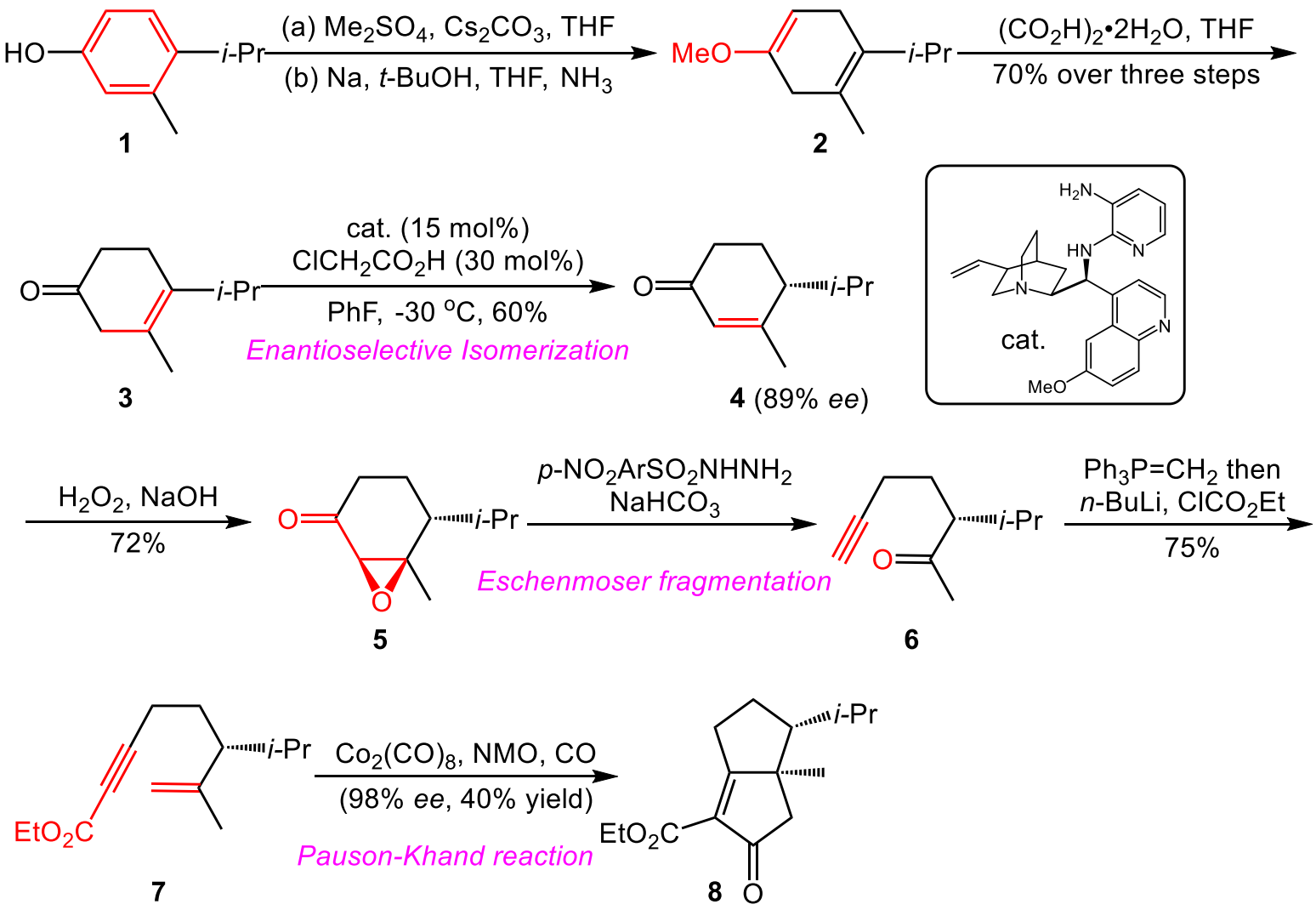


Retrosynthetic analysis

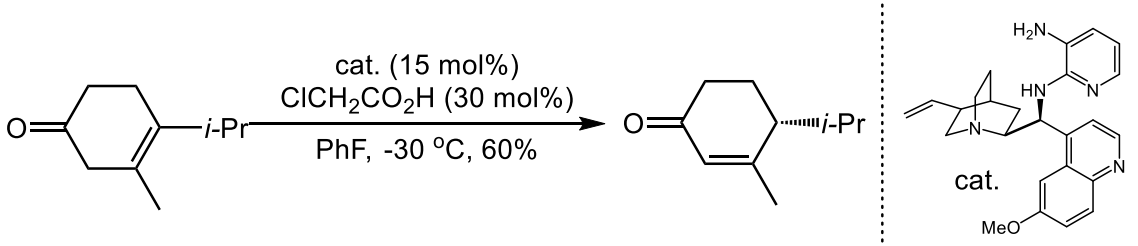


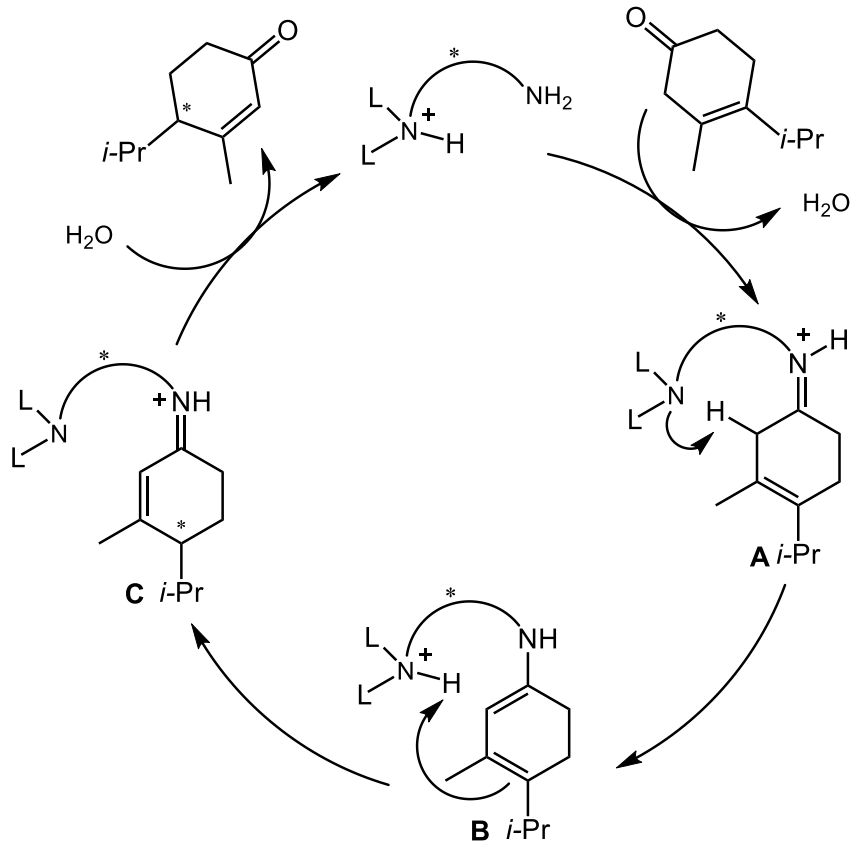
Yang, Z. *et al. Angew. Chem. Int. Ed*. **2018**, *57*, 8874.

Synthesis of the enyne



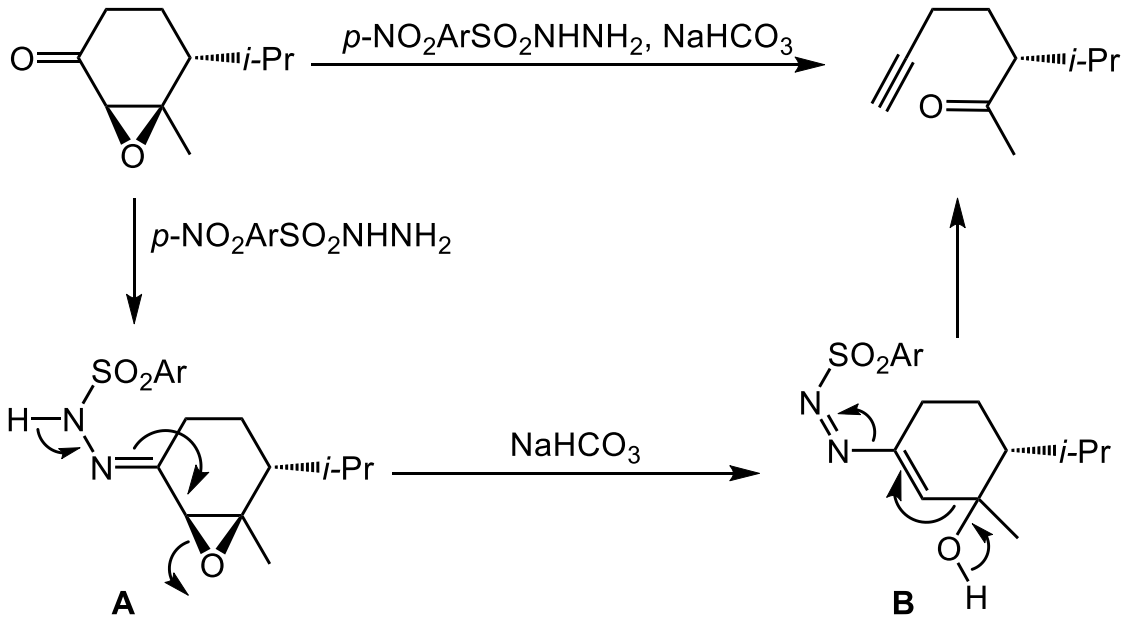
Enantioselective Isomerization



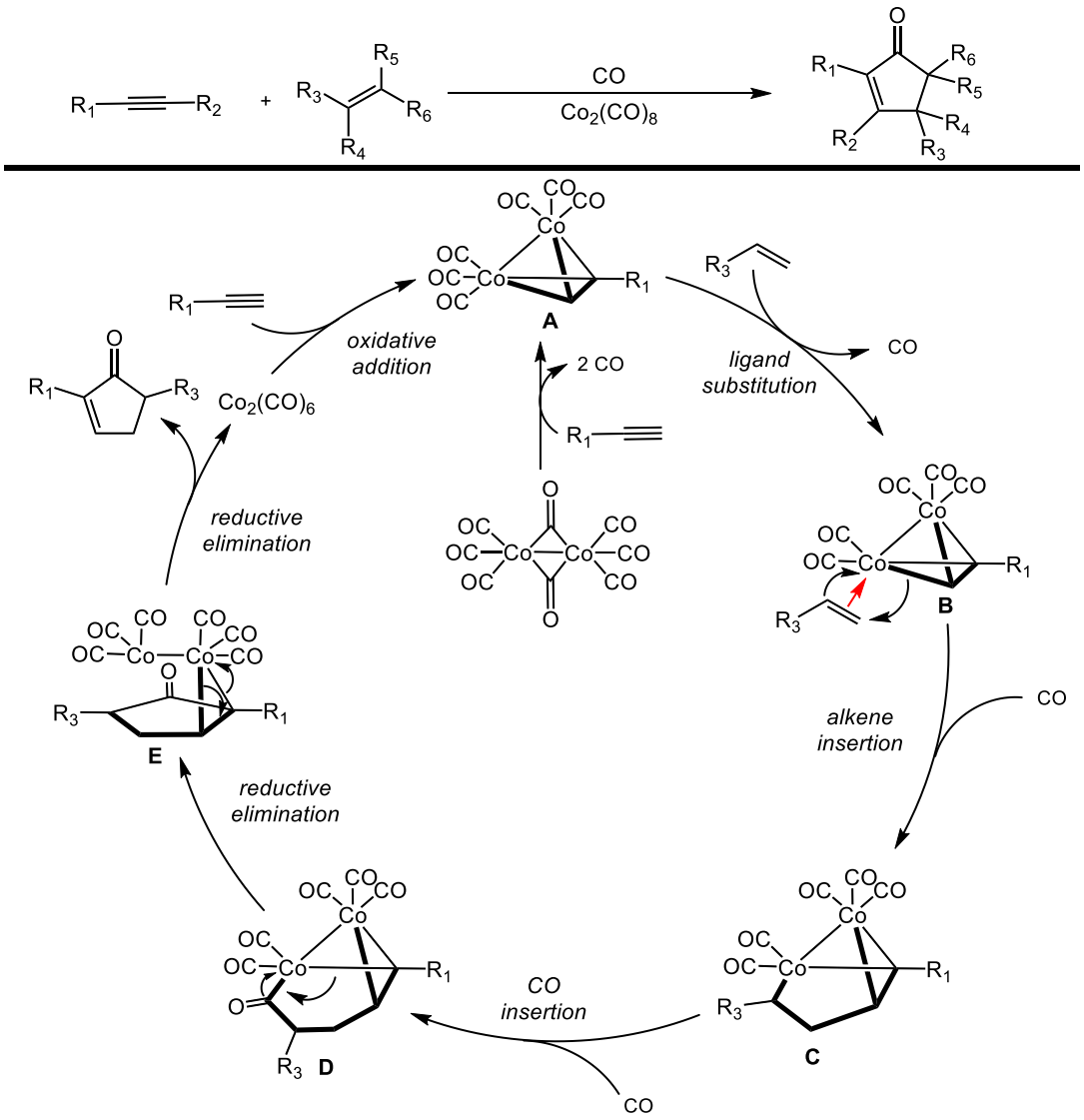


Deng, L. *et al. J. Am. Chem. Soc.* **2012**, *134*, 18209.

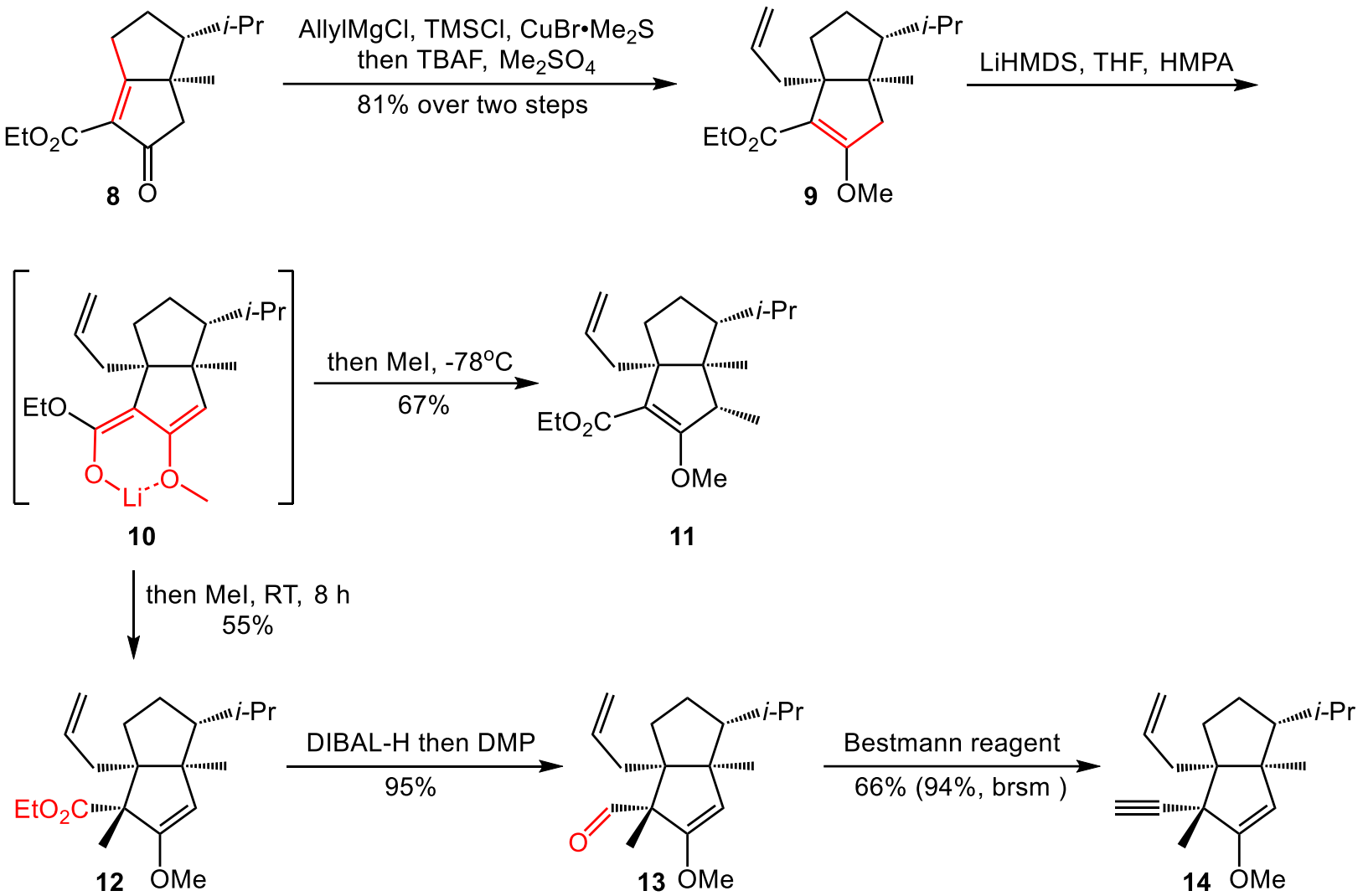
Eschenmoser fragmentation



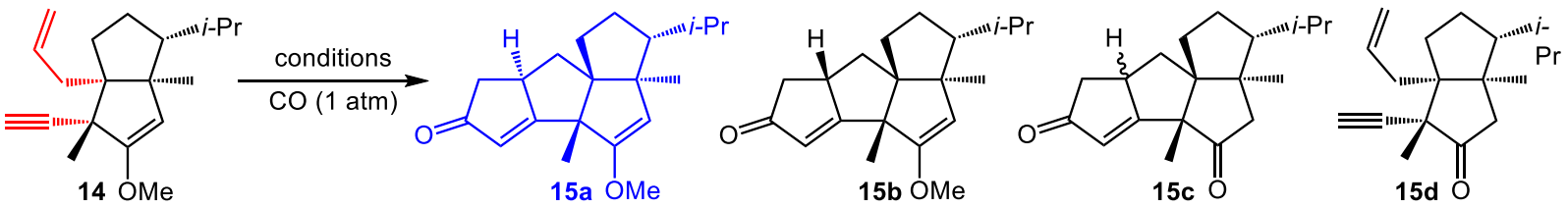
Pauson-Khand reaction



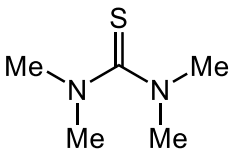
Synthesis of the enyne



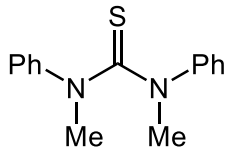
The intramolecular Pauson-Khand reaction



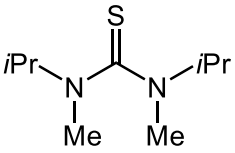
Entry[a]	Conditions	Yield (**a**)	Yield (**b**)	Yield (**c**)	Yield (**d**)
1	$Co_2(CO)_8$ (10 mol%), TMTU (60 mol%), PhMe, 60°C, 12 h	21	42	-	-
2	$[Rh(CO)_2Cl]_2$ (10 mol%), DCE, 60 °C, 12 h,	-	45	-	-
3	$[Rh(CO)_2Cl]_2$ (10 mol%), tBu$_2$O, 130 °C,12 h	6	30	-	-
4	[RhCl(dppp)] (10 mol%), tBu$_2$O, 130 °C, 12 h	trace	trace	-	-
5	$PdCl_2$ (20 mol%), TMTU (20 mol%), THF, 50 °C, 50 h	trace	trace	-	-
6	$PdCl_2$ (20 mol%), LiCl (1.2 equiv), THF, 50 h, 50 °C	-	-	-	50
7	$PdCl_2(CH_3CN)_2$ (20 mol%), LiCl (1.2 equiv), THF, 50 h, 50 °C	-	-	30	20



(TMTU)

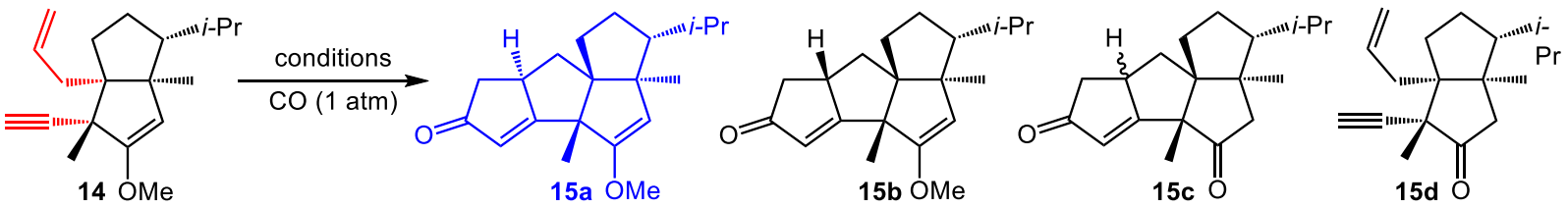


(TU-1)

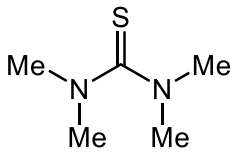


(TU-2)

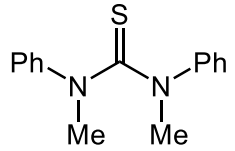
The intramolecular Pauson-Khand reaction



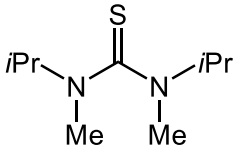
Entry[a]	Conditions	Yield (**a**)	Yield (**b**)	Yield (**c**)	Yield (**d**)
1	$PdCl_2$ (20 mol%), TMTU (20 mol%), LiCl (1.2 equiv), THF, 50 °C, 50 h	30	20	-	-
2	$PdCl_2$ (10 mol%), TU-1 (11 mol%), THF, 42 h, 50 °C	29	7	40	-
3	$PdCl_2$ (10 mol%), TU-2 (10 mol%), THF, 18 h, 50 °C	10	8	-	-
4	$PdCl_2$ (30 mol%), TU-1 (30 mol%), Na_2CO_3 (1.0 equiv), THF, 36 h, 50 °C	49	16	-	-
5	$PdCl_2$ (30 mol%), TU-1 (30 mol%) $NaHCO_3$, THF, 36 h, 50 °C	61	16	-	-



(TMTU)

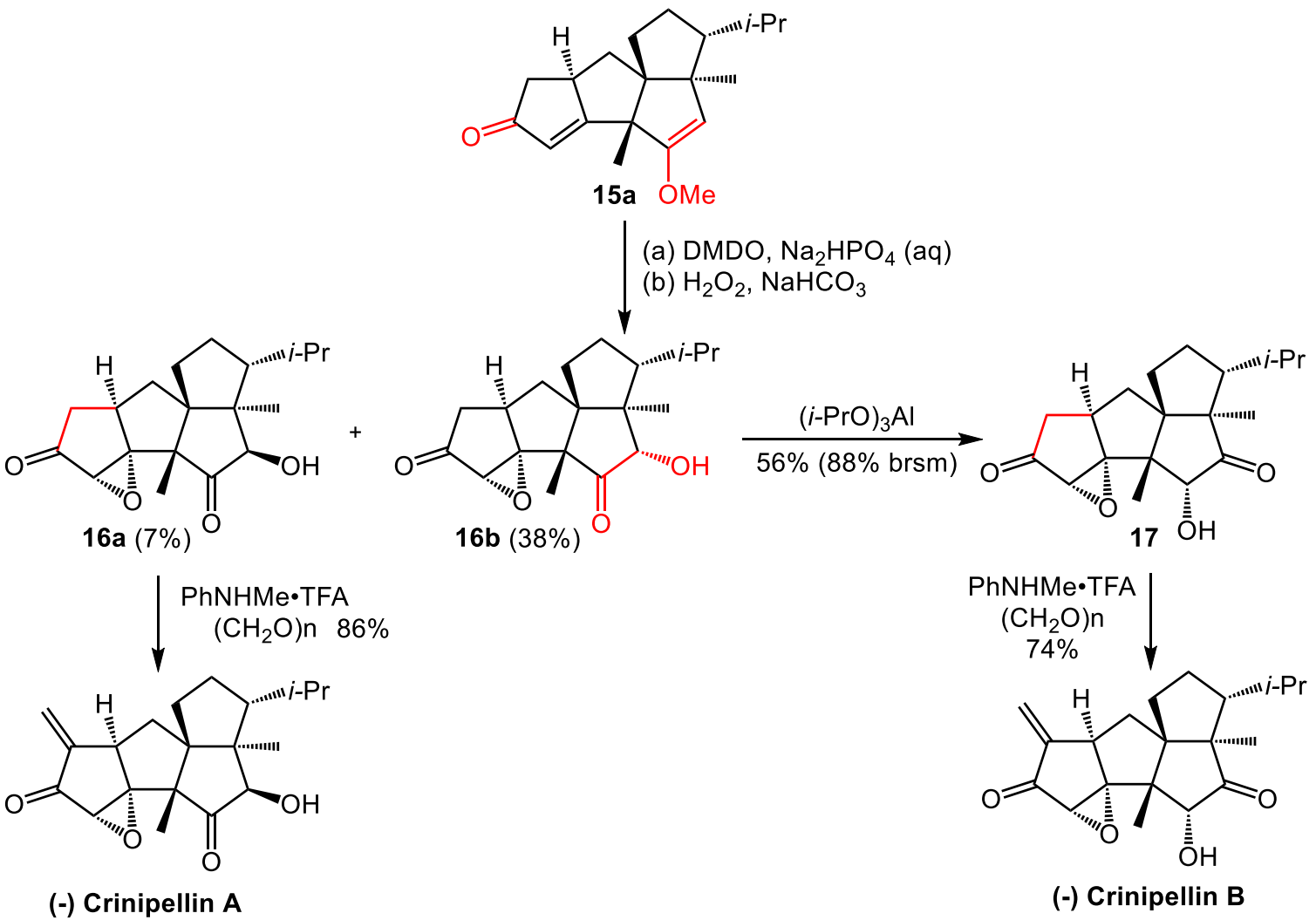


(TU-1)

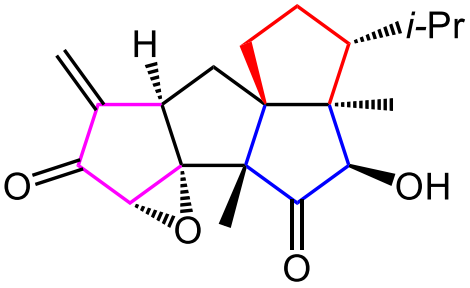


(TU-2)

Total Synthesis of 6



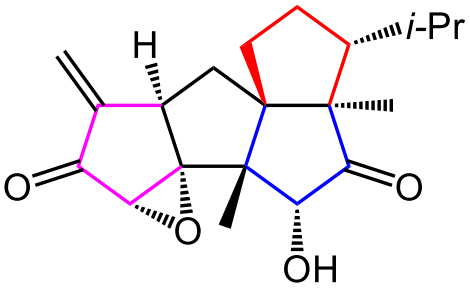
Summary



(-) Crinipellin A

- (-)-Crinipellin A : 25 Steps, 1.01% overall yield;
- The first catalytic enantioselective total synthesis of (-)-Crinipellin A;
- The tandem [2+3] cycloaddition reaction.

Lee, H.-Y. *et al. J. Am. Chem. Soc.* **2014**, *136*, 10274.



(-) Crinipellin B

- (-)-Crinipellin A: 17 Steps, 0.06% overall yield;
- (-)-Crinipellin B: 18 Steps, 0.16% overall yield;
- Cobalt-catalyzed PK reaction；
- Thiourea/palladium-catalyzed PK reaction;
- Tactical placement of substituents and functionalities.

Yang, Z. *et al. Angew. Chem. Int. Ed*. **2018**, *57*, 8874.

The first paragraph

Crinipellin A is one of several related diterpenoids isolated from the fungus Crinipellis stipitaria (Agaricales) by Steglich and co-workers in 1979. It has an α methylene ketone motif and a unique tetraquinane core, which bears eight stereogenic centers, of which three are contiguous all-carbon quaternary carbon atoms. In terms of biological activity, 1 and 2 were originally reported to have antibiotic activities. 1a could completely inhibit the syntheses of DNA, RNA, and proteins in Ehrlich carcinoma cells at a concentration of 5 mg/mL. The α methylene ketone motif in crinipellins A and B makes them a potential irreversible probes in the field of drug discovery and chemical biology.

The last paragraph

In summary, we achieved the asymmetric total syntheses of (-)-crinipellin A and (-)-crinipellin B in 17 and 18 steps, respectively, from the commercially available phenol. The key features of our synthesis include use of our developed thiourea/palladium-catalyzed intramolecular PK reaction for diastereoselective construction of the tetraquinane core of the naturally occurring crinipellins. Tactical placement of substituents and functionalities will enable the protocol developed here to be used in the synthesis of tetraquinane cores having various substituents. This strategy will therefore be useful in the collective synthesis of analogues of the crinipellins.

Thanks for your attention