Literature Report

Enantioselective Total Synthesis of (-)-Pavidolide B

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Checker: Hong-Qiang Shen
Date: 2017-10-16

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J. Am. Chem. Soc. **2017**, *139,* 13989-13992.

CV of Zhen Yang

Education:

- 1978-1982 B.S .; Shenyang Pharmaceutical University
- 1983-1986 M. S.; Shenyang Pharmaceutical University
- 1989-1992 Ph.D., The Chinese University of Hong Kong
- 1992-1995 Postdoc., The Scripps Research Institute
- 1998-2001 Professor, Harvard University School of Medicine

Research:

Our research interests span many fields, ranging from total synthesis of natural product, synthetic methodology, combinatorial chemistry and small molecule based chemical biology.

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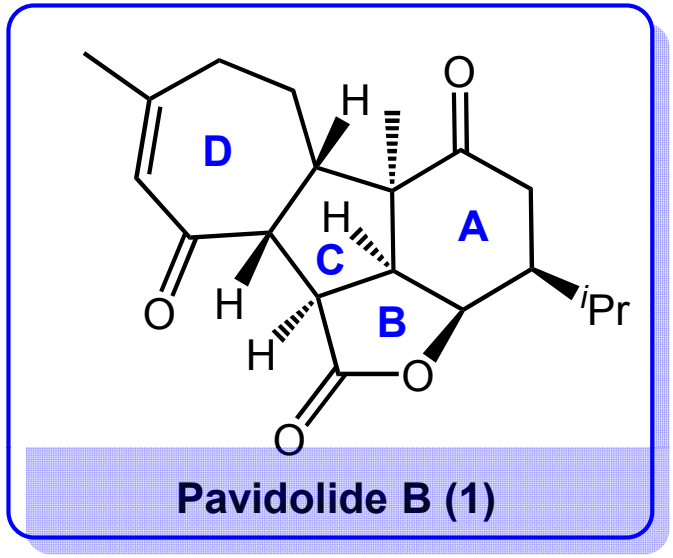
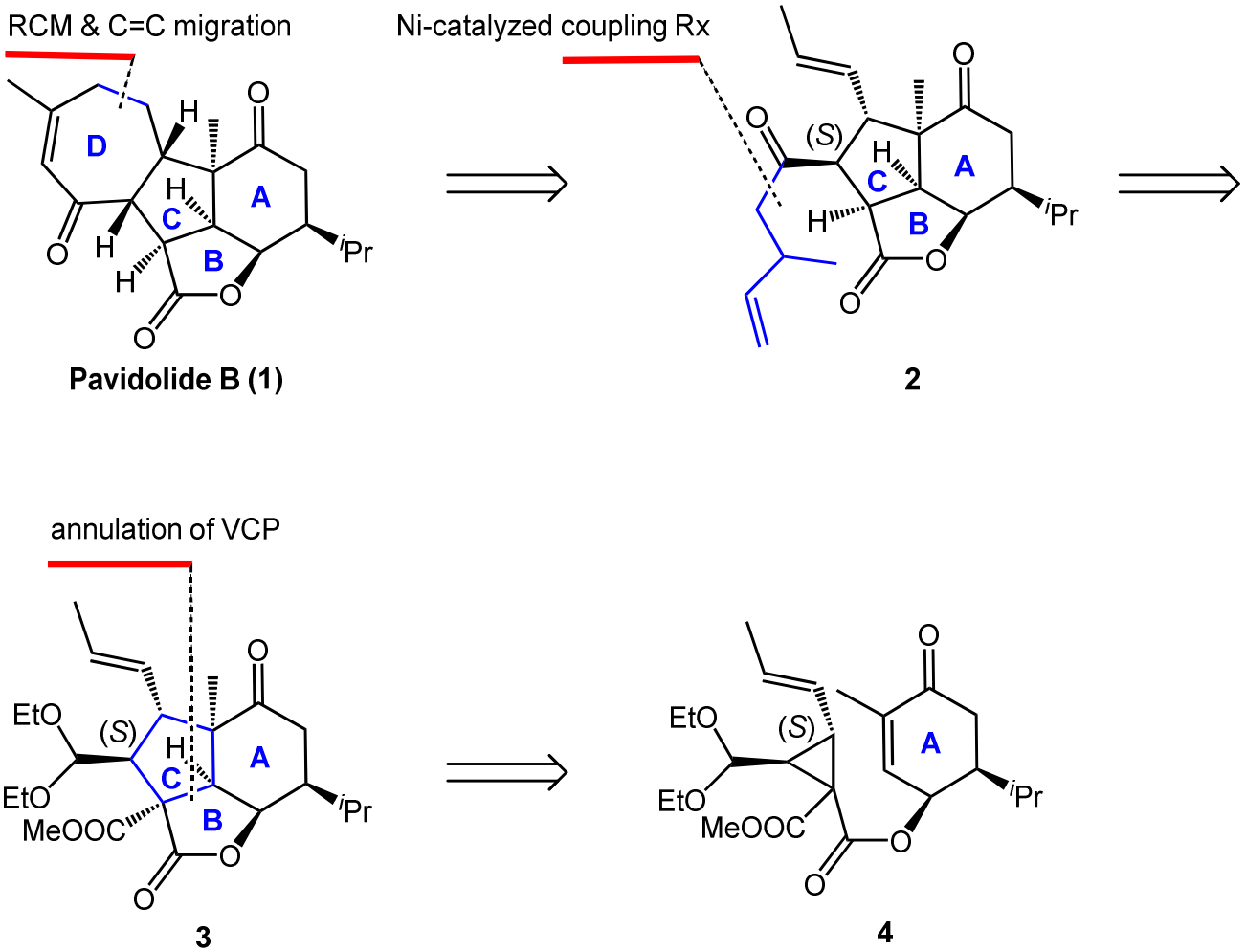
Introduction



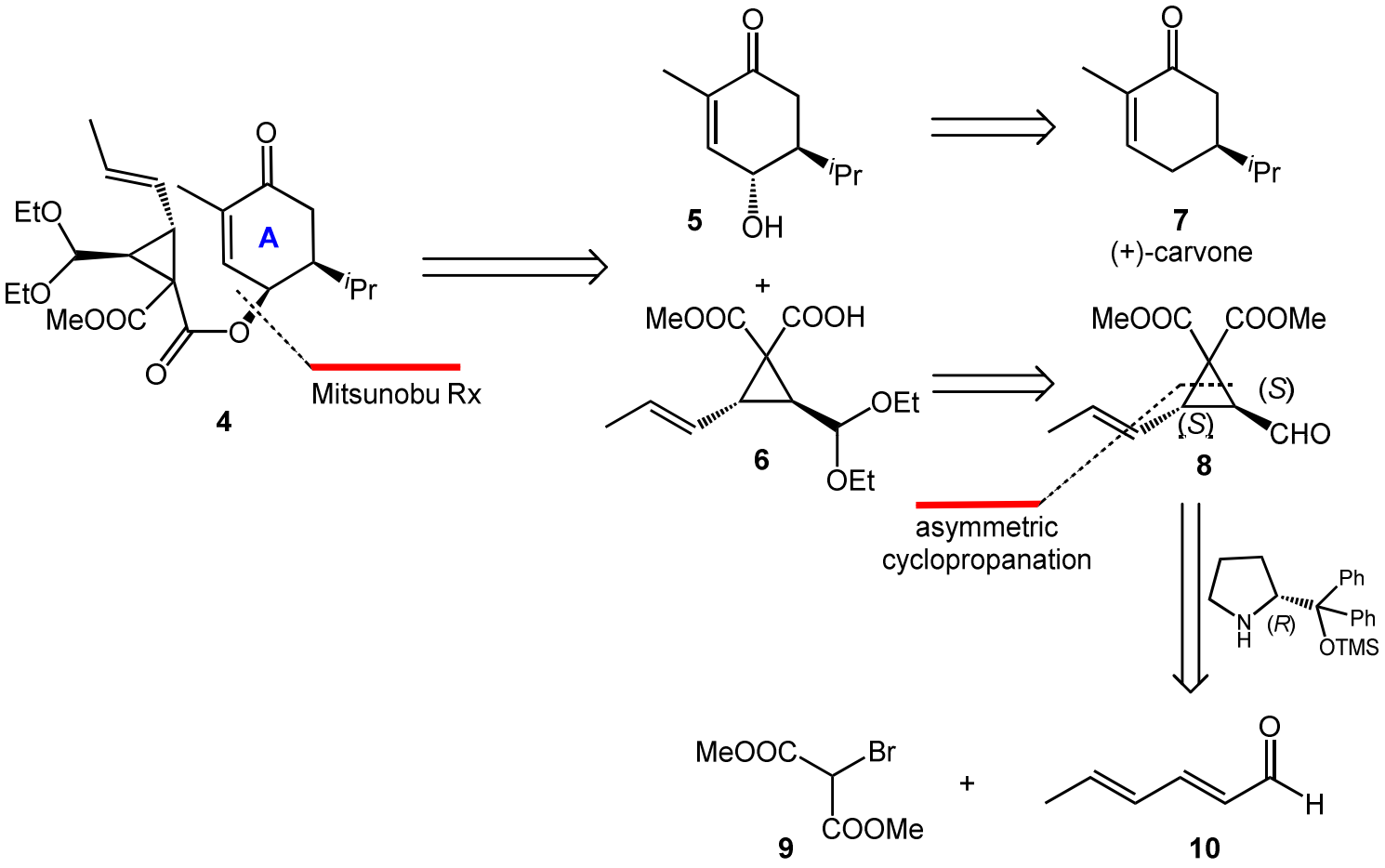
Pavidolide B (1)

- It was isolated from the marine soft coral *Sinularia pavida* by Lin group in 2012;
- It features a dome-sharped 6/5/7 fused-ring system and fully functionalized C ring of pavidolide B, with seven contiguous stereocenters (one quaternary);
- The molecule shows high selective inhibitory activity against a number of human promyelocytic leukemia cell lines.

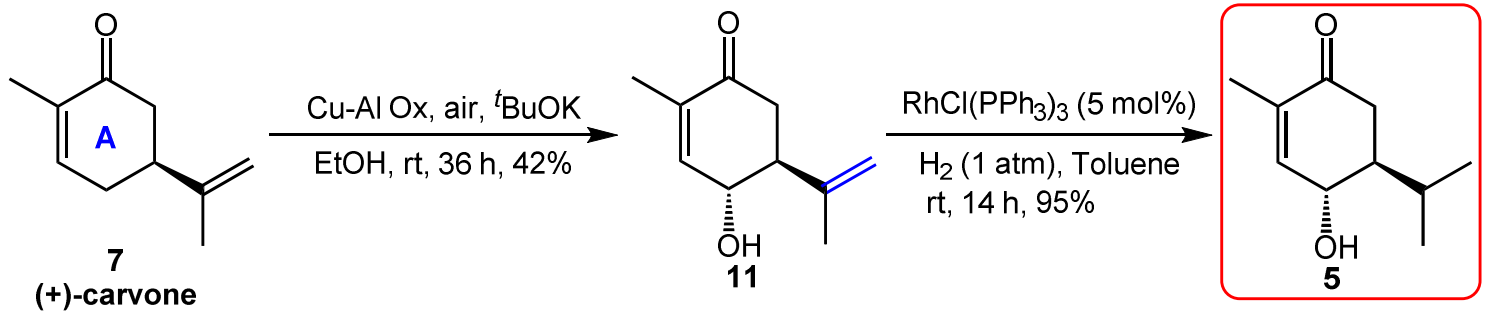
Retrosynthetic analysis of Pavidolide B (1)



Retrosynthetic analysis of Pavidolide B (1)



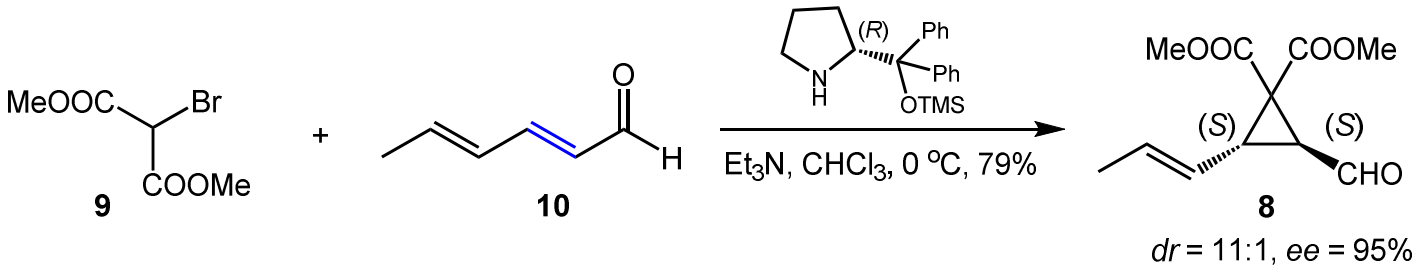
Asymmetric synthesis of Precursor 4



7
(+)-carvone

11

5



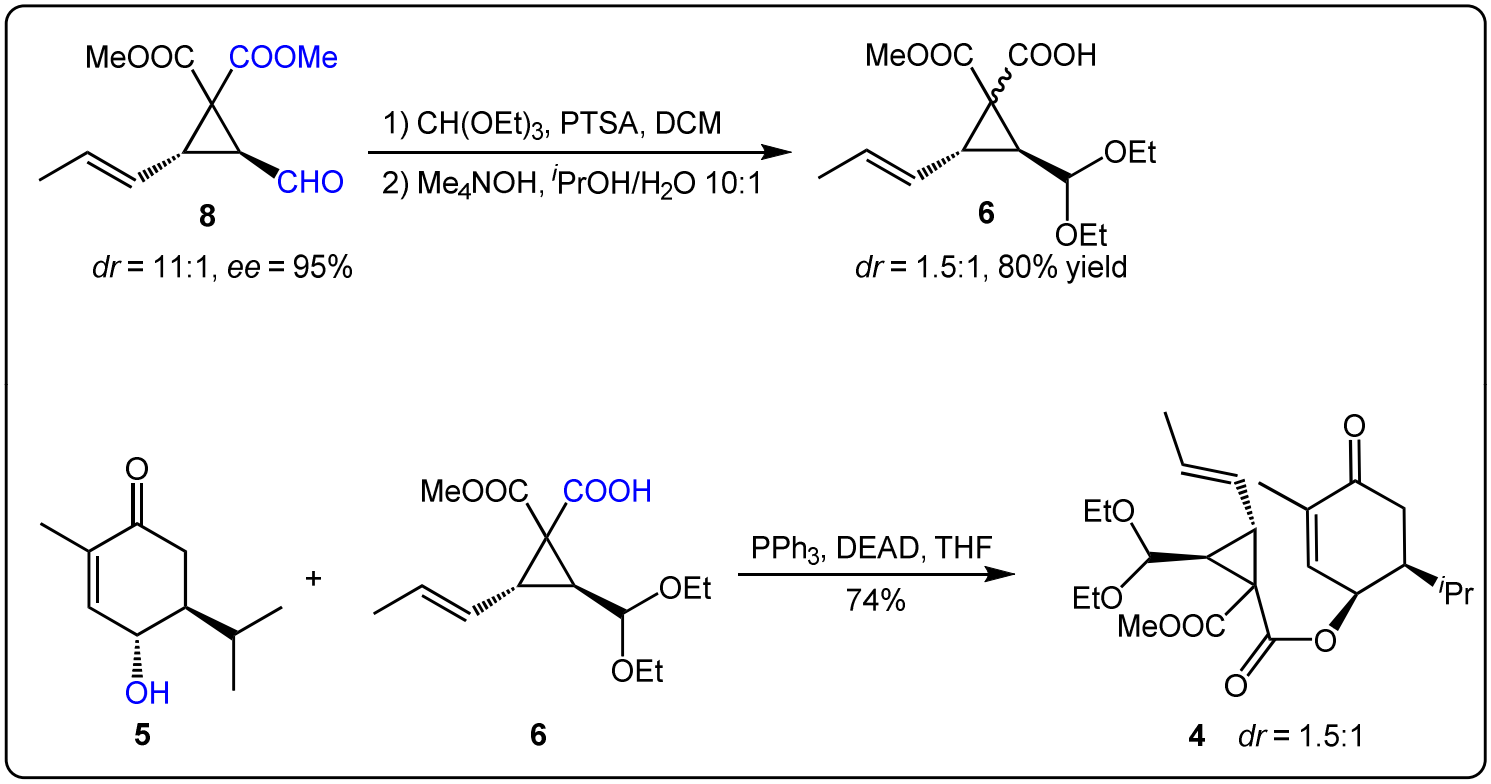
9

10

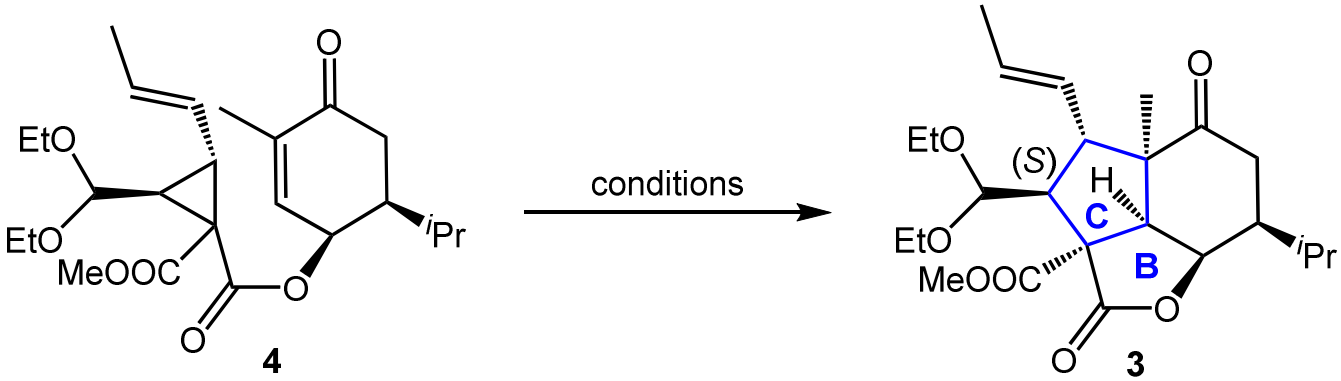
8

dr = 11:1, *ee* = 95%

Asymmetric synthesis of Precursor 4



Screening of the reaction of conditions



entry	conditions	solvent	time (h)	temp. (°C)	yield [a] (%)
1	PhSH, AIBN	toluene	9	60	trace
2	PhSH, AIBN	toluene	6	80	32
3	PhSH, AIBN	toluene	3	100	31
4	PhSH, AIBN	toluene	3	120	35
5	PhSSPh, AIBN, UV (250 W)	toluene	5	25	32
6	PhSSPh, AIBN, UV (250 W), $AlMe_3$	toluene	3	25	40-48
7	PhSSPh, BPO, UV (250 W)	toluene	5	25	23

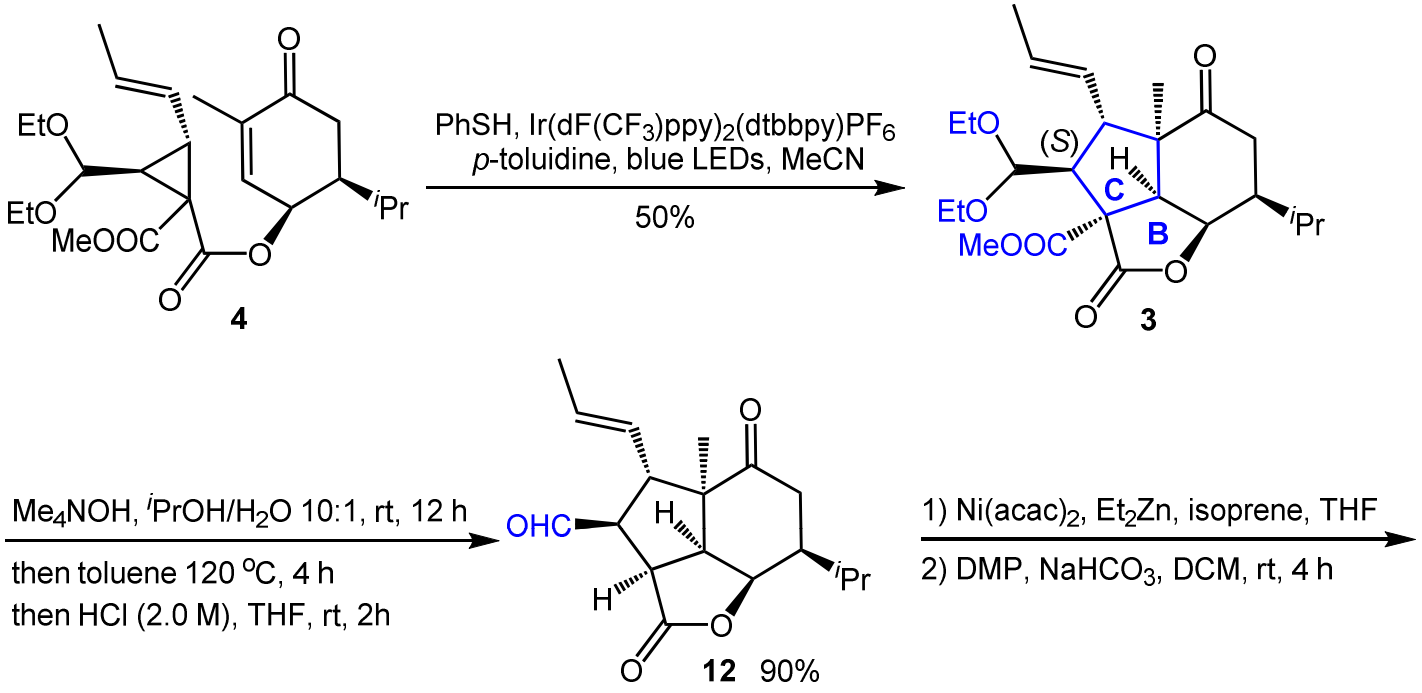
[a] Isolated yield

Screening of the reaction of conditions

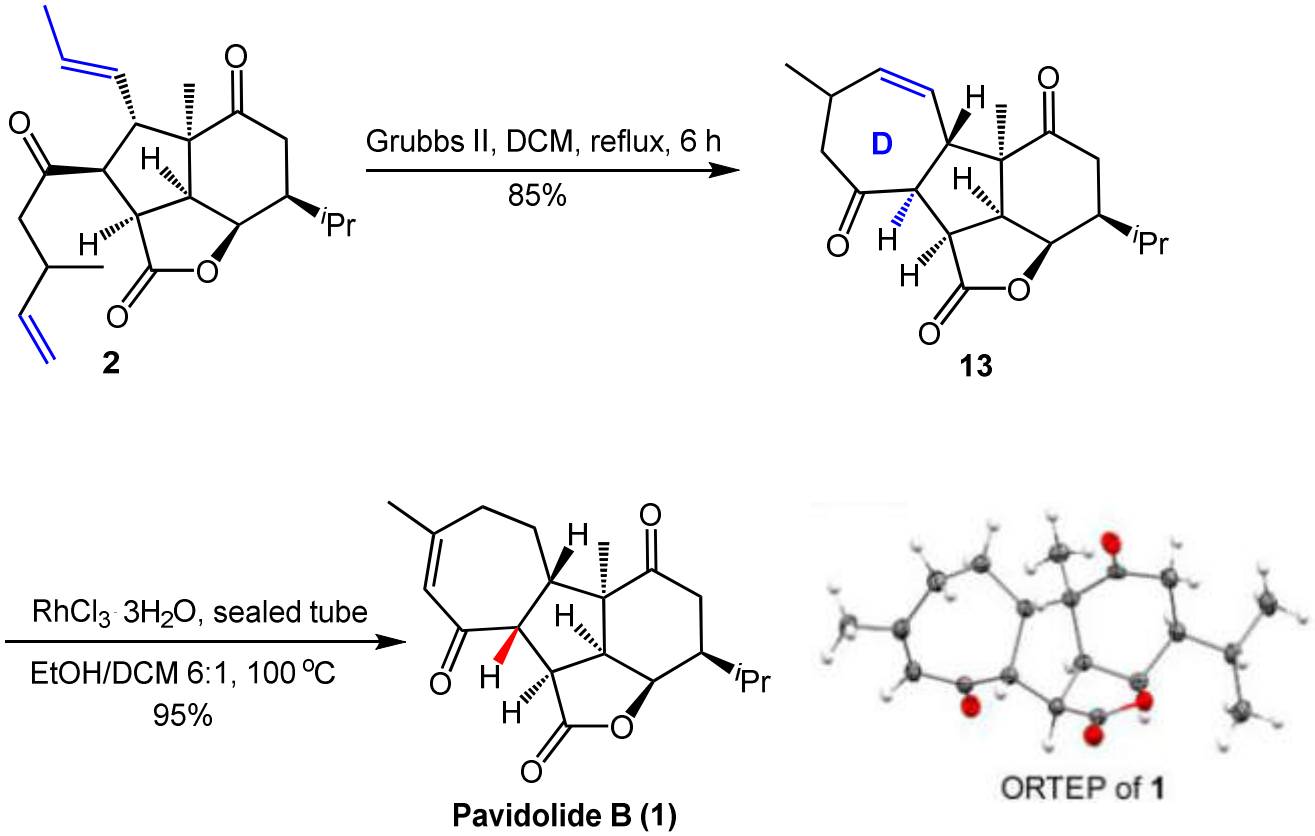
entry	conditions	solvent	time (h)	temp (^{o}C)	yield [a] (%)
8	PhSH, $Ru(bpy)_3Cl_2$, *p*-toluidine, blue LEDs	MeCN	4	25	30
9	PhSH, $Ir(ppy)_2(dtbbpy)PF_6$, *p*-toluidine, blue LEDs	MeCN	5	25	47
10	PhSH, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine, blue LEDs	MeCN	2	25	50
11	benzyl mercaptan, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine, blue LEDs	MeCN	5	25	23
12	methyl thiolgycolate, $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, *p*-toluidine, blue LEDs	MeCN	2	25	25

[a] Isolated yield

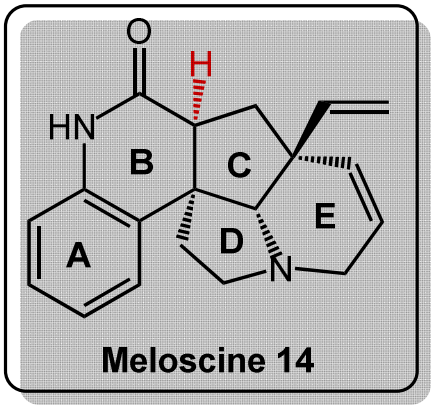
Asymmetric total synthesis of Pavidolide B (1)



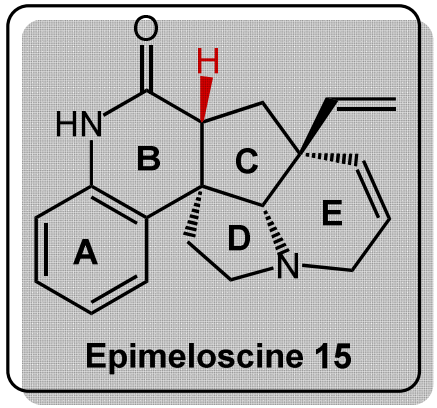
Asymmetric total synthesis of Pavidolide B (1)



Total synthesis of (±)-Meloscine and (±)-Epimeloscine



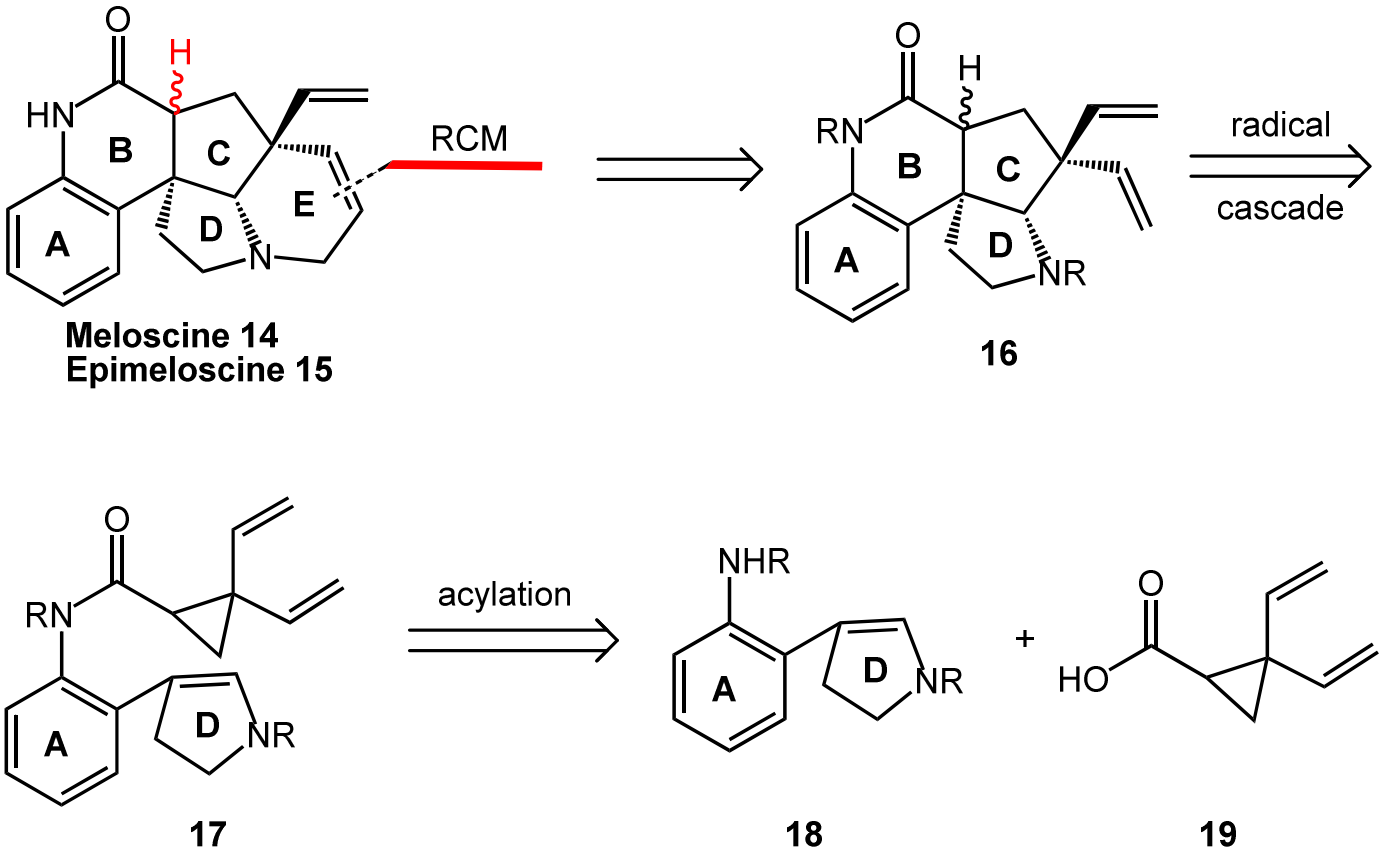
Meloscine 14



Epimeloscine 15

Hanmo Zhang, Dennis P. Curran *J. Am. Chem. Soc*. **2011**, *133*, 10376.

Retrosynthetic analysis of 14 & 15



Meloscine 14
Epimeloscine 15

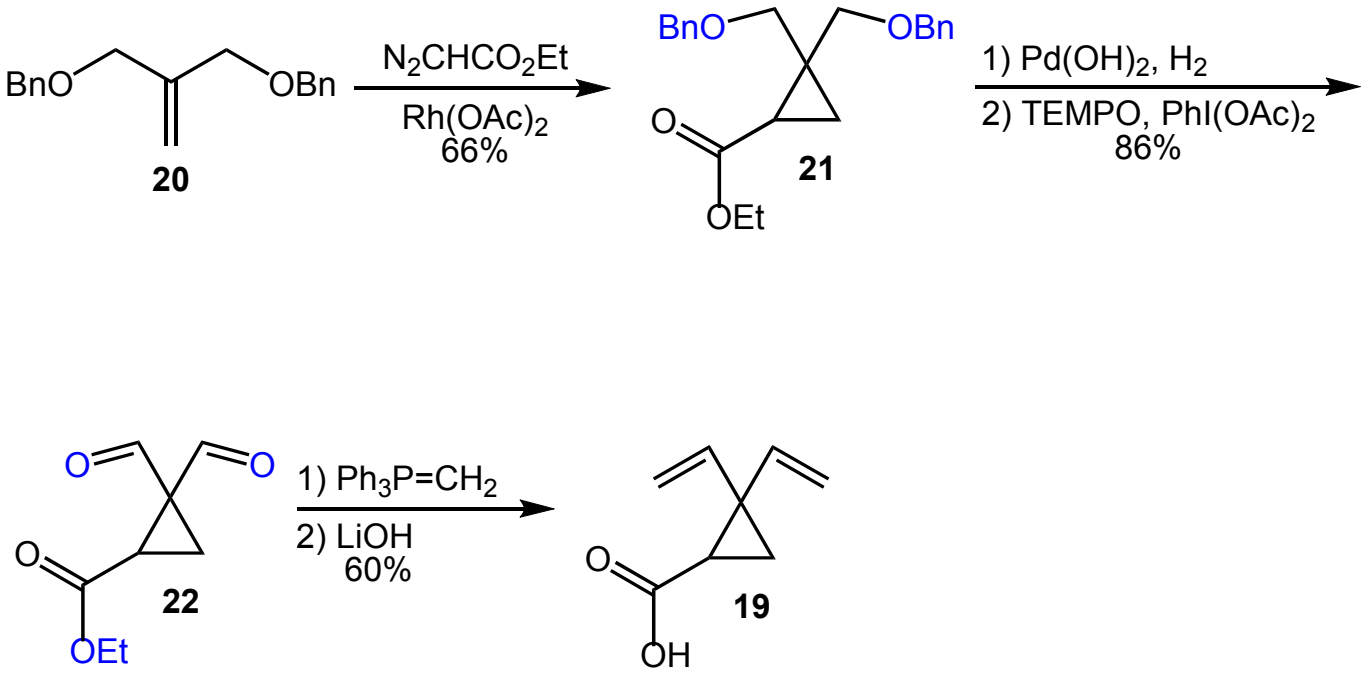
16

17

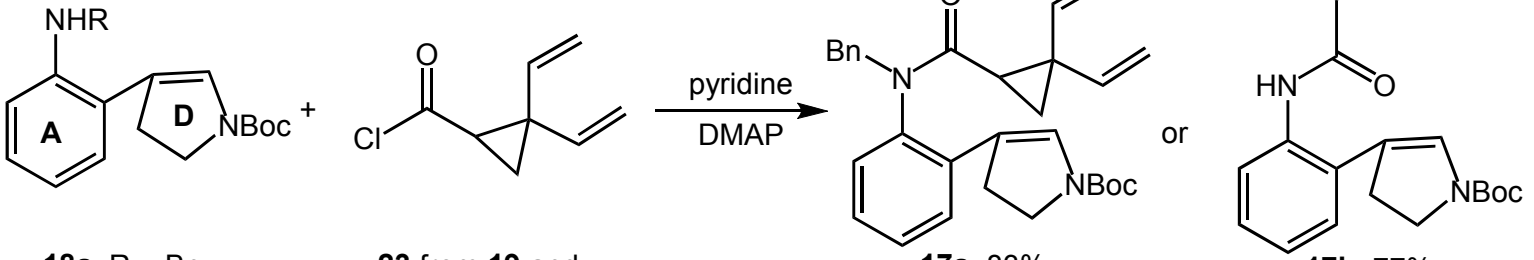
18

19

Synthesis of divinylcyclopropanecarboxylic acid



Synthesis of (±)-Epimeloscine and (±)-Meloscine

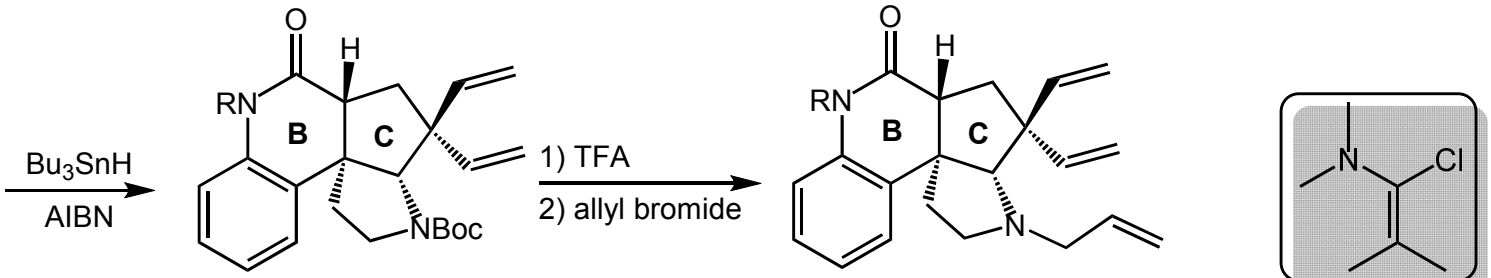


18a, R = Bn
18b, R = H

23 from **19** and Ghosez reagent

17a, 83%
E-rotamer favored

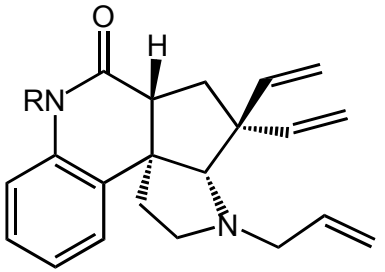
17b, 77%
Z-rotamer favored



16a, R = Bn, 55%
16b, R = H, 38%

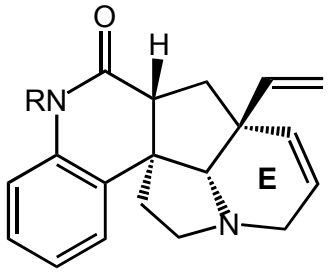
24a, R = Bn, 83%
24b, R = H, 73%

Synthesis of (±)-Epimeloscine and (±)-Meloscine



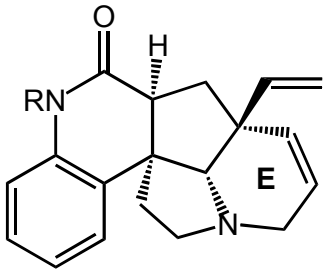
24a, R = Bn, 83%
24b, R = H, 73%

Grubbs II



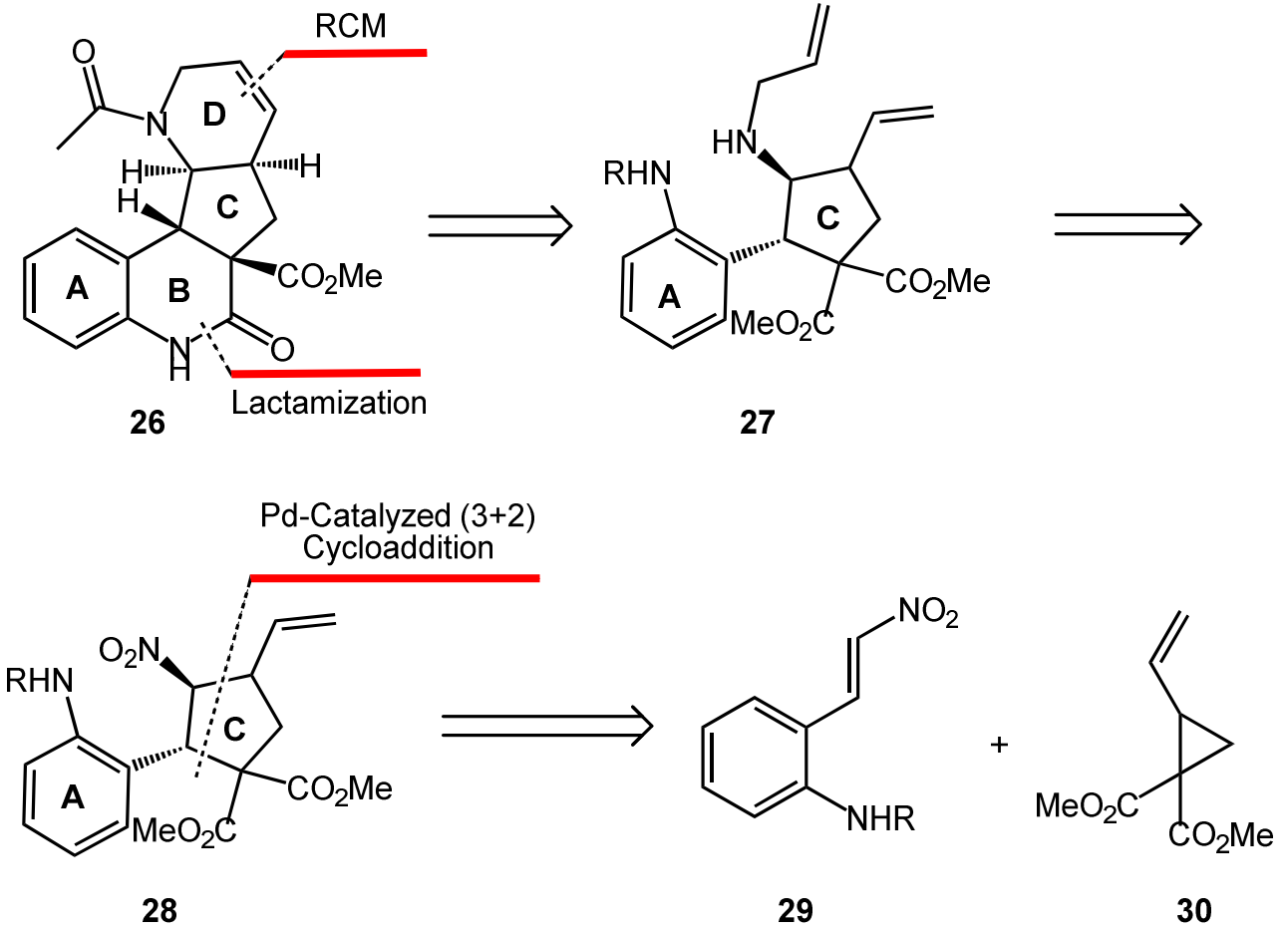
25a, R = Bn, 94%, roadblock
Epimeloscine 15, R = H, 89%

KO^tBu
R = H



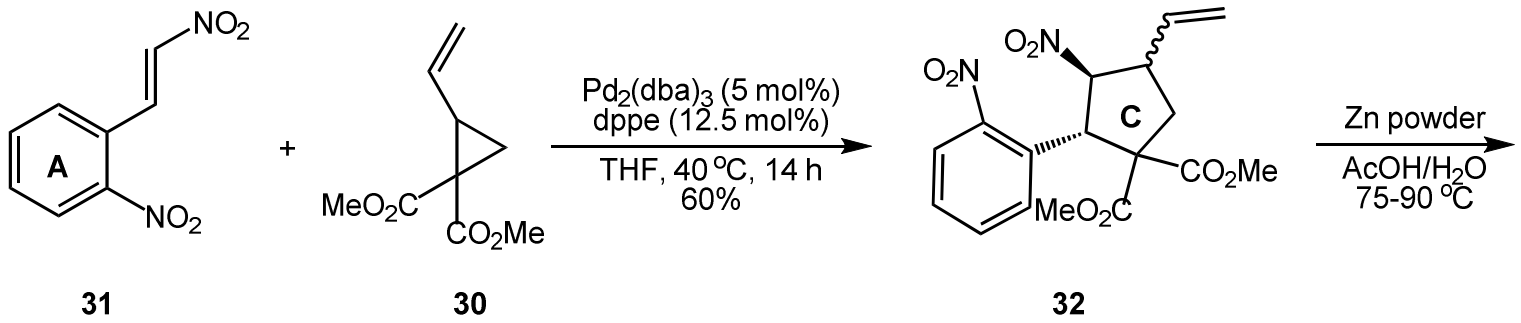
Meloscine 14, 83%

Retrosynthetic analysis of Melodinus Alkaloids

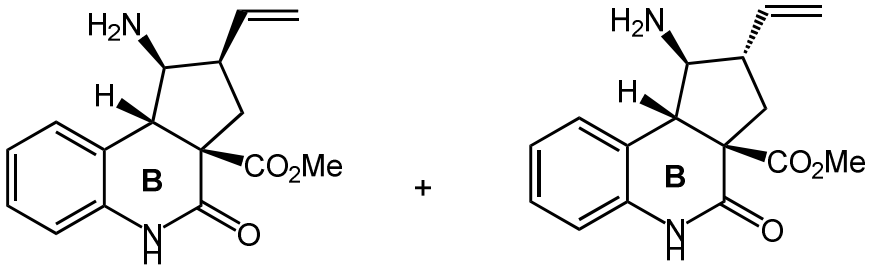


Alexander F. G. Goldberg, Brian M. Stoltz. *Org. Lett*. **2011**, *13*, 4474.

Synthesis of the ABC ring system

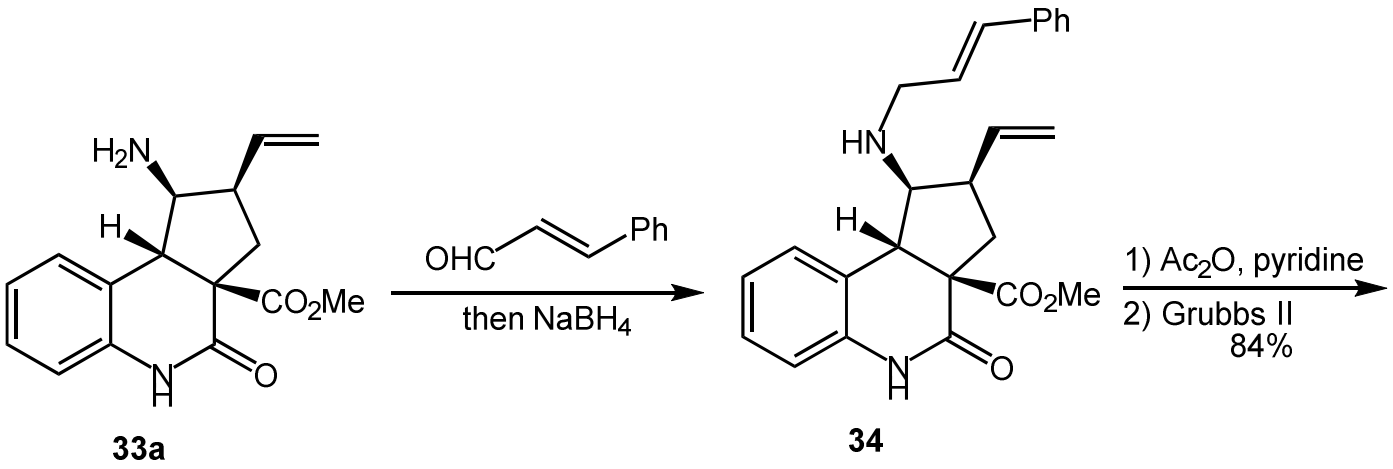


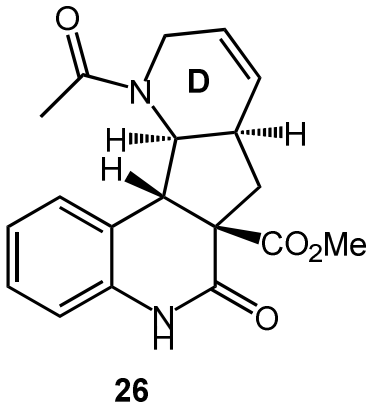
31 **30** **32**



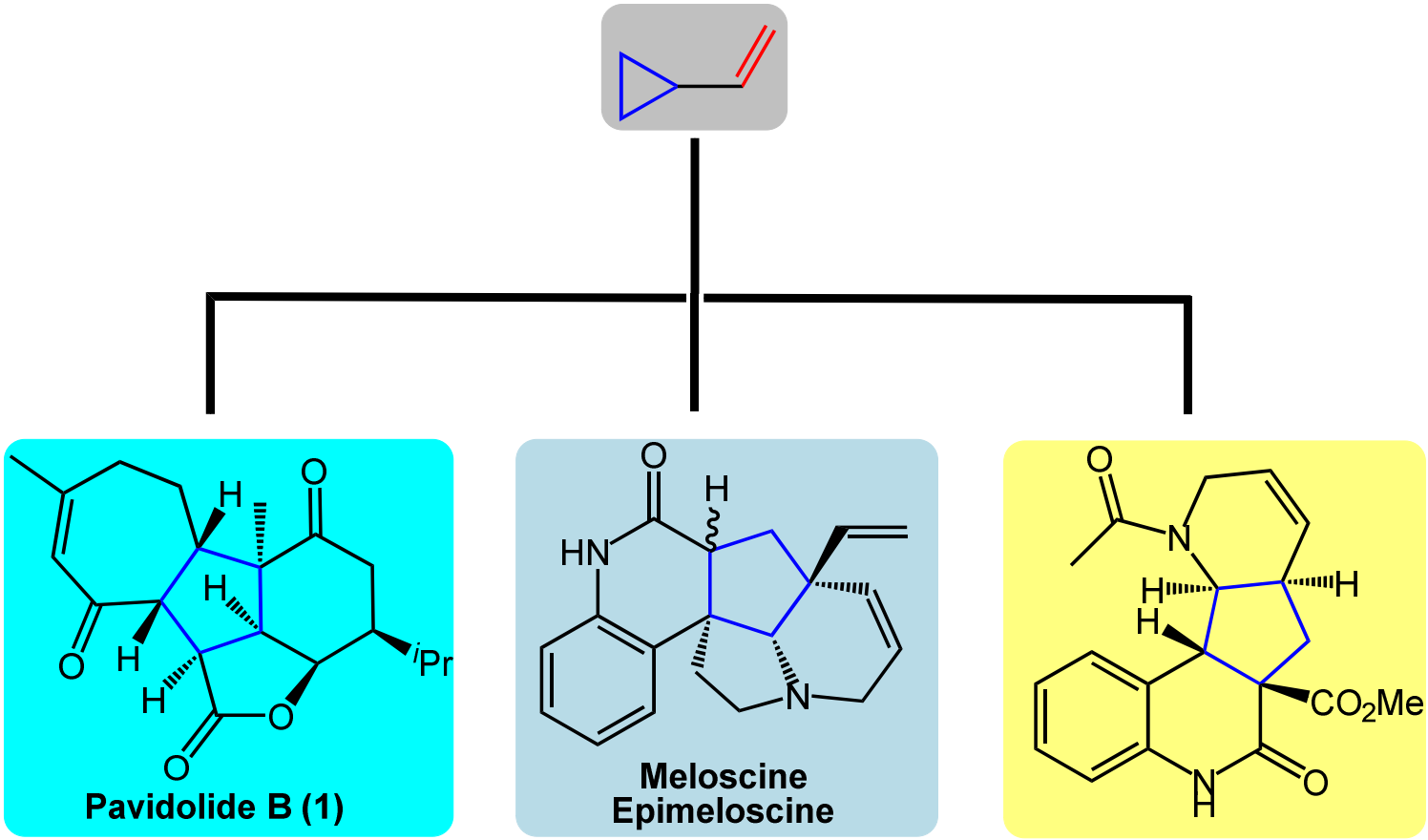
33a (1:2 *dr*, 79%) **33b**

Closure of D ring





Summary



Introduction

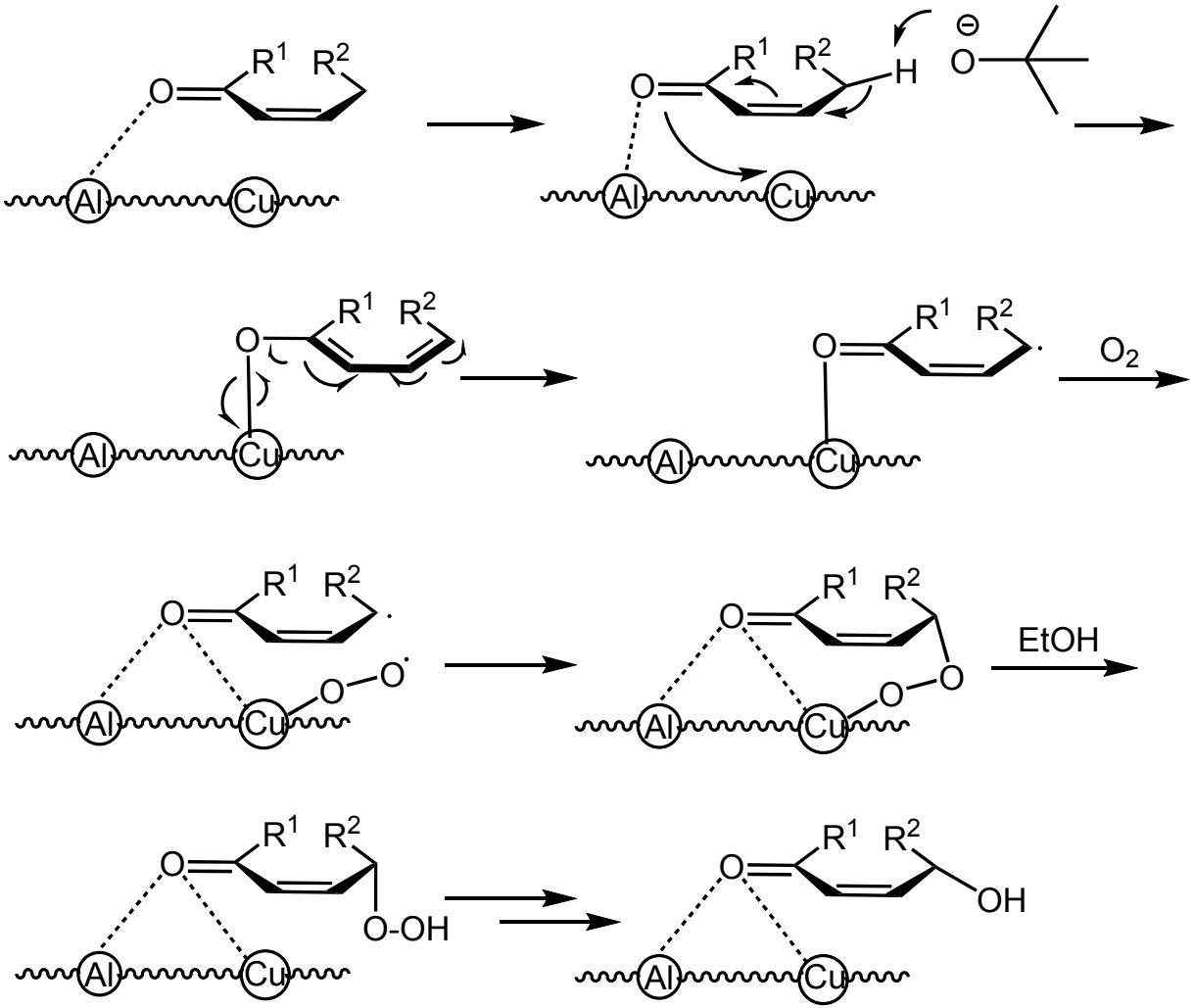
The (-)-pavidolide B, a tetracyclic diterpenoid, was isolated in a small quantity from the marine soft coral *Sinularia pavida* by Lin and co-workers in 2012. This molecule shows high selective inhibitory activity against a number of human promyelocytic leukemia cell lines.

The efficient synthesis of the dome-shaped 5/5/6 fused-ring system and fully functionalized C ring of pavidolide B, with seven contiguous stereocenters (one of which is quaternary), poses huge challenges, and efficient strategies for successful execution need to be designed.

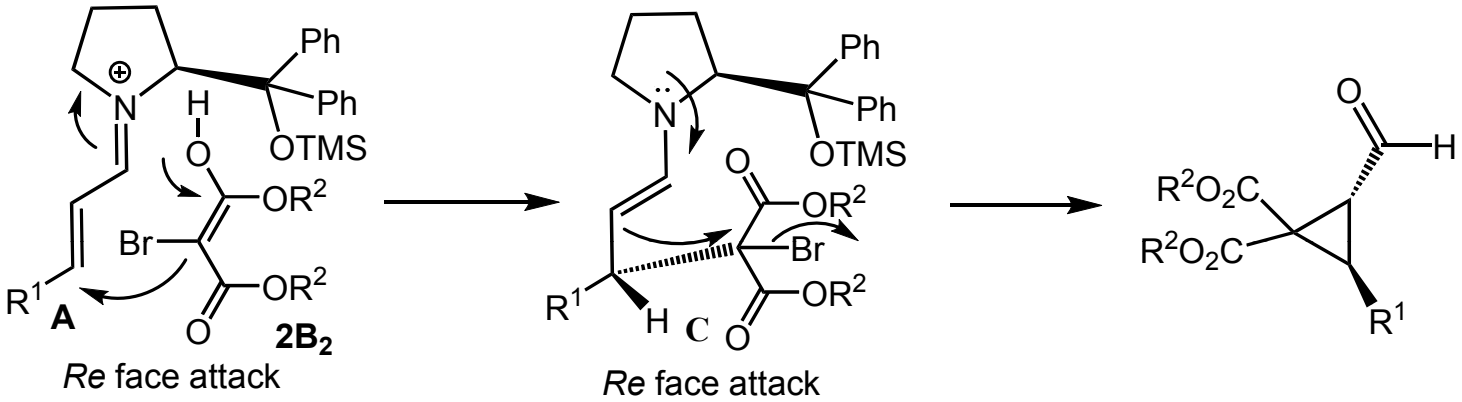
Summary

In summary, the asymmetric total synthesis of pavidolide B (1) was achieved for the first time in 10 linear steps with 16% overall yield. The key step is a radical-based cascade annulation of ester **4**. This reaction assembles the fully functionalized tricyclic C ring of pavidolide B with formation of two C−C bonds, two rings in a single step, and four stereocenters including the C4 quaternary center.

Selective Cu-Al Ox mediated enone allylic hydroxylation



Synthesis of cyclopropane



Synthesis of 18