Christian A. Kuttruff

Johann Mulzer

Group Meeting
12/07/2013

Prof. Dr. Johann Mulzer, born August 5th, 1944 in Prien/Chiemsee (Germany)

Education

1969: Diploma in chemistry, University of Munich (LMU)

1969-1974: Ph.D., University of Munich (LMU), (with Rolf Huisgen)

1974-1975: Postdoc, Harvard University, (with E. J. Corey)

Academic Career

1980-1982: Assistant Professor, University of **Munich**

1982-1984: Associate Professor, University of **Düsseldorf**

1984-1995: Full Professor, Free University of **Berlin**

1995-1996: Full Professor, University of **Frankfurt**

1996-2012: Full Professor, University of **Vienna** (Austria)

Selected Awards and Memberships

1981: Grant for a University Lecturer in Chemistry, Chemical Industry Fund (FCI)
1983: Jost Henkel Memorial Prize
1994: Leibniz Prize, German Research Foundation (DFG)
1997: Ernst Schering Prize, Ernst Schering Research Foundation
1999: Erwin Schrödinger Prize of the Austrian Academy of Science
2002: Member of the Austrian Academy of Science
2010: Emil-Fischer-Medaille, Gesellschaft Deutscher Chemiker (GDCh)

Publications (as of December 2013)

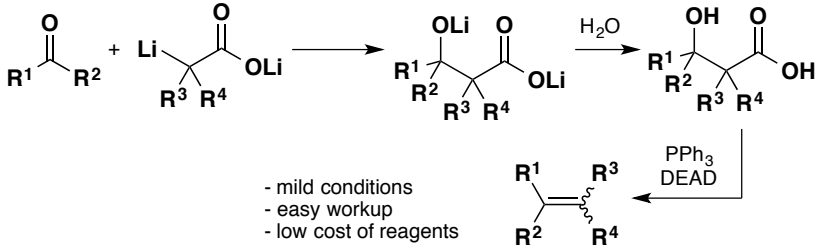
- 321 publications
- 49 reviews
- 13 patents
- many books and book chapters

"Die Guad'n haltens aus!" (Mulzer)

Disclaimer: this presentation represents a presonal selection of the published work of Johann Mulzer and is not intended to be comprehensive by any means.

The early days in Munich:

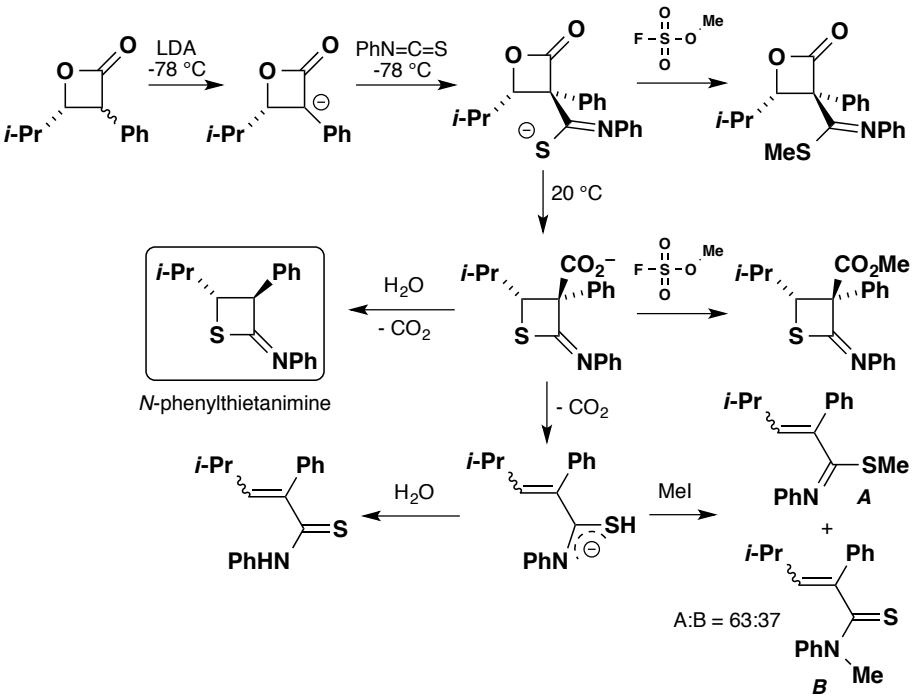
Decarboxylative dehydration of β-hydroxycarboxylic acids
Angew. Chem. Int. Ed. **1977**, *16*, 255–256.



new olefin synthesis

→ methodology expanded to synthesis of 1,3-dienes: *Tetrahedron Lett.* **1978**, *19*, 2953–2954.

2-thietanimines from α-deprotonated β-lactones and phenyl isothiocyanate
Angew. Chem. Int. Ed. **1980**, *19*, 466–467.



N-phenylthietanimine

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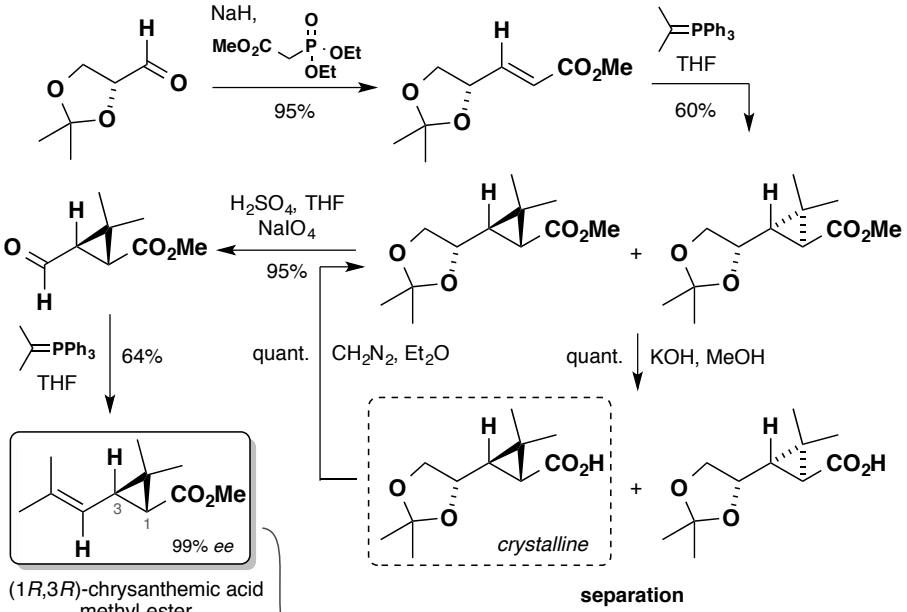
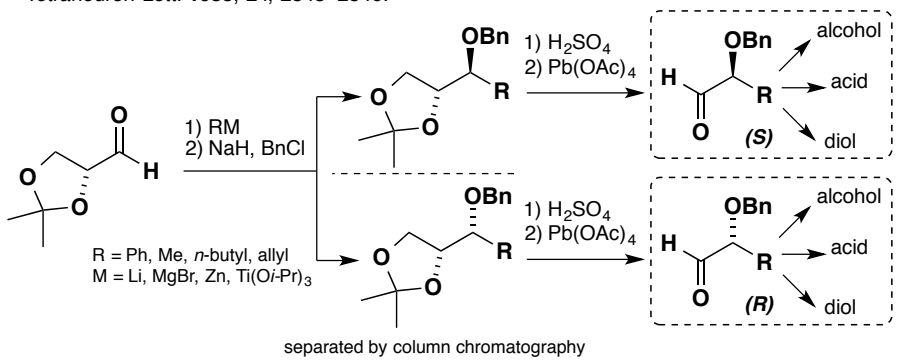
Some work from the Düsseldorf, Berlin and Frankfurt period:

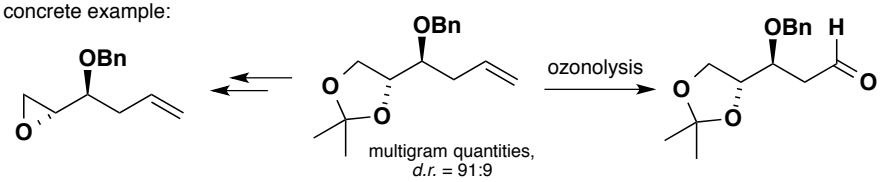
Diastereo- and enantioselective synthesis of chrysanthemic acid methyl ester
Angew. Chem. Int. Ed. **1983**, *22*, 63–64.



Synthesis of optically active building blocks from (*R*)-2,3-isopropylidene glyceraldehyde
Tetrahedron Lett. **1983**, *24*, 2843–2846.



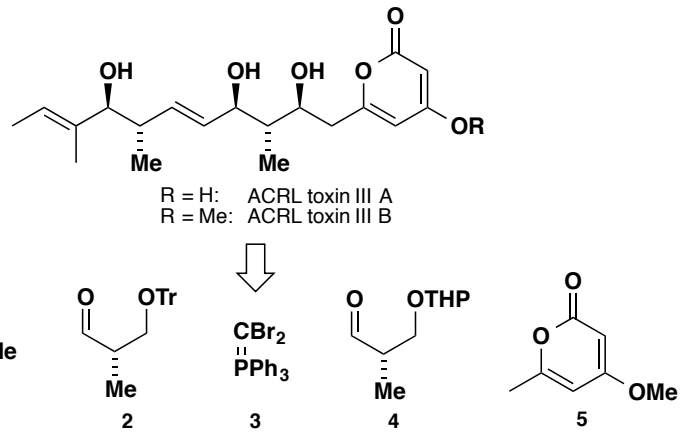
concrete example:



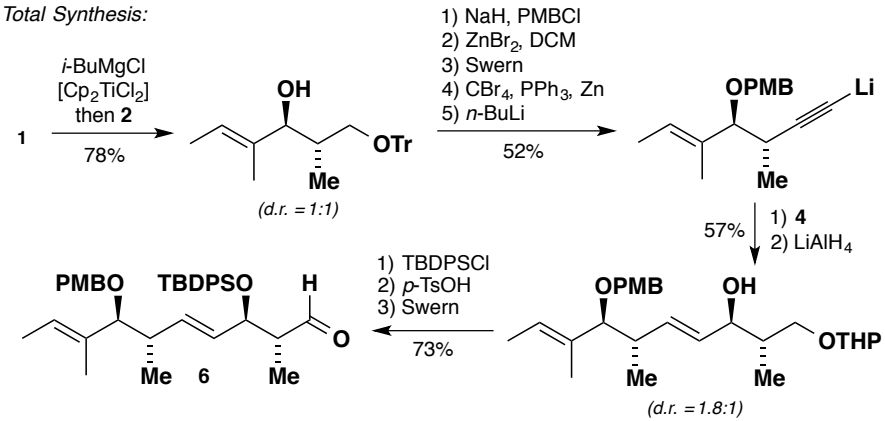
First total synthesis of (–)-ACRL Toxin III B
Angew. Chem. Int. Ed. **1993**, *32*, 1452–1454.

- ACRL toxin III A present in a fungus which causes brown spot disease on citrus
- unknown mechanism of action

Retrosynthesis:



Total Synthesis:



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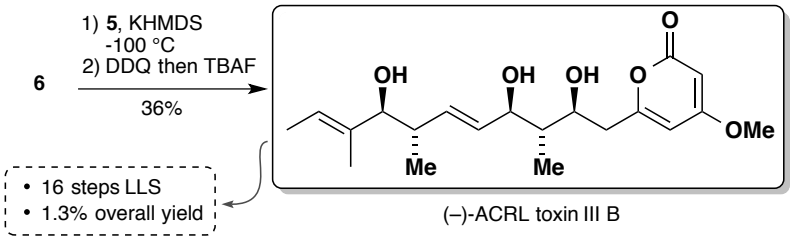
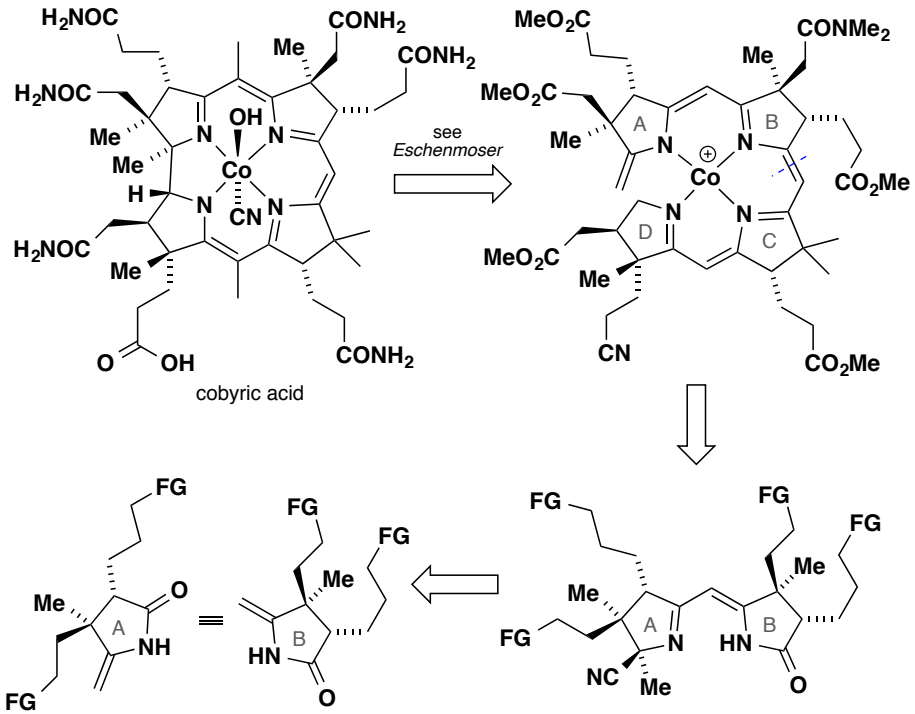
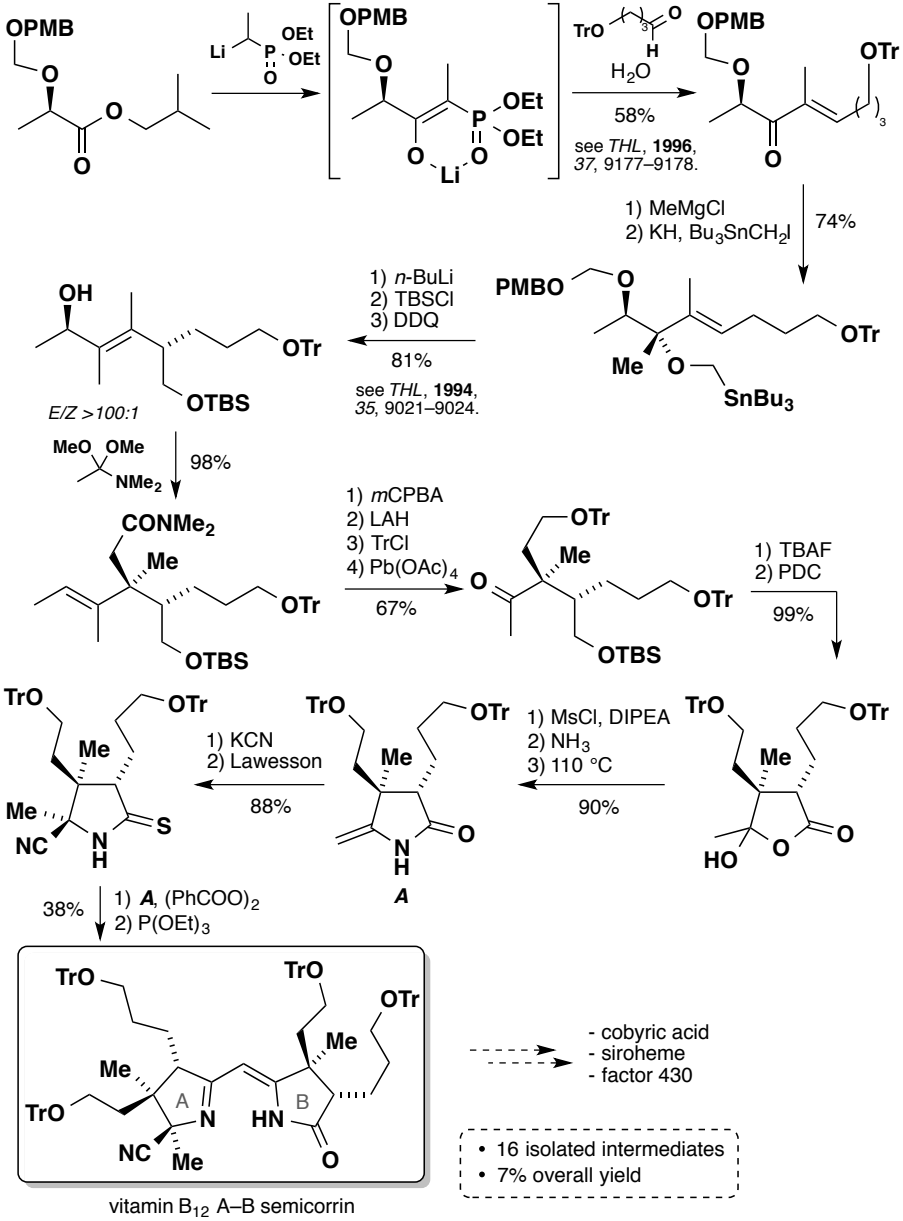


Synthesis of a Vitamin B_{12} A–B-semicorrin
J. Am. Chem. Soc. **1997**, *119*, 5512–5518.

Retrosynthesis:



Forward Synthesis:



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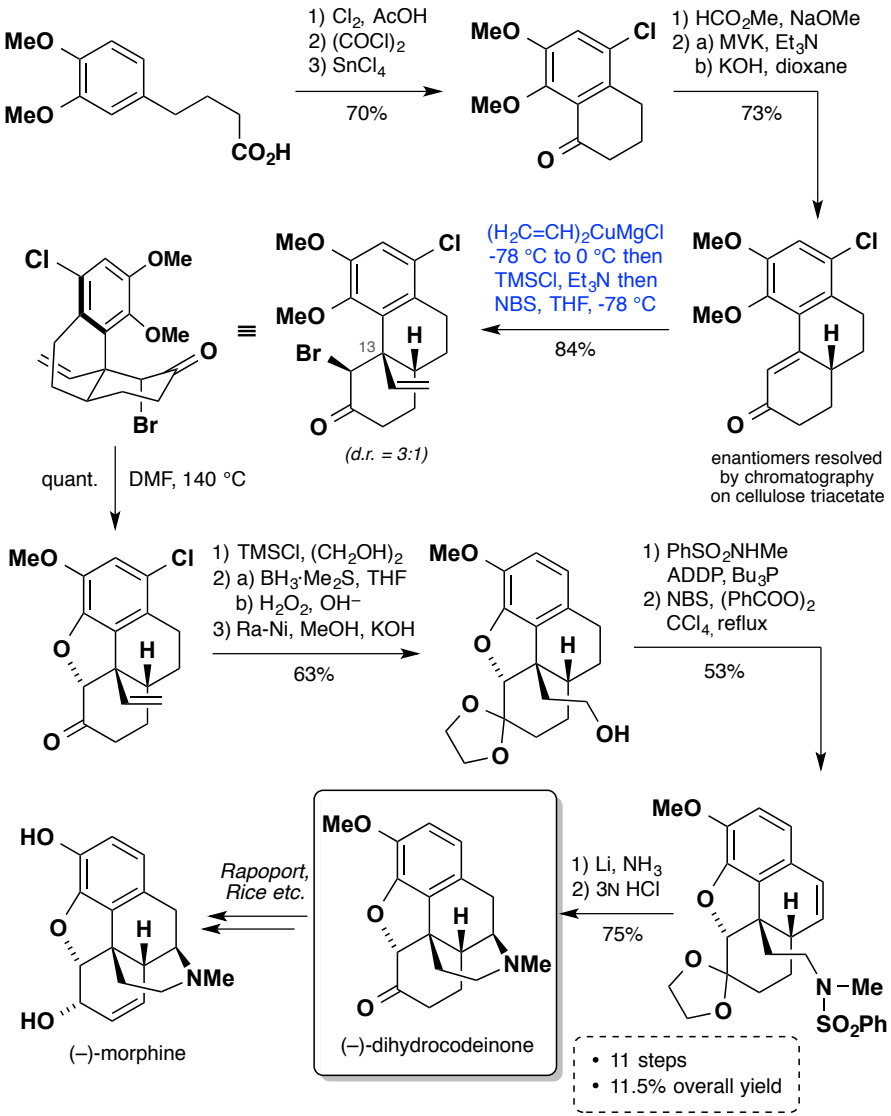
The Vienna Era:

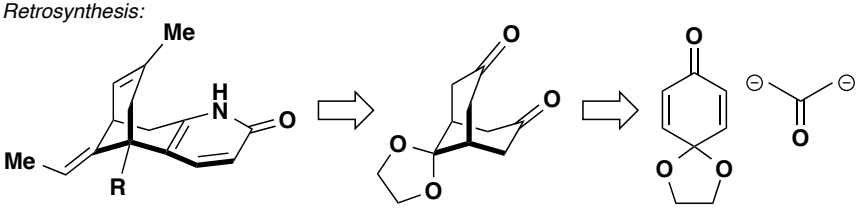
(–)-Morphine
Angew. Chem. Int. Ed. **1996**, *35*, 2830–2832.

Total Synthesis:



(±)-desamino huperzine A
Tetrahedron Lett. **2000**, *41*, 9229–9232

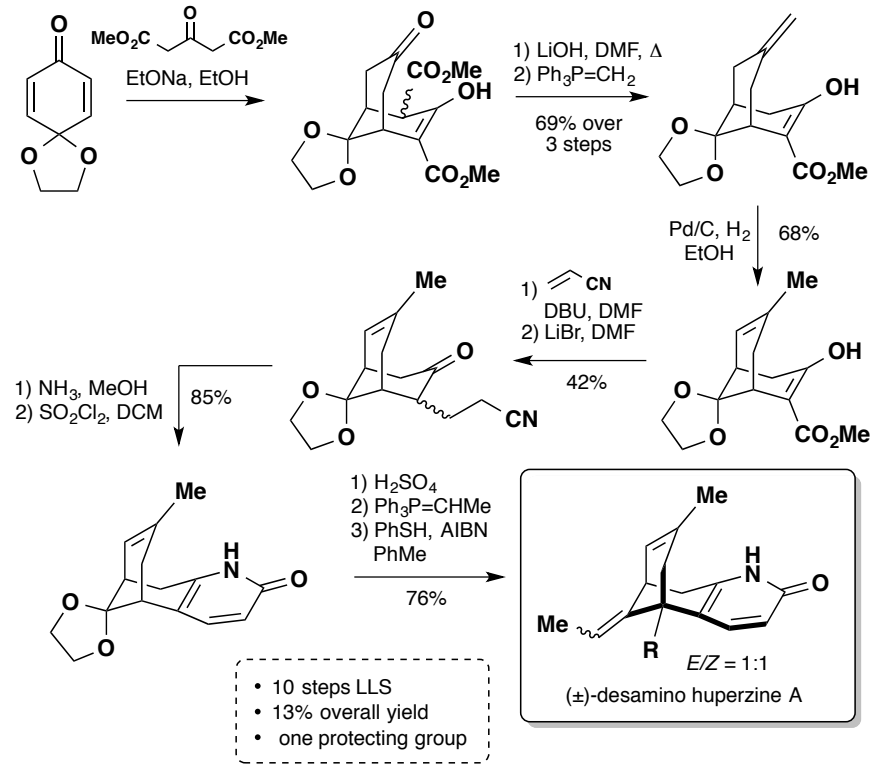
Retrosynthesis:



R = NH_2: huperzine A
R = H: desamino huperzine A

- huperzine A is a AChE inhibitor and a potential lead for treatment of Alzheimer's disease
- great potential in synthetic derivatives of huperzine A

Total Synthesis:



→ synthesis and biological activity of more derivatives: *BMCL* **2001**, *11*, 2627–2630.

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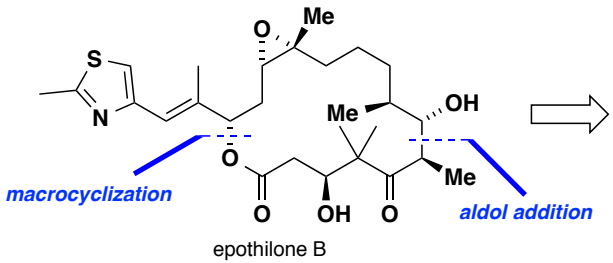
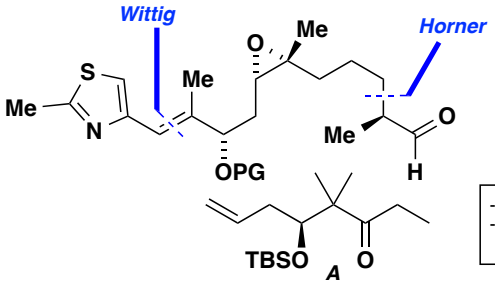
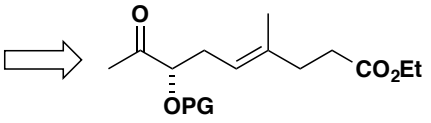
Epothilone B
Angew. Chem. Int. Ed. **2000**, *39*, 581–583.

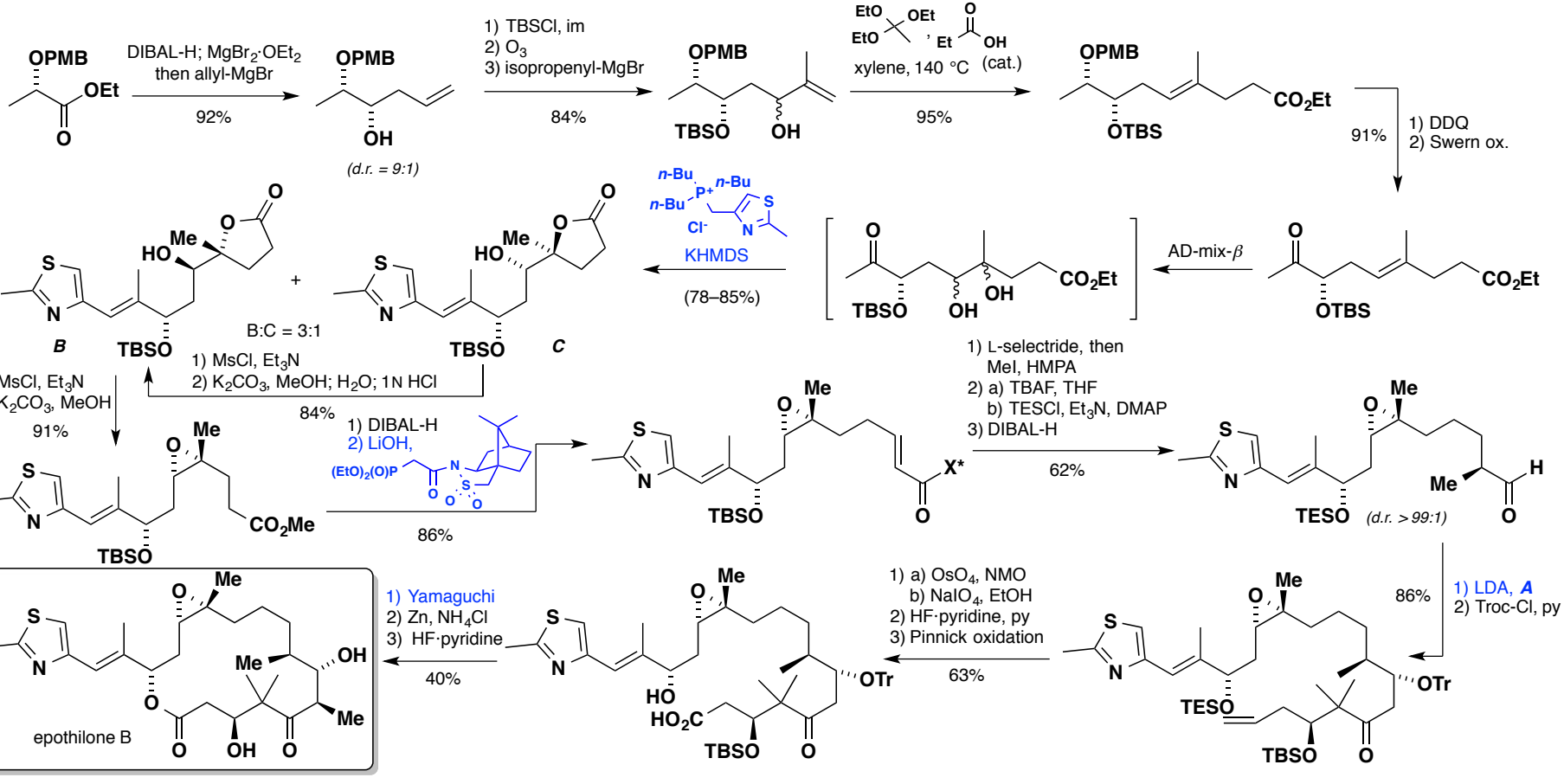


epothilone B





- epothilones are antitumor compounds that inhibit microtubule function
- aza-epothilone B (ixabepilone) was FDA-approved in 2007 for the treatment of aggressive metastatic breast cancer



→ subsequent work about epothilones and derivatives: *THL* **2000**, *41*, 7635; *JOC* **2000**, *65*, 7456; *Chem. Eur. J.* **2001**, *7*, 2261; *OL*, **2005**, *7*, 1311; *JOC*, **2006**, *15*, 3372.

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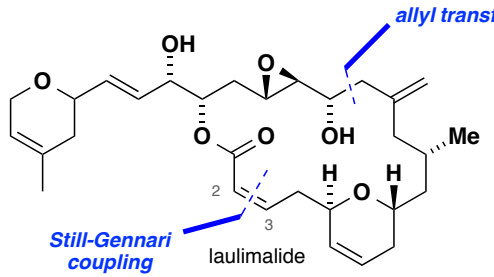
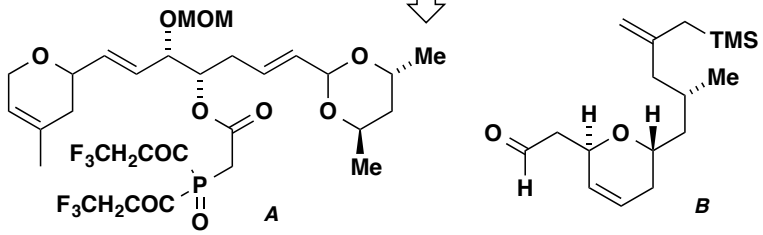
Laulimalide
JACS **2001**, *123*, 10764–10765.

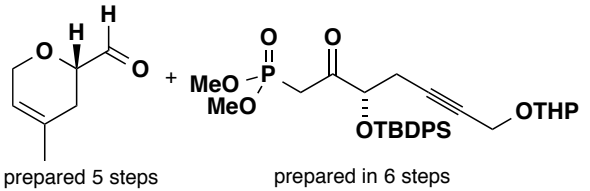
- laulimalide is a metabolite from marine sponges that promotes abnormal tubulin polymerization
- displays unusually high activity against multidrug resistant cancer cell lines

Retrosynthesis:



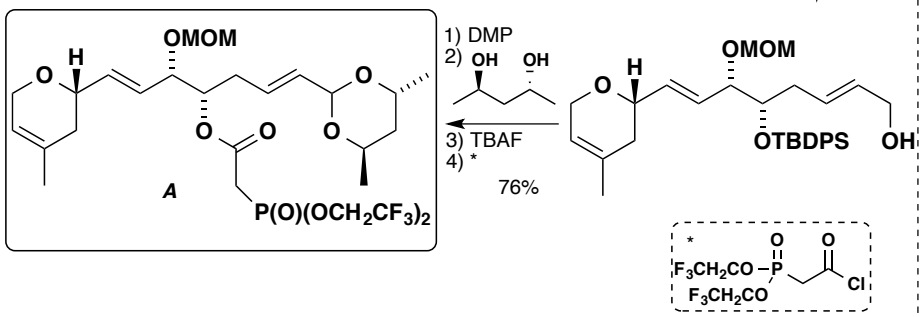


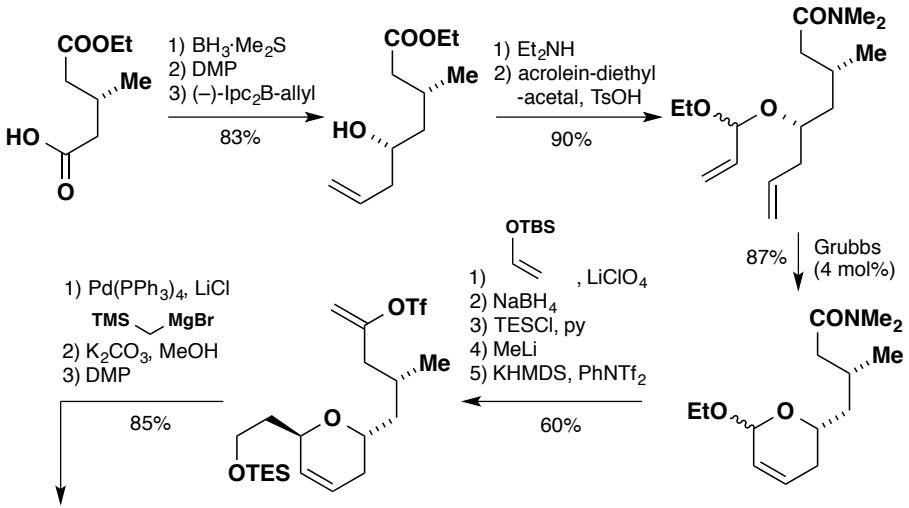
Total Synthesis:

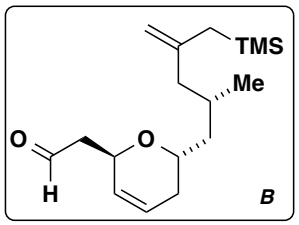


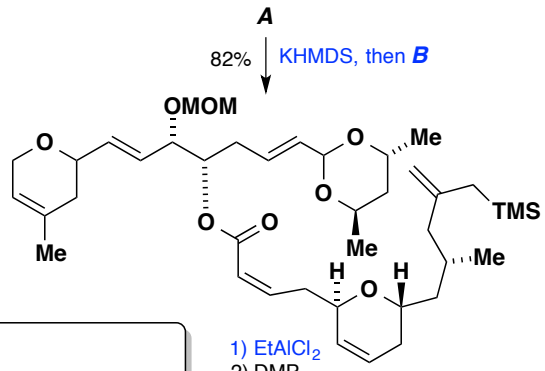
1) LiOH
2) $NaBH_4$, $CeCl_3$
3) MOMCl, DIPEA
4) HCl, MeOH
5) Red-Al

40%



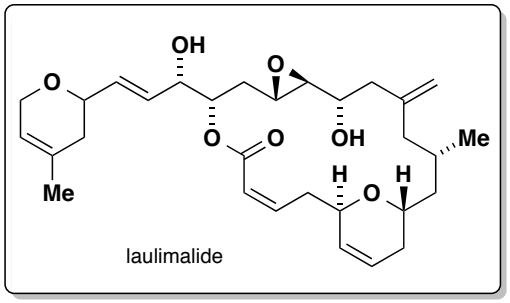






1) $EtAlCl_2$
2) DMP
3) TsOH
4) Me_2BBr
5) SAE

31%



- 19 steps LLS
- 21% overall yield
- 1st fully stereocontrolled synthesis

→ subsequent work about laulimalide and analogs: *THL* **2002**, *43*, 3381; *JOC* **2003**, *68*, 3026; *OL* **2008**, *10*, 4701; *Chem. Eur. J.* **2009**, *15*, 5979; *THL*, **2009**, *50*, 5790.

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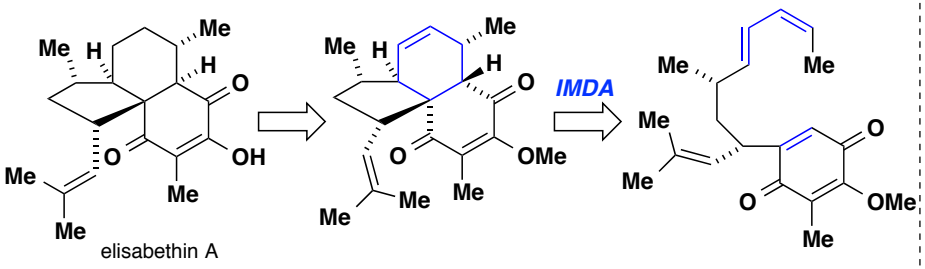
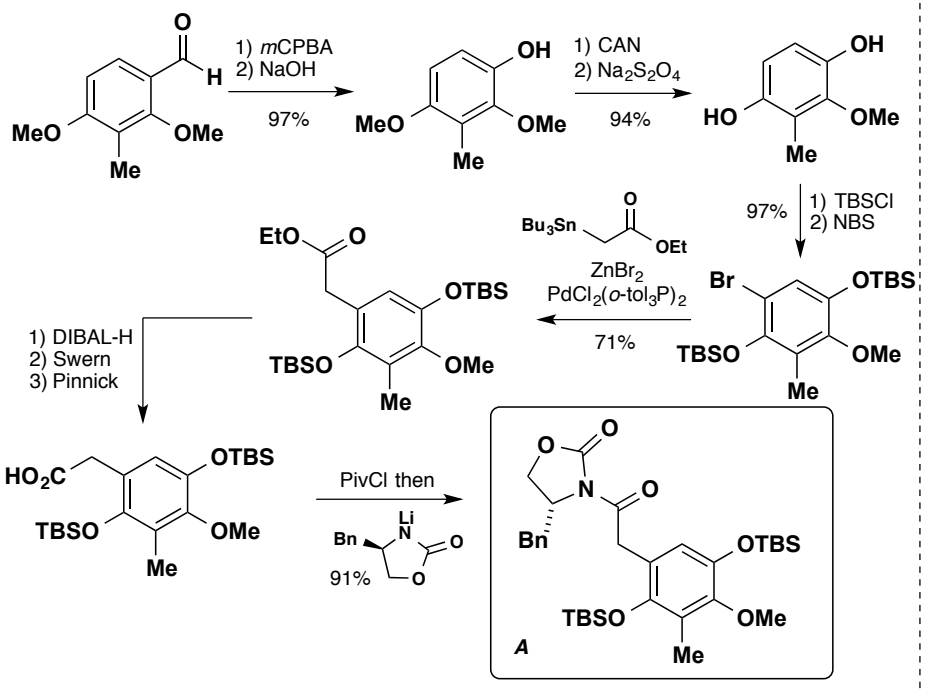
Elisabethin A
JACS **2003**, *125*, 4680–4681.

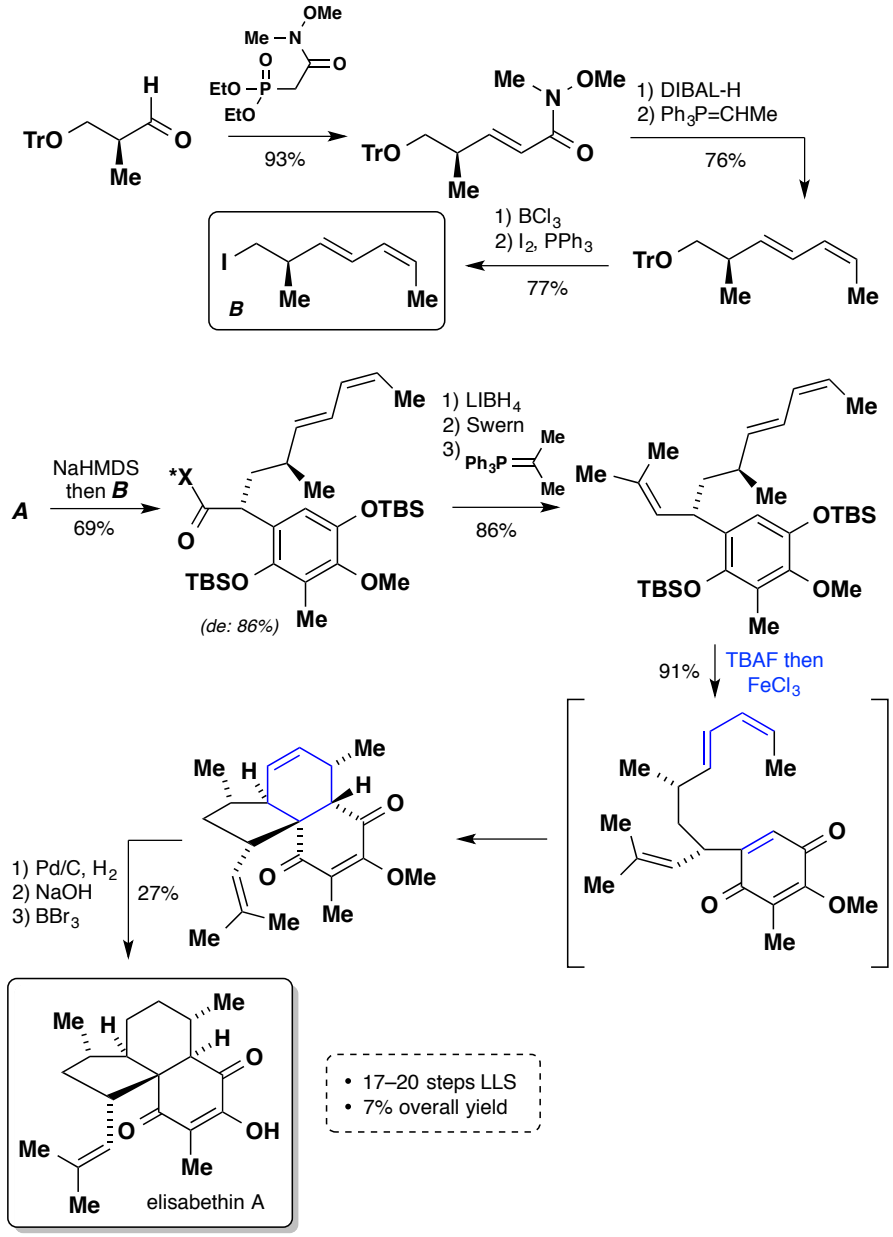
- isolated from the Carribean gorgonian *Pseudopterogorgia elisabethae*
- some members of the elisabethane class show significant activity agains *Mycobacterium tuberculosis*

Retrosynthesis:



Total Synthesis:



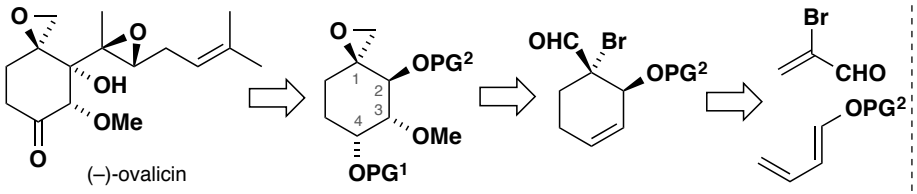


- 17–20 steps LLS
- 7% overall yield

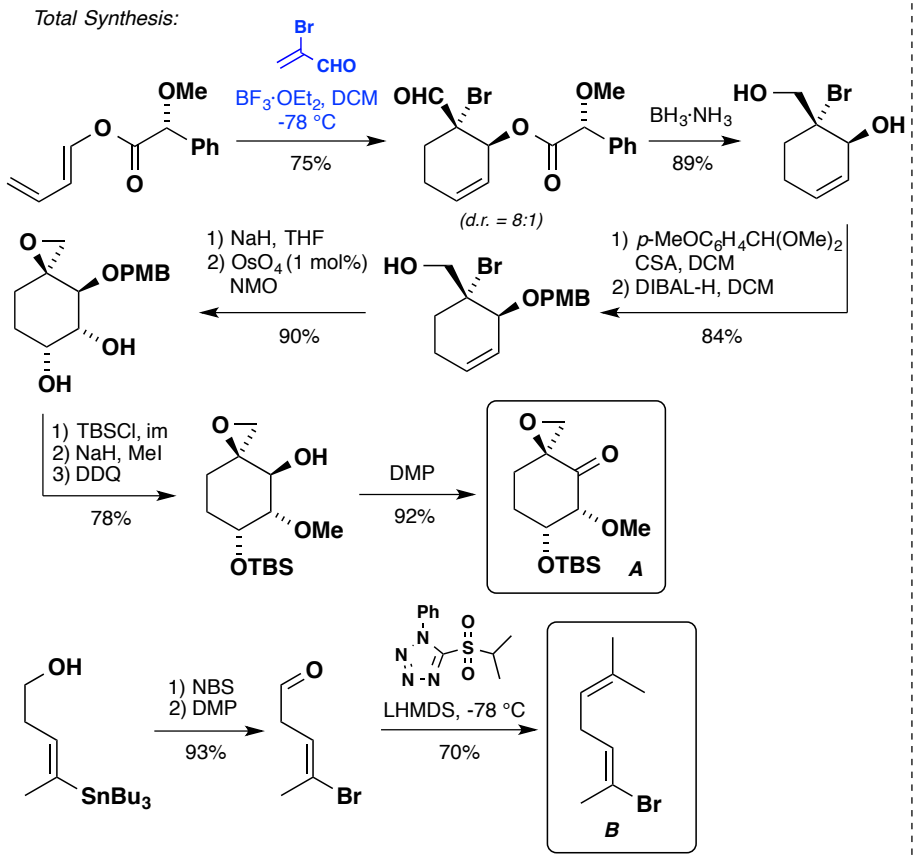
(–)-Ovalicin
Angew. Chem. Int. Ed. **2007**, *46*, 2690–2693

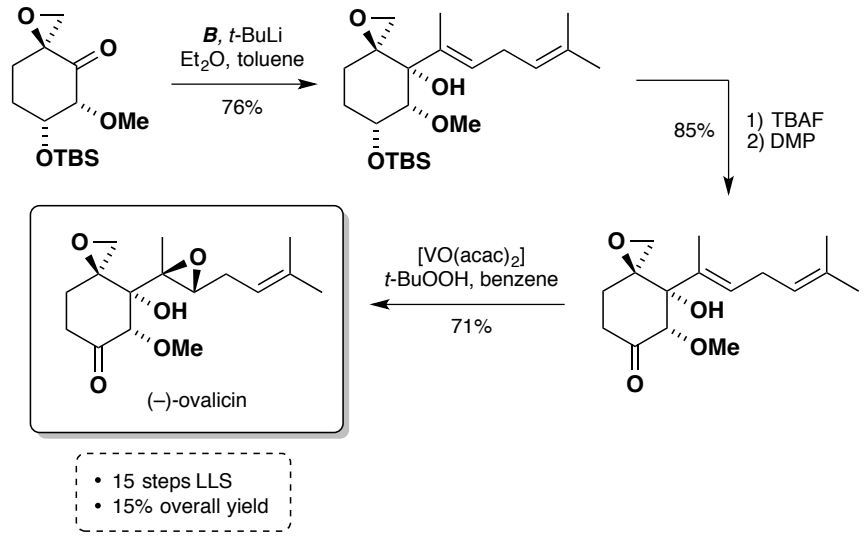
- ovalicin and the structurally closely related fumagillin show potent antiangiogenic activity
- ovalicin is also a promising agent against microsporidiosis

Retrosynthesis:



Total Synthesis:



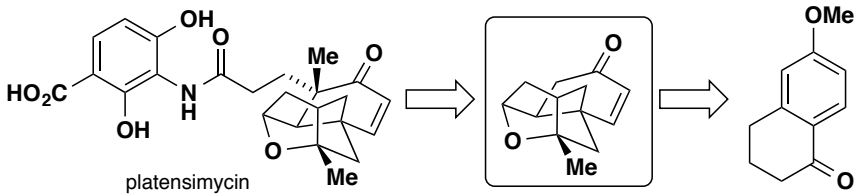


- 15 steps LLS
- 15% overall yield

Formal synthesis of platensimycin
Angew. Chem. Int. Ed. **2007**, *46*, 8074–8075.

- originally isolated by a Merck group from a strain of *Streptomyces platensis*
- inhibits β-ketoacyl-ACP synthase I/II (Fab F/B) which is involved in fatty acid biosynthesis
- its novel scaffold and extraordinary antibacterial activity have drawn great attention

Retrosynthesis:



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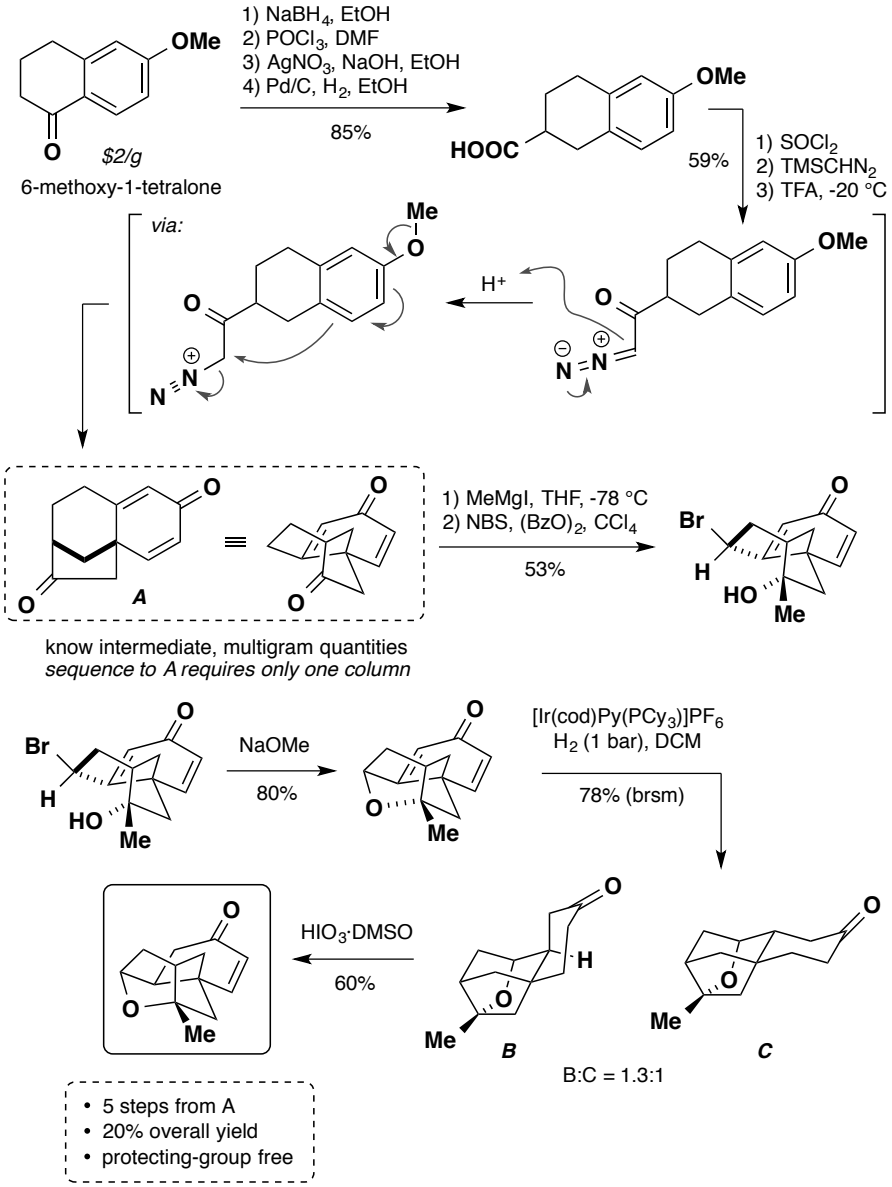
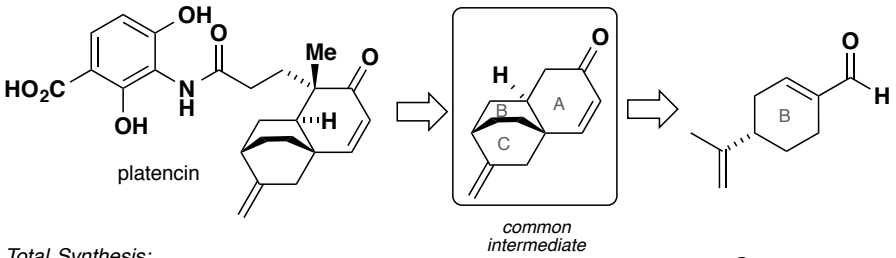
Total Synthesis:



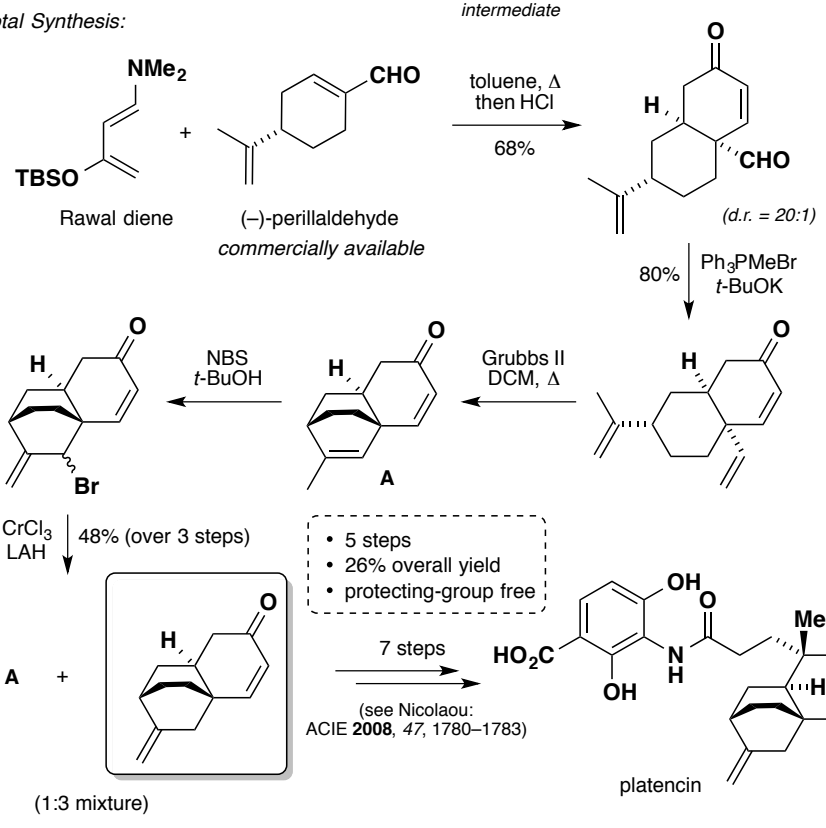
Formal synthesis of (–)-platencin
Angew. Chem. Int. Ed. **2008**, *47*, 6199–6200.

- isolated along with platensimycin
- exhibits broad-spectrum antibacterial activity against many pathogens that show resistance to current antibiotics

Retrosynthesis:



Total Synthesis:



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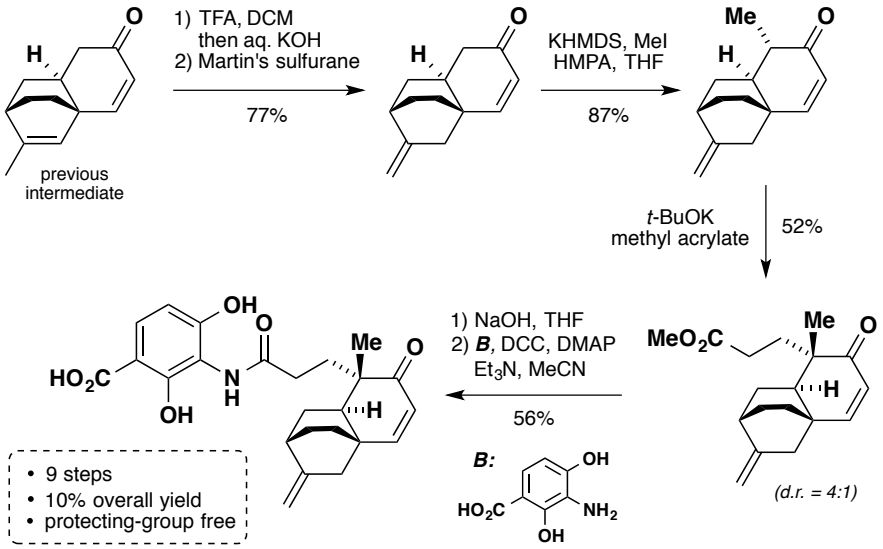
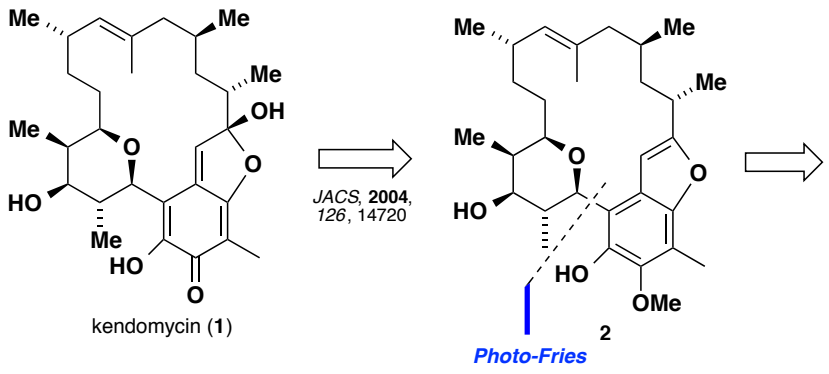
Total synthesis of (–)-platencin
J. Org. Chem. **2009**, *74*, 2937–2941.

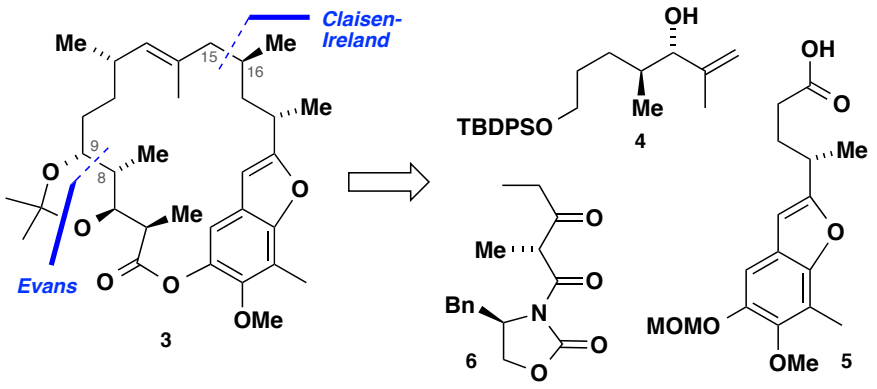


Kendomycin
Angew. Chem. Int. Ed. **2009**, *48*, 6032–6036.

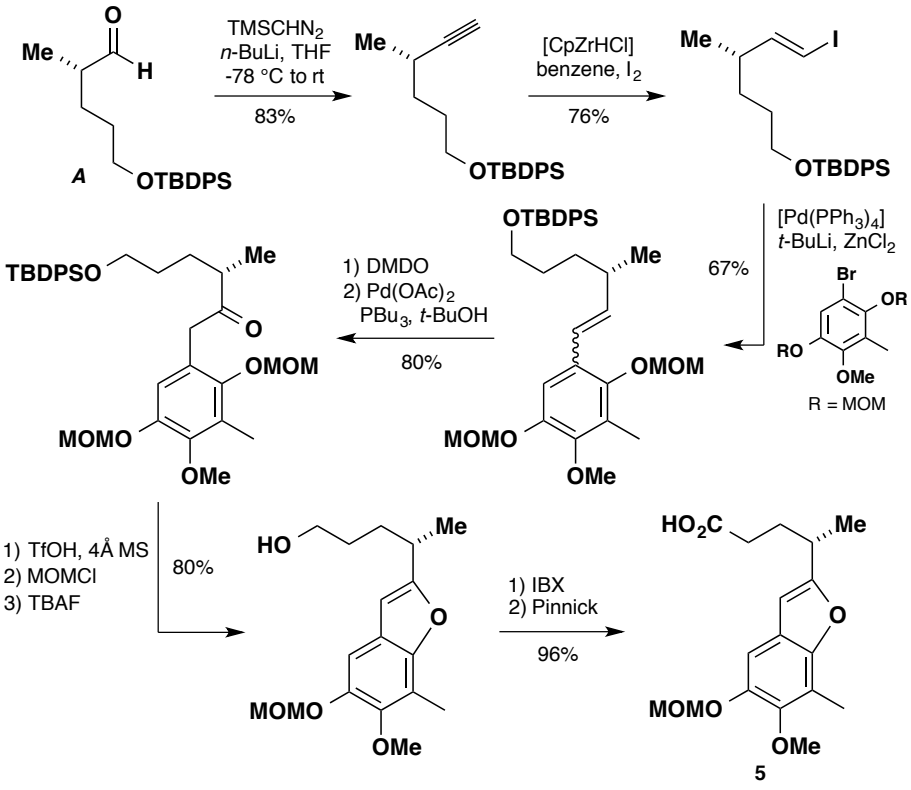
- antitumor macrolide first isolated in 2000 from the bacteria *Streptomyces violaceoruber*
- potent endothelin receptor antagonist and antiosteoperotic compound with remarkable antibacterial and cytostatic activity

Photo-Fries approach:





Total Synthesis:



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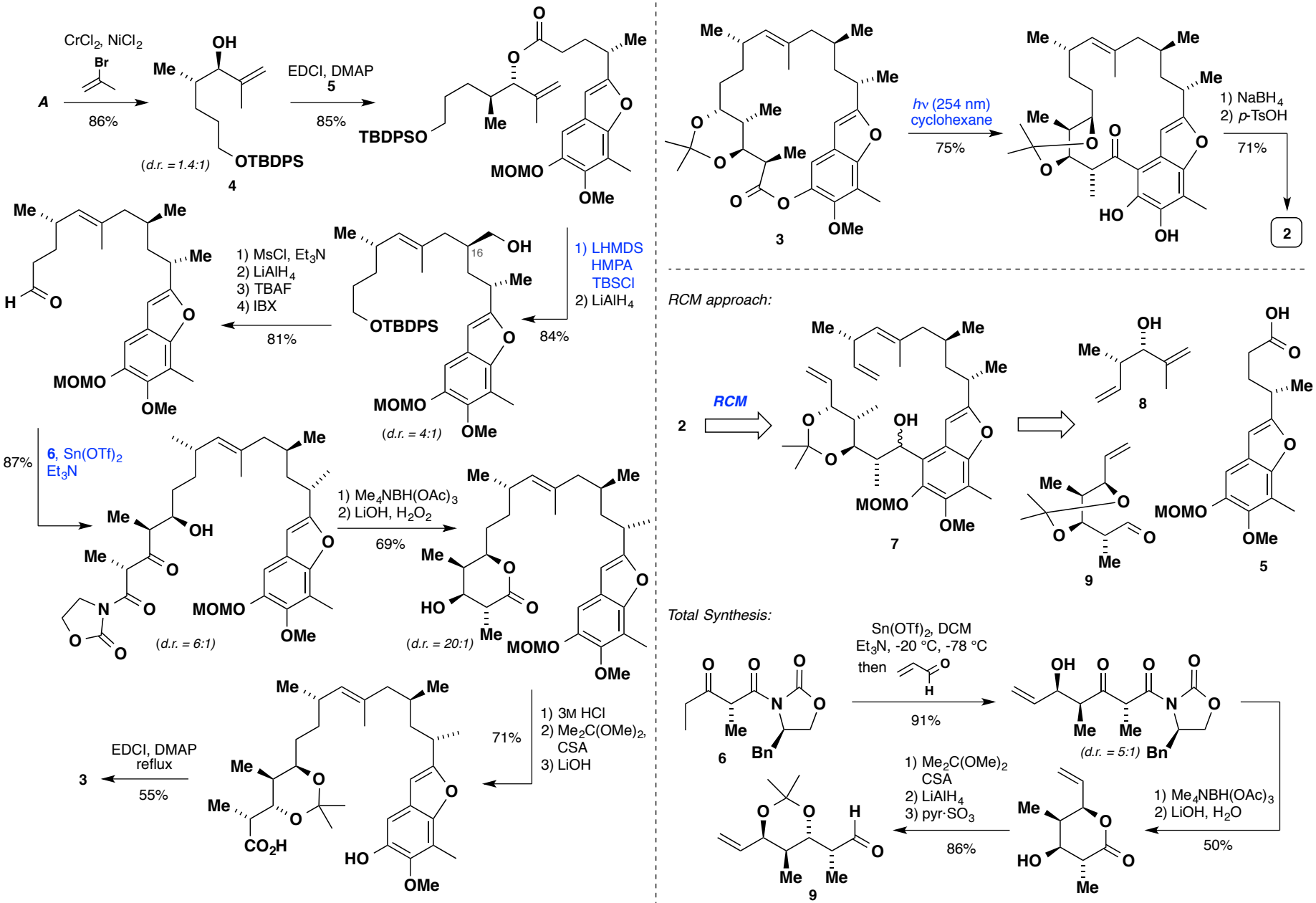

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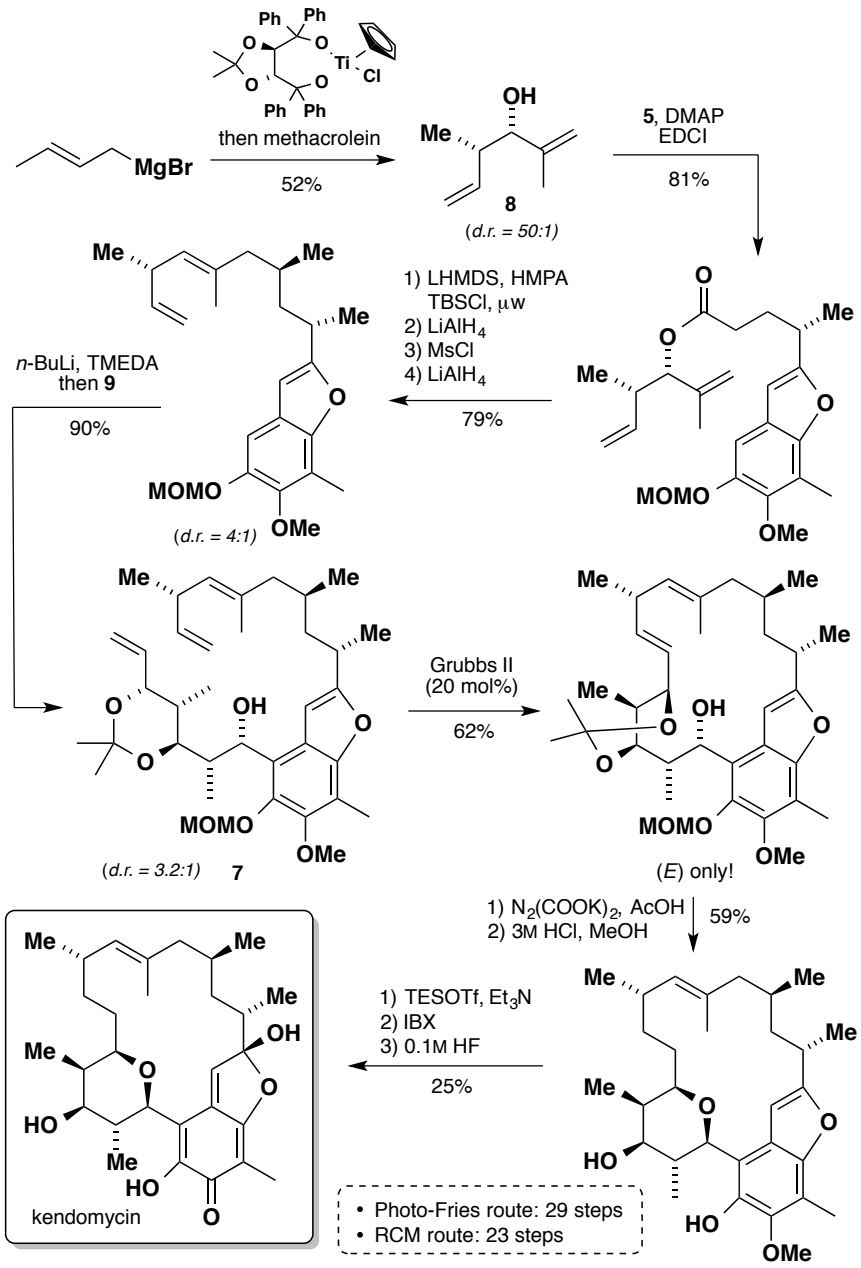
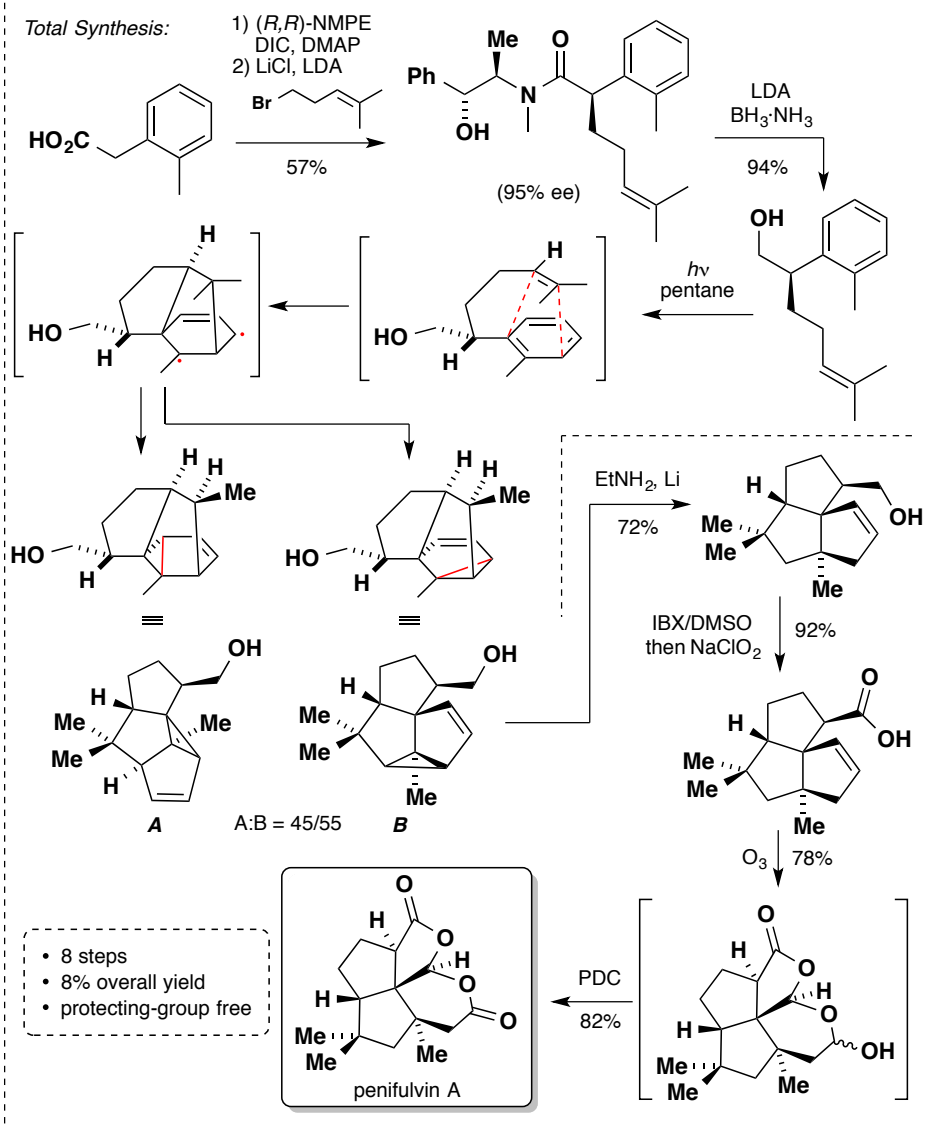


(–)-Penifulvin A
J. Am. Chem. Soc. **2009**, *131*, 452–453.

- shows strong insecticidal activity against the fall armyworm, one of the most significant pest of corn



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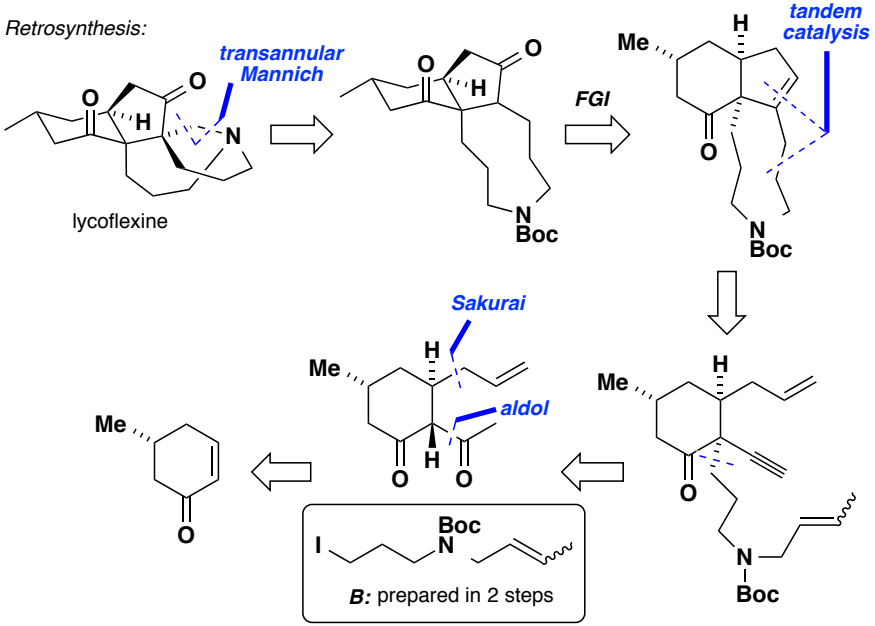
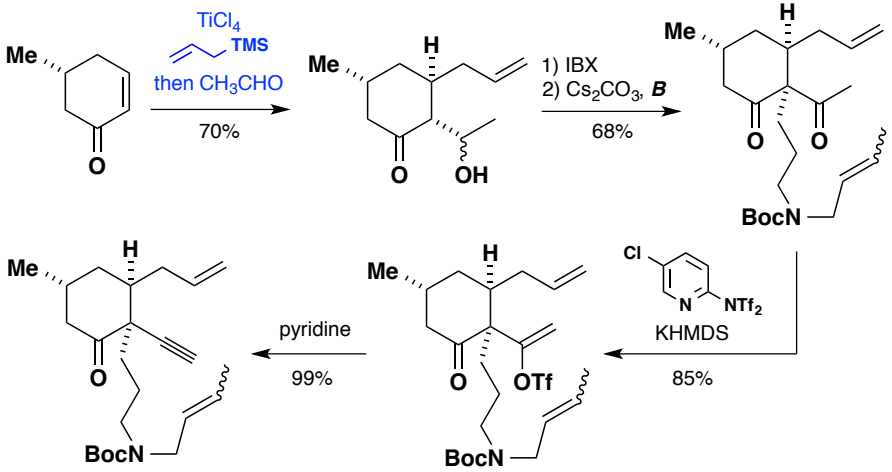
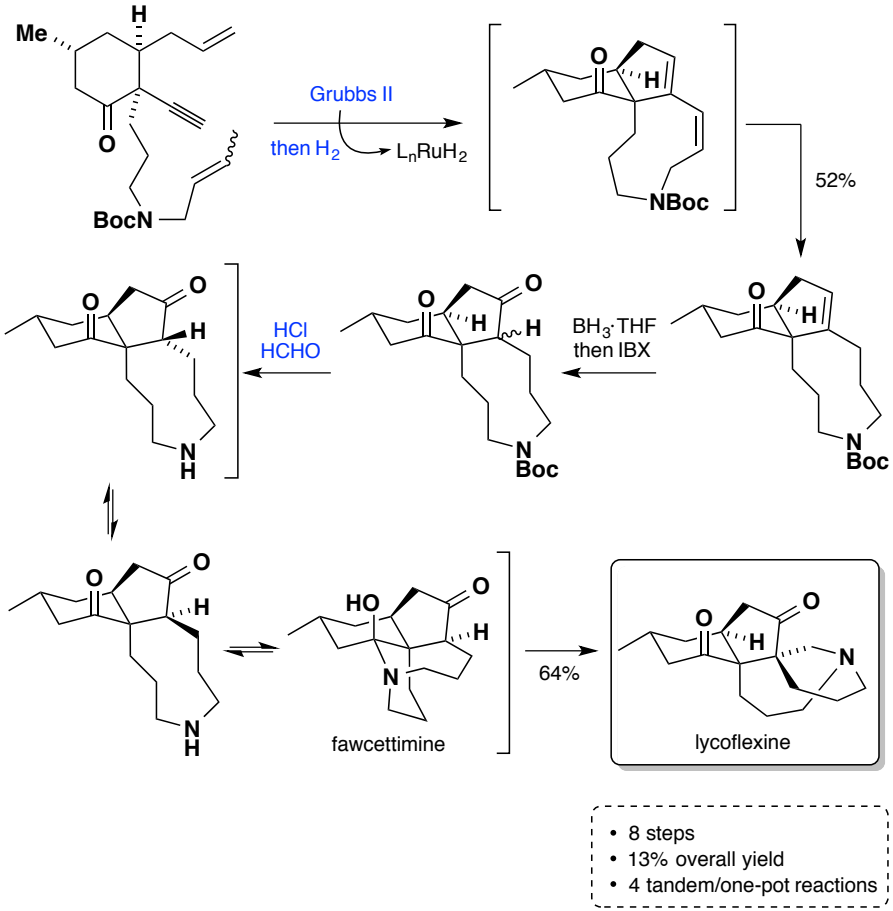
(+)-Lycoflexine
J. Am. Chem. Soc. **2010**, *132*, 14338–14339.

Retrosynthesis:



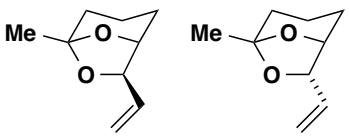
Total Synthesis:



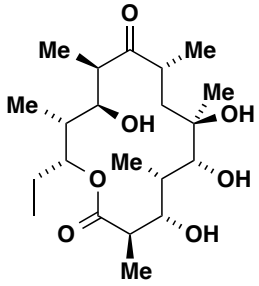


- 8 steps
- 13% overall yield
- 4 tandem/one-pot reactions

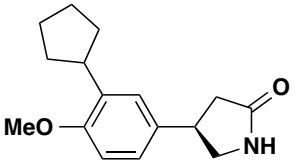
A selection of further completed targets by the Mulzer group:



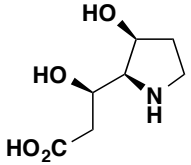
exo- and *endo*-**brevicomin**
Liebigs Ann. Chem. **1986**, 825–838.



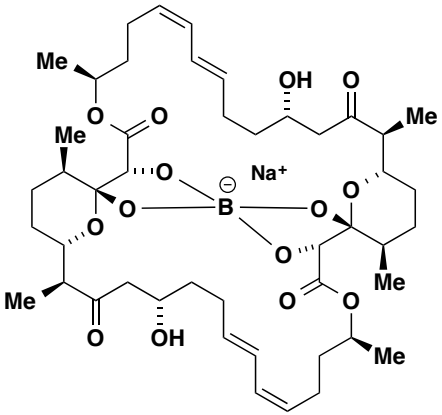
erythronolide B
JACS **1991**, *113,* 910–923.



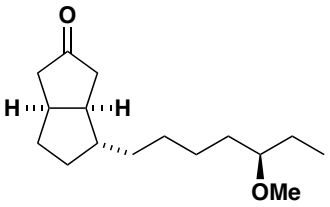
rolipram
ACIE **1992**, *31,* 870–872.



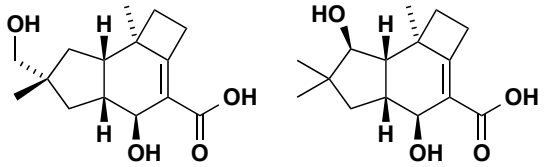
(+)-detoxinine
JOC **1996**, *61,* 566–572.



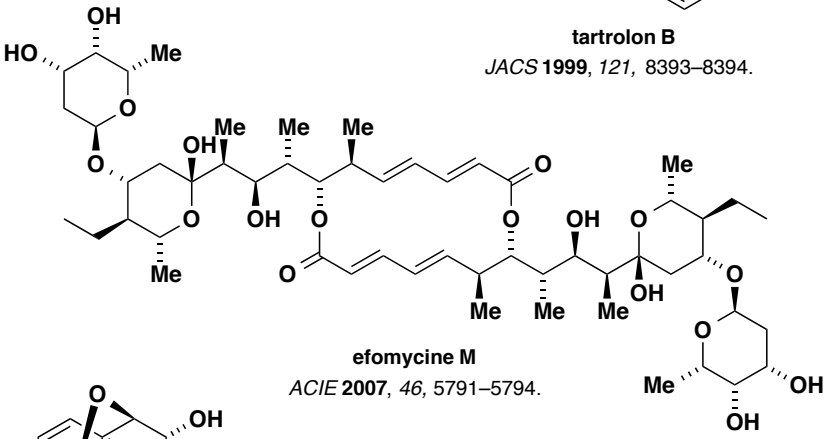
tartrolon B
JACS **1999**, *121,* 8393–8394.



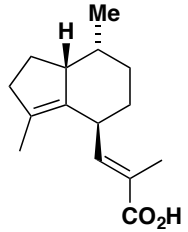
cyoctol
TH **2004**, *60,* 9599–9614.



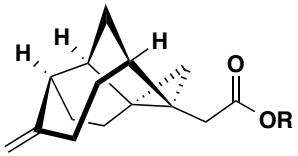
pasteurestin A and B
ACIE **2007**, *46,* 9320–9322.



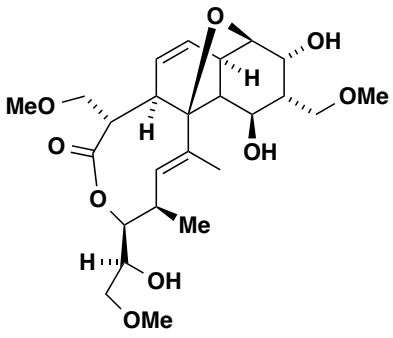
efomycine M
ACIE **2007**, *46,* 5791–5794.



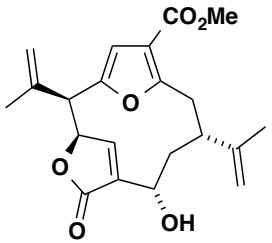
valerenic acid
OL **2009**, *11,* 1151–1153.



echinopine A: R = H
echinopine B: R = Me
OL **2009**, *11,* 5306–5309.

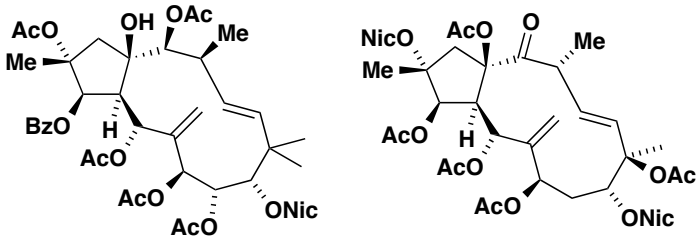


branimycin
ACIE **2010**, *49,* 2050–2053.

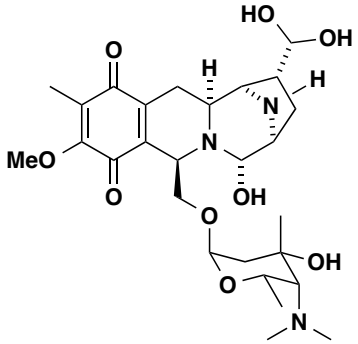


11-gorgiacerol
OL **2012**, *14,* 2834–2837.

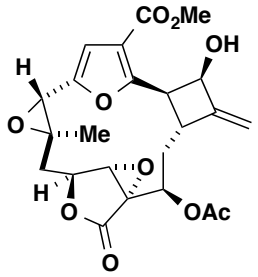
Some studies towards:



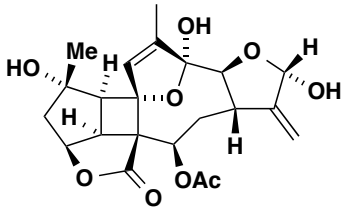
pepluanin A and **euphosalicin**
Synlett **2004**, 2258–2562.



lemonomycin
Synlett **2008**, 2443–2446



providencin
Synlett **2009**, 1357–1366.



bielschowskysin
OL **2012**, *14*, 2195–2197.
OL **2013**, *15*, 3098–3101.