

# **Chemistry in Germany - The Young Generation**

***... a personal selection***

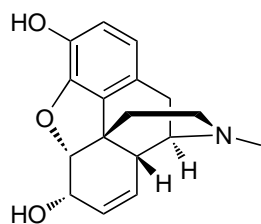
**Dirk Trauner**

- born: April 17th 1967, Linz, Austria
- studies in biology and biochemistry, University of Vienna
- 1997 PhD with Johann Mulzer, Free University of Berlin
- 1998-2000 Postdoc with S. Danishefsky, New York
- 2000-2006 Assistant Professor, UC Berkeley
- 2006-2010 Associate Professor, UC Berkeley
- since 2008 Professor of Chemical Biology and Chemical Genetics, LMU Munich, Germany
- 113 publications (15 PhD and Postdoc)

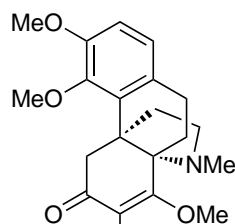
**"I find it amazing that ... I am getting paid for sitting in my office and playing with toys and that my imagination occasionally corresponds to the material world."**

**"In a nutshell, my research involves ... natural products and neurons."**  
(Total synthesis of bioactive natural products, synthetic methodology, and chemical neurobiology)

**Total Synthesis of Morphine and Hasubanan Alkaloids:  
The Hydrophenanthrenone Approach**

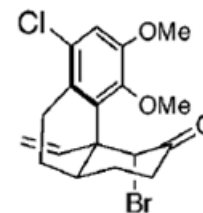
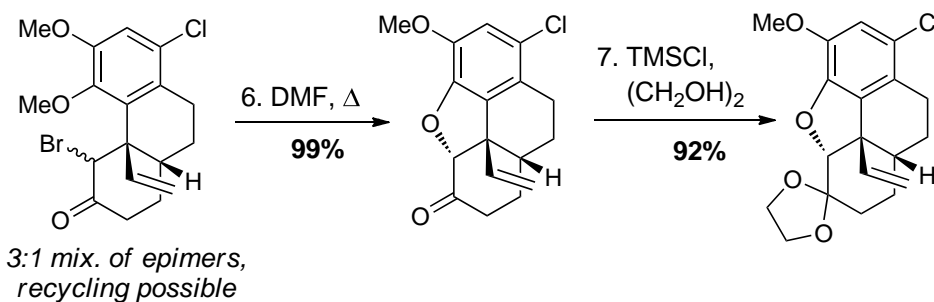
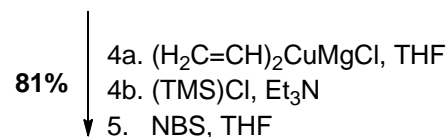
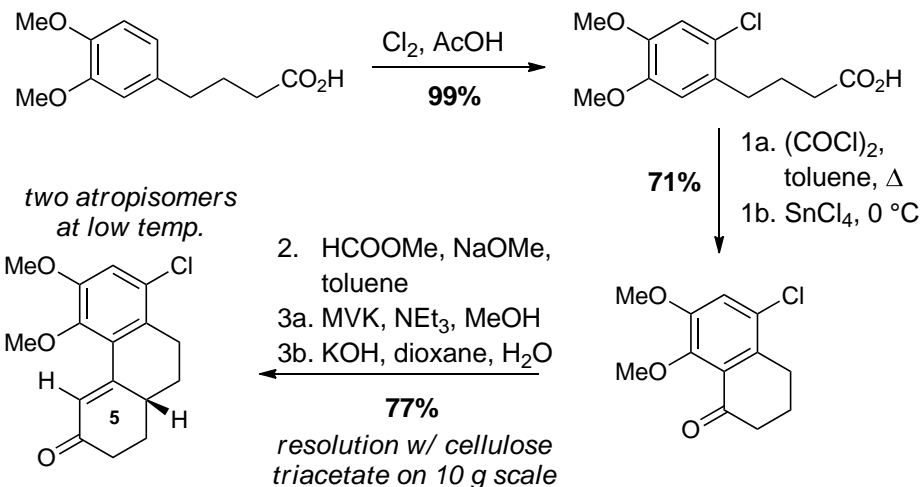


(-)-morphine

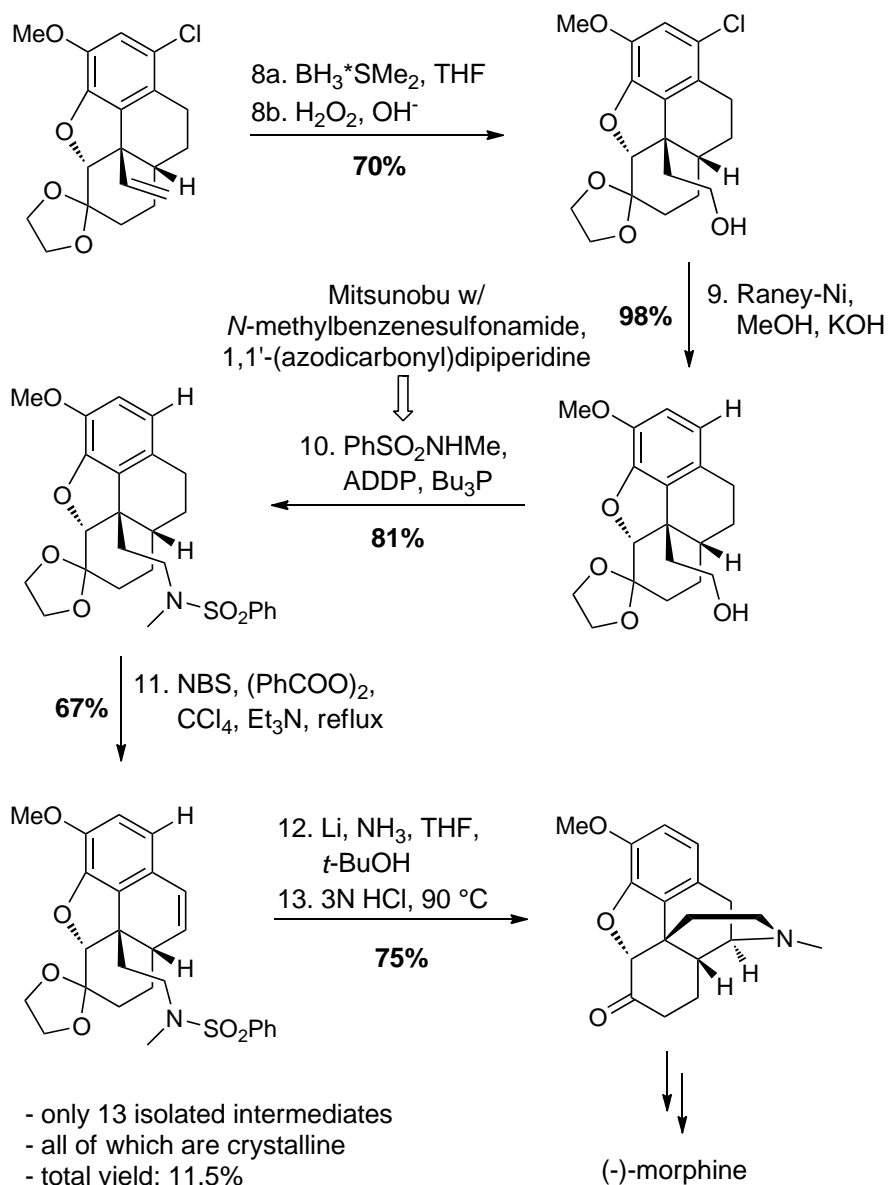


(-)-hasubanonine

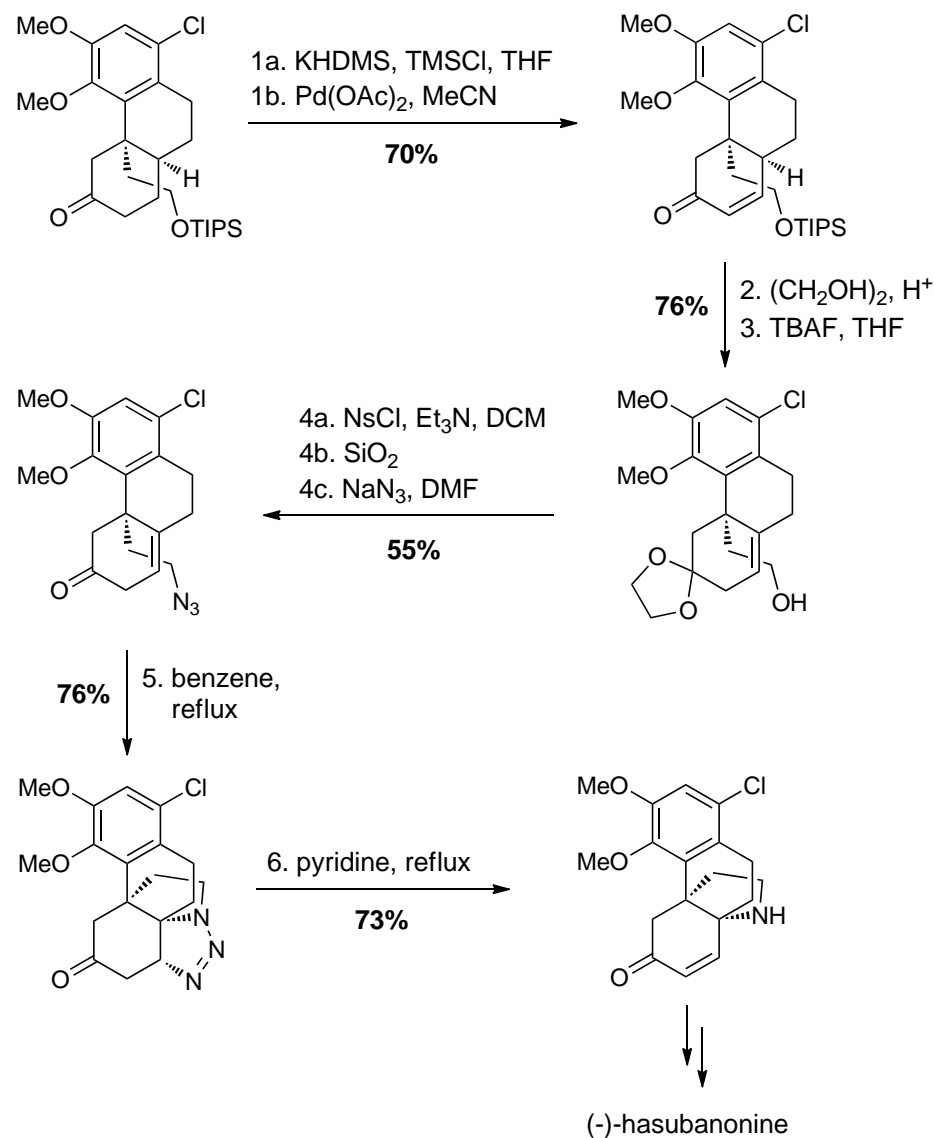
*Angew. Chem., Int. Ed.* **1997**, 35, 2830.  
*Synlett* **1997**, 5, 441.  
*Synthesis* **1998**, 653.  
*J. Org. Chem.* **1998**, 63, 5908.  
*Chirality* **1999**, 11, 475.



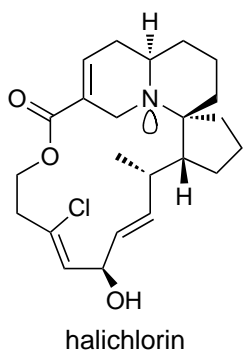
***α-haloketone effect***  
α-bromocyclohexanones prefer a conformation with axial bromine in order to minimize electrostatic interaction of the dipolar C–Br and C=O bonds or maximize overlap between the corresponding σ\* and p- orbitals



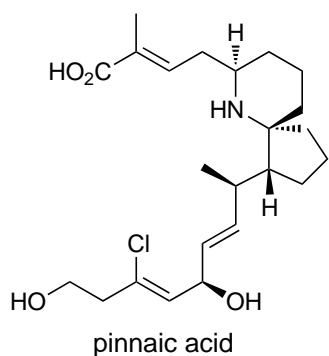
- only 13 isolated intermediates
- all of which are crystalline
- total yield: 11.5%
- inexpensive and readily available sm
- recycling of undesired isomers



## Total Synthesis of Halichlorin



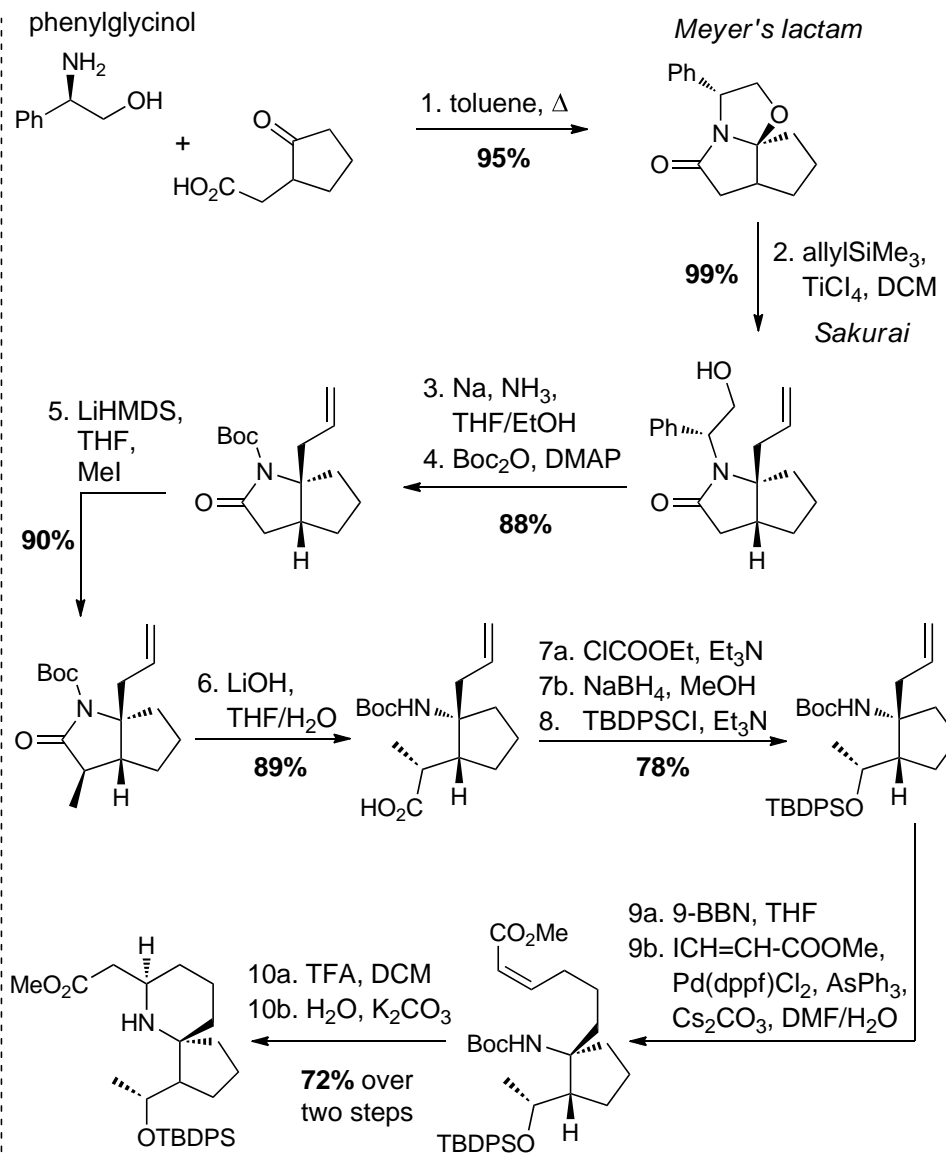
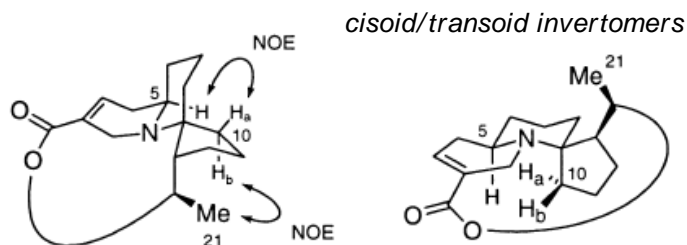
*Angew. Chem., Int. Ed.* **1999**, 38, 3542.  
*Tetrahedron Lett.* **1999**, 40, 6513.



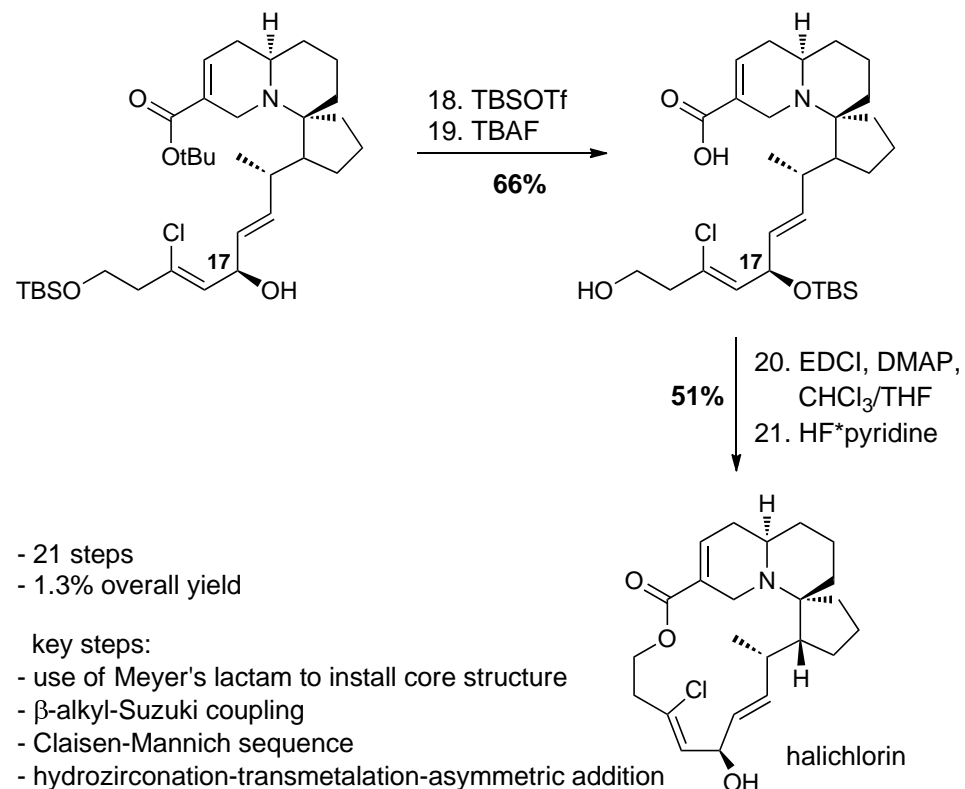
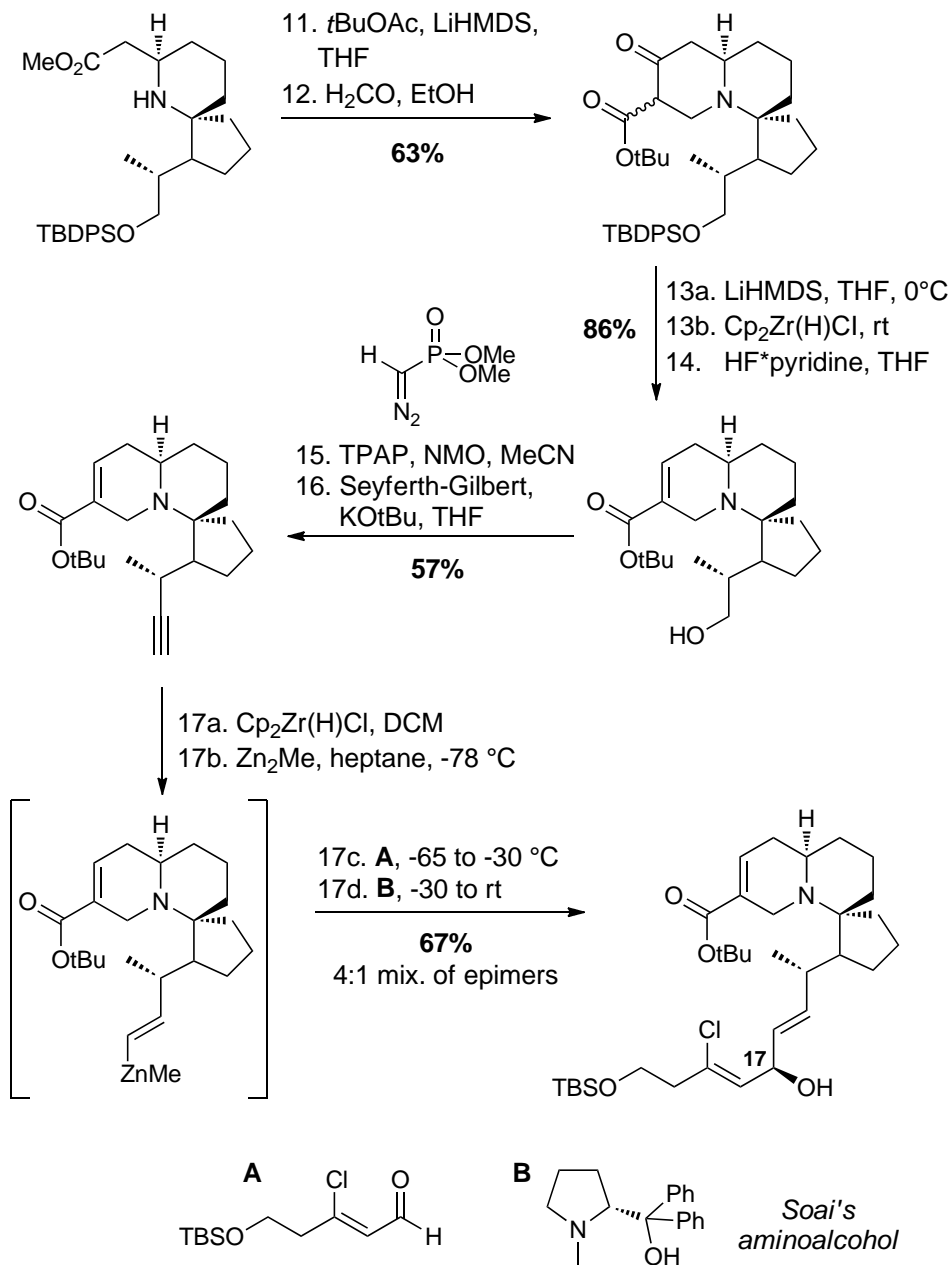
*Helv. Chim. Acta* **2000**, 83, 2344.  
*Angew. Chem., Int. Ed.* **2001**, 40, 4450.  
*Angew. Chem. Int. Ed.* **2001**, 40, 4453.

(structure elucidated by combination  
of spectroscopy, total synthesis,  
and degradation experiments)

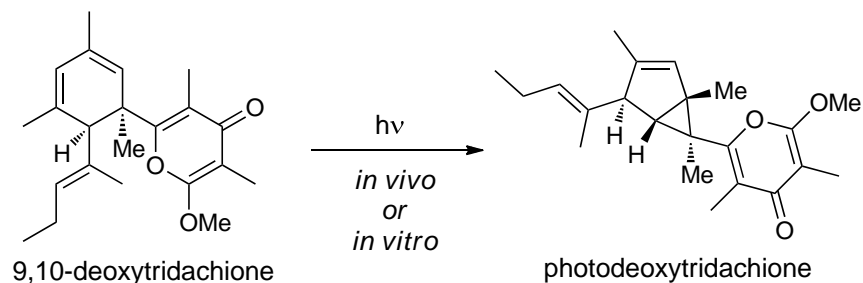
- halichlorin exhibit considerable structural homology (e.g. quinolizidine subunit), but act upon different biological targets (VCAM-1 vs. cPLA<sub>2</sub>)
- VCAM-1 has recently emerged as a potential target for drug discovery since it is supposed to be involved in regulating leukocyte trafficking
- derivatives for SAR studies



excellent review on  $\beta$ -alkyl Suzuki-Miyaura cross-coupling reactions:  
*Angew. Chem., Int. Ed.* **2001**, 40, 4544

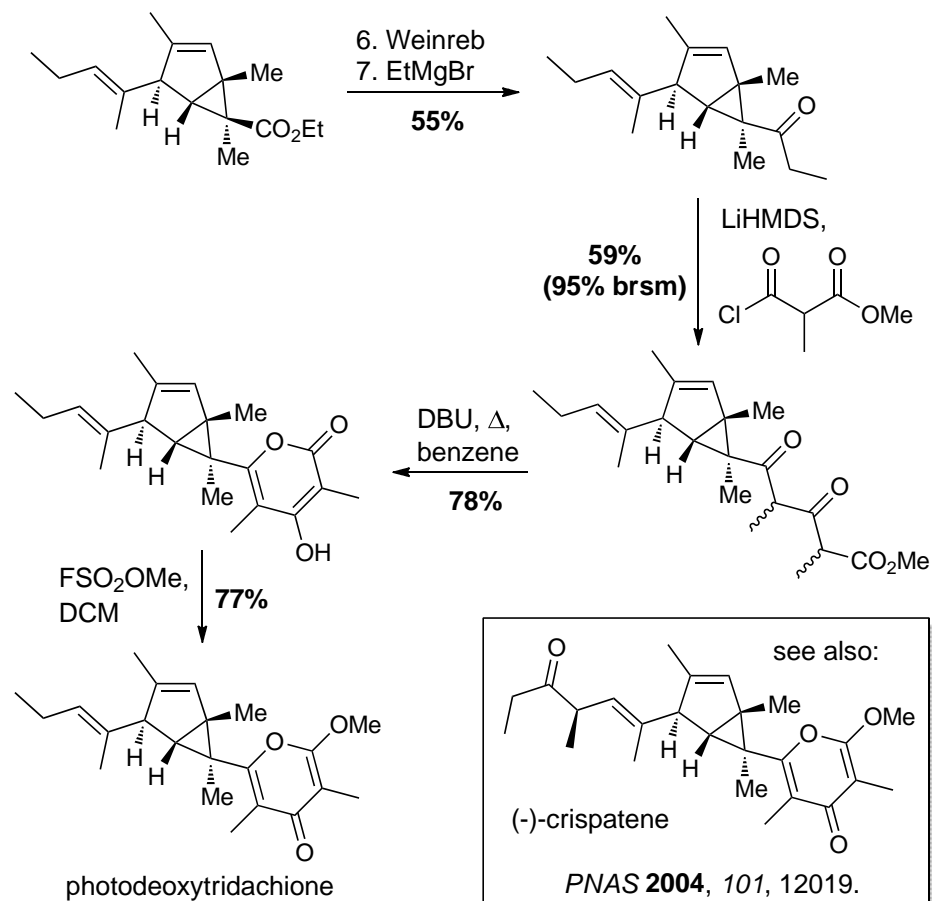
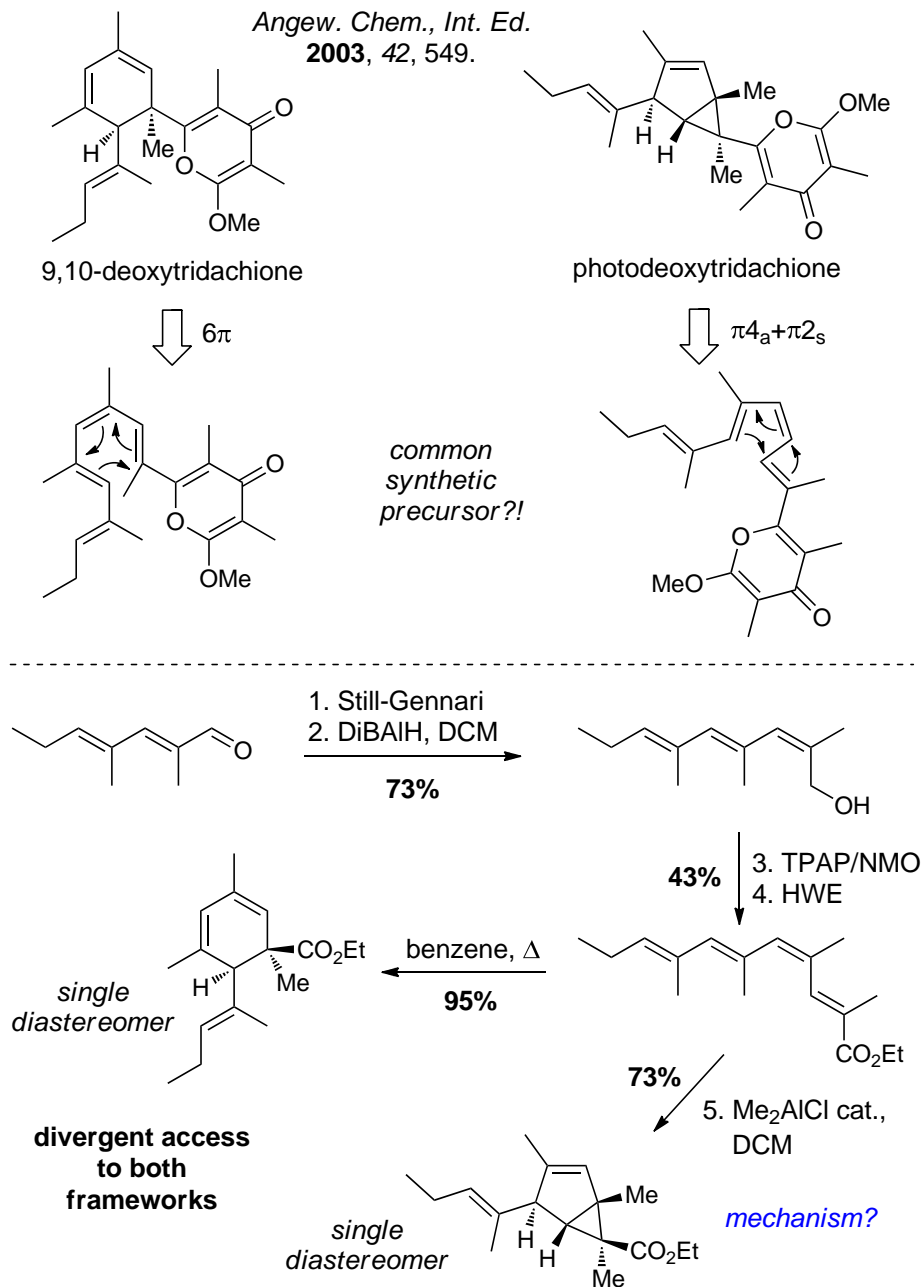


### Biomimetic Syntheses applying Electrocyclization Cascades

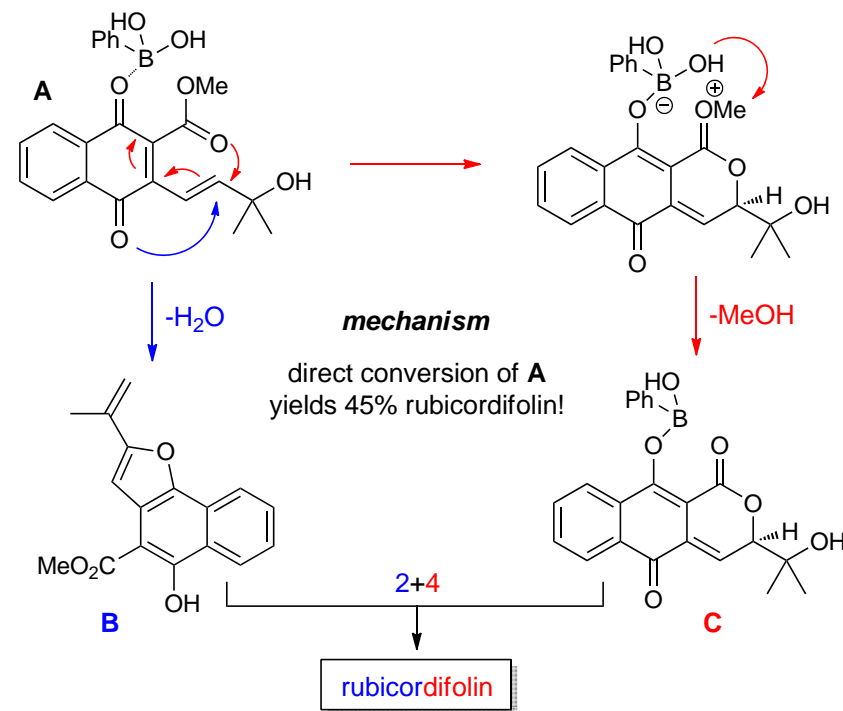
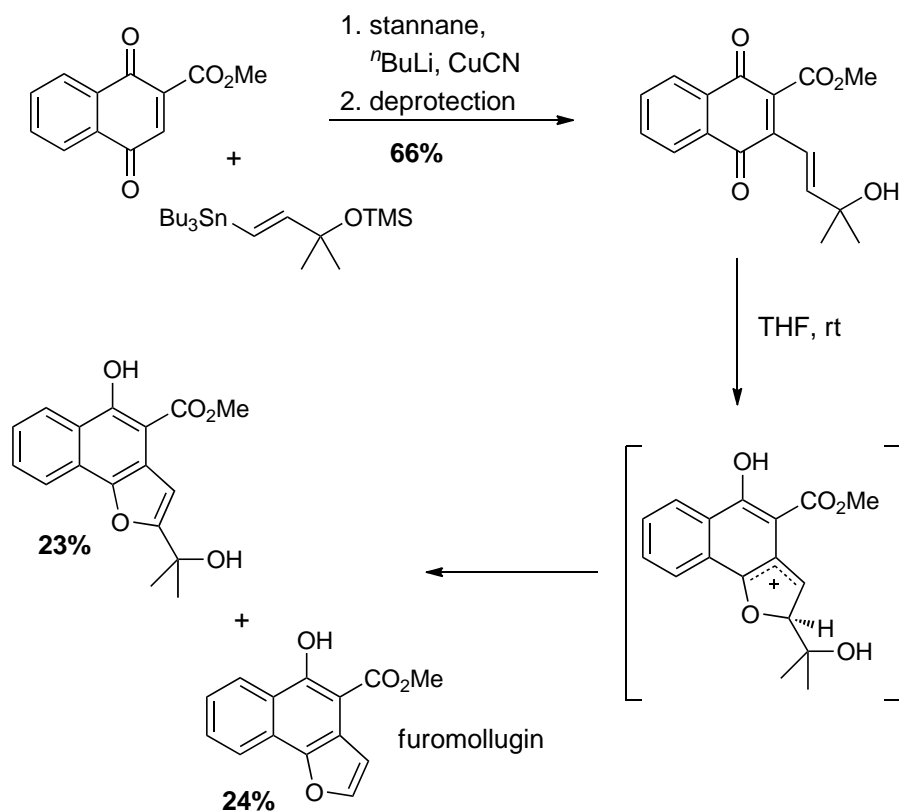
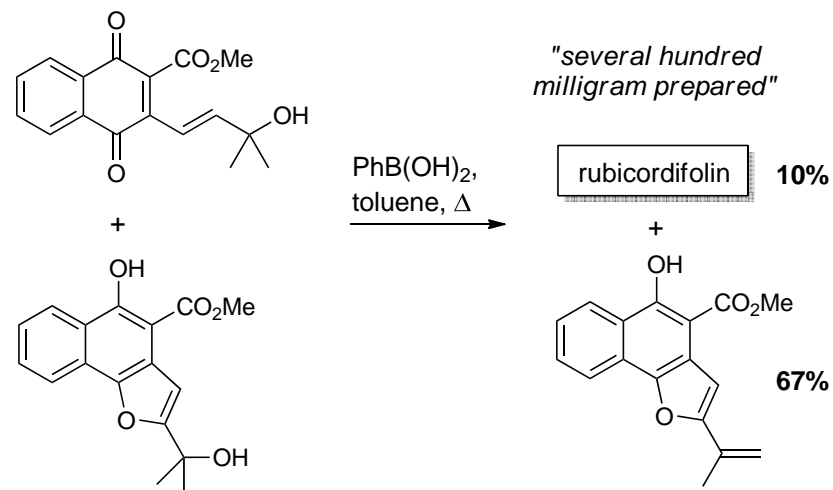
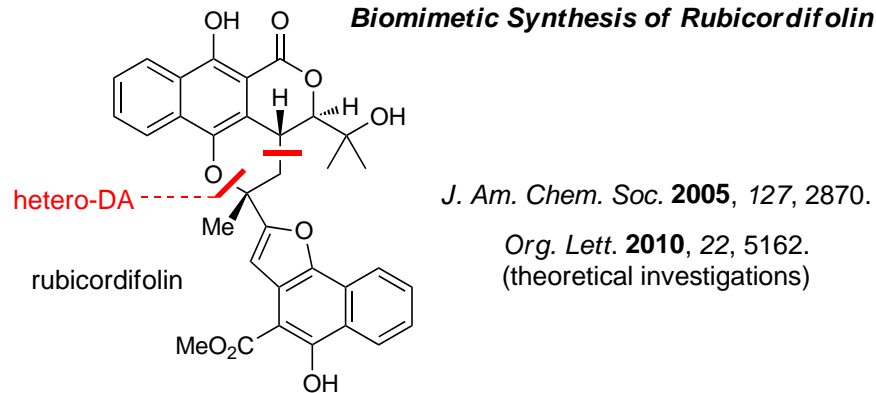


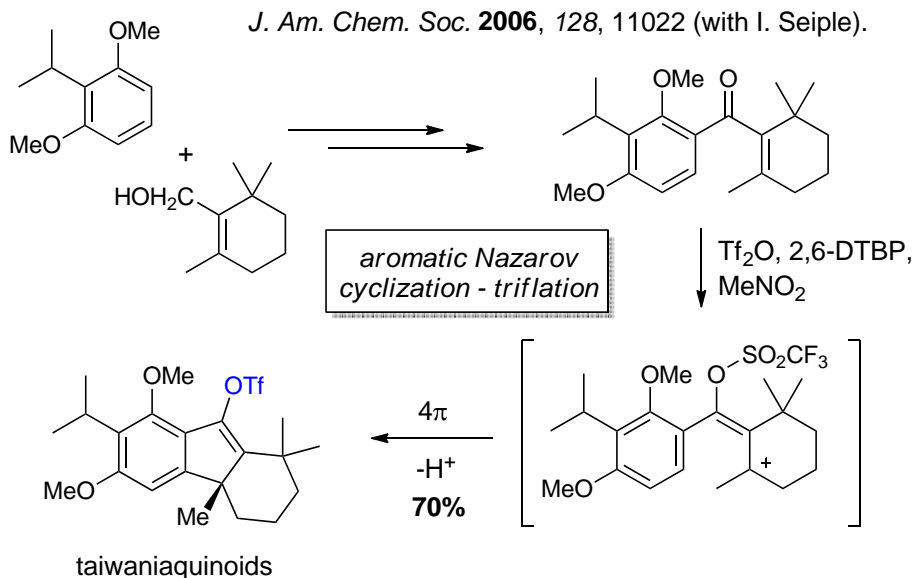
### biosynthetic relationship

via triplet state, diradical mechanism: *Org. Lett.* **2005**, *7*, 4959.

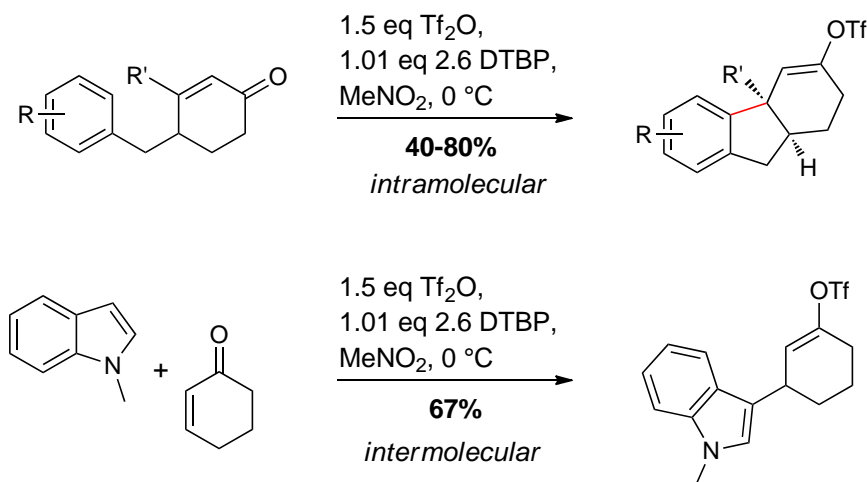


## Biomimetic Synthesis of Rubicordifolin

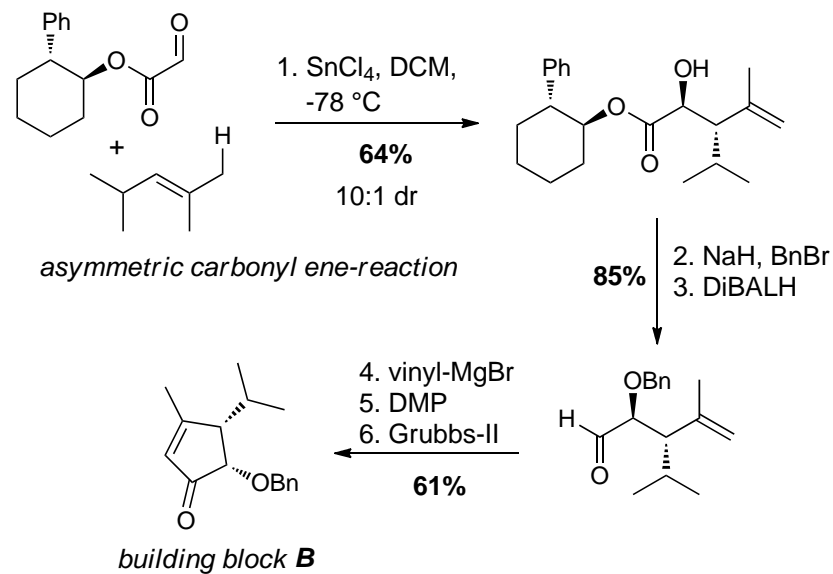
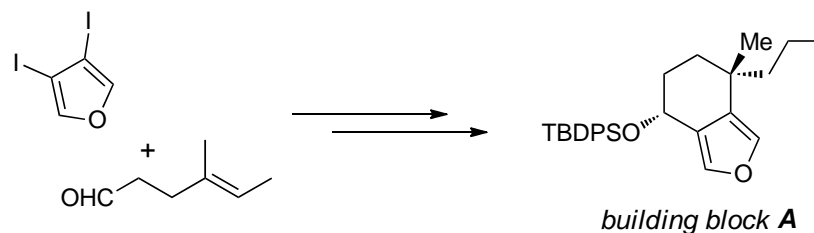
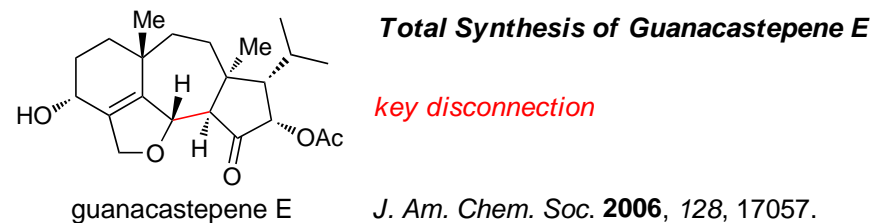


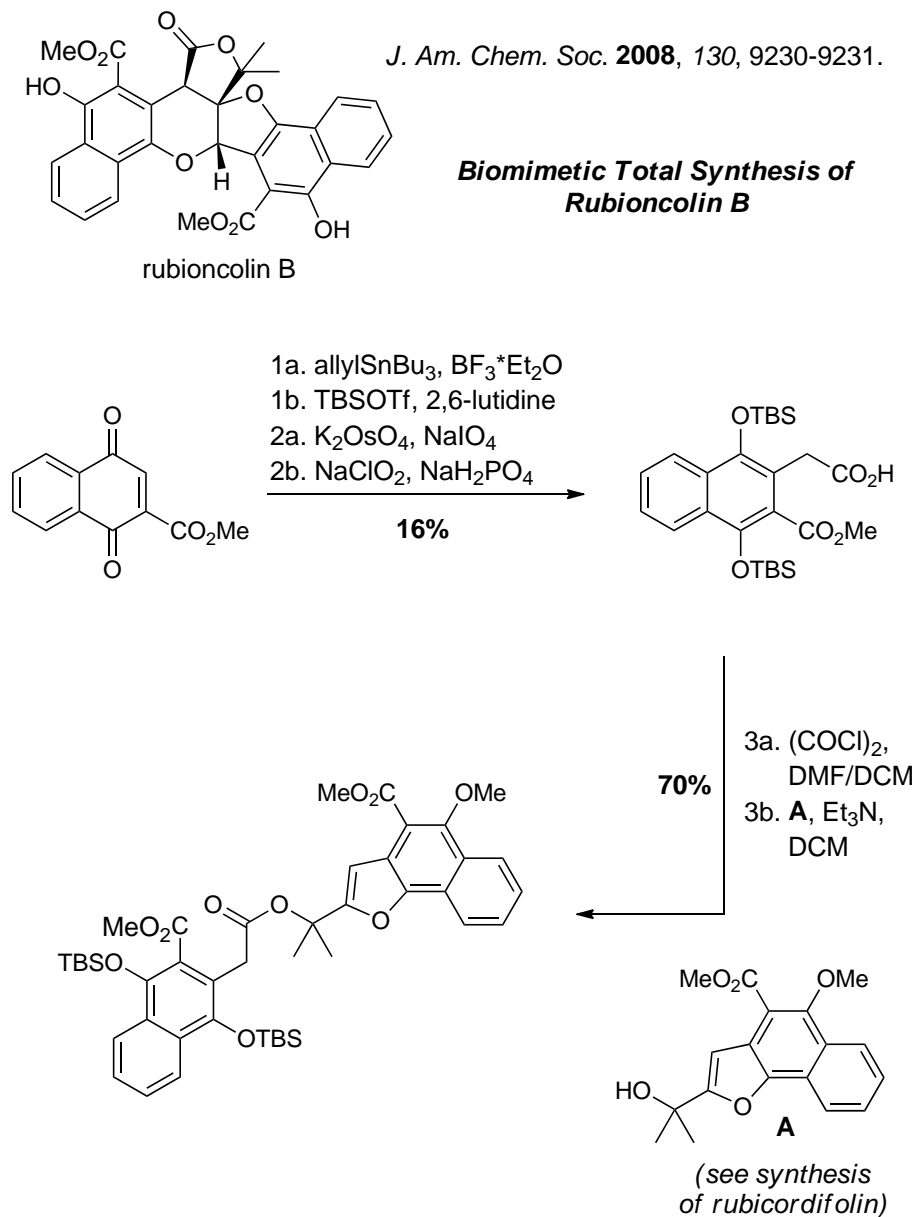
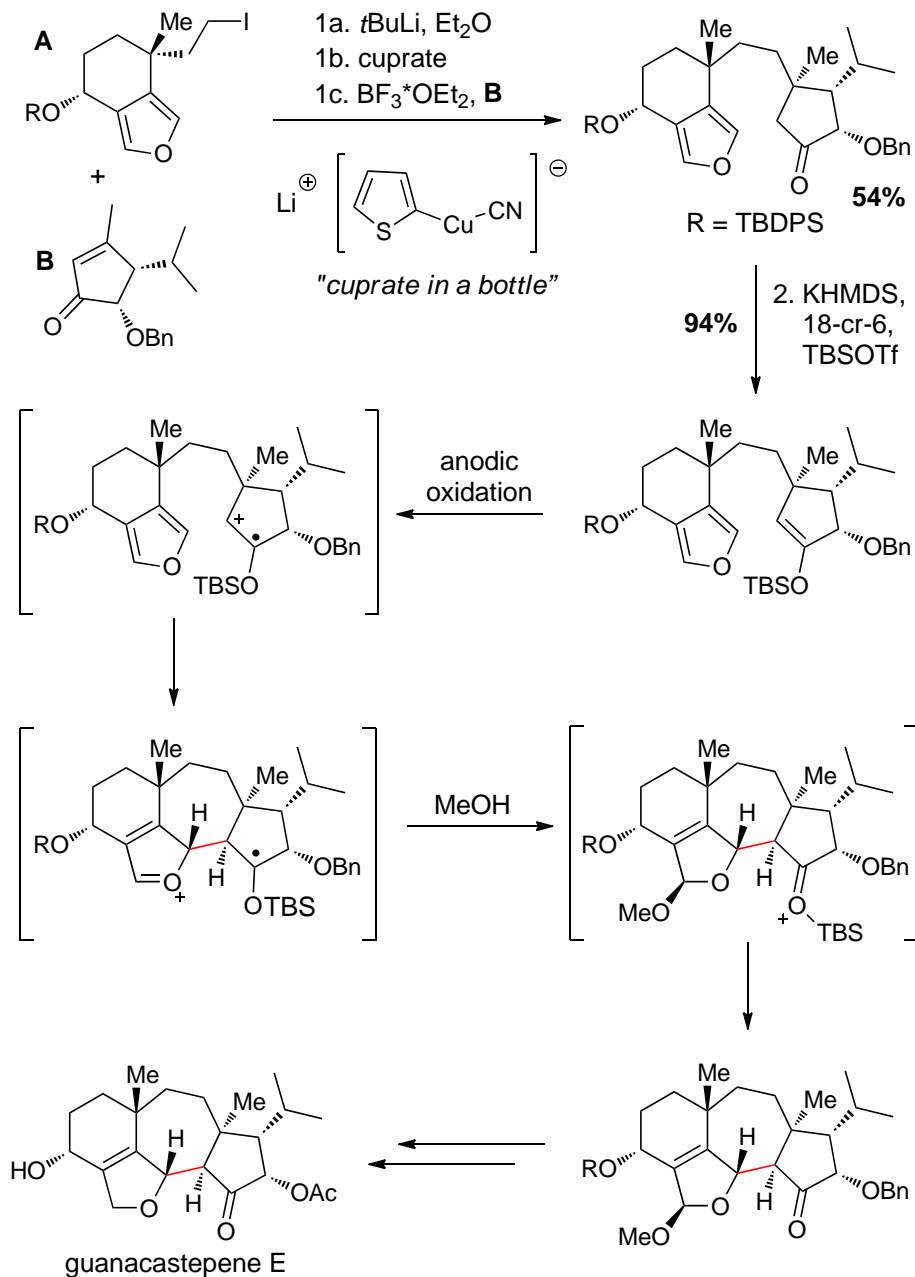


## also: Friedel-Crafts triflation



*Org. Lett.* **2006**, 8, 5429.



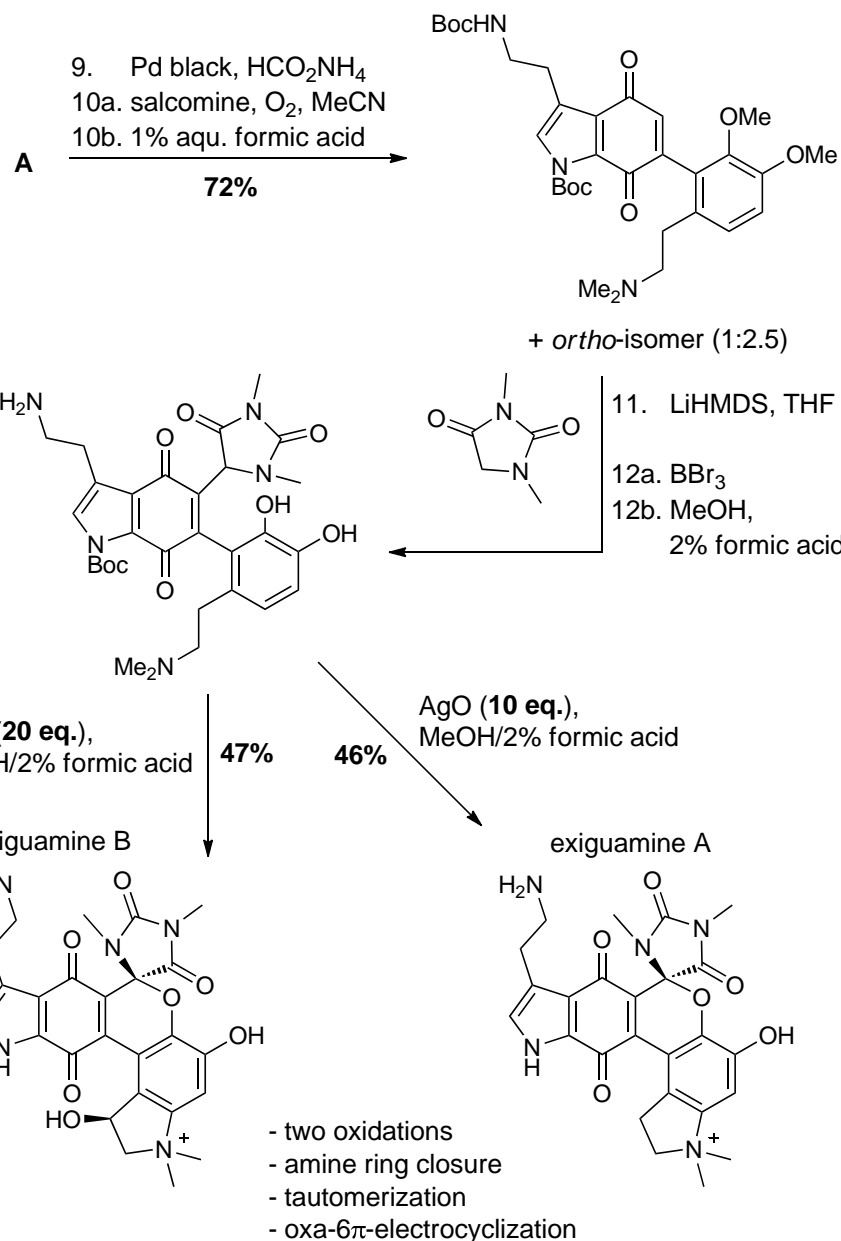
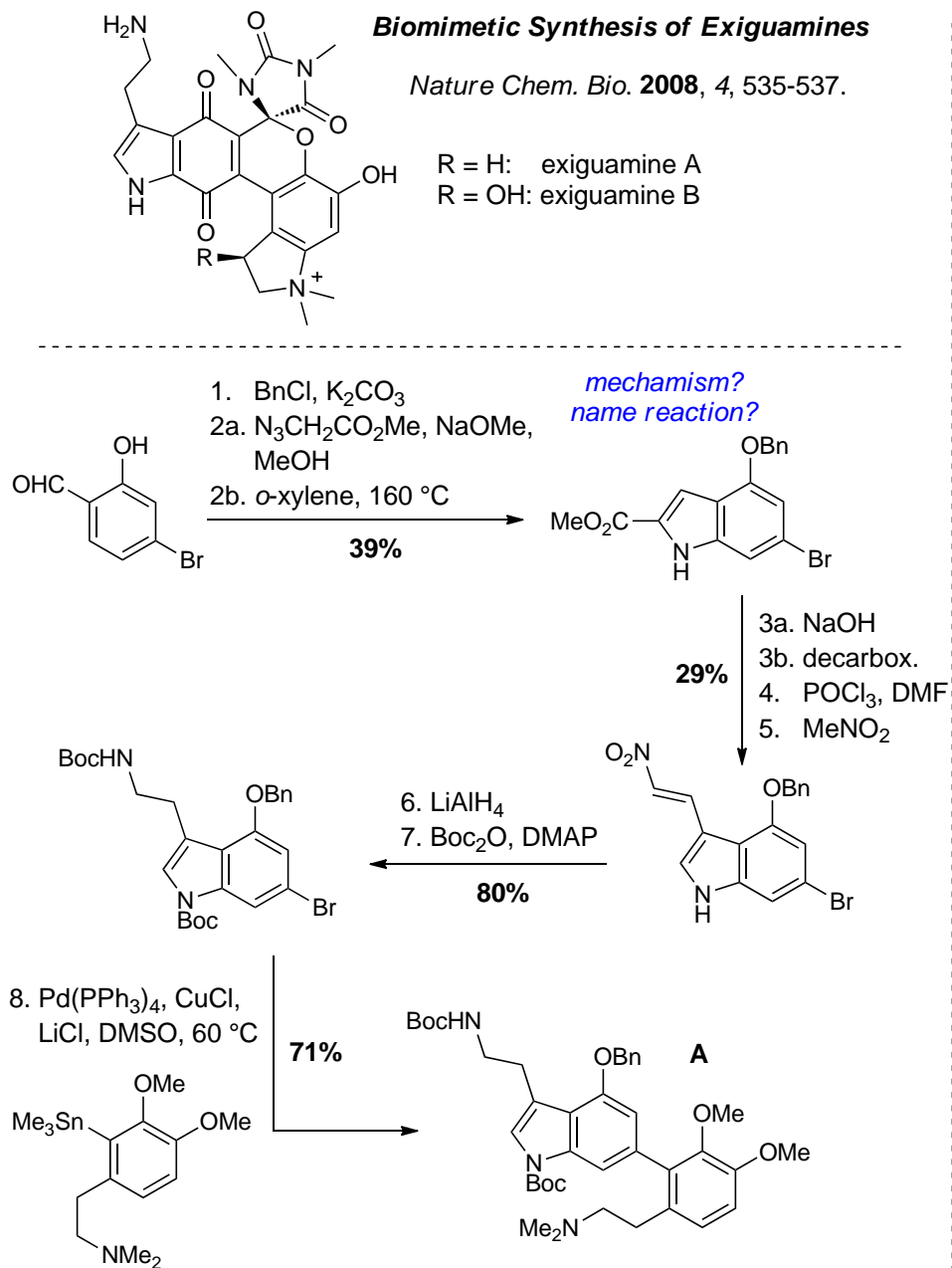


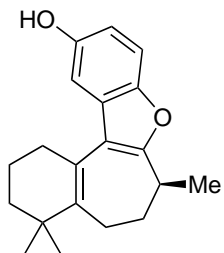


## Biomimetic Synthesis of Exiguamines

Nature Chem. Bio. 2008, 4, 535-537.

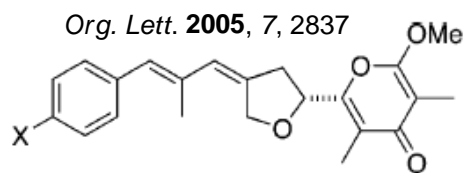
R = H: exiguamine A  
R = OH: exiguamine B





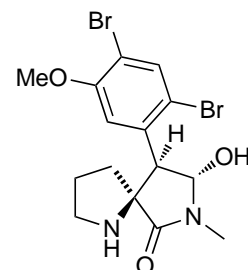
S-(+)-frondosin B

*Angew. Chem., Int. Ed.* **2002**, *41*, 1569.



*Org. Lett.* **2005**, *7*, 2837

X = NO<sub>2</sub>: aureothin  
 X = NHAc: N-acetylaureothamine  
 X = CN: aureonitrile

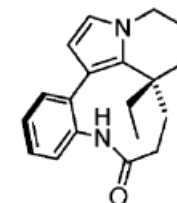


amathaspiramide F

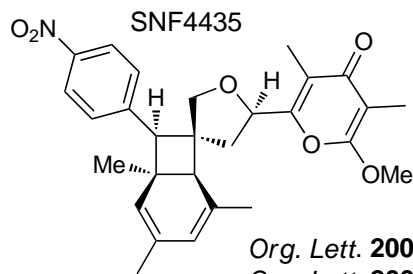
*Angew. Chem., Int. Ed.* **2002**, *41*, 4556

*J. Org. Chem.* **2009**, *74*, 1581.

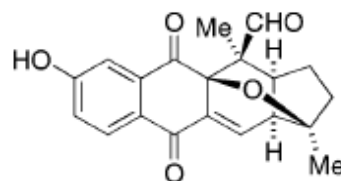
*Org. Lett.* **2005**, *7*, 5207.



rhazinilam



*Org. Lett.* **2002**, *4*, 2221.  
*Org. Lett.* **2005**, *7*, 4475.

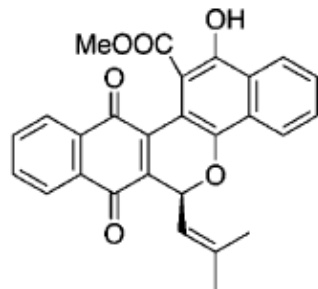


pinnatal (1)

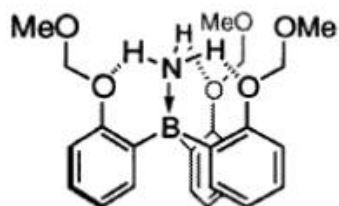
*J. Am. Chem. Soc.* **2005**, *127*, 6276.

**REVIEW:** "Biosynthetic and Biomimetic Electrocyclizations."  
*Chem. Rev.* **2005**, *105*, 4757.

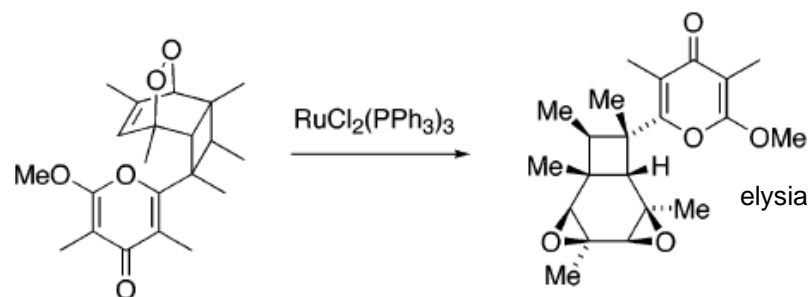
*Org. Lett.* **2005**, *7*, 5865.



microphyllaquinone



*Org. Lett.* **2002**, *4*, 4109.

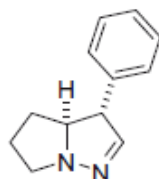


*Org. Lett.* **2005**, *7*, 2901.

*Angew. Chem., Int. Ed.* **2005**, *44*, 4602.

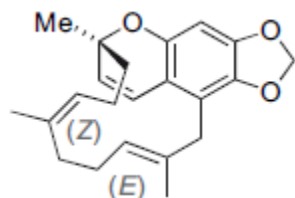
Studies Toward the Haouamines: *Org. Lett.* **2006**, 8, 23.

Studies Toward Maoecrystal V: *Org. Lett.* **2010**, 12, 5656-5659.



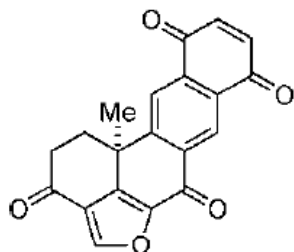
newbouldine

*Tetrahedron* **2010**, 66, 6626-6631.



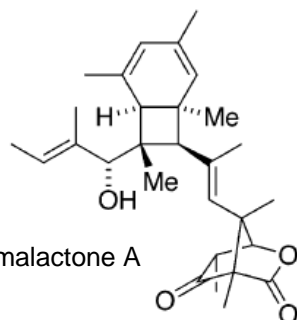
smenochromene B

*Tetrahedron* **2007**, 63, 6529.



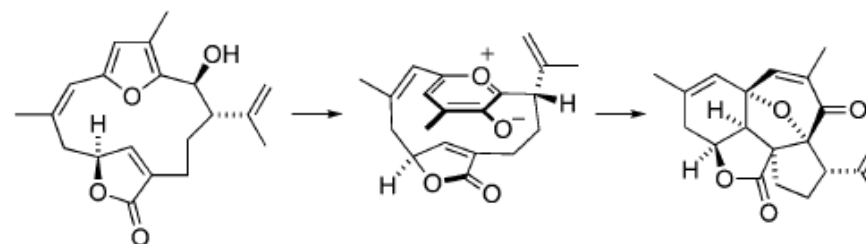
halenaquinone

*J. Am. Chem. Soc.* **2008**, 130, 8604-8605.  
(Vinyl Quinones as Diels-Alder Dienes)



shimalactone A

*Org. Lett.* **2008**, 10, 149.

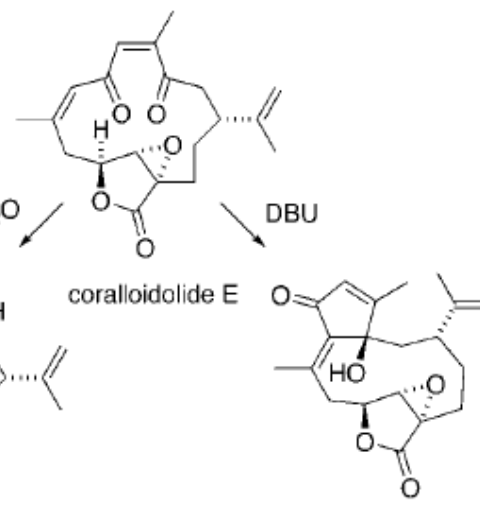


bipinnatin J

*Org. Lett.* **2006**, 8, 345.

*Org. Lett.* **2006**, 8, 5901.

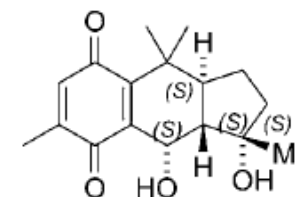
intricarene



coralloidolide B

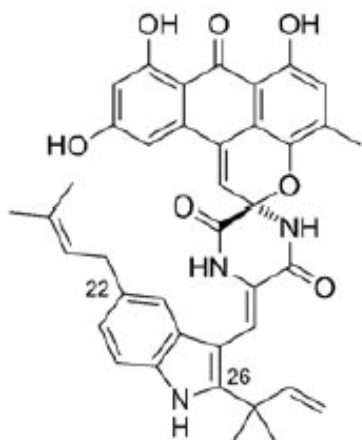
coralloidolide C

*Angew. Chem. Int. Ed.* **2010**, 49, 2619-2621.



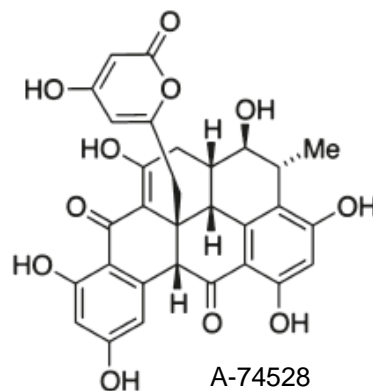
pycnanthuquinone C

*Angew. Chem. Int. Ed.*  
**2010**, 49, 6199-6202.

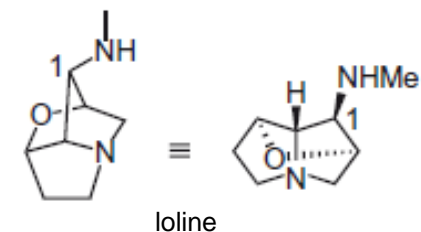


variecolortide A

*Angew. Chem. Int. Ed.* **2011**, *50*, 1402-1405.



*Org. Lett.* **2011**, *13*, 1386-1389.

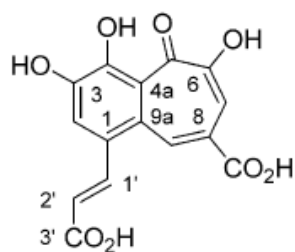


*Nat. Chem.* **2011**, *3*, 543-545.

not covered: "**Chemical Neurobiology**"

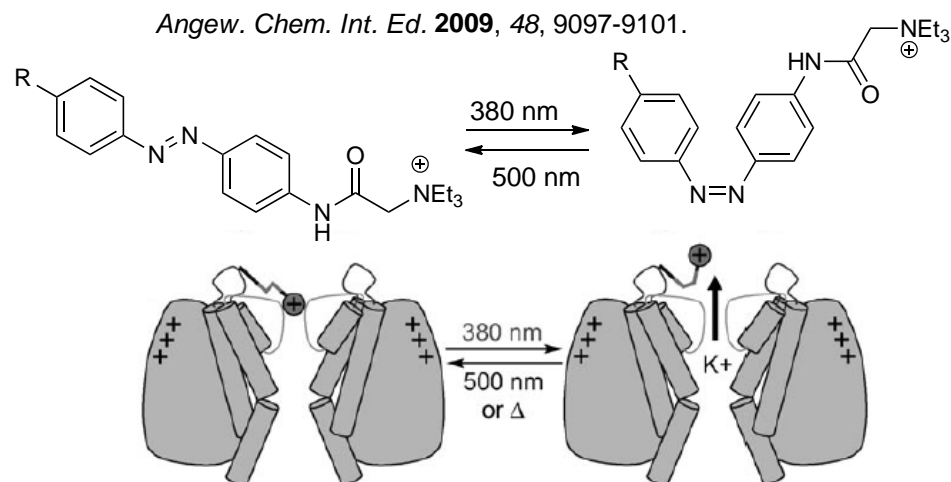
excellent review: *Introduction: Chemical Approaches to Neurobiology*,  
*Chem. Rev.* **2008**, *105*, 1499.

*Angew. Chem. Int. Ed.* **2009**, *48*, 9097-9101.



crocipodin

*Tetrahedron* **2011**, *67*, 1536-1539.



... don't miss the zebra-fish experiment!  
(*Nature* **2009**, *461*, 407-410.)

**Thorsten Bach:**

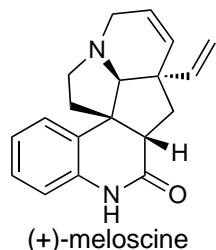
- born: 1965, Ludwigshafen, Germany  
 - studies in chemistry, University of Heidelberg / USC LA  
 - 1991 PhD with Manfred Reetz, University of Marburg  
 ("Enantioselective C-C Coupling Using Chiral Catalysts")

- 1991-1992 Postdoc with D. Evans, Harvard University  
 ("Histidine Analogs by Pd-mediated C,C Bond Formation")

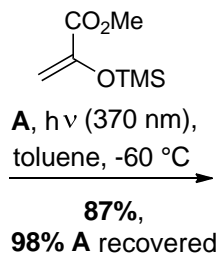
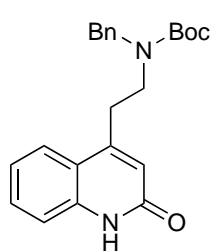
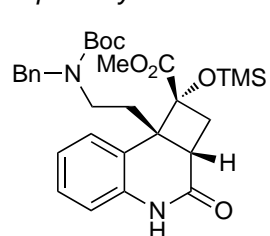
- 1992-1996 Habilitation, University of Münster  
 - 1997-2000 Full Professor, University of Marburg  
 - since 2000 Chair of Organic Chemistry I, TU Munich  
 - 188 publications

**main research interests:**

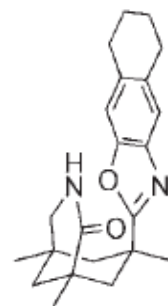
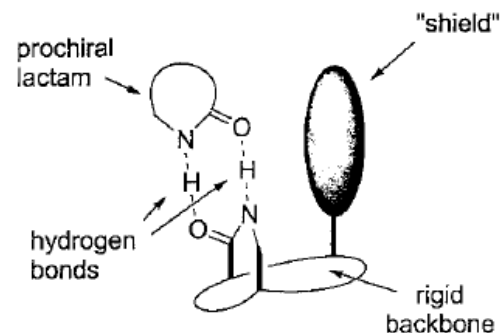
- **photochemistry**
- **catalysis**
- **chemistry of heterocycles**
- **total synthesis**

**Total Synthesis of Meloscine**

*Angew. Chem. Int. Ed.* **2008**, 47, 5082-5084.  
*Chem. Eur. J.* **2009**, 15, 3509-3525.

**enantioselective [2+2] photocycloaddition**

79% ee  
 >99% ee (after HPLC)

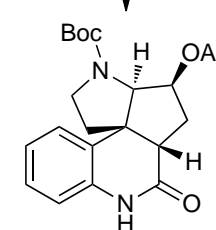
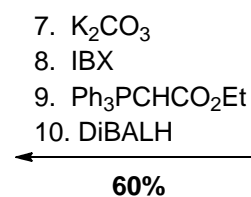
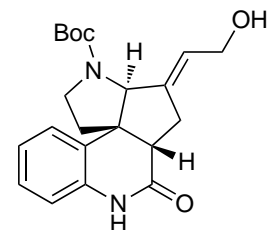
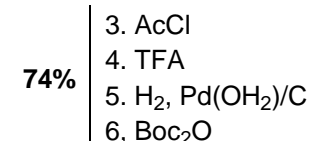
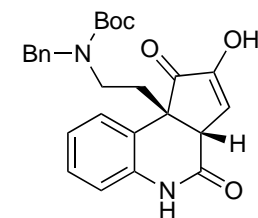
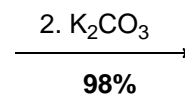
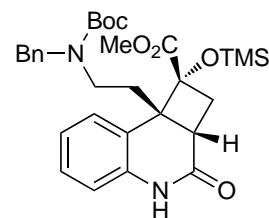
chiral host **A**

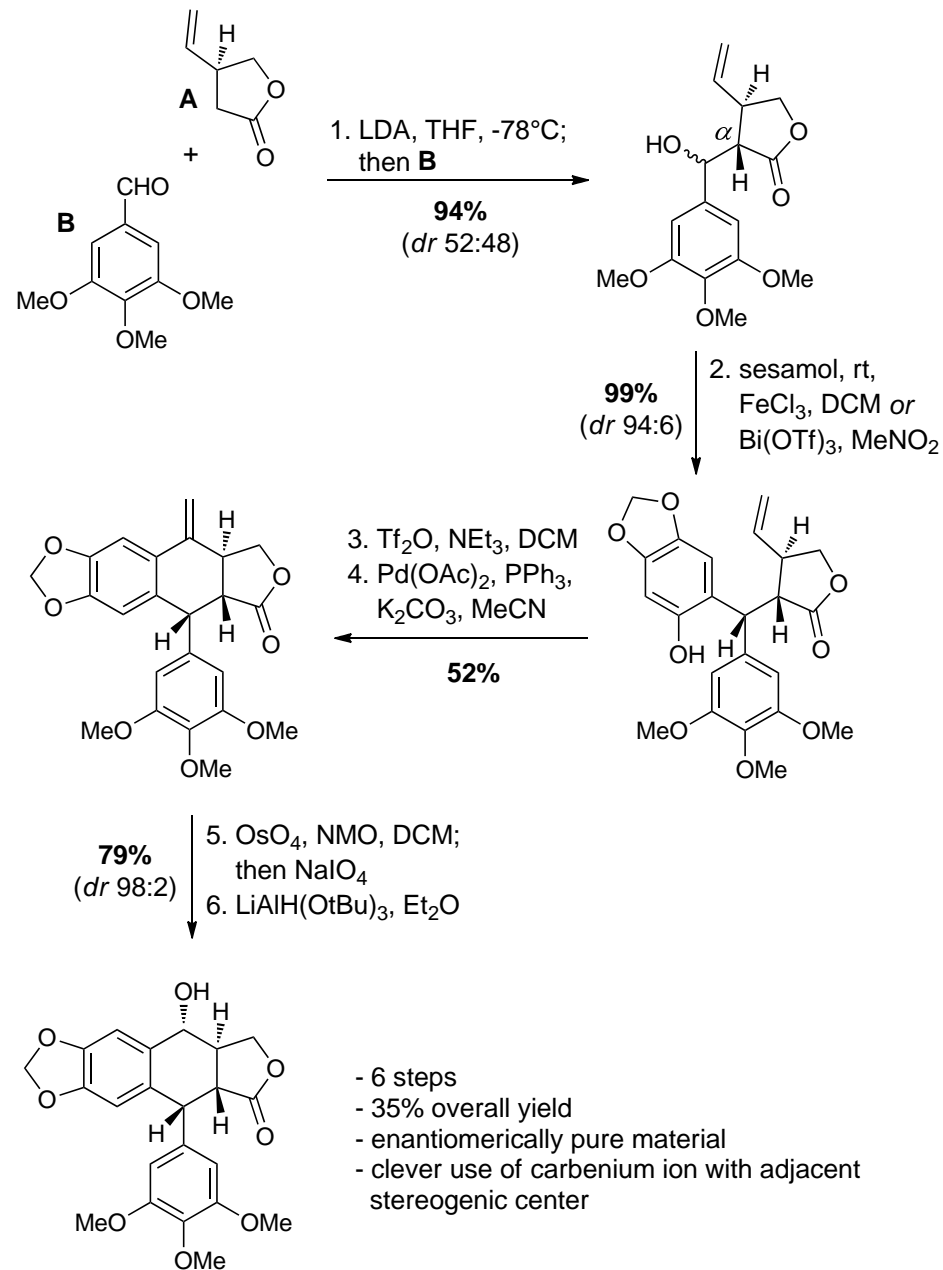
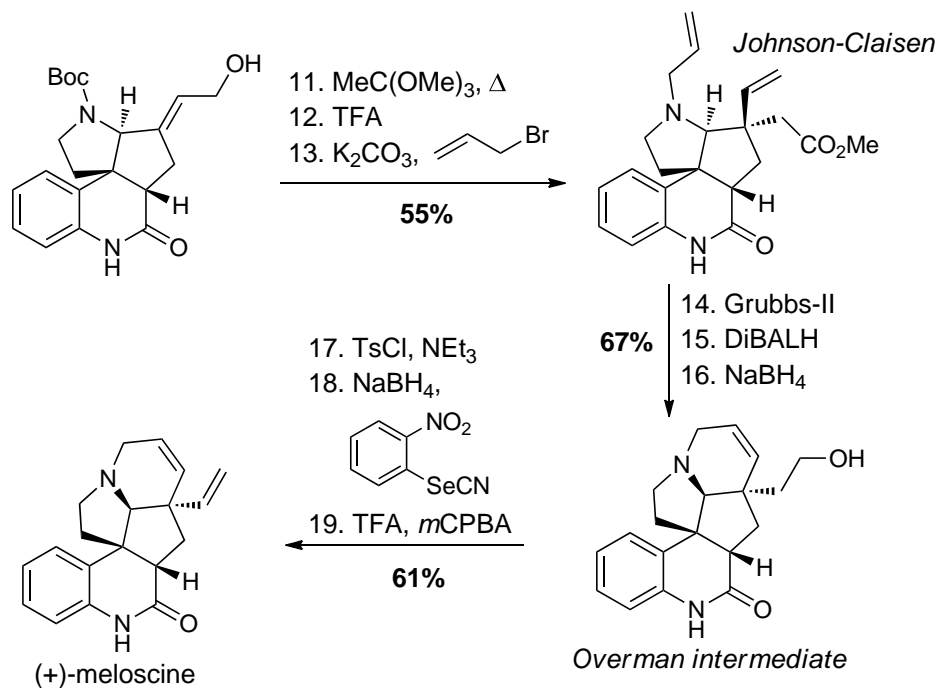
*Angew. Chem. Int. Ed.* **2000**, 39, 2302-2304.

*J. Org. Chem.* **2006**, 71, 5662-5673.

*Synlett* **2004**, 2588-2509.

*Synthesis* **2001**, 1395-1405 (preparation of host).

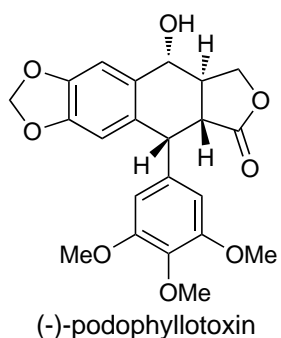


**Total Synthesis of Podophyllotoxin**

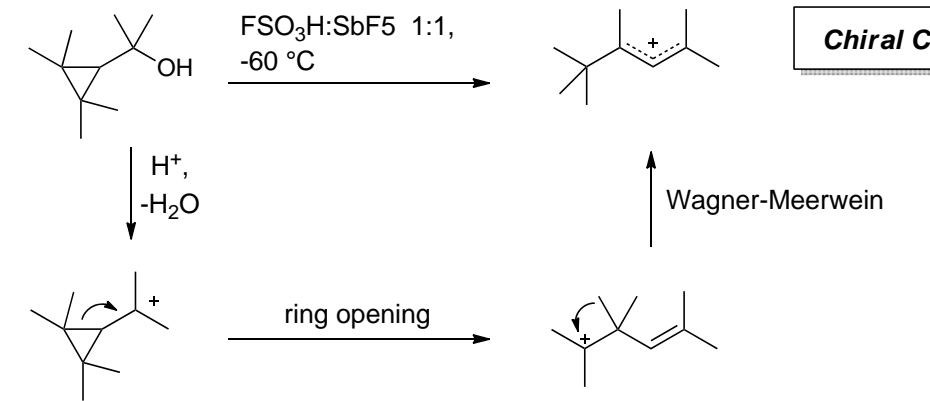
*Angew. Chem. Int. Ed.* **2008**, 47, 7557-7559.

*J. Org. Chem.* **2009**, 74, 312-318.  
(*chiral carbocations, theoretical investigations*)

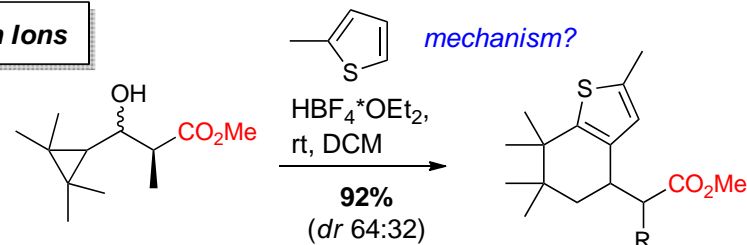
*Synlett* **2011**, 1235-1238.  
(*enantioselective FC with chiral Broensted acids*)



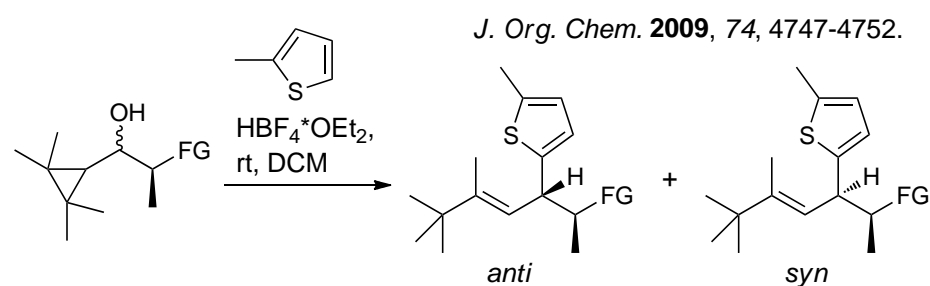
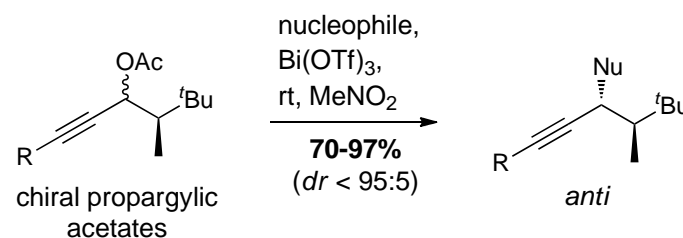
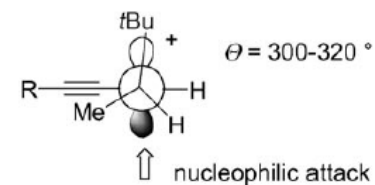
- lignane class of natural products
- antiviral properties
- several total syntheses (e.g. 1<sup>st</sup> synthesis by Meyers, 24 steps)



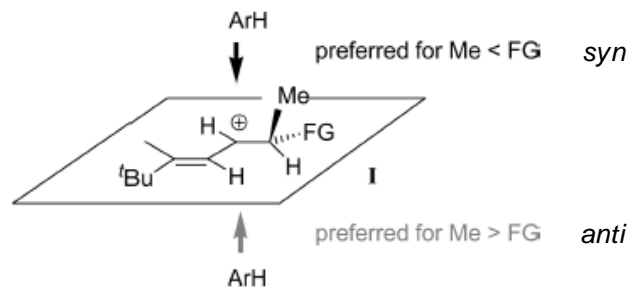
## Chiral Carbenium Ions



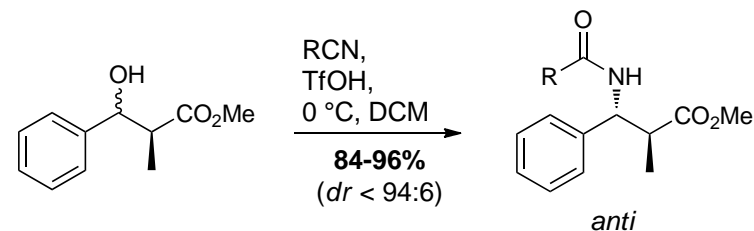
mechanism?

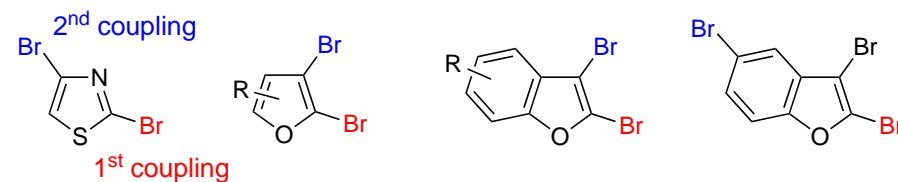
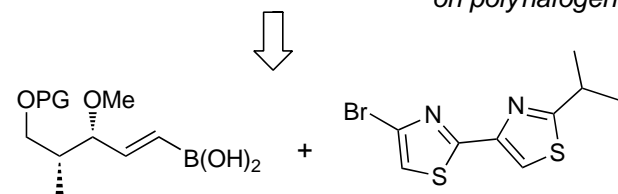
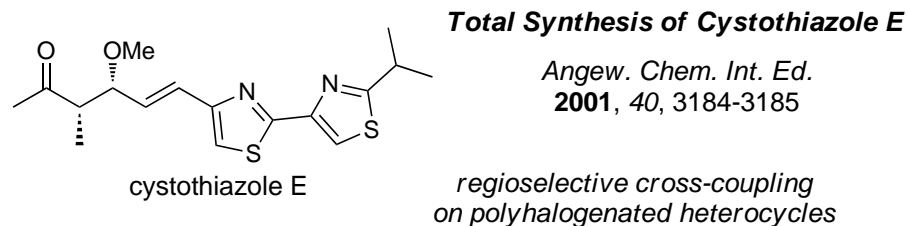
*J. Org. Chem.* **2009**, *74*, 4747-4752.simple model  
for predicting  
the outcome*Angew. Chem. Int. Ed.* **2008**, *47*, 10106-10109.

entry <sup>a</sup>	alcohol	FG	product	yield [%]	d.r. <sup>b</sup> ( <i>anti</i> : <i>syn</i> )
1	3a	<sup>t</sup> Bu	17a	84	3:97
2	4a	Ph	18a	97	77:23
3	5a	CN	19a	86	76:24
4	6a	PO(OEt) <sub>2</sub>	20a	87	74:26

simple model  
for predicting  
the outcome

diastereoselective Ritter reactions:

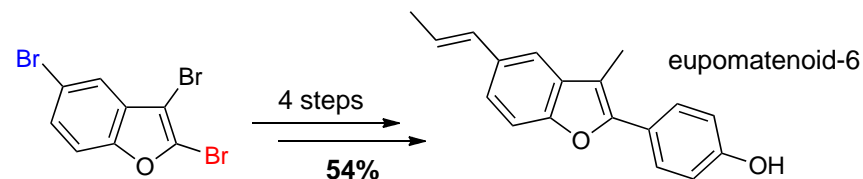
*Chem. Commun.* **2009**, 2130-2132.



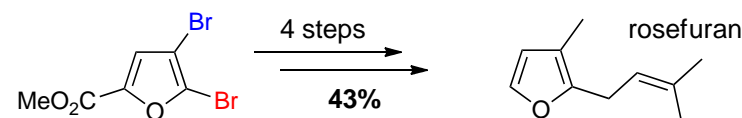
Thiazoles: *Tetrahedron Lett.* **2000**, 41, 1707-1710.  
*J. Org. Chem.* **2002**, 67, 5789-5795.  
*Synthesis* **2011**, 199-206.

Pyrrroles: *Synlett* **2005**, 1957-1959.  
*Heterocycles* **2007**, 74, 569-594.

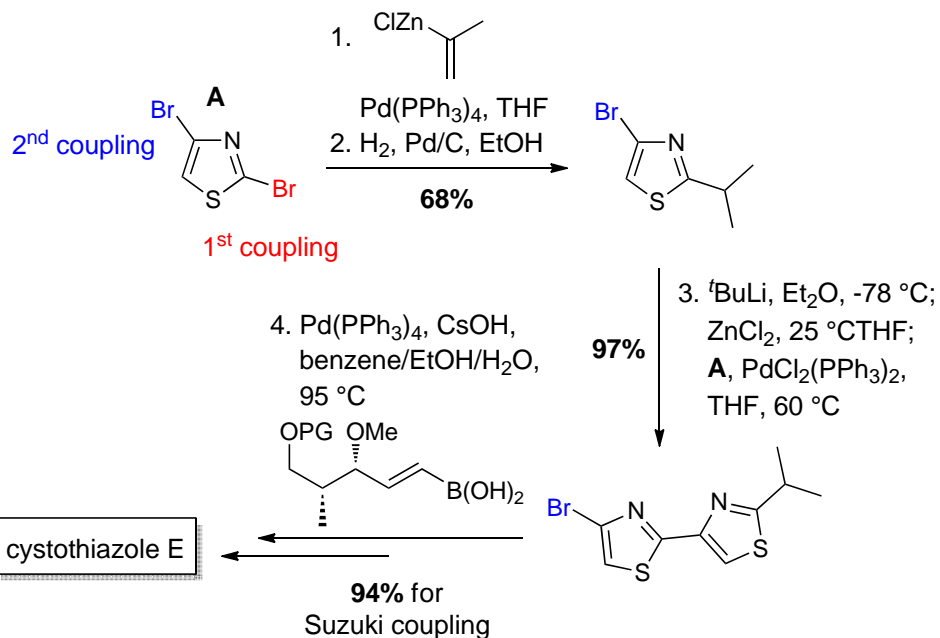
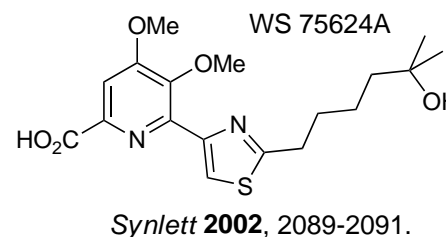
review: *Tetrahedron* **2005**, 61, 2245-2267.



*Tetrahedron Lett.* **2002**, 43, 9125-9127.  
*Synlett* **2001**, 1284-1286.  
*Synthesis* **2003**, 925-939.

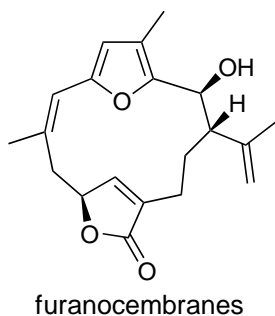


*Eur. J. Org. Chem.* **1999**, 2045-2057.

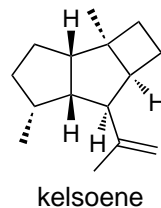


- 10 steps
- 21% overall yield
- three sequential couplings as key sequence
- usually bithiazole core established by classical Hantzsch thiazole methodology (e.g. Boger's bleomycin synthesis; *Angew. Chem. Int. Ed.* **1999**, 38, 448-476.)

**Regioselective C,C Coupling Reactions on Polyhalogenated Heterocycles**

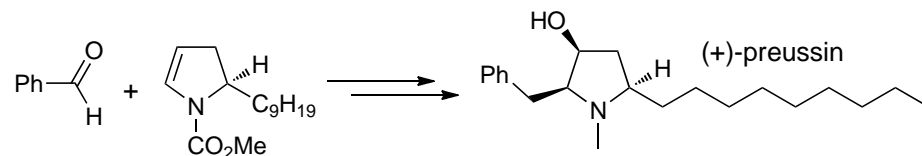


*Synlett* **2005**, 511-513.  
*J. Org. Chem.* **2001**, 66, 3427-3434.

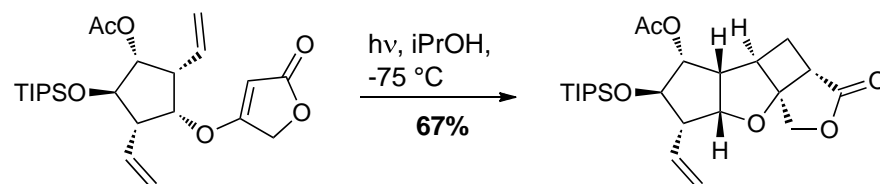


*Synlett* **2002**, 1305-1307.  
*Top. Curr. Chem.* **2005**, 243, 1-42.

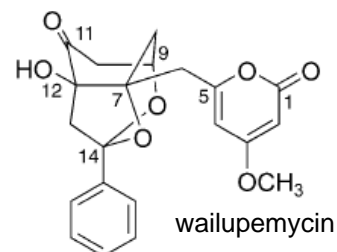
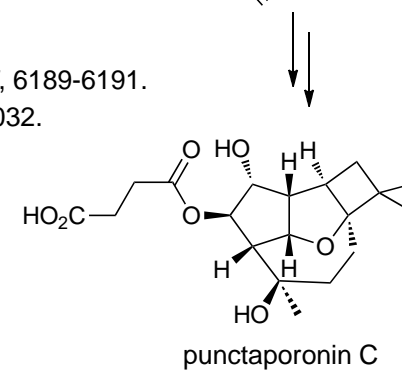
**Stereoselective [2+2] Photocycloadditions (e.g. Paterno-Büchi Reactions)**



*Angew. Chem. Int. Ed.* **1998**, 37, 3400-3402.



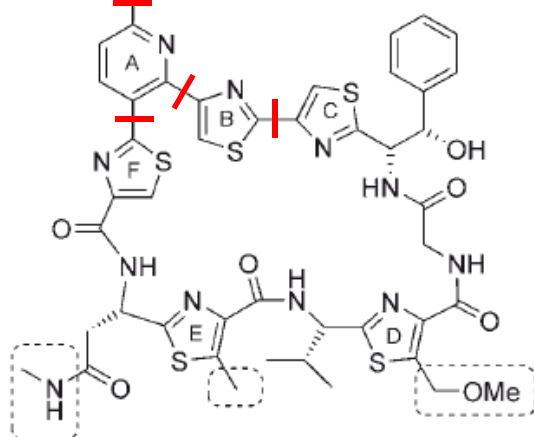
*Angew. Chem. Int. Ed.* **2008**, 47, 6189-6191.  
*Chem. Eur. J.* **2010**, 16, 6015-6032.



*Angew. Chem. Int. Ed.* **2003**, 42, 4685-4687.  
*Chem. Eur. J.* **2005**, 11, 7007-7023.

GE2270 A

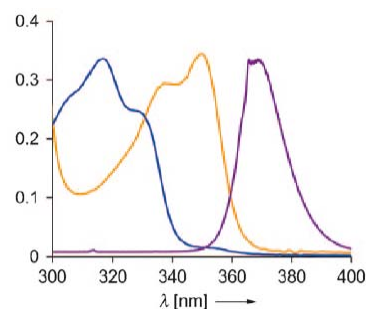
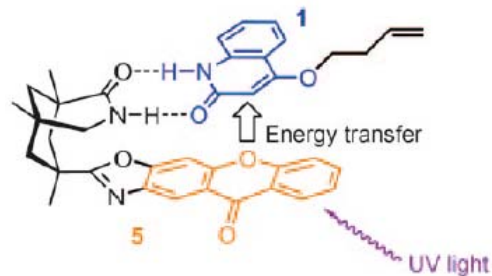
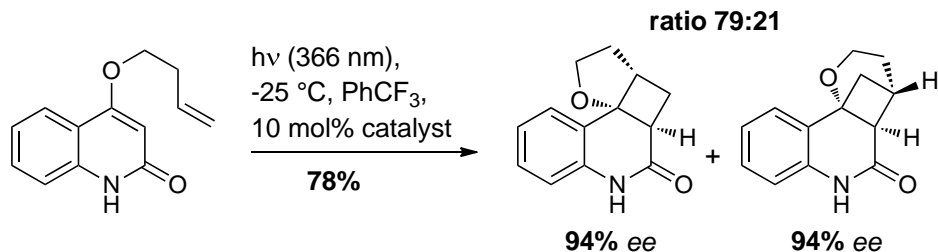
... a potent antibiotic thiazolylpeptide



structure variation in other GE2270 antibiotics

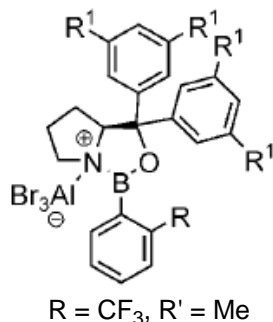
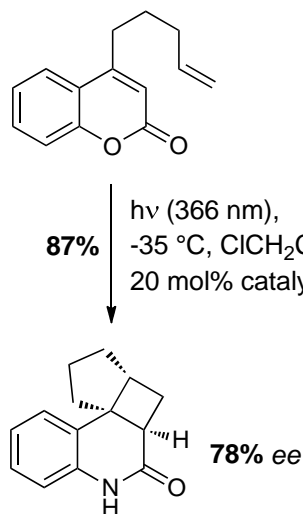
*Chem. Eur. J.* **2008**, 14, 2322-2339.  
*Angew. Chem. Int. Ed.* **2007**, 46, 4771-4774.

## Light-Driven Organocatalysis



*Angew. Chem. Int. Ed.* **2009**, 48, 6640-6642.

## Chiral Lewis Acids in Enantioselective Photochemistry



*Angew. Chem. Int. Ed.* **2010**, 49, 7782-7785.

## Stefan Bräse:



- born: November 30<sup>th</sup> 1967, Kiel, Germany
- studies in chemistry, University of Göttingen
- 1995 PhD with Armin de Meijere
- 1995-1996 Postdoc with J. Bäckvall, University of Uppsala
- 1996-1997 Postdoc with K.C. Nicolaou, TSRI, La Jolla  
(*Total synthesis of vancomycin*)
- 1997-2001 Habilitation, RWTH Aachen (mentor: D. Enders)
- 2001-2003 Full Professor, University of Bonn, Germany
- since 2003 KIT, Karlsruhe, Germany
- around 110 publications

## main research interests:

- **combinatorial chemistry**
- **solid-phase chemistry**
- **nanstructures**
- **total synthesis**

"If I were a car... I would be an Audi RS6."

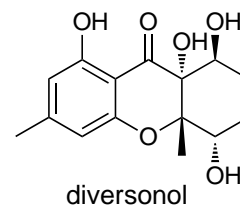
My motto is... "I know!".

Hobbies: Chemistry...

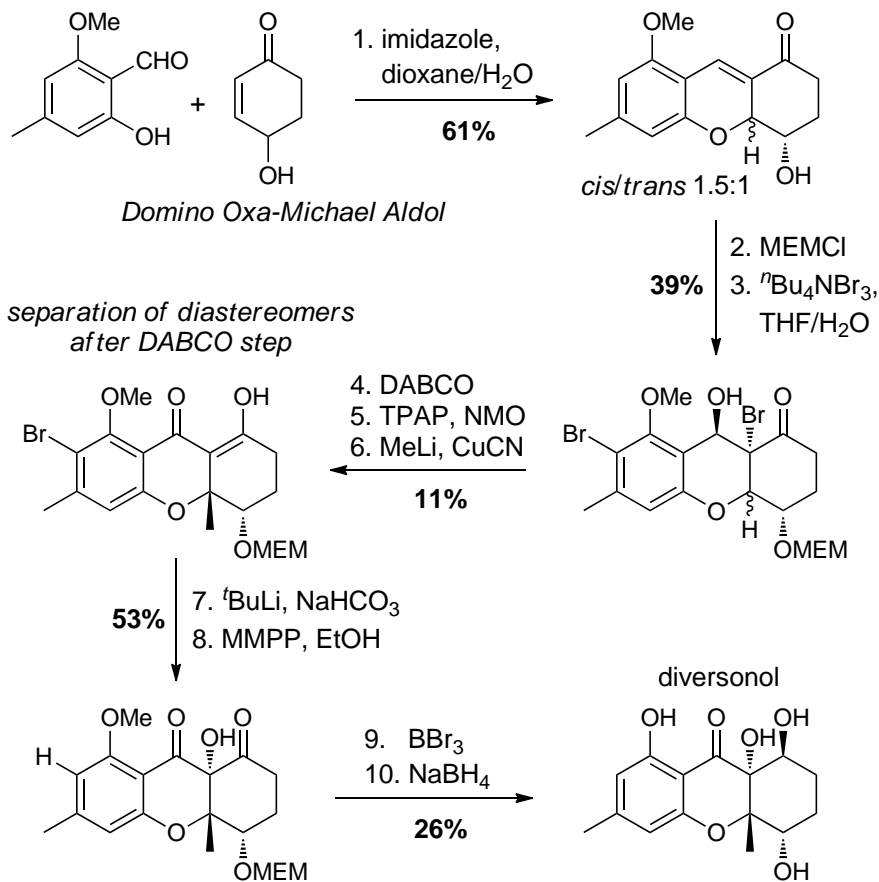
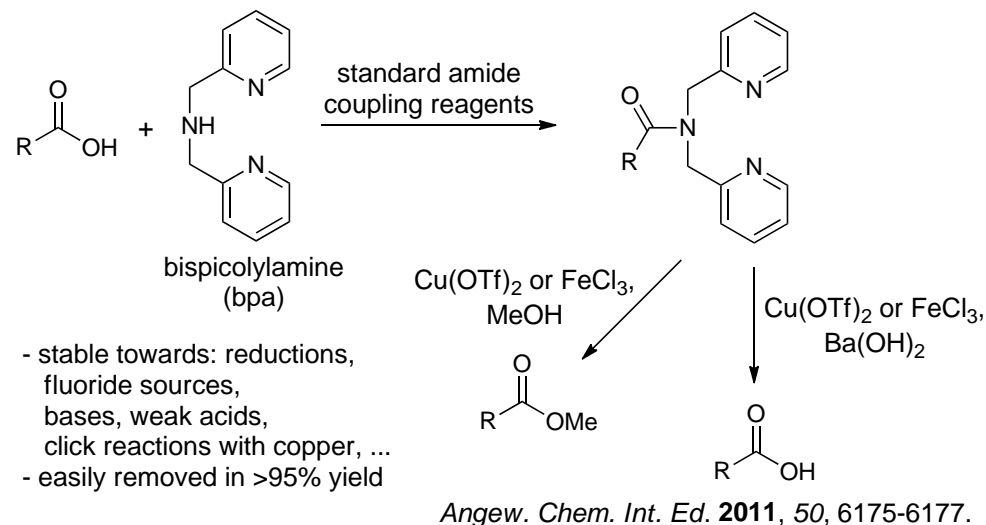
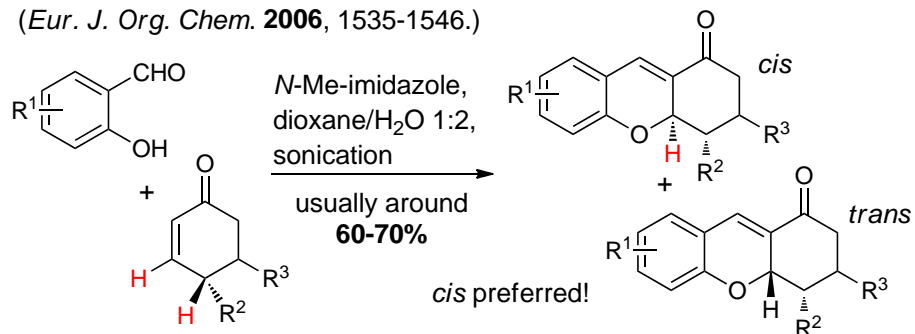
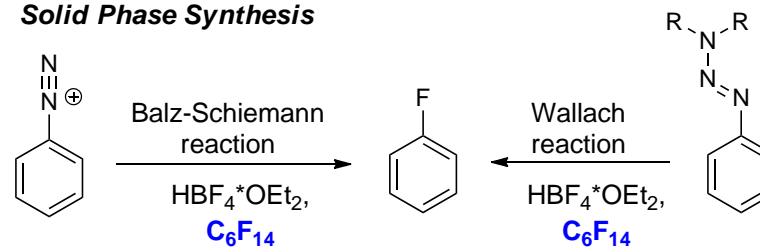


## Total Synthesis of Diversonol

*Angew. Chem. Int. Ed.* **2006**, 45, 307-309.



- isolated from *Penicillium diversum*
- absolute configuration unknown

**A Novel Protecting Group for RCOOH****Domino Oxa-Michael Aldol Reaction**(Eur. J. Org. Chem. **2006**, 1535-1546.)**Solid Phase Synthesis**perfluorohexanes C<sub>6</sub>F<sub>14</sub> as magic solvent:

- suppression of side product formation
- mild reactions conditions (80 °C)
- applicable to solid phase and in solution

*Angew. Chem. Int. Ed.* **2010**, 49, 5986-5988.**... also worth reading:**

*Angew. Chem. Int. Ed.* **1999**, 38, 1071 (C,C couplings w/ immobilized substrates).  
*Angew. Chem. Int. Ed.* **2008**, 47, 8120-8122 (solid phase synthesis of simple NP).  
*Eur. J. Org. Chem.* **2009**, 4494-4502 (fluorinating cleavage from solid support).

**Frank Glorius:**

- born: XX. XX. 1972, XX, Germany.
- studies in chemistry, University of Hannover
- 1995-1996 Research with Paul A. Wender, Stanford
- 2000 PhD with Andreas Pfaltz, MPI/University of Basel
- 2000-2001 Postdoc with D. A. Evans, Harvard University
- 2001-2004 Habilitation, MPI Mülheim (mentor: A. Fürstner)
- 2004 Associate Professor, University of Marburg, Germany
- since 2007 Full Professor, University of Münster, Germany
- 91 publications

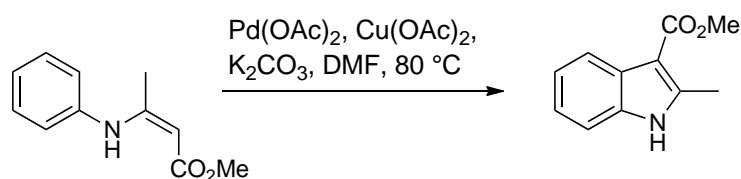
**main research topics:**

- sterically demanding NHCs
- functional MOFs
- challenging cross-couplings
- CH activation
- asymmetric organocatalysis
- heterocyclic chemistry

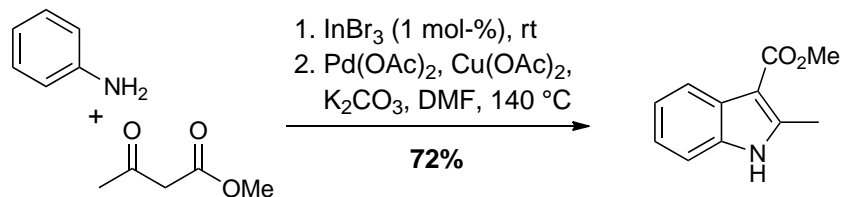
*"When I wake up I... can't believe it's that time already."*

**Indoles from Enamines by CH Activation**

*Angew. Chem. Int. Ed.* **2008**, *47*, 7230-7233.

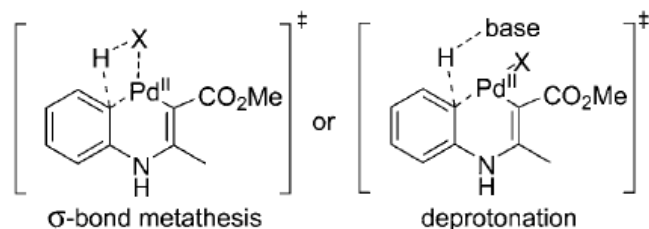


- very wide substrate scope
- steric demand determines outcome, not electronic influence; rarely regioisomers
- good yields, scalable
- one-pot reaction possible (see below)



Entry	Product	Yield <sup>[b]</sup> [%]	Entry	Product	Yield <sup>[b]</sup> [%]
1 <sup>[c]</sup>		72	11 <sup>[d]</sup>		74
2 <sup>[d]</sup>		82	12 <sup>[c]</sup>		53
3 <sup>[d]</sup>		68	13 <sup>[c]</sup>		76
	(6-Me/4-Me)	(92:8 <sup>[e]</sup> )		(6-Cl/4-Cl)	(88:12 <sup>[e]</sup> )
4 <sup>[c]</sup>		72	14 <sup>[c]</sup>		64
5 <sup>[d]</sup>		62	15 <sup>[f]</sup>		54
					(>99:1 <sup>[e]</sup> )
6 <sup>[f]</sup>		64	16 <sup>[f]</sup>		52
7 <sup>[f]</sup>		68	17 <sup>[f]</sup>		64
		(>99:1 <sup>[e]</sup> )			
8 <sup>[f]</sup>		64	18 <sup>[f]</sup>		70
9 <sup>[d]</sup>		78	19 <sup>[f]</sup>		65
10 <sup>[d]</sup>		74	20 <sup>[c]</sup>		85
	(6-F/4-F)	(53:47 <sup>[e]</sup> )			(>99:1 <sup>[e]</sup> )

proposed mechanism:

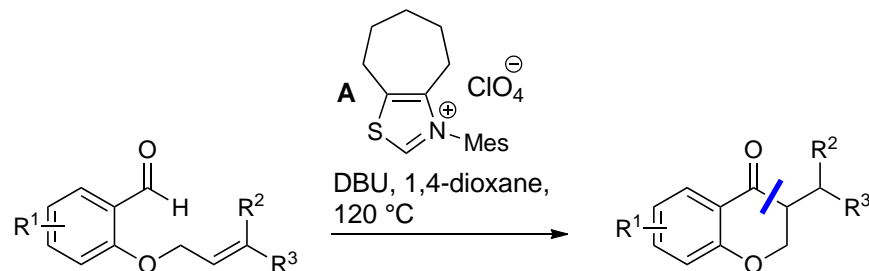


Initial mechanistic investigations unambiguously support a  $\sigma$ -bond metathesis or deprotonation pathway and not an electrophilic aromatic palladation of the aniline ring.

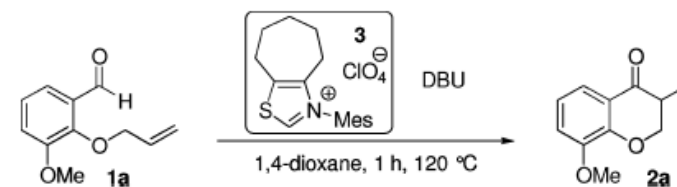
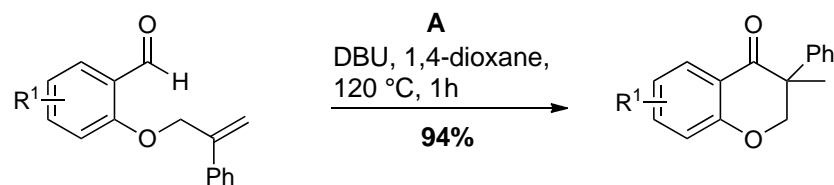
### NHC-Catalyzed Hydroacylation of Unactivated Double Bonds (*cp.* Stetter reaction)

*J. Am. Chem. Soc.* **2009**, *131*, 14190-14191.

*Org. Lett.* **2008**, *10*, 4243-4246 (synthesis of NHC **A**).

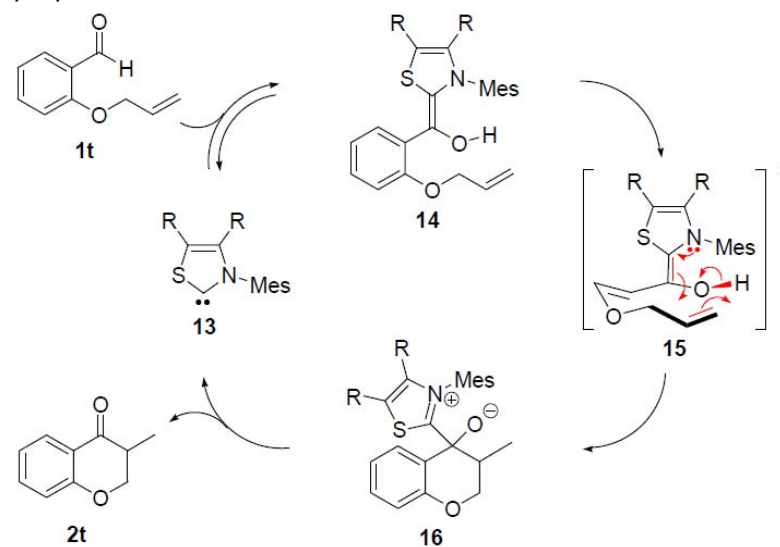


- very wide substrate scope
- good yields (70-96%)
- scalable
- formation of quaternary centers possible
- useful disconnection



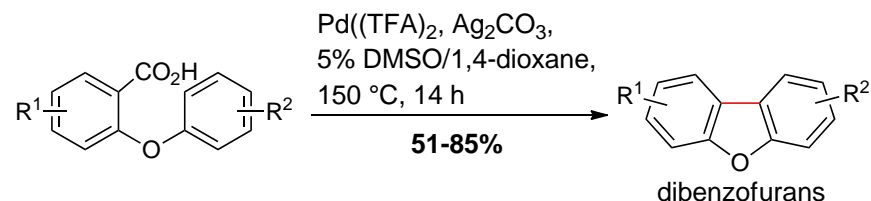
entry	variation of the standard conditions <sup>a</sup>	yield of <b>2a</b> (%) <sup>b</sup>
1	none	69
2	<b>4</b> instead of <b>3</b>	2
3	<b>5</b> instead of <b>3</b>	21
4	<b>6</b> instead of <b>3</b>	2
5	<b>7</b> instead of <b>3</b>	11
6	DBU: 20 mol % instead of 40 mol %	34
7	TEA instead of DBU	3
8	K <sub>2</sub> CO <sub>3</sub> instead of DBU	32
9	KOt-Bu instead of DBU	69
10	10 mol % of <b>3</b> , 20 mol % DBU	65
11	reaction time: 2 h instead of 1 h	81 (85) <sup>c</sup>

proposed mechanism:



### Intramolecular Direct Arylation of Benzoic Acids by Tandem Decarboxylation/C-H Activation

*J. Am. Chem. Soc.* **2009**, *131*, 4194-4195.



### Mathias Christmann:

- born: XX. XX. 1972, Peine, Germany.
- studies in chemistry, University of Braunschweig
- 2000 PhD with M. Kalesse, University of Hannover (*Total Synthesis of (+)-Ratjadone*)
- 2001-2002 Postdoc with C. J. Forsyth, Univ. of Minnesota
- 2003-2007 Habilitation, RWTH Aachen (mentor: D. Enders)
- since 2008 Associate Professor, TU Dortmund, Germany
- 36 independent publications

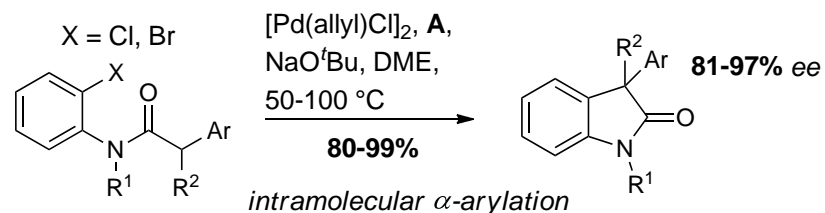
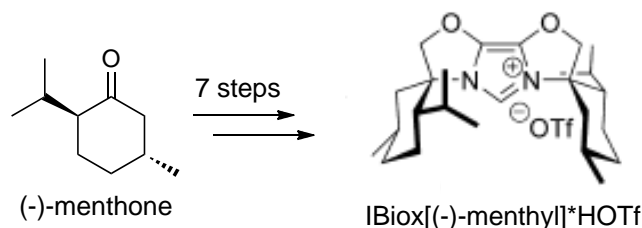
### main research topics:

- total synthesis
- method development
- organocatalysis
- catalytic transformations of renewable resources

We have recently initiated a program that is aimed at making larger substructures within natural products available from terpene feedstock. Using simple bulk terpenes such as geranyl and neryl acetate or nepetalactone we are aiming to find efficient ways to modify the carbon skeleton using oxidations, organocatalytic and metal-catalyzed reactions such as hydroformylations.

### A Sterically Demanding Chiral NHC Ligand

*J. Am. Chem. Soc.* **2009**, *131*, 8344-8345.

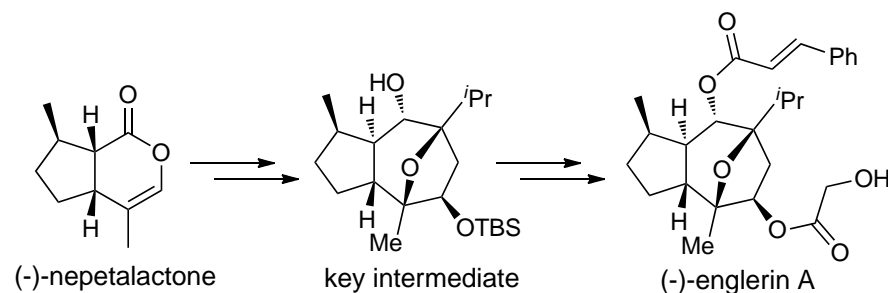


- rigid geometry of NHC leads to excellent ee's
- high yields
- aryl chlorides (X = Cl) can be used for the first time
- *N*-benzyl give higher ee's than *N*-methyl
- highest ee's for *ortho*-substituted aryls (Ar)

### The Concept - e.g. (-)-Englerin A from (-)-Nepetalactone:

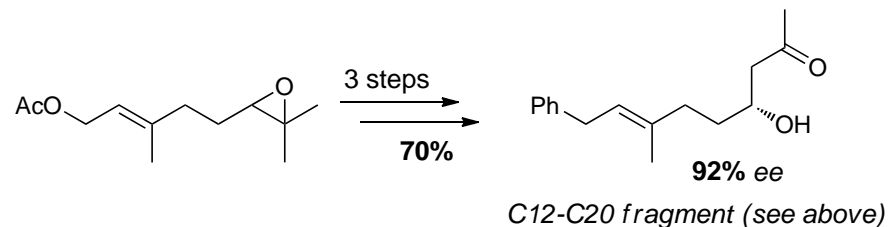
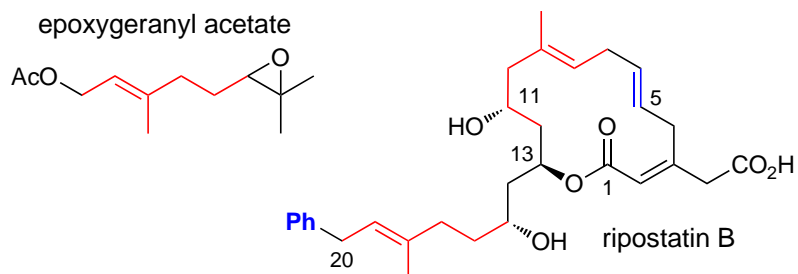
*Angew. Chem. Int. Ed.* **2009**, *48*, 9105 (1<sup>st</sup> generation synthesis).

*Angew. Chem. Int. Ed.* **2011**, *50*, 3998 (2<sup>nd</sup> generation synthesis).



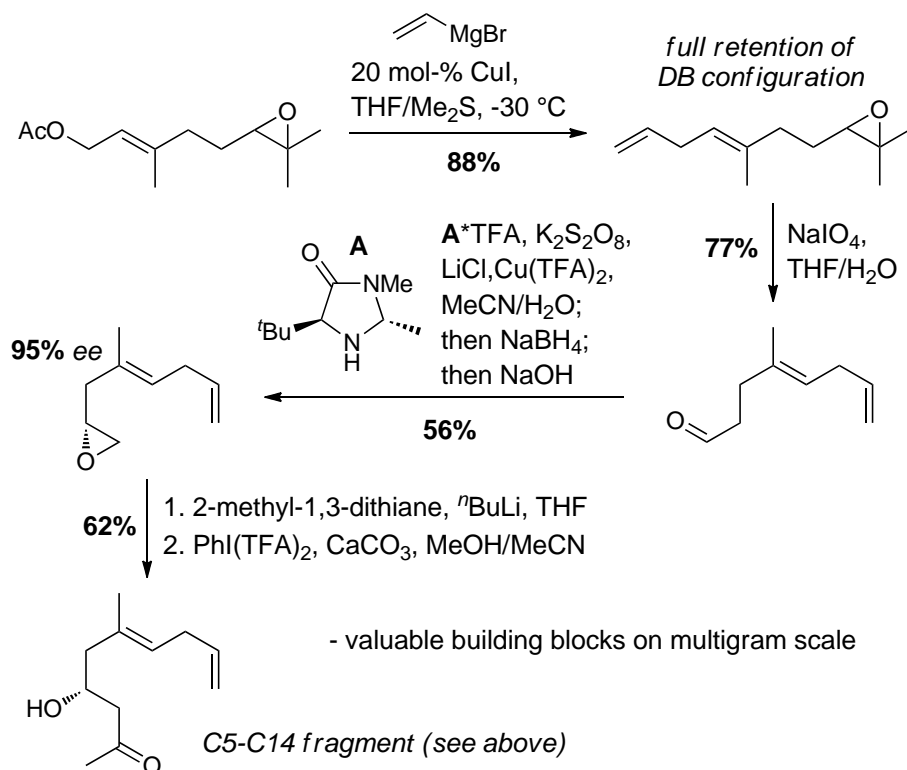
- multigram quantities of key intermediate available
- route allows for various late stage modifications for SAR studies
- derivatives with improved activity against renal cancer cell lines

**The Concept - continued...** Chem. Commun. 2011, 47, 394-396.



... the end!

selected examples of prepared building blocks:



not covered:

- Magnus Rüping, RWTH Aachen
- Dirk Menche, University of Heidelberg
- Armino Studer, University of Münster
- Benjamin List, MPI Mühlheim
- Christian Hertweck, HKI Jena
- Lutz Ackermann, University of Heidelberg
- ...

... part II to come ...