

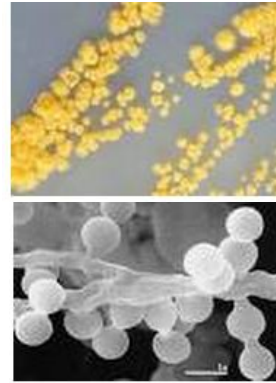


> Karl Gademann, born in 1972

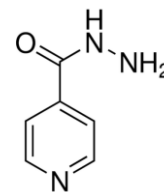
- Ph.D. at ETH under the supervision of Prof. Dr. Dieter Seebach (1997-2000)
- Postdoctoral Fellow at Givaudan (2000) and in Harvard University with Prof. Dr. Eric N. Jacobsen (2000-2001)
- Habilitation with Prof. Dr. Erick M. Carreira (2002-2006)
- Full Professor and Dean of research at the University of Basel

> Research Interests :

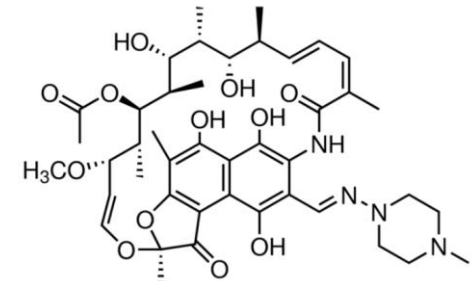
- Total synthesis of natural products
- Bioprospecting and Neuroengineering



- > First isolation through fermentation of *Actinoplanes deccanensis* in 1975 by Parenti and co-workers
- > First antimicrobial agent approved by the FDA for the treatment of *Clostridium difficile* infection (2011, Optimer, Dificid®)
- > Bacterial activity against *Mycobacterium tuberculosis*
- > But low bioavailability and instability of the compound under acidic conditions
- > First total enantioselective synthesis : give access to structurally diverse analogues
- > Each year : 9 million new cases and 2 million deaths
- > Two drugs already developed



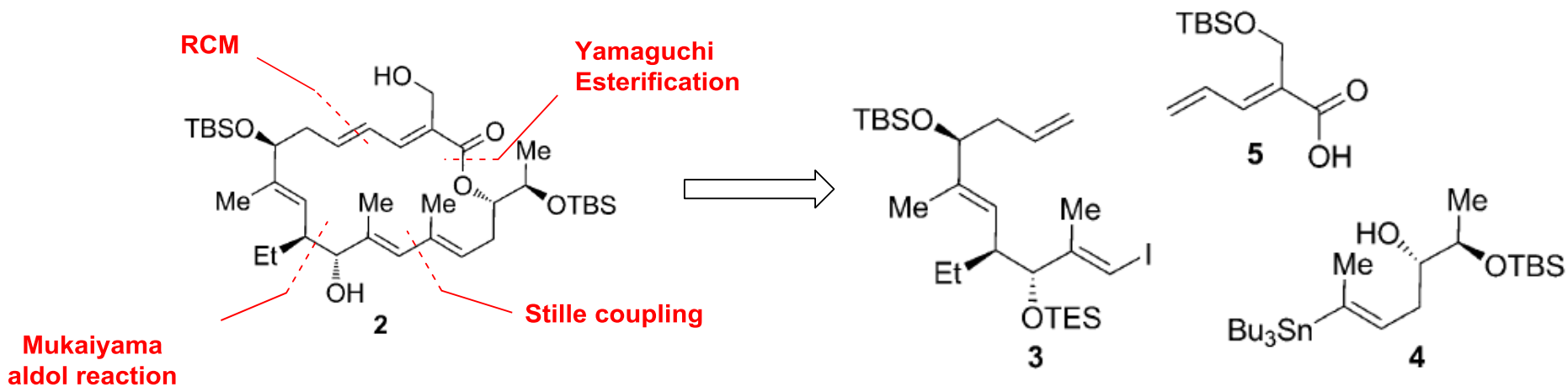
Isoniazid



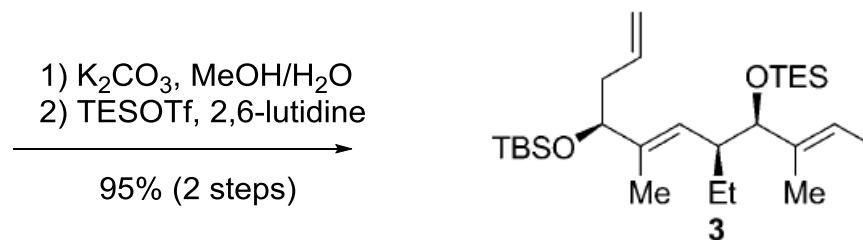
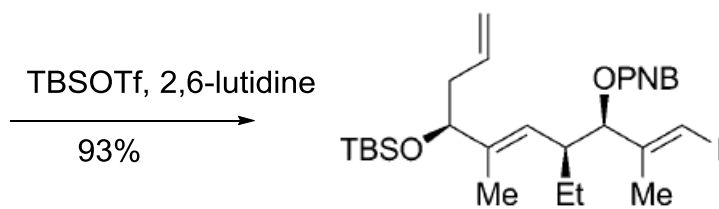
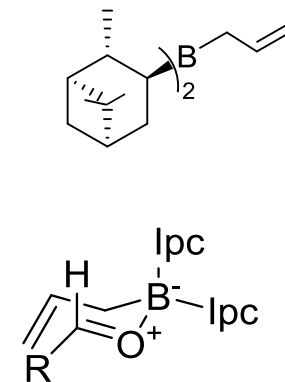
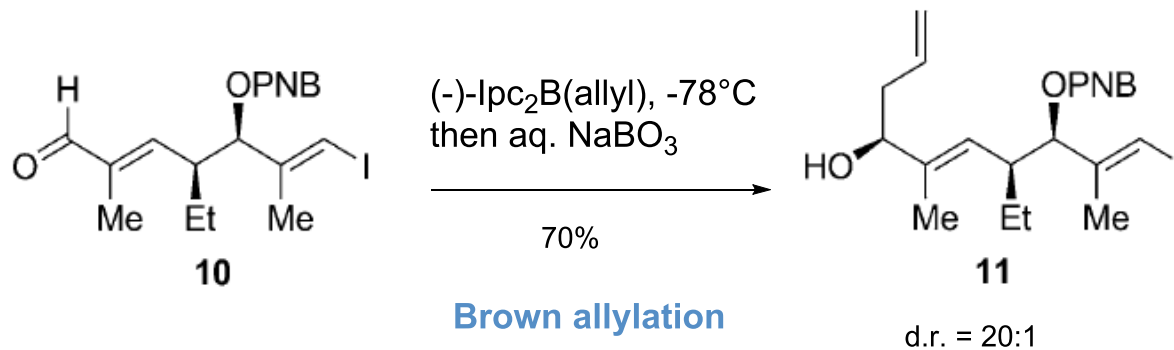
Rifampicin

Retrosynthetic Analysis

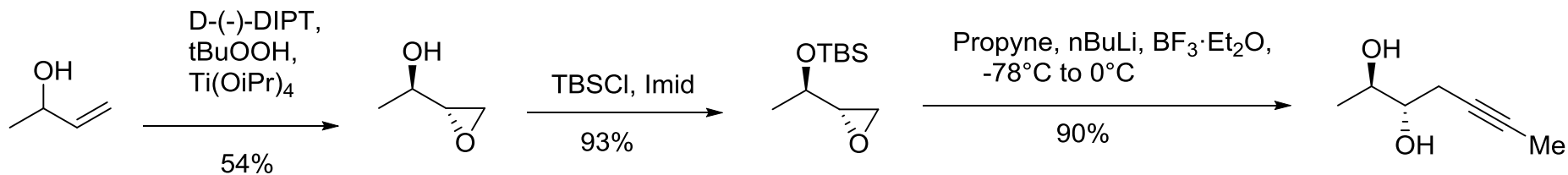
- > 18-membered Macrolactone **2**, central aglycon of fidaxomicin
 - Short and highly convergent synthetic route
 - Three main building blocks: vinyl iodide **3**, vinyl stannane **4**, and dienoic acid **5**
 - Five chiral centers



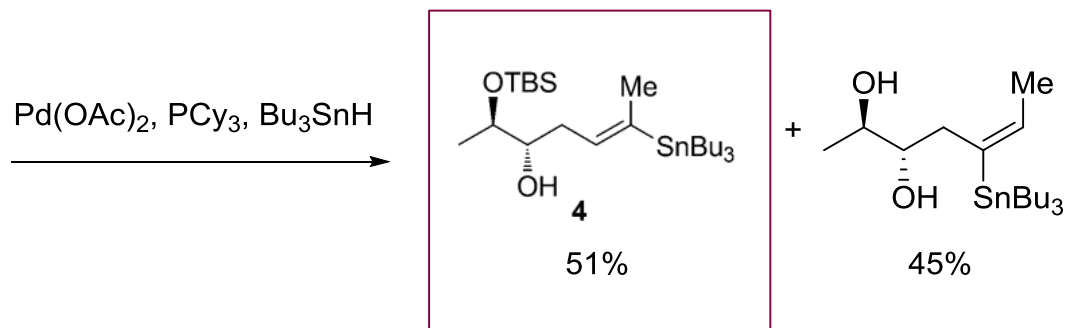
Synthesis of building block 3



Synthesis of building block 4

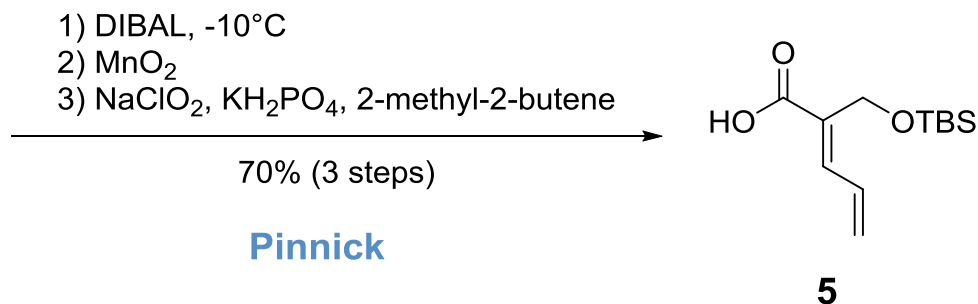
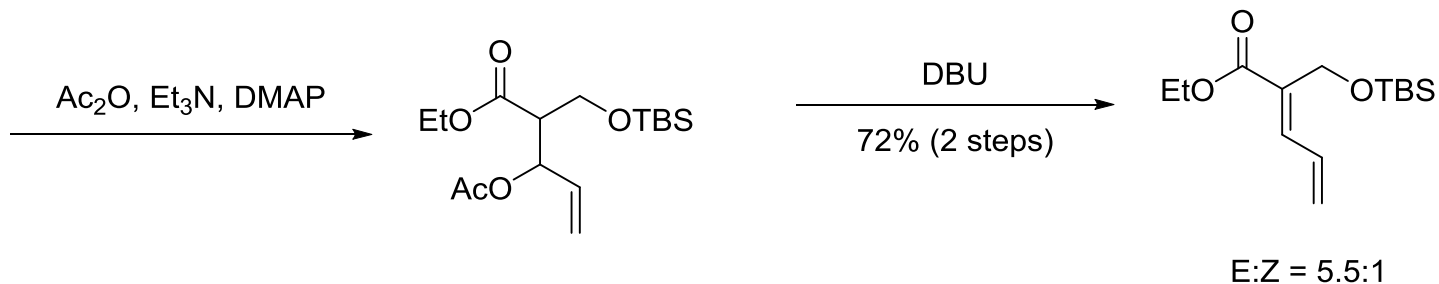
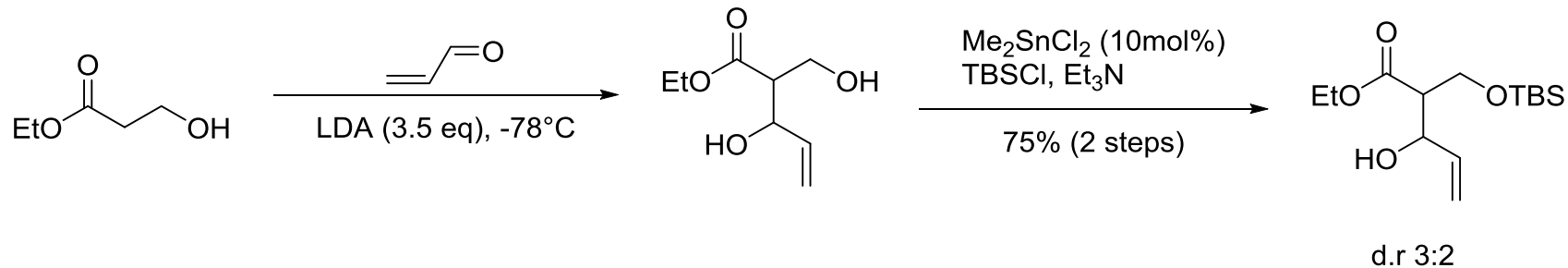


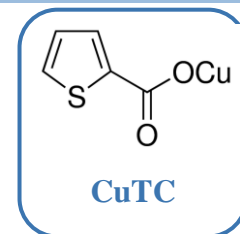
Sharpless epoxidation



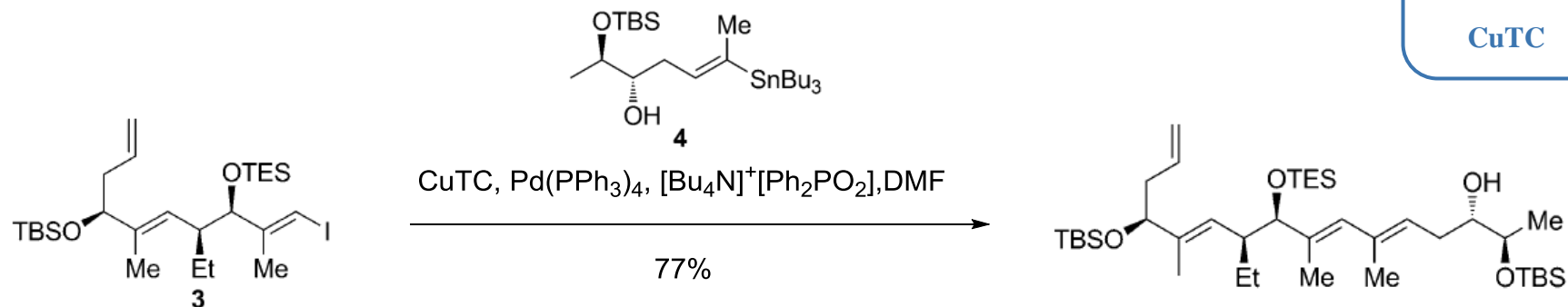
Desired regioisomer

Synthesis of building block 5

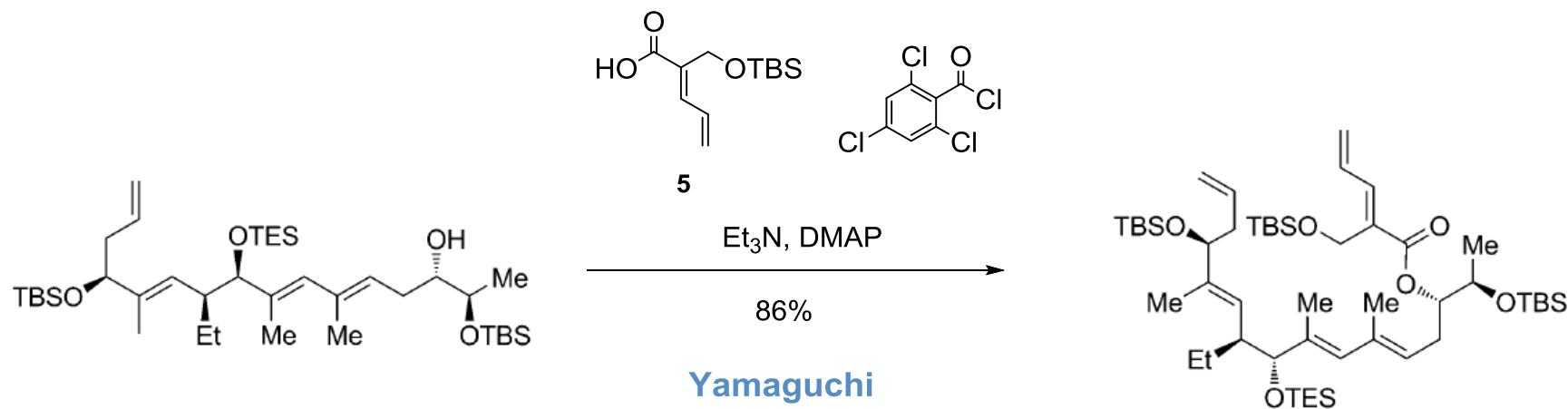




Synthesis of Macrolactone 2

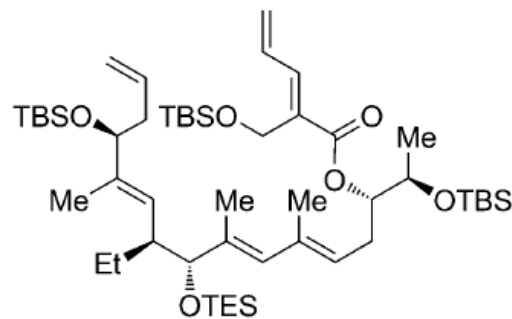


Stille coupling



Yamaguchi

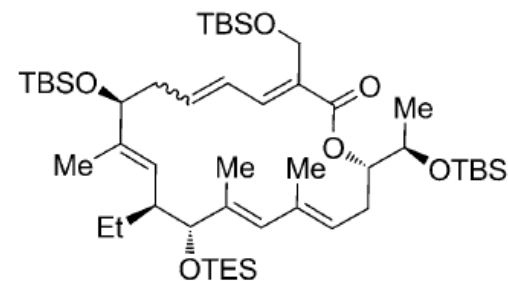
Synthesis of Macrolactone 2



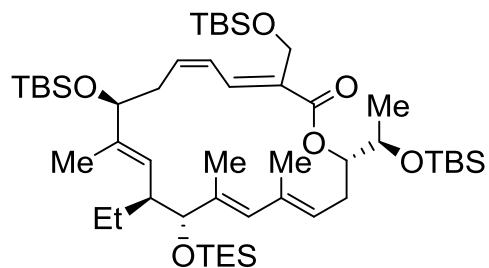
1) Grubbs cat. II (15 mol%),
40°C (microwave irradiation), 10 min, E/Z=2:3
2) 100°C, 18 h, E/Z=2:1

90%

RCM

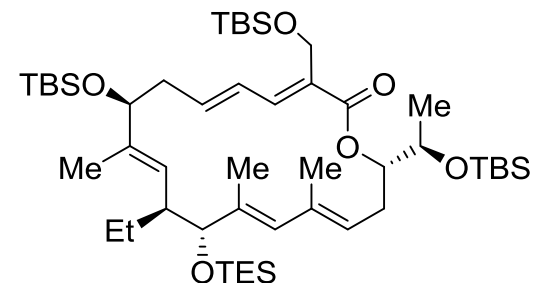


E/Z=2:1



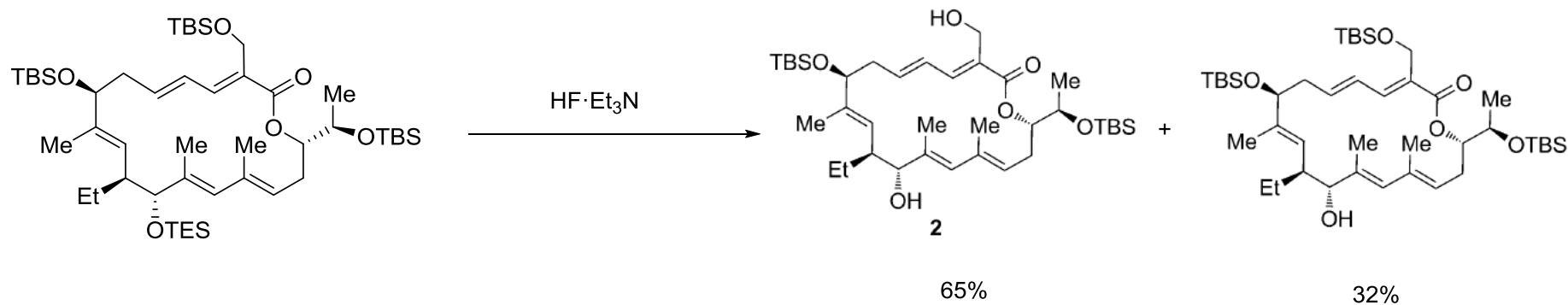
Grubbs cat. II (15 mol%), 100°C, 18 h

92%



E/Z=2:1

Synthesis of Macrolactone 2



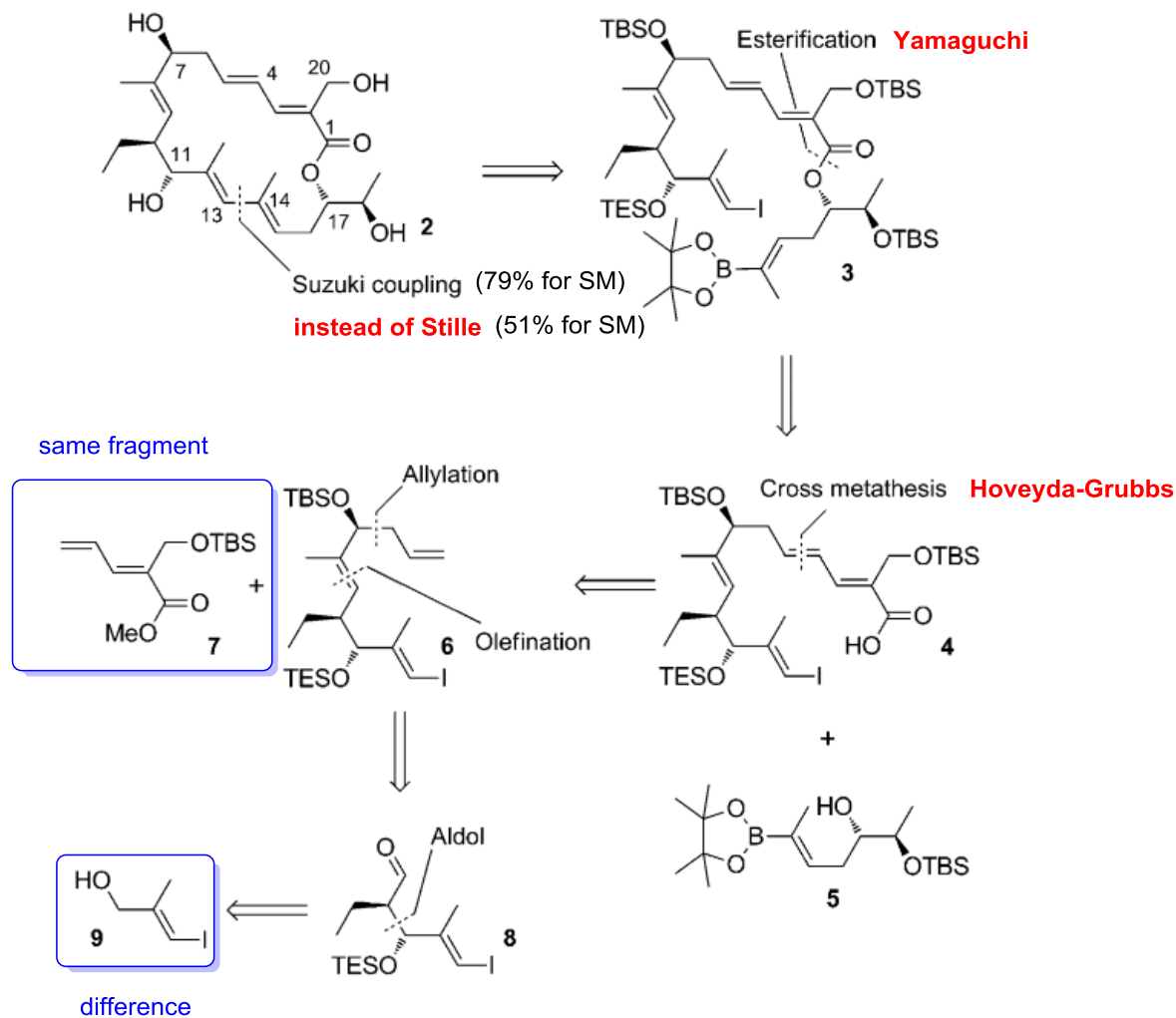
- > Possible recycling of TES-deprotected product
- > Free hydroxy groups for following glycosylations

- > Synthesis in 18 steps via three main fragments in 0.7% yield
- > Stereoselective synthesis
- > Highlights of the strategy
 - RCM for macrocyclization
 - Diastereoselective VMAR
 - Stille coupling with sterically hindered substrates
- > Structures established the structures unambiguously
- > Preparation of the noviose, rhamnose and resorcinol units in progress

Other Synthesis

> F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 1937–1940;

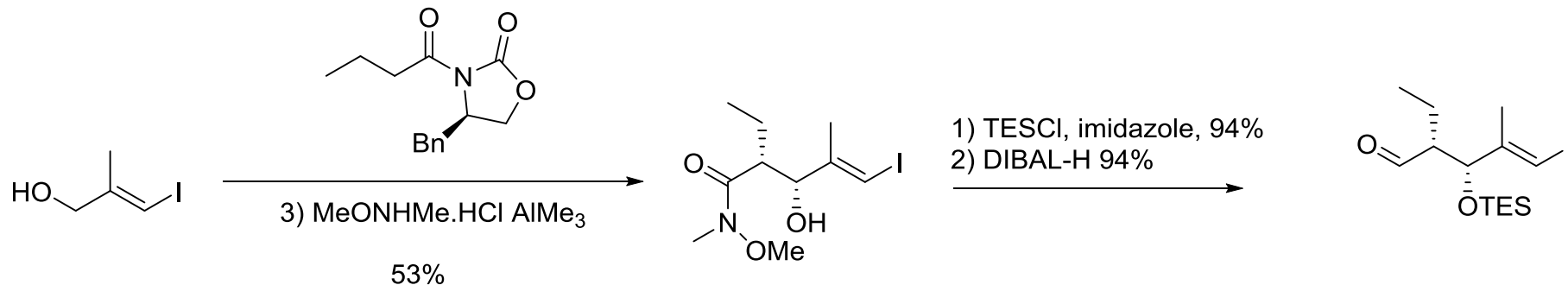
- 17 steps
- 0,1% yield



Other Synthesis

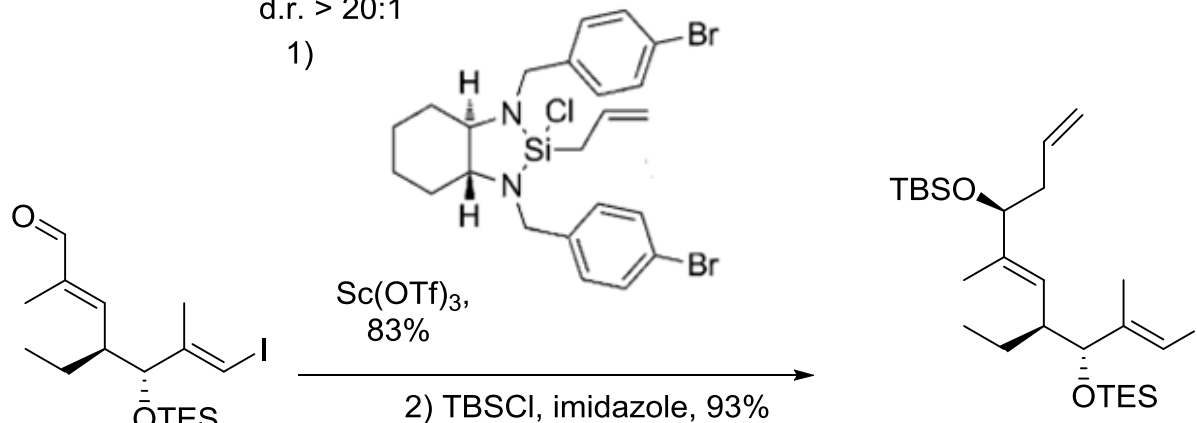
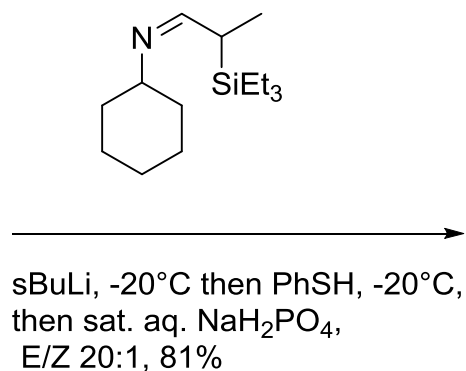
> Synthesis fragment 6

- 1) MnO₂
- 2) Bu₂BOTf, NEt₃, -78 °C



- 1) TESCl, imidazole, 94%
- 2) DIBAL-H 94%

d.r. > 20:1
1)



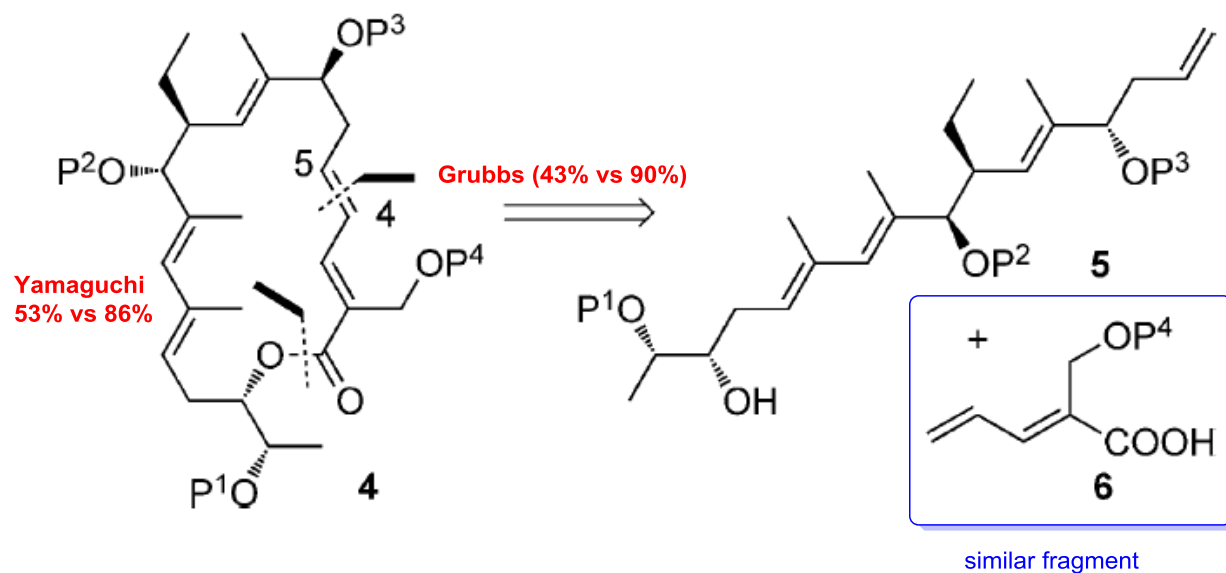
- 2) TBSCl, imidazole, 93%

d.r. > 20:1

Corey-Peterson

Other Synthesis

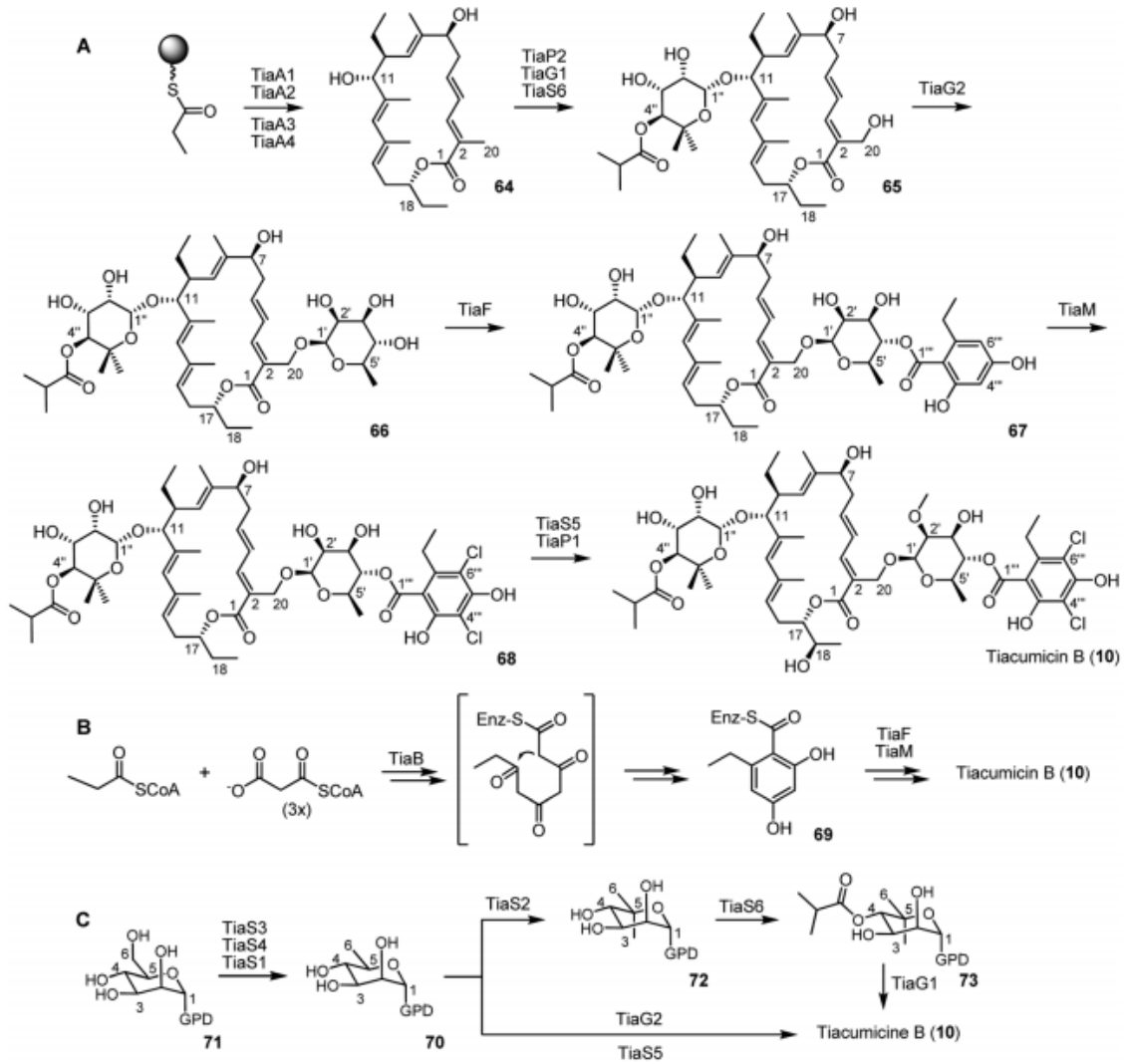
- > W. Erb, J.-M. Grassot, D. Linder, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.*- **2015**, *54*, 1929–193
 - 29 steps
 - 0.0002%



- > To construct **5** : several oxidation/HWE/reduction sequence repeated
use of Evan's copule and allylboration

Thank you for your attention!

Biosynthesis



Previous synthesis of resorcylic acid:

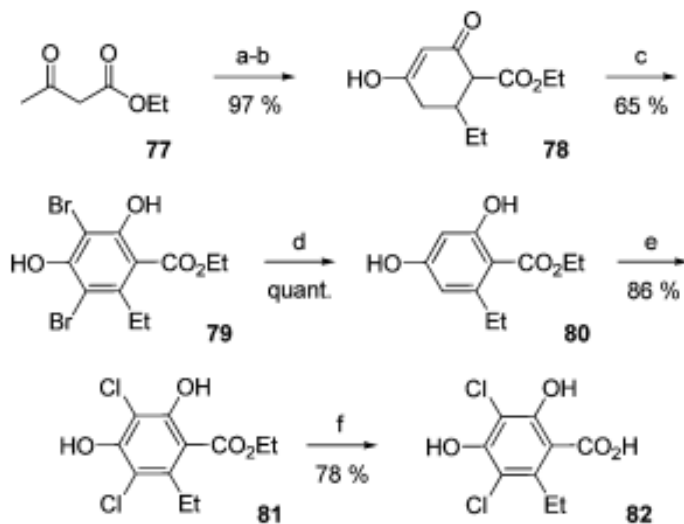


Fig. 10 The synthesis of homodichloro-orsellinic acid. (a) (*E*)-Ethyl pent-2-enoate, Na, EtOH, reflux. (b) HCl aq., $-10\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$. (c) Br_2 , AcOH, $40\text{ }^{\circ}\text{C}$. (d) Ni/Al, NaOH aq., $0\text{ }^{\circ}\text{C}$. (e) SO_2Cl_2 , Et_2O , reflux. (f) H_2SO_4 conc.

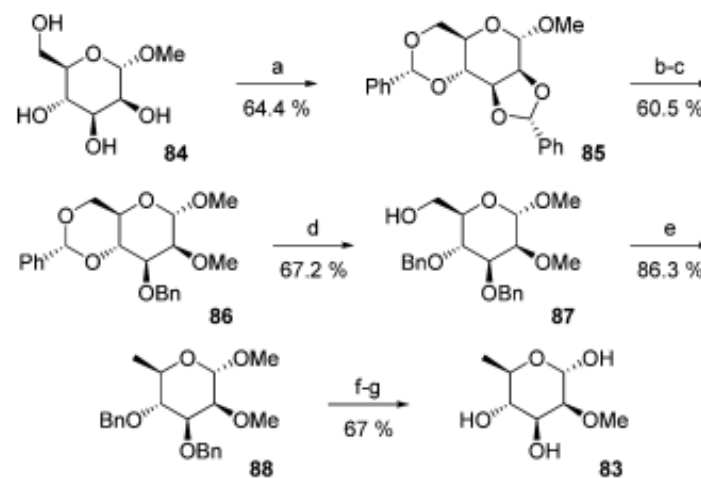
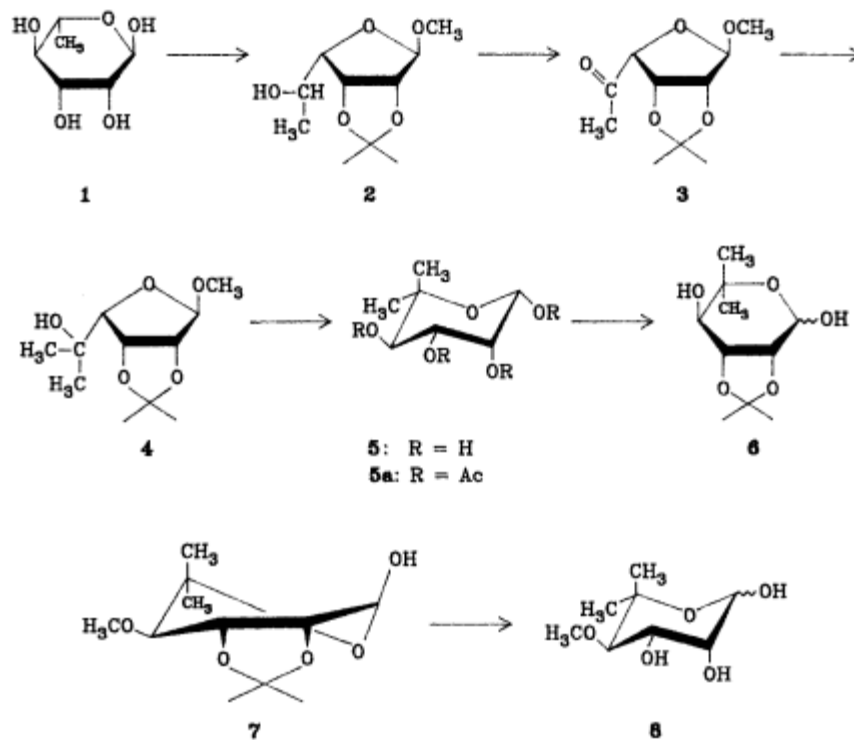


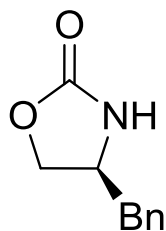
Fig. 11 The synthesis of 2-O-methyl- β -D-rhamnose. (a) α,α -Dimethoxytoluene, PTSA, DMF, $65\text{--}75\text{ }^{\circ}\text{C}$. (b) LiAlH_4 , AlCl_3 , Et_2O , DCM. (c) MeI, Ag_2O , DMF. (d) LiAlH_4 , AlCl_3 , Et_2O , DCM. (e) TsCl. (f) LiAlH_4 , benzene, Et_2O , reflux. (g) H_2 , Pd/C, EtOH, AcOH. (h) H_2SO_4 (1 M), $100\text{ }^{\circ}\text{C}$.

Previous synthetic studies on noviose:



Synthesis Evans auxiliary

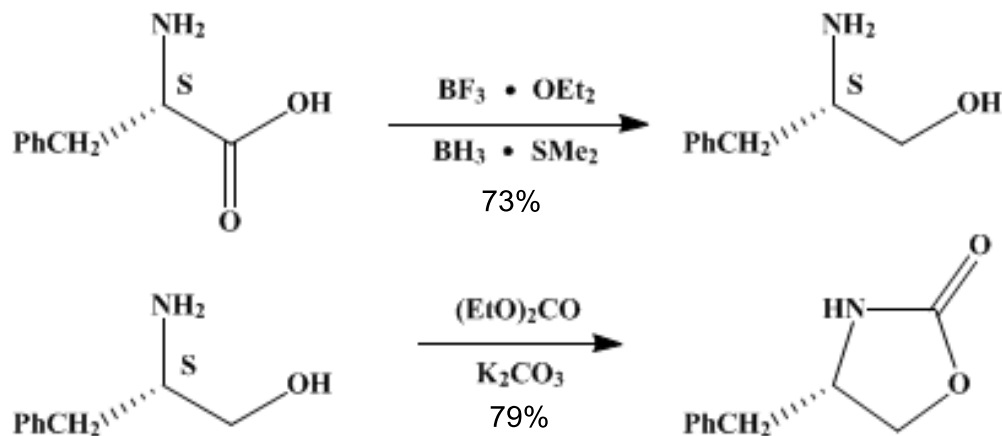
> Commercially available:



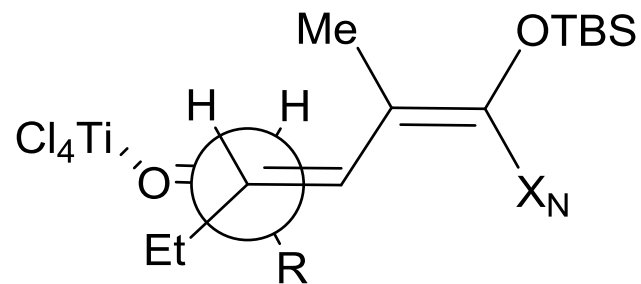
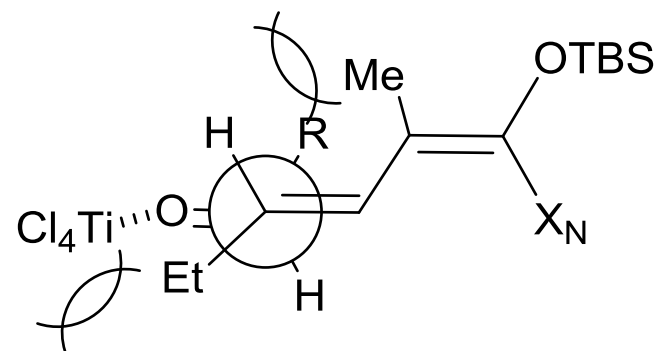
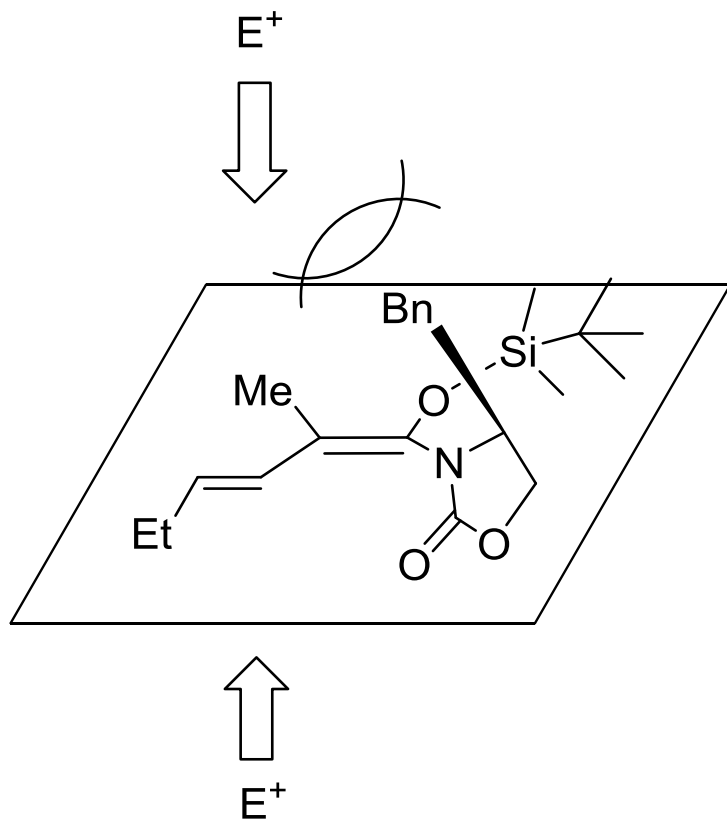
■ TCI : 5g, 62 €

■ Aldrich : 5g, 249 CHF

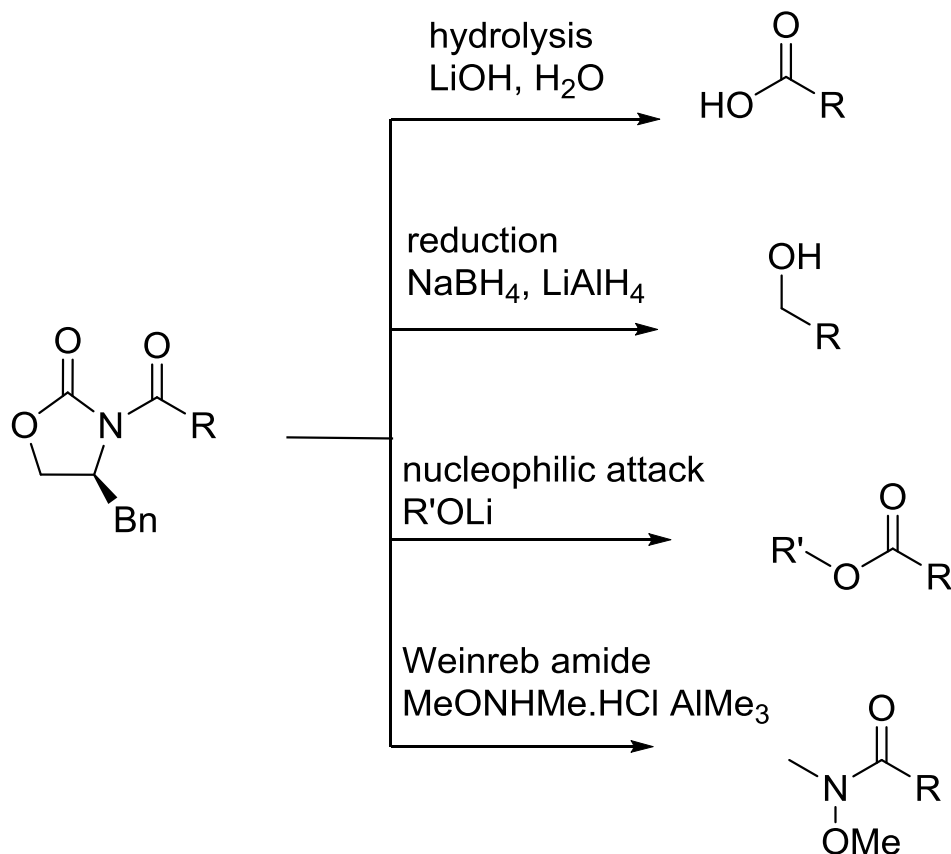
> Starting from (*S*)-phenylalanine



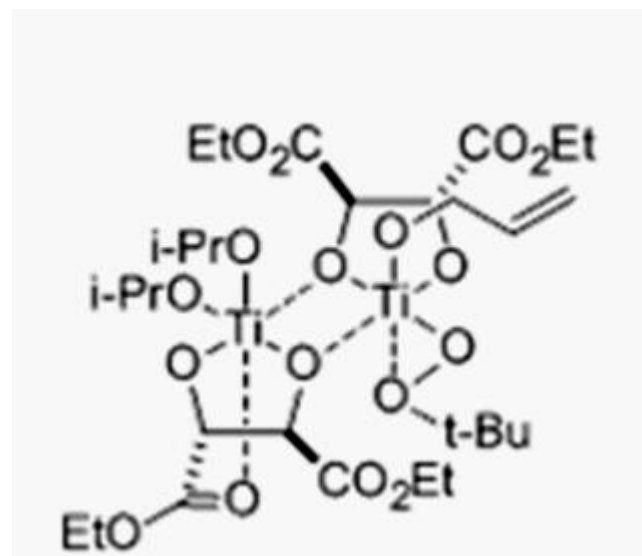
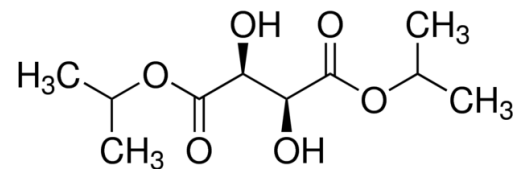
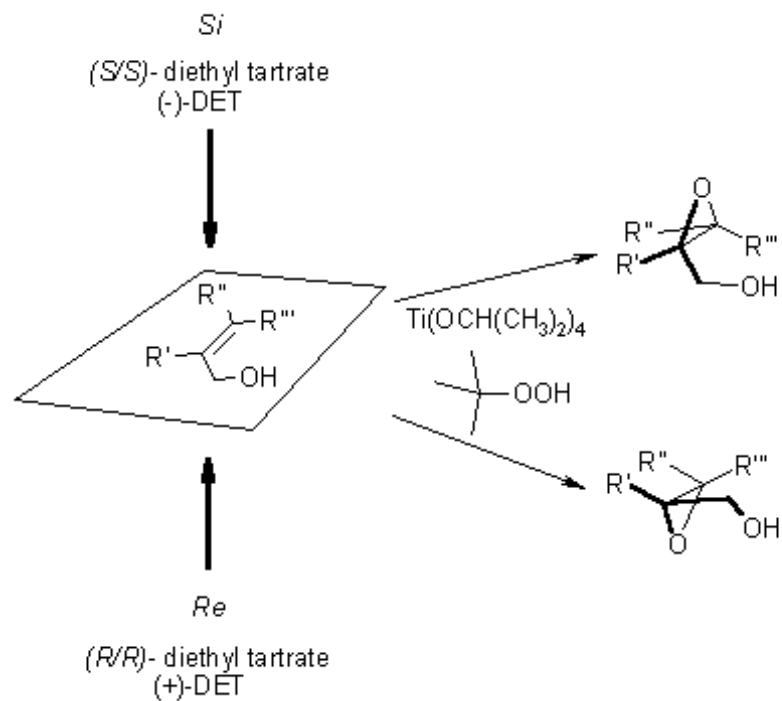
Stereoselectivity



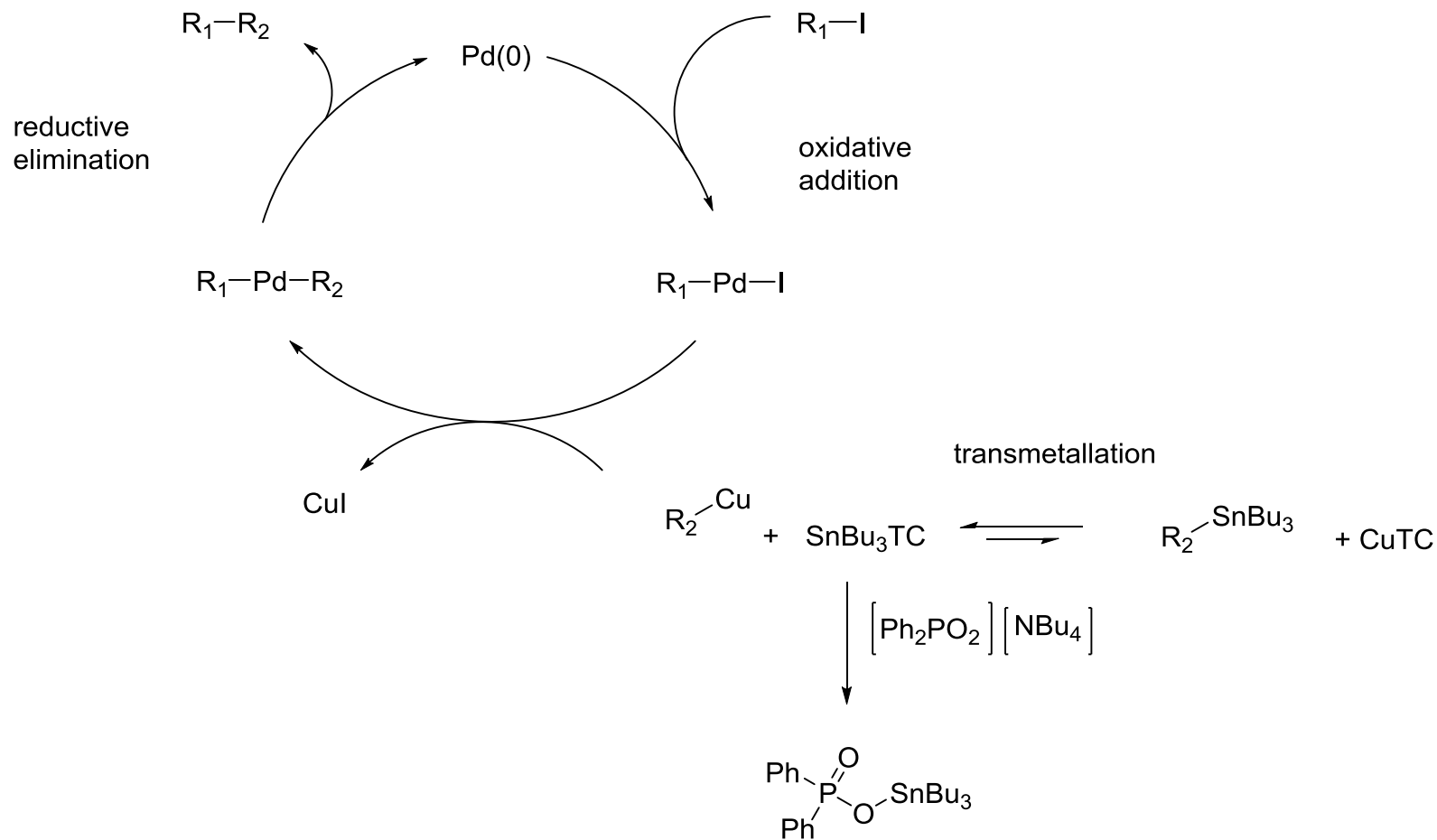
Removal of auxiliary



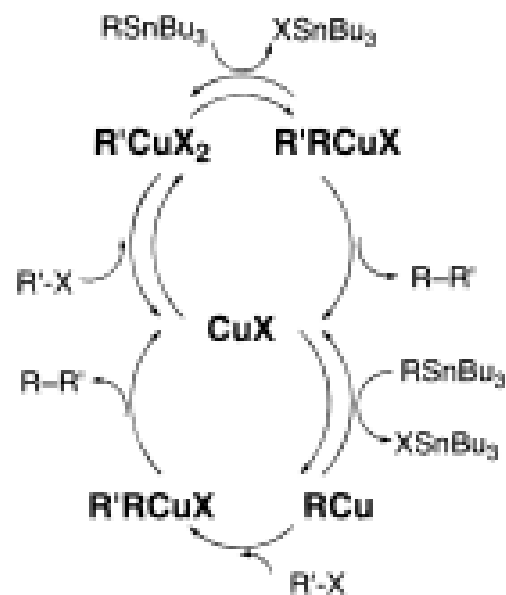
Sharpless epoxydation



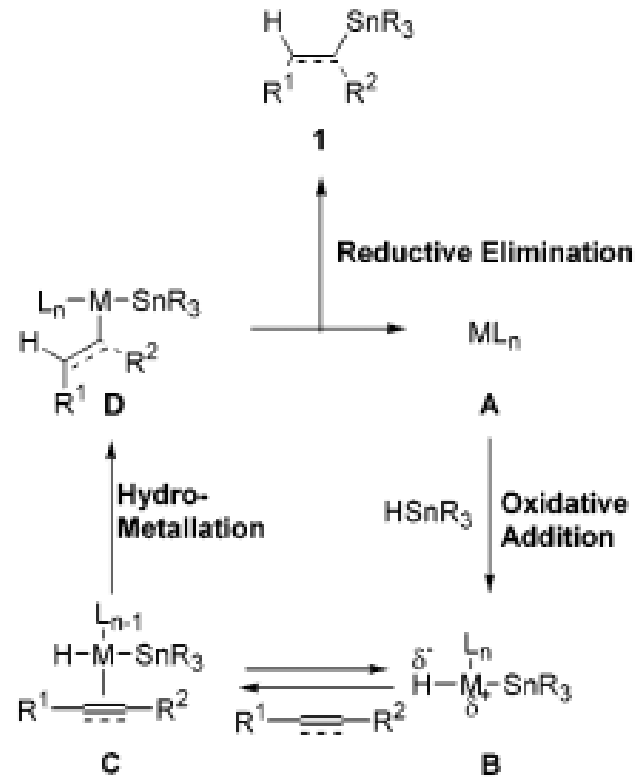
Stille coupling



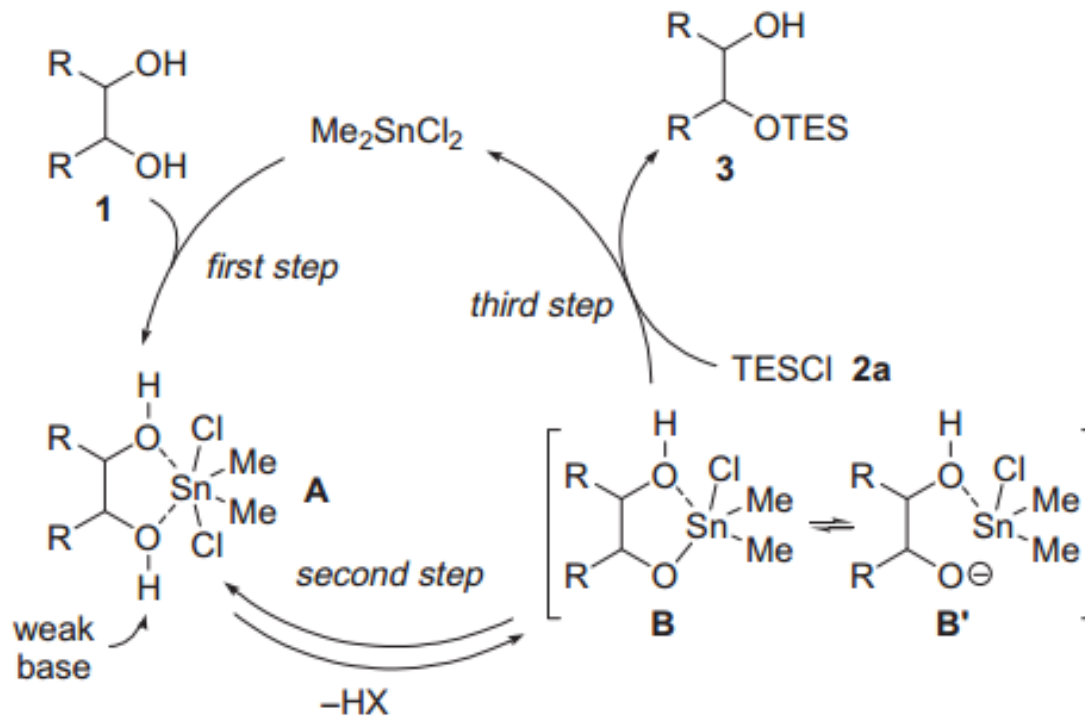
Stille coupling



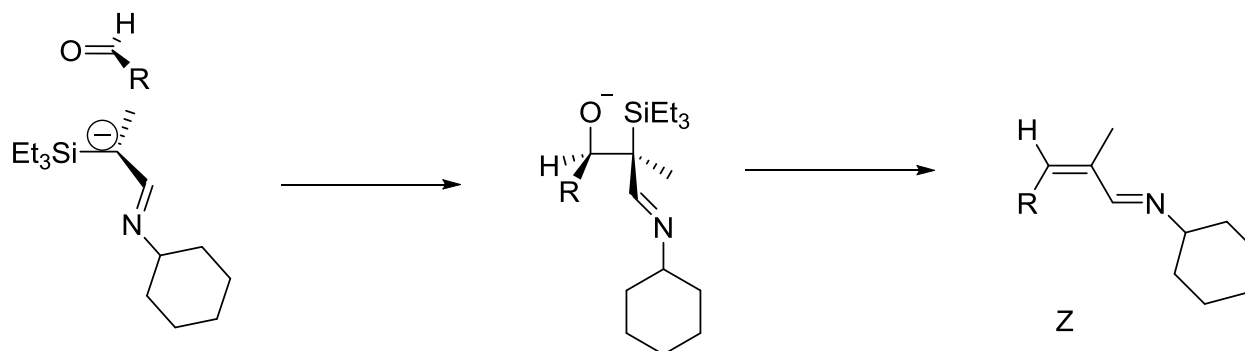
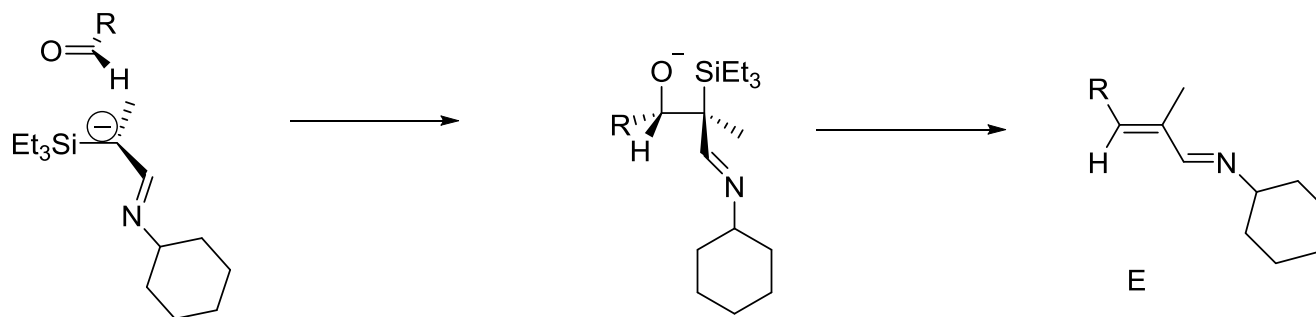
Hydrostannation



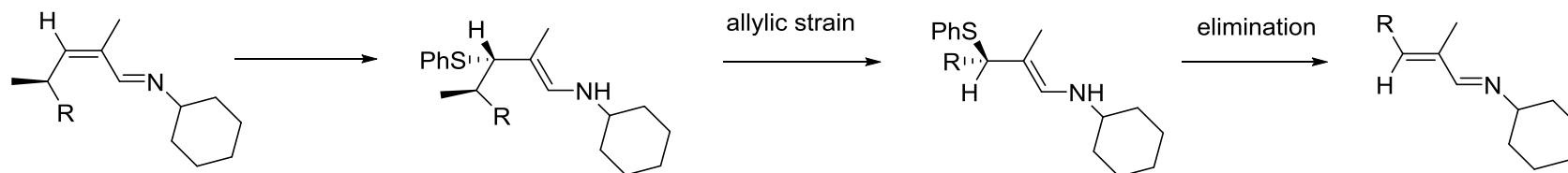
Monoselective TBDimethylsilylation



Corey Peterson olefination



> Conversion Z to E with thiophenol



Stereoselective aldol reaction - Altmann

