Total Synthesis of (+)-Pleuromutilin

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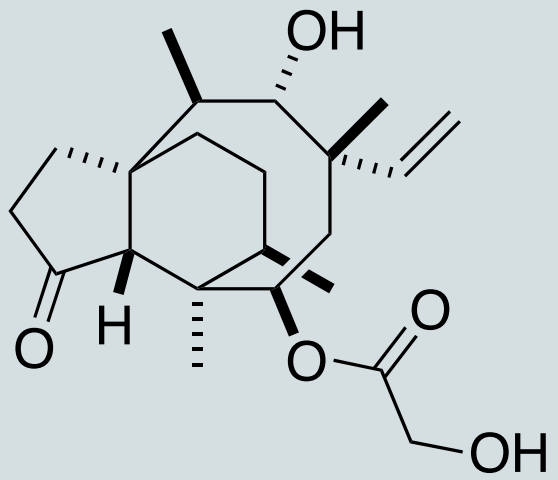

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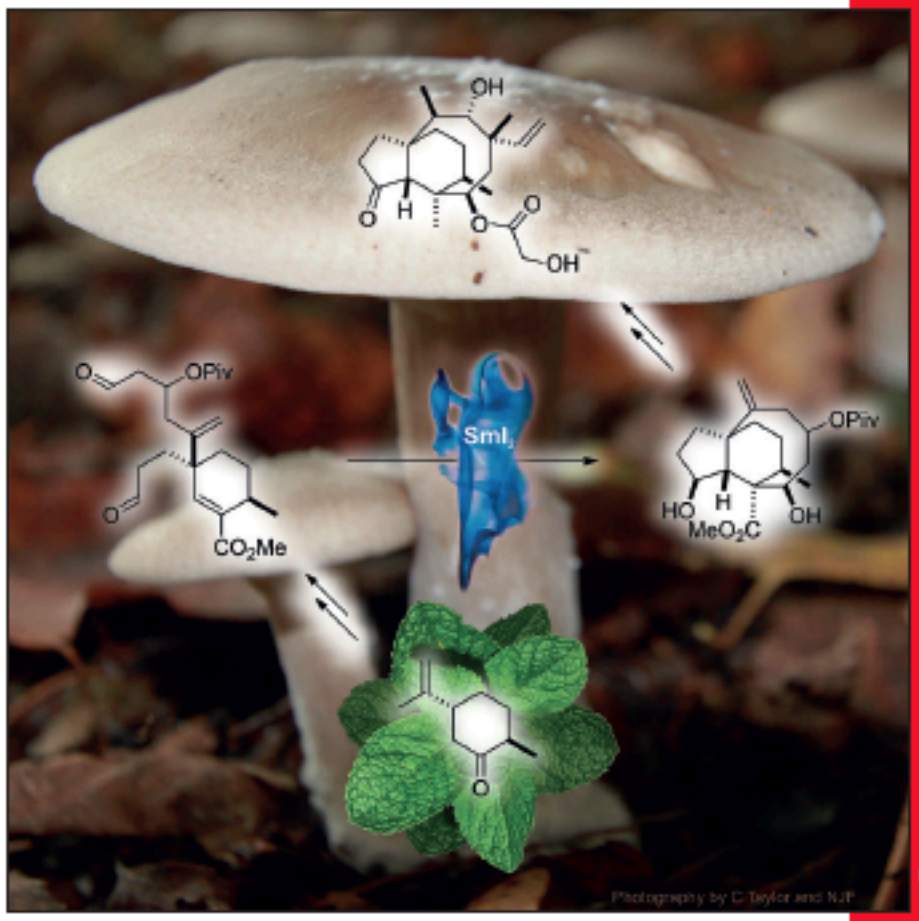

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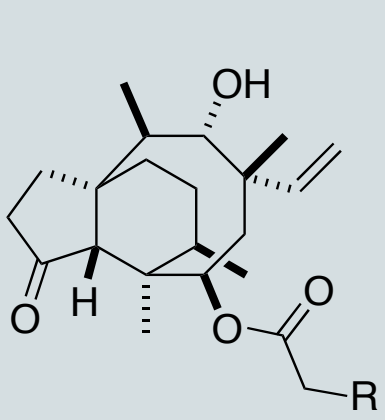
Introduction – Pleuromutilin

- **Fungal** secondary metabolite **(+)-Pleuromutilin** was first isolated from *Clitopilus passeckerianus* in 1951 by Kavangh and co-workers
- **Antibacterial acitivity** through a novel mode of action involving binding to the prokaryotic ribosome
- **First enantiospecific total synthesis** of natural compound by David Procter
- **Two racemic synthesis** by Gibbons (*JACS* **1982**) and Boekman (*JACS* **1989**)
- Two elegant **routes to the trycyclic core** by Zard (*Org. Lett.* **2003**) and Sorensen (*Chem. Commun.* **2011**)

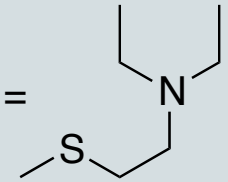
Introduction – Pleuromutilin Analogues

- Analogues derived by semi-synthesis from pleuromutilin, including tiamulin (**2;** Denegard® by Novartis Animal Health) and retapamulin (**3**; Altargo® by GlaxoSmithKline)

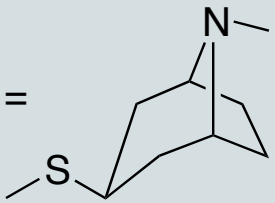


1, R = OH

2, R =



3, R =



Manufacture

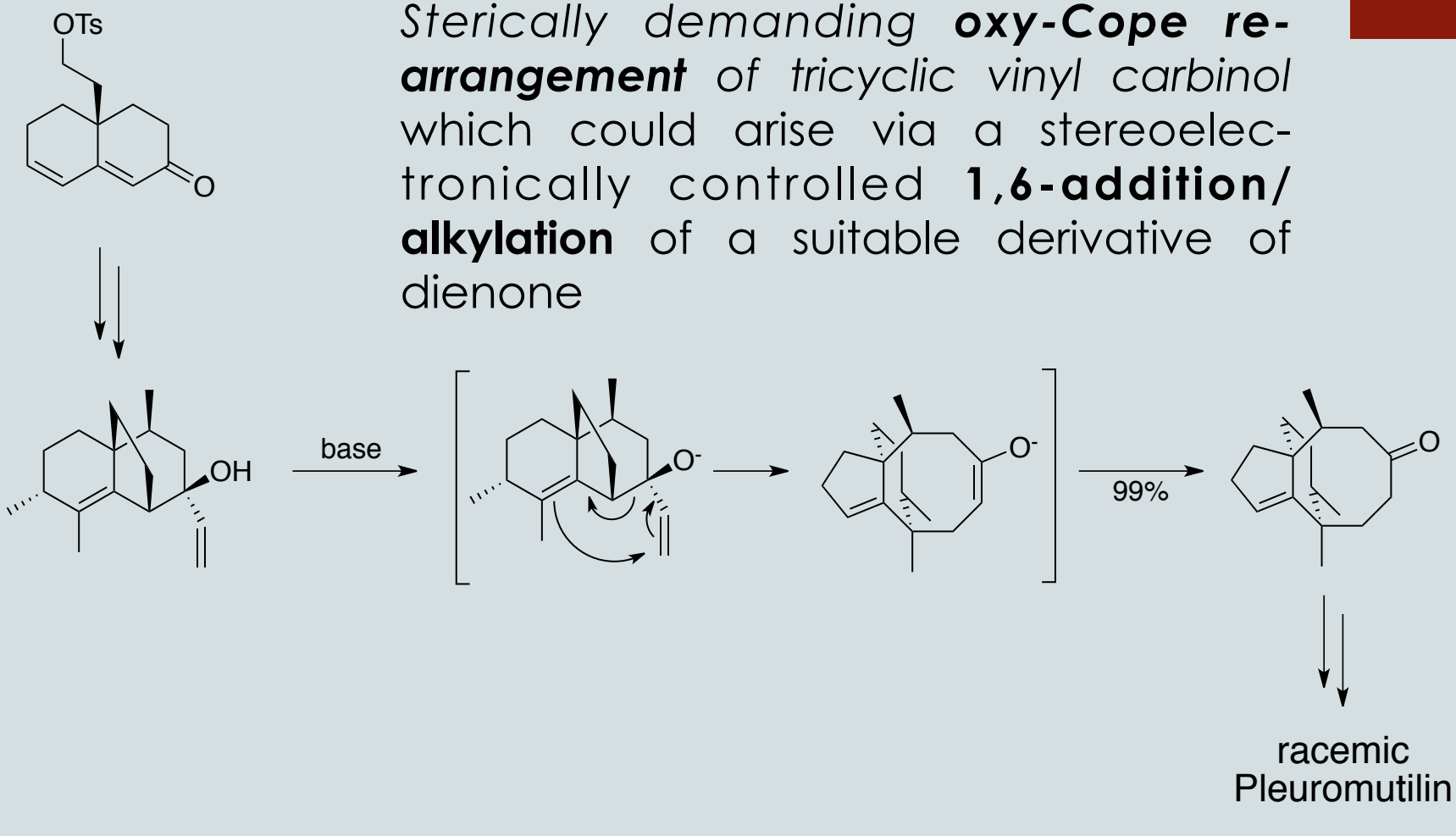
Retapamulin is manufactured by a semi-synthetic process, starting with a fermentation step from *Clitopilus passeckerianus* CP2 to yield the key intermediate pleuromutilin and then progressing via a 5-step synthetic process to give retapamulin.

Details and spectra were provided for elemental analysis, ^{1}H-NMR, ^{13}C-NMR, MS, IR and X-ray crystallography for the primary reference standard of retapamulin. The data confirmed the proposed structure.

→ Abstract of **INN** register (**I**nternational **N**onproprietary **N**ames) by **WHO**

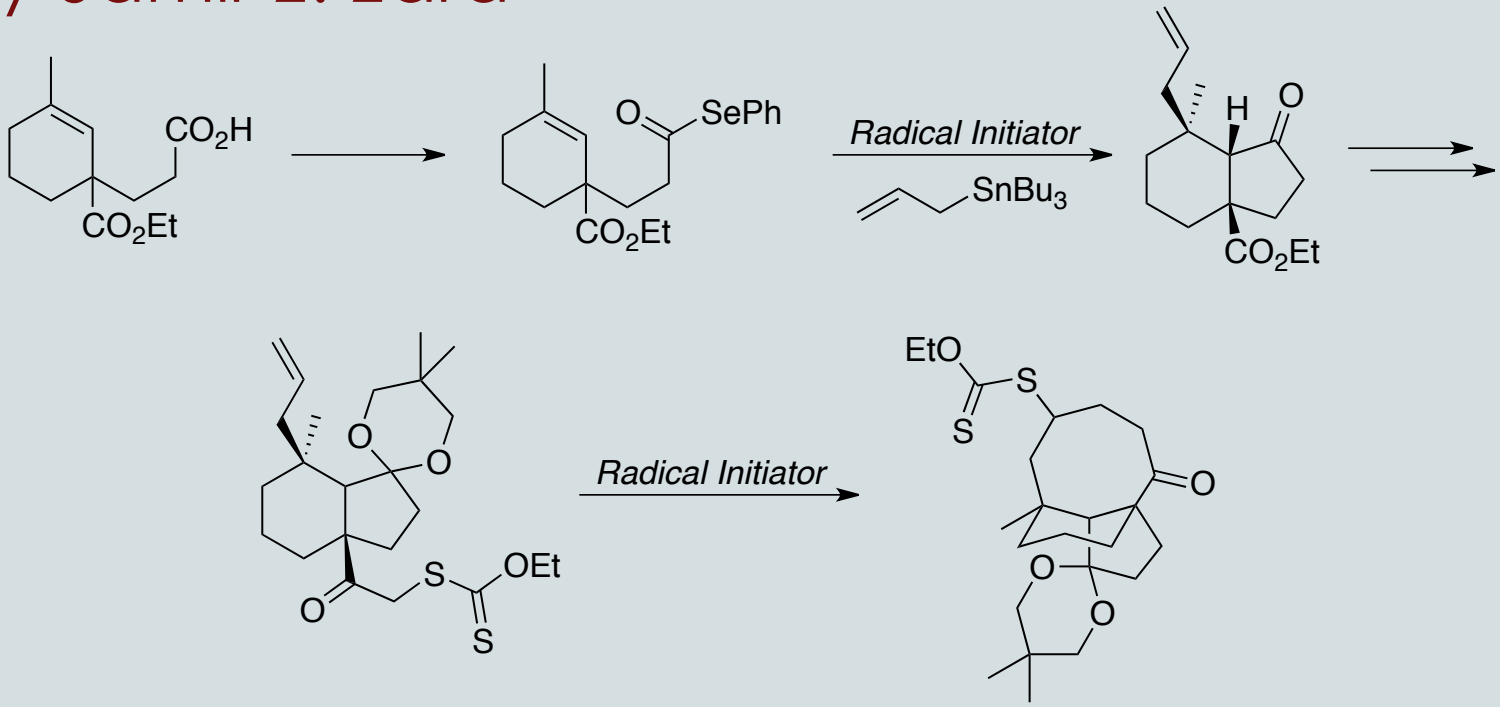
Key Step of Racemic Total Synthesis by Boeckman and co-workers

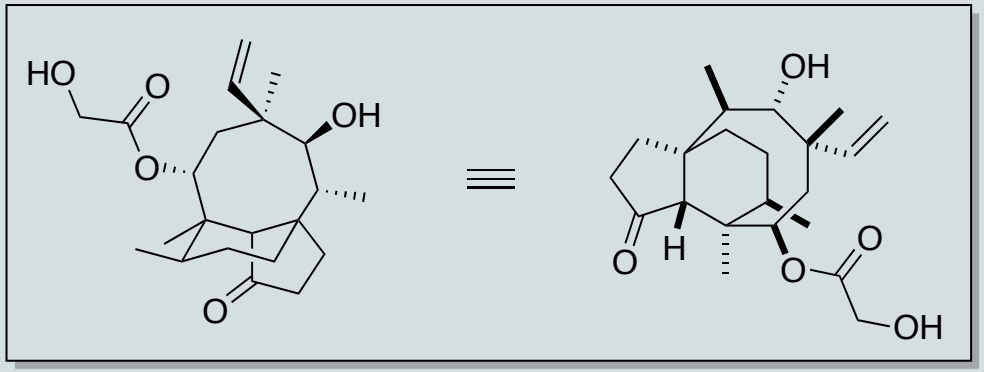
Sterically demanding ***oxy-Cope re-arrangement*** *of tricyclic vinyl carbinol* which could arise via a stereoelectronically controlled **1,6-addition/ alkylation** of a suitable derivative of dienone



R. K. Boeckman *et al. J. Am. Chem. Soc.* **1989**, *111*, 8284.

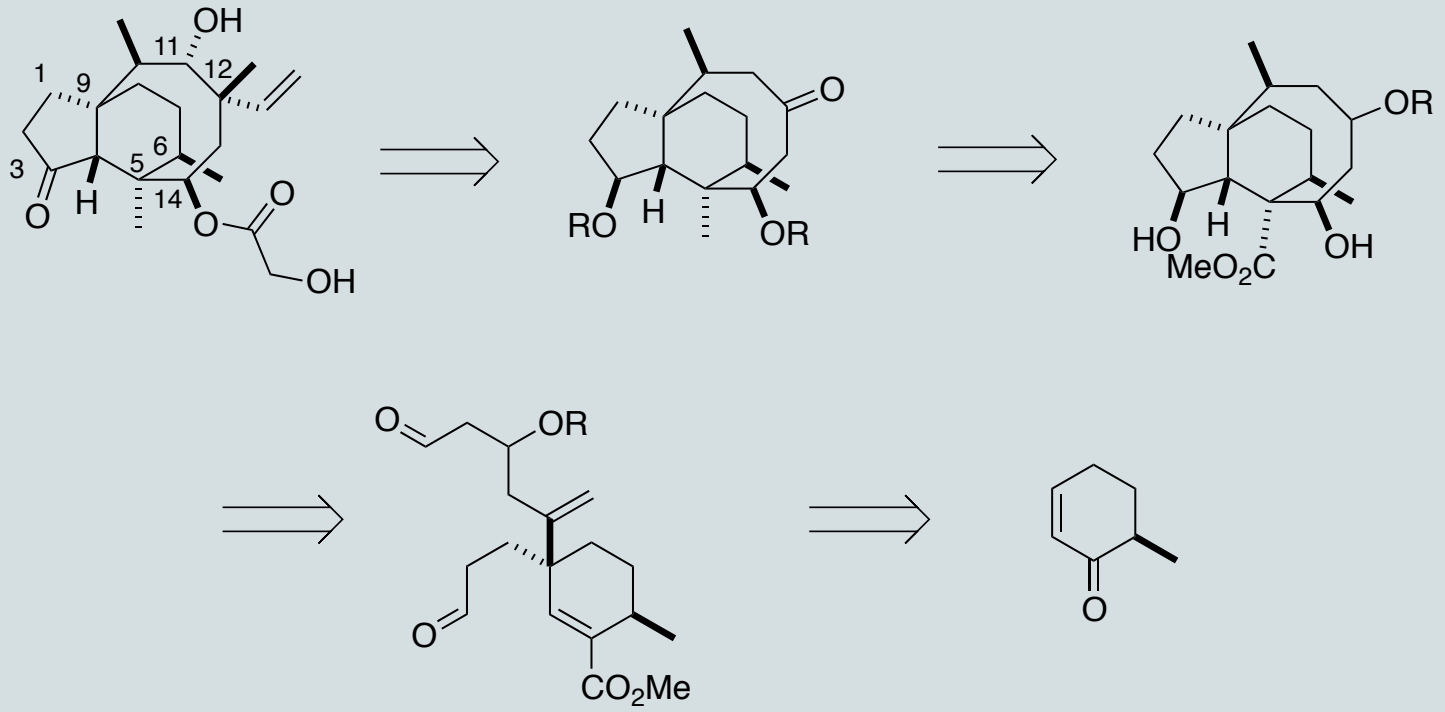
Route to Tricyclic Core of Pleuromutilin by Samir Z. Zard



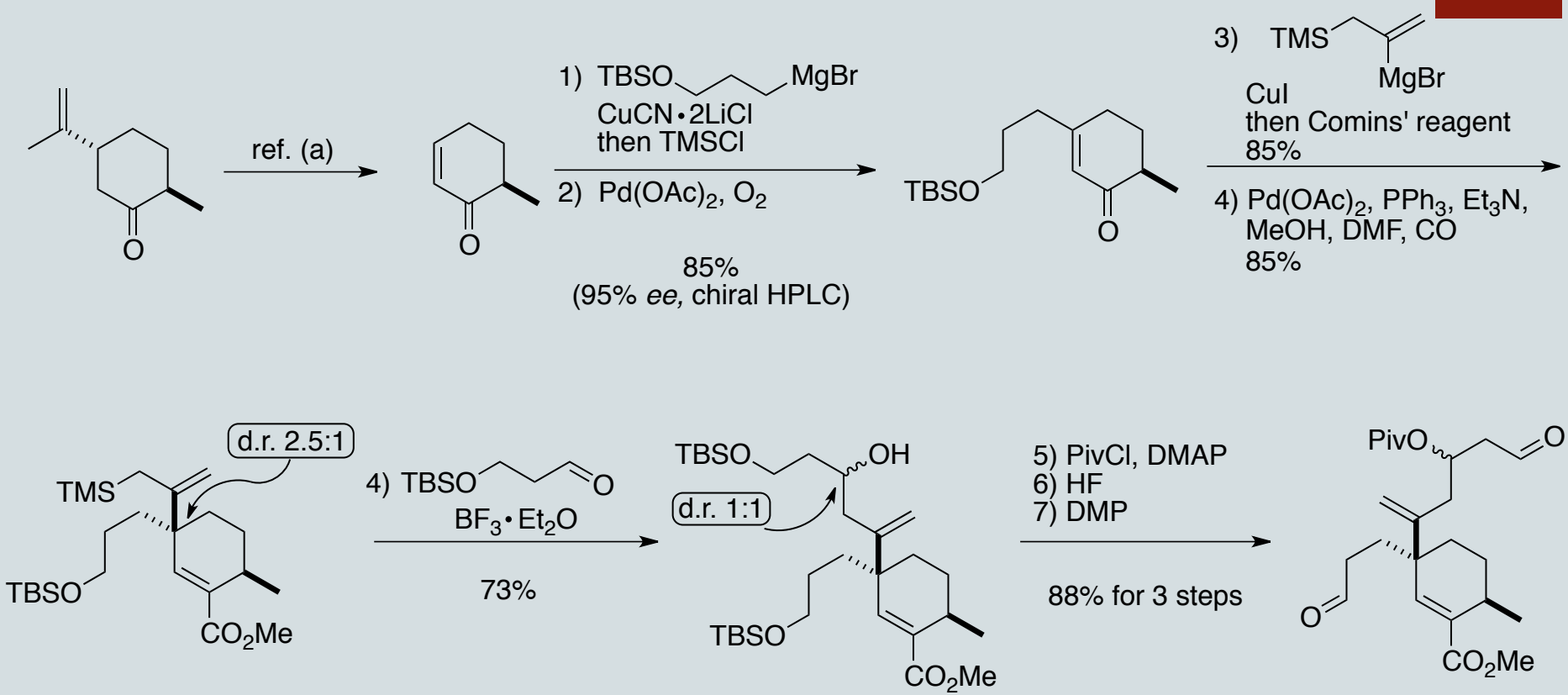


Org. Lett. **2003**, *5*, 325-328.

Retrosynthetic Analysis

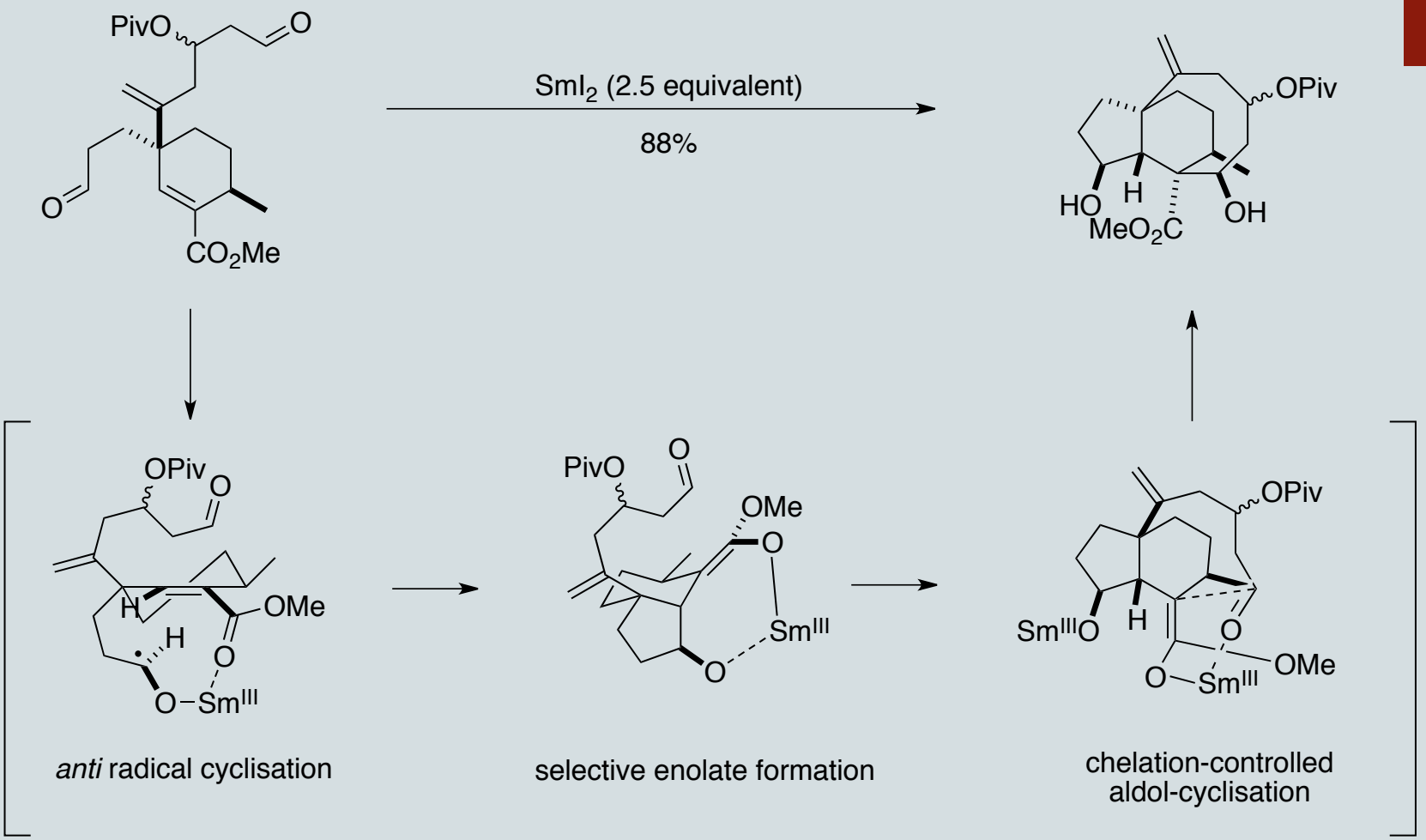


Synthesis of the Cascade Cyclisation Substrate



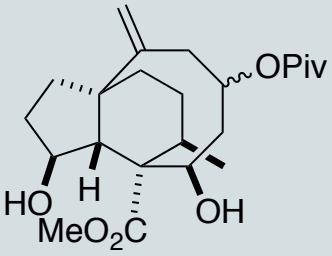
(a) S. L. Schreiber *J. Am. Chem. Soc.* **1980**, *102*, 6163.

SmI_2-mediated Cyclisation Cascade



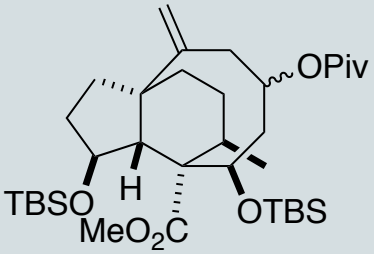
Procter *et al. ACIE* **2009**, *48*, 9315.

Protection/Deprotection, Reduction of Double Bond



1) TBSOTf

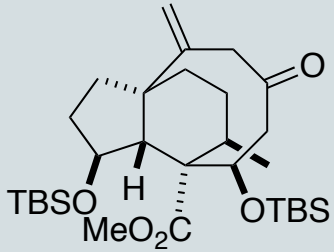
76%



d.r. 2.5:2.5:1:1

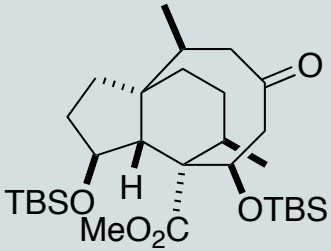
2) $LiAlH_4$, rt
3) DMP

63%



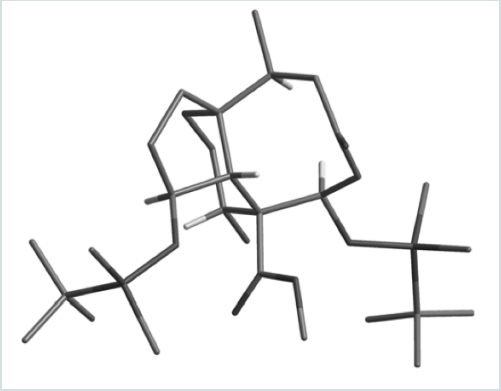
(> 98% *ee*, chiral HPLC)

4) Pd/C, H_2

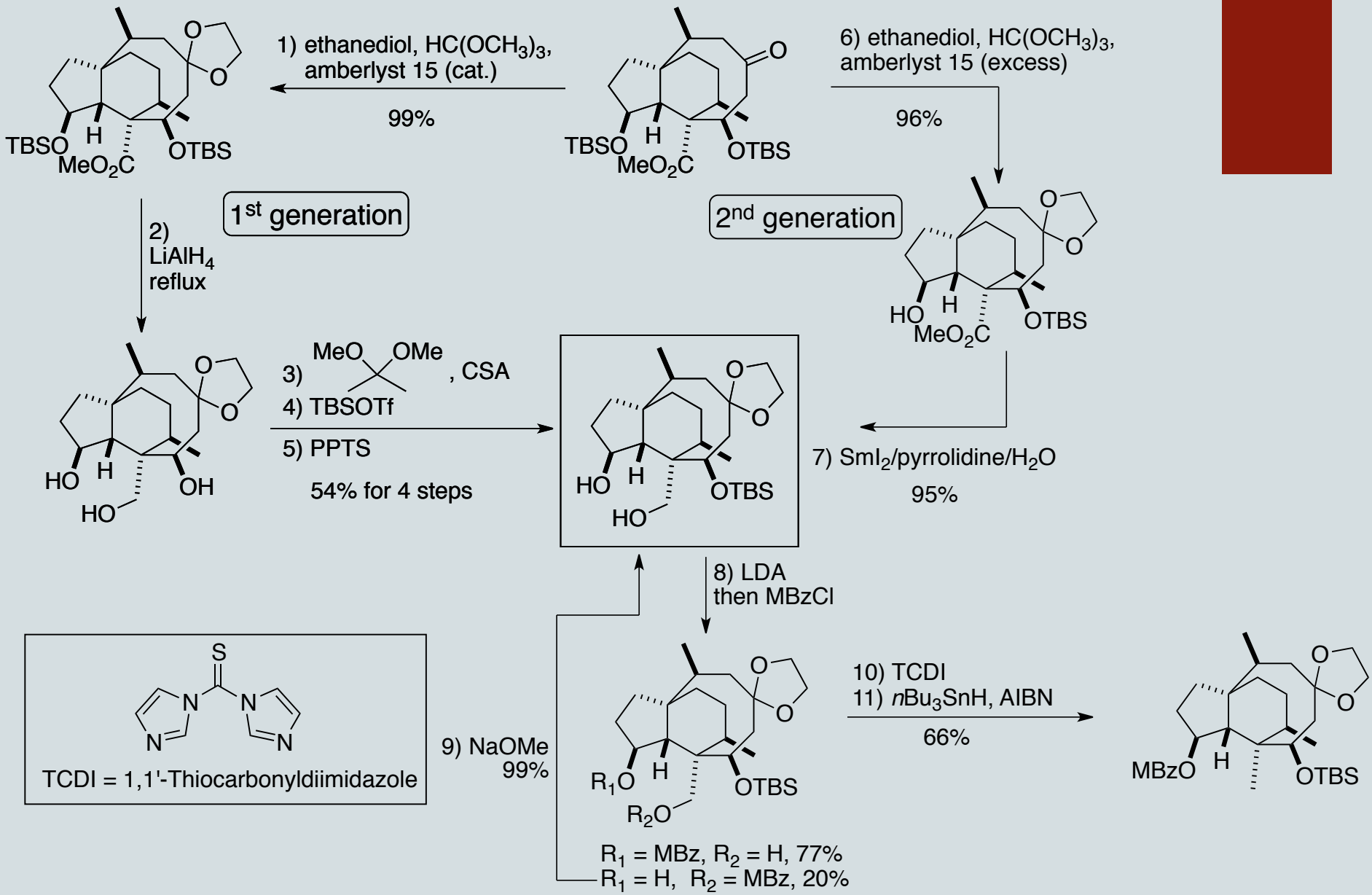


d.r. 3:1, but major was isolated in 75% yield

≡

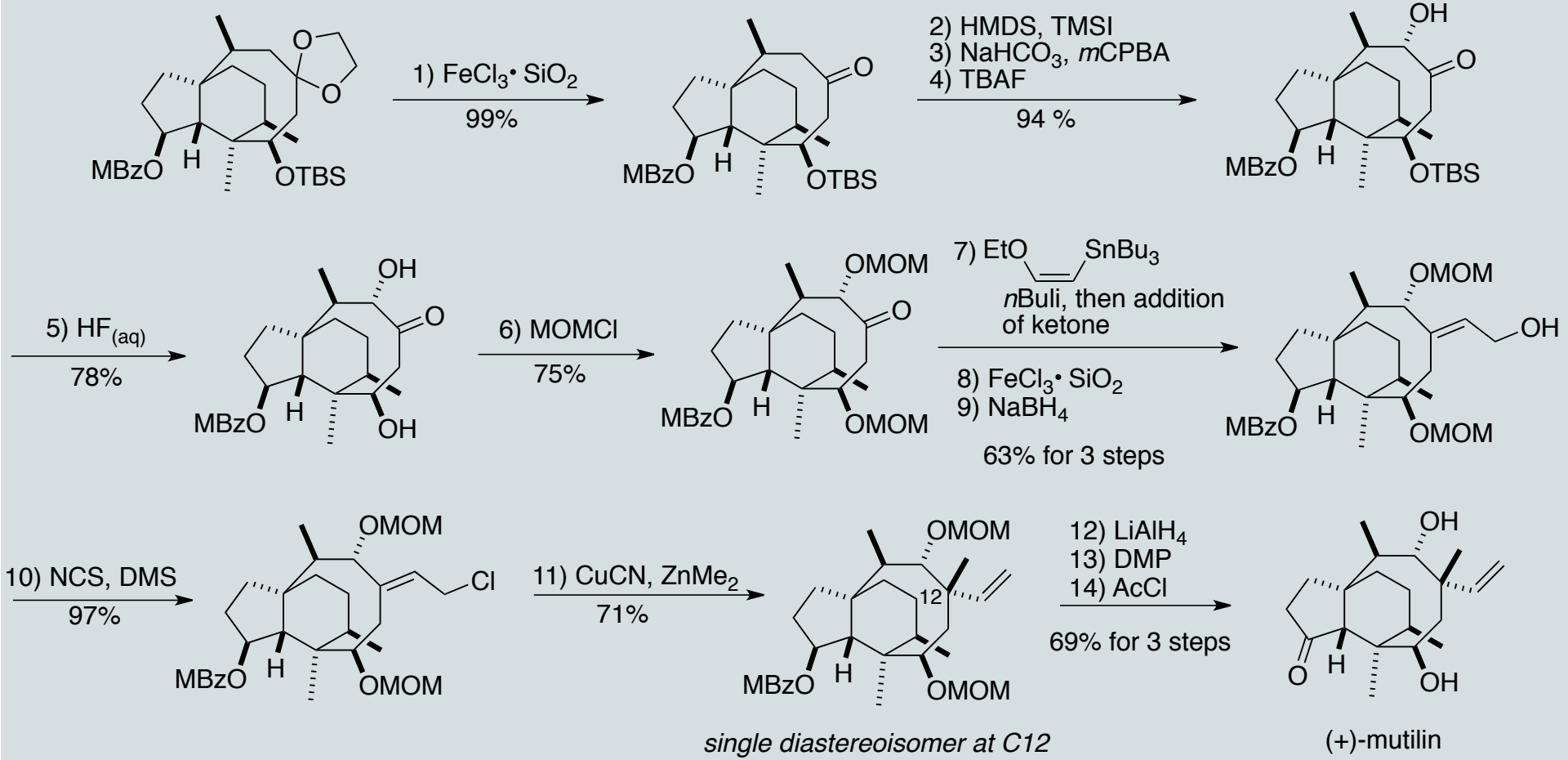


Reduction of C5 Methyl Ester



Reduction of hind. esters with SmI_2: D. J. Procter *Chem Commun* **2011**, *47*, 10254.

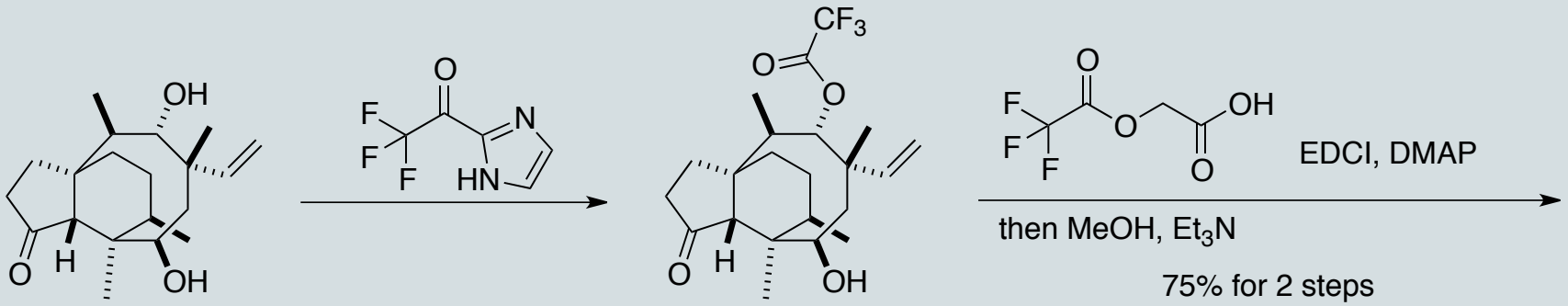
Elaboration of the Eight-Membered Ring



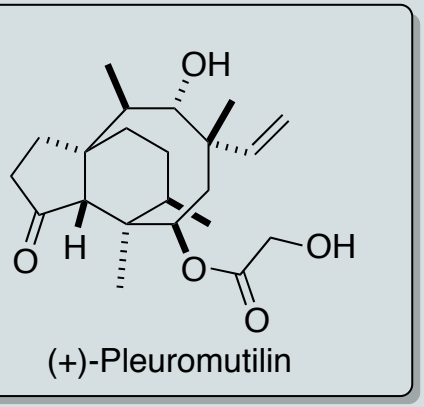
single diastereoisomer at C12

(+)-mutilin

Completion of the Synthesis



(+)-mutilin



(+)-Pleuromutilin

Conclusion

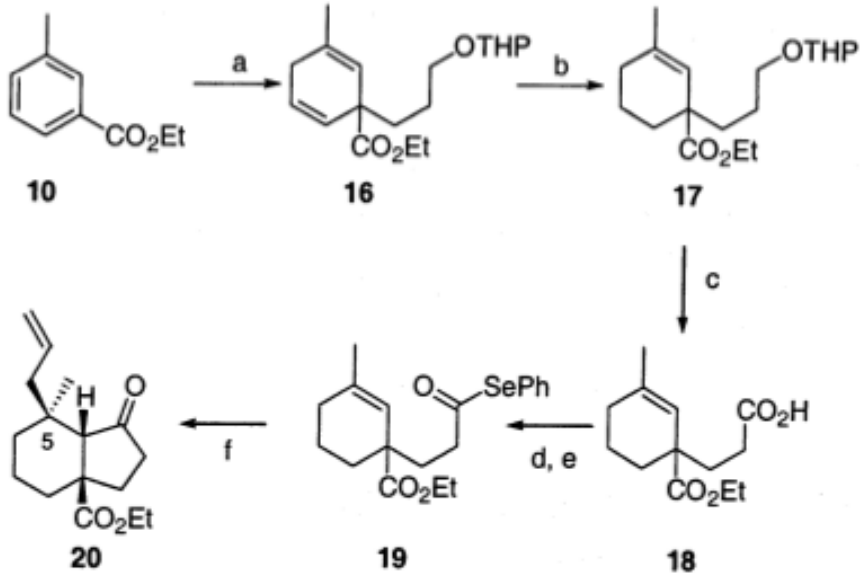
- First entantiospecific total synthesis (but long)

- Key Steps including SmI_2:
  1) SmI_2-mediated cyclisation cascade
  2) SmI_2/pyrrolidine/H_2O-based ester reduction

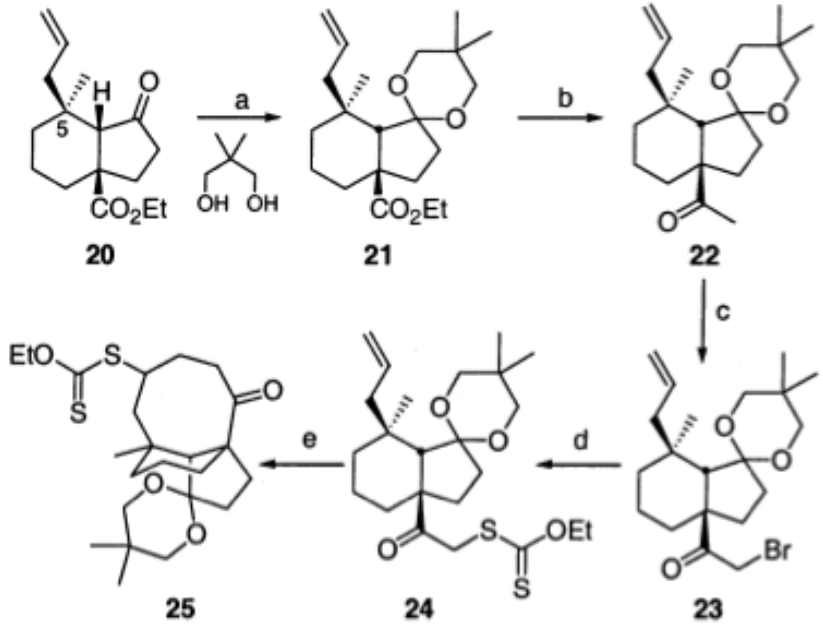
- Efficient conversion of (+)-mutilin to (+)-pleuromutilin

- This approach is currently being used to expand the pleuromutilin class of antibiotics through the synthesis of novel analogues that are inaccessible from the natural compound

Preparation of Starting Carboxylic Acid (Zard Synthesis)

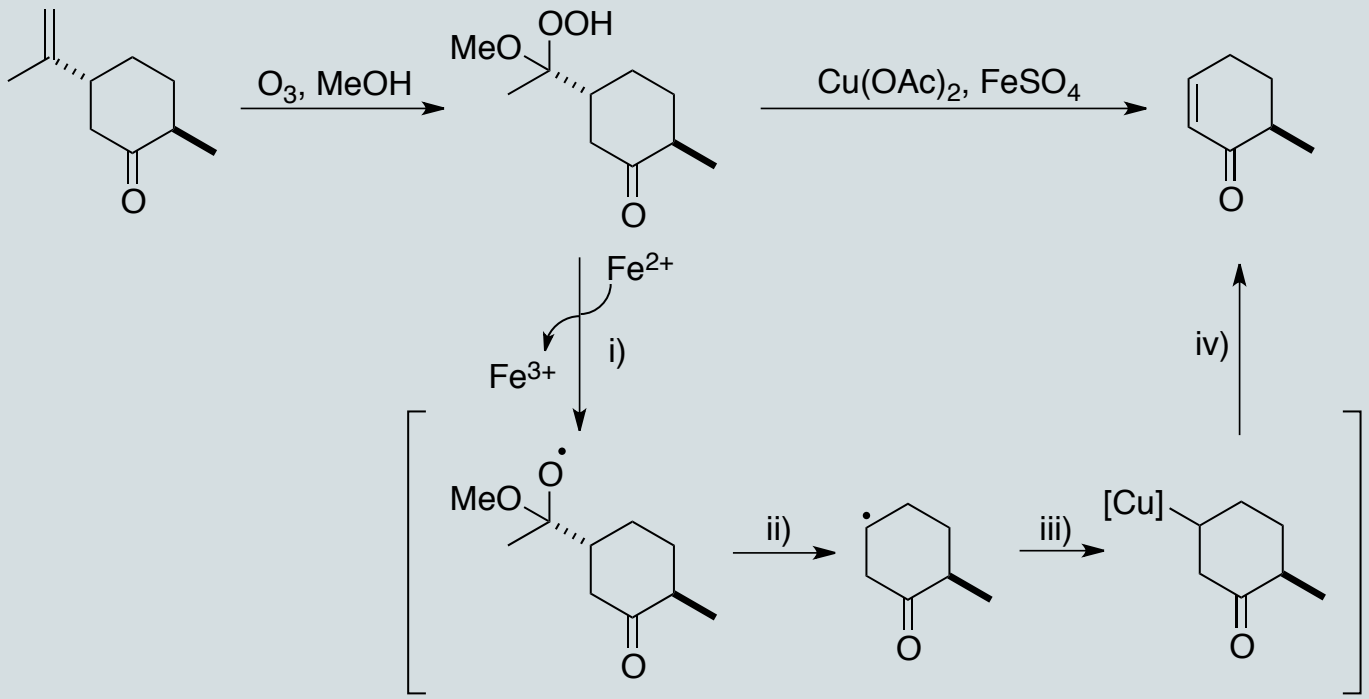


[a] Reagents and conditions: (a) Li, NH_3 liq., *t*BuOH, THF, $Br(CH_2)_3OTHP$ (72%); (b) H_2, $ClRh(PPh_3)_3$ cat., rt (quantitative); (c) CrO_3, H_2SO_4, acetone, −10 °C (80%); (d) $(COCl)_2$, CH_2Cl_2, rt; (e) PhSeSePh, $NaBH_4$, EtOH 0 °C (75% 2 steps); (f) $AllylSnBu_3$, ACCN cat., heptane (55%).



[a] Reagents and conditions: (a) PTSA, $HC(OEt)_3$, benzene, reflux (85%); (b) MeLi (5 equiv), THF, reflux (80%); (c) (i) LDA, TMSCl, THF, −78 °C, (ii) NBS, THF, $NaHCO_3$, −10 °C (80% 2 steps); (d) KSC(S)OEt, acetone, rt (quantitative); (e) DLP, 1,2-dichloroethane, reflux (60%).

S. L. Schreiber *J. Am. Chem. Soc.* **1980**, *102*, 6163.



i)Transfer of an electron from $Fe^{2+}$to peroxide to form oxy-radical
ii) Fragmentation to form carbon-radical
iii) Oxidative coupling with $Cu(OAc)_2$
iv) β -elimination

Reduction of Ester with SmI_2/amine/ H_2O by Procter (proposed Mechanism)