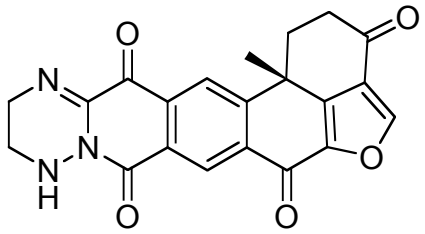
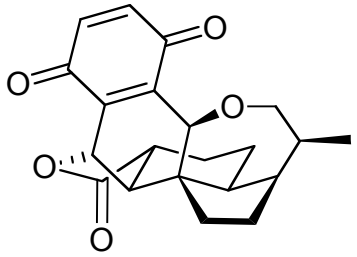
Studies toward the Total Synthesis of Noelaquinone and Pleurotin





Stephan Elzner
Research Topic Seminar
July 29th, 2006

Outline

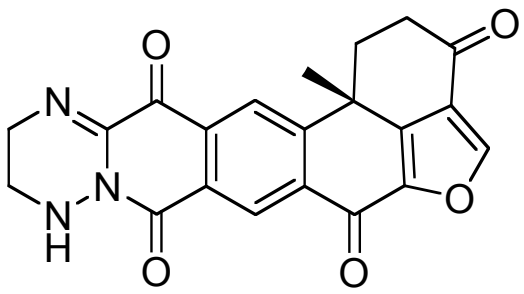
Part 1: Noelaquinone

- Isolation and Characterization
- Studies toward the DEF-Ring System of Noelaquinone

Part 2: Pleurotin

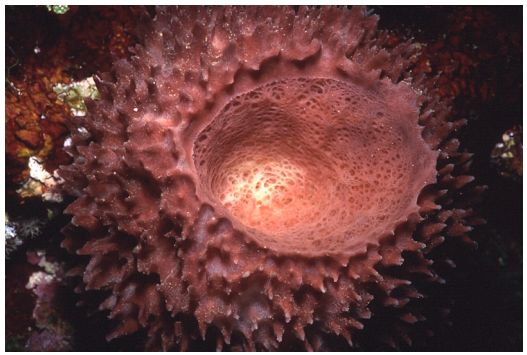
- Isolation, Characterization and Biological Properties
- Synthetic Approaches towards Pleurotin and Analogues
- Previous Studies in the Wipf Group
- Current Approach

Part 1: Noelaquinone

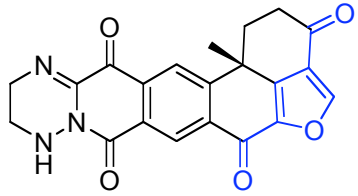


Isolation and Characterization of Noelaquinone

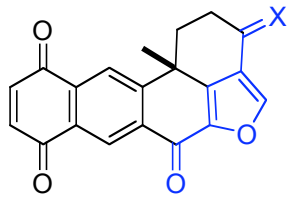
- First isolated in 1998 from an unidentified *Xestospongia* sp. (Indonesia) by Paul Scheuer. 67 g sponge yielded 6 mg natural product
- Structure determination based upon NMR-analysis and biological activity is still waiting to be further investigated
- Structurally related to a class of marine metabolites isolatable from the same *Xestospongia sp*.
  - *(+)*-halenaquinone and *(+)*-xestoquinone
- The thermodynamically stable naphthoquinone is replaced by a tetrahydro-1,2,4-triazine moiety
  - sole example in a natural product
- *(+)*-Halenaquinone and *(+)*-xestoquinone show antiproliferative activity at nanomolar concentrations *in vivo* through the blocking of PI-3 kinase. Common origin of the biological potency of these compounds is presumably the tricyclic furan moiety, also present in noelaquinone



Xestospongia sp.
(California Academy of Sciences
www.calacademy.org)



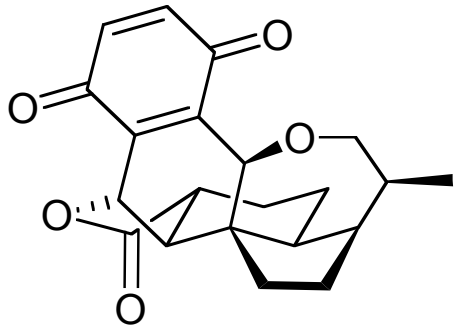
Noelaquinone



X = O : Halenaquinone
X = H_2: Xestoquinone

Y. Zhu, W.Y. Yoshida, M. Kelly-Borges, P. J. Scheuer, *Heterocycles* **1998**, *49*, 355-360
P. Wipf et al., *Org. Biomol. Chem.* **2004**, *2*, 1911-1920
N. Ihle et al. *Mol. Cancer Therap.* **2004**, *3*, 763-772

Part 2: Pleurotin



Isolation and Characterization

- First isolated 1947 from the fungus *pleurota griseus*, the compound could also be found in extracts from *Hohenbruehelia geogenius* and *Hohenbruhelia atrocaerulea*

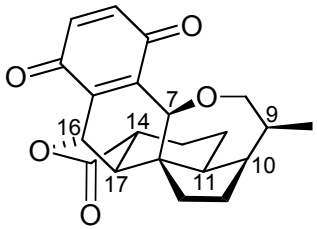
  W. J. Robbins, F. Kavanaugh, A. Hervey, *Proc. Natl. Acad. Sci. U.S.A.* **1947**, *33*, 171
  J. Riondel, H. Beriel, A. Dardas, G. Carraz, L. Oddoux, Arzneim. Forsch. **1981**, *31*, 293
  S. M. Shipley, A. L. Barr, S. J. Graf, R. P. Collins, T. G. McCloud, D. J. Newman, *J. Ind. Microbiol. Biotechnol.* **2006**, *33*, 463

Hohenbruhelia atrocaerulea
(www.mykoweb.com)

- Strucure was assigned by degradative studies in 1968 and later confirmed by X-ray crystallographic analysis

  H. Schelling, Ph.D. thesis, ETH Zürich, Switzerland, **1968**
  J. Grandjean, R. Huls, *Tetrahedron Lett.* **1974**, *15*, 1893
  P. C. Cohen-Addad, J. Rionel, *Acta Crystallogr.* **1981**, *B37*, 1309

- Structure: - Hexacyclic framework containing 8 stereocenters
  - Quinone moiety substituted with two benzylic leaving groups, which play an inmportant role in the biological activity



Pleurotin

Biological Activity

- Antibiotic activity against gram-positive bacteria

  W. J. Robbins, F. Kavanagh, A. Hervey, *Proc. Natl. Acad. Sci. U.S.A.* **1947**, *33*, 171

- Antitumor activity against Ehrlich ascites, L-1210 lymphoid carcinoma and mammary carcinoma

  J. Riondel, H. Beriel, A. Dardas, G. Carraz, L. Oddoux, Arzneimittel Forschung **1981**, *31*, 293

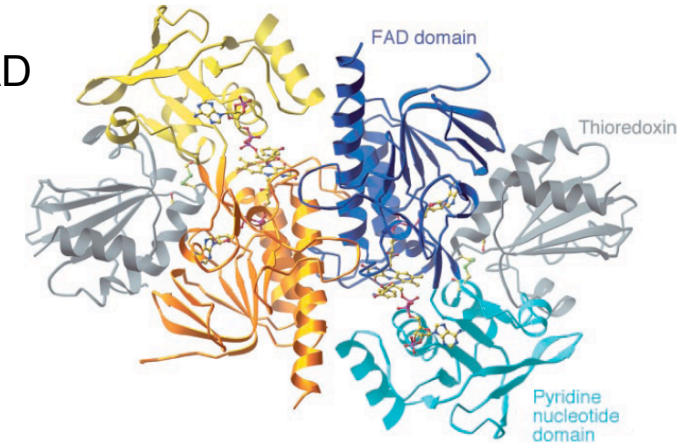
- Potent inhibitor of the thioredoxin-thioredoxin reductase system (IC_{50} = 170 nM)

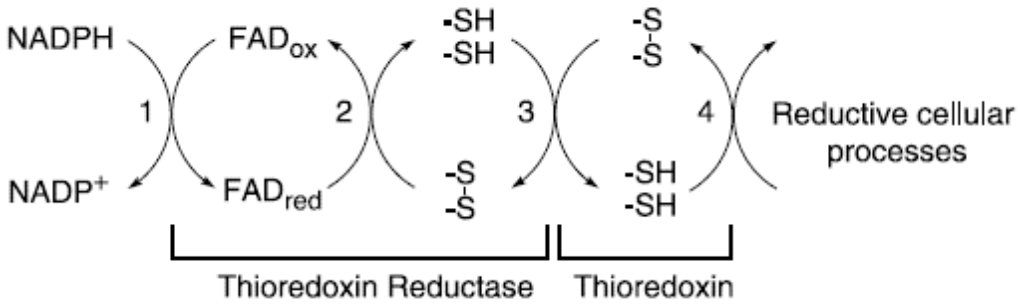
  S. J. Welsh, R. R. Williams, A. Birmingham, D. J. Newman, D. Kirkpatrick, G. Powis, *Mol. Cancer Ther.* **2003**, 235-243
  P. Wipf, S. M. Lynch, A. Birmingham, G. Tamayo, A. Jiménez, N. Campos, G. Powis, *Org. Biomol. Chem.* **2004**, *2*, 1651-1658

Thioredoxin-Thioredoxin Reductase Redox System

Thioredoxin

- 12 kDa protein containing cystein residues, which can switch between reduced (-SH) and oxidized (-S-S-) state
- Regenerated by thioredoxin-reductase, which is autoreduced in a mechanism involving NADPH and FAD
- Regulates several transcription factors (e.g. NFκ-B)
- Overexpressed in human solid tumors (lung, colon)
- Growth factor playing a role in tumor promotion
- Stimulates tumor growth and inhibits apoptosis *in vivo*
  ⇒ target for the developement of anti-cancer agents



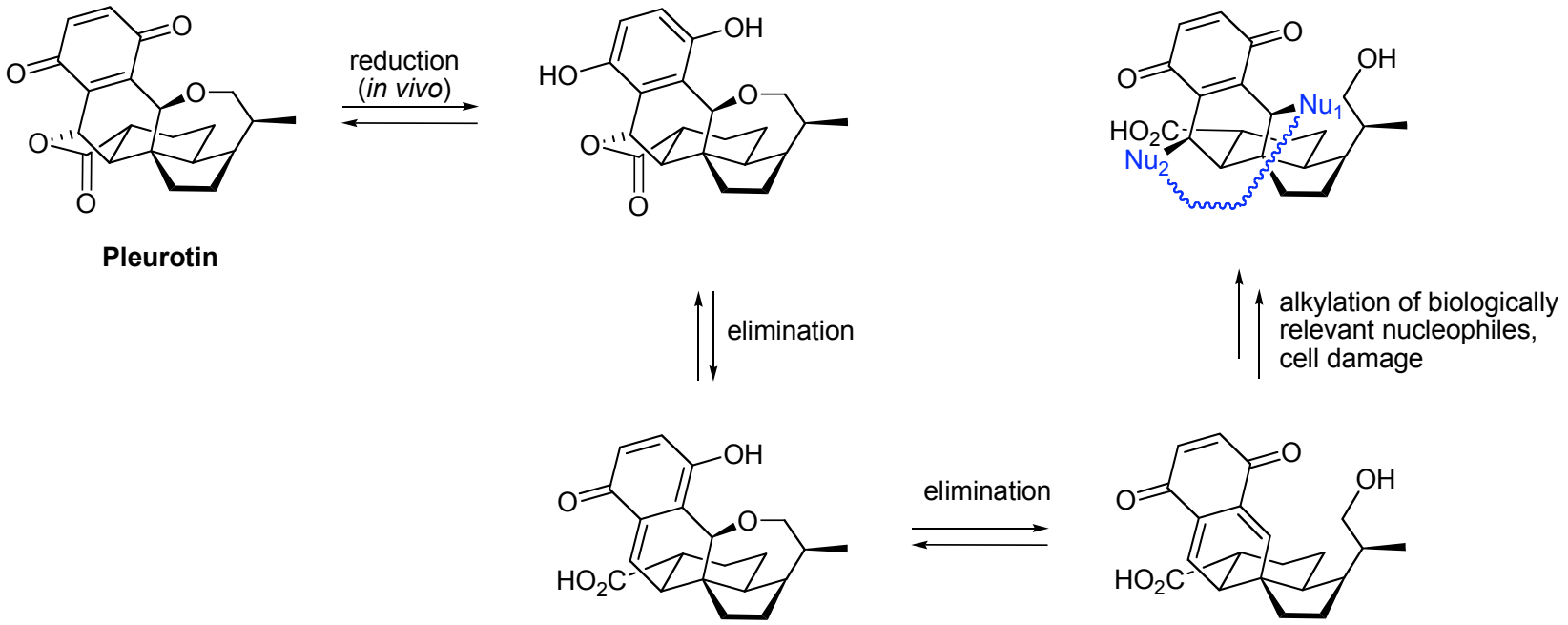


B. W. Lennon, C. H. Williams, M. L. Ludwig, *Science* **2000**, *289*, 1190
G. Powis, D. L. Kirkpatrick, M. Angulo, A. Baker, *Chem.-Biol. Interact.* **1998**, *111*, 23

Proposed Bioactivation of Pleurotin

Bioreductive bisalkylating agent:

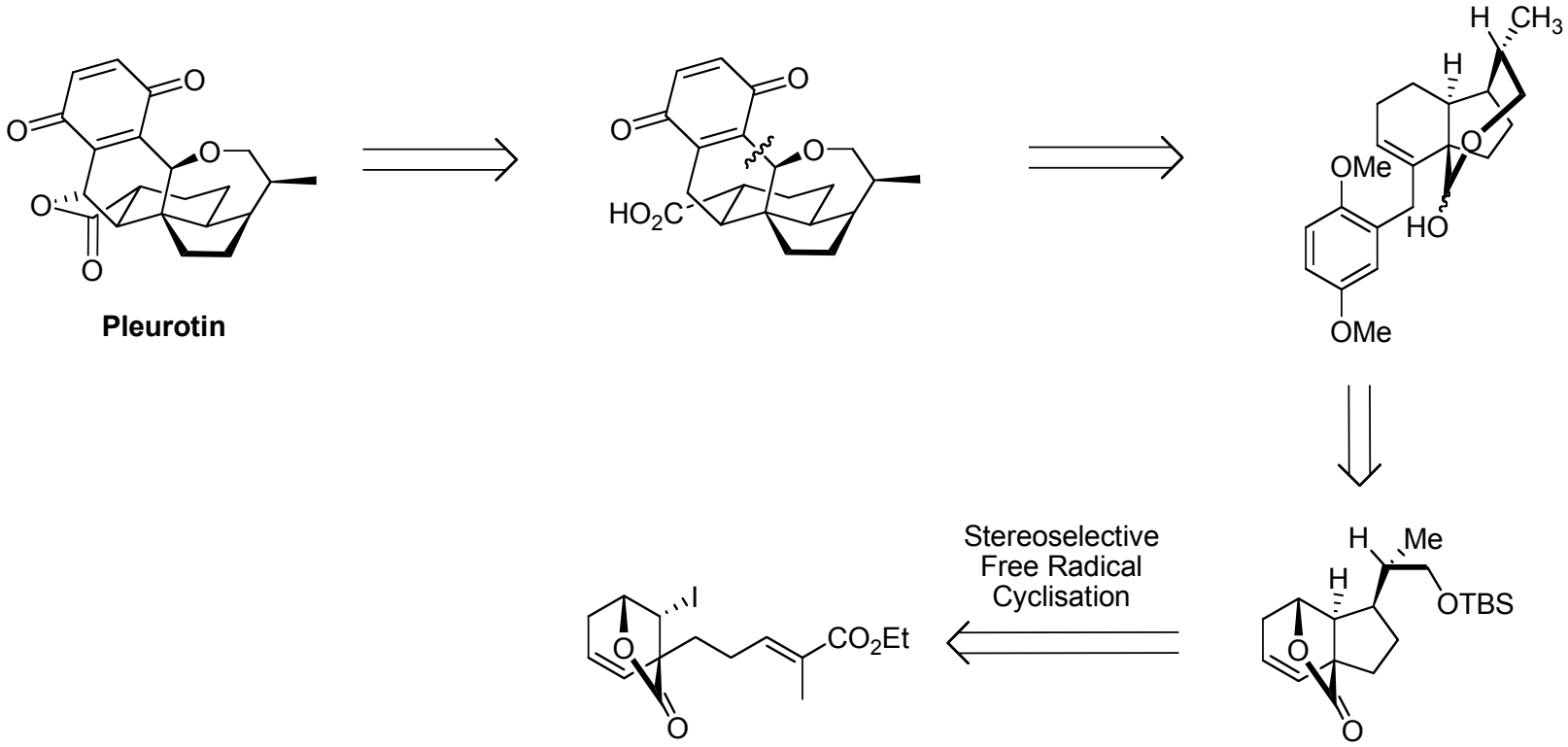
Conversion of the inactive form to a potent alkylating agent through *in vivo* transformation



Pleurotin

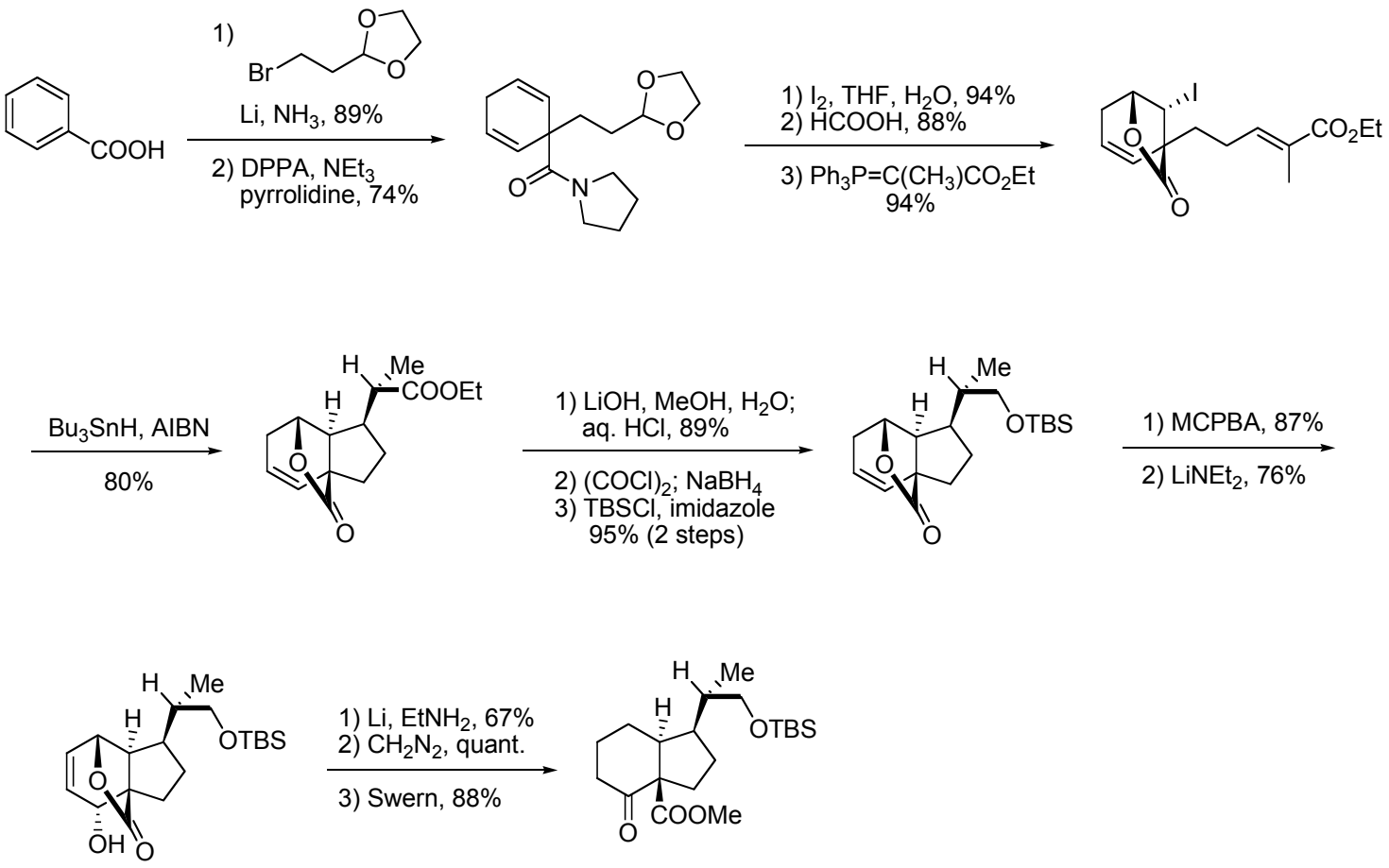
H. W. Moore, *Science* **1977**, *197*, 527
D. J. Hart, H.C. Huang, R. Krishnamurthy, T. Schwartz, *J. Am. Chem. Soc* **1989**, *111*, 7507

Hart: First Racemic Total Synthesis of Pleurotin



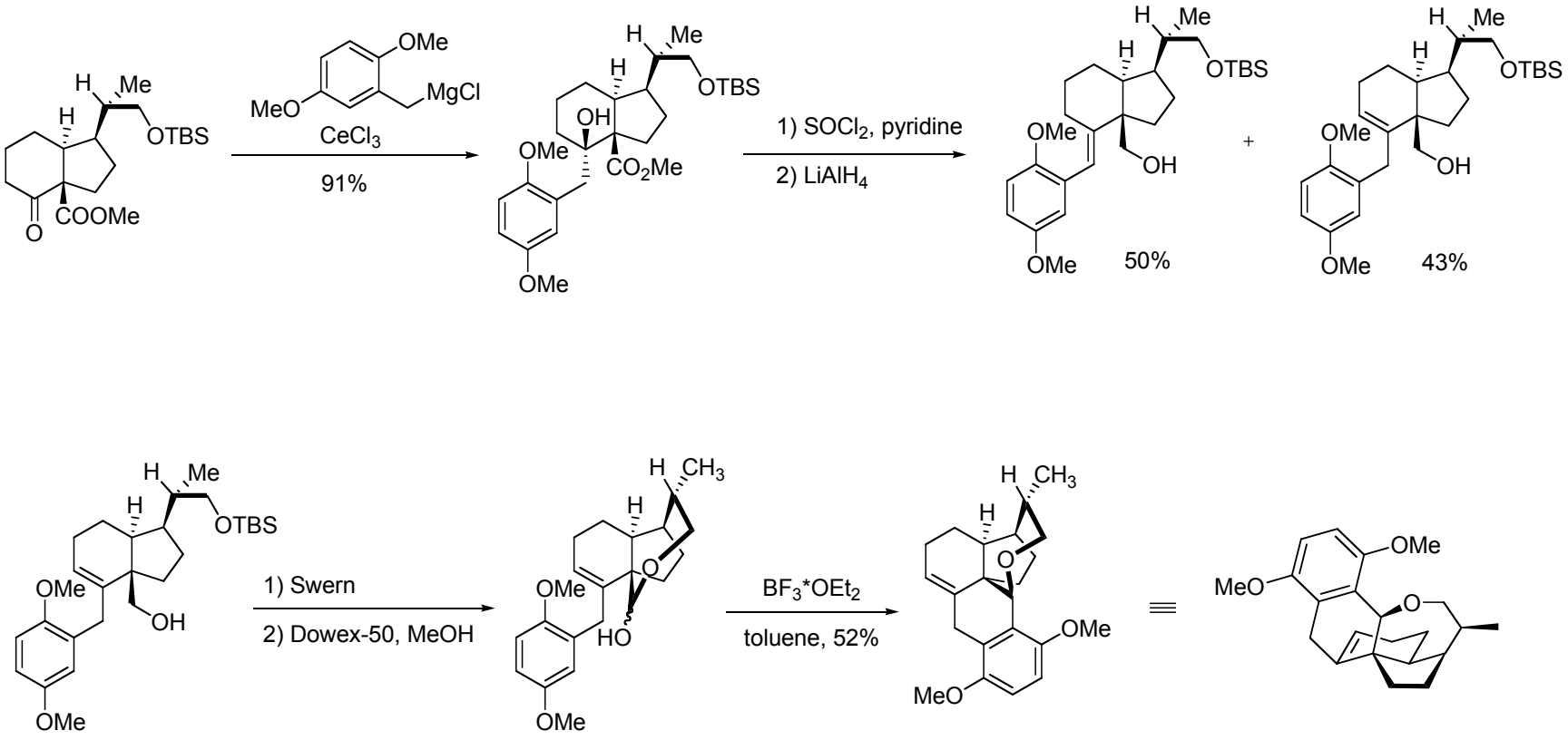
D. J. Hart, H.C. Huang, *J. Am. Chem. Soc* **1988**, *110*, 1634
D. J. Hart, H.C. Huang, R. Krishnamurthy, T. Schwartz, *J. Am. Chem. Soc* **1989**, *111*, 7507

Hart: Synthesis of Pleurotin (cont.)



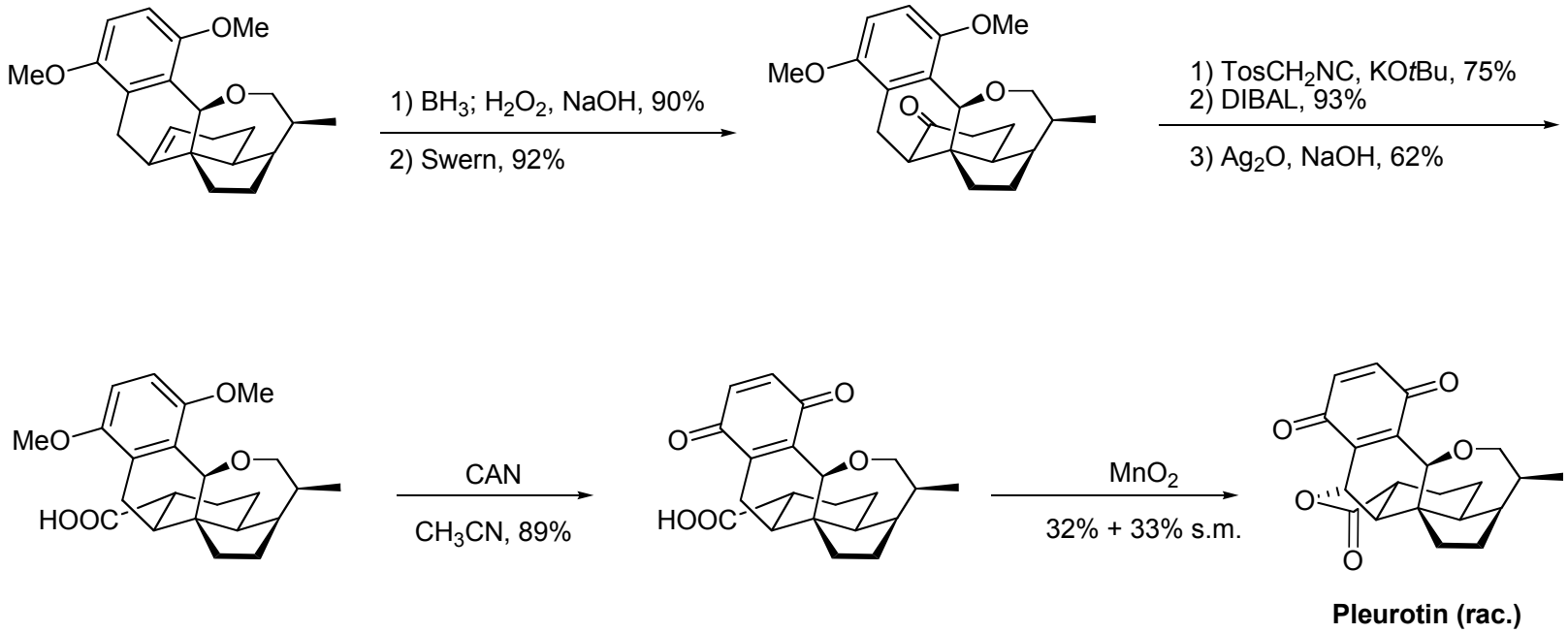
D. J. Hart, H.C. Huang, *J. Am. Chem. Soc* **1988**, *110*, 1634
D. J. Hart, H.C. Huang, R. Krishnamurthy, T. Schwartz, *J. Am. Chem. Soc* **1989**, *111*, 7507

Hart: Synthesis of Pleurotin (cont.)



D. J. Hart, H.C. Huang, *J. Am. Chem. Soc* **1988**, *110*, 1634
D. J. Hart, H.C. Huang, R. Krishnamurthy, T. Schwartz, *J. Am. Chem. Soc* **1989**, *111*, 7507

Hart: Synthesis of Pleurotin (cont.)



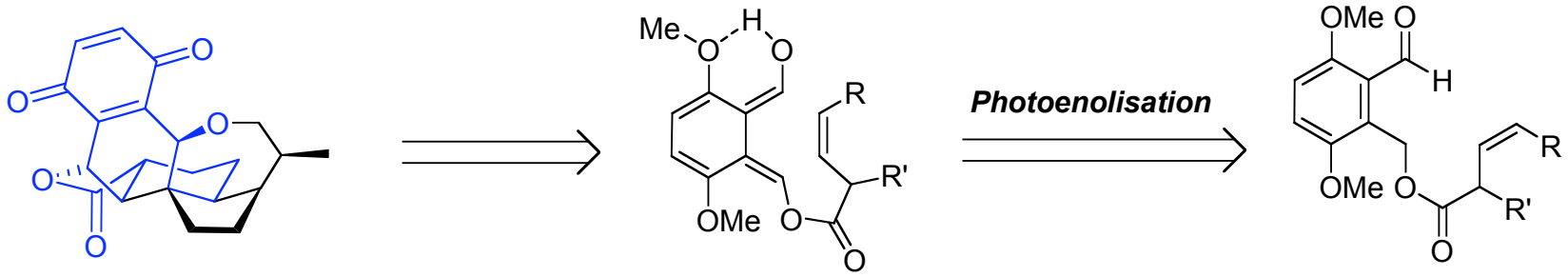
Pleurotin (rac.)

- 26 steps
- Average 80% yield per step
- 0.3 % overall yield

D. J. Hart, H.C. Huang, *J. Am. Chem. Soc* **1988**, *110*, 1634
D. J. Hart, H.C. Huang, R. Krishnamurthy, T. Schwartz, *J. Am. Chem. Soc* **1989**, *111*, 7507

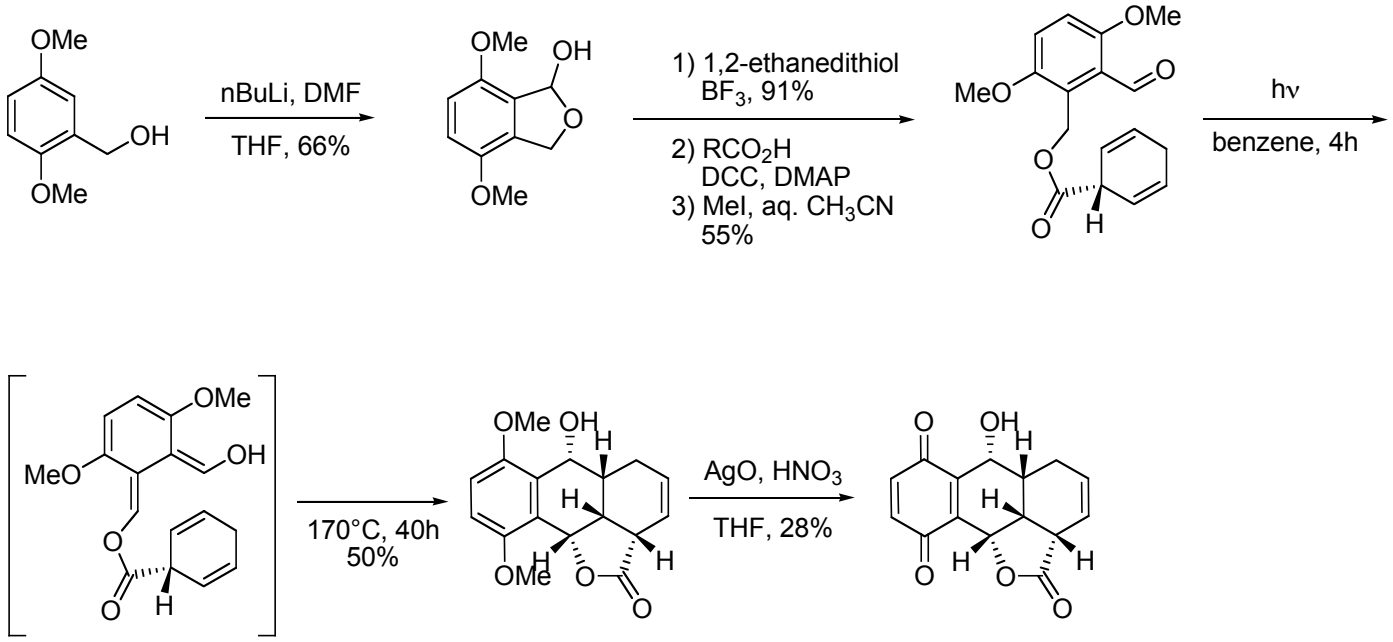
Kraus: Synthesis of Pleurotin Core

Tandem Photoenolisation/Diels-Alder



G. A. Kraus, L. Chen, *Synlett* **1991**, 89
G. A. Kraus, L. Chen, *Synth. Commmun.* **1993**, *23*, 2041

Kraus: Pleurotin Core (cont.)



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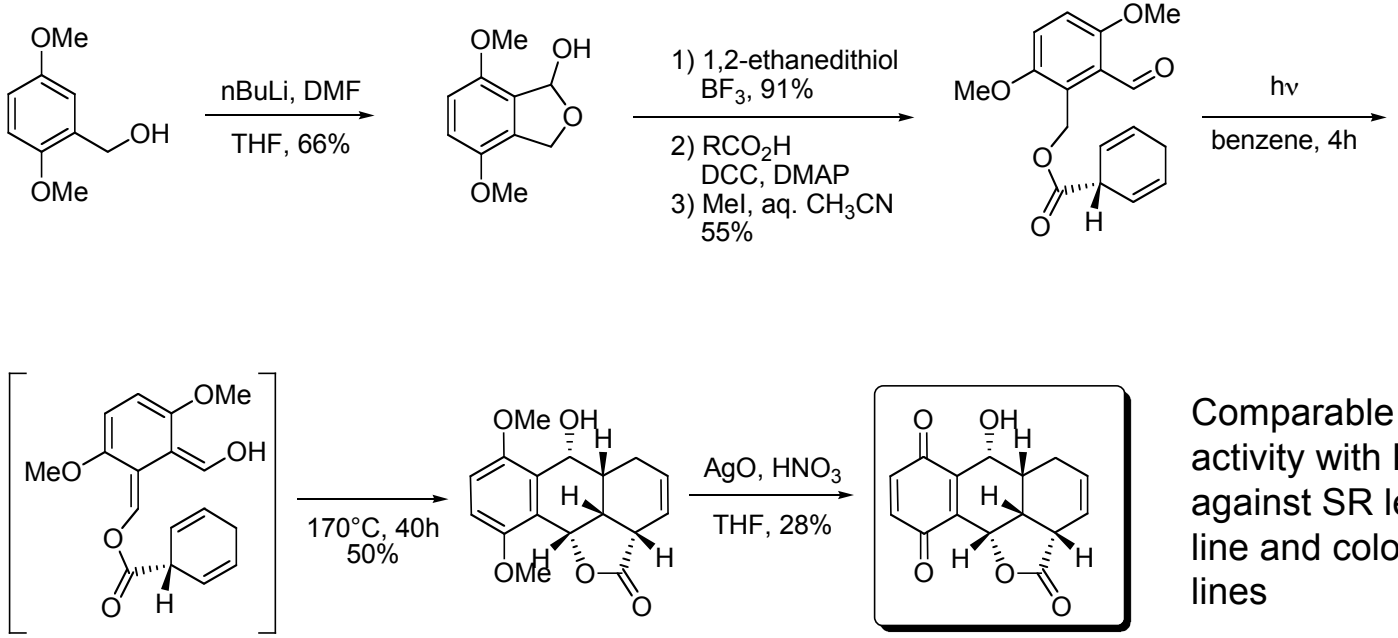
G. A. Kraus, L. Chen, *Synth. Commmun.* **1993**, *23*, 2041

Kraus: Pleurotin Core (cont.)



Comparable biological activity with Pleurotin against SR leukemia cell line and colon cancer cell lines

G. A. Kraus, L. Chen, *Synlett* **1991**, 89
G. A. Kraus, L. Chen, *Synth. Commmun.* **1993**, *23*, 2041

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