Enantioselective Total Synthesis of (+)-Salvileucalin B

Sergiy Levin, Roger R. Nani, and Sarah E. Reisman

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Presented by: Jared Hammill
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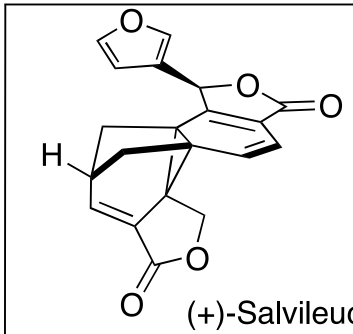
(+)-Salvileucalin B

- Salvia genus has rich history of natural products, derived from *salvare* (to heal)
  - Several biologically active natural products have been isolated including the potent hallucinogen salvinorin A.

- Isolated in 2008 by Takeya and co-workers
  - Active against human lung & colon cancer IC_{50} 5.23 and 1.88 µg/mL

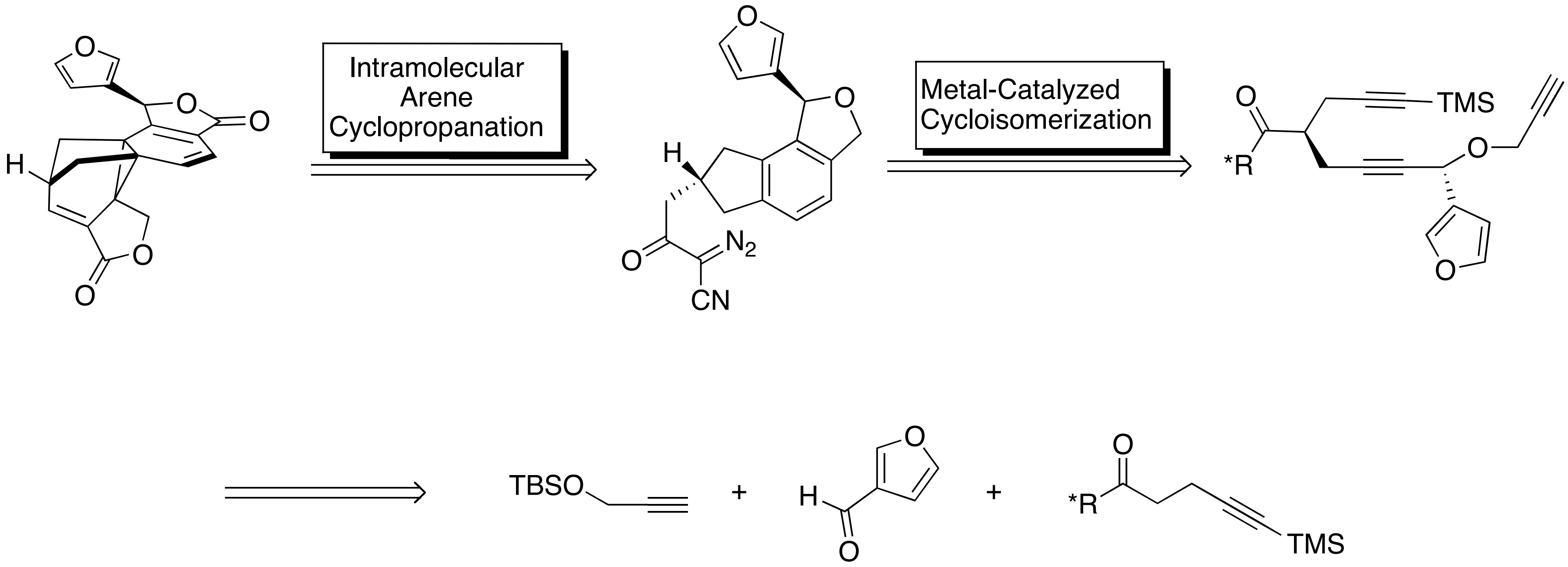
- Contains stable norcaradiene core
  - Fully substituted cyclopropane
  - Structure confirmed by X-ray crystallography



(+)-Salvileucalin B

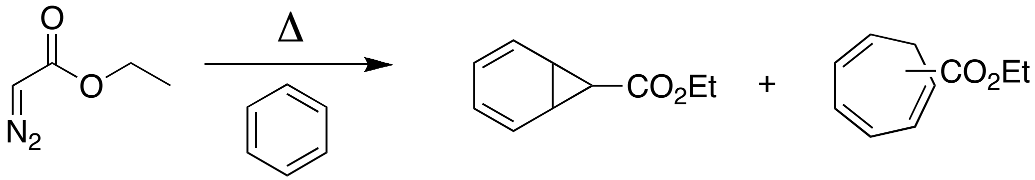
Aoyagi, T.; Yamazaki, A.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, 10, 4429

Retrosynthetic Analysis

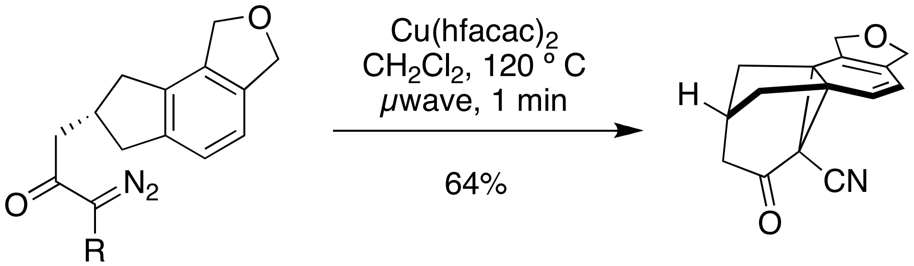


Previous Work

- Buchner and Curtius first described the cyclopropanation of arenes in 1885 with the thermolysis of ethyl diazoacetate in benzene



Note: often when Rh^{II} favors C-H insertion (i.e. benzylic or geometrically favored) Cu^{II} catalysis provides selectivity for cyclopropanation

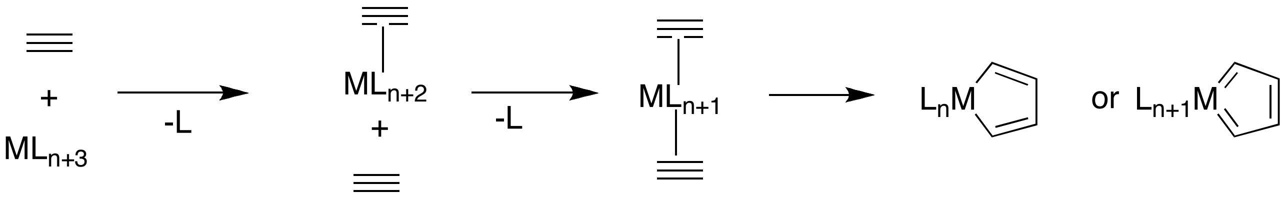


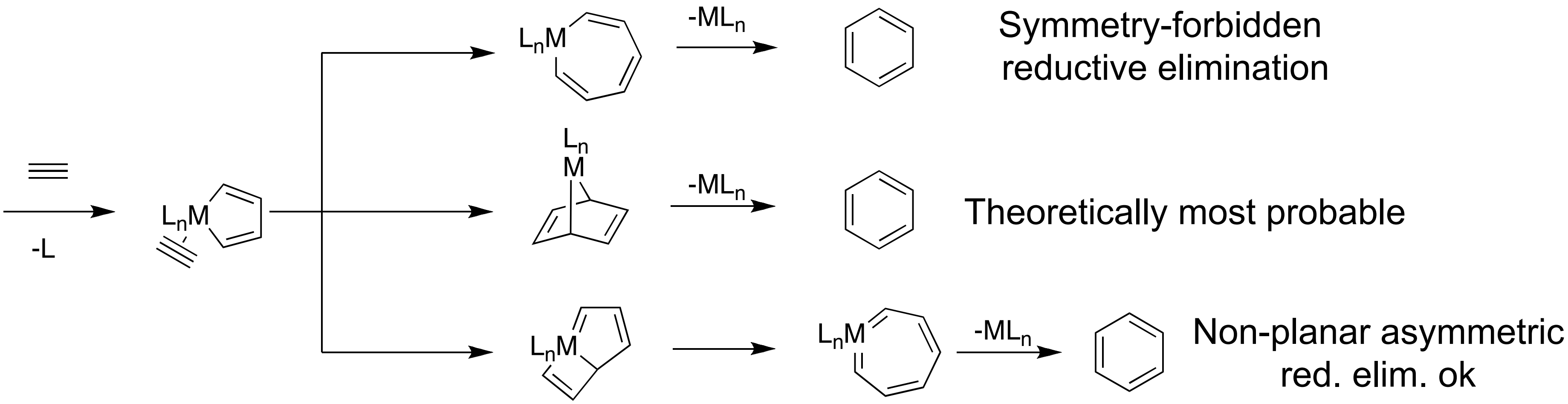
Note: R = Me, CO_2Me, → dimerization and C-H insertion pathways favored
R = CN,→ ↓ reactivity but desired cyclopropanation

Buchner E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2377
Levin, S; Nani, R., R.; Reisman, S. E. *Org. Lett.* **2010**, *12,* 780

Cyclopropanation Reviews:
Padwa, A.; Austin, D. J. *ACIE*, **1994**, *33*, 1797
Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

Cyclotrimerization





Symmetry-forbidden reductive elimination

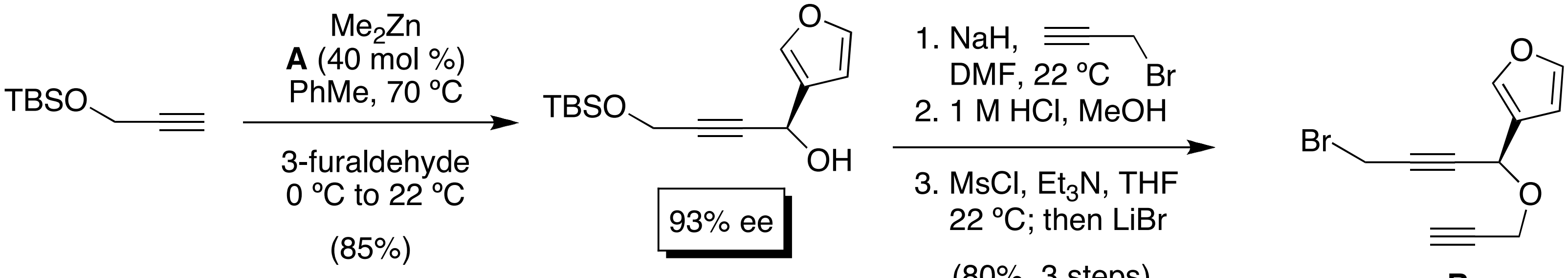
Theoretically most probable

Non-planar asymmetric red. elim. ok

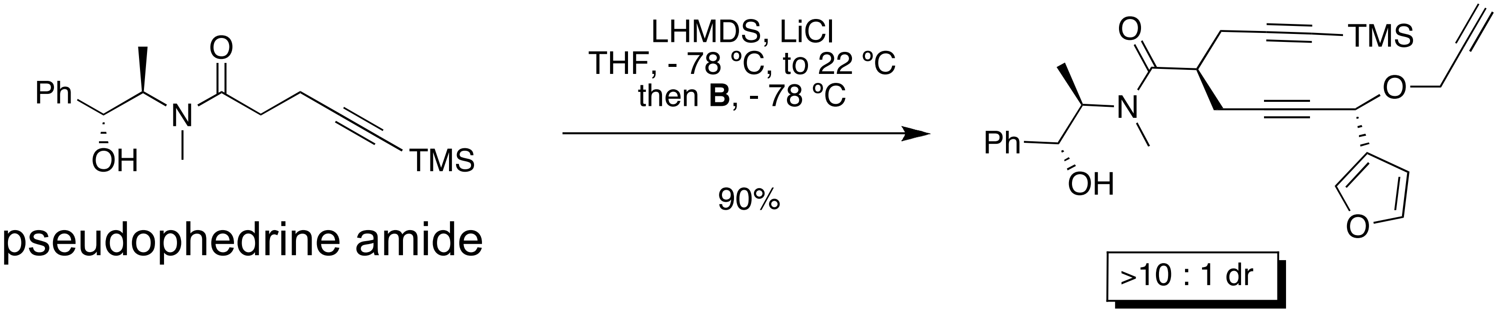
- •1866 by Berthelot → conversion of acetylene to benzene (>400 °C)
- •Since catalyzed by >15 metals (Ti, V, Mo, W, Fe, Os, Cu, Pd, **Ru, Rh, Ir, Co)**

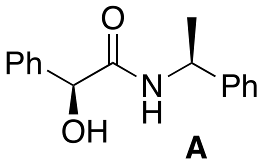
Schetter, M.C.R. *Hebd. Seances Acad. Sci.* ***1866**, 62*, 905.
Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G. B. *J. Am. Chem. Soc.* **1999,** *121*, 6055.
Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003** *125,* 11721.

Synthesis of triyne



B



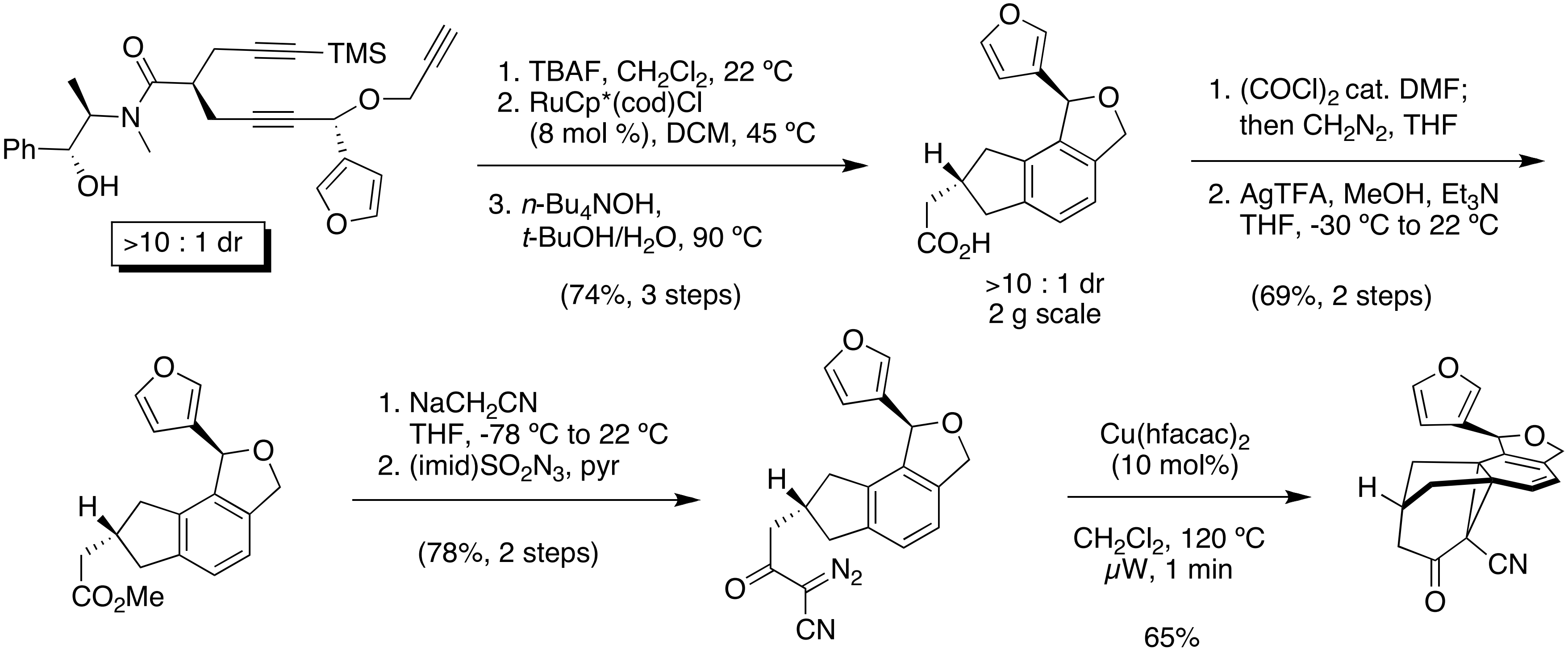


A

(S,S,)-mandelamide **III**

Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *JACS* **1997**, *119*, 6496.

Cyclotrimerization & Cyclopropanation



1. TBAF, CH_2Cl_2, 22 ºC
2. RuCp*(cod)Cl (8 mol %), DCM, 45 ºC
3. *n*-Bu_4NOH, *t*-BuOH/H_2O, 90 ºC

(74%, 3 steps)

>10 : 1 dr
2 g scale

1. $(COCl)_2$ cat. DMF; then CH_2N_2, THF
2. AgTFA, MeOH, Et_3N THF, -30 ºC to 22 ºC

(69%, 2 steps)

1. $NaCH_2CN$ THF, -78 ºC to 22 ºC
2. (imid)SO_2N_3, pyr

(78%, 2 steps)

$Cu(hfacac)_2$ (10 mol%)

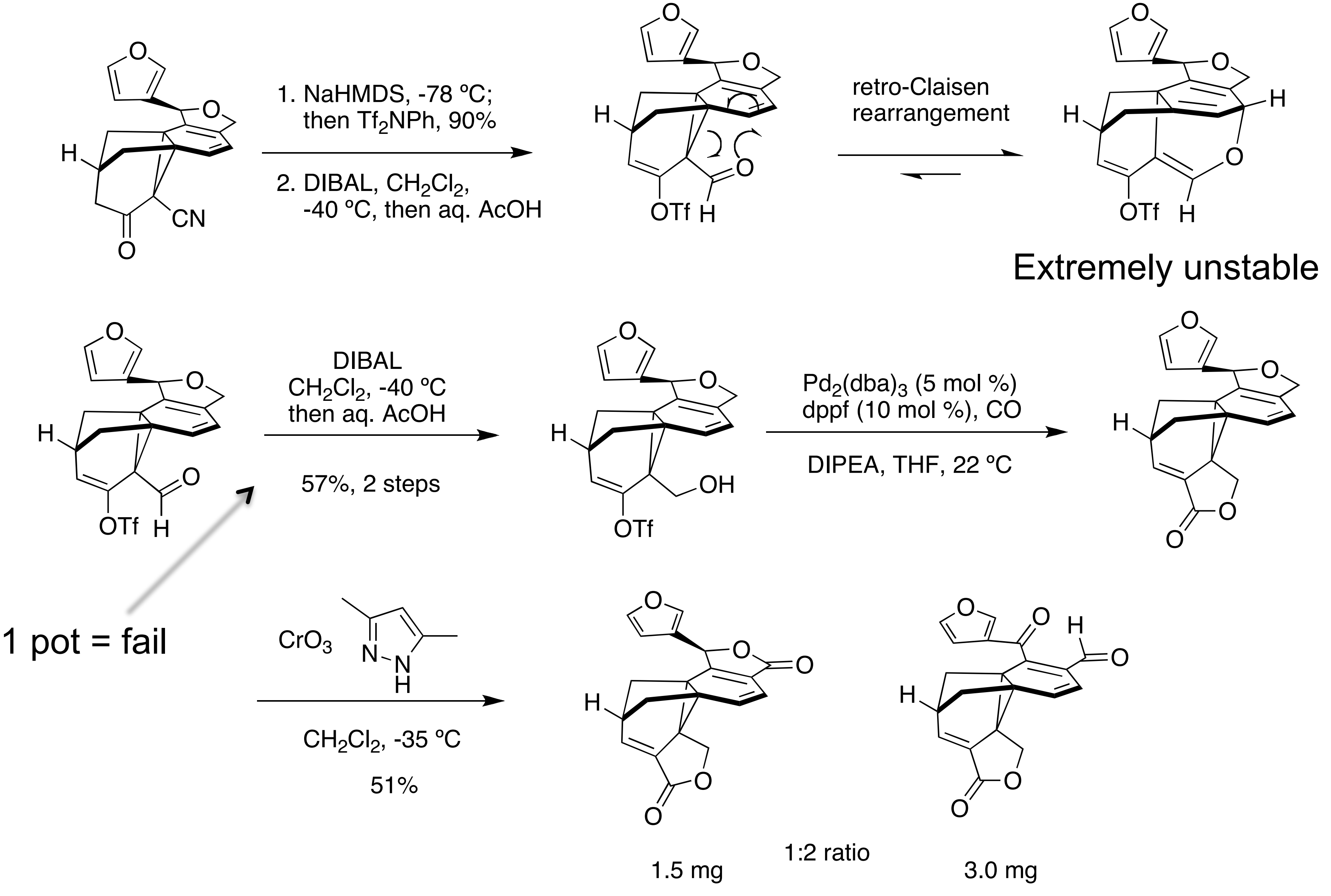
CH_2Cl_2, 120 ºC
μW, 1 min

65%

Note: simultaneous desilylation and saponification led to an erosion in dr

Goddard-Borger, E. D.; Stick, R. V. *Org. Lett*. **2007**, *9*, 3797.

Completion



1. NaHMDS, -78 ºC; then Tf_2NPh, 90%
2. DIBAL, CH_2Cl_2, -40 ºC, then aq. AcOH

retro-Claisen rearrangement

Extremely unstable

DIBAL
CH_2Cl_2, -40 ºC
then aq. AcOH

57%, 2 steps

1 pot = fail

$Pd_2(dba)_3$ (5 mol %)
dppf (10 mol %), CO

DIPEA, THF, 22 ºC

CrO_3

CH_2Cl_2, -35 ºC

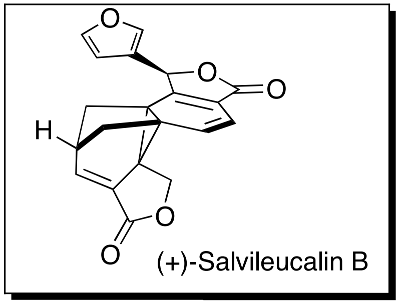
51%

1.5 mg

1:2 ratio

3.0 mg

Conclusions



(+)-Salvileucalin B

- 1st total synthesis (+)-salvileucalin B in 18 steps (4% yield)
- Copper catalyzed cyclotrimerization provided rapid access to cyclopropanation precursor
- Successfully constructed a fully substituted cyclopropane via a copper catalyzed arene cyclopropanation
- The molecule was completed via a selective allylic C-H oxidation