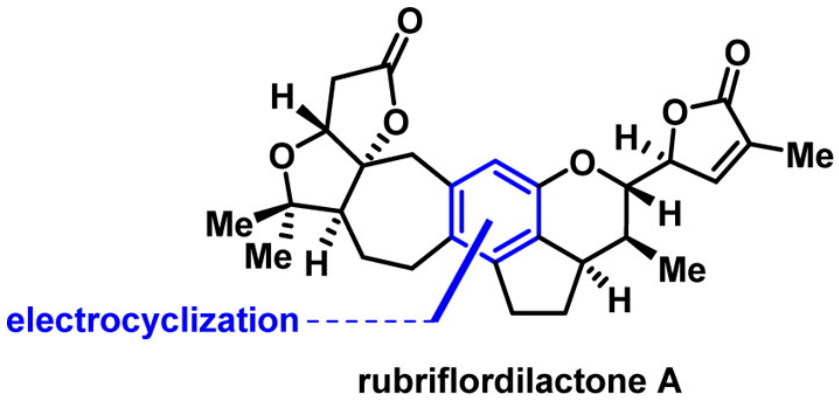
Total Synthesis of Rubriflordilactone A

Jian Li , Peng Yang , Ming Yao , Jun Deng , and Ang Li.
J. Am. Chem. Soc., **2014**, *136* (47), pp 16477–16480

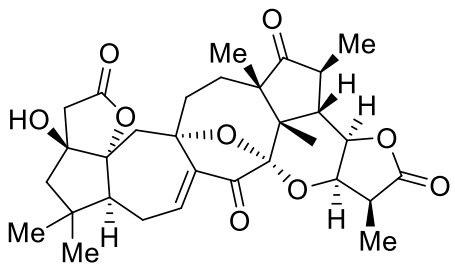


rubriflordilactone A

Liming Cao
Wipf Group Current Literature
1/3/2015

Schisandraceae triterpenoids

- *Schisandraceae* is a family of climbing plants and contains the genera *Schisandra* and *Kadsura*.
- The family consists of 50 species mainly distributed in southeast Asia and North America.
- Many species have a long history of use as folk medicines in China and are hot topic since 1970's because of their remarkable medicinal functions.
- *Schisandraceae* triterpenoids embody complex and dense polycyclic frameworks and are embellished with diverse oxy-functionalities and intricate stereochemical patterns.
- Only example: (±)-Schindilactone A (29 steps, 0.2%)

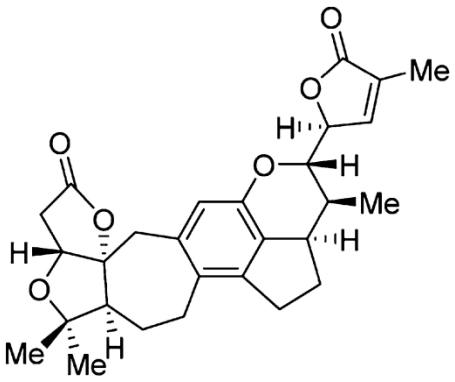


(±)-Schindilactone A

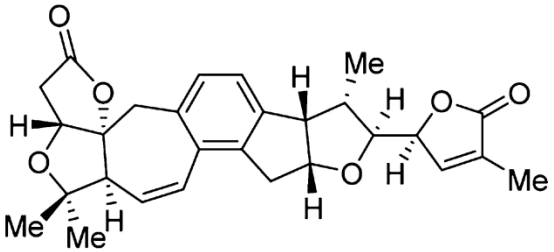
Nat. Prod. Rep. **2008**, 25, 871
Phytochem. Rev. **2014**, DOI: 10.1007/s11101-014-9343-7.
Angew. Chem., Int. Ed. **2011**, 50, 7373

Rubriflordilactone A and B

- *Schisandra rubriflora* is a deciduous Climber in the forests and shrubberies to 3300 meters in the Himalayas and is widely used in the traditional Chinese medicine.
- Rubriflordilactone A and B were isolated from the leaves and stems of *Schisandra rubriflora* by Sun et al. in 2006 and characterized by 2D NMR and X-ray crystallography.
- Rubriflordilactone A and B possess a multisubstituted arene motif in their pentacyclic frame work.
- Rubriflordilactone **B** exhibited promising anti-HIV activity.



1: rubriflordilactone A

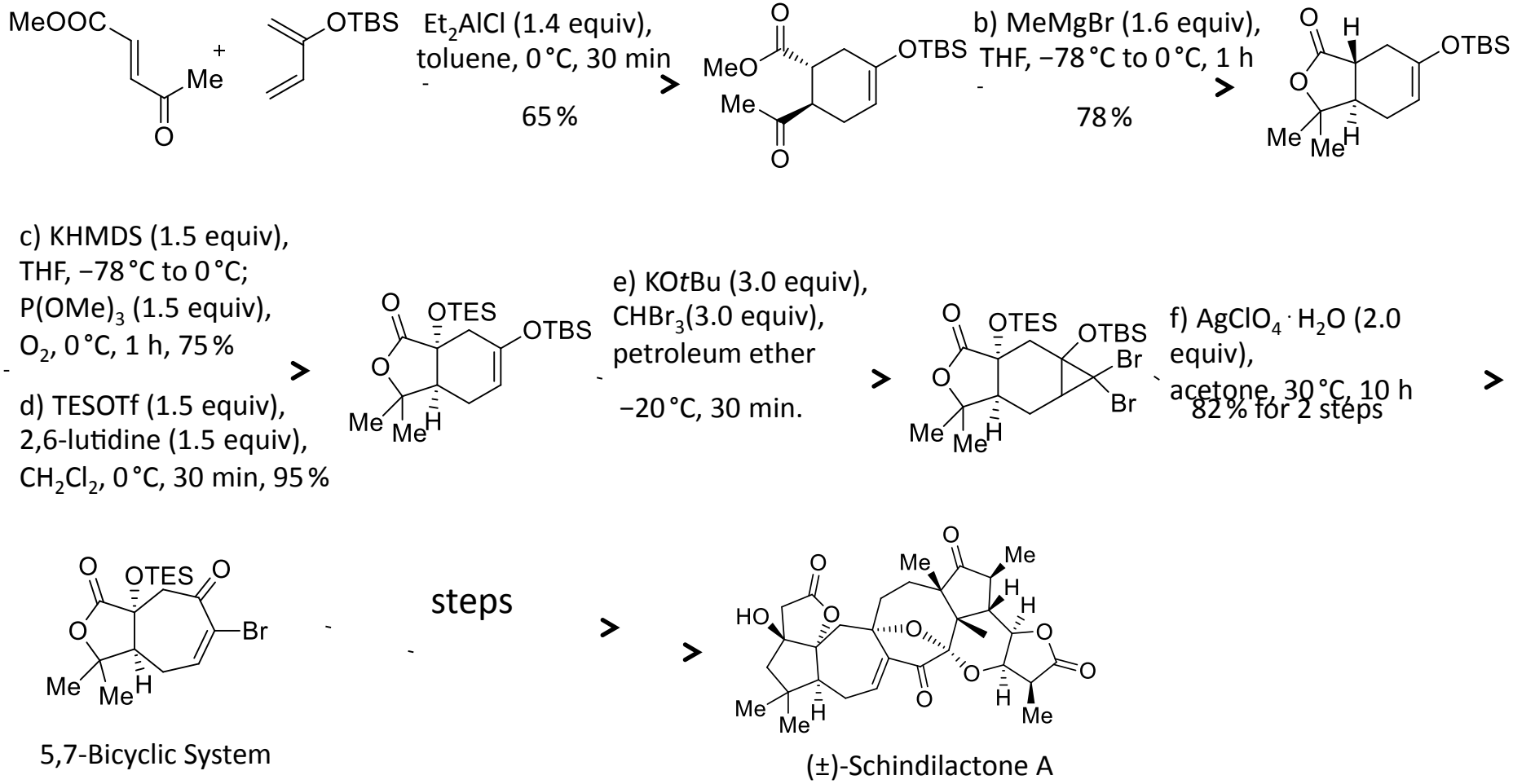


2: rubriflordilactone B

www.flickr.com/photos/12017190@N06

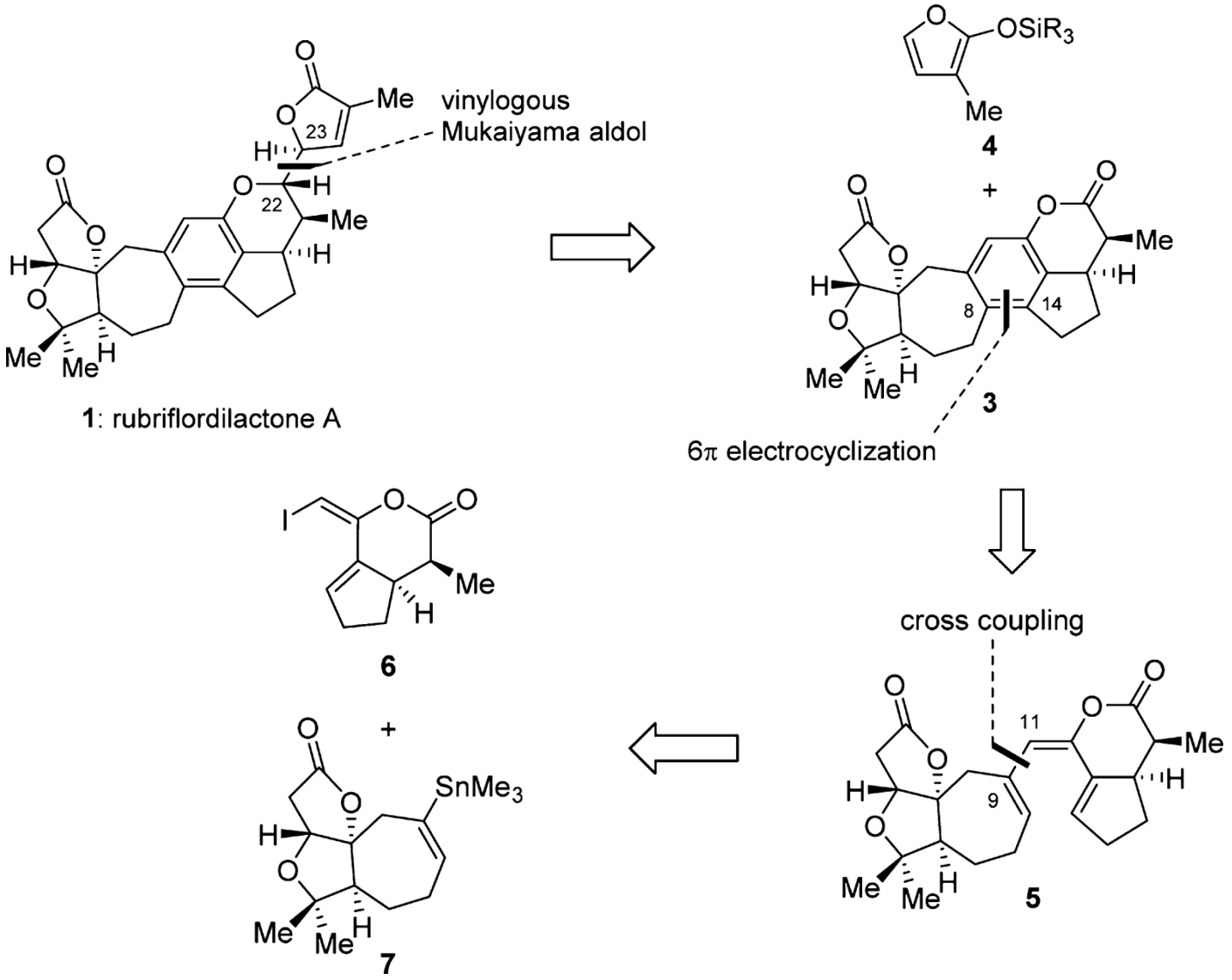
Org. Lett. **2006**, 8, 991
http://www.pfaf.org/user/plant.aspx?latinname=Schisandra+rubriflora

Yang's Synthesis of the Racemic 5,7-Bicyclic System



Angew. Chem., Int. Ed. **2011**, 50, 7373

Retrosynthetic Analysis



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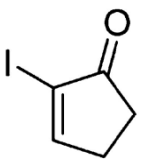
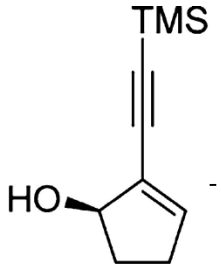
Synthesis of the Right-Hand Segment



9

a) **8** (5 mol %), BH_3·THF (0.67 equiv), THF, 0 °C, 30 min, 82%, > 99% ee

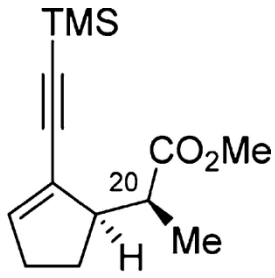
b) $Pd(PPh_3)_2Cl_2$ (0.5 mol %), CuI (1 mol %), TMS-acetylene (3.0 equiv), toluene, 50 °C, 2 h, 99%



10

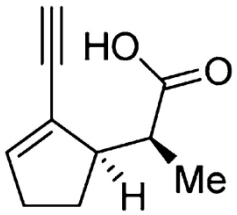
c) 2-nitrophenol (2 mol %), $EtC(OMe)_3$ (1.7 equiv), 100 °C, 48 h

90%, 7.5:1 dr at C20



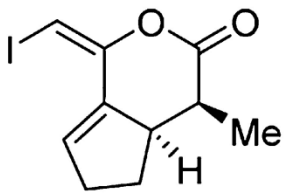
11

d) aq LiOH (1.0 M)/THF (1:1), 60 °C, 4 h, 93%



12

e) NIS (1.0 equiv), $NaHCO_3$ (2.0 equiv), acetonitrile, 22 °C, 1.5 h, 52%



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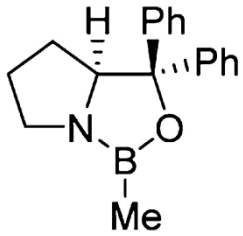

8

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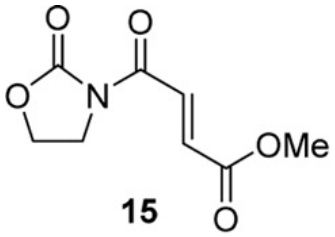
Synthesis of the Left-Hand Segment



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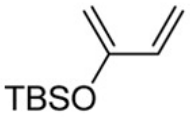
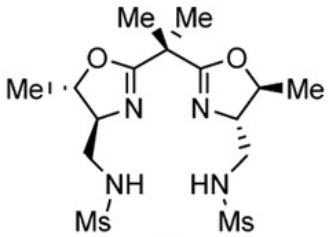


14

a) $Cu(OTf)_2$ (5 mol %), **16** (5.5 mol %), 4 Å MS, CH_2Cl_2, 0 °C, 2 d, 80%, 76% ee



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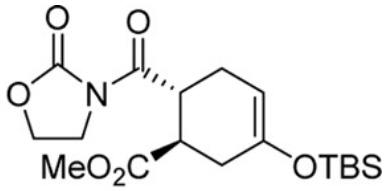
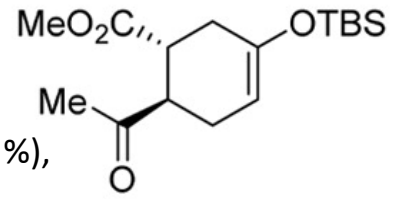


13

b) EtSH (3.0 equiv), BuLi (2.5 equiv), THF, 0 °C, 30 min, 96%

c) $Pd_2(dba)_3$ (1 mmol %), *S*-Phos (5 mmol %), MeZnI (5.0 equiv), NMP/THF (1.5:1), 65 °C, 1.5 h, 80%

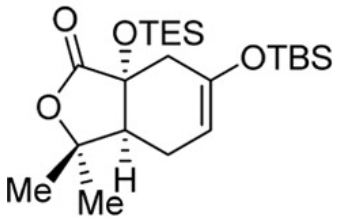


17

d) MeMgCl (1.1 equiv), THF, −40 °C, 1 h, then −20 °C, 45 min, 83%

e) KHMDS (1.1 equiv), THF, −78 °C, 30 min; then $P(OMe)_3$ (1.5 equiv), O_2, −78 °C, 20 min, 83%

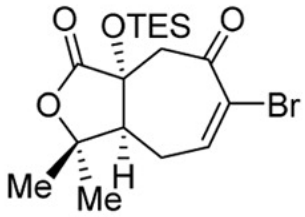
f) TESOTf (1.5 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 94%



19

g) $CHBr_3$ (3.0 equiv), *t*-BuOK (3.0 equiv), petroleum ether, −20 °C, 1 h

h) $AgClO_4 \cdot H_2O$ (2.0 equiv), $CaCO_3$ (5.0 equiv), acetone, 30 °C, 10 h, 66% (2 steps)



18

recrystallized to give the enantioenriched form (73%, > 99% ee) after removal of the essentially racemic crystals

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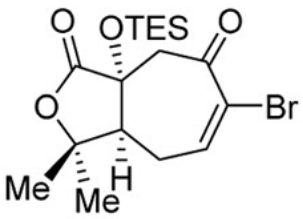
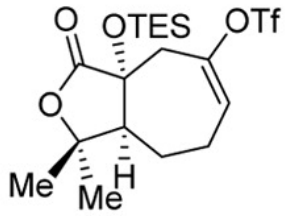
Synthesis of the Left-Hand Segment



18

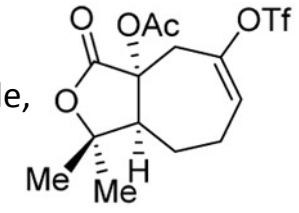
i) Pd/C (4 mol %), H_2 (1 atm), MeOH/EtOAc (1:1), 22 °C, 1.5 h, 97%

j) LiHMDS (2.5 equiv), $PhNTf_2$ (1.8 equiv), THF, −25 °C, 2 h, 89%



20

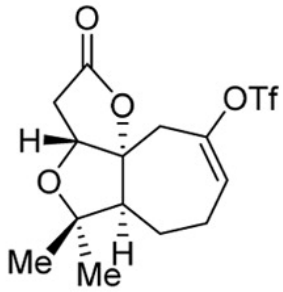
k) $Sc(OTf)_3$ (10 mol %), Ac_2O (5.0 equiv), acetonitrile, 10 min, 96%



21

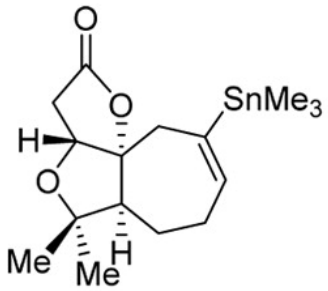
l) LiHMDS (1.6 equiv), THF, 0 °C, 5 min, 93%

m) Et_3SiH (25.0 equiv), $BF_3{\cdot}OEt_2$ (20.0 equiv), 35 °C, 3 h, 65% (29% for the recovered SM)



22

n) $Pd(PPh_3)_4$ (10 mol %), $Me_3SnSnMe_3$ (1.5 equiv), LiCl (1.5 equiv), THF, 60 °C, 15 min, 75%



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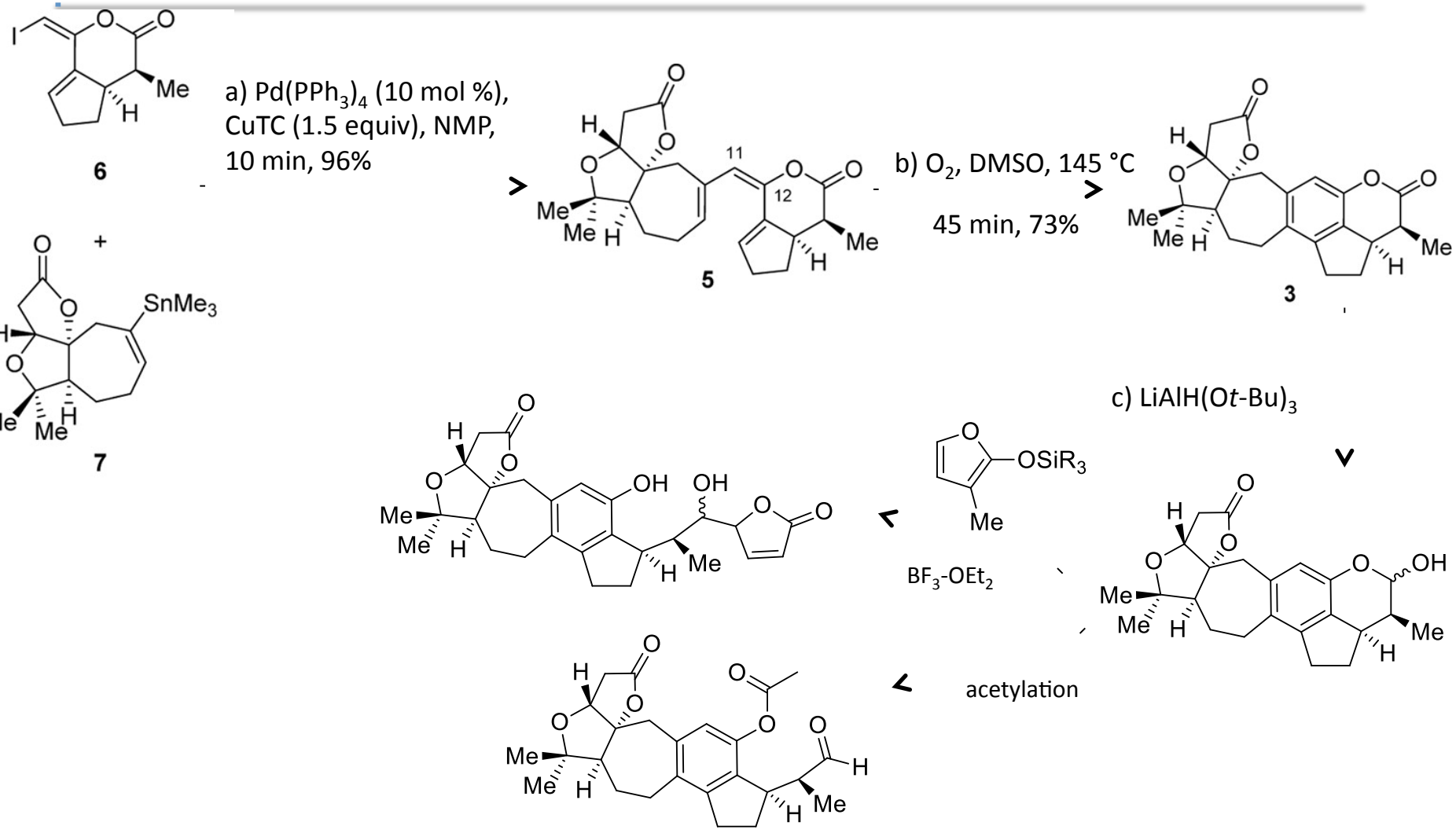
J. Am. Chem. Soc., **2014**, *136*, 16477

Completion of the Synthesis



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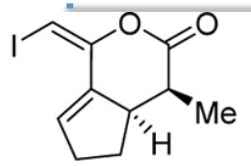
Completion of the Synthesis



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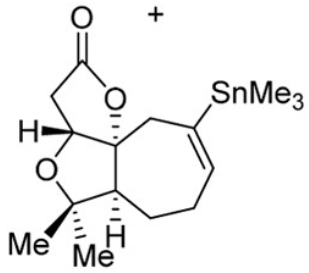
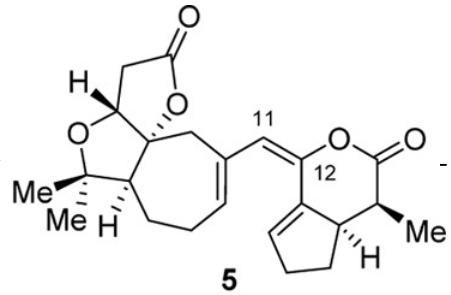


7

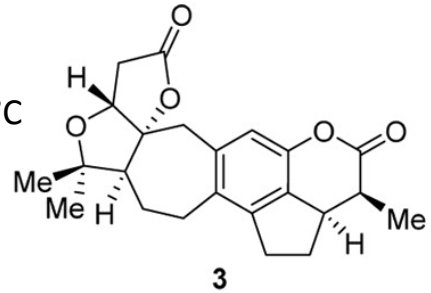
a) $Pd(PPh_3)_4$ (10 mol %), CuTC (1.5 equiv), NMP, 10 min, 96%



5

b) O_2, DMSO, 145 °C

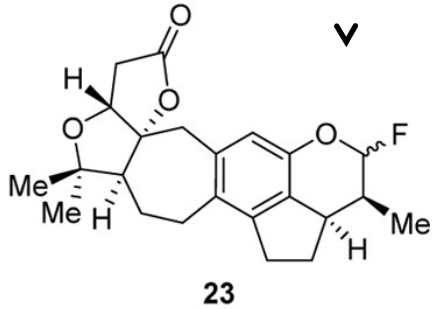
45 min, 73%



3

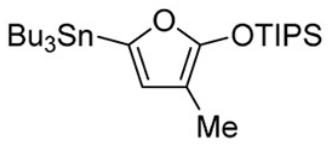
c) $LiAlH(Ot\text{-}Bu)_3$ (1.1 equiv), THF, 5 °C, 10 min

d) DAST (2.0 equiv), CH_2Cl_2, 22 °C, 10 min, 62% (2 steps)



23

e) $BF_3{\cdot}OEt_2$ (3.2 equiv), CH_2Cl_2, 22 °C, 5 min, 66%



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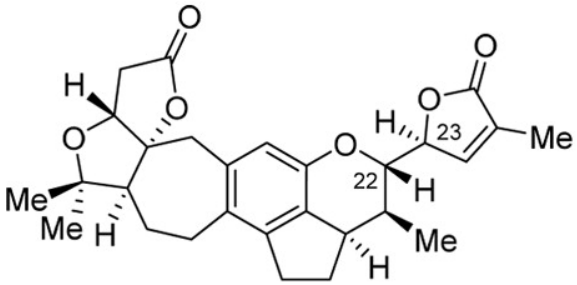

1: rubriflordilactone A

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conclusion

- The first and asymmetric total synthesis of Rubriflordilactone A in 19 steps (2%).
- The two segments were prepared in essentially enantiopure forms and assembled through Stille–Migita coupling; the geometry of the triene was secured.
- A one-pot 6π-electrocyclization/oxidative aromatization served as the key step of the synthesis..
- A formal vinylogous Mukaiyama aldol reaction installed the butenolide side chain at the final stage.