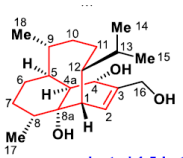
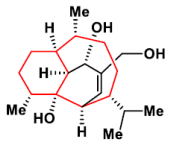
Asymmetric Total Synthesis of (-)-Vinigrol



unprecedented 1,5-butano-decahydronaphthalene core



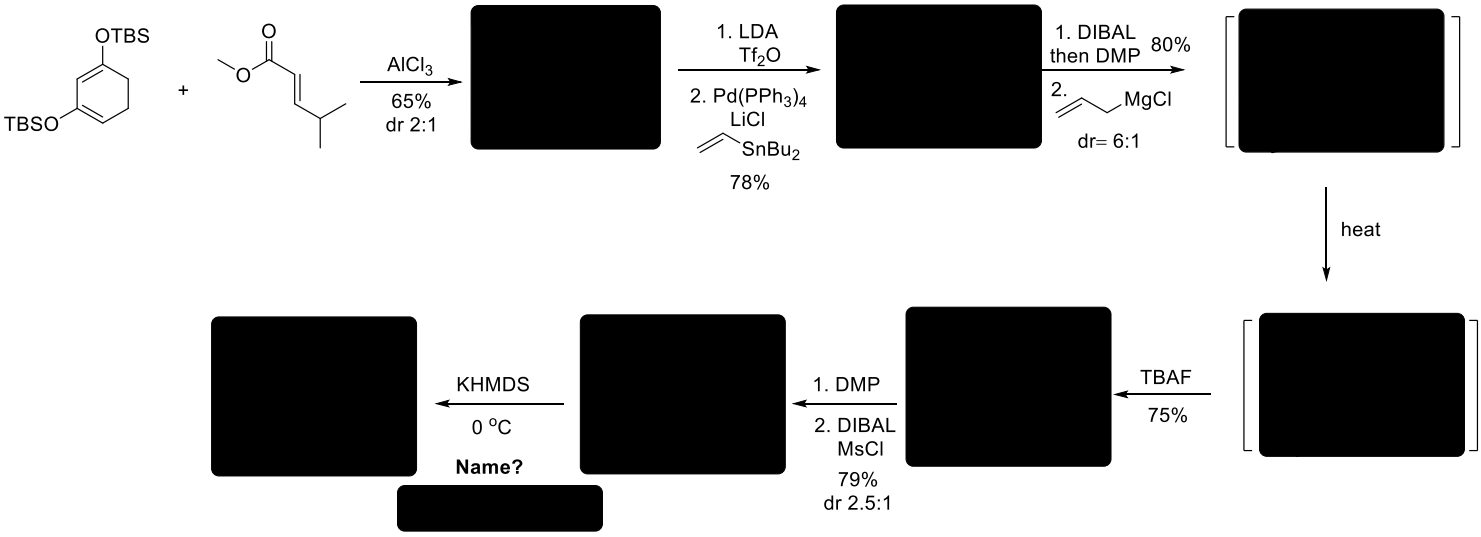
"taxol-like" bicyclo[5.3.1]undecane

***Review**: The conquest of vinigrol. Creativity, frustrations, and hope.*
Org. Prep. Proced. Int. **2007**, *39*, 311-353.
Before Baran's total synthesis: 17 publications and 4 dissertations, no total synthesis had been reported

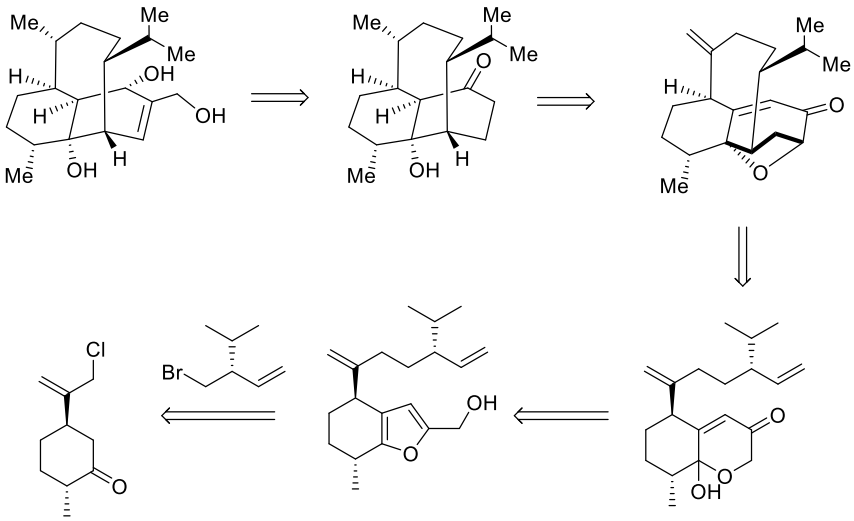
Racemic synthesis
Phil S. Baran *J. Am. Chem. Soc.* **2009**, *131*, 17066–17067. 23 steps
Barriault *Angew. Chem., Int. Ed.* **2012**, *51*, 2111-2114. 24 steps
Njardarson *Angew. Chem., Int. Ed.* **2013**, *52*, 8648-8651. 38 steps

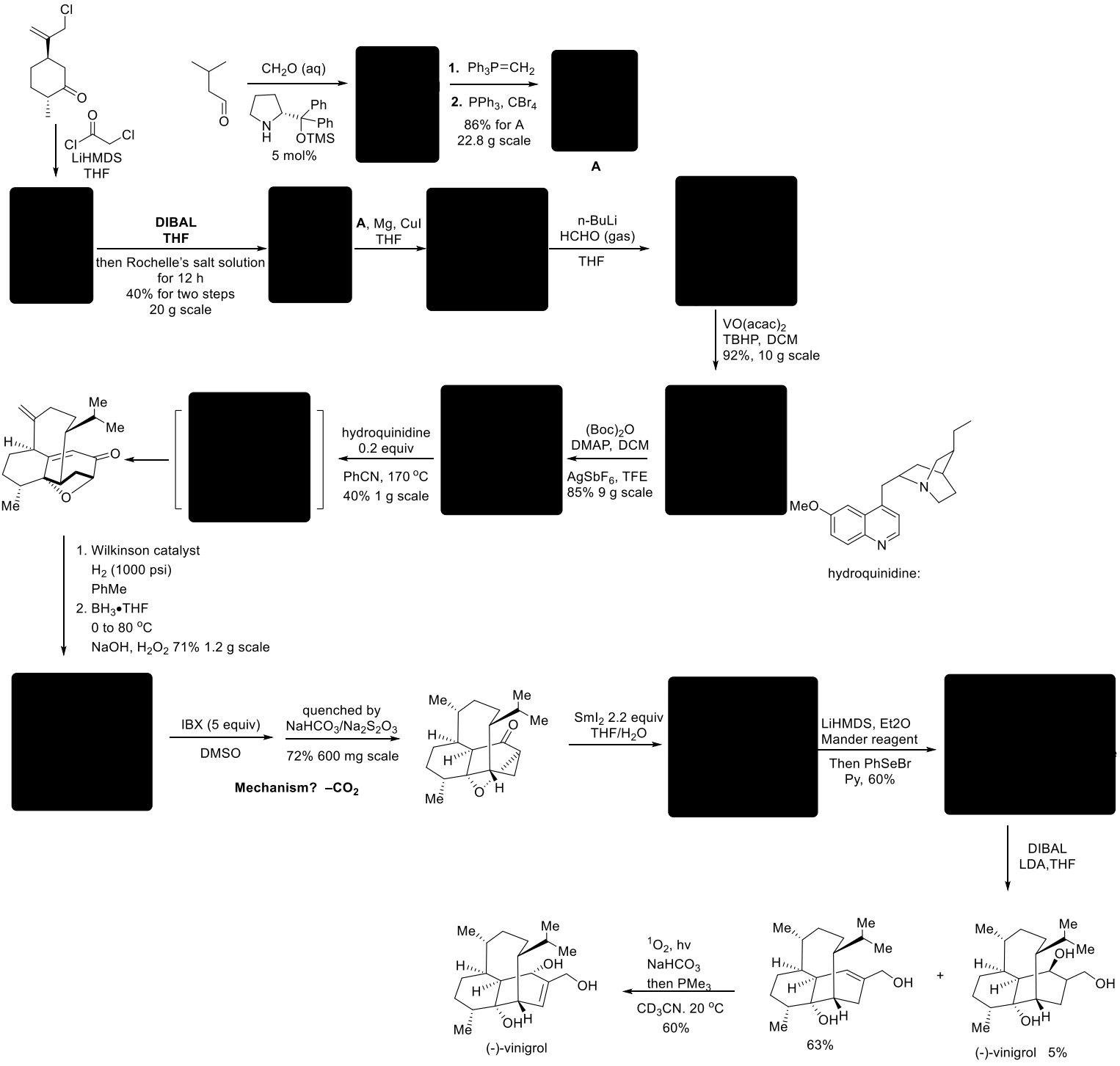
Asymmetric synthesis
Tuoping Luo *J. Am. Chem. Soc.* **2019**, *141*, 3440-3443. 20 steps
Chuang-Chuang Li *J. Am. Chem. Soc.* **2019**, *141*, 15773-15778. 15 steps

Baran's approach to the key decahydro-1,5-butanonaphthalene

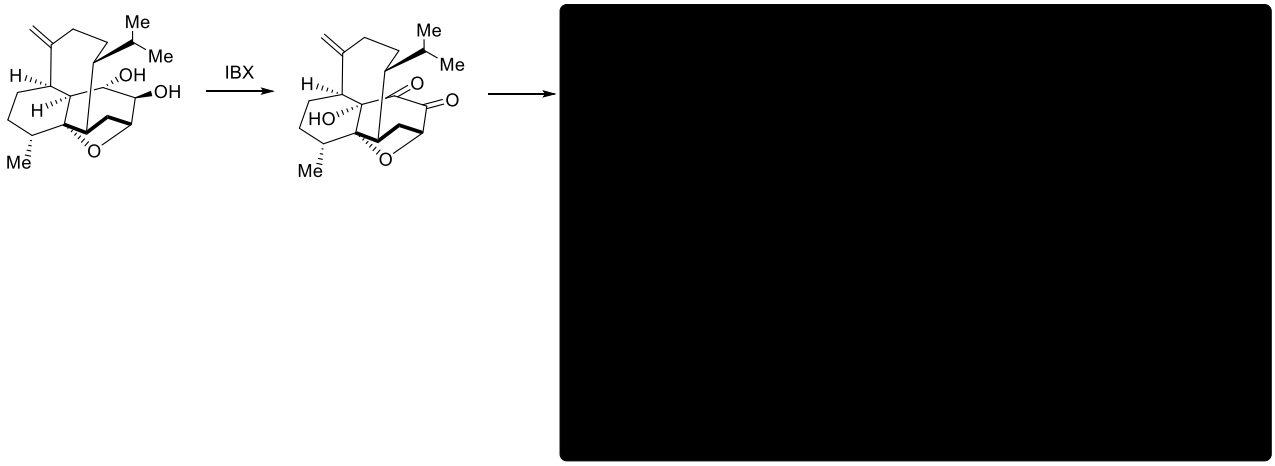


Li's retrosynthetic analysis



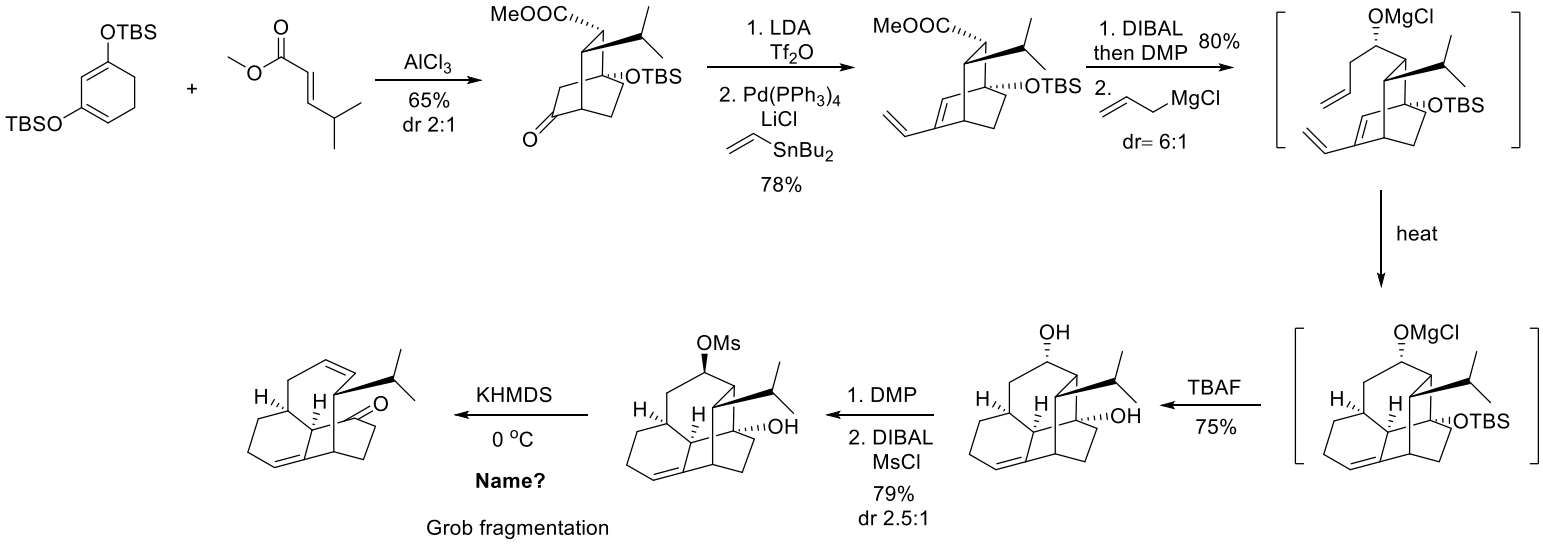

Cl
O
Cl
O
Cl
LiHMDS
THF
CH2O (aq)
O
N
H
Ph
Ph
OTMS
5 mol%
1. Ph3P=CH2
2. PPh3, CBr4
86% for A
22.8 g scale
A
DIBAL
THF
then Rochelle's salt solution
for 12 h
40% for two steps
20 g scale
A, Mg, CuI
THF
n-BuLi
HCHO (gas)
THF
VO(acac)2
TBHP, DCM
92%, 10 g scale
(Boc)2O
DMAP, DCM
AgSbF6, TFE
85% 9 g scale
hydroquinidine
0.2 equiv
PhCN, 170 °C
40% 1 g scale
Me
Me
H
O
O
Me
MeO
N
N
hydroquinidine:
1. Wilkinson catalyst
H2 (1000 psi)
PhMe
2. BH3•THF
0 to 80 °C
NaOH, H2O2 71% 1.2 g scale
IBX (5 equiv)
DMSO
quenched by
NaHCO3/Na2S2O3
72% 600 mg scale
Mechanism? –CO2
Me
Me
Me
H
H
O
O
H
Me
SmI2 2.2 equiv
THF/H2O
LiHMDS, Et2O
Mander reagent
Then PhSeBr
Py, 60%
DIBAL
LDA,THF
Me
Me
Me
H
H
OH
OH
OH
H
Me
(-)-vinigrol
1O2, hv
NaHCO3
then PMe3
CD3CN. 20 °C
60%
63%
+
OH
(-)-vinigrol 5%

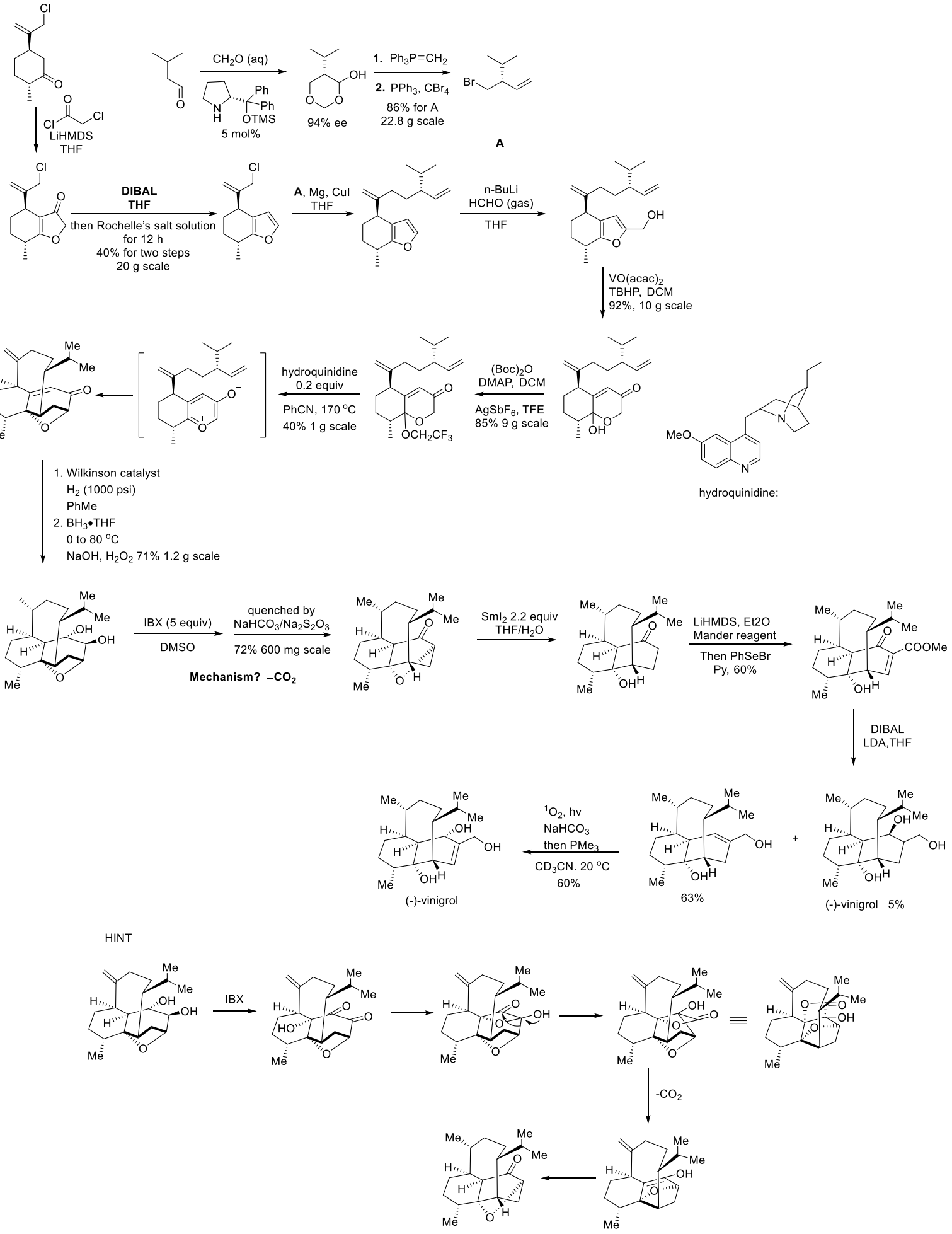
HINT



SOLUTION

Baran's approach to the key decahydro-1,5-butanonaphthalene




CH2O (aq)
5 mol%
94% ee
1. Ph3P=CH2
2. PPh3, CBr4
86% for A
22.8 g scale
A
LiHMDS
THF
DIBAL
THF
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for 12 h
40% for two steps
20 g scale
A, Mg, CuI
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HCHO (gas)
THF
VO(acac)2
TBHP, DCM
92%, 10 g scale
(Boc)2O
DMAP, DCM
AgSbF6, TFE
85% 9 g scale
hydroquinidine
0.2 equiv
PhCN, 170 °C
40% 1 g scale
hydroquinidine:
1. Wilkinson catalyst
H2 (1000 psi)
PhMe
2. BH3•THF
0 to 80 °C
NaOH, H2O2 71% 1.2 g scale
IBX (5 equiv)
DMSO
quenched by
NaHCO3/Na2S2O3
72% 600 mg scale
Mechanism? –CO2
SmI2 2.2 equiv
THF/H2O
LiHMDS, Et2O
Mander reagent
Then PhSeBr
Py, 60%
DIBAL
LDA,THF
1O2, hv
NaHCO3
then PMe3
CD3CN. 20 °C
60%
(-)-vinigrol
63%
(-)-vinigrol 5%
HINT
IBX
-CO2