10.1002/anie.202009562

WILEY-VCH

COMMUNICATION

Asymmetric Total Synthesis of Cephanolide A

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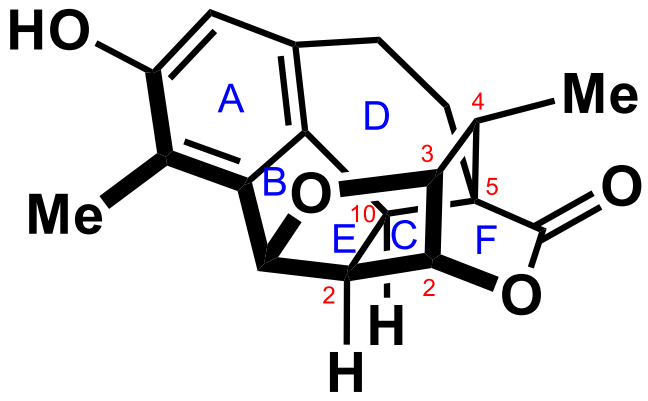
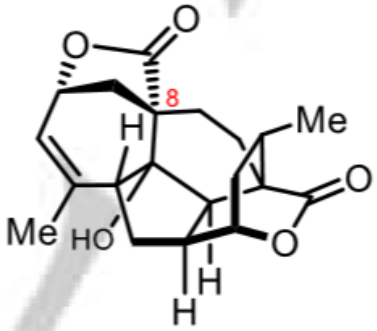
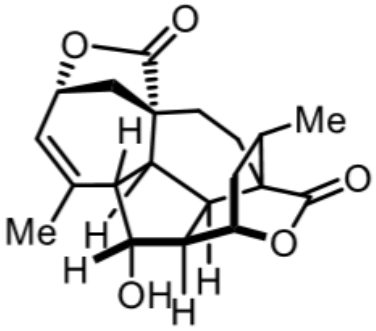


cephanolide A

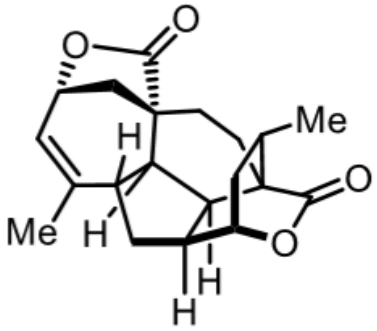
C_{20} diterpenoids



mannolide A (**1**)

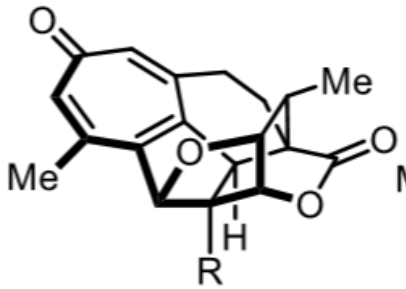


mannolide B (**2**)

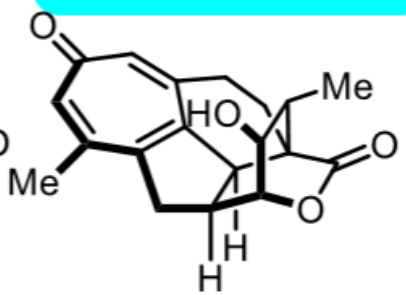


mannolide C (**3**)

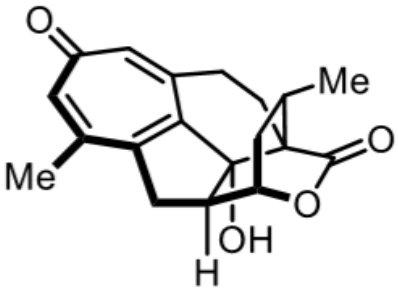
C_{19} norditerpenoids



R=H, harringtonolide (**4**)
R=OH, fortunolide B (**5**)

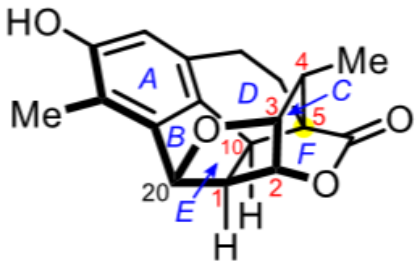


hainanolidol (**6**)

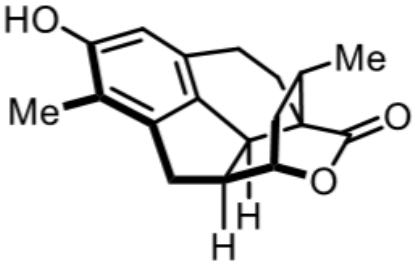


fortunolide A (**7**)

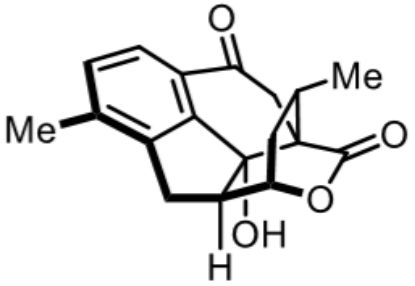
C_{18} dinorditerpenoids



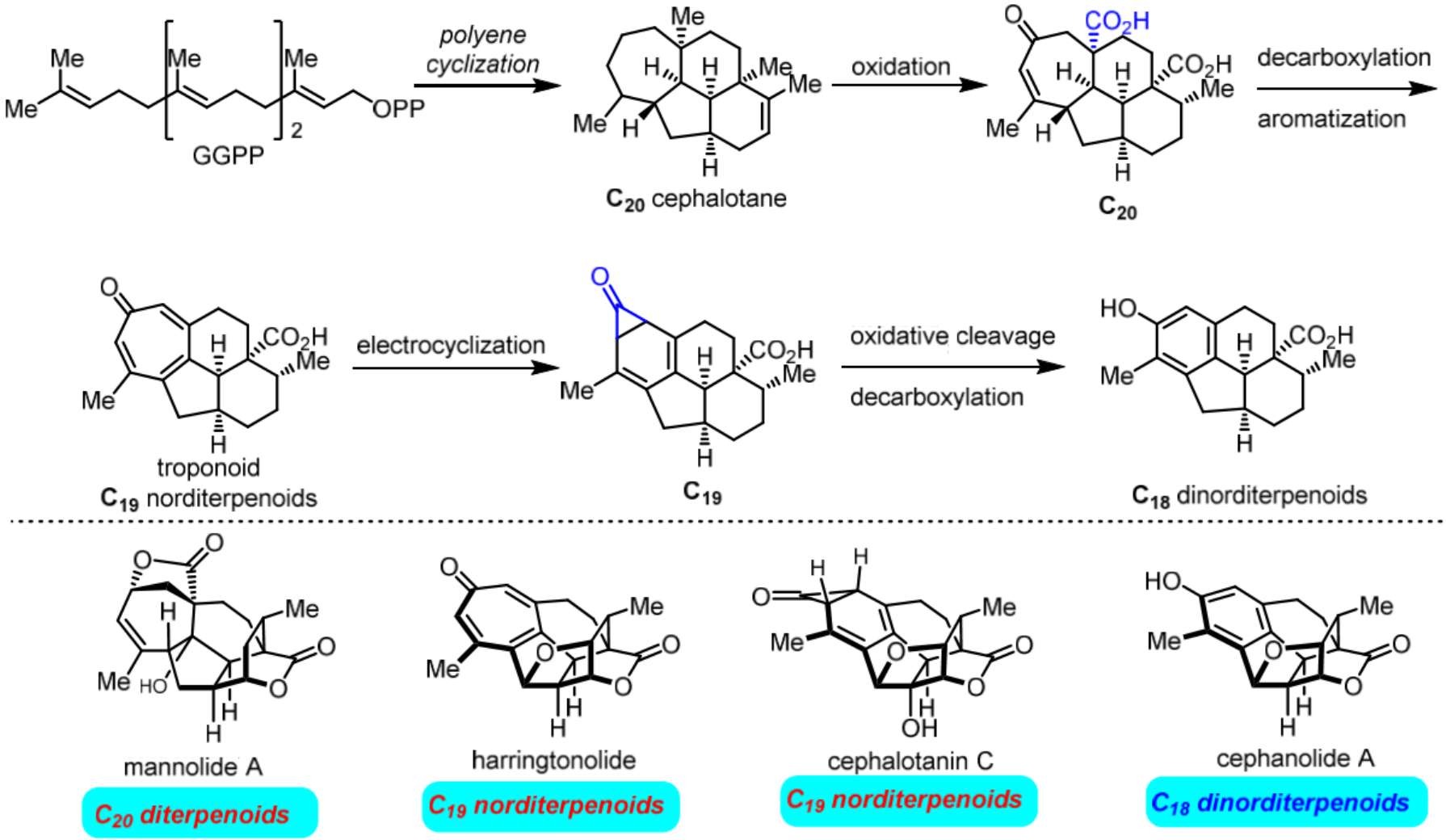
cephanolide A (**8**)



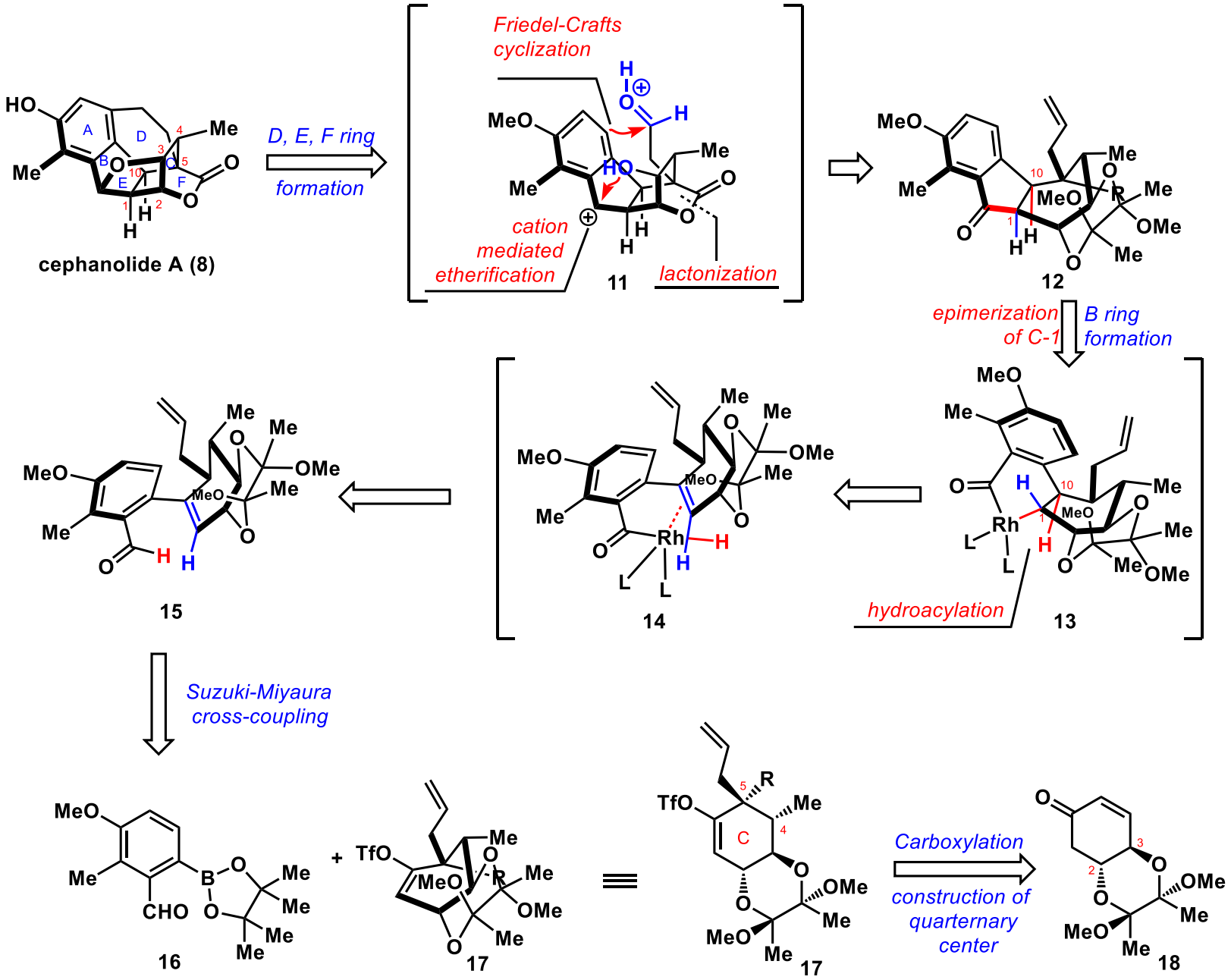
cephanolide B (**9**)

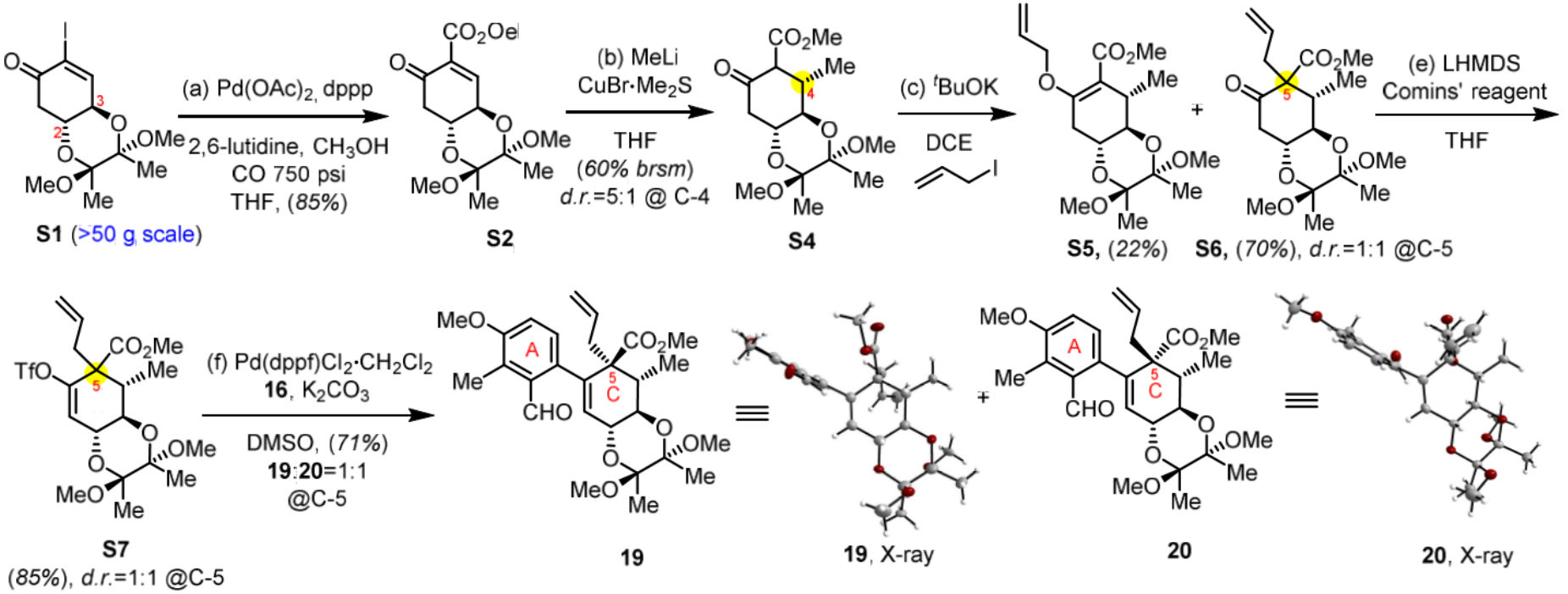


cephanolide C (**10**)

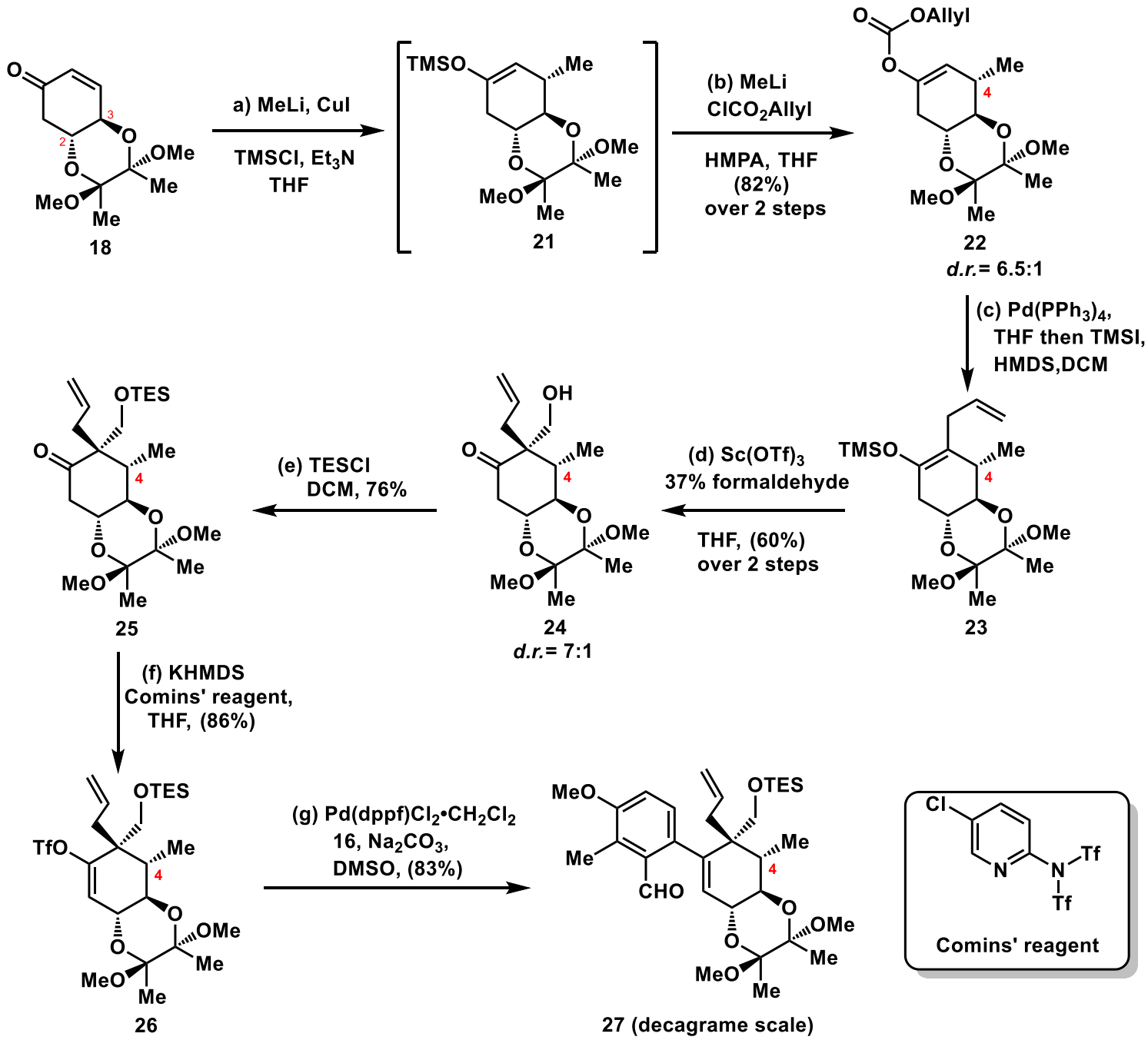


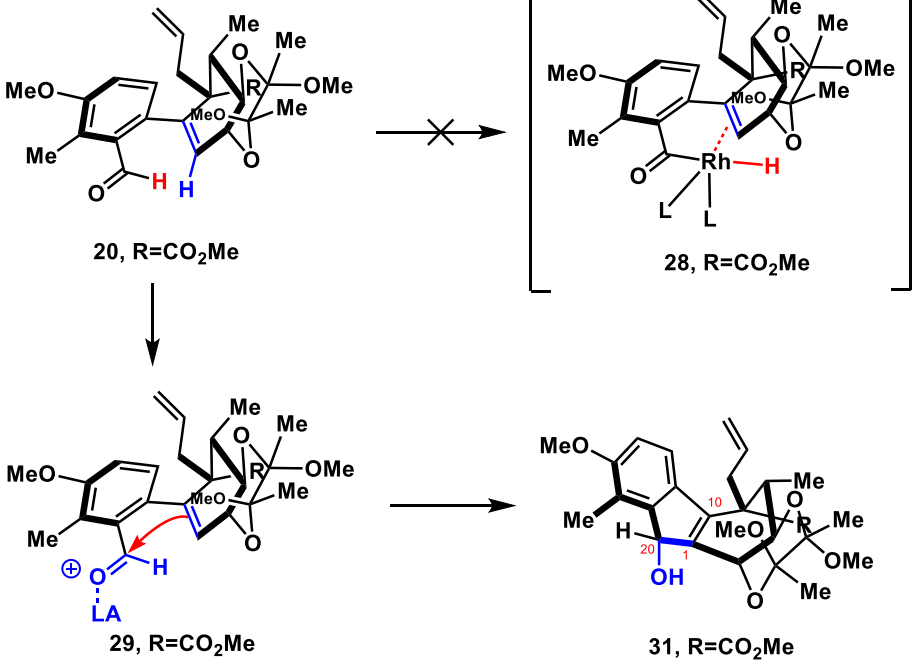
Scheme 1. Plausible biogenetic pathways of *cephalotaxus* diterpenoids


cephanolide A (8)
D, E, F ring formation
Friedel-Crafts cyclization
cation mediated etherification
lactonization
11
12
epimerization of C-1
B ring formation
13
hydroacylation
14
15
Suzuki-Miyaura cross-coupling
16
17
17
Carboxylation
construction of quarternary center
18

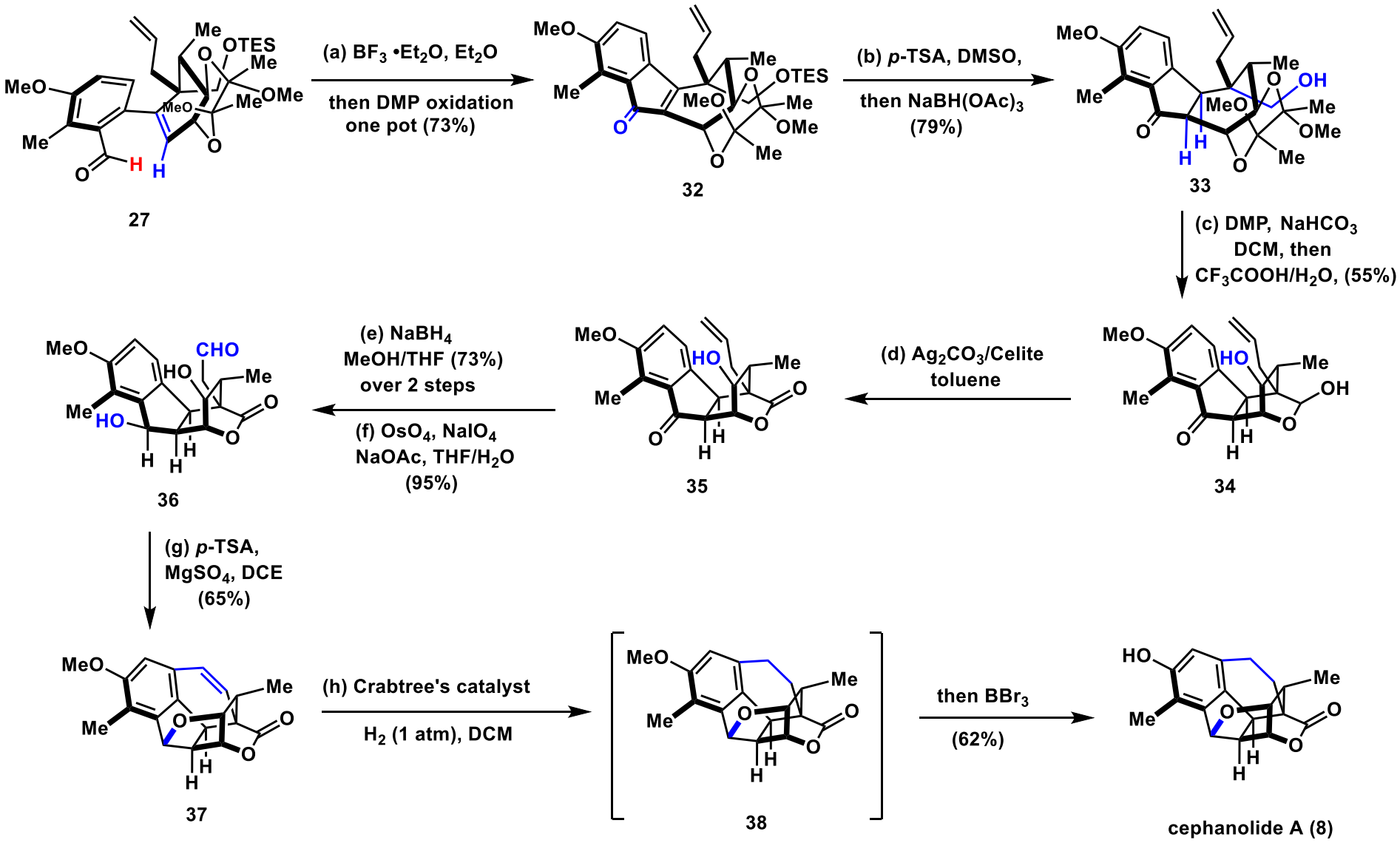


Scheme 2. First generation of preparation and cross coupling of rings A and C


18
a) MeLi, CuI
TMSCl, Et3N
THF
21
(b) MeLi
ClCO2Allyl
HMPA, THF
(82%)
over 2 steps
22
d.r.= 6.5:1
(c) Pd(PPh3)4,
THF then TMSI,
HMDS,DCM
23
(d) Sc(OTf)3
37% formaldehyde
THF, (60%)
over 2 steps
24
d.r.= 7:1
(e) TESCl
DCM, 76%
25
(f) KHMDS
Comins' reagent,
THF, (86%)
26
(g) Pd(dppf)Cl2•CH2Cl2
16, Na2CO3,
DMSO, (83%)
27 (decagrame scale)
Comins' reagent



entry	*conditions*	*results*
1	$[Rh(COD)Cl]_2$, PPh_3, NaBARF, 1,4-dioxane, 100 °C, 12 h	**31**, *20%*
2	$[Rh(COD)Cl]_2$, PPh_3, NaBARF, DCE, 40 °C 2.5 h	**31** and **31'**, *58%* *d.r.*=1:6 @ C-20
3	$[Rh(COD)Cl]_2$, dppp, $AgBF_4$, DCE, 40 °C 2.5 h	messy
4	$AgBF_4$, DCE, 40 °C, 24 h	NR
5	$Rh(PPh_3)_2Cl$, benzene, 100 °C, 12 h	NR
6	$[Rh(COD)Cl]_2$, PPh_3, DCE, 40 °C, 12 h	NR
7	NaBARF, DCE, 80 °C, 7 h	**31**, *30%*
8	NaBARF, dioxane, 100 °C, 20 h	**31**, **31'**, *27%*, *d.r.*=1:1 @ C-20
9	$BF_3{\cdot}Et_2O$, Et_2O, 0 °C, 30 min	**31**, *84%*


(a) $BF_3 \cdot Et_2O$, Et_2O
then DMP oxidation
one pot (73%)
(b) *p*-TSA, DMSO,
then $NaBH(OAc)_3$
(79%)
(c) DMP, $NaHCO_3$
DCM, then
CF_3COOH/H_2O, (55%)
(d) Ag_2CO_3/Celite
toluene
(e) $NaBH_4$
MeOH/THF (73%)
over 2 steps
(f) OsO_4, $NaIO_4$
NaOAc, THF/H_2O
(95%)
(g) *p*-TSA,
$MgSO_4$, DCE
(65%)
(h) Crabtree's catalyst
H_2 (1 atm), DCM
then BBr_3
(62%)
27
32
33
34
35
36
37
38
cephanolide A (8)