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Communication

Asymmetric Total Synthesis of Pedrolide

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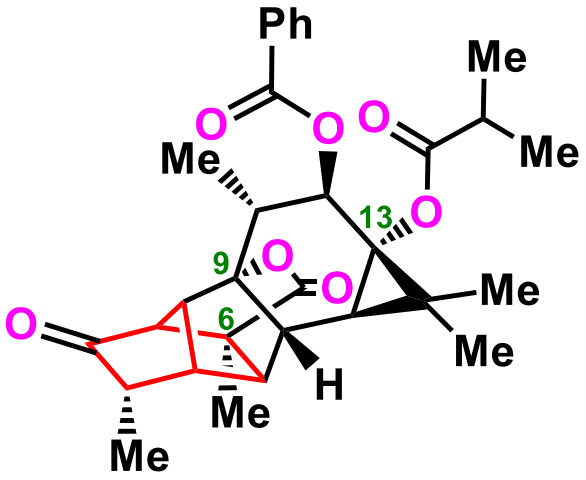


Pedrolide (1, 5.0 mg isolated)

structural features:

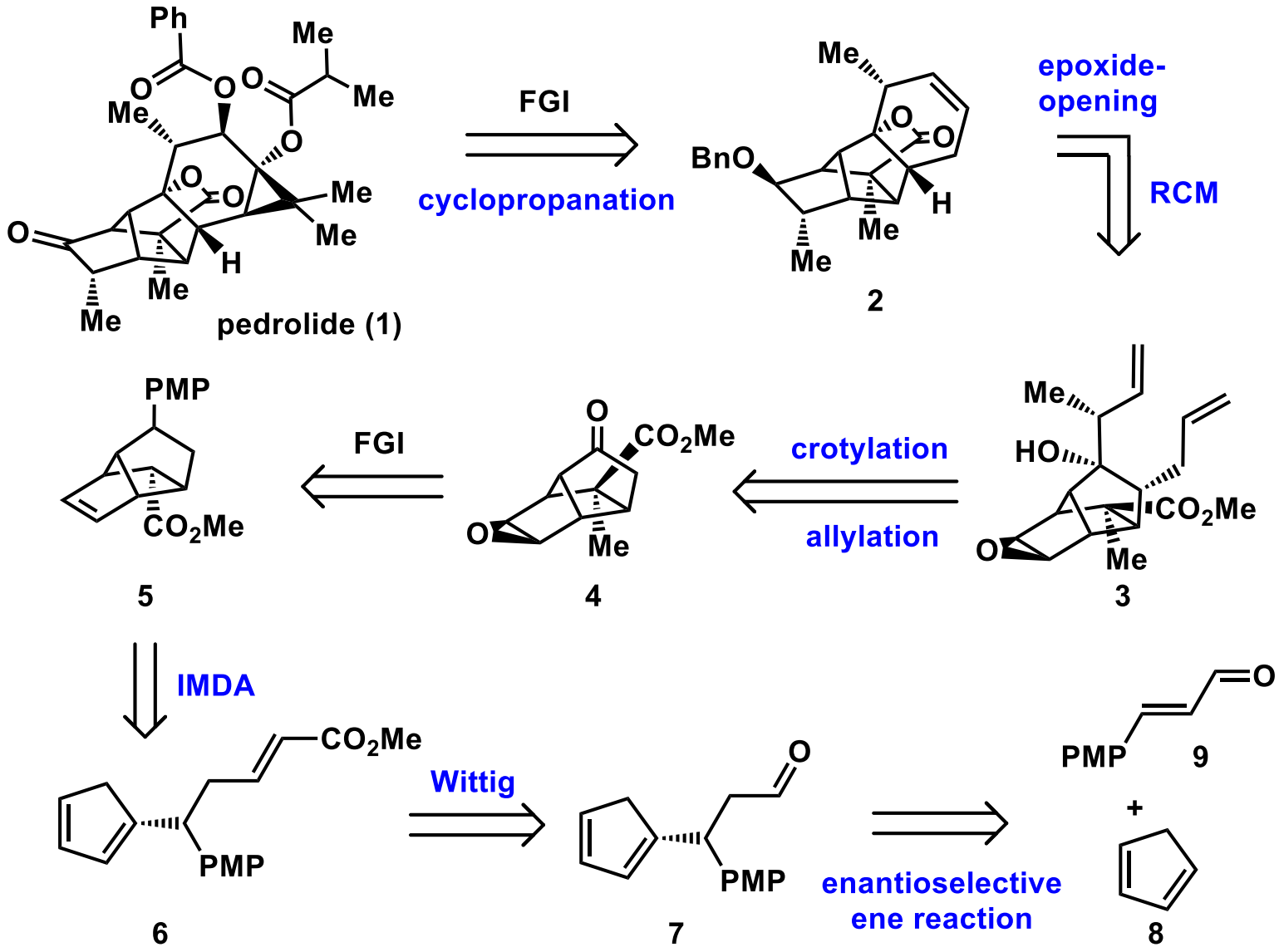
- unprecedented skeleton: pedrolane
- [5-5-5-6-6-3] hexacyclic core: bicyclo[2.2.1]heptane
- 12 contiguous stereocenters: 3 quaternary
- highly oxygenated

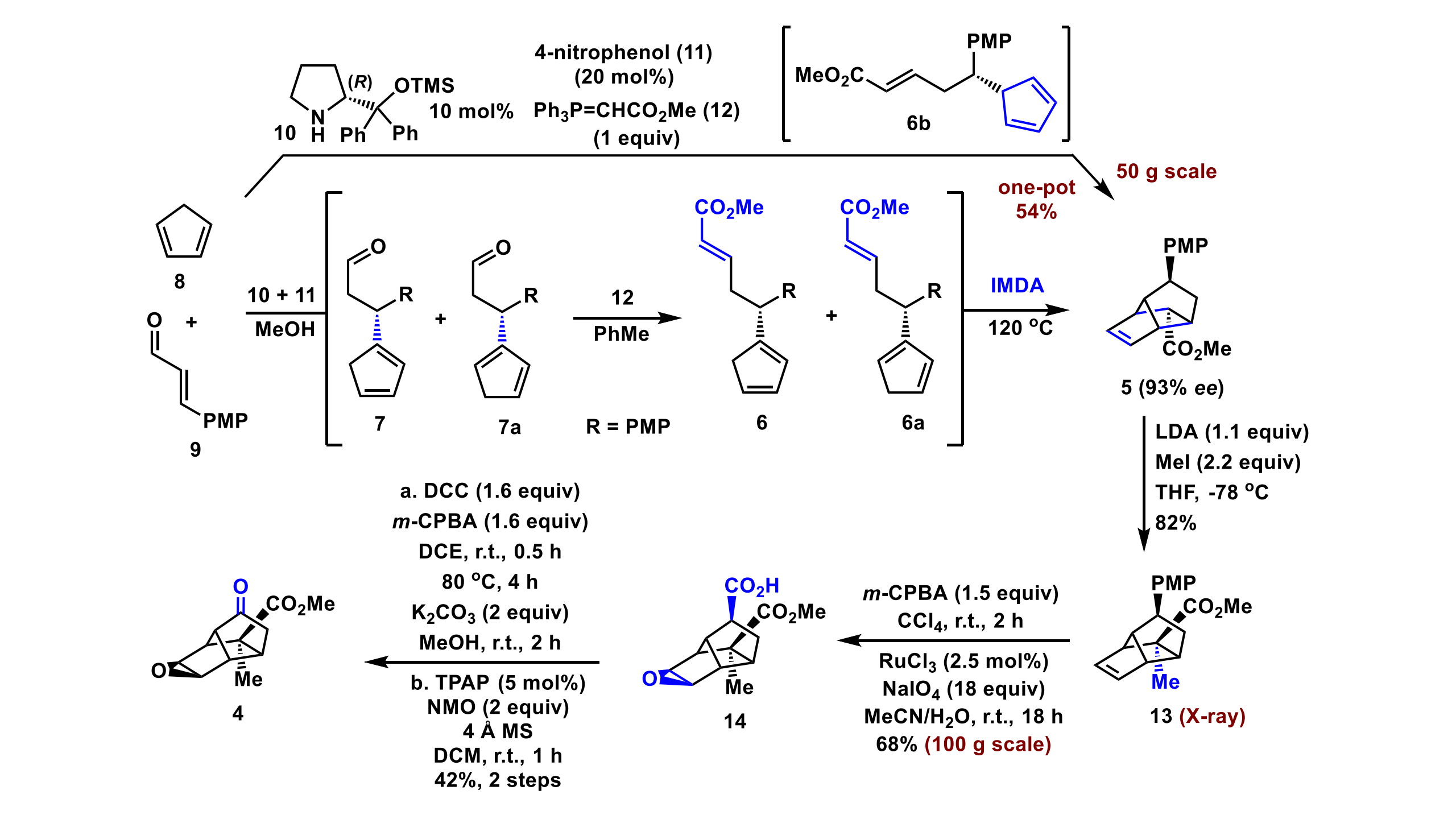
total syntheses:

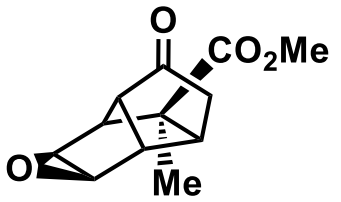
- Carreira (first synthesis, 20 steps)
- this work (>200 mg)

J. Am. Chem. Soc., **2024**, *146*, 2928.

Scheme 1. Retrosynthetic Analysis of Pedrolide (1)



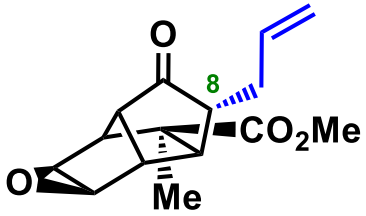

10
(R)
OTMS
N
H
Ph
Ph
10 mol%
4-nitrophenol (11)
(20 mol%)
Ph3P=CHCO2Me (12)
(1 equiv)
PMP
MeO2C
6b
50 g scale
one-pot
54%
8
O
+
PMP
9
10 + 11
MeOH
O
R
7
+
O
R
7a
12
PhMe
R = PMP
CO2Me
R
6
+
CO2Me
R
6a
IMDA
120 °C
PMP
CO2Me
5 (93% ee)
LDA (1.1 equiv)
MeI (2.2 equiv)
THF, -78 °C
82%
PMP
CO2Me
Me
13 (X-ray)
m-CPBA (1.5 equiv)
CCl4, r.t., 2 h
RuCl3 (2.5 mol%)
NaIO4 (18 equiv)
MeCN/H2O, r.t., 18 h
68% (100 g scale)
CO2H
CO2Me
O
Me
14
a. DCC (1.6 equiv)
m-CPBA (1.6 equiv)
DCE, r.t., 0.5 h
80 °C, 4 h
K2CO3 (2 equiv)
MeOH, r.t., 2 h
b. TPAP (5 mol%)
NMO (2 equiv)
4 Å MS
DCM, r.t., 1 h
42%, 2 steps
O
CO2Me
O
Me
4



4

KHMDS (1.1 equiv)
allyl iodide (1.2 equiv)

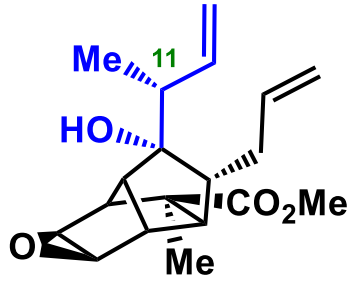
KHMDS (1.2 equiv)
CPME, -50 °C, 71%
(10 g scale)



15

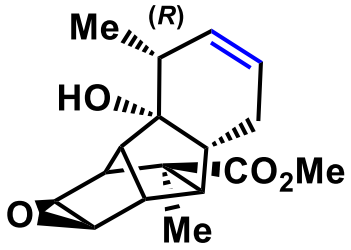
16, 70% for 3/3' (1:2)
or
BF_3•OEt_2 (0.5 equiv)
DCM, -50 °C

17a (5 equiv), 85% for 3 (desired)
17b (5 equiv), 70% for 3'



3 (11*R*)
3' (11*S*)

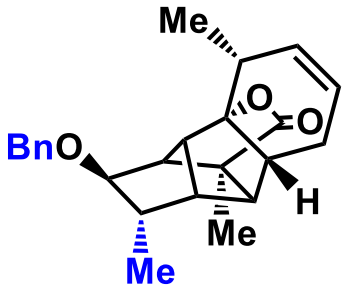
HG II (5 mol%)
DCM, 40 °C, 48 h, 81%



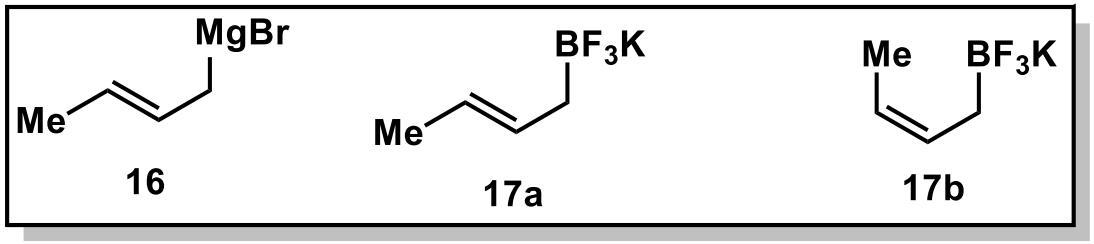
18

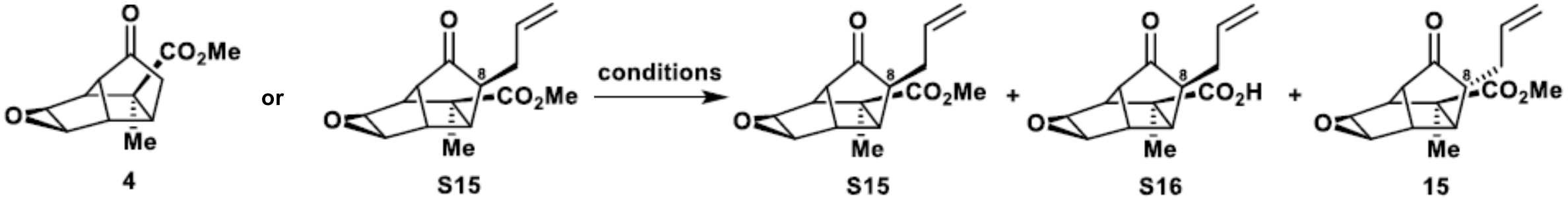
$LiCuMe_2$ (1.1 equiv), Et_2O
r.t., 6 h

NaH (2.0 equiv)
BnBr (2.5 equiv)
TBAI (0.3 equiv)
THF, overnight
75% (10 g scale)

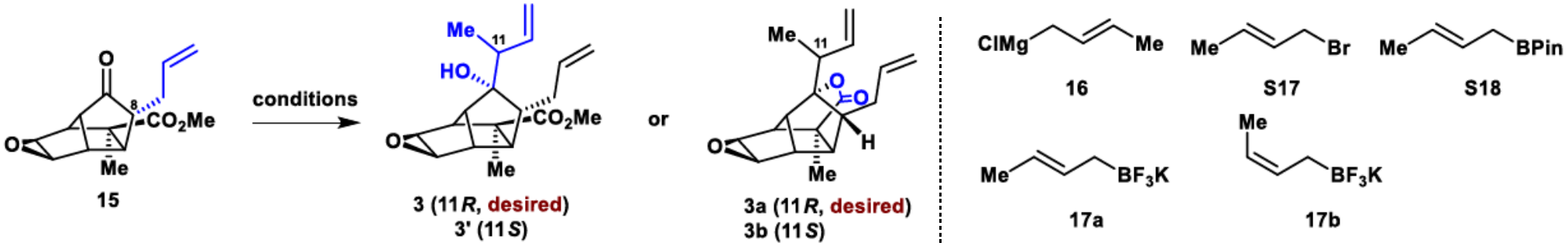


2 (>80 g produced)

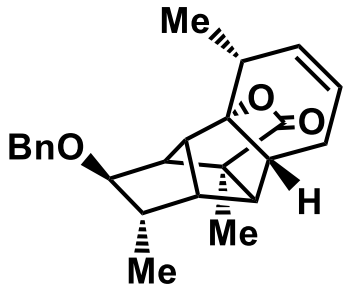




Entry[a]	Substrate	Reagent	Solvent/Temp. (°C)	Products (Yield(%))
1	**4**	KHMDS, allyl iodide	THF/-78	**S15** (90)
2	**S15**	KHMDS	THF/-78	NR
3	**S15**	KHMDS	THF/-60	**15** (20) + **S16** (60)
4	**S15**	KHMDS	THF/-30	**S16** (30)
5	**S15**	NaHMDS	THF/-30	NR
6	**S15**	LDA	THF/-30	decomposed
7	**S15**	LHMDS	THF/-30	NR
8	**S15**	KO*t*-Bu	THF/-30	**S16** (70)
9	**S15**	KHMDS	THF-Et_2O (1:1) -50	**15** (trace)
10	**S15**	KHMDS	Et_2O/-50	**15** (trace)
11	**S15**	KHMDS	CPME-THF (4:1) -50	**15** (74)
12	**4**	KHMDS, allyl iodide; KHMDS	CPME-THF (4:1) -50	**15** (71)



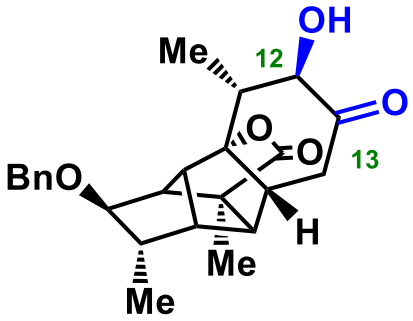
Entry[a]	Reagent	Solvent/Temp. (°C)	*R*:*S*	Yield (%)	Products
1	**16**	THF/-30	1:2.0	70	**3a+3b**
2	**16**, $TiCl_4$	THF/-78	1:2.1	no determined	**3a+3b**
3	**16**, $CeCl_3$	THF/-78	\	NR	\
4	**16**, $ZnBr_2$	THF/-78	\	NR	\
5	**S17** Cp_2TiCl_2	THF/25	\	no desired product	\
6	**S17**, In	THF-H_2O/reflux	\	low conversion	**3a+3b**
7	**S18**, In	THF or DCM/ reflux	\	NR	\
8	**17a** K-catalyst	DCM-H_2O/25	\	NR	\
9	**17a** $BF_3{\cdot}OEt_2$	DCM/-50	*R* only	85	**3**
10	**17a** $BF_3{\cdot}OEt_2$	DCM/-30	\	epoxide-opening side products	\
11	**17b** $BF_3{\cdot}OEt_2$	DCM/-50	*S* only	70	**3'**



2

$K_2OsO_4•2H_2O$ (1 mol%)
NMO (1.5 equiv)
THF-H_2O, r.t., 36 h

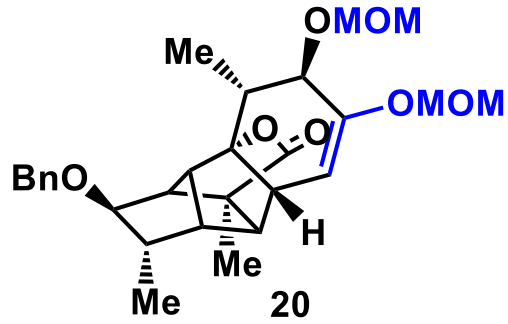
TEMPO (0.4 equiv)
KBr (0.4 equiv)
NaClO (2 equiv)
$NaHCO_3$ (5%)
DCM, 0 °C, 12 h
85% (4 g scale)



19

KHMDS, DIPEA
MOMBr, HMPA

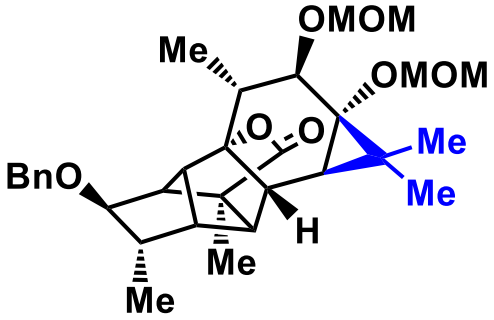
THF
-78 °C to -30 °C
60%



20

a. NaO^tBu (25 equiv)
$CHBr_3$ (30 equiv)
PE, 0 °C, 10 h

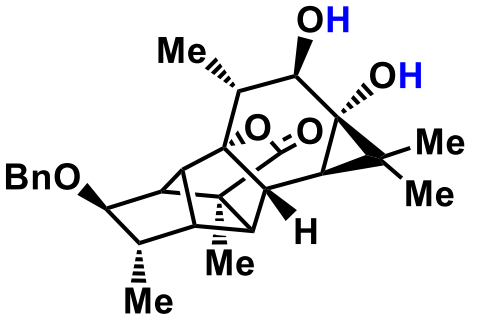
b. $LiCuMe_2$ (15 equiv)
HMPA, Et_2O, -20 °C, 8 h
MeI (40 equiv), r.t.
overnight
40% 2 steps



21 (>1.5 g produced)

3N HCl, THF, 45 °C, 16 h

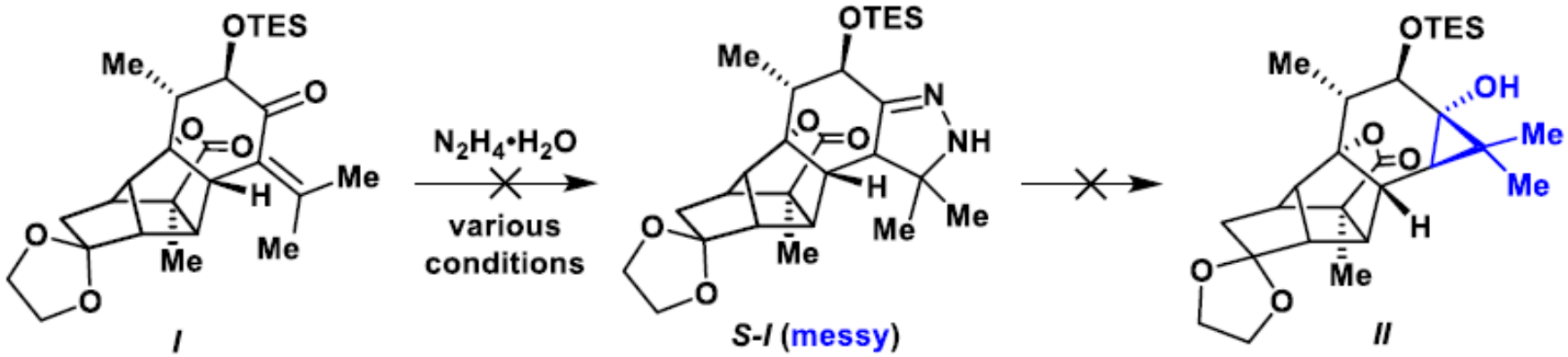
87%
(>600 mg scale)



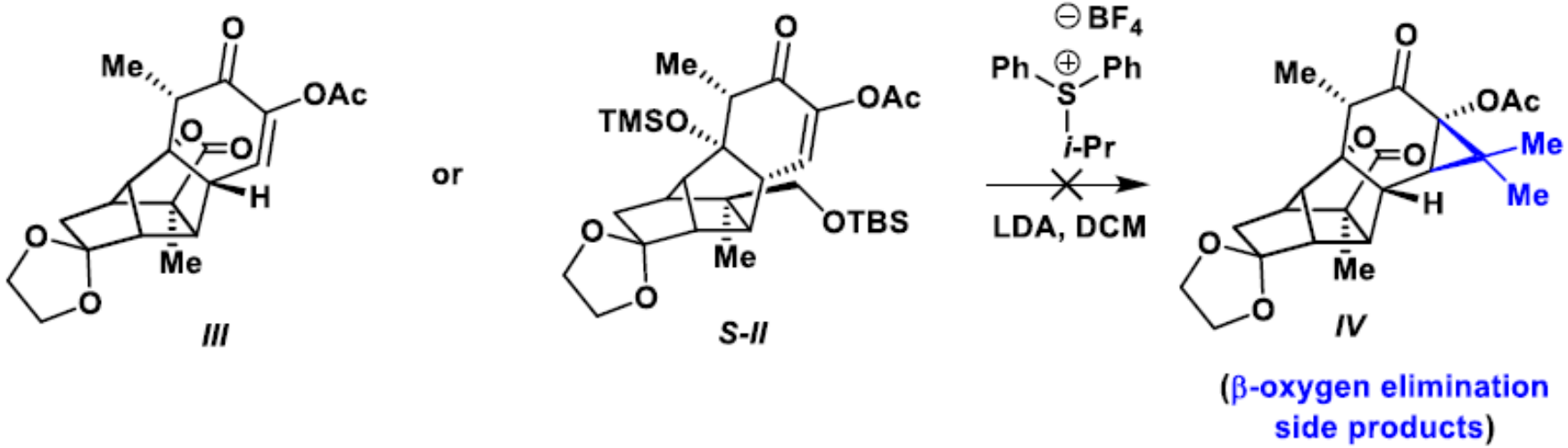
22

Scheme S4. Unsuccessful attempts to construct the desired cyclopropane ring.

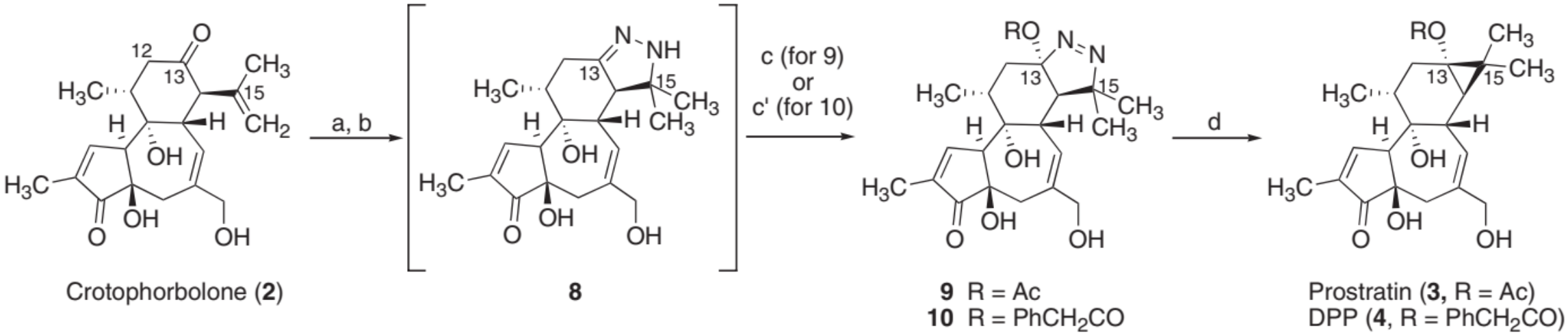
a) Photolysis of cyclic diazene (Wender)



b) Diphenylisopropylsulfonium ylide addition (Wender)



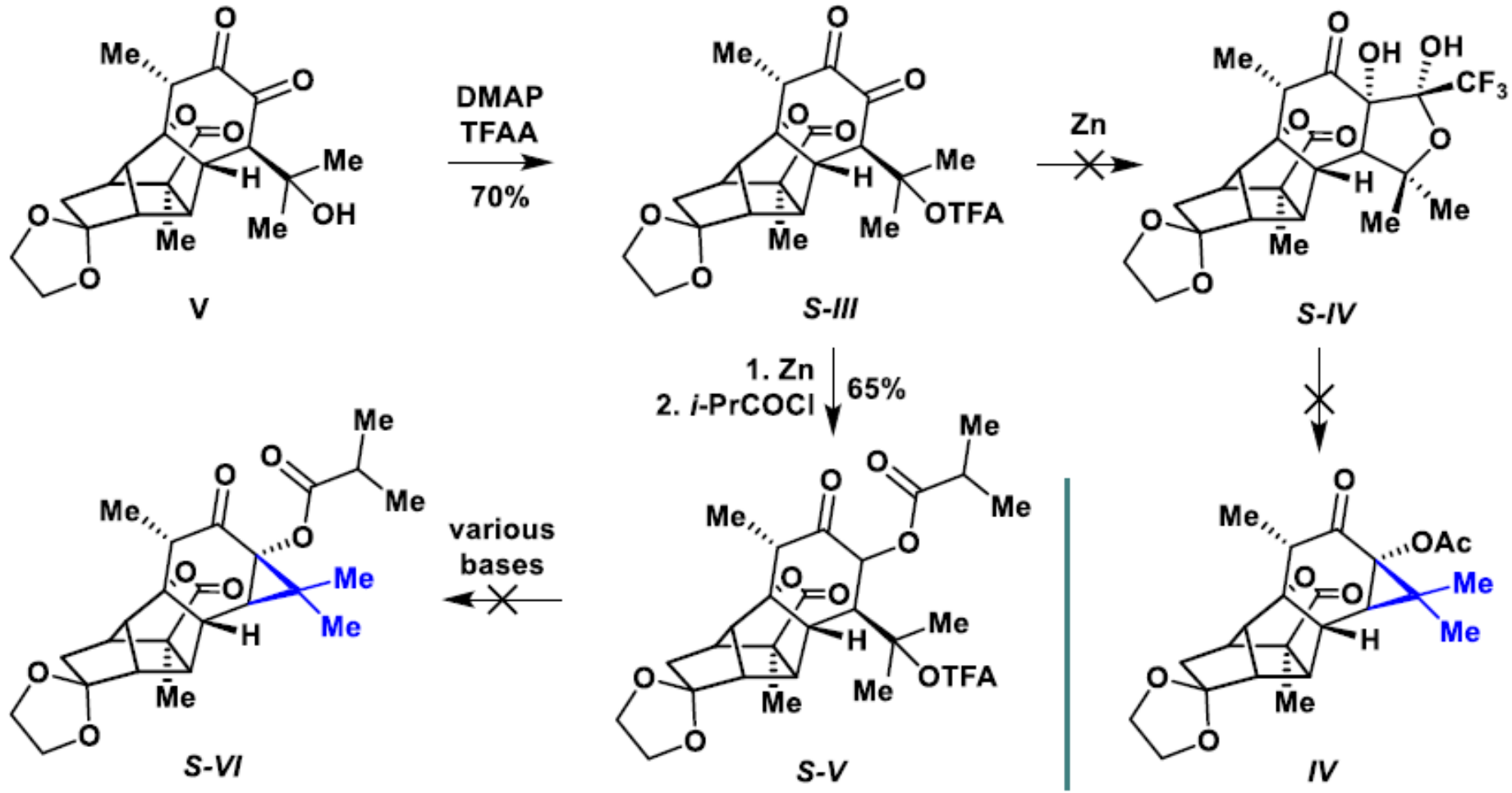
(β-oxygen elimination side products)

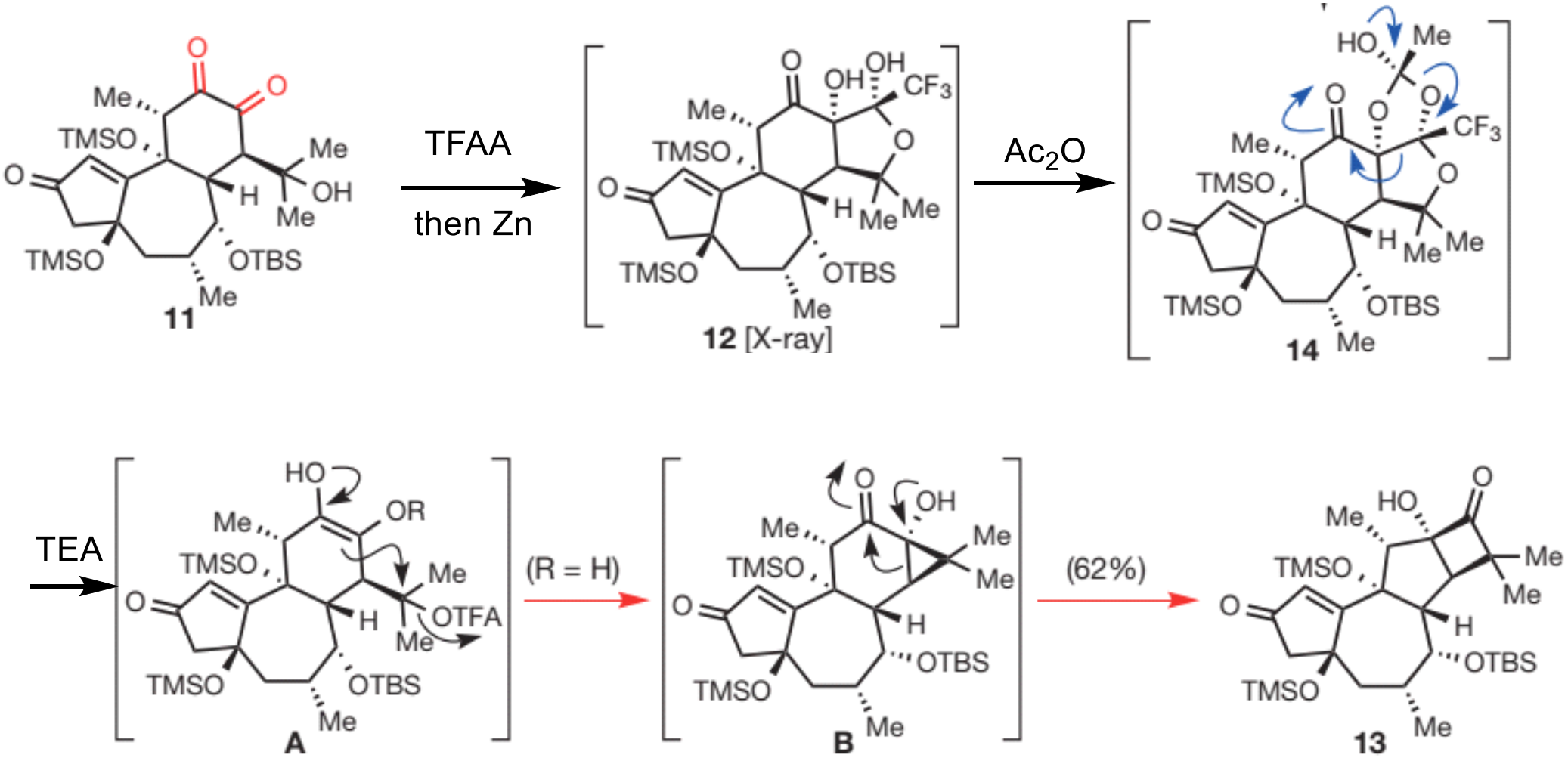


(a) $H_4N_2 \cdot H_2O$ (2 equiv.), AcOH (5 equiv.), MeOH, 25 °C, 45 min; (b) pyridine/DIPEA (9:1), 150 °C, 48 h; (c) $Pb(OAc)_4$ (1.1 equiv.), CH_2Cl_2, 0 °C, 30 min (43% of **9** from **2**); (c') $Pb(OAc)_4$ (1.2 equiv.), $PhCH_2COOH$ (50 equiv.) (premixed), CH_2Cl_2, 0 °C, 30 min. (36% of **10** from **2**); (d) $h\upsilon$ (300 nm), EtOAc/benzene (1:1) or MeOH, 25 °C (67–92% for **3**, 90% for **4**)

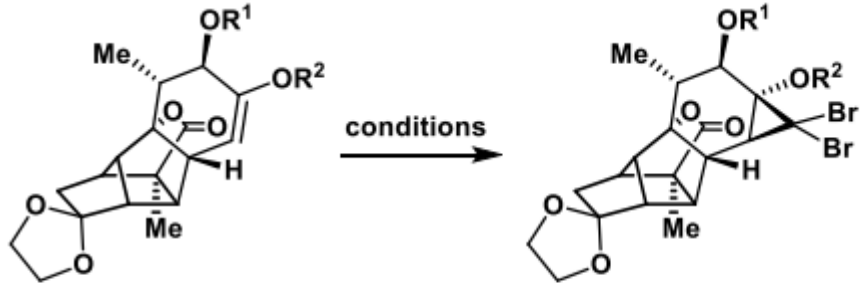
Science, **2008**, *320*, 649.

c) Cascade rearrangement (Baran)



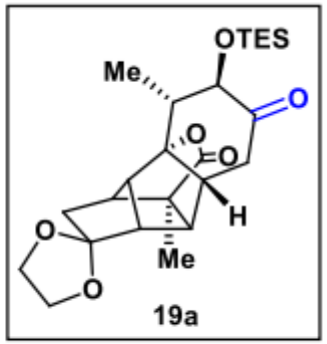


Nature, **2016**, *532*, 90.



G: (R^1 = TES, R^2 = TES)
G1: (R^1 = TES, R^2 = *i*-PrCO)
G2: (R^1 = TES, R^2 = MOM)

G3: (R^1 = TES, R^2 = TES)
G4: (R^1 = TES, R^2 = *i*-PrCO)
G5: (R^1 = TES, R^2 = MOM)



19a

Entry[a]	Substrate	Reagent	Solvent/Temp. (°C)	Yield (%)	Product
1	**G**	KO*t*-Bu $CHBr_3$	pentane/-30	NR	\
2	**G**	Br_2CMe_2 *n*-BuLi	pentane/-78	NR	\
3	**G**	Br_2CMe_2 *n*-BuLi	pentane/ -78 to 25	decomposed	\
4	**G1**	KO*t*-Bu $CHBr_3$	pentane/-30	\	**19a**
5	**G2**	Br_2CMe_2 *n*-BuLi	pentane/ -78 to 25	NR, slightly decomposed	\
6	**G2**	KO*t*-Bu $CHBr_3$	pentane/-30	20	**G5**
7	**G2**	KO*t*Bu $CHBr_3$	pentane/-40	low conversion	**G5**
8	**G2**	KO*t*-Bu $CHBr_3$	hexane/-30	74	**G5**

20a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
20: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
20b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

S2a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
S2: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
S2b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

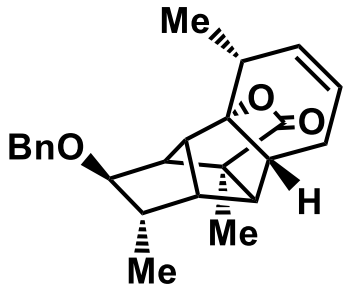
Entry[a]	Sub-strate	Reagent	Solvent/Temp. (°C)	Yield (%)	Conversion (%)	Product
1	**20a**	KO*t*-Bu $CHBr_3$	hexane/-30 to 25	NR	0	\
2	**20**	KO*t*-Bu $CHBr_3$	hexane/-30	20	50	**S2**
3	**20**	KO*t*-Bu $CHBr_3$	PE/-30	33	60	**S2**
4	**20**	KO*t*-Bu $CHBr_3$	CPME/-30	17	25	**S2**
5	**20**	KO*t*-Bu $CHBr_3$	CPME/0	trace	\	**S2**
6	**20**	KHMDS $CHBr_3$	PE/-30	decom-posed	\	\
7	**20**	NaOH TEBAC $CHBr_3$	DCM-H_2O/25	\	10, slow	**S2**

20a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
20: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
20b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

S2a: (R^1 = MOM, R^2 = TES, R^3 = TBS)
S2: (R^1 = MOM, R^2 = MOM, R^3 = Bn)
S2b: (R^1 = MOM, R^2 = MOM, R^3 = TBS)

8	**20**	NaOH TEBAC $CHBr_3$	DCM-H_2O/40	decom- posed	\	\
9	**20**	NaO*t*-Bu $CHBr_3$	PE/-30	NR	0	\
10	**20**	NaO*t*Bu $CHBr_3$	PE/-10	36	60	**S2**
11	**20**	NaO*t*-Bu $CHBr_3$	PE/0	50	80	**S2**
12	**20b**	KO*t*-Bu $CHBr_3$	PE/-30	48	100	**S2b**
13[b]	**20b**	NaO*t*-Bu $CHBr_3$	PE/0	61	90	**S2b**

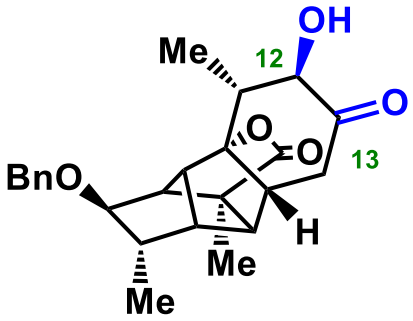
[a] Reactions performed on 0.05 mmol scale. [b] Although **20b** provided a slightly higher yield, however, TBS group was not compatible when removing MOM group. Therefore, we continued our total synthesis with **S2**; PE (petroleum ether). CPME (cyclopentyl methyl ether); TEBAC (benzyltriethylammonium chloride).



2

$K_2OsO_4•2H_2O$ (1 mol%)
NMO (1.5 equiv)
THF-H_2O, r.t., 36 h

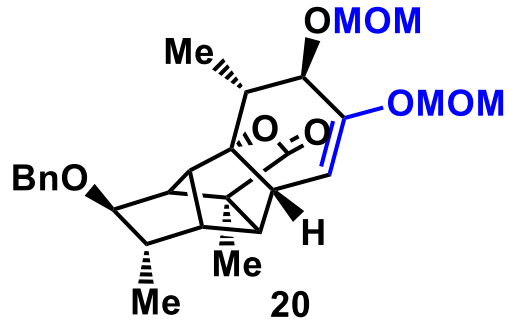
TEMPO (0.4 equiv)
KBr (0.4 equiv)
NaClO (2 equiv)
$NaHCO_3$ (5%)
DCM, 0 °C, 12 h
85% (4 g scale)



19

KHMDS, DIPEA
MOMBr, HMPA

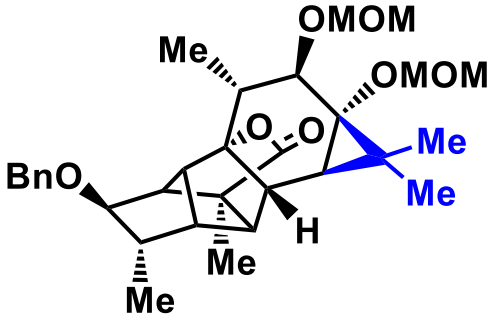
THF
-78 °C to -30 °C
60%



20

a. NaO*t*-Bu (25 equiv)
$CHBr_3$ (30 equiv)
PE, 0 °C, 10 h

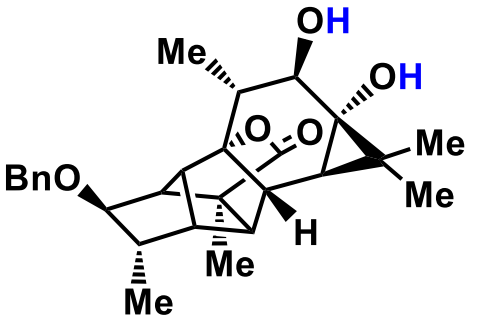
b. $LiCuMe_2$ (15 equiv)
HMPA, Et_2O, -20 °C, 8 h
MeI (40 equiv), r.t.
overnight
40% 2 steps



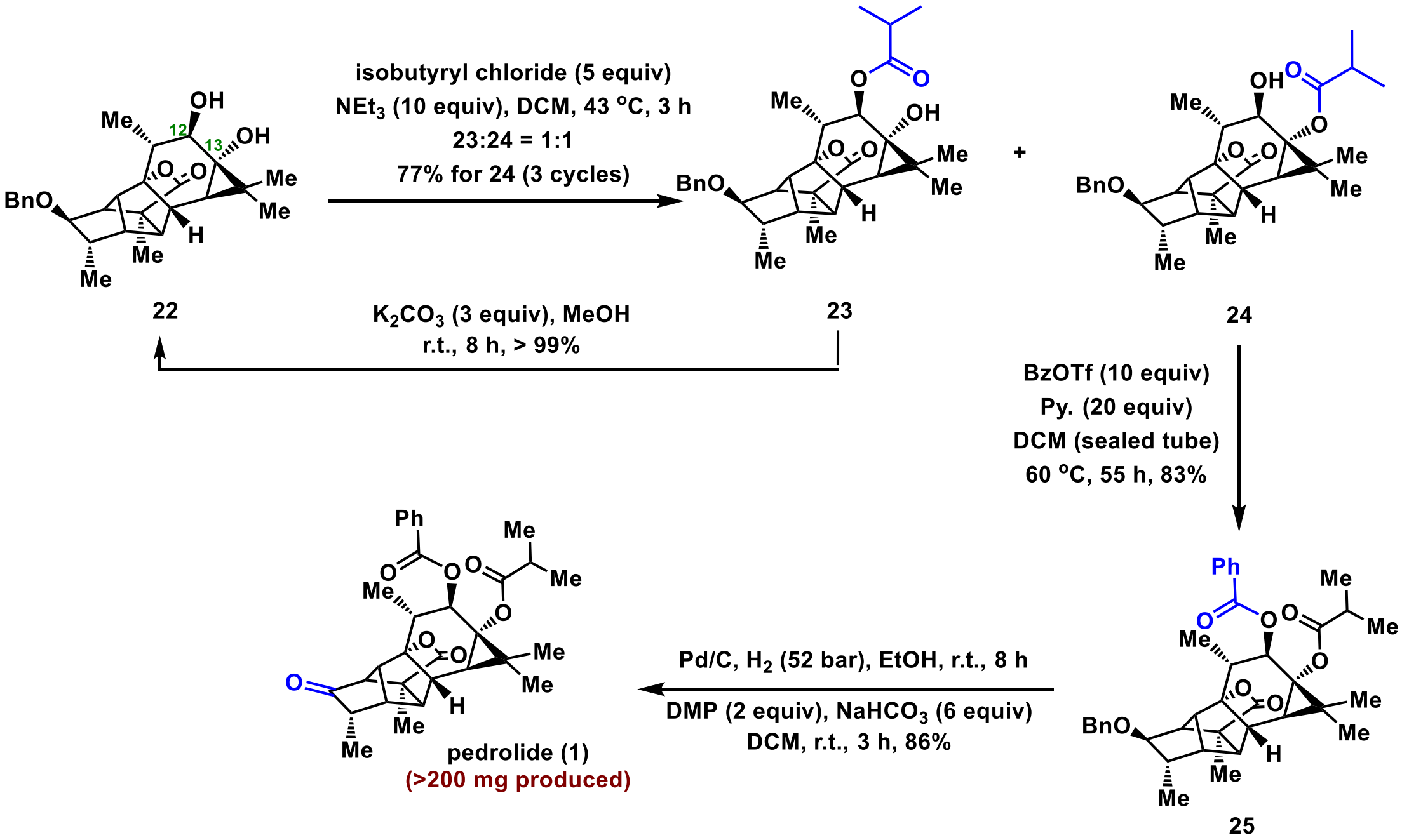
21 (>1.5 g produced)

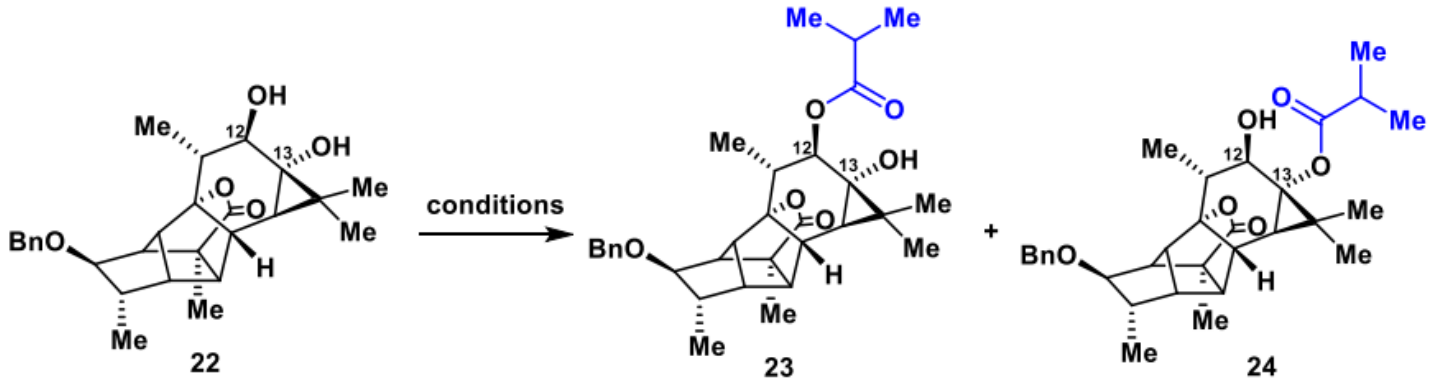
3N HCl, THF, 45 °C, 16 h

87%
(>600 mg scale)

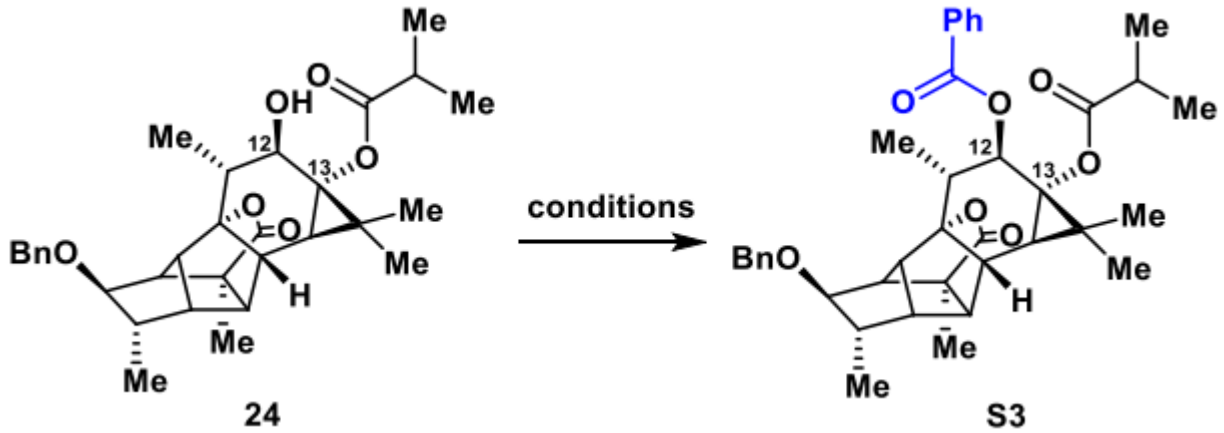


22

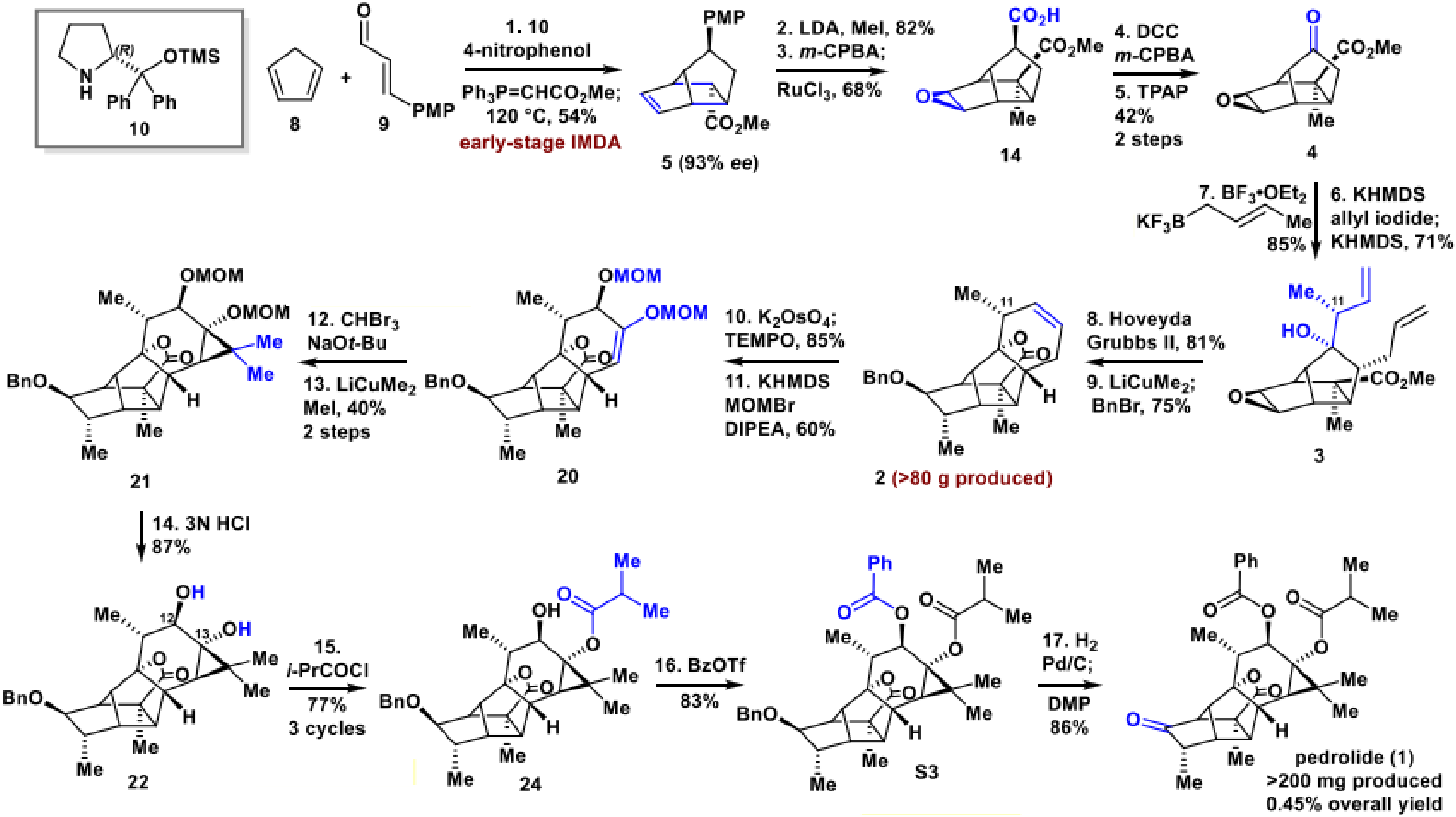

isobutyryl chloride (5 equiv)
NEt3 (10 equiv), DCM, 43 °C, 3 h
23:24 = 1:1
77% for 24 (3 cycles)
22
23
24
+
K2CO3 (3 equiv), MeOH
r.t., 8 h, > 99%
BzOTf (10 equiv)
Py. (20 equiv)
DCM (sealed tube)
60 °C, 55 h, 83%
25
Pd/C, H2 (52 bar), EtOH, r.t., 8 h
DMP (2 equiv), NaHCO3 (6 equiv)
DCM, r.t., 3 h, 86%
pedrolide (1)
(>200 mg produced)



Entry[a]	Reagent	Solvent/Temp. (°C)	23/24	Yield (%)
1	EDCI, DMAP *i*-PrCOOH	DCM/40	**23** only	50 (incomplete reaction)
2	NaH, *i*-PrCOCl	THF/0 to 25	**23** only	20
3	DMAP *i*-PrCOCl	DCM/40	**23** only	90
4	NEt_3, *i*-PrCOCl	DCM/40	1:1	92 (**23** + **24**)
5	NEt_3, *i*-PrCOCl	DCM/50	2:1	90 (**23** + **24**)
6	NEt_3, *i*-PrCOCl	THF/50	\	decomposed
7	NEt_3, DMAP *i*-PrCOCl	DCM/40	1.5:1	90 (**23** + **24**)
8	NEt_3 $(i\text{-PrCO})_2O$	DCM/40	\	NR
9	NaHMDS, NEt_3 *i*-PrCOCl	THF/-20	**23** only	trace
10	NaHMDS *i*-PrCOCl	THF/-20	\	NR



Entry[a]	Reagent	Solvent/Temp. (°C)	Yield (%)
1[b]	Py, DMAP, Bz_2O	DCM/40	NR
2	Py, DMAP, Bz_2O	DMF/80	NR
3	Py, DMAP, BzCl	DCM/40	NR
4	Py, DMAP, BzCl	DMF/40	NR
5	Py, DMAP, BzCl	DMF/80	NR
6	EDCI, DMAP, BzOH	DCM/40	NR
7	EDCI, DMAP, BzOH	DMF/40	NR
8	NEt_3, DMAP, BzCl	DCM/40	NR
9	NEt_3, DMAP, Bz_2O	DCM/40	NR
10	2,4,6-trichlorobenzoyl chloride NEt_3, DMAP, BzOH	PhMe/80	20
11	Py, BzOTf	DCM/0 to 25	NR
12	Py, BzOTf	DCM/40	NR
13	Py, BzOTf	DCM/60	83


10
8
9
1. 10
4-nitrophenol
$Ph_3P=CHCO_2Me$;
120 °C, 54%
early-stage IMDA
5 (93% ee)
2. LDA, MeI, 82%
3. m-CPBA;
$RuCl_3$, 68%
14
4. DCC
m-CPBA
5. TPAP
42%
2 steps
4
7. BF_3•OEt_2
85%
6. KHMDS
allyl iodide;
KHMDS, 71%
3
8. Hoveyda
Grubbs II, 81%
9. $LiCuMe_2$;
BnBr, 75%
2 (>80 g produced)
10. K_2OsO_4;
TEMPO, 85%
11. KHMDS
MOMBr
DIPEA, 60%
20
12. $CHBr_3$
NaOt-Bu
13. $LiCuMe_2$
MeI, 40%
2 steps
21
14. 3N HCl
87%
22
15.
i-PrCOCl
77%
3 cycles
24
16. BzOTf
83%
S3
17. H_2
Pd/C;
DMP
86%
pedrolide (1)
>200 mg produced
0.45% overall yield