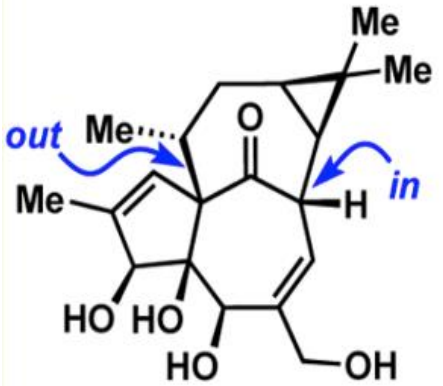
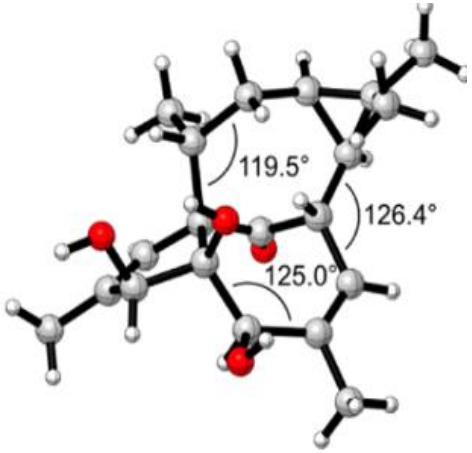
Total Synthsis of (±)-Ingenol

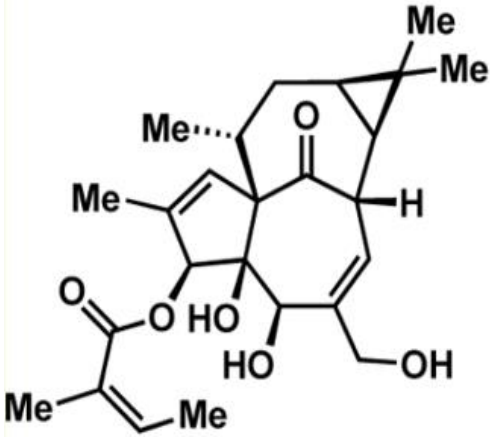


ingenol (**1**)

- **unique *in/out* stereochemistry**
- **3 prior syntheses: 37-46 steps**



20-deoxyingenol (**2**)
(X-ray)



ingenol mebutate (**3**)
(Picato®)

- **FDA approved (2012) first-in-class topical treatment for actinic keratosis**
- **in clinical trials for basal cell carcinoma**
- **1.1 mg/kg isolated yield from *E. peplus***
- **3 step semi-synthesis from Ingenol**

时间：2024.4.25
汇报人：王振洋

常见特殊试剂的淬灭及处理

药明康德 WuXi PharmaTech

LAH

Lithium Aluminum Hydride

(x g):

1. 用适量乙醚稀释后冷却到0 ^{0}C；
2. 慢慢加入x mL 水；
3. 加入x mL 15 % 氢氧化钠水溶液；
4. 再加入3x mL 水；
5. 升温到室温搅拌15分钟；
6. 加入一些无水$MgSO_4$；
7. 搅拌15分钟后过滤除盐。

DIBAL-H

Diisobutyl Aluminum Hydride

(x mmol):

1. 用适量乙醚稀释后冷却到0 ^{0}C；
2. 慢慢加入0.04x mL 水；
3. 加入0.04x mL 15% 氢氧化钠水溶液；
4. 加入0.1x mL 水；
5. 升温到室温搅拌15分钟；
6. 加入一些无水$MgSO_4$；
7. 搅拌15分钟后过滤除盐。

易燃易爆或剧毒品的后处理

药明康德 WuXi PharmaTech

《常见危险废物的销毁方法》

种类	处理方法
酰氯、三氯氧磷、氯化亚砜	在搅拌下，加到大量冰水中，再用碱中和
硫酸二甲酯	在搅拌下，滴加到稀NaOH或氨水中，中和
有机锂化物	溶于THF中，慢慢加入过量一倍mol的EtOH，再加水稀释，最后加稀HCl至溶液变清
氰化物	调pH > 9，加入饱和NaClO溶液 (1 mol 约需0.4 L) 过夜，用亚硝酸盐试纸证实NaClO已过量
叠氮物	调pH > 9，按1：50以上的浓度配成稀的水溶液，搅拌下慢慢加入NaClO淬灭
过氧化物	在酸性水溶液中，用Fe^{2+}、亚硫酸盐或二硫化物还原至淀粉KI试纸呈阴性，中和
碱金属氢化物、钠屑	悬浮在干燥四氢呋喃中，搅拌下慢慢加乙醇或异丙醇至不再放出氢气、澄清为止

常见特殊试剂的淬灭及处理

药明康德 WuXi PharmaTech

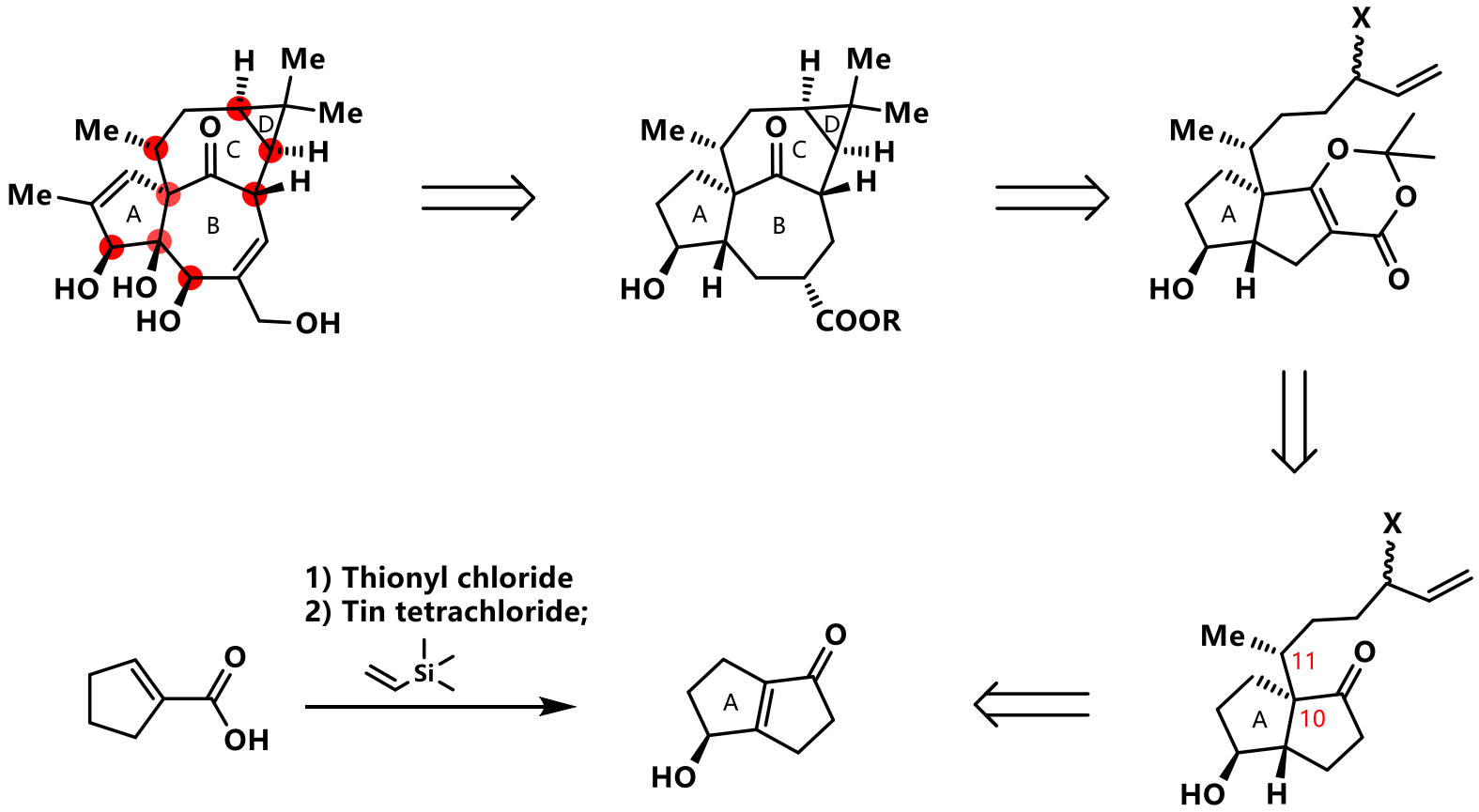
种类	处理方法 *
Boron Compounds	加入MeOH，生成了$(MeO)_3B$，旋蒸除去 (含硼化合物)
PCC/PDC	通过硅藻土、硅酸镁载体等过滤除去 (吡啶和CrO3/重铬酸吡啶)
Jones **Reagent**	加入异丙醇直至反应体系颜色从橙色或红色变成绿色 （琼斯试剂)
Copper Salts	用饱和NH_4Cl水溶液来淬灭反应，再在室温下搅拌一段时间至溶液成深蓝色，分掉水相 （铜盐)
R_3Sn-X Byproducts	可以通过KF与硅藻土的混合物过滤，也可以通过硅胶短柱，以反应溶剂（加~2-5%的Et_3N）为洗脱剂来除去
Metal Salts	许多过渡态金属可以与硫化物生成沉淀除去。通常可以用Na_2S水溶液来洗涤（金属盐)

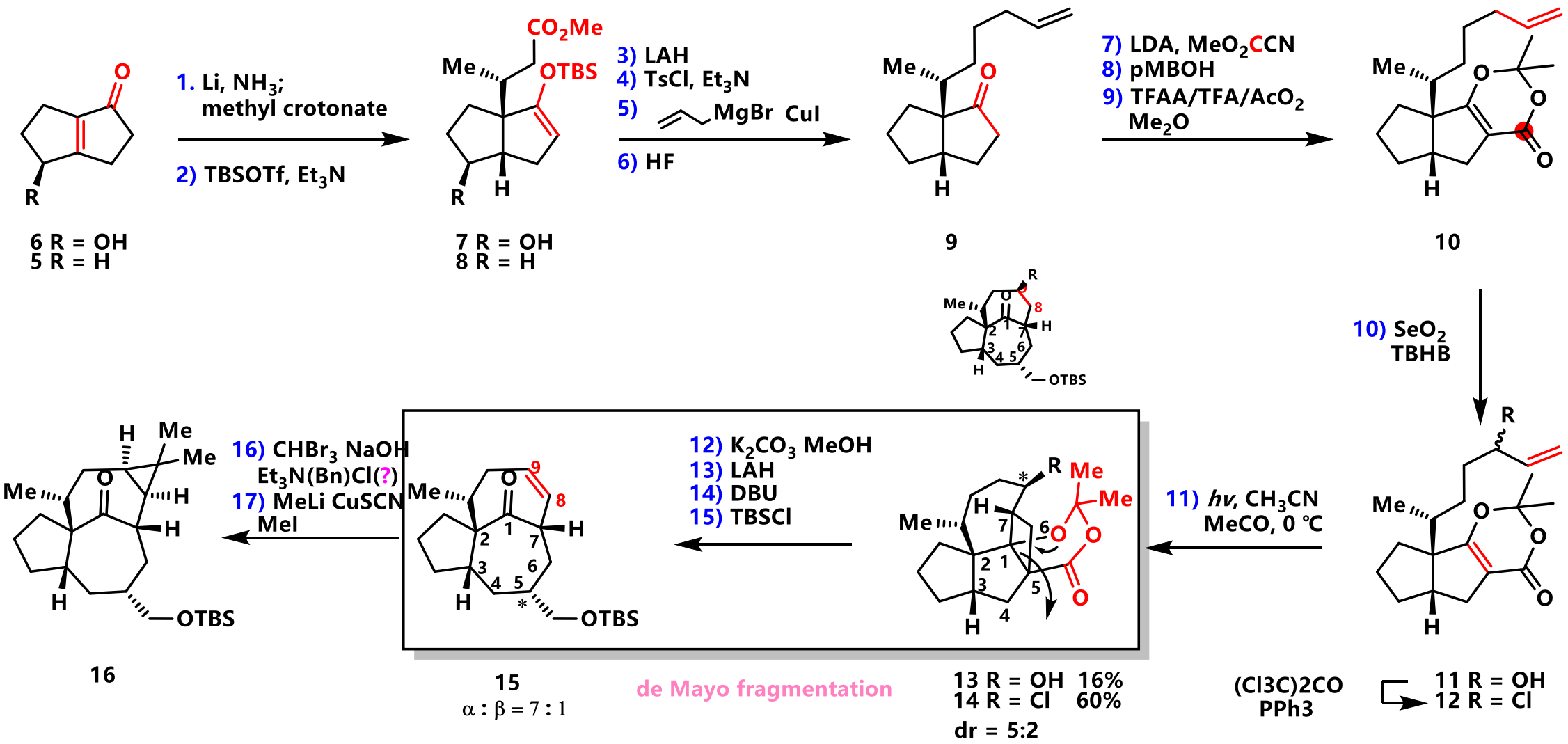
* From Not Voodoo Website

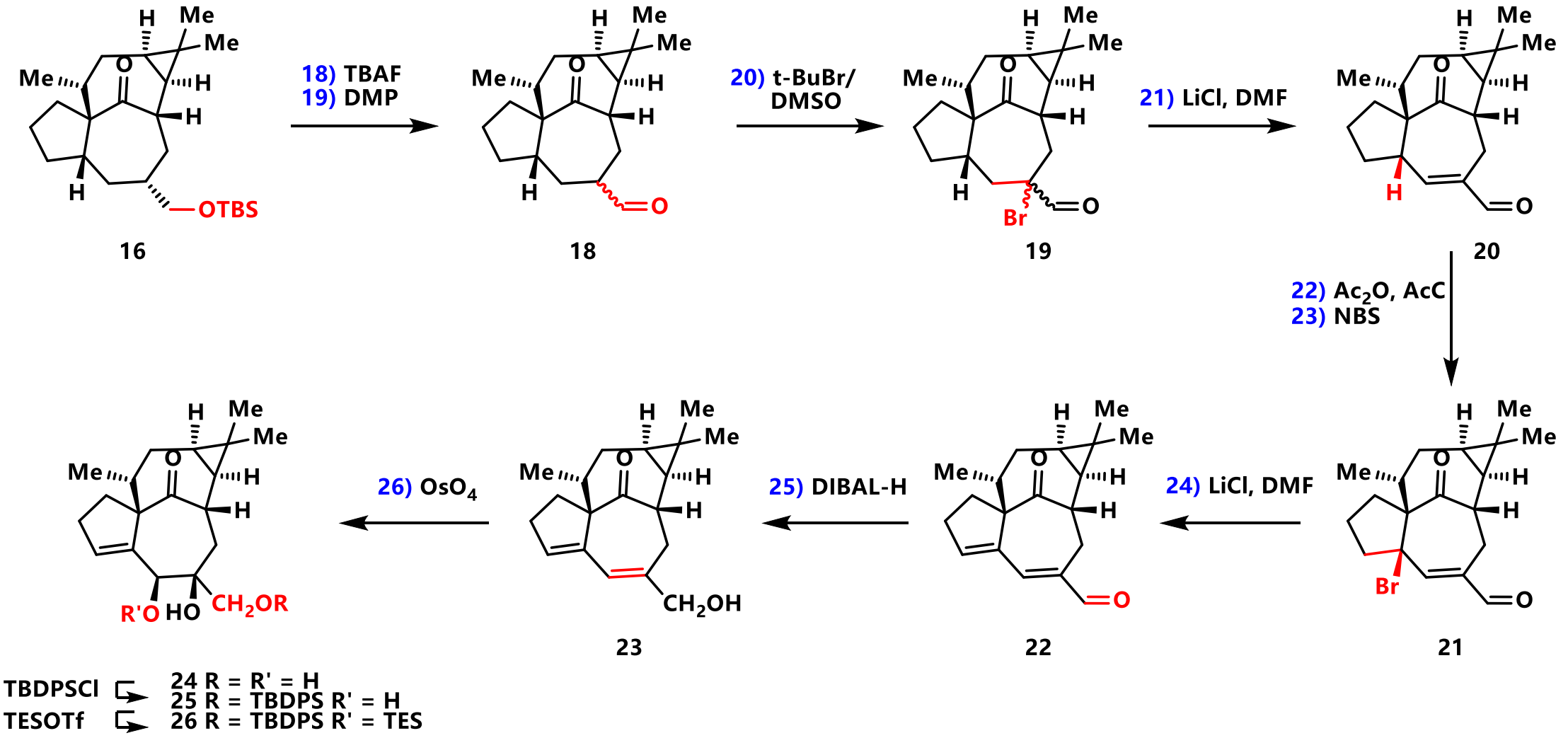
J. Org. Chem. 1989, 54, 13, 3140–3157
Chem. Commun. , 2010, 46, 6335。DOI: 10.1039/c0cc01328e

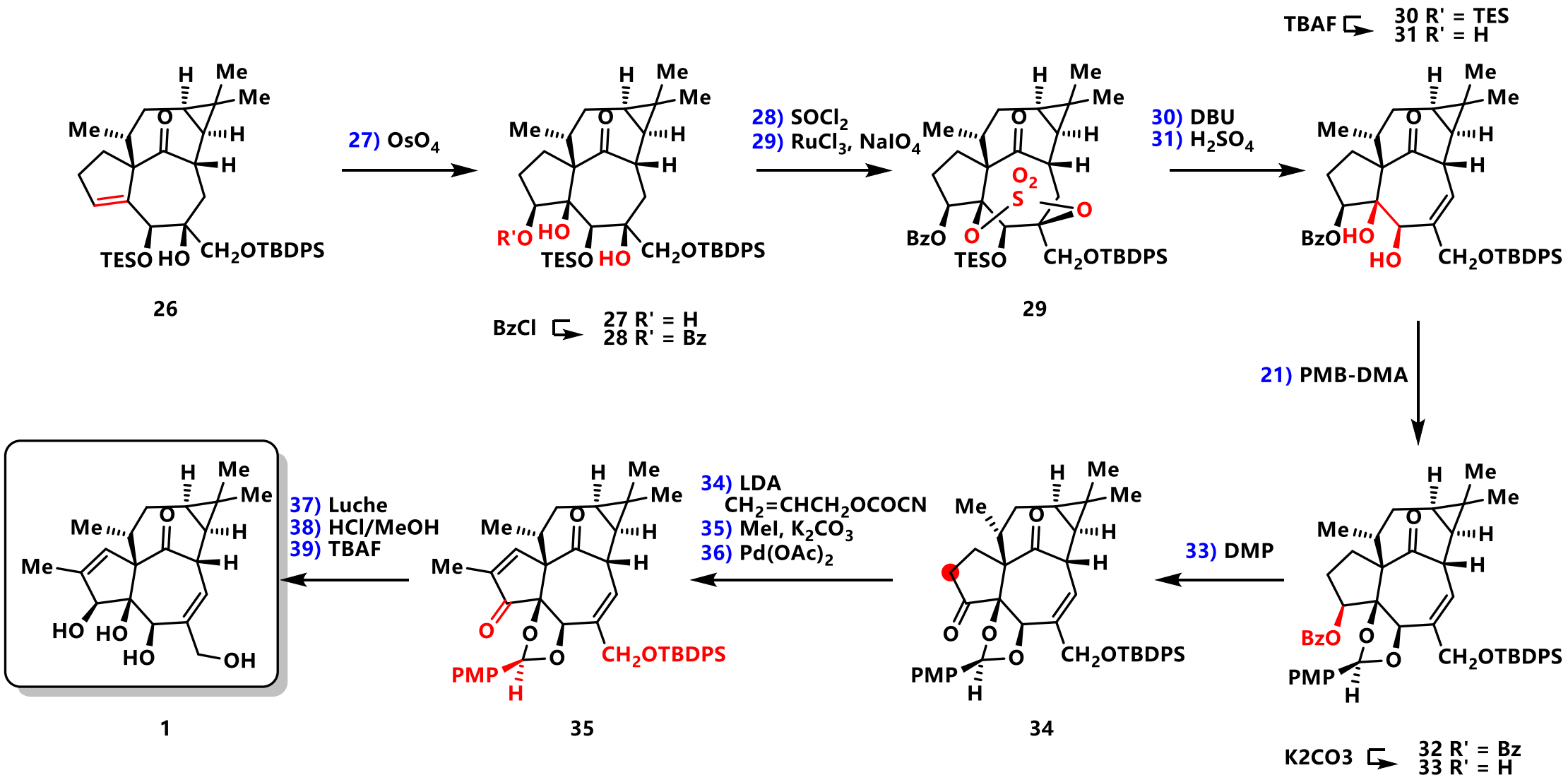
♦**Winkler课题组的工作**（J. Am. Che*m. Soc.,* **2002**, *124*, 9726–9728.）

♦**The First Total Synthsis of (±)-Ingenol 【43 steps from 6】**



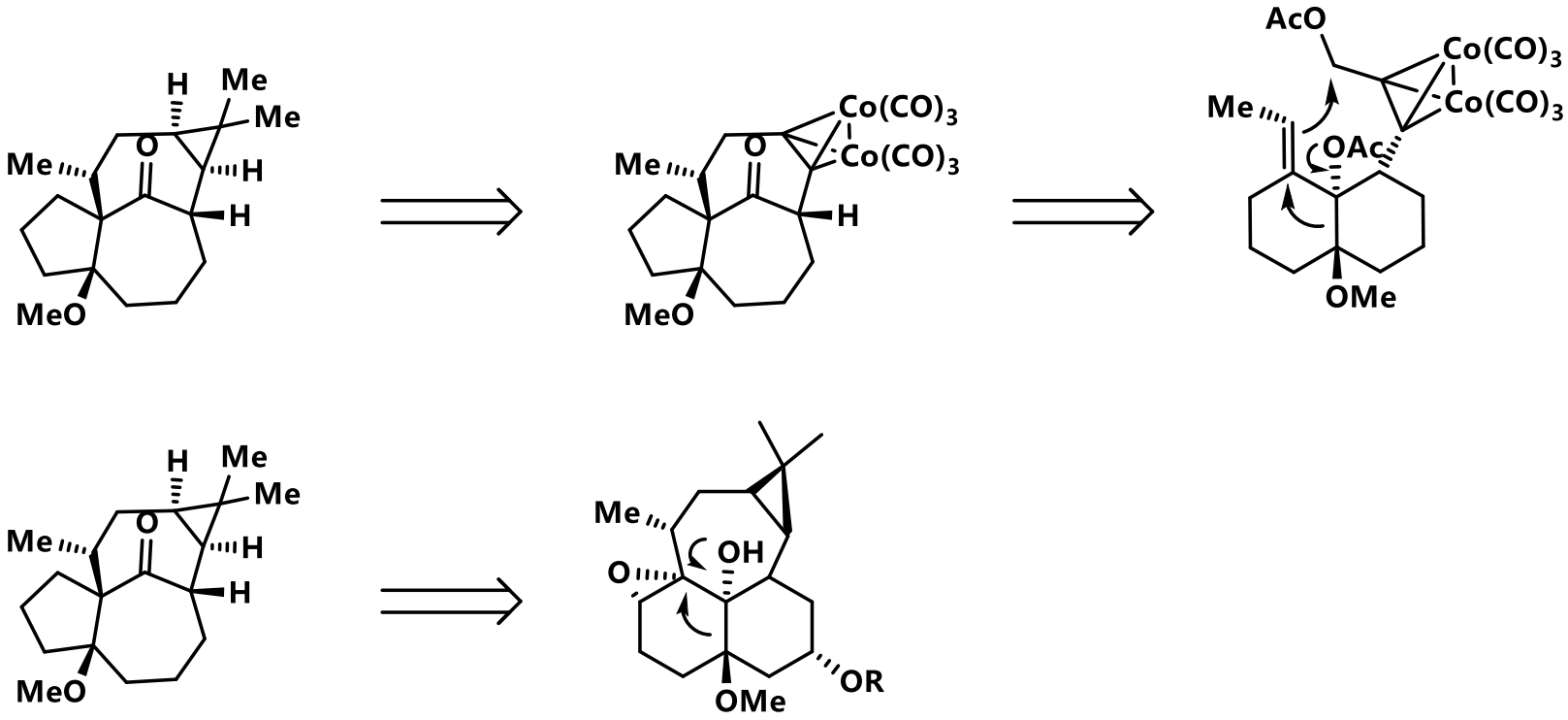

1. Li, NH3;
methyl crotonate
2) TBSOTf, Et3N
3) LAH
4) TsCl, Et3N
5) MgBr CuI
6) HF
7) LDA, MeO2CCN
8) pMBOH
9) TFAA/TFA/AcO2
Me2O
10) SeO2
TBHB
11) hv, CH3CN
MeCO, 0 ℃
12) K2CO3 MeOH
13) LAH
14) DBU
15) TBSCl
16) CHBr3 NaOH
Et3N(Bn)Cl(?)
17) MeLi CuSCN
MeI
6 R = OH
5 R = H
7 R = OH
8 R = H
9
10
11 R = OH
12 R = Cl
(Cl3C)2CO
PPh3
13 R = OH 16%
14 R = Cl 60%
dr = 5:2
de Mayo fragmentation
15
α : β = 7 : 1
16

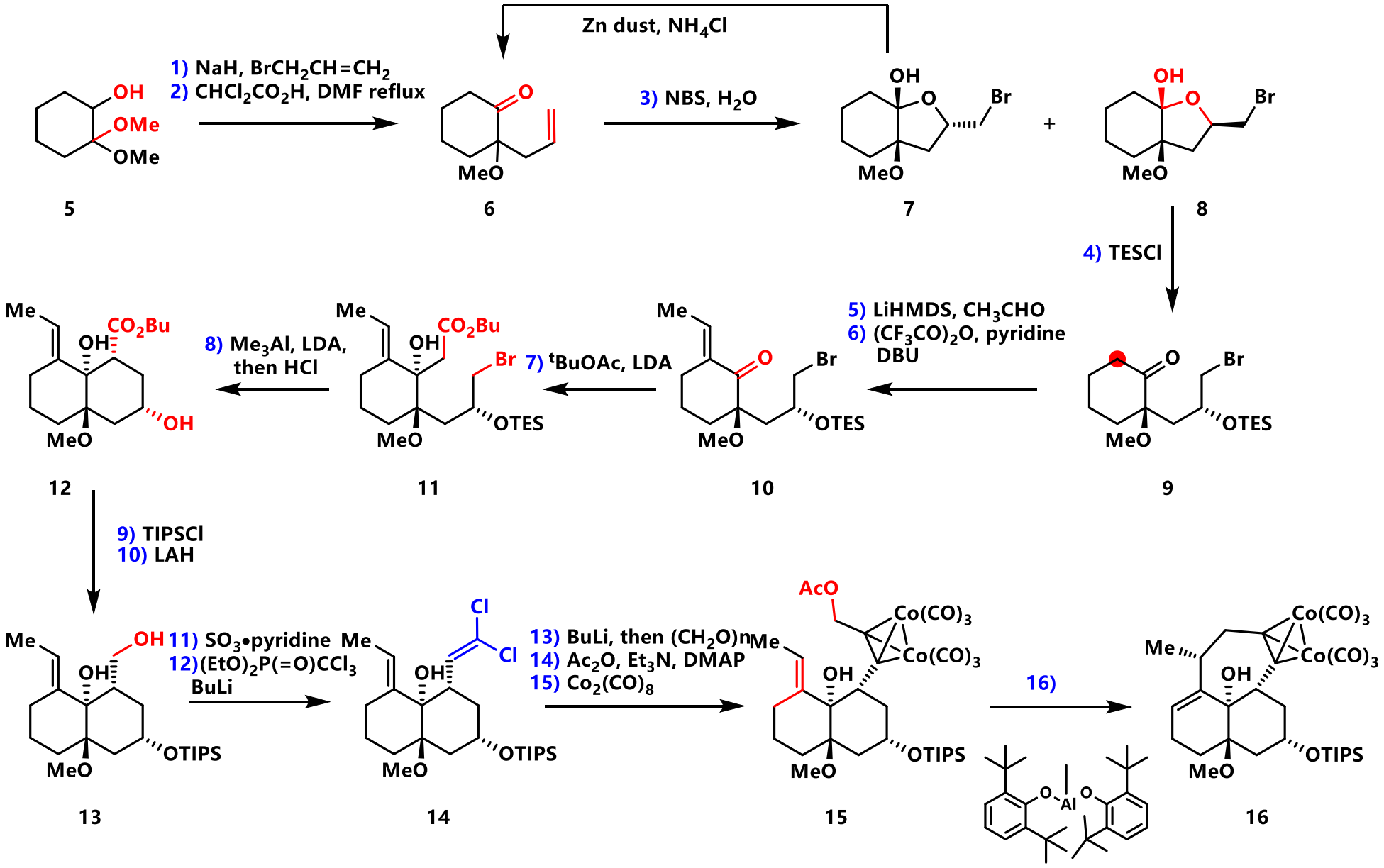

18) TBAF
19) DMP
20) t-BuBr/
DMSO
21) LiCl, DMF
22) Ac2O, AcC
23) NBS
24) LiCl, DMF
25) DIBAL-H
26) OsO4
16
18
19
20
21
22
23
TBDPSCl
TESOTf
24 R = R' = H
25 R = TBDPS R' = H
26 R = TBDPS R' = TES

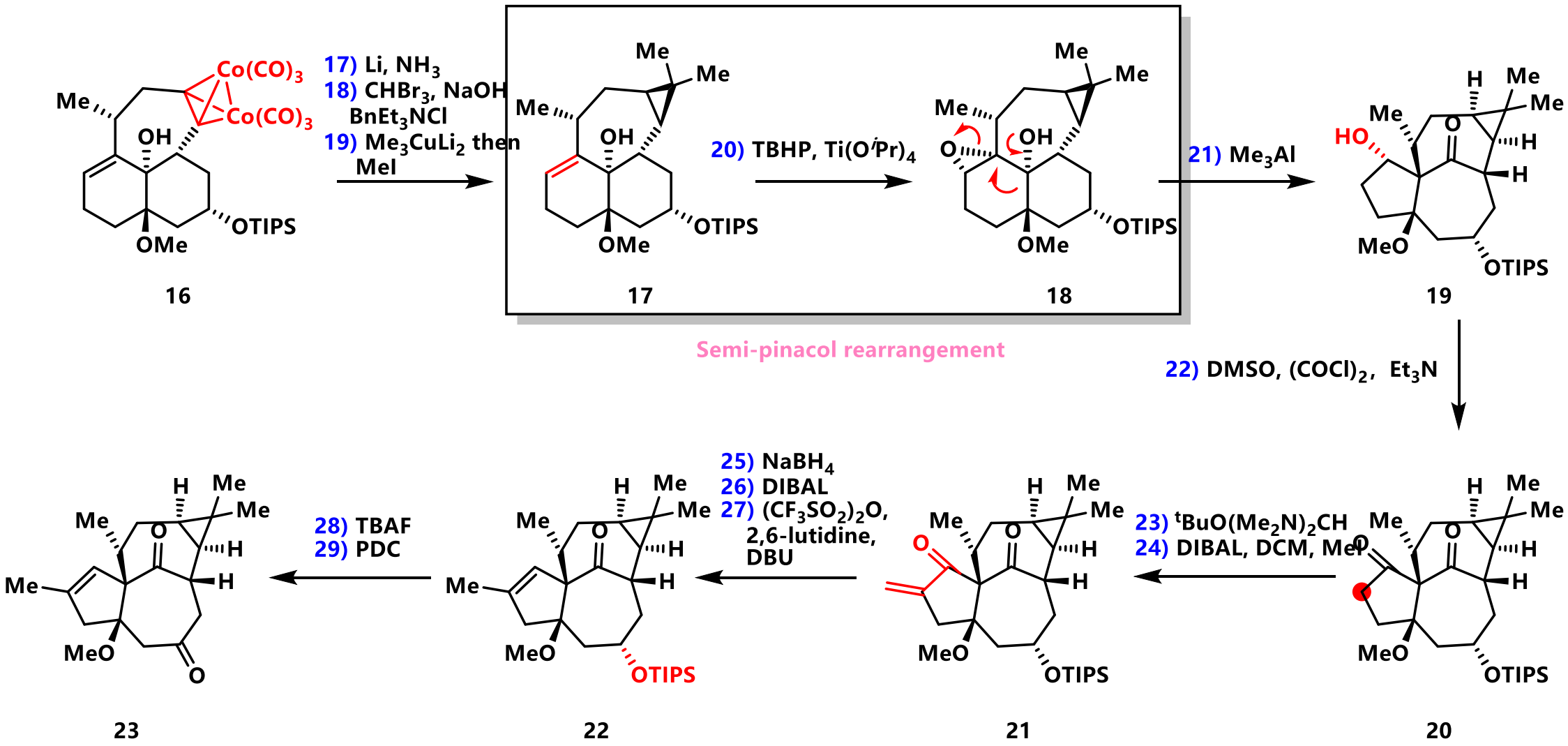

TBAF
30 R' = TES
31 R' = H
27) OsO4
28) SOCl2
29) RuCl3, NaIO4
30) DBU
31) H2SO4
BzCl
27 R' = H
28 R' = Bz
21) PMB-DMA
K2CO3
32 R' = Bz
33 R' = H
33) DMP
34) LDA
CH2=CHCH2OCOCN
35) MeI, K2CO3
36) Pd(OAc)2
37) Luche
38) HCl/MeOH
39) TBAF
26
29
34
35
1

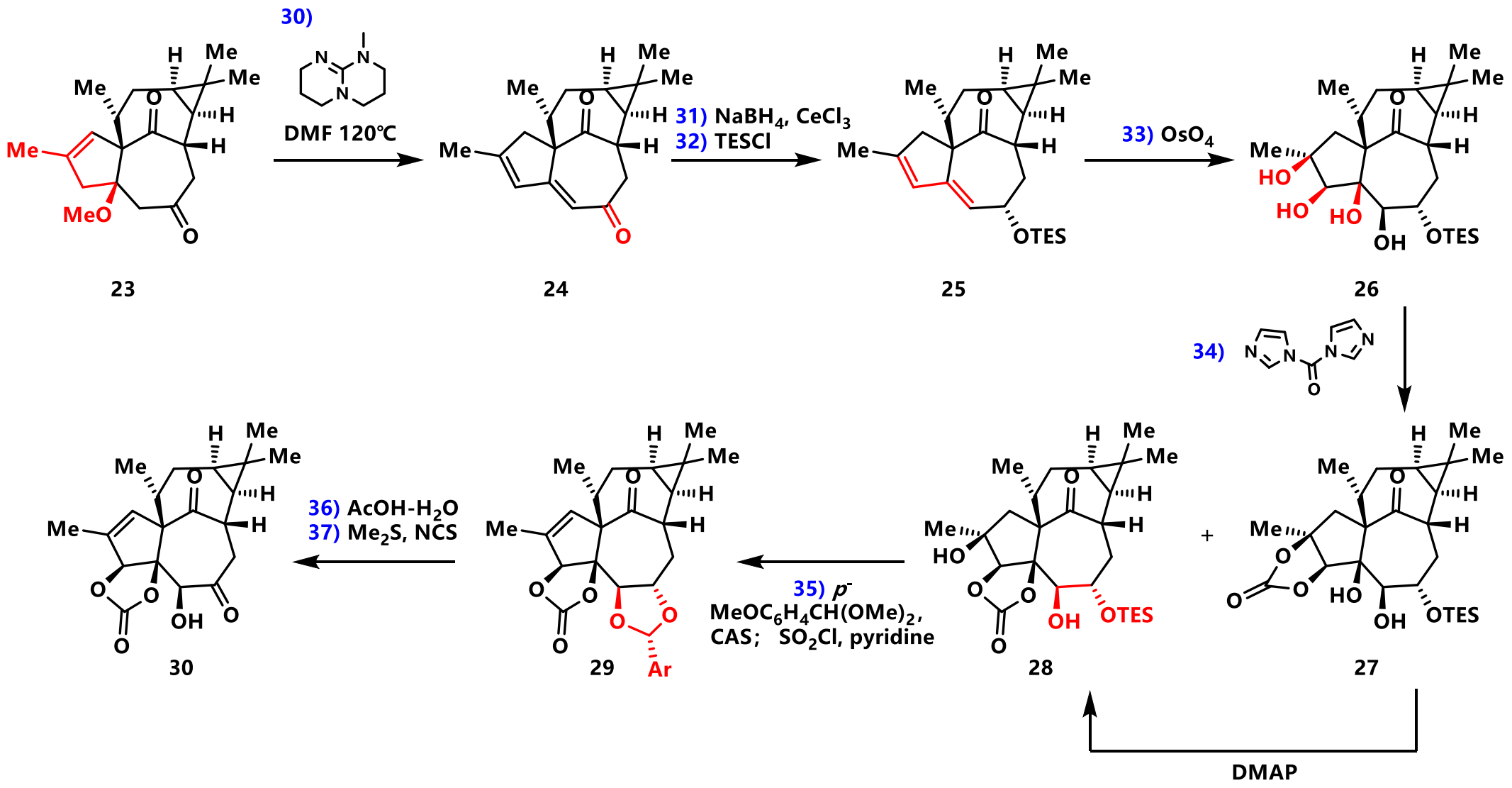
♦Kuwajima.课题组的工作（J. Am. *Chem. Soc.*, **2003**, *125*, 1498–1500）

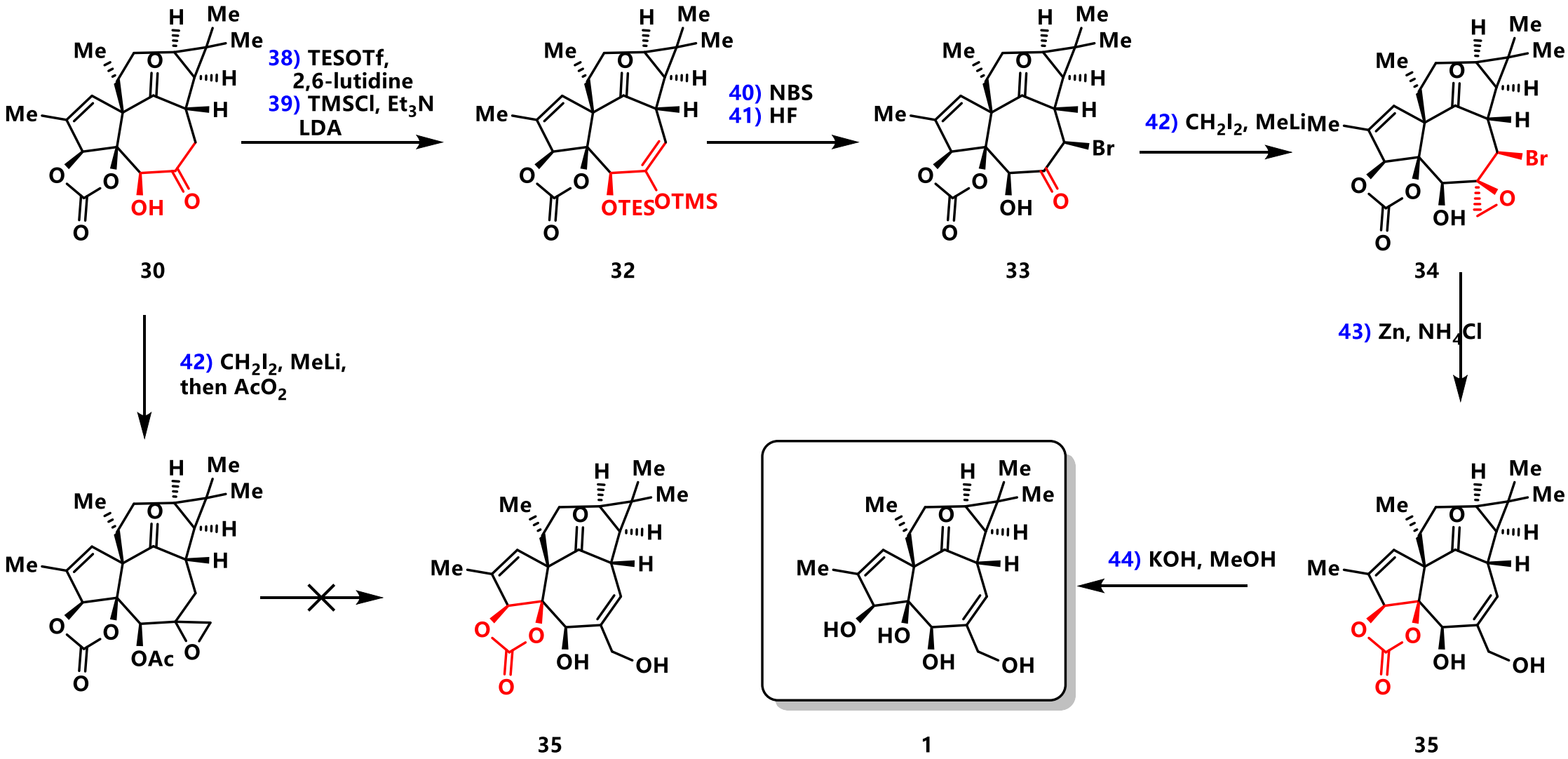
♦**Total Synthsis of Ingenol 【45 steps】**




Zn dust, NH4Cl
1) NaH, BrCH2CH=CH2
2) CHCl2CO2H, DMF reflux
3) NBS, H2O
4) TESCl
5) LiHMDS, CH3CHO
6) (CF3CO)2O, pyridine
DBU
7) tBuOAc, LDA
8) Me3Al, LDA,
then HCl
9) TIPSCl
10) LAH
11) SO3•pyridine
12) (EtO)2P(=O)CCl3
BuLi
13) BuLi, then (CH2O)n
14) Ac2O, Et3N, DMAP
15) Co2(CO)8
16)
5
6
7
8
9
10
11
12
13
14
15
16

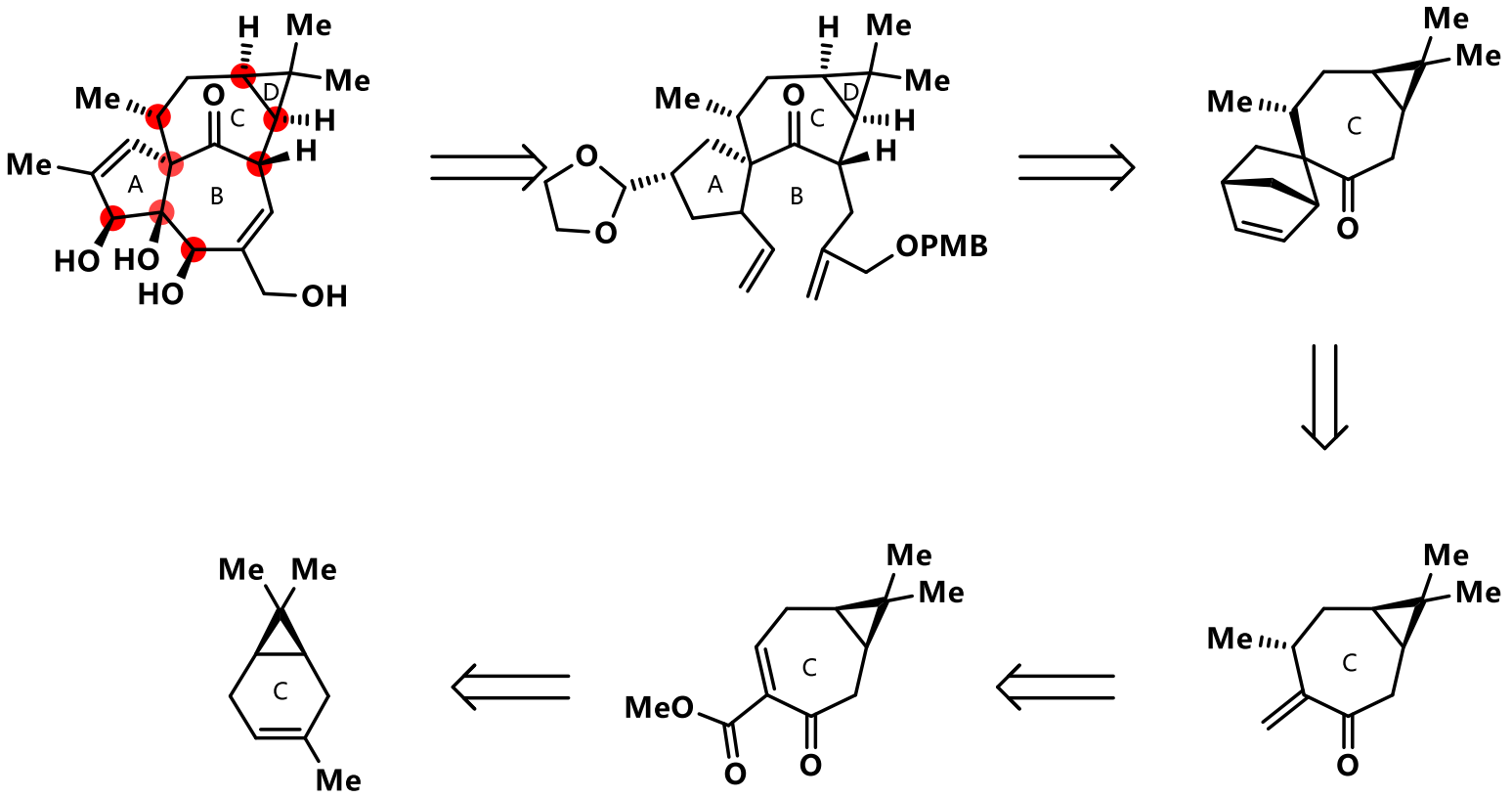

Co(CO)3
Co(CO)3
Me
OH
OTIPS
OMe
16
17) Li, NH3
18) CHBr3, NaOH
BnEt3NCl
19) Me3CuLi2 then
MeI
Me
Me
Me
OH
OTIPS
OMe
17
20) TBHP, Ti(OiPr)4
Me
Me
Me
O
OH
OTIPS
OMe
18
21) Me3Al
H
Me
Me
HO
O
H
H
MeO
OTIPS
19
Semi-pinacol rearrangement
22) DMSO, (COCl)2, Et3N
23) tBuO(Me2N)2CH
24) DIBAL, DCM, MeI
O
20
25) NaBH4
26) DIBAL
27) (CF3SO2)2O,
2,6-lutidine,
DBU
21
28) TBAF
29) PDC
OTIPS
22
O
23

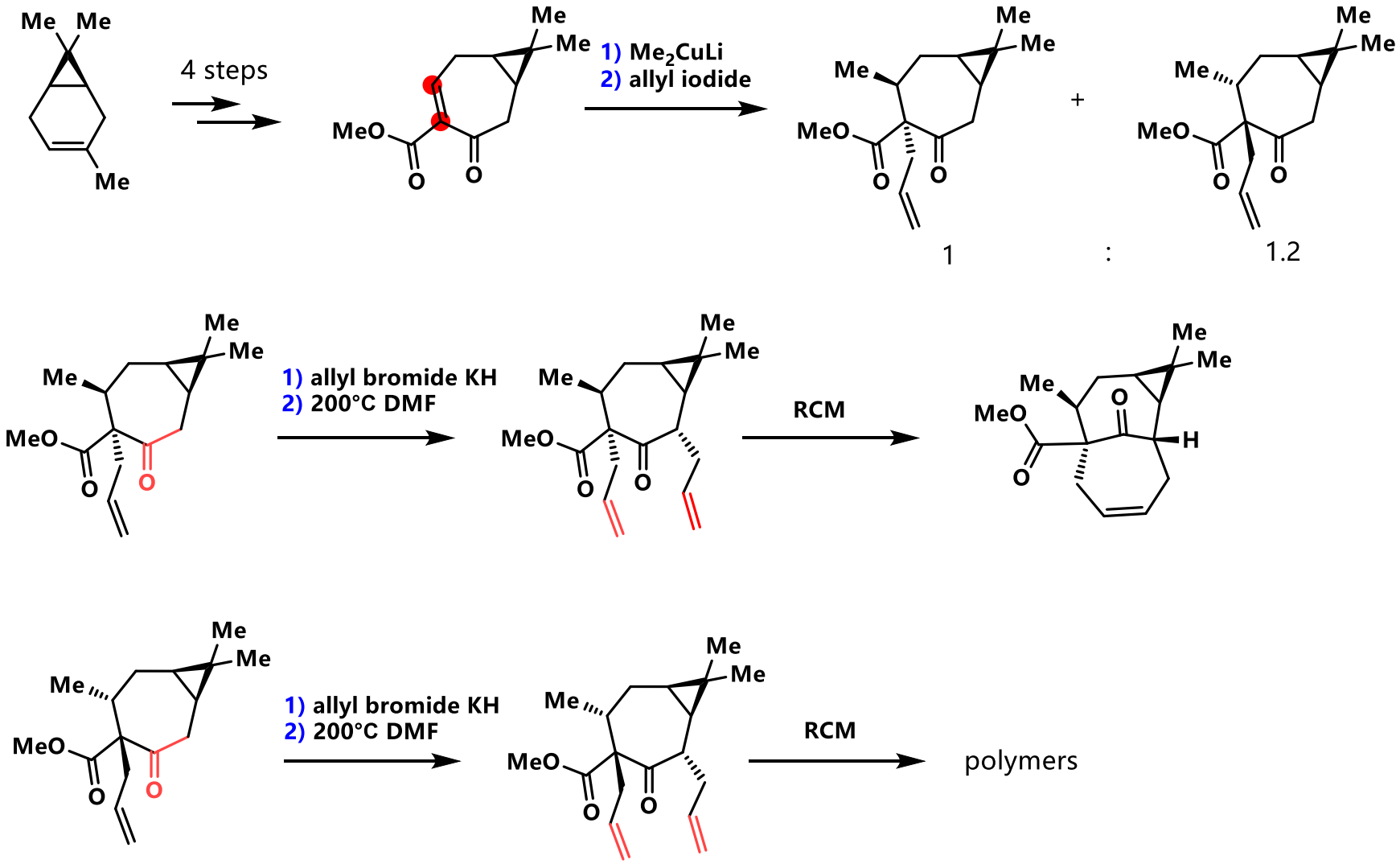

30)
DMF 120℃
31) NaBH4, CeCl3
32) TESCl
33) OsO4
34)
35) p-
MeOC6H4CH(OMe)2,
CAS; SO2Cl, pyridine
36) AcOH-H2O
37) Me2S, NCS
DMAP
23
24
25
26
27
28
29
30

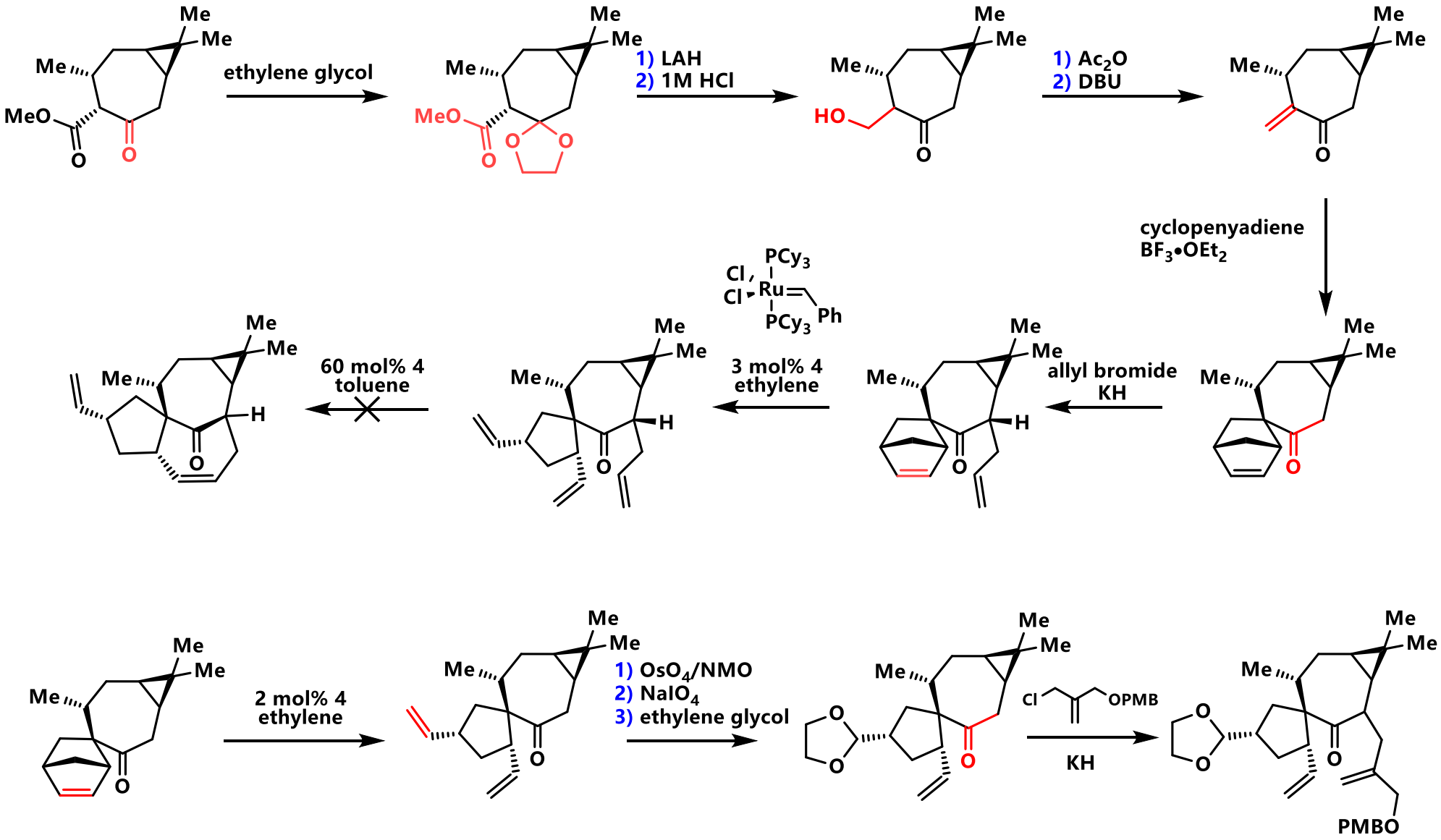

38) TESOTf,
2,6-lutidine
39) TMSCl, Et3N
LDA
40) NBS
41) HF
42) CH2I2, MeLi
43) Zn, NH4Cl
42) CH2I2, MeLi,
then AcO2
44) KOH, MeOH
30
32
33
34
35
1
35

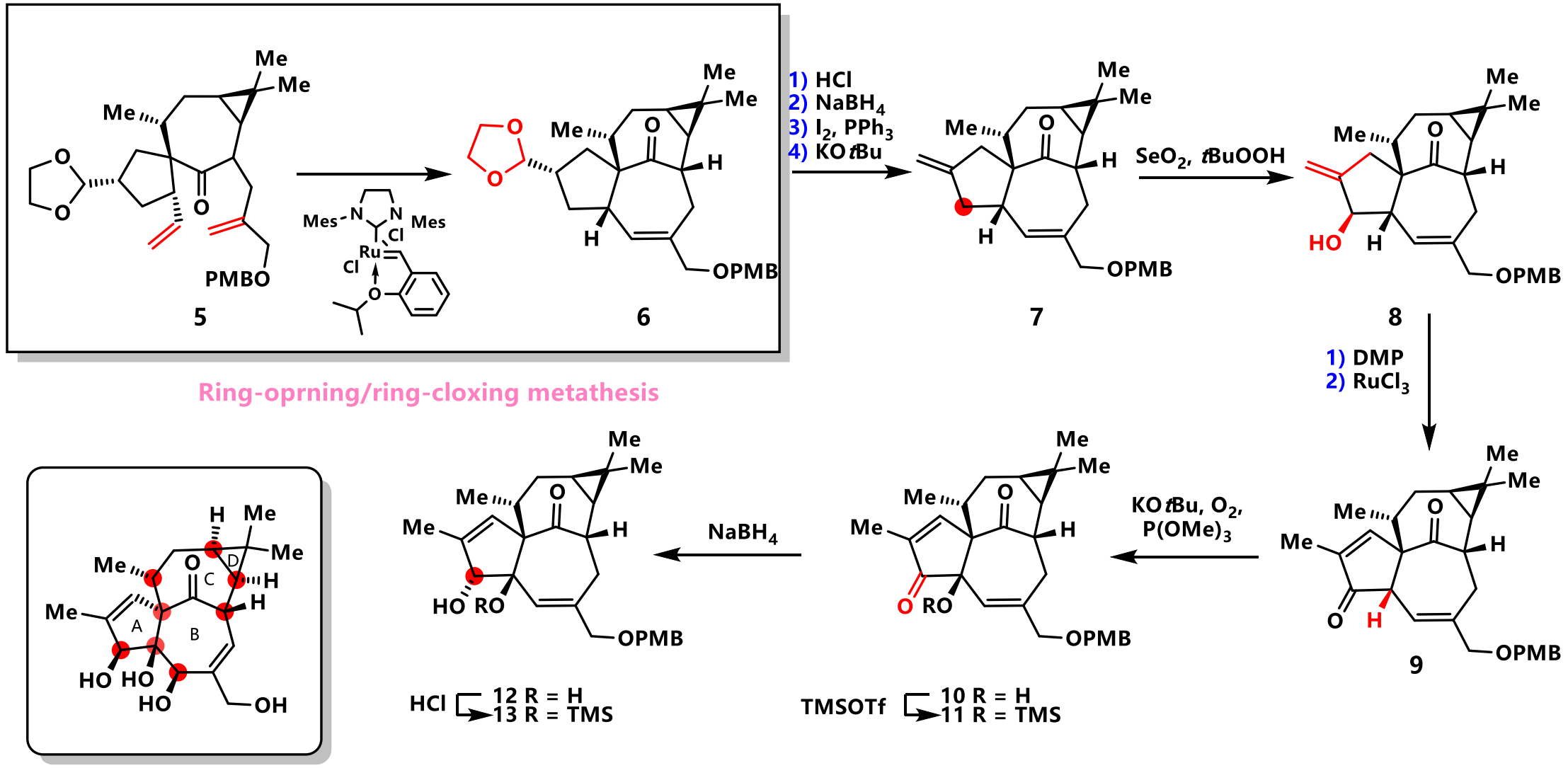
♦**John L. Wood 课题组的工作**（J. Am. *Chem. Soc.*, **2004**, *126*, 16300–16301）

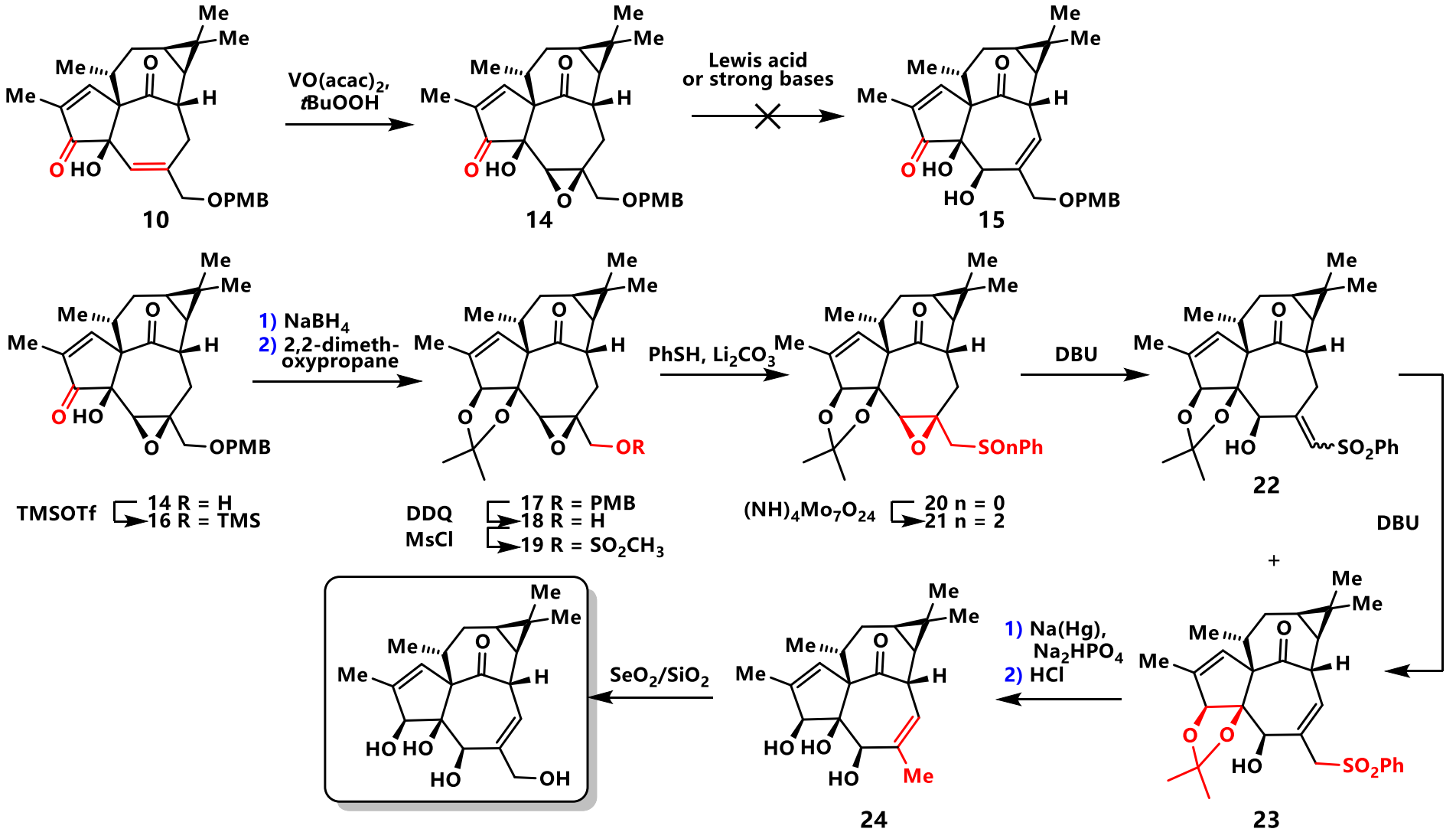
♦**Total Synthsis of Ingenol 【32 steps from 2】**



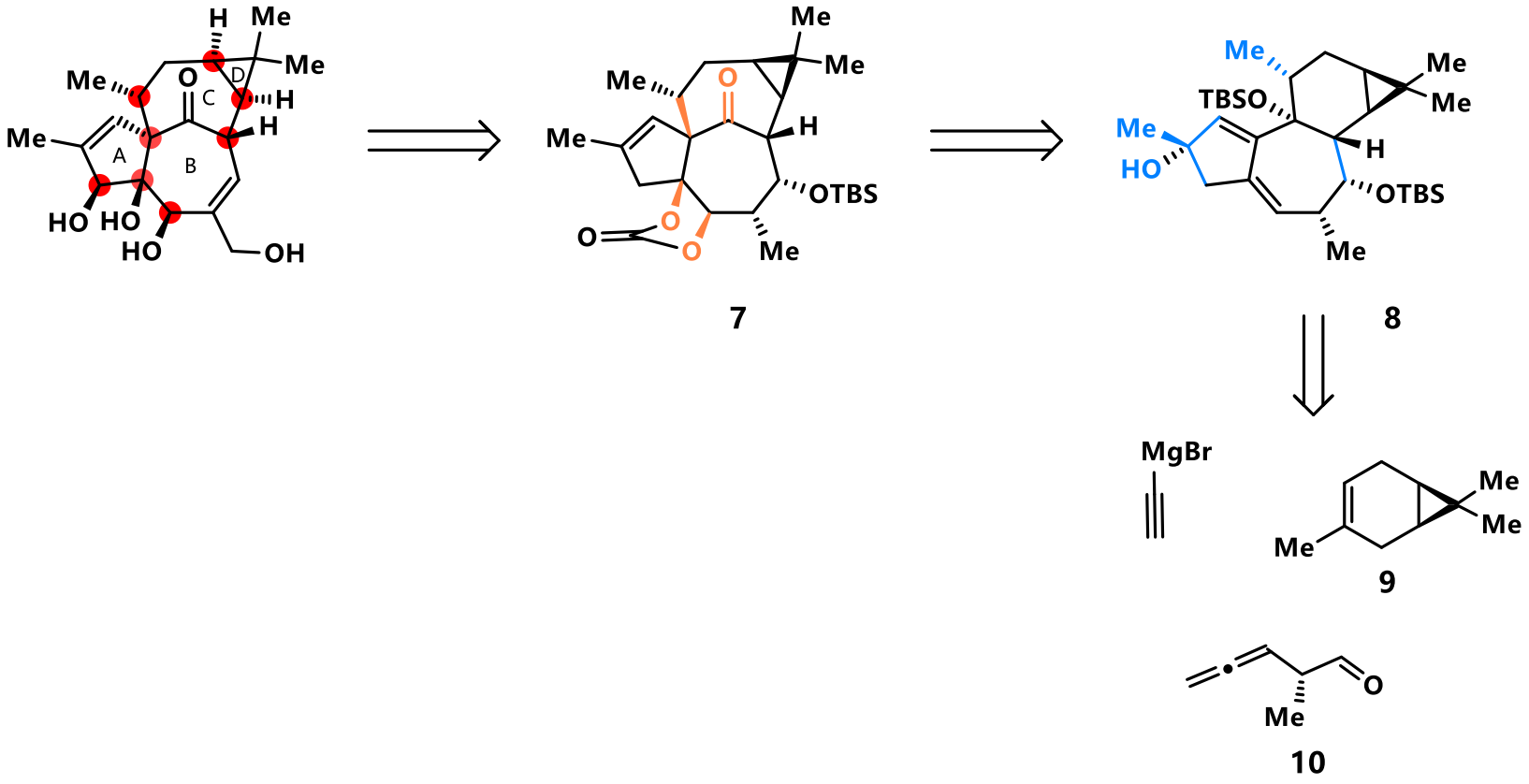

Me
Me
Me
4 steps
MeO
O
O
1) Me2CuLi
2) allyl iodide
+
1 : 1.2
1) allyl bromide KH
2) 200°C DMF
RCM
H
1) allyl bromide KH
2) 200°C DMF
RCM
polymers


ethylene glycol
1) LAH
2) 1M HCl
1) Ac_2O
2) DBU
cyclopenyadiene
$BF_3•OEt_2$
allyl bromide
KH
3 mol% 4
ethylene
60 mol% 4
toluene
2 mol% 4
ethylene
1) OsO_4/NMO
2) $NaIO_4$
3) ethylene glycol
KH
OPMB
PMBO

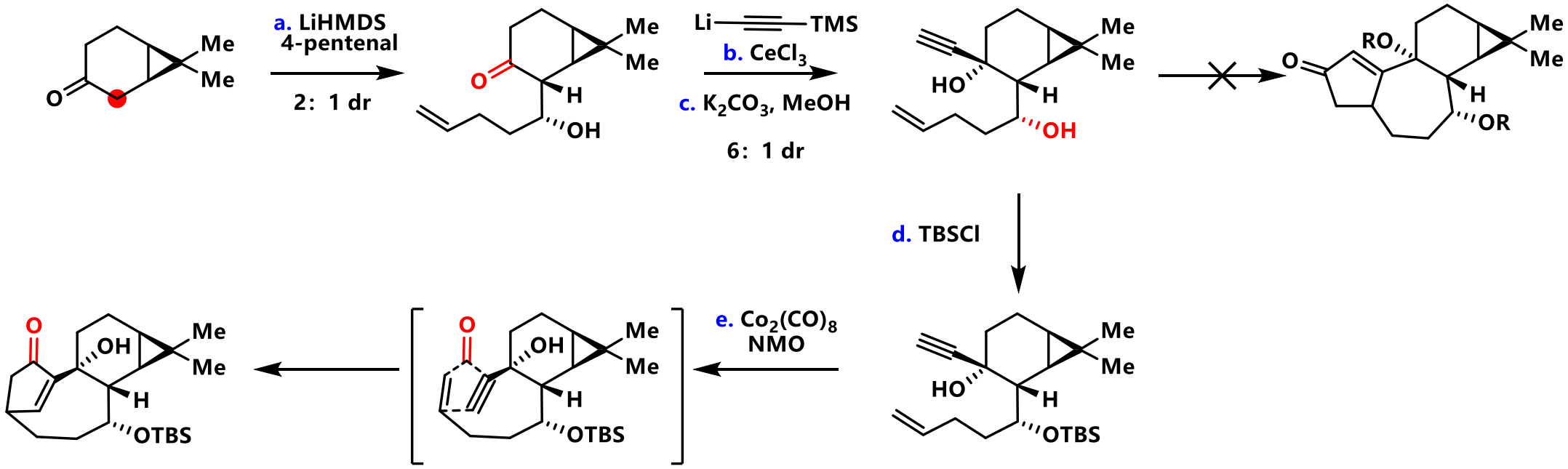

Me
Me
Me
O
O
O
PMBO
5
Mes
N
N
Mes
Cl
Ru
Cl
O
6
OPMB
1) HCl
2) NaBH4
3) I2, PPh3
4) KOtBu
7
SeO2, tBuOOH
HO
8
1) DMP
2) RuCl3
9
KOtBu, O2,
P(OMe)3
10 R = H
11 R = TMS
TMSOTf
NaBH4
12 R = H
13 R = TMS
HCl
HO RO
A
B
C
D
OH
Ring-oprning/ring-cloxing metathesis

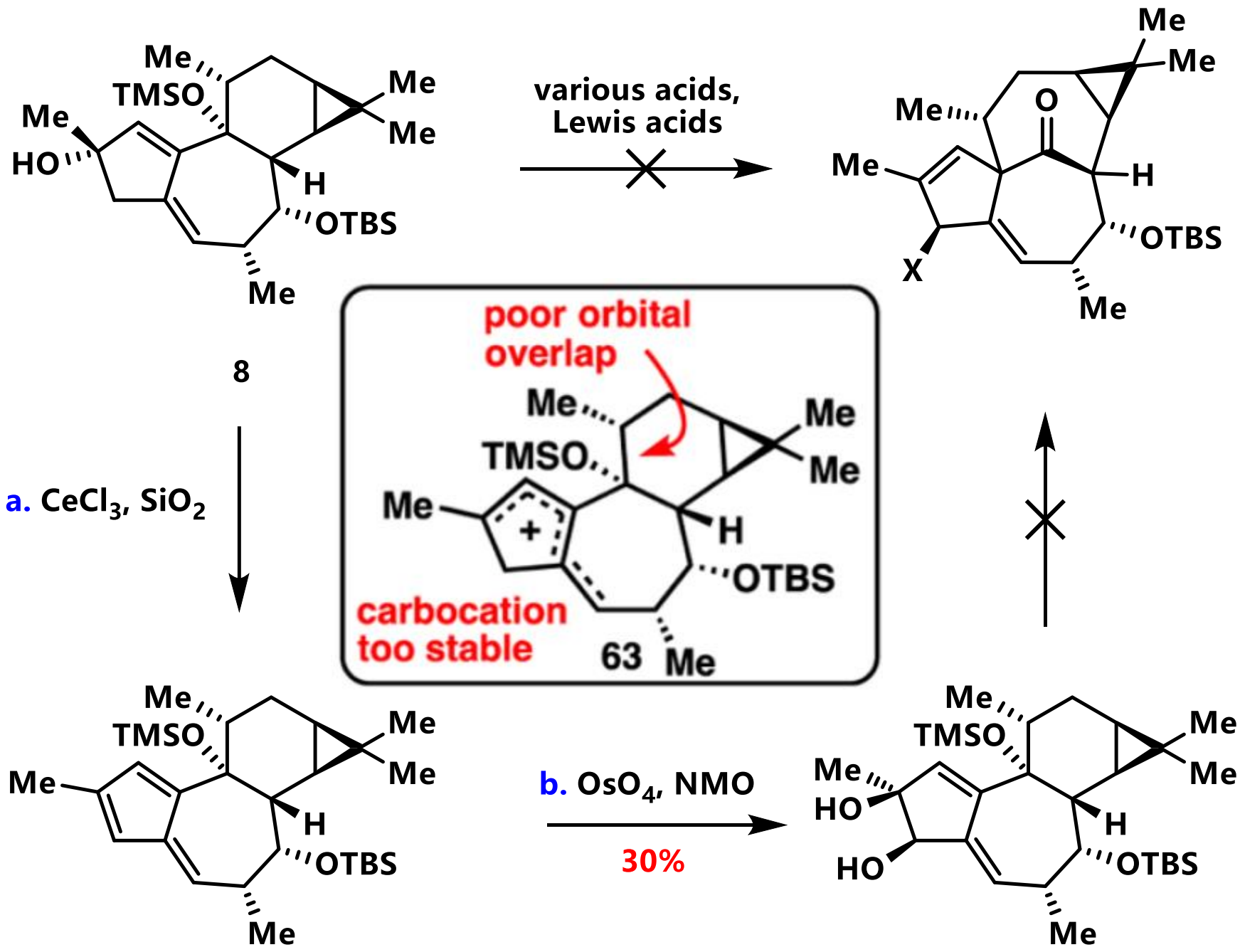

VO(acac)2, tBuOOH
Lewis acid or strong bases
10
14
15
1) NaBH4
2) 2,2-dimeth-oxypropane
PhSH, Li2CO3
DBU
TMSOTf
14 R = H
16 R = TMS
DDQ
MsCl
17 R = PMB
18 R = H
19 R = SO2CH3
(NH)4Mo7O24
20 n = 0
21 n = 2
22
DBU
1) Na(Hg), Na2HPO4
2) HCl
SeO2/SiO2
24
23

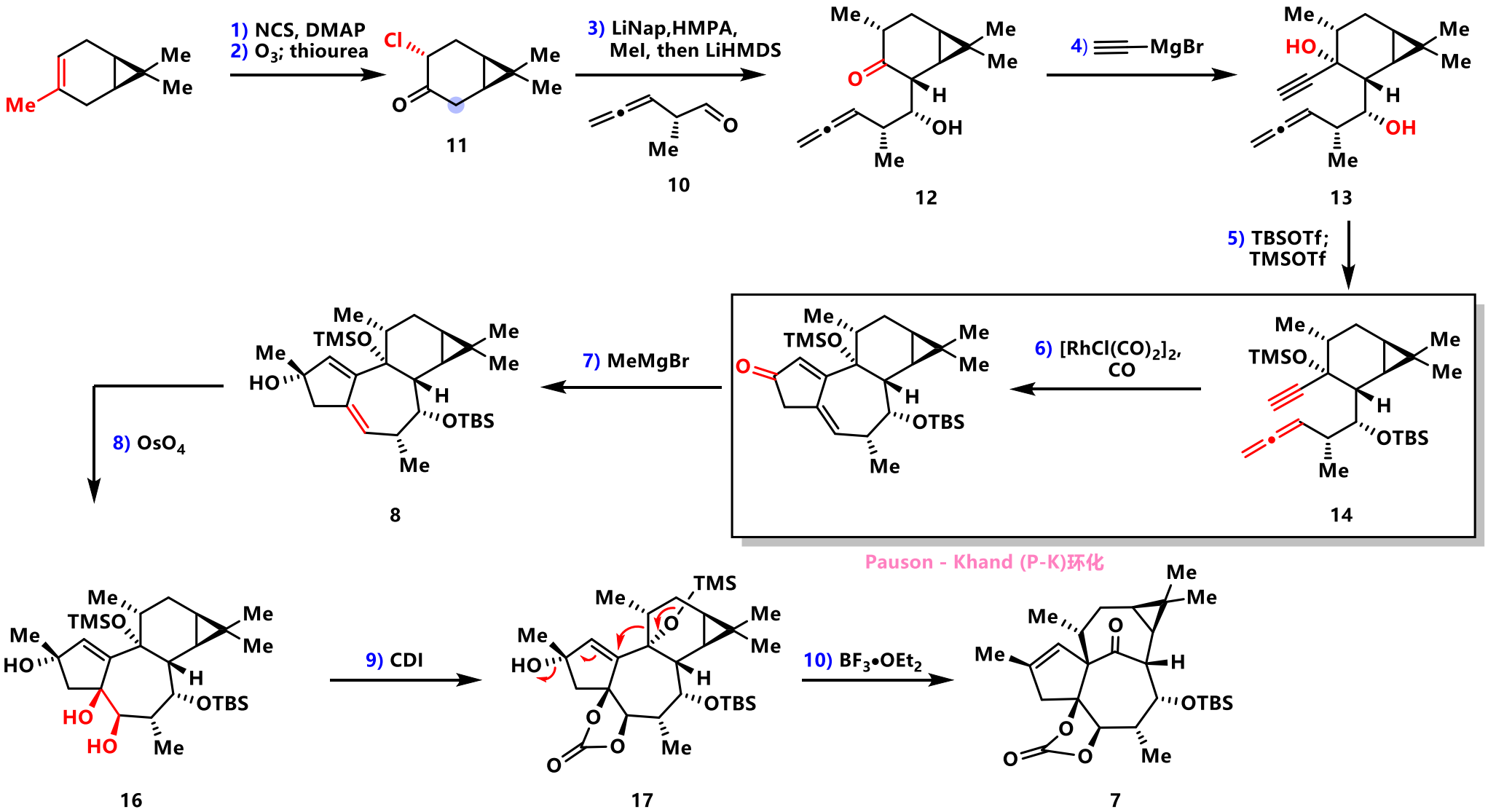
♦**Baran 课题组的工作**（Science341,878-882(2013)）
♦**14-Step Synthsis of (+)-Ingenol from (+)-Carene**

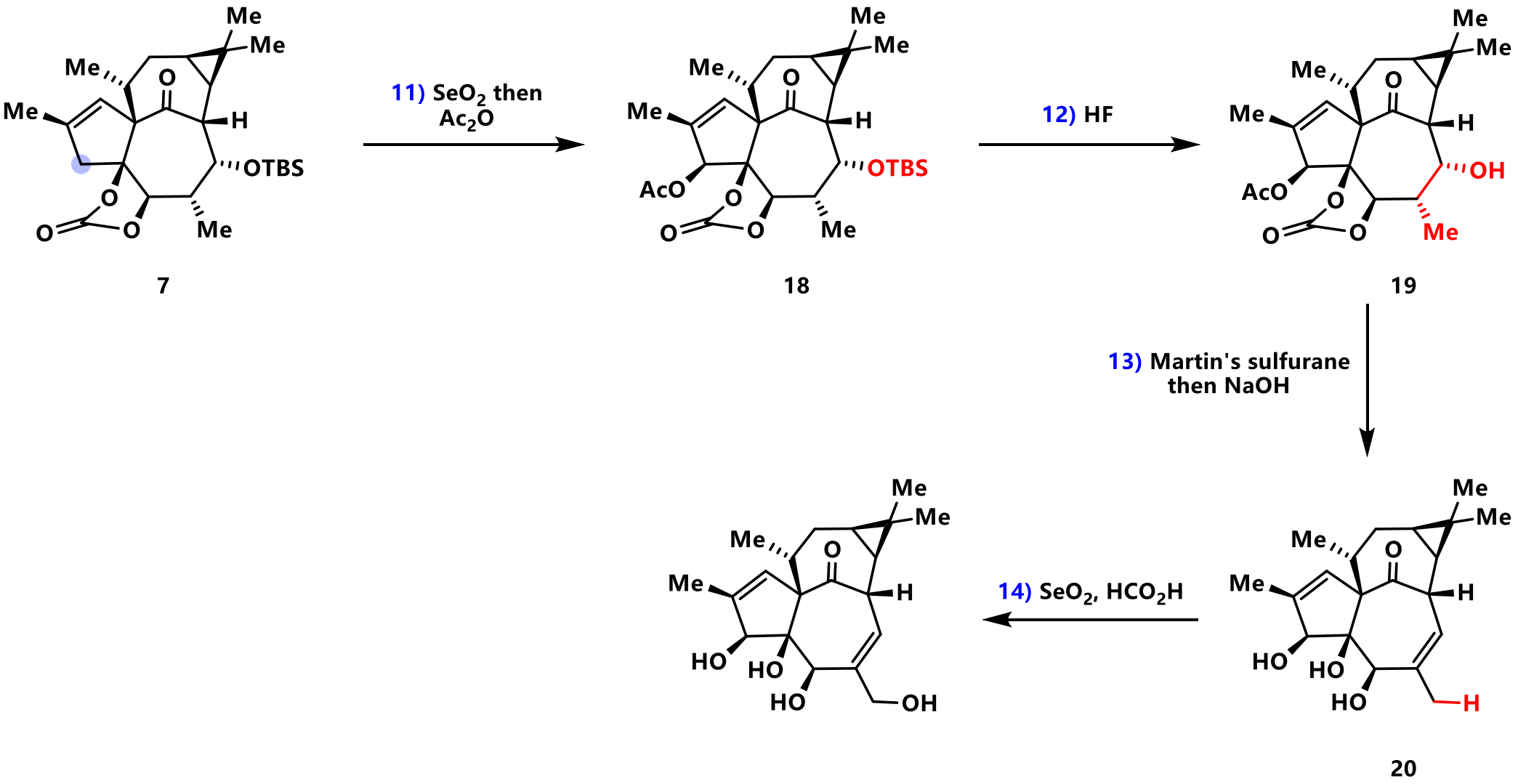


7　　8　　9　　10


a. LiHMDS
4-pentenal
2: 1 dr
b. CeCl3
c. K2CO3, MeOH
6: 1 dr
d. TBSCl
e. Co2(CO)8
NMO
Me
Me
O
OH
H
HO
OTBS
RO
OR
TMS
Li


Me
TMSO
Me
Me
HO
H
OTBS
Me
8
various acids,
Lewis acids
Me
Me
Me
O
Me
H
OTBS
X
Me
a. CeCl3, SiO2
poor orbital
overlap
Me
TMSO
Me
Me
Me
+
H
OTBS
carbocation
too stable
63
Me
Me
TMSO
Me
Me
Me
H
OTBS
Me
b. OsO4, NMO
30%
Me
TMSO
Me
Me
HO
H
HO
OTBS
Me


1) NCS, DMAP
2) O3; thiourea
11
3) LiNap,HMPA,
MeI, then LiHMDS
10
12
4) MgBr
13
5) TBSOTf;
TMSOTf
14
6) [RhCl(CO)2]2,
CO
7) MeMgBr
8) OsO4
8
9) CDI
16
17
10) BF3•OEt2
7
Pauson - Khand (P-K)环化


Me
Me
Me
Me
O
H
OTBS
O
O
O
Me
11) SeO_2 then Ac_2O
AcO
12) HF
OH
13) Martin's sulfurane then NaOH
HO
14) SeO_2, HCO_2H
OH

7 18 19 20

感谢聆听