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Communication

Total Synthesis of Ganoapplanin Enabled by a Radical Addition/Aldol Reaction Cascade

Nicolas Müller,[§] Ondřej Kováč,[§] Alexander Rode, Daniel Atzl, and Thomas Magauer*

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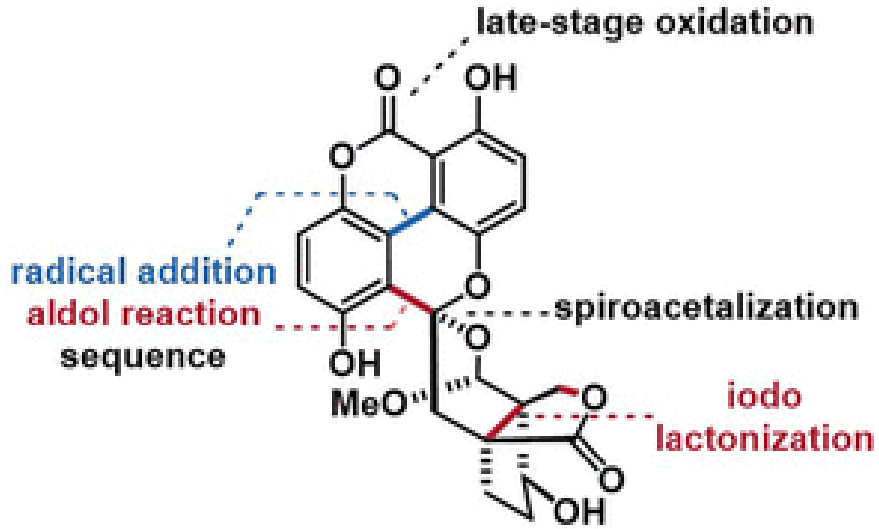
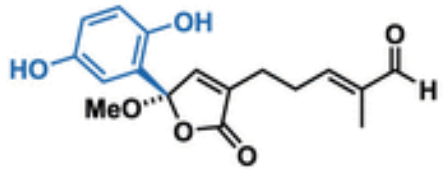
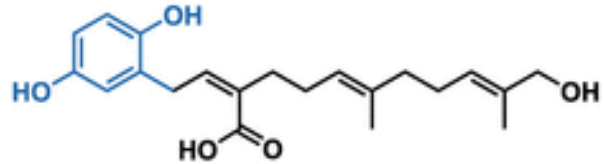


- isolated from *Ganoderma applanatum*
- 6/6/6/6 tetracyclic system
- dioxatricyclo[4.3.3.0]dodecane
- spiro bisacetal

linear *Ganoderma* meroterpenoids

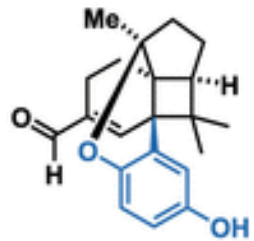


lucidulactone B (1)

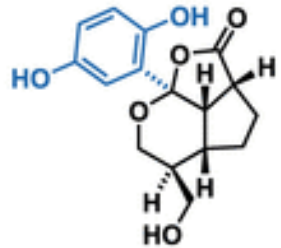


ganomycin A (2)

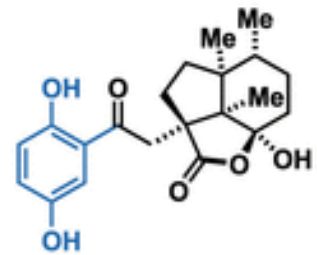
polycylic *Ganoderma* meroterpenoids



cochlearol B (3)

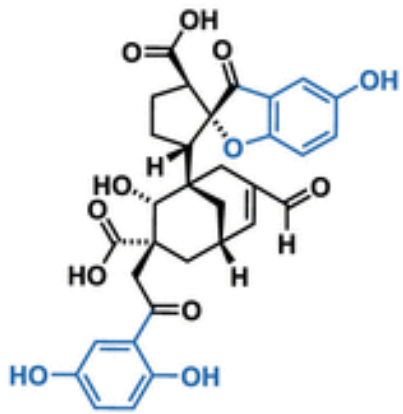


applanatumol B (4)

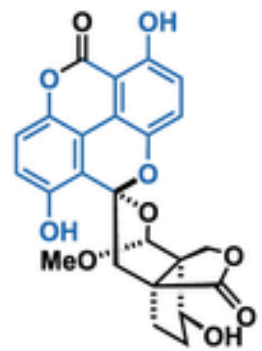


ganodermaone A (5)

dimeric *Ganoderma* meroterpenoids



applanatumin A (6)

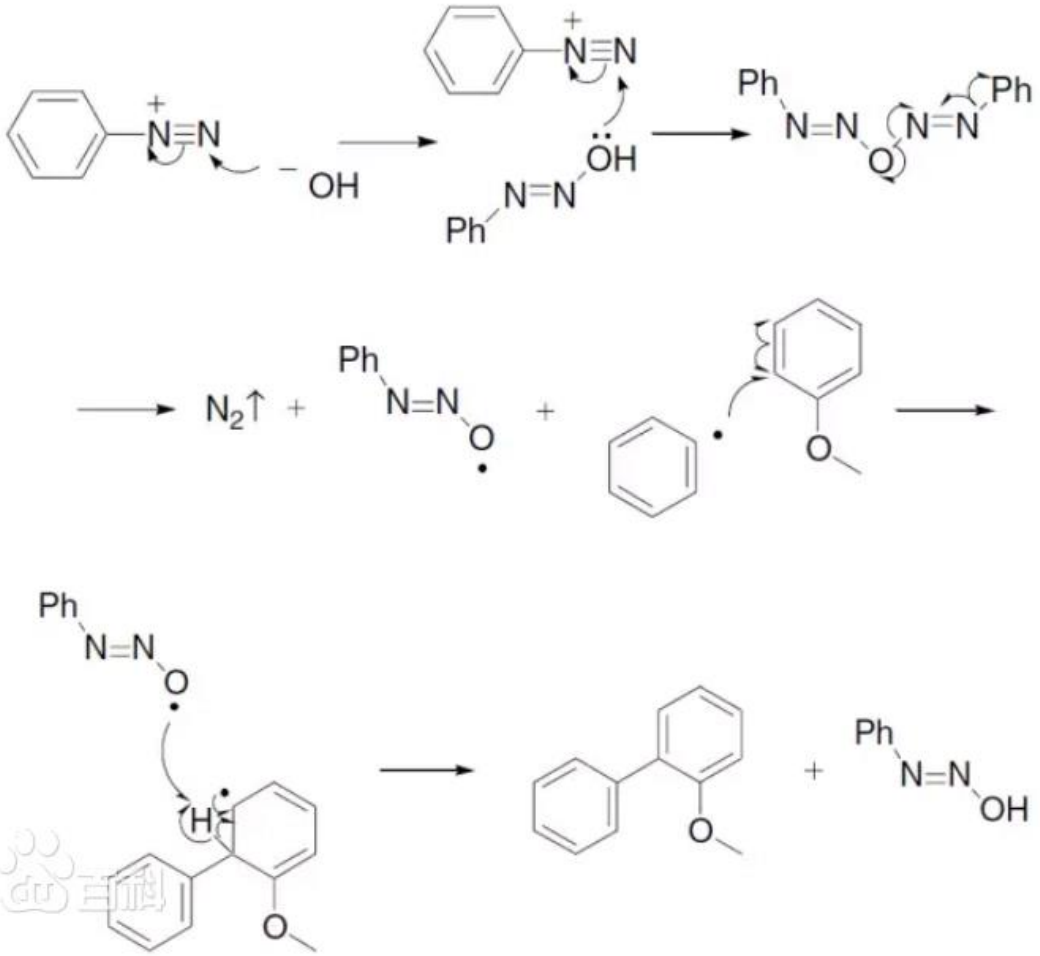


ganoapplanin (7)

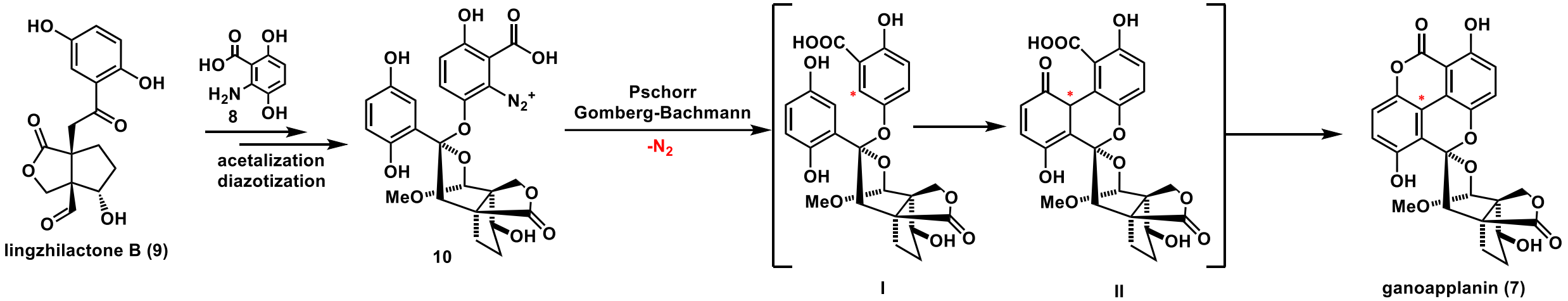
- isolated in 2016 from *Ganoderma applanatum*
- inhibition of T-type voltage-gated Ca^{2+} channels (IC_{50} = 36.6 μM)
- 6/6/6/6 tetracyclic system
- dioxatricyclo[4.3.3.0]dodecane
- spiro bisacetal
- five stereocenters

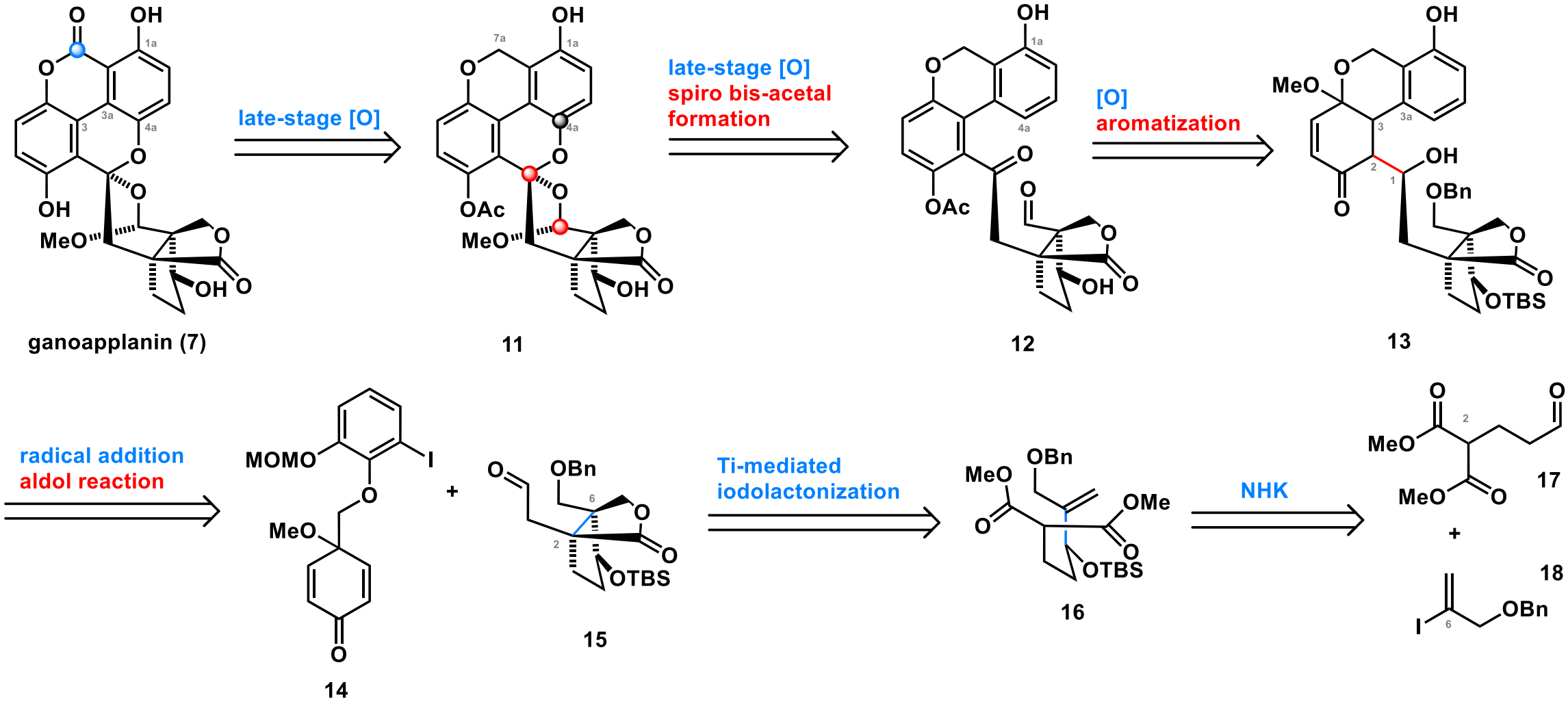
Gomberg–Bachmann反应

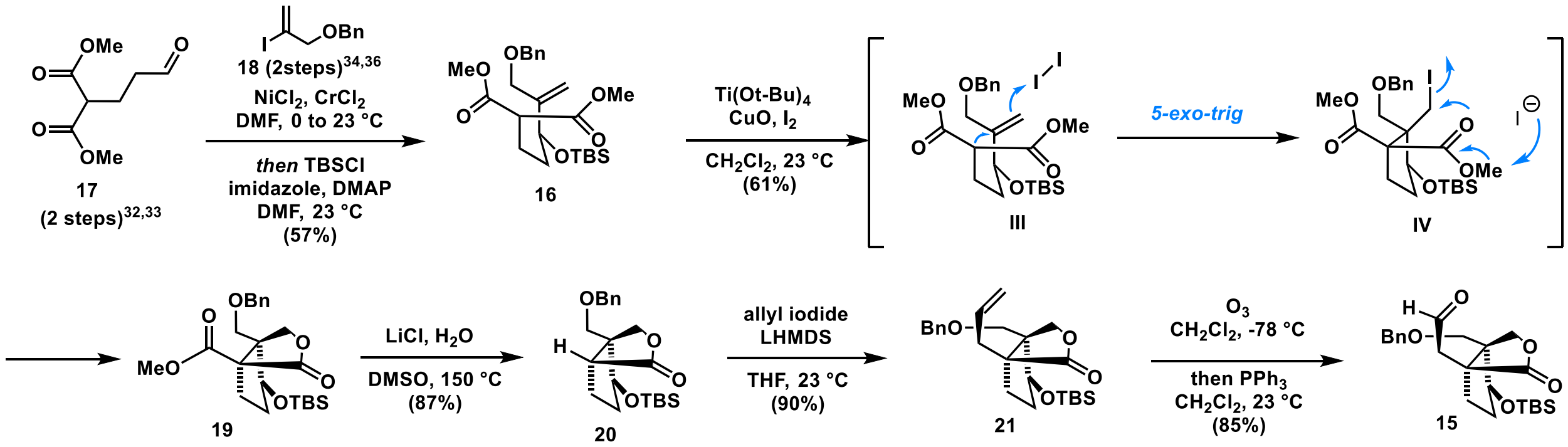
Gomberg–Bachmann反应是指重氮盐的酸性溶液用氢氧化钠或乙酸钠的水溶液处理时，发生芳基的偶联反应，生成联芳烃的衍生物的反应。



J. Am. Chem. Soc. **1924,** *46, 2339*

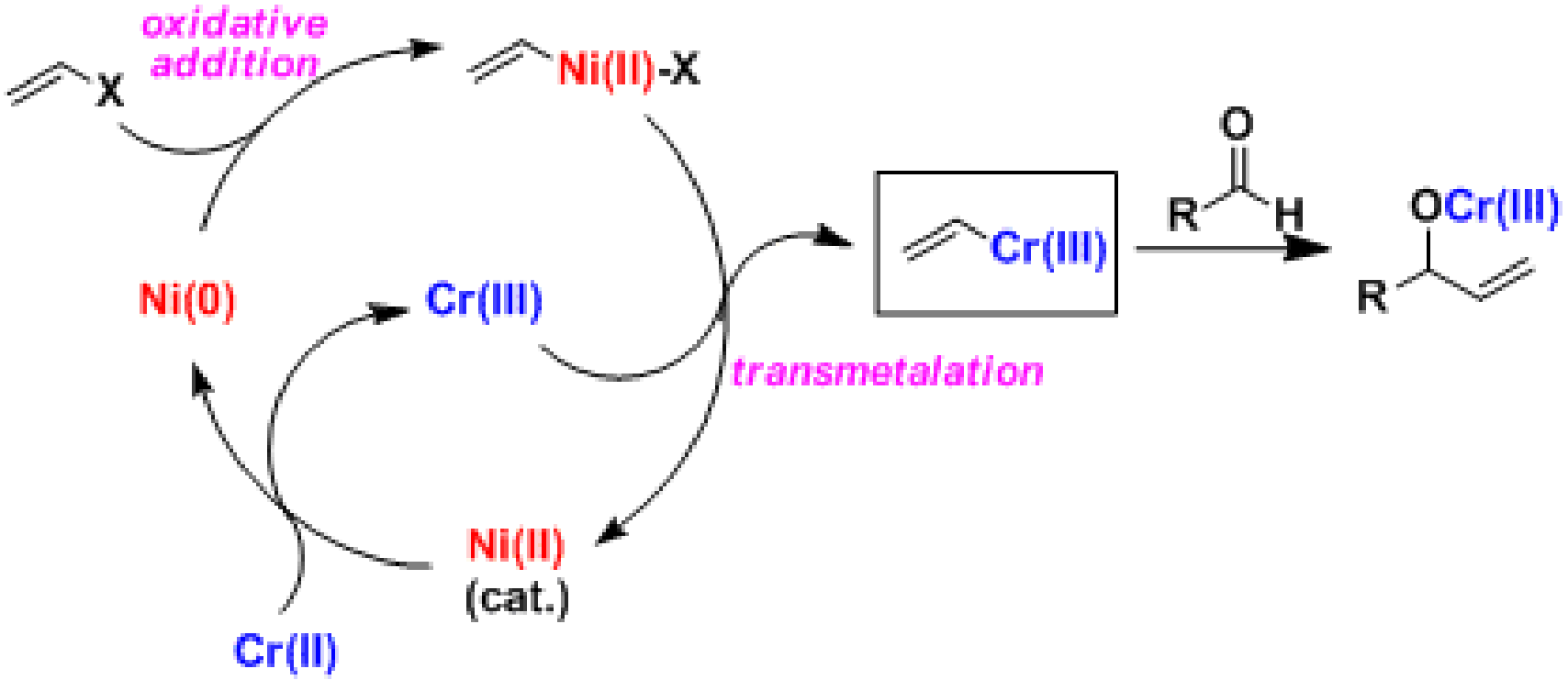

lingzhilactone B (9)
8
acetalization
diazotization
10
Pschorr
Gomberg-Bachmann
-N2
I
II
ganoapplanin (7)


late-stage [O]
late-stage [O]
spiro bis-acetal
formation
[O]
aromatization
radical addition
aldol reaction
Ti-mediated
iodolactonization
NHK
ganoapplanin (7)
11
12
13
14
15
16
17
18

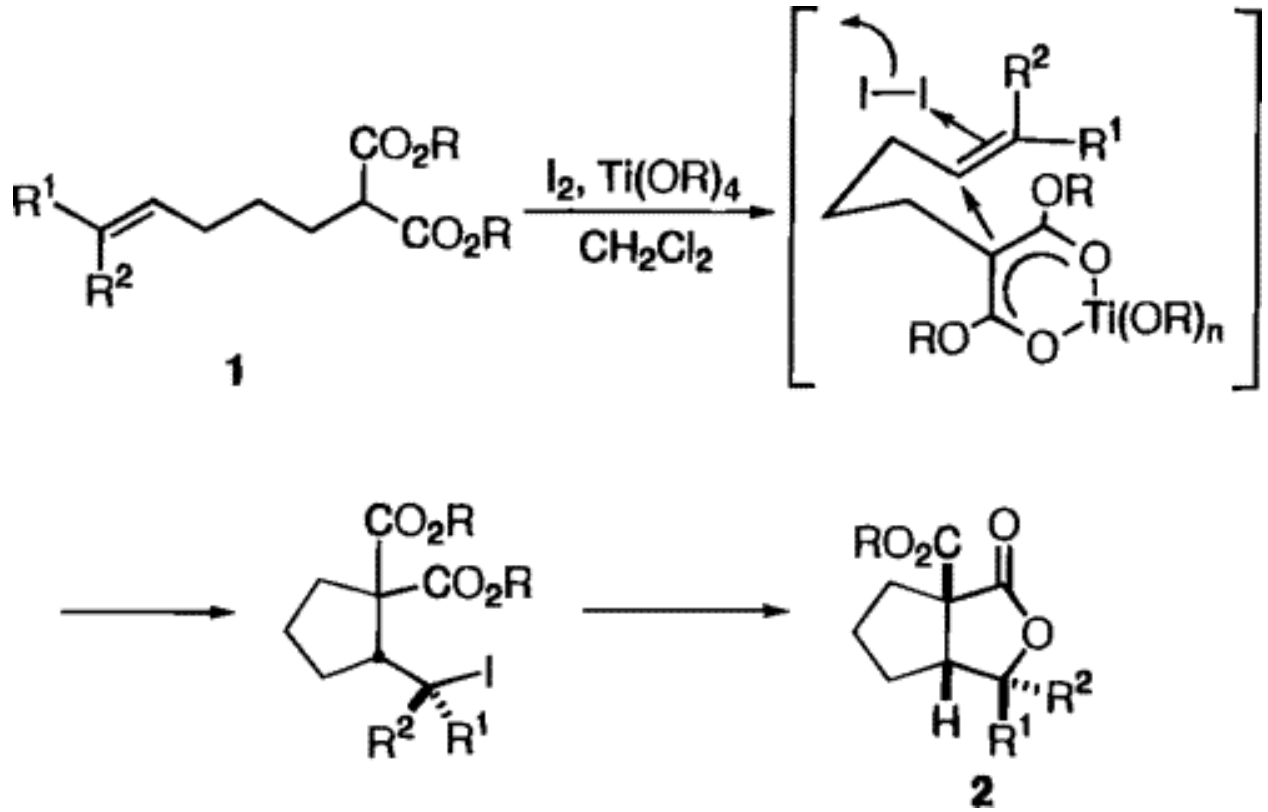

17
(2 steps)[32,33]
18 (2steps)[34,36]
NiCl2, CrCl2
DMF, 0 to 23 °C
then TBSCl
imidazole, DMAP
DMF, 23 °C
(57%)
16
Ti(Ot-Bu)4
CuO, I2
CH2Cl2, 23 °C
(61%)
III
5-exo-trig
IV
19
LiCl, H2O
DMSO, 150 °C
(87%)
20
allyl iodide
LHMDS
THF, 23 °C
(90%)
21
O3
CH2Cl2, -78 °C
then PPh3
CH2Cl2, 23 °C
(85%)
15

Nozaki-Hiyama偶联反应 / Nozaki-Hiyama-Kishi反应

烯基卤化物或烯基三氟甲磺酸与醛之间的偶联反应。反应用到二价镍催化剂以及摩尔当量的二价铬还原剂。不饱和醛的情况时选择性发生1,2-加成。



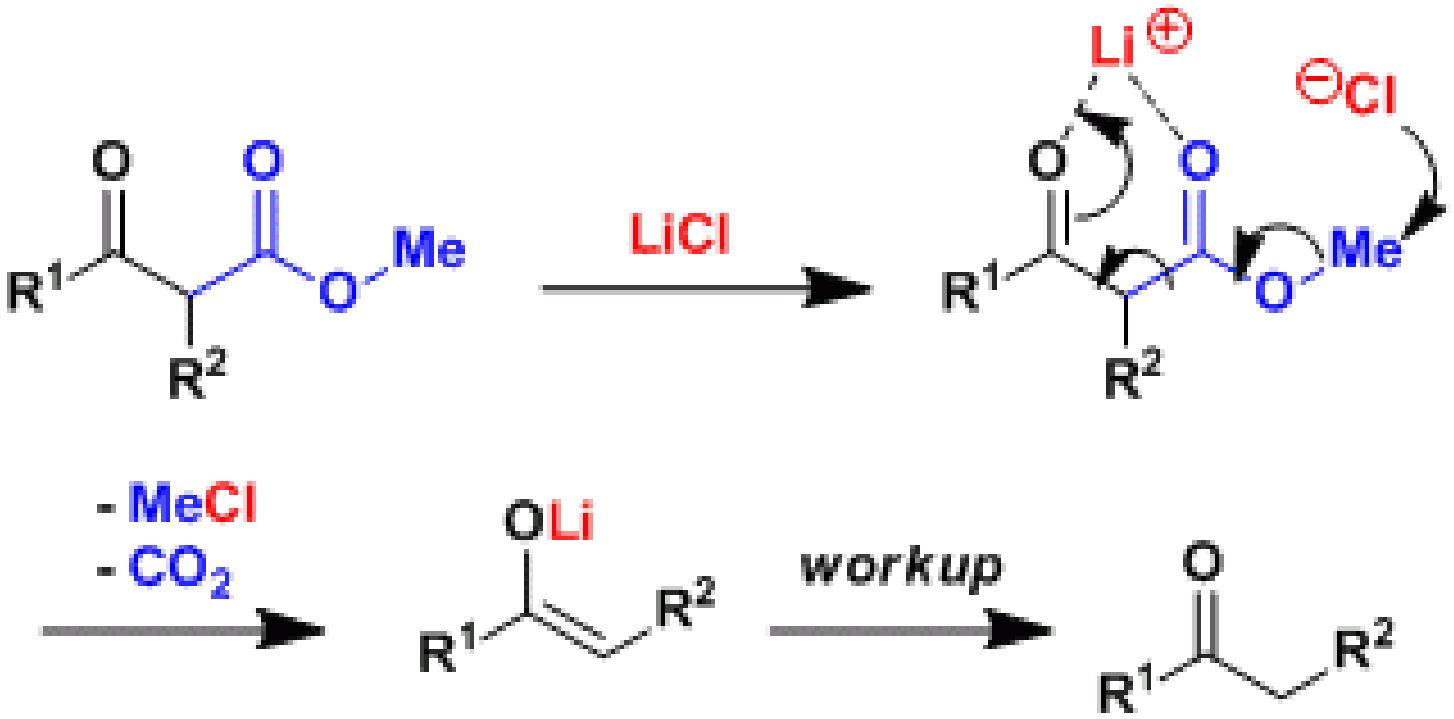
钛（IV）介导的烯烃的碘内酯化

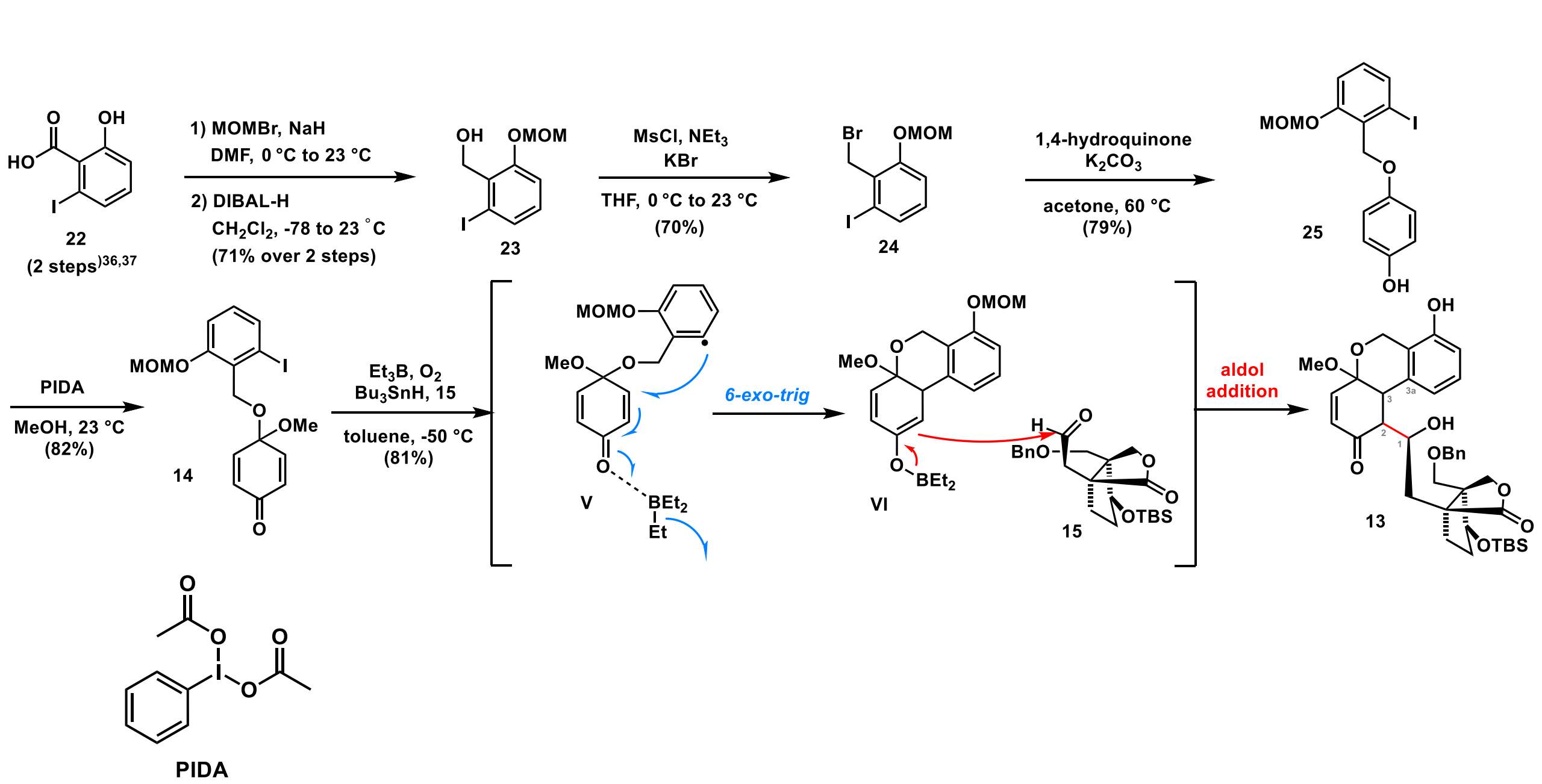


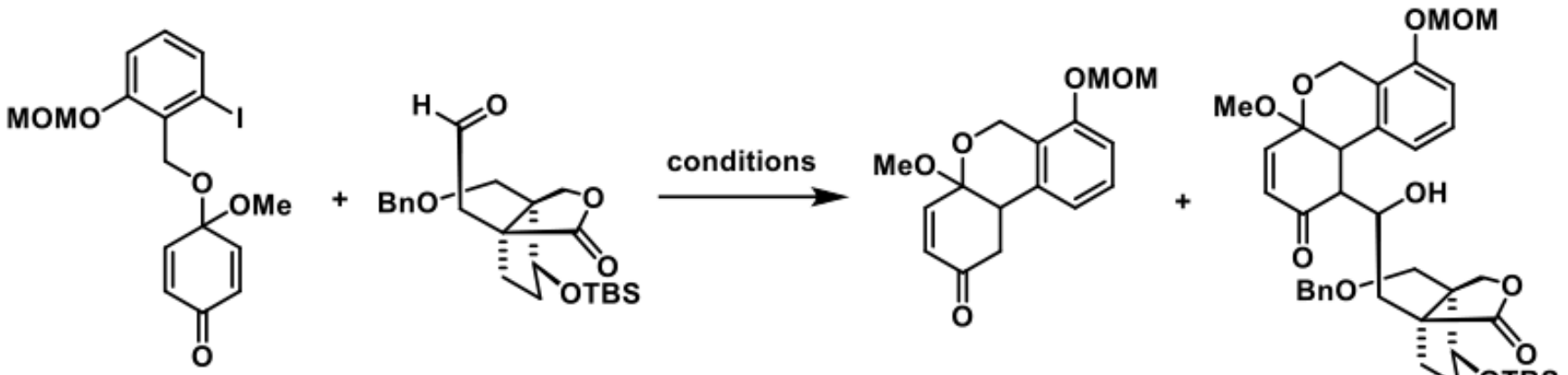
J. Org. Chem. **1996,** *61*, *23*, 8256–8263

Krapcho脱碳酸反应

β-酮酸甲酯与LiCl在DMSO中加热，在基本中性条件下引发脱碳酸的反应。

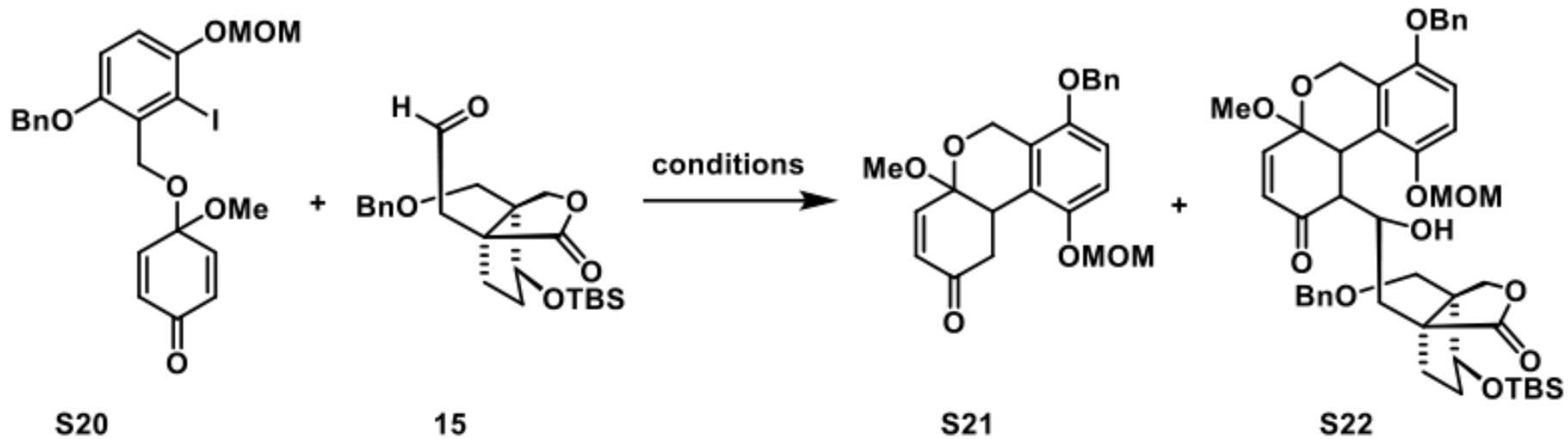



22
(2 steps)[36,37]
1) MOMBr, NaH
DMF, 0 °C to 23 °C
2) DIBAL-H
CH2Cl2, -78 to 23 °C
(71% over 2 steps)
23
MsCl, NEt3
KBr
THF, 0 °C to 23 °C
(70%)
24
1,4-hydroquinone
K2CO3
acetone, 60 °C
(79%)
25
PIDA
MeOH, 23 °C
(82%)
14
Et3B, O2
Bu3SnH, 15
toluene, -50 °C
(81%)
V
6-exo-trig
VI
15
aldol
addition
13
PIDA



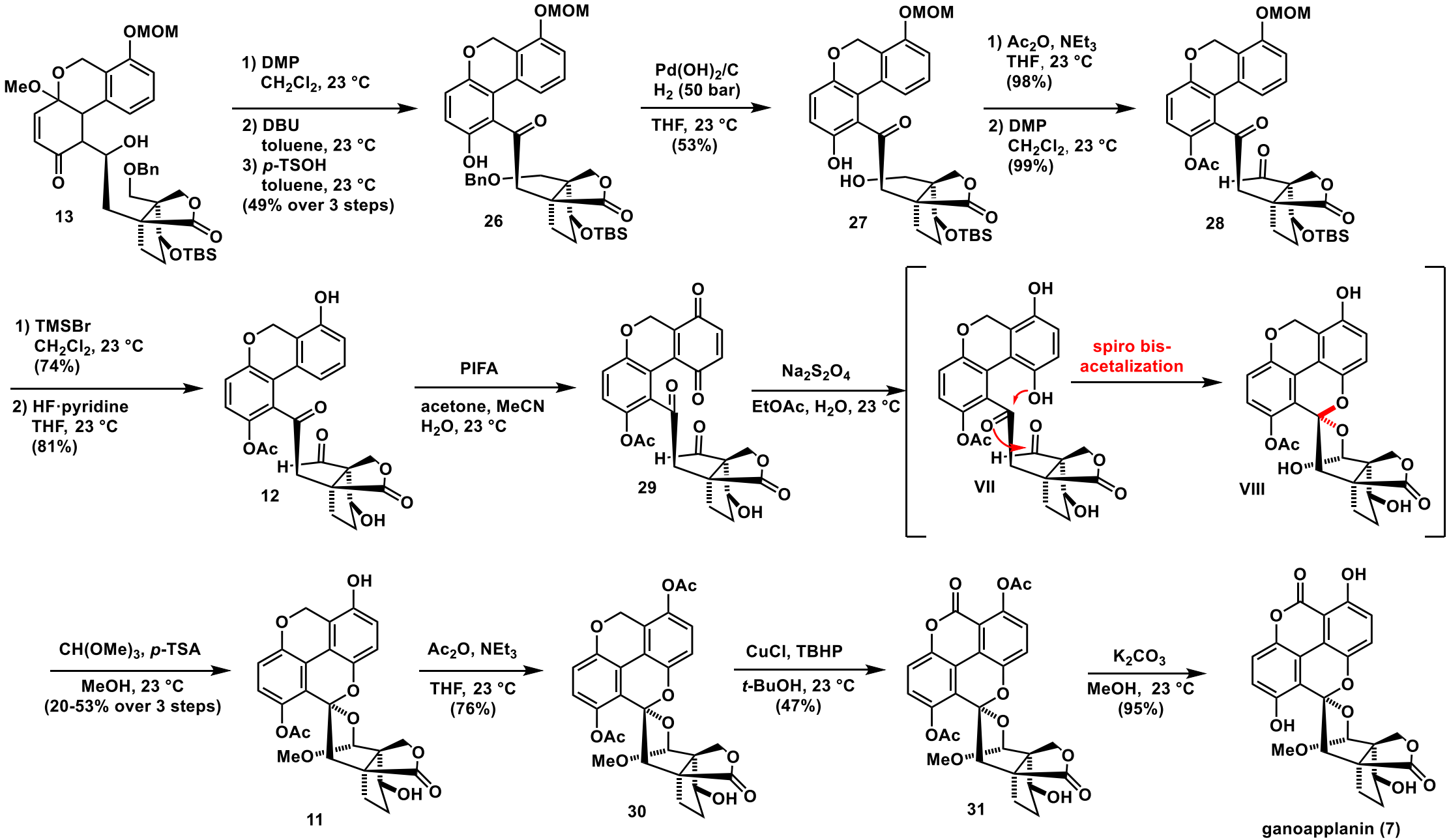
14 **15** **S11** **13**

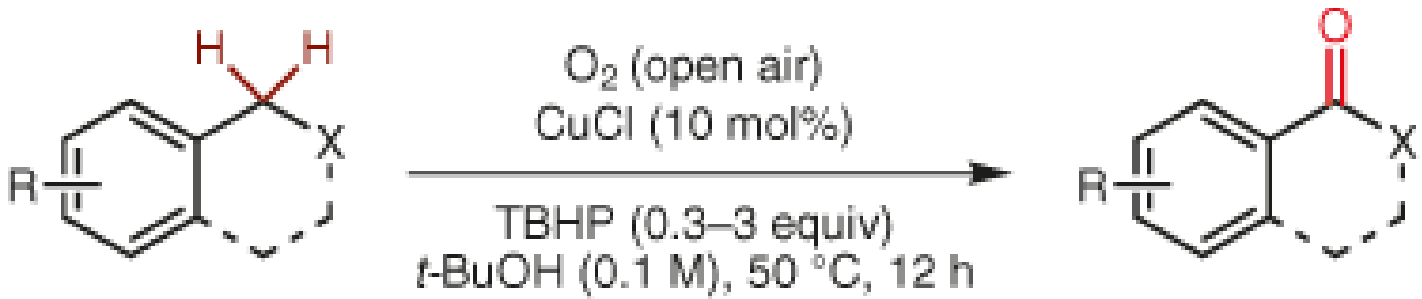
Entry	14	15	Reagents	Temp.	Result
1	1 equiv	-	*t*-BuLi (2.2 equiv), THF	–78 °C	Decomposition
2	1 equiv	-	*t*-BuLi (2.2 equiv), DMPU, THF	–78 °C	Decomposition
3	1 equiv	-	*t*-BuLi (2.2 equiv), HMPA, THF	–78 °C	Decomposition
4	1 equiv	-	*i*PrMgCl (1.1 equiv), THF	0 °C	Decomposition
5	1 equiv	-	AIBN (0.5 equiv), $HSnBu_3$ (1.2 equiv), toluene	50 °C	**S11** (70%)
6	1.6 equiv	1 equiv	AIBN (0.5 equiv), $HSnBu_3$ (1.2 equiv), toluene	50 °C	**S11** (70%), **13** not formed
7	1.6 equiv	1 equiv	AIBN (0.5 equiv), $HSnBu_3$ (1.2 equiv), BEt_3 (2.0 equiv), toluene	50 °C	Decomposition
8	1 equiv	-	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	–50 °C	**S11** (up to 90%)
9	1 equiv	-	BEt_3 (4.0 equiv), air, toluene	–50 °C	Decomposition
10	1 equiv	-	BEt_3 (4.0 equiv), air, benzene	23 °C	Decomposition
11	1 equiv	-	$HSnBu_3$ (1.2 equiv), air, toluene	–50 °C	No consumption of **14**
12	1.6 equiv	1 equiv	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	–50 °C	**13** (up to 81%), + **S11**



S20 **15** **S21** **S22**

Entry	35	15	Reagents	Temp.	Result
1	1.6 equiv	1 equiv	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	–78 °C	recovered **15**, + **S21** (not isolated), **S22** not formed
2	1.6 equiv	1 equiv	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	–50 °C	recovered **15**, + **S21** (40%), **S22** not formed
3	1.6 equiv	1 equiv	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	0 °C	recovered **15**, + **S21** (not isolated), **S22** not formed
4	1.6 equiv	1 equiv	BEt_3 (4.0 equiv), $HSnBu_3$ (1.2 equiv), air, toluene	23 °C	recovered **15** + decomposition, **S22** not formed


OMOM
MeO
OH
OBn
13
1) DMP
CH_2Cl_2, 23 °C
2) DBU
toluene, 23 °C
3) *p*-TSOH
toluene, 23 °C
(49% over 3 steps)
OMOM
OH
BnO
26
OTBS
$Pd(OH)_2/C$
H_2 (50 bar)
THF, 23 °C
(53%)
OMOM
OH
HO
27
OTBS
1) Ac_2O, NEt_3
THF, 23 °C
(98%)
2) DMP
CH_2Cl_2, 23 °C
(99%)
OMOM
OAc
28
OTBS
1) TMSBr
CH_2Cl_2, 23 °C
(74%)
2) HF·pyridine
THF, 23 °C
(81%)
OH
OAc
12
OH
PIFA
acetone, MeCN
H_2O, 23 °C
OAc
29
OH
$Na_2S_2O_4$
EtOAc, H_2O, 23 °C
OH
OAc
VII
OH
spiro bis-
acetalization
OH
OAc
HO
VIII
OH
$CH(OMe)_3$, *p*-TSA
MeOH, 23 °C
(20-53% over 3 steps)
OH
OAc
MeO
11
OH
Ac_2O, NEt_3
THF, 23 °C
(76%)
OAc
OAc
MeO
30
OH
CuCl, TBHP
t-BuOH, 23 °C
(47%)
OAc
OAc
MeO
31
OH
K_2CO_3
MeOH, 23 °C
(95%)
OH
OH
MeO
OH
ganoapplanin (7)



- ligand-free
- inexpensive CuCl as catalyst
- mild conditions
- simple operation