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Total Synthesis

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Stereoselective Total Synthesis of (−)-Thallusin for Bioactivity Profiling

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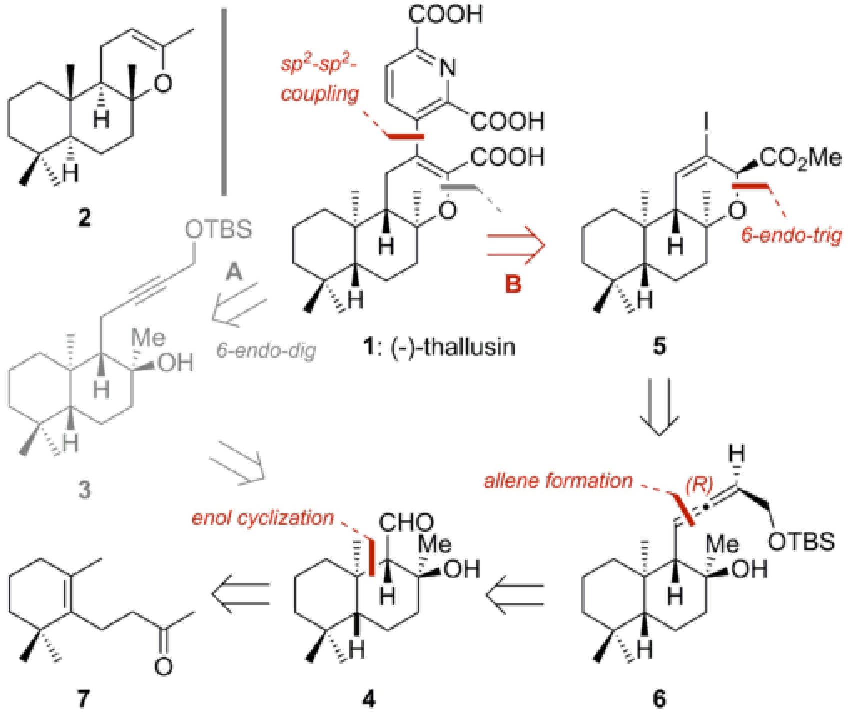
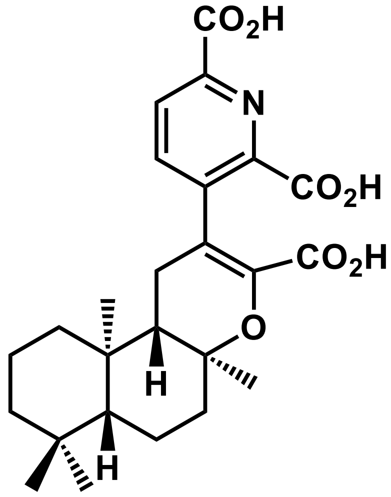
Dedicated to Professor Herbert Waldmann on the occasion of his 65th birthday.

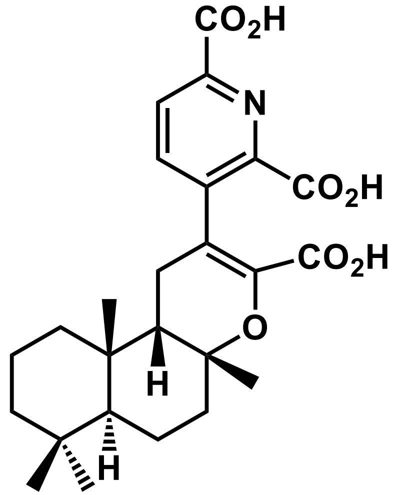
Abstract: Chemical mediators are key compounds for controlling symbiotic interactions in the environment. Here, we disclose a fully stereoselective total synthesis of the algae differentiation factor (−)-thallusin that utilizes sophisticated 6-*endo*-cyclization chemistry and effective late-stage sp^2–sp^2-couplings using non-toxic reagents. An EC_{50} of 4.8 pM was determined by quantitative phenotype profiling in the green seaweed *Ulva mutabilis* (Chlorophyte), underscoring this potent mediator's enormous, pan-species bioactivity produced by symbiotic bacteria. SAR investigations indicate that (−)-thallusin triggers at least two different pathways in *Ulva* that may be separated by chemical editing of the mediator compound structure.



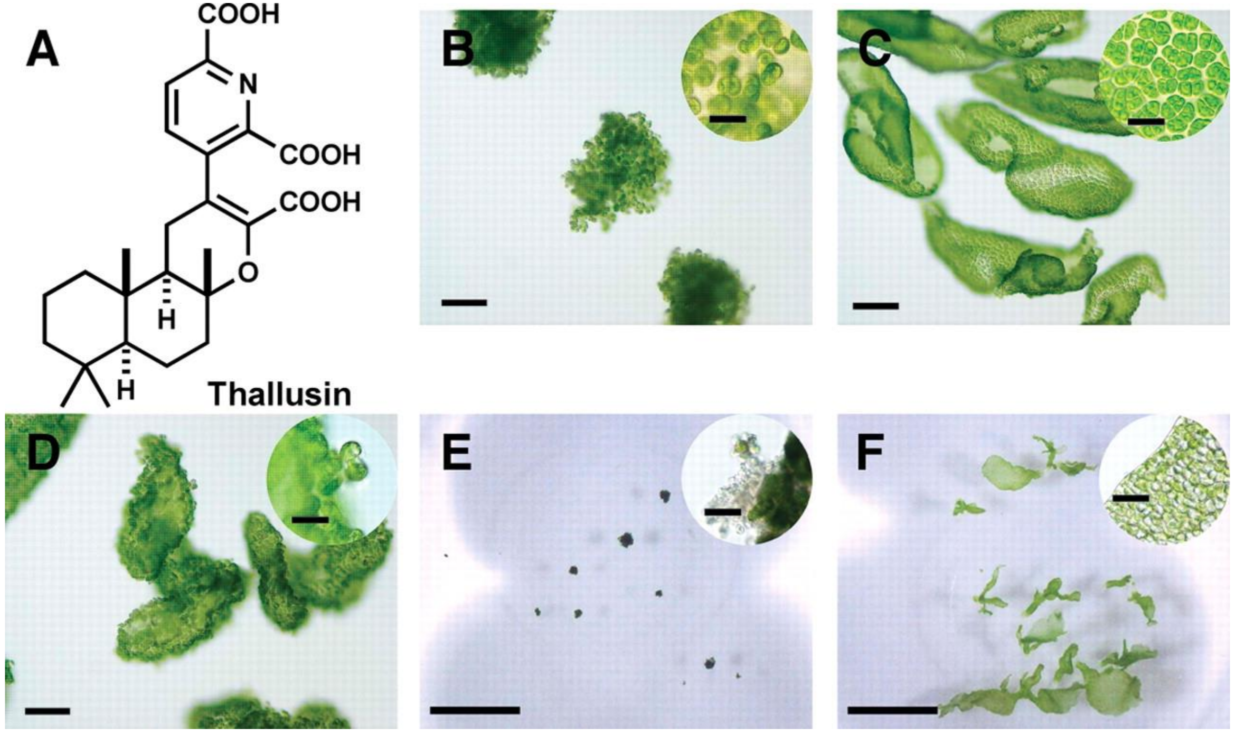
Chemosynthetic symbioses of microorganisms are central

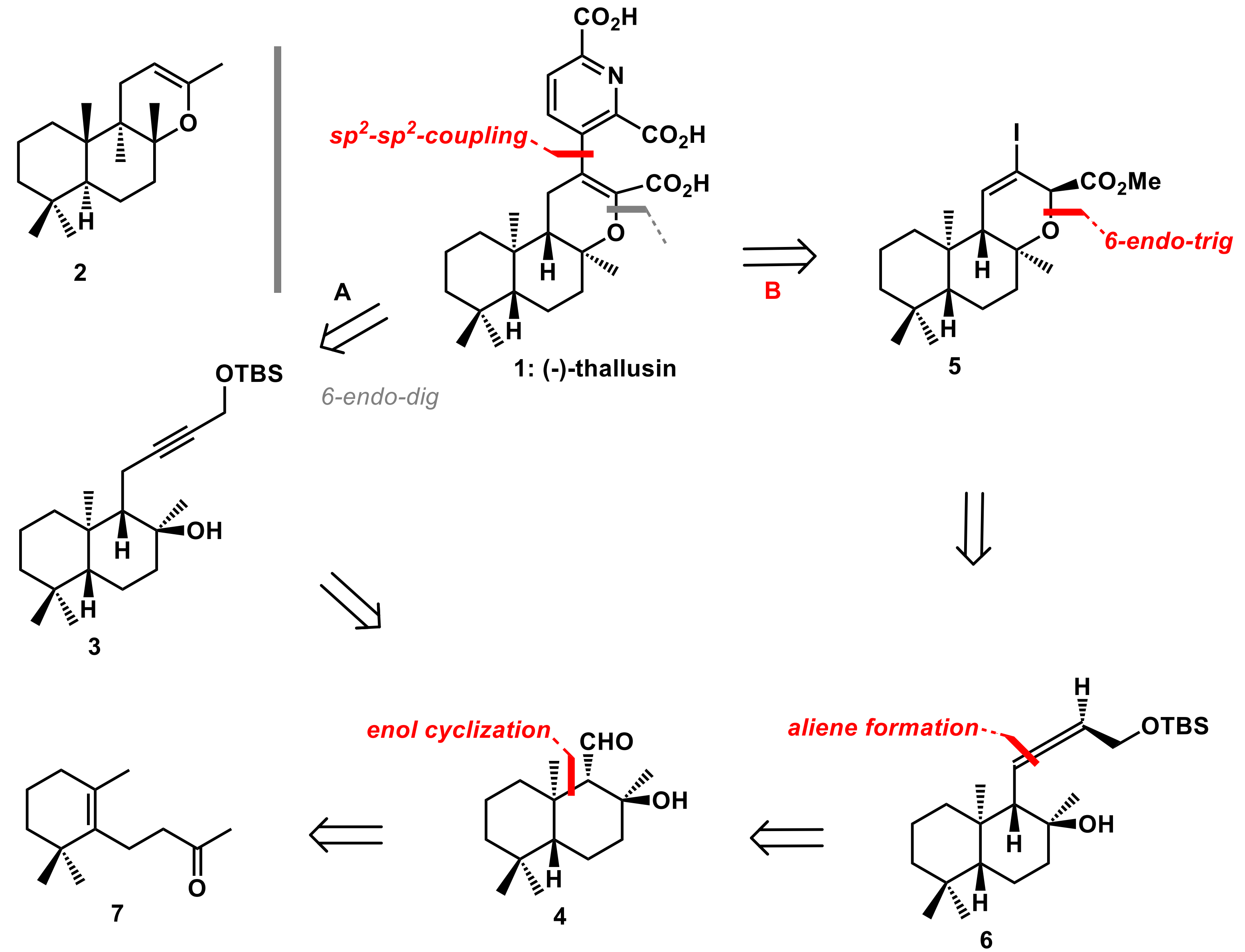


(-)-thallusin

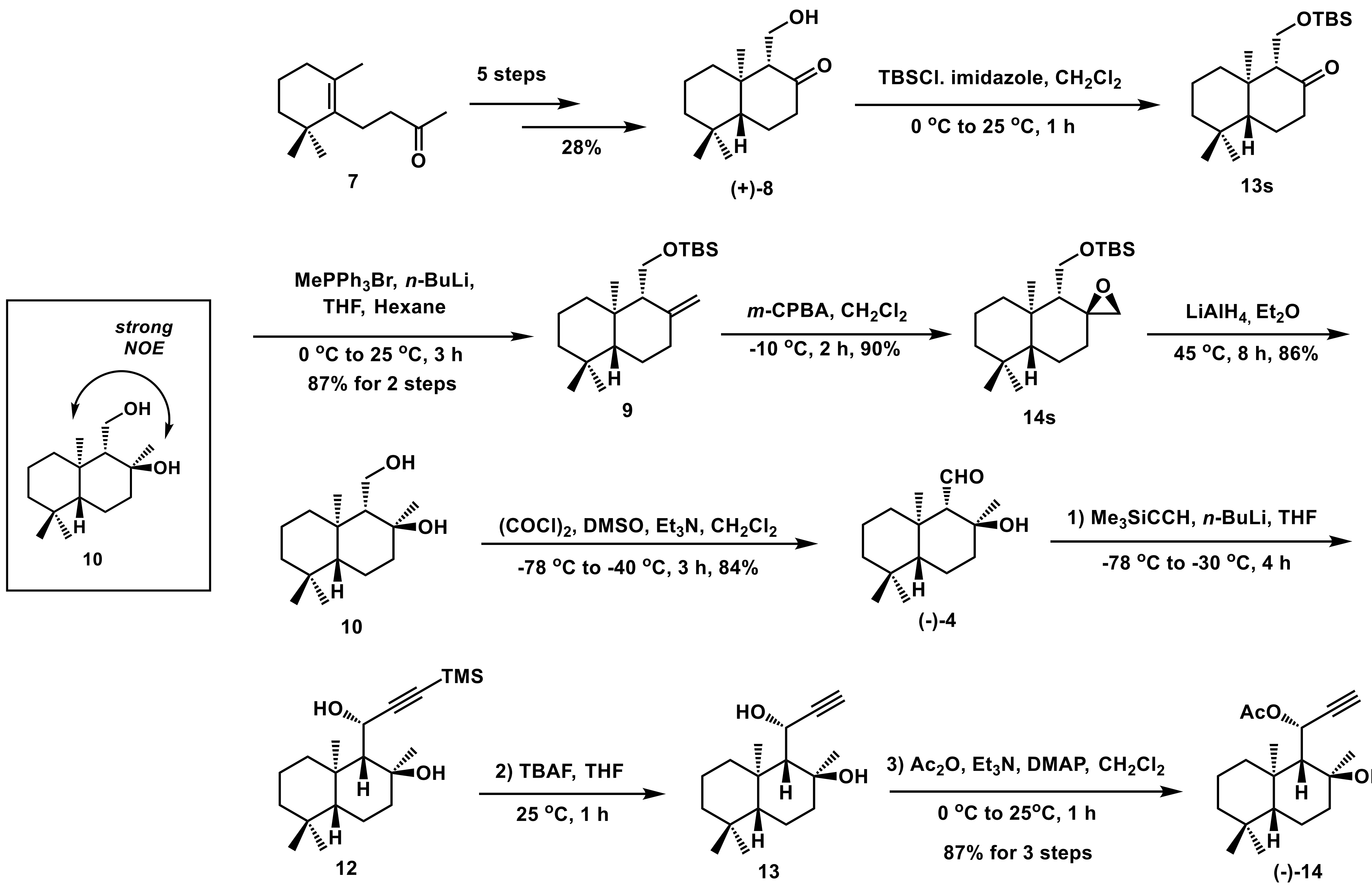


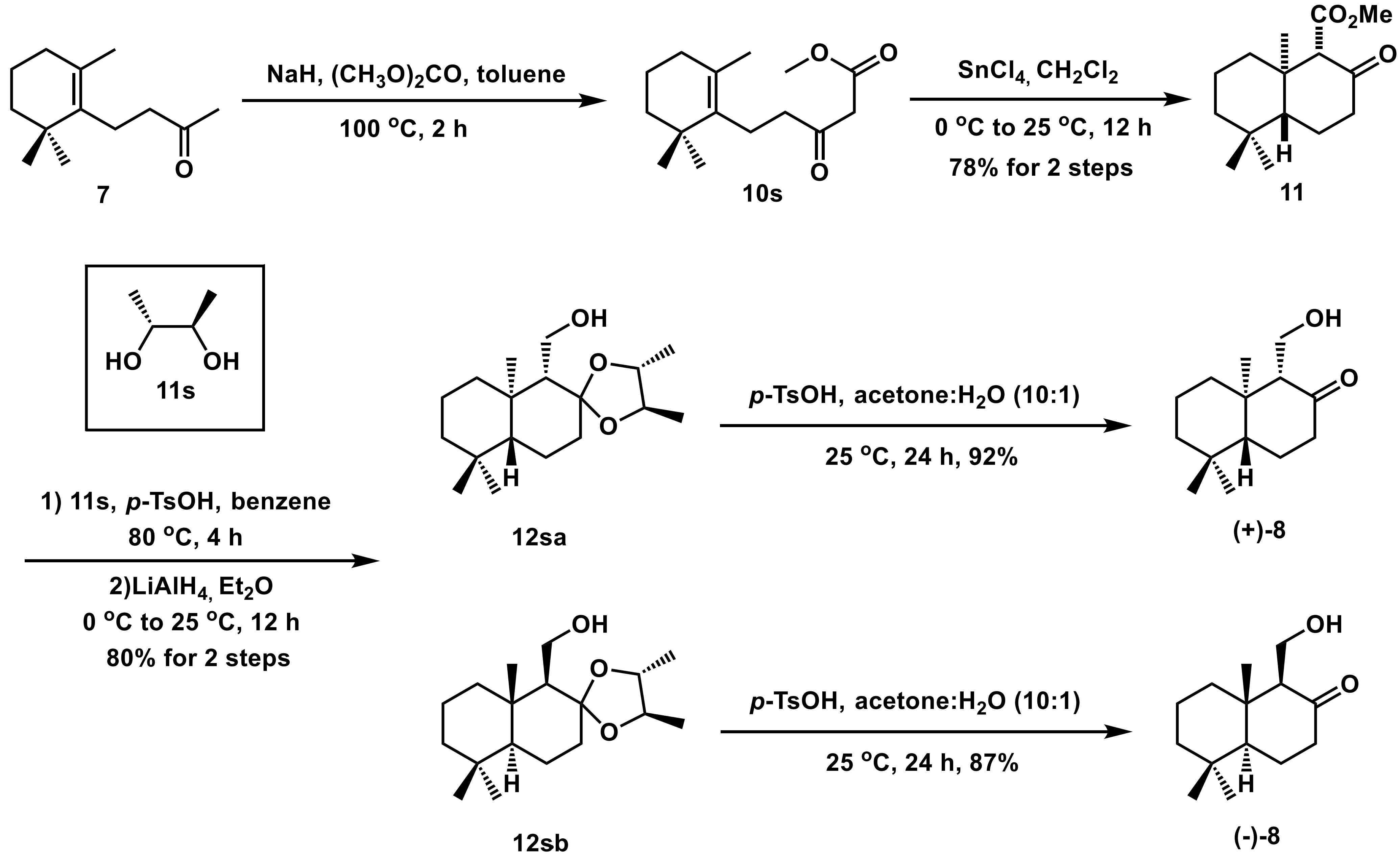
(+)-thallusin



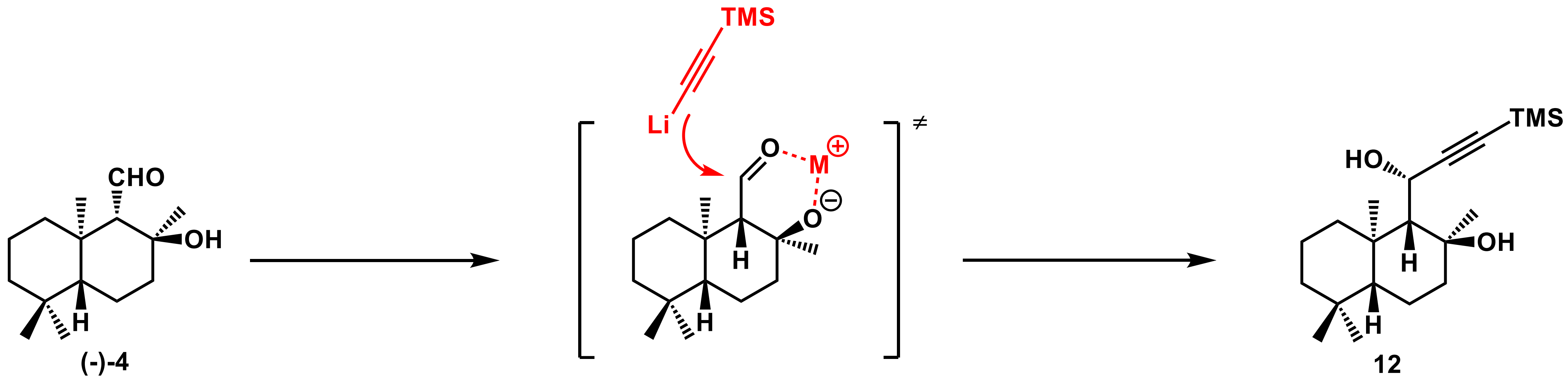


CO2H
N
CO2H
CO2H
sp2-sp2-coupling
O
H
H
1: (-)-thallusin
O
H
2
A
B
6-endo-dig
OTBS
OH
H
H
3
I
CO2Me
O
6-endo-trig
H
H
5
enol cyclization
CHO
OH
H
4
O
7
aliene formation
H
OTBS
OH
H
H
6

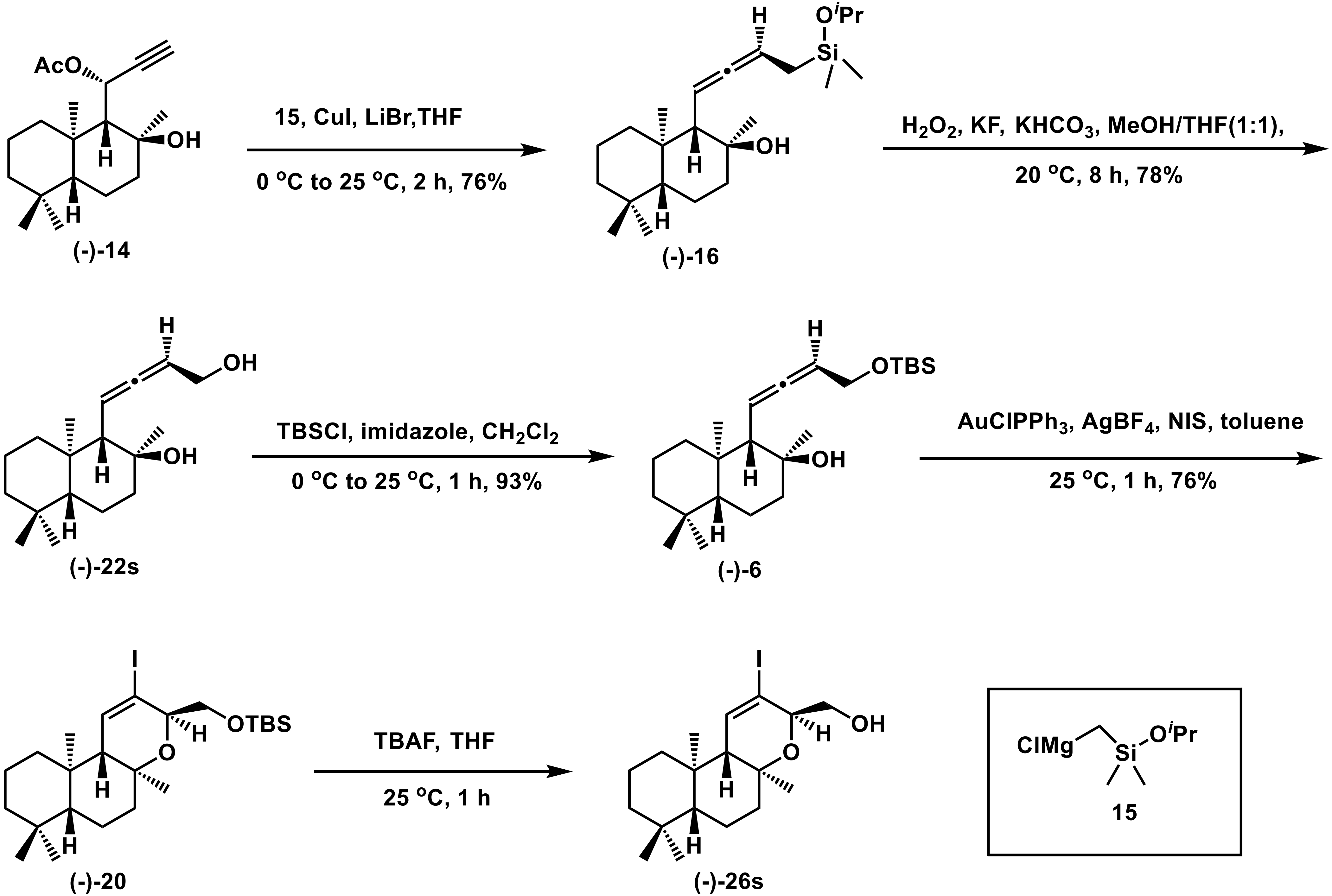

5 steps
28%
7
(+)-8
TBSCl. imidazole, CH2Cl2
0 °C to 25 °C, 1 h
13s
strong NOE
10
MePPh3Br, n-BuLi, THF, Hexane
0 °C to 25 °C, 3 h
87% for 2 steps
9
m-CPBA, CH2Cl2
-10 °C, 2 h, 90%
14s
LiAlH4, Et2O
45 °C, 8 h, 86%
10
(COCl)2, DMSO, Et3N, CH2Cl2
-78 °C to -40 °C, 3 h, 84%
(-)-4
1) Me3SiCCH, n-BuLi, THF
-78 °C to -30 °C, 4 h
12
2) TBAF, THF
25 °C, 1 h
13
3) Ac2O, Et3N, DMAP, CH2Cl2
0 °C to 25°C, 1 h
87% for 3 steps
(-)-14



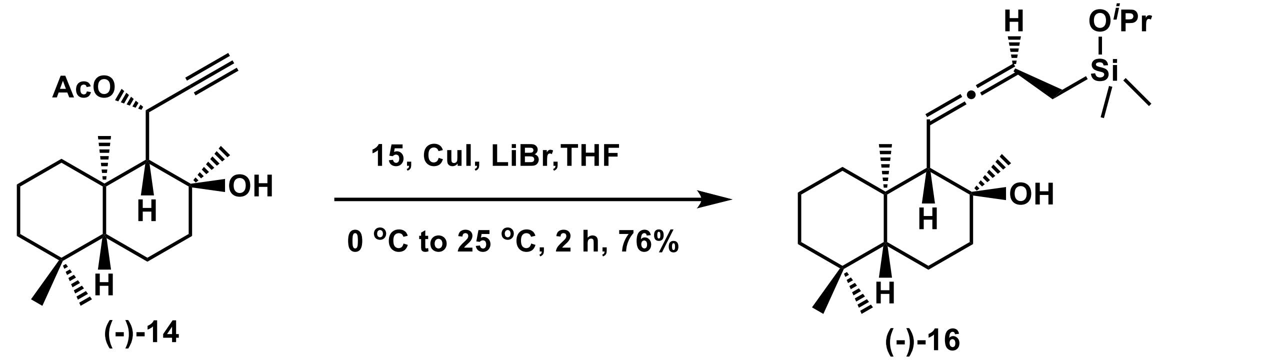
NaH, $(CH_3O)_2CO$, toluene
100 °C, 2 h
$SnCl_4$, CH_2Cl_2
0 °C to 25 °C, 12 h
78% for 2 steps
CO_2Me
7
10s
11
11s
1) 11s, *p*-TsOH, benzene
80 °C, 4 h
2) $LiAlH_4$, Et_2O
0 °C to 25 °C, 12 h
80% for 2 steps
12sa
12sb
p-TsOH, acetone:H_2O (10:1)
25 °C, 24 h, 92%
p-TsOH, acetone:H_2O (10:1)
25 °C, 24 h, 87%
(+)-8
(-)-8



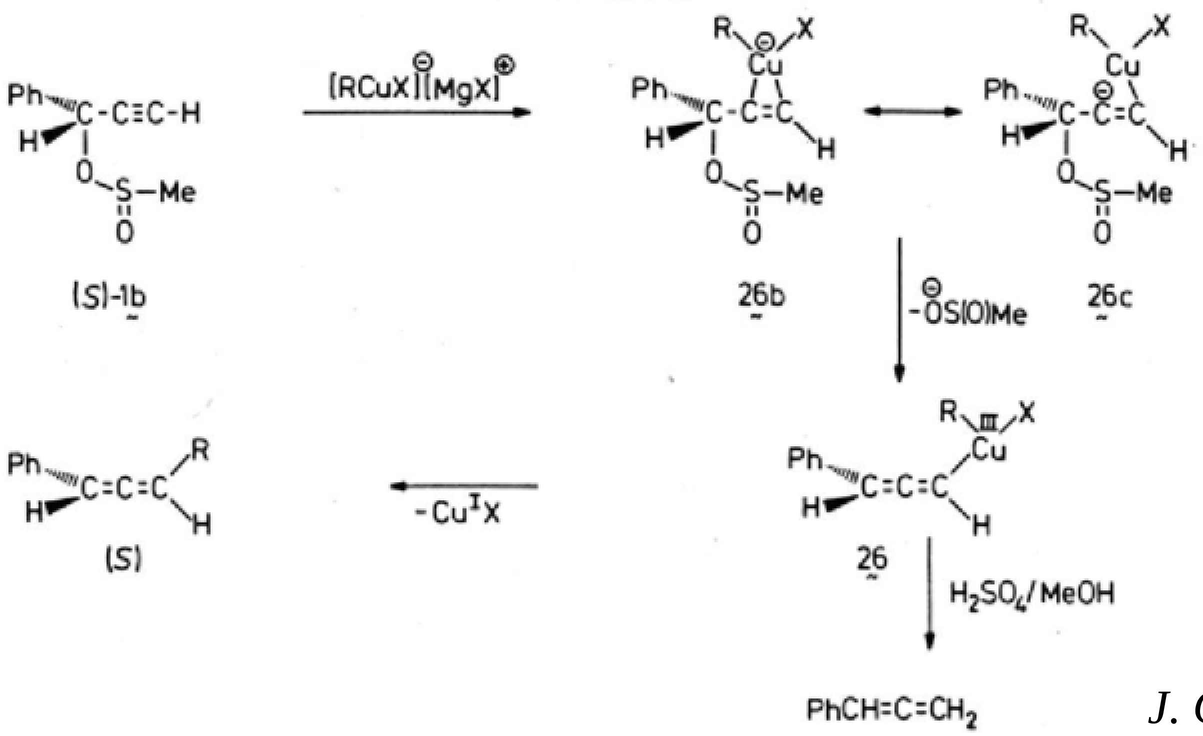
CHO
OH
H
(-)-4
TMS
Li
O
M
O
H
H
≠
TMS
HO
OH
H
H
12



AcO
OH
H
(-)-14
15, CuI, LiBr,THF
0 °C to 25 °C, 2 h, 76%
O^{i}Pr
Si
(-)-16
H$_2$O$_2$, KF, KHCO$_3$, MeOH/THF(1:1),
20 °C, 8 h, 78%
(-)-22s
TBSCl, imidazole, CH$_2$Cl$_2$
0 °C to 25 °C, 1 h, 93%
OTBS
(-)-6
AuClPPh$_3$, AgBF$_4$, NIS, toluene
25 °C, 1 h, 76%
I
O
(-)-20
TBAF, THF
25 °C, 1 h
(-)-26s
ClMg
15



$$CuX + LiX \longrightarrow LiCuX_2 \xrightarrow{R-MgX} [\{RCuX\}MgX \cdot LiX]$$



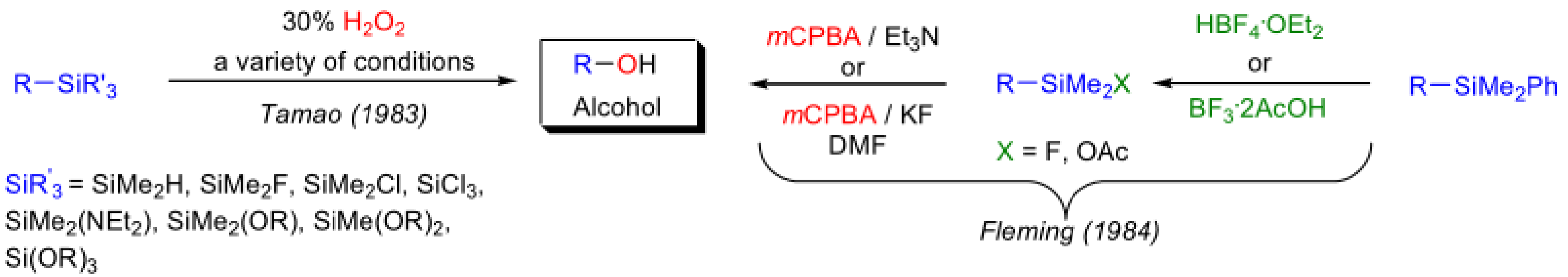
J. Org. Chem., **1989**, *15*, 54.

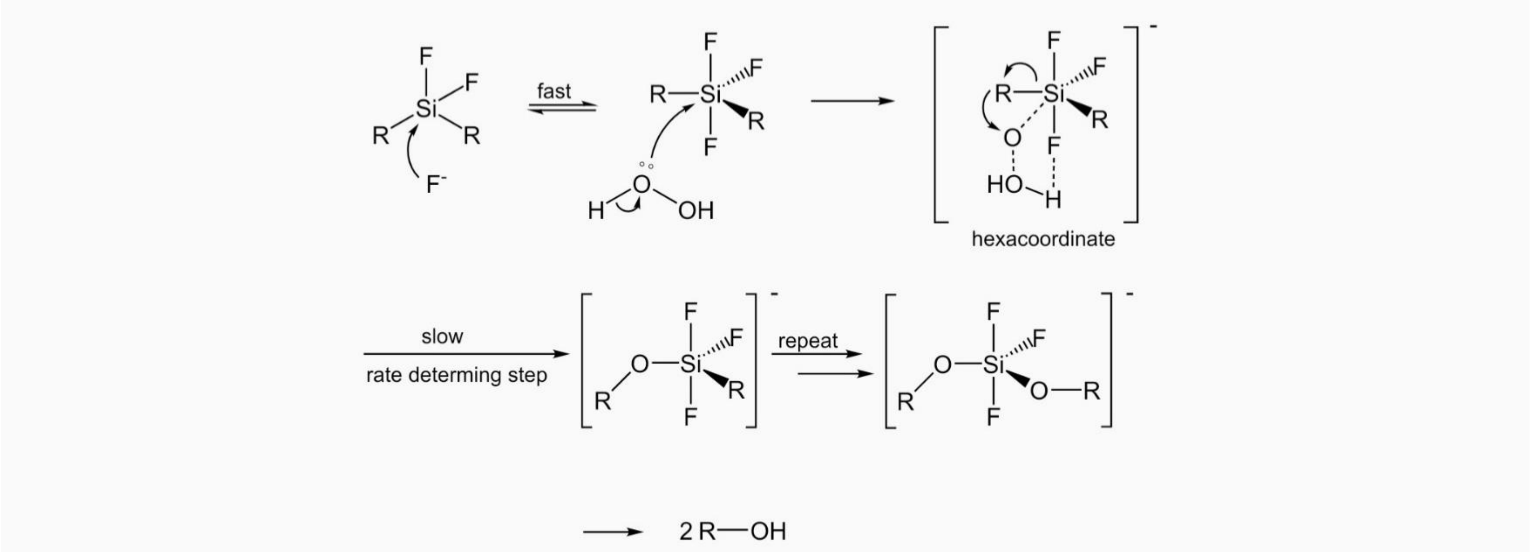
FLEMING-TAMAO OXIDATION

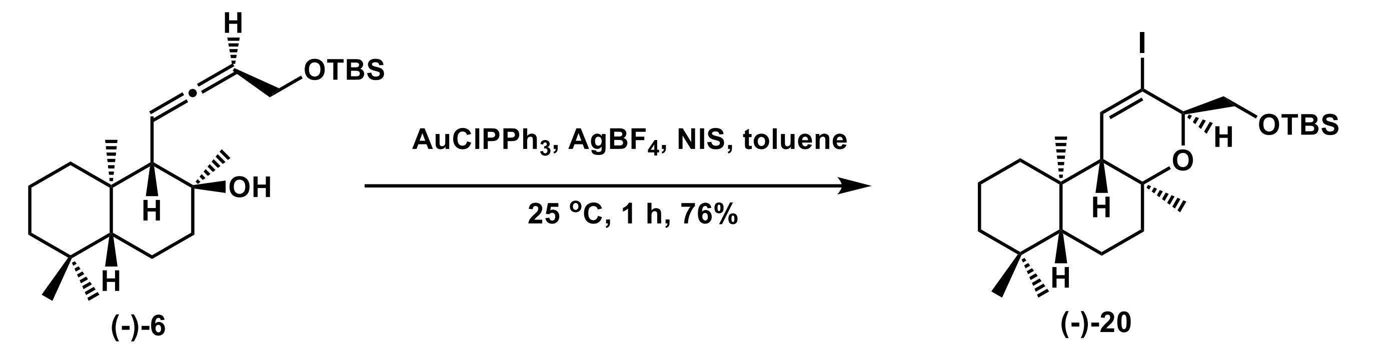
(References are on page 588)

Importance:

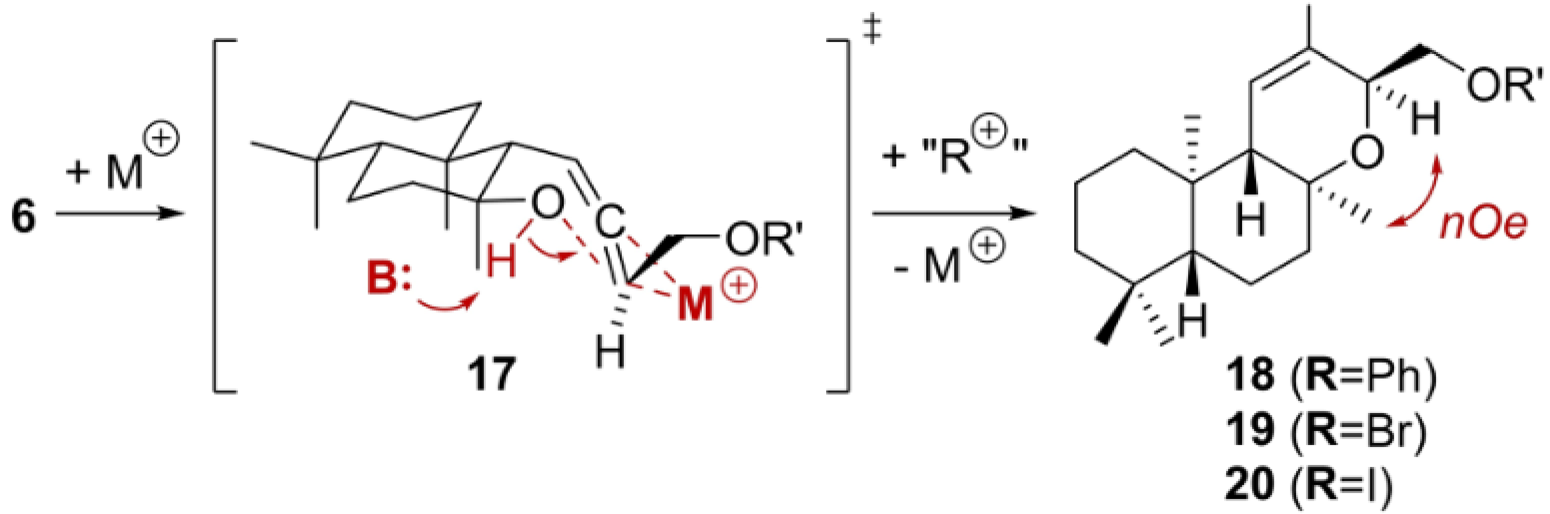
[*Seminal Publications*[1-7]; *Reviews*[8-12]; *Modifications & Improvements*[13-17]; *Theoretical Studies*[18,19]]



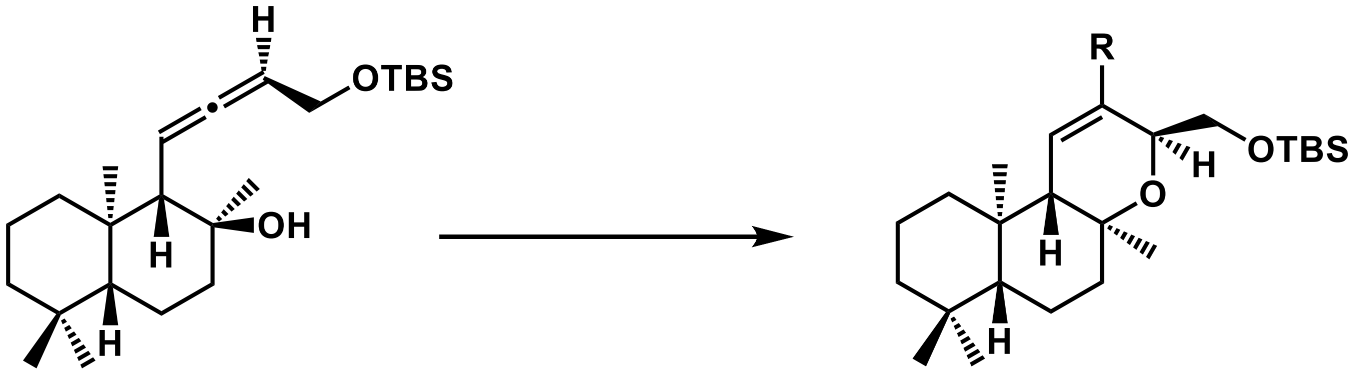




OTBS
OH
H
AuClPPh3, AgBF4, NIS, toluene
25 °C, 1 h, 76%
I
O
(-)-6
(-)-20



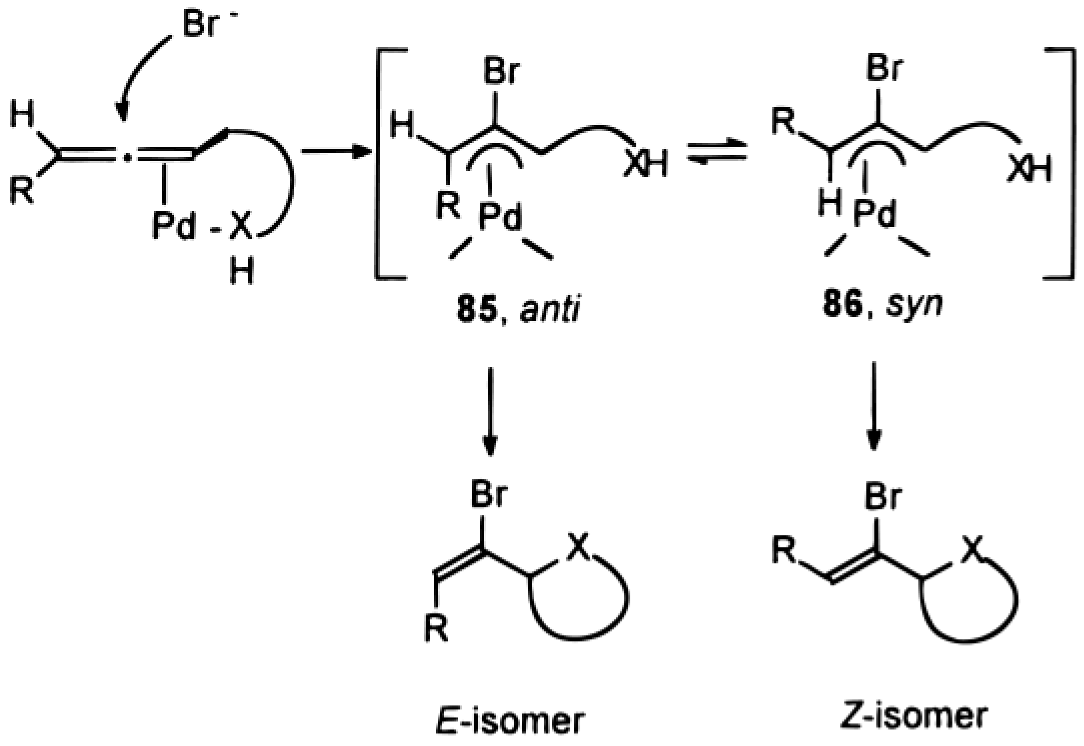
6
+ M⊕
B:
H
O
C
OR'
M⊕
17
‡
+ "R⊕"
- M⊕
R
nOe
18 (R=Ph)
19 (R=Br)
20 (R=I)



(-)-6

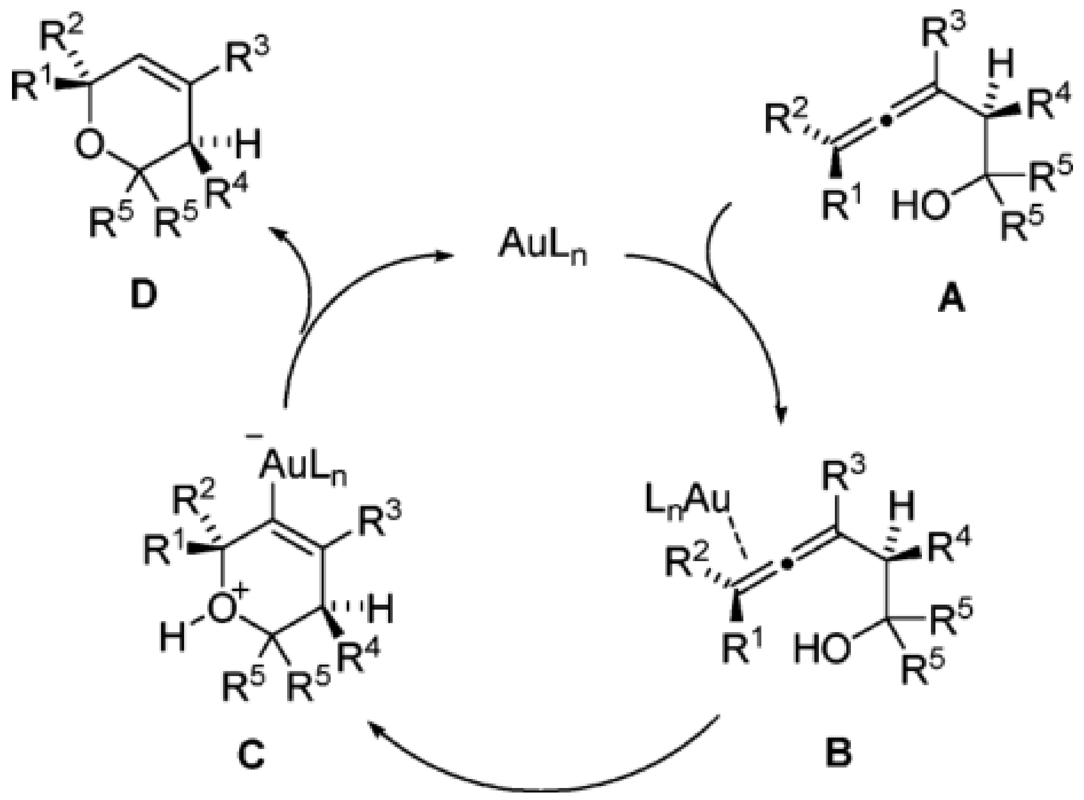
18 (R=Ph)
19 (R=Br)
20(R=I)

Entry	Catalyst	Reagents and conditions	Yield [%][a]
1	$Pd(PPh_3)_4$	K_2CO_3, PhI; DMF, 80 °C	0 (**18**)[b]
2	$Pd_2(dba)_3$	dppe (5 mol%), Cs_2CO_3, PhI; DMF, 80 °C	0 (**18**)[b]
3	$AuClPPh_3$	Cs_2CO_3, $[PhN_2][BF_4]$; Acn, 50 °C	0 (**18**)[c]
4	$AuClPPh_3$	$NaHCO_3$, $[PhN_2][BF_4]$; Acn, 50 °C	0 (**18**)[c]
5	$Pd(OAc)_2$	$Cu(OAc)_2 \times 2\,H_2O$ (2 equiv), LiBr (5 equiv), K_2CO_3 (1.2 equiv), O_2 (1 atm); Acn, 25 °C	56 (**19**) (d.r. 5:1)[d]
6	$Pd(Acn)_2Cl_2$	$Cu(OAc)_2 \times 2\,H_2O$ (2 equiv), LiBr (5 equiv), K_2CO_3 (1.2 equiv), O_2 (1 atm); Acn, 25 °C	42 (**19**) (d.r. 5:1)[d]
7	$AuClPPh_3$	$AgBF_4$ (5 mol%), I_2; Acn, 25 °C	0 (**20**)[b]
8	$AuClPPh_3$	$AgBF_4$ (5 mol%), NIS; CH_2Cl_2, −20 °C	0 (**20**)[b]
9	$AuClPPh_3$	$AgBF_4$ (5 mol%), NIS; Acn, 25 °C	30 (**20**) (d.r. > 95:5)[d]
10	$AuCl_3$	AgOTf (5 mol%), NIS; Acn, 25 °C	20 (**20**) (d.r. > 95:5)[d]
11	$AuClPPh_3$	$AgBF_4$ (5 mol%), NIS; **toluene**; 25 °C	76 (**20**) (d.r. > 95:5)[d]

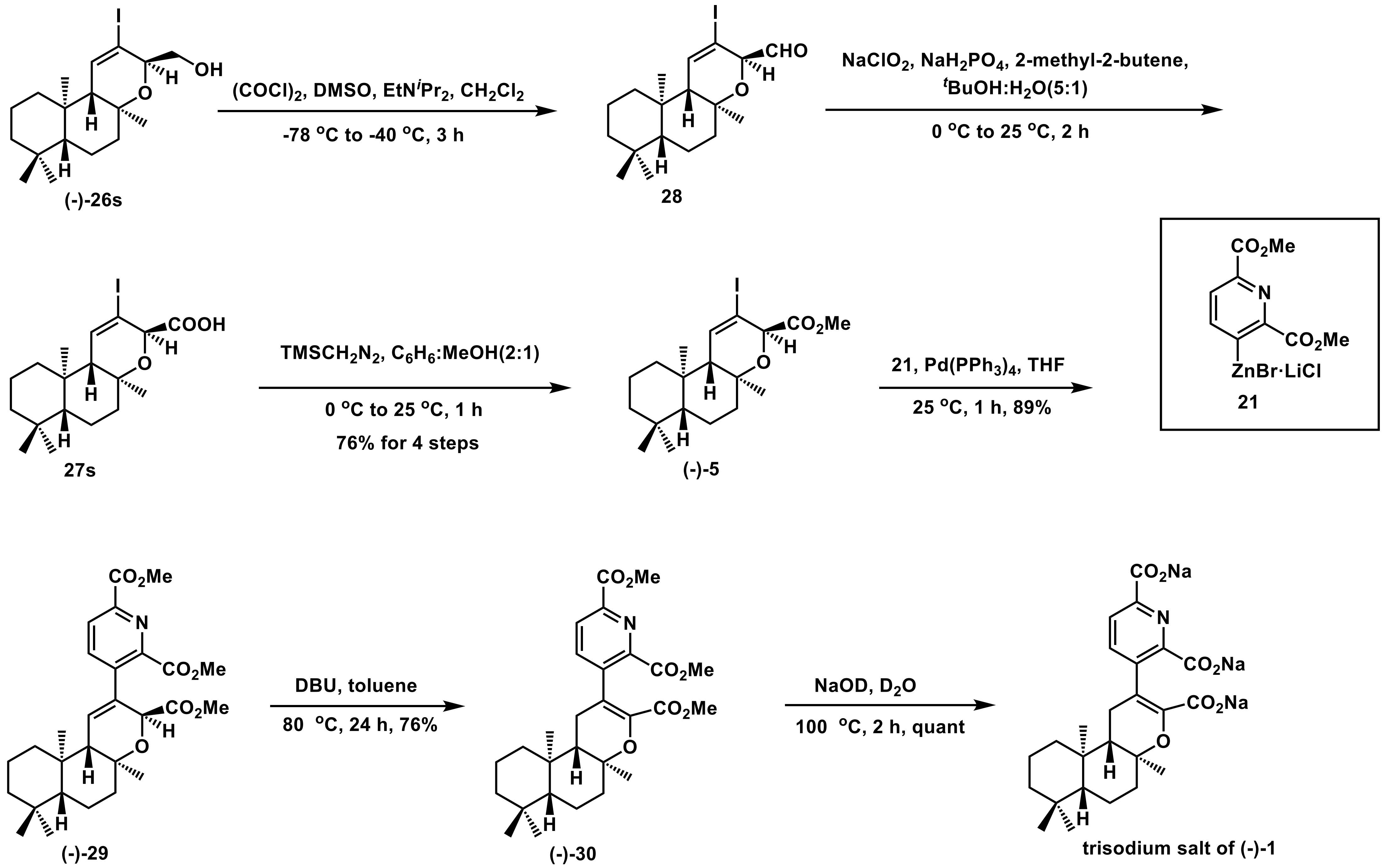


XH = COOH, OH, NHR, OCONHR

J. Am. Chem. Soc., **2000,** *122,* 9600.



Org. Lett., **2006**, *8*, 20.


(COCl)2, DMSO, EtNiPr2, CH2Cl2
-78 oC to -40 oC, 3 h
NaClO2, NaH2PO4, 2-methyl-2-butene,
tBuOH:H2O(5:1)
0 oC to 25 oC, 2 h
(-)-26s
28
TMSCH2N2, C6H6:MeOH(2:1)
0 oC to 25 oC, 1 h
76% for 4 steps
21, Pd(PPh3)4, THF
25 oC, 1 h, 89%
27s
(-)-5
21
DBU, toluene
80 oC, 24 h, 76%
NaOD, D2O
100 oC, 2 h, quant
(-)-29
(-)-30
trisodium salt of (-)-1

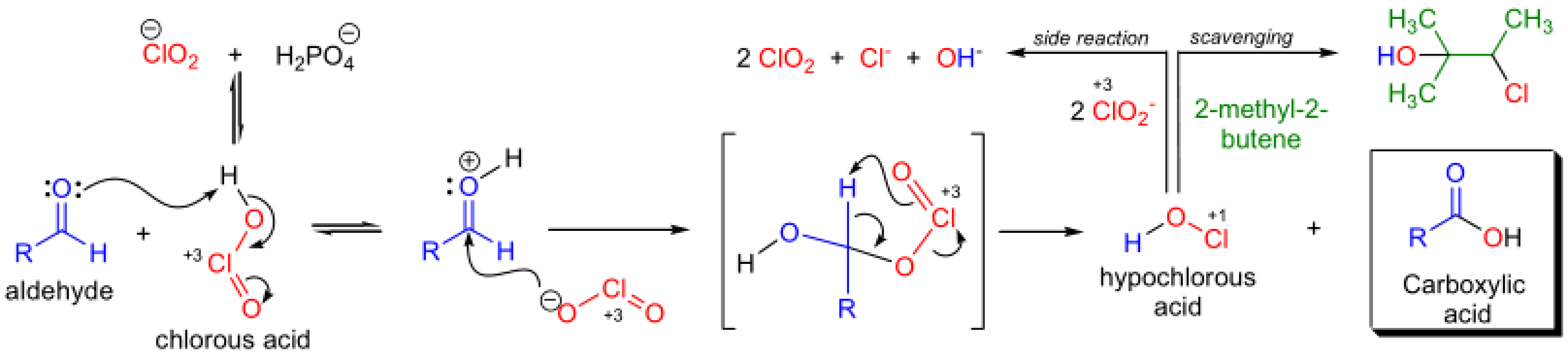
PINNICK OXIDATION

(References are on page 655)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5]; *Modifications & Improvements*[6,5,7]]

Mechanism: [10,6]



NEGISHI CROSS-COUPLING

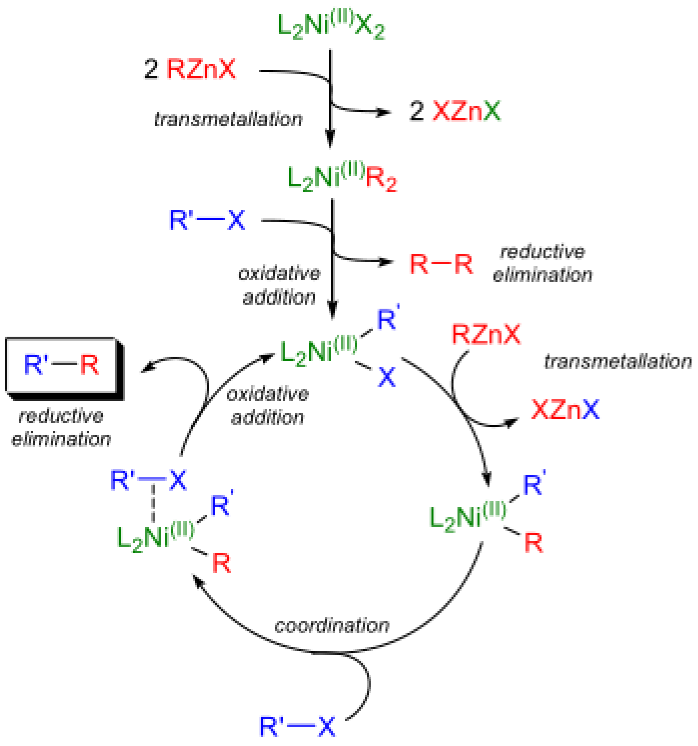
(References are on page 637)

Importance:

[*Seminal Publications*[1-6]; *Reviews*[7-24]; *Modifications & Improvements*[25-32]]

Mechanism: [10]

Ni-catalyzed process:



Pd-catalyzed process: