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Communication

Total Synthesis of Yuzurine-type Alkaloid Daphgraciline

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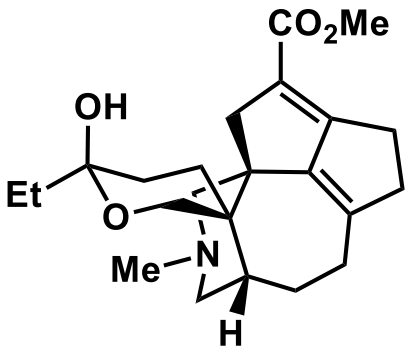
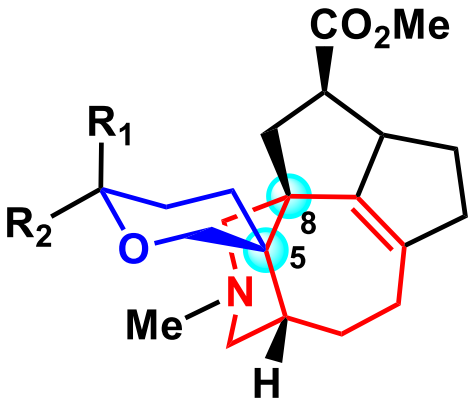


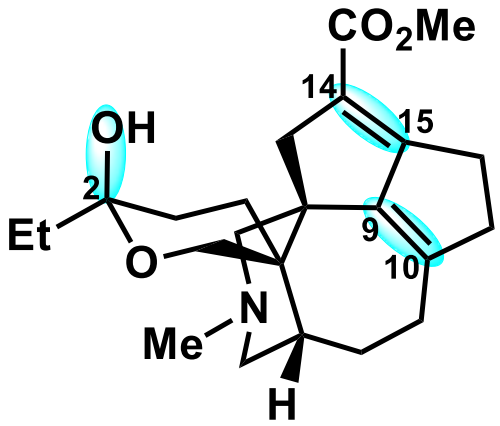
daphgraciline



yuzurine-type (1), 50 members
no total synthesis reported

structural features:

- [6-7-5-5-6] pentacyclic core
- unique azabicyclo[4.3.1] ring system
- unusual spiro tetrahydropyran
- multiple stereocenters

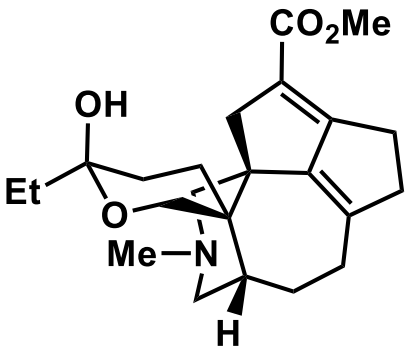


daphgraciline (2)

additional structural features:

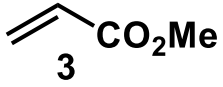
- 2 tetrasubstituted double bonds
- hemiketal moiety

Retrosynthetic Analysis of Daphgraciline (2)



daphgraciline (2)

reductive epoxide coupling



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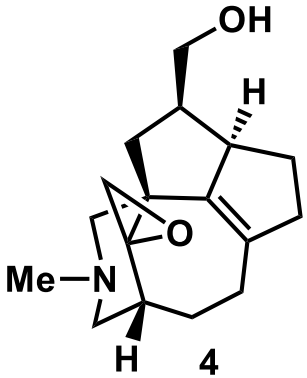
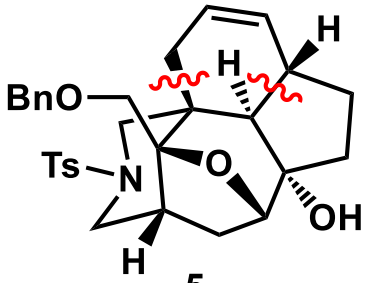


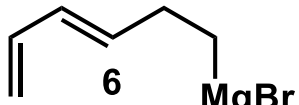
4

ring contraction

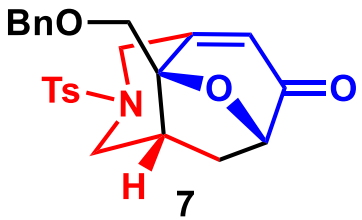


5

1,2-addition

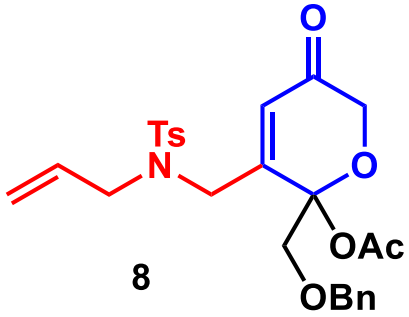


IMDA



7

type II [5+2]



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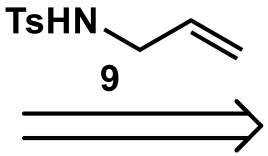

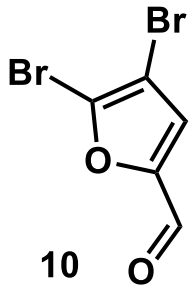

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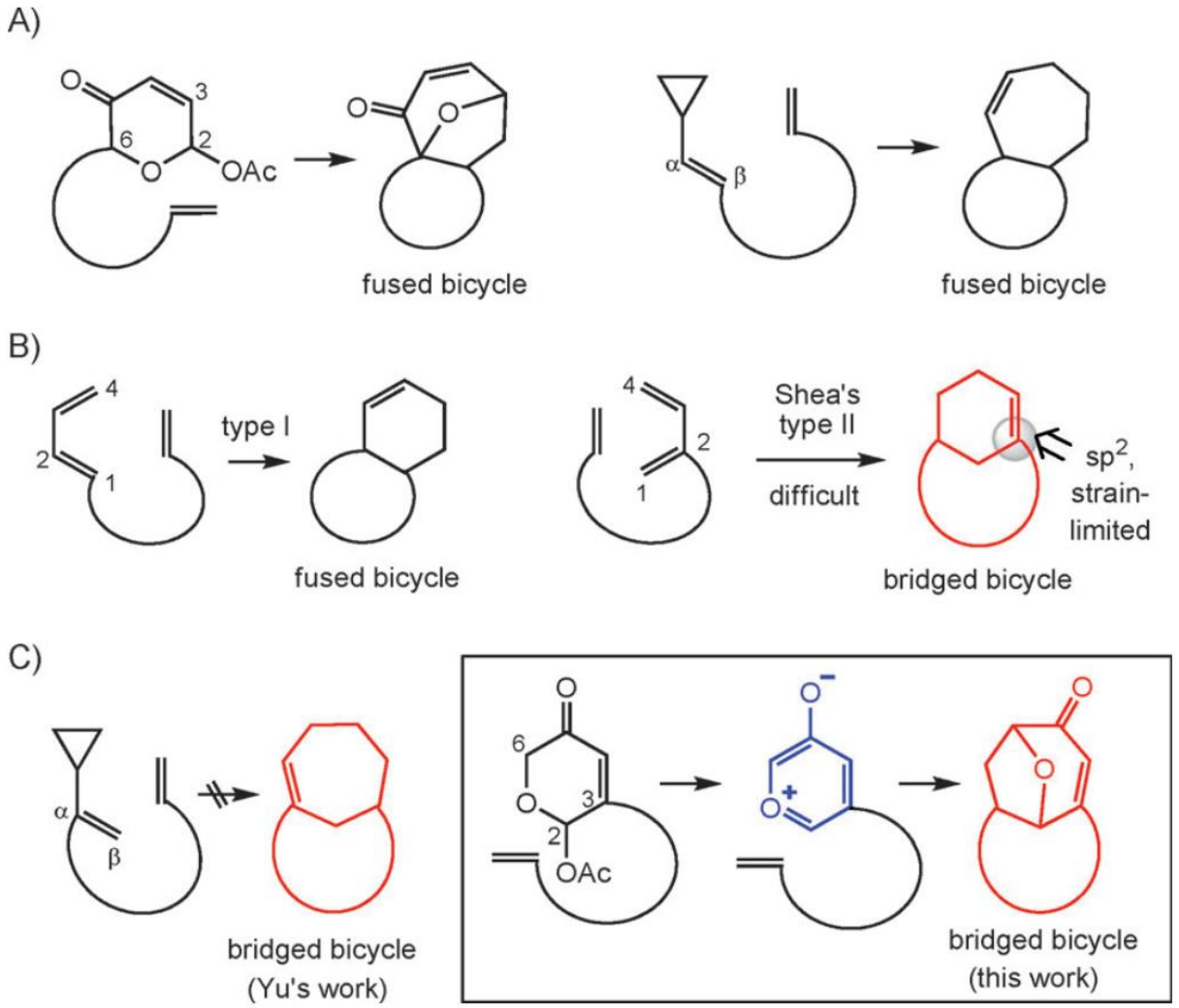


Scheme 1. A) Type I intramolecular [5+2] cycloaddition reactions. B) Type I and type II IMDA reaction. C) Type II intramolecular [5+2] cycloaddition to bridged cycloheptane bicycles.

Angew. Chem., Int. Ed., **2015**, *54*, 1754.

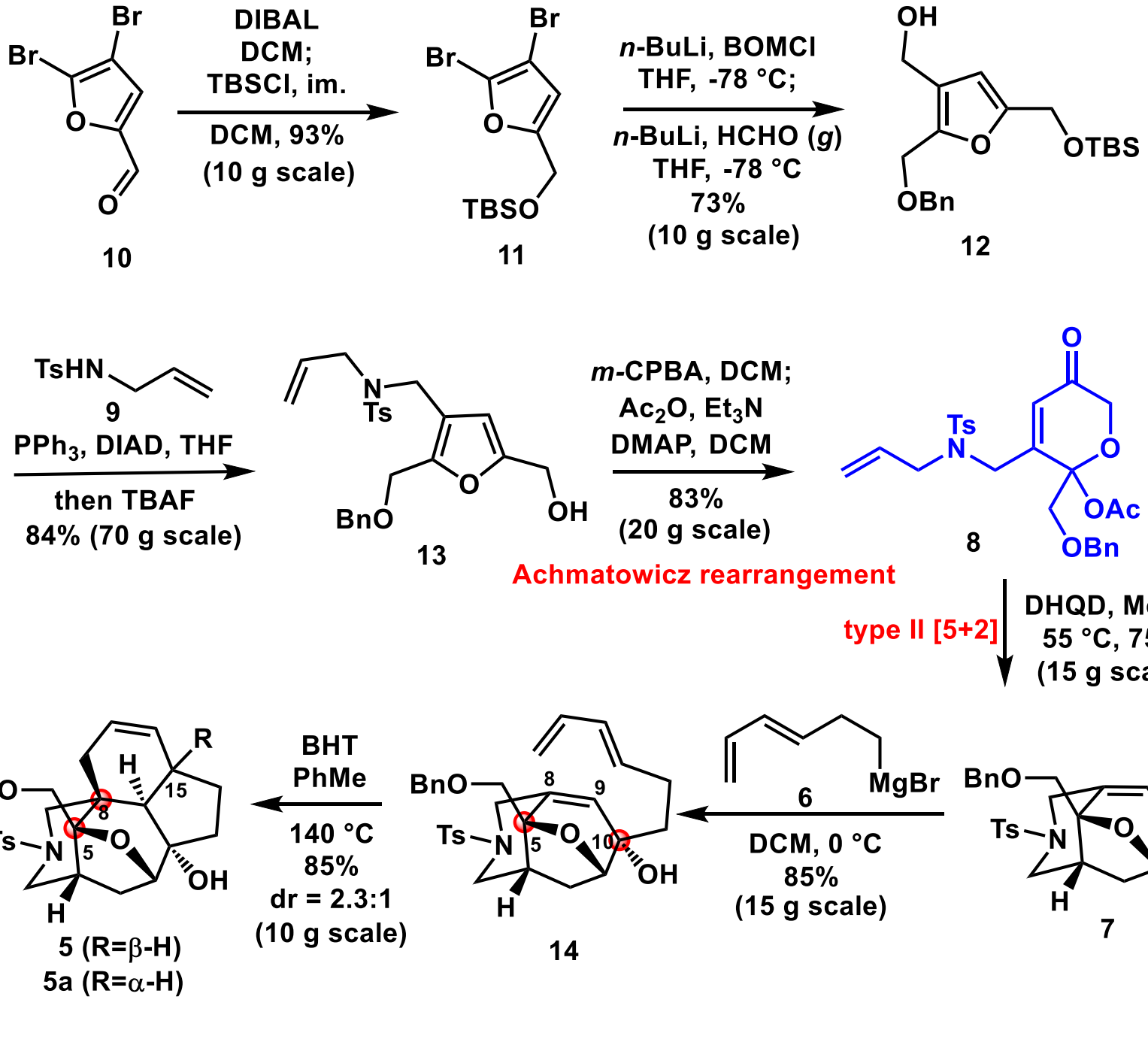
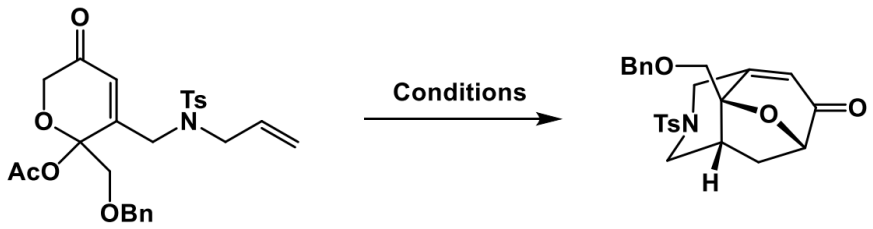

Br
Br
O
O
10
DIBAL
DCM;
TBSCl, im.
DCM, 93%
(10 g scale)
Br
Br
O
TBSO
11
n-BuLi, BOMCl
THF, -78 °C;
n-BuLi, HCHO (g)
THF, -78 °C
73%
(10 g scale)
OH
O
OTBS
OBn
12
TsHN
9
PPh3, DIAD, THF
then TBAF
84% (70 g scale)
N
Ts
O
BnO
OH
13
m-CPBA, DCM;
Ac2O, Et3N
DMAP, DCM
83%
(20 g scale)
O
Ts
N
O
OAc
OBn
8
Achmatowicz rearrangement
type II [5+2]
DHQD, MeCN
55 °C, 75%
(15 g scale)
BnO
Ts
N
O
O
H
7
MgBr
6
DCM, 0 °C
85%
(15 g scale)
BnO
8
9
Ts
N
5
O
10
OH
H
14
BHT
PhMe
140 °C
85%
dr = 2.3:1
(10 g scale)
BnO
H
R
15
8
Ts
N
5
O
OH
H
5 (R=β-H)
5a (R=α-H)

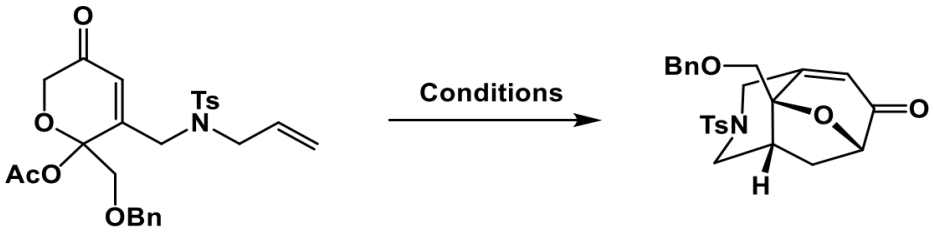
Table S1. Optimization of Type II [5+2] cycloaddition of 8



8 7[a]

Entry	Base	Equiv.	Solvent	T (°C)	t (h)	Yield(%)[b]
1	DBU	1.5	DCM	25	12	62
2	DBN	2.0	DCM	25	15	Decomposed
3	DABCO	2.0	DCM	25	15	0
4	Pyrrolidine	2.0	DCM	25	15	Decomposed
5	Pyrrole	2.0	DCM	25	15	0
6	Et_3N	4.0	DCM	25	15	0
7	Et_3N	4.0	DCM	60	15	25
8	Et_3N	2.0	MeCN	80	15	58

Table S1. Optimization of Type II [5+2] cycloaddition of 8

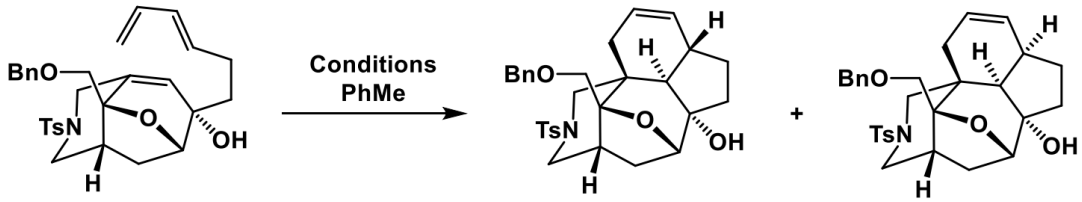


8 7[a]

Entry	Base	Equiv.	Solvent	T (°C)	t (h)	Yield(%)[b]
9	TMP	2.0	DCM	25	15	0
10	TMP	1.5	MeCN	160	12	59
11	K_2CO_3	3.0	MeCN	120	12	Decomposed
12	DHQD	0.5	DCM	35	12	65
13	DHQD	0.5	MeCN	55	12	75
14	DHQD	0.1	MeCN	55	12	60

[a]Reaction conditions: **8** (30 mg), solvent (25 mL). [b]Isolated yield.

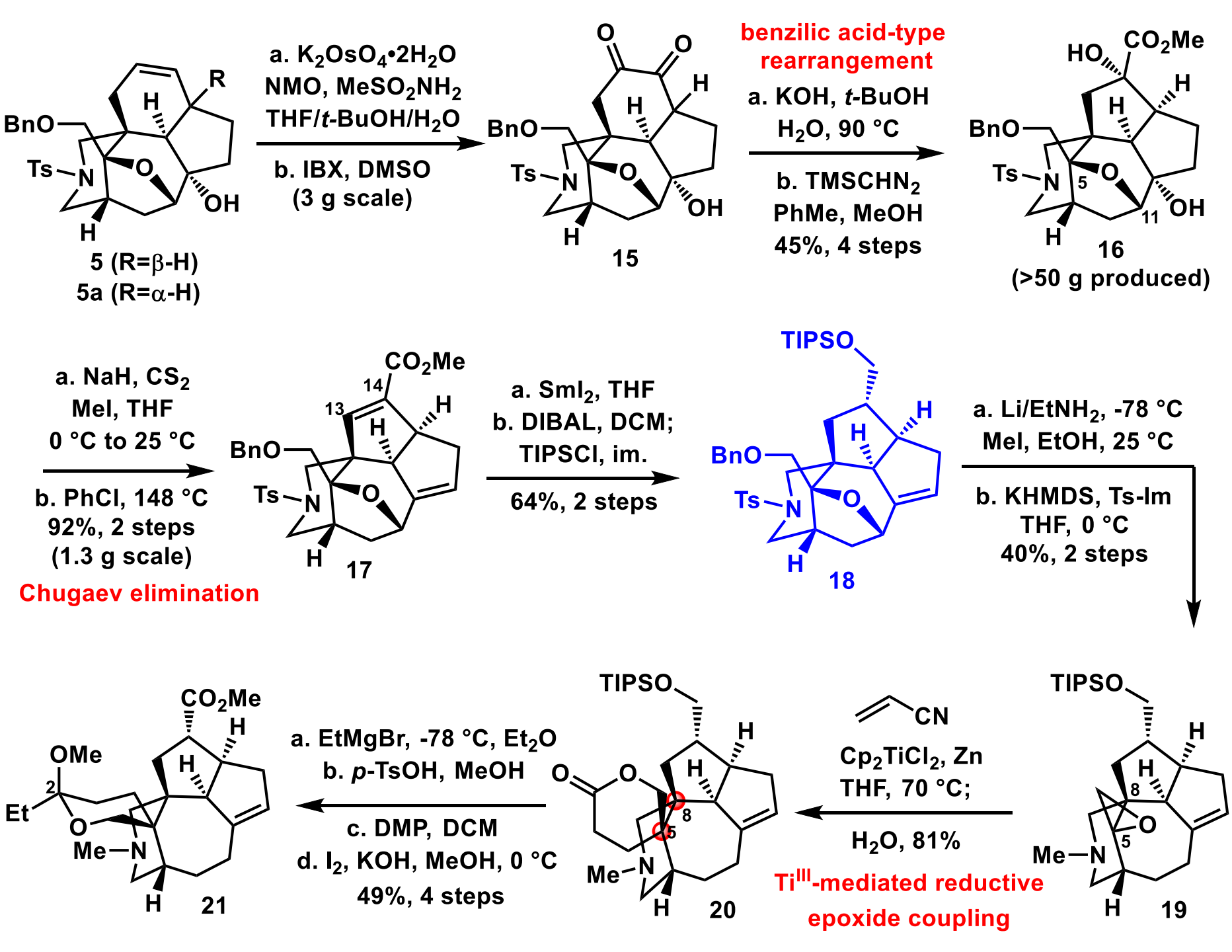
Table S2. Optimization of IMDA reaction of 14



14[a] 5 5a

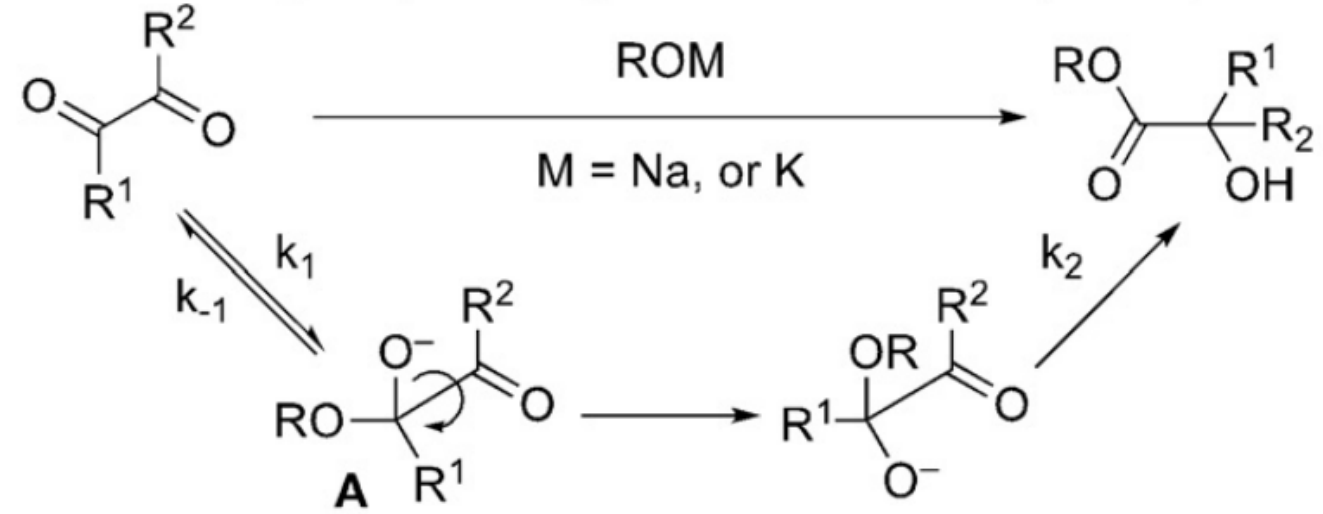
Entry	T(°C)	Additive	t(h)	Solvent	Ratio(**5**:**5a**)	Yield(%)[b]
1	80	-	5	PhMe	-	0
2[c]	120	-	5	PhMe	2.5:1	64
3	120	BHT	12	PhMe	2.5:1	81
4	140	-	12	PhMe	2.3:1	83
5	140	BHT	12	PhMe	2.3:1	85
6	160	-	12	PhMe	2:1	75
7[d]	180	-	3	PhMe	2:1	70
8	140	-	12	MeCN	1.7:1	74
9	140	-	12	PhCl	1.7:1	76
10	140	-	12	Dioxane	1.7:1	74

[a]Reaction conditions: **14** (30 mg), PhMe (8 mL). [b]Isolated yield. [c]85% conversion. [d]91% conversion.


a. $K_2OsO_4•2H_2O$
NMO, $MeSO_2NH_2$
THF/*t*-BuOH/H_2O
b. IBX, DMSO
(3 g scale)
5 (R=β-H)
5a (R=α-H)
15
benzilic acid-type rearrangement
a. KOH, *t*-BuOH
H_2O, 90 °C
b. $TMSCHN_2$
PhMe, MeOH
45%, 4 steps
16
(>50 g produced)
a. NaH, CS_2
MeI, THF
0 °C to 25 °C
b. PhCl, 148 °C
92%, 2 steps
(1.3 g scale)
Chugaev elimination
17
a. SmI_2, THF
b. DIBAL, DCM;
TIPSCl, im.
64%, 2 steps
18
a. Li/$EtNH_2$, -78 °C
MeI, EtOH, 25 °C
b. KHMDS, Ts-Im
THF, 0 °C
40%, 2 steps
19
Cp_2TiCl_2, Zn
THF, 70 °C;
H_2O, 81%
Ti^{III}-mediated reductive epoxide coupling
20
a. EtMgBr, -78 °C, Et_2O
b. *p*-TsOH, MeOH
c. DMP, DCM
d. I_2, KOH, MeOH, 0 °C
49%, 4 steps
21

benzilic acid-type rearrangement

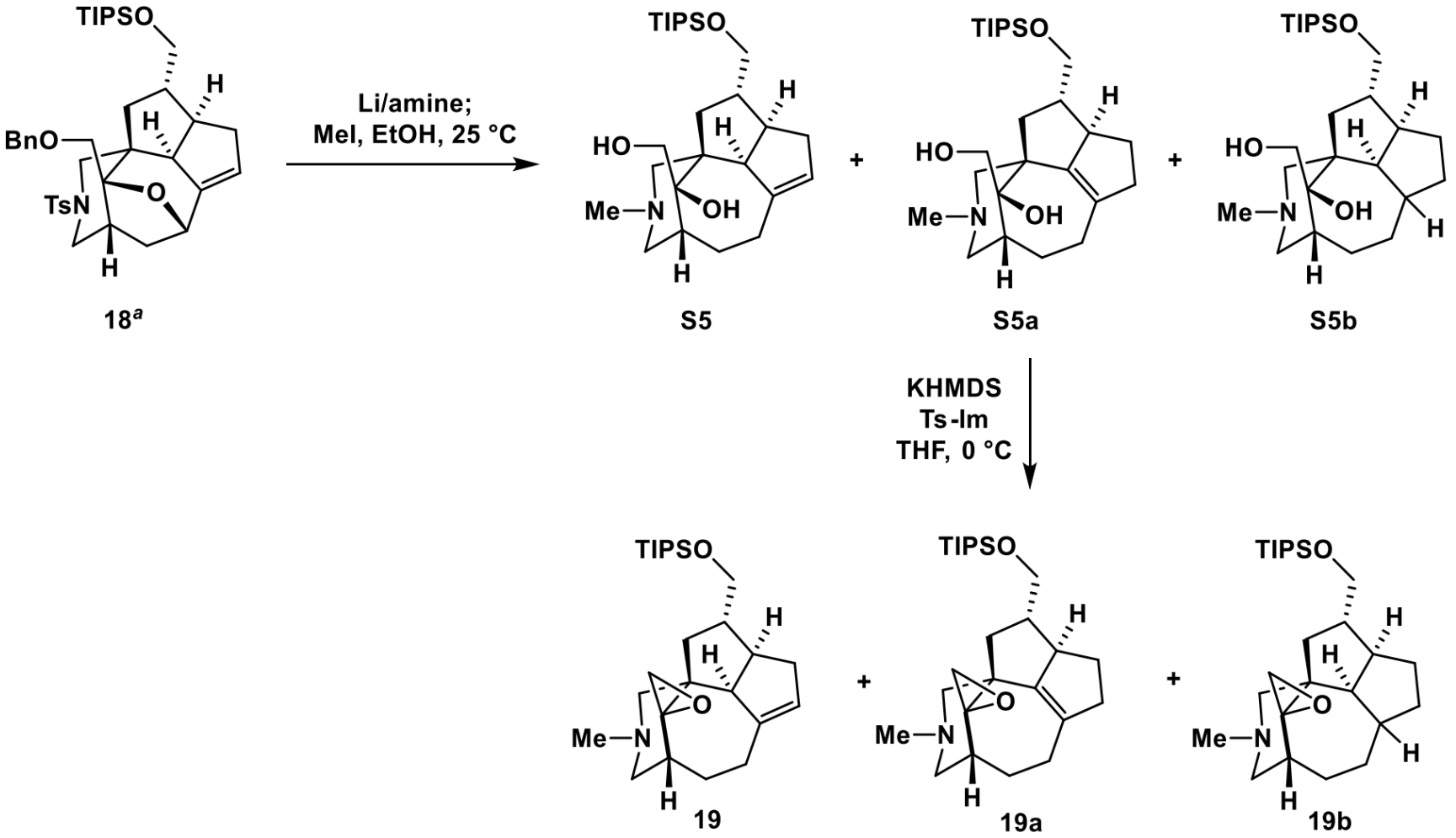
Benzilic acid (ester) rearrangement and reaction pathway



$R^1 = R^2$ = arene, alkyl, ester, R = H or alkyl

established kinetics: $k_1 \geq k_2 \leq k_{-1}$

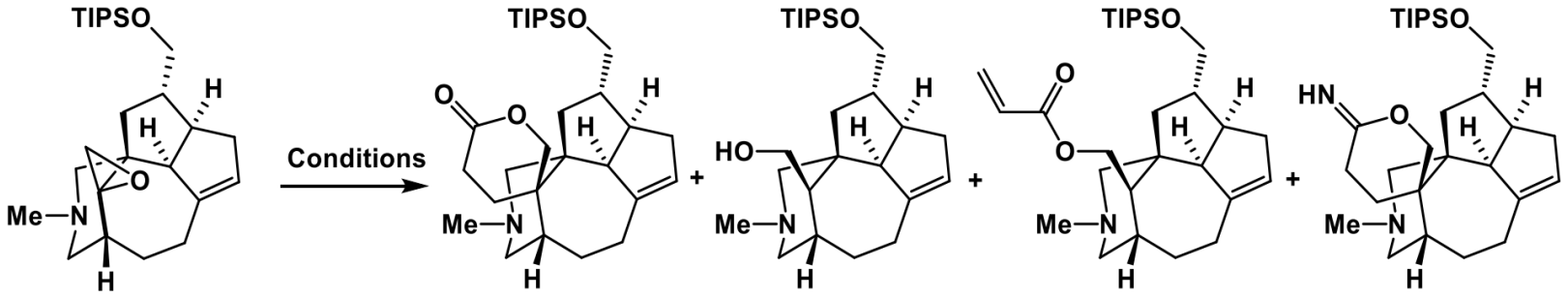
Table S3. Screened oxa-bridged ring opening conditions of 18



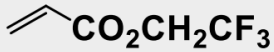
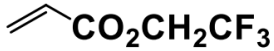
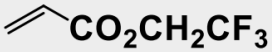
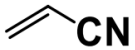
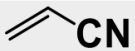
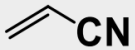
Entry	Solvent	Additive	T (°C)	t (min)	Ratio (**19**:**19a**:**19b**)	Yield (**19**)(%)[b]
1	$EtNH_2$	-	0	20	Mainly **19b**	<5
2	$EtNH_2$	-	-78	5	3:1:0	41
3	$EtNH_2$	-	-78	60	3:1:0	40
4	NH_3	-	-78	60	decomposed	0
5	$MeNH_2$	-	-78	5	3:1:0	31
6	$EtNH_2$/THF(2:1)	-	-78	5	2:1:0	30
7	$EtNH_2$	*t*-BuOH	-78	5	7.5:1:3	28
8	$EtNH_2$	EtOH	-78	5	3:1:2	22
9	$EtNH_2$/Me_2NH(1:1)	-	-78	5	3:1:0	35

[a]Reaction conditions: **18** (100 mg), amine (5 mL). [b]Isolated yield.

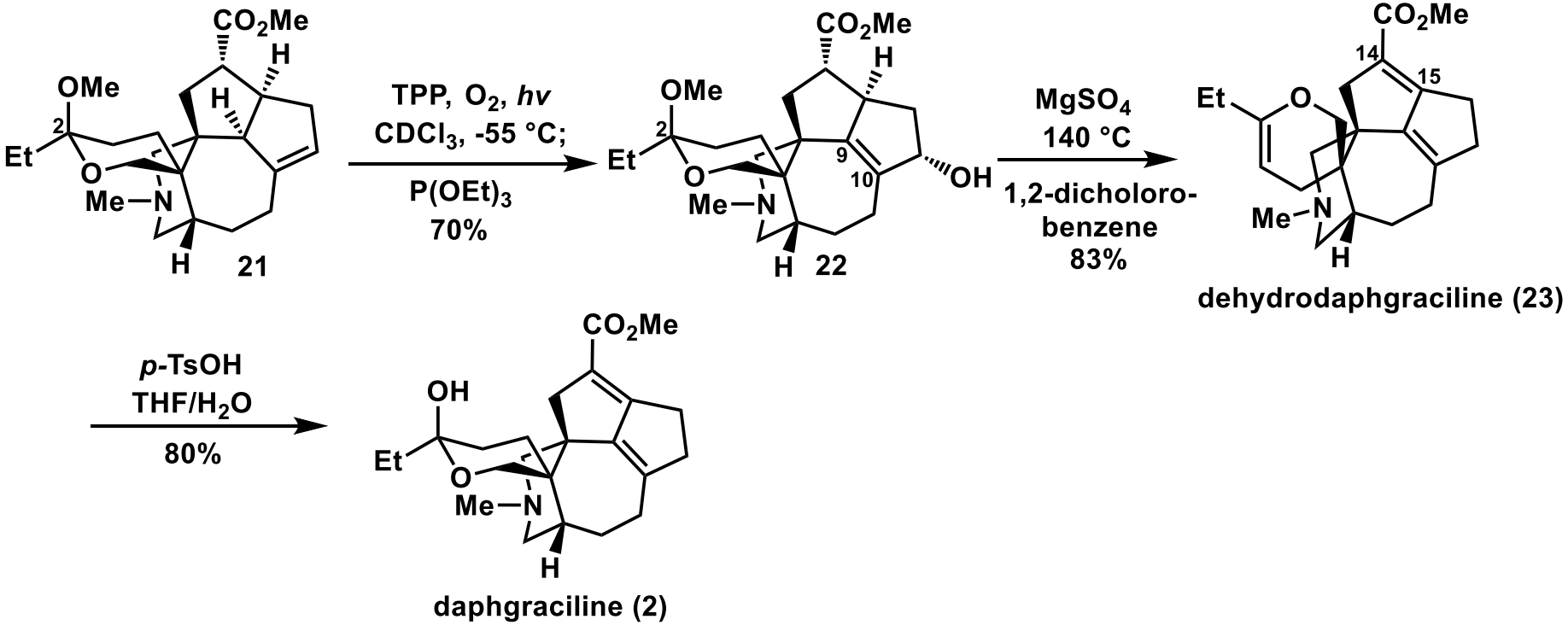
Table S4. Condition screening of Ti^{III}-mediated reductive epoxide coupling reaction of 19



Entry	Conditions[a]	Ratio (**19**/**20**/**20a**/**20b**/**20c**)	Yield (**20**) (%)[b]
1	Cp_2TiCl_2 (1.6 eq.), Zn (1.5 eq.), $CO_2CH_2CF_3$ (10 eq.), 2,4,6-collidine·HCl (3 eq.), 25 °C, 12 h	-	0
2	Cp_2TiCl_2 (3 eq.), Zn (12 eq) CO_2Me (10 eq.), 25 °C, 2 h	-	0
3	Cp_2TiCl_2 (4 eq.), Zn (6 eq.), $CO_2CH_2CF_3$ (10 eq.), 60 °C, 5 h	1.2:1:2.1:0.4:0	12

4	Cp_2TiCl_2 (4 eq.), Zn (6 eq.),  (20 eq.), 60 °C, 7 h	0.7:1:1.4:0.4:0	20
5	Cp_2TiCl_2 (5 eq.), Zn (10 eq.),  (50 eq.), 70 °C, 7 h	0.1:1:0.7:0.4:0	31
6	Cp_2TiCl_2 (5 eq.), Zn (10 eq.),  (50 eq.), 70 °C, 20 h	0:1:0.04:0.4:0	42
7	Cp_2TiCl_2 (5 eq.), Zn (10 eq.),  (50 eq.), 2,4,6-collidine·HCl (3 eq.), 70 °C, 16 h	1.6:1:0:0:0	44
8	Cp_2TiCl_2 (6 eq.), Zn (15 eq.),  (12 eq.), 70 °C, 16 h	1:8:0:0:0	71
9[c]	Cp_2TiCl_2 (6 eq.), Zn (15 eq.),  (12 eq.), 70 °C, 16 h	1:5.6:0:0:4.4	44
10[c]	Cp_2TiCl_2 (6 eq.), Zn (15 eq.),  (12 eq.), 70 °C, 16 h; H_2O (2 eq.), 6 h	1:10:0:0:0	81

[a]Reaction Conditions: **19** (20 mg), THF (1.5 mL); [b]Isolated yield. [c]Run with 90 mg **19**.



ene reaction

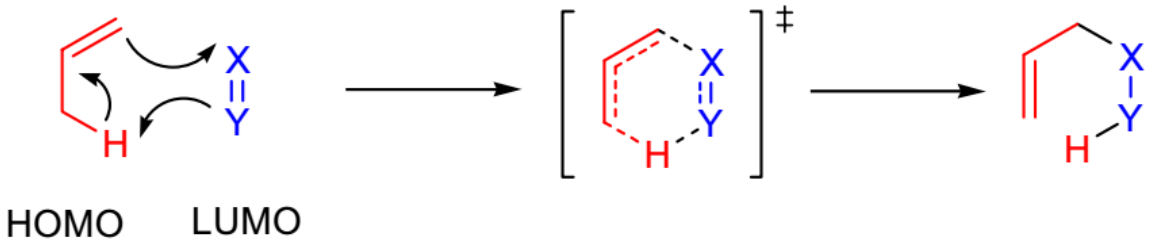
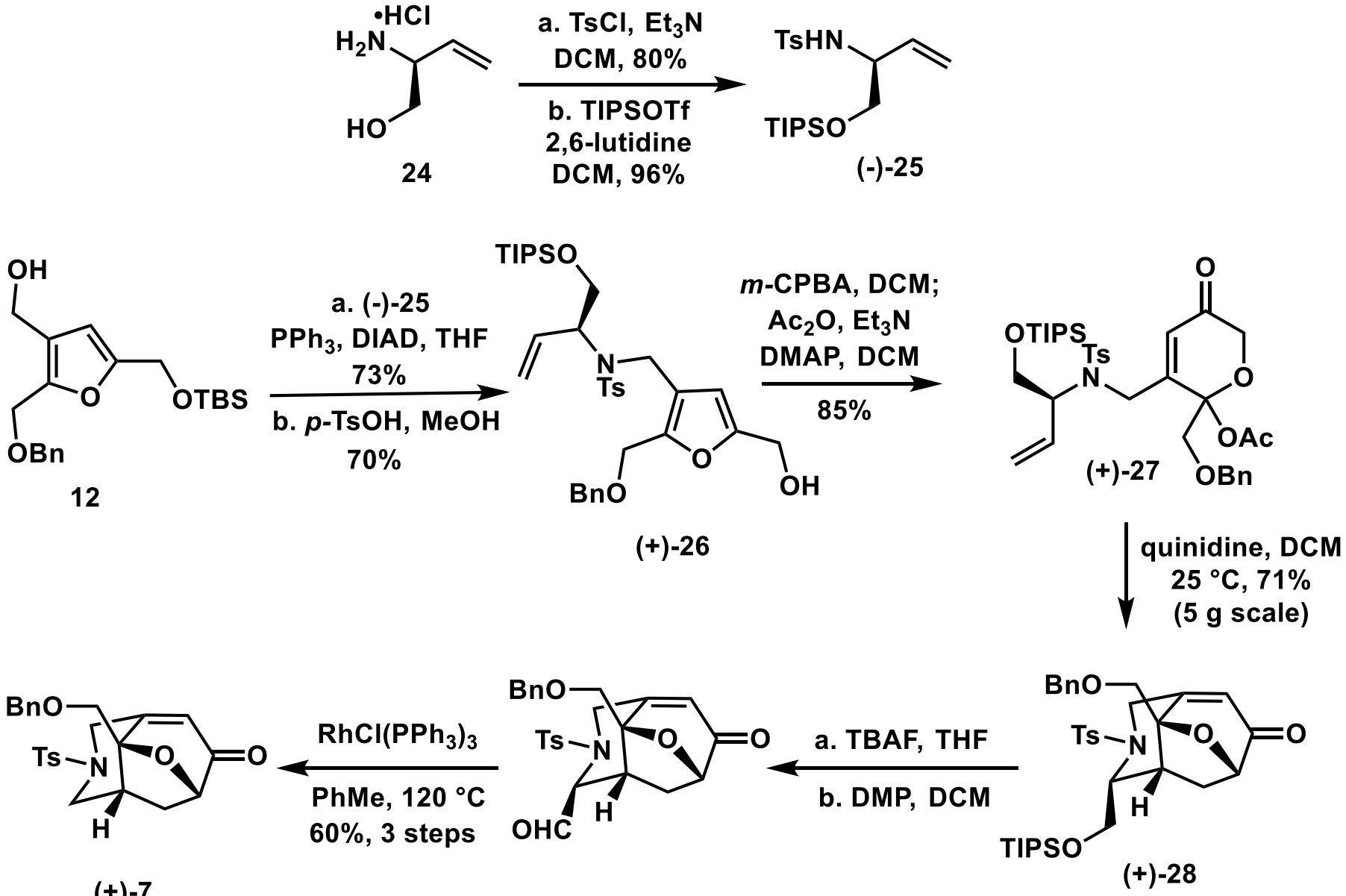


Table 1. Singlet Oxygen Lifetimes, τ_Δ, at High and Low Temperature Extremes and at Room Temperature[a]

solvent	$\tau_\Delta^{high}/\mu s$ (T/°C)	$\tau_\Delta^{RT}/\mu s$ (T/°C)	$\tau_\Delta^{low}/\mu s$ (T/°C)
toluene-h_8	26.3 (80)	30.3 (20)	31.2 (10)
toluene-d_8	127 (80)	264[b] (20)	303 (10)
benzene-h_6	30.4 (75)	30.3 (20)	30.2 (10)
benzene-d_6	490 (75)	802 (20)	857 (10)
cyclohexane-h_{12}	22.9 (75)	23.8 (20)	24.0 (10)
cyclohexane-d_{12}	501 (75)	482[b] (20)	478 (10)
methanol-h_4	10.4 (60)	9.8 (20)	9.1 (−15)
methanol-d_4	258 (60)	285 (20)	290 (10)
CH_3CN	81.5 (60)	81.8 (20)	81.9 (5)
CD_3CN	1590 (60)	1625 (20)	1635 (5)
H_2O	3.3 (50)	3.5 (20)	3.6 (5)
D_2O	50 (85)	69 (20)	77 (5)

J. Am. Chem. Soc., **2010**, *132*, 8098.


•HCl
H2N
HO
24
a. TsCl, Et3N
DCM, 80%
b. TIPSOTf
2,6-lutidine
DCM, 96%
TsHN
TIPSO
(-)-25
OH
OTBS
OBn
12
a. (-)-25
PPh3, DIAD, THF
73%
b. p-TsOH, MeOH
70%
TIPSO
N
Ts
BnO
OH
(+)-26
m-CPBA, DCM;
Ac2O, Et3N
DMAP, DCM
85%
O
OTIPS
Ts
N
O
OAc
OBn
(+)-27
quinidine, DCM
25 °C, 71%
(5 g scale)
BnO
Ts
N
O
O
H
TIPSO
(+)-28
a. TBAF, THF
b. DMP, DCM
BnO
Ts
N
O
O
H
OHC
RhCl(PPh3)3
PhMe, 120 °C
60%, 3 steps
BnO
Ts
N
O
O
H
(+)-7