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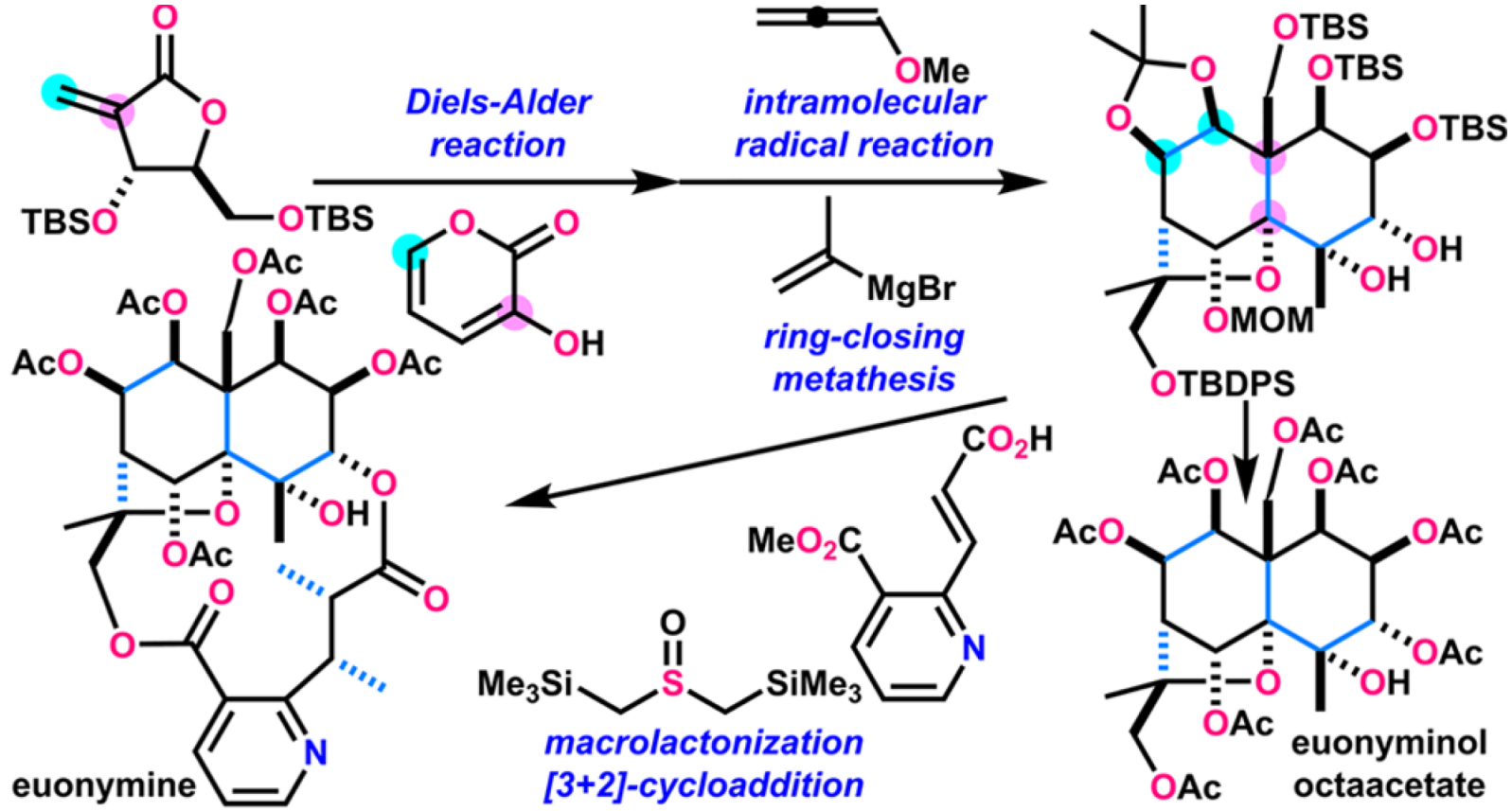
Total Synthesis of Euonymine and Euonyminol Octaacetate

Yinghua Wang,† Toshiya Nagai,† Itsuki Watanabe, Koichi Hagiwara, and Masayuki Inoue*



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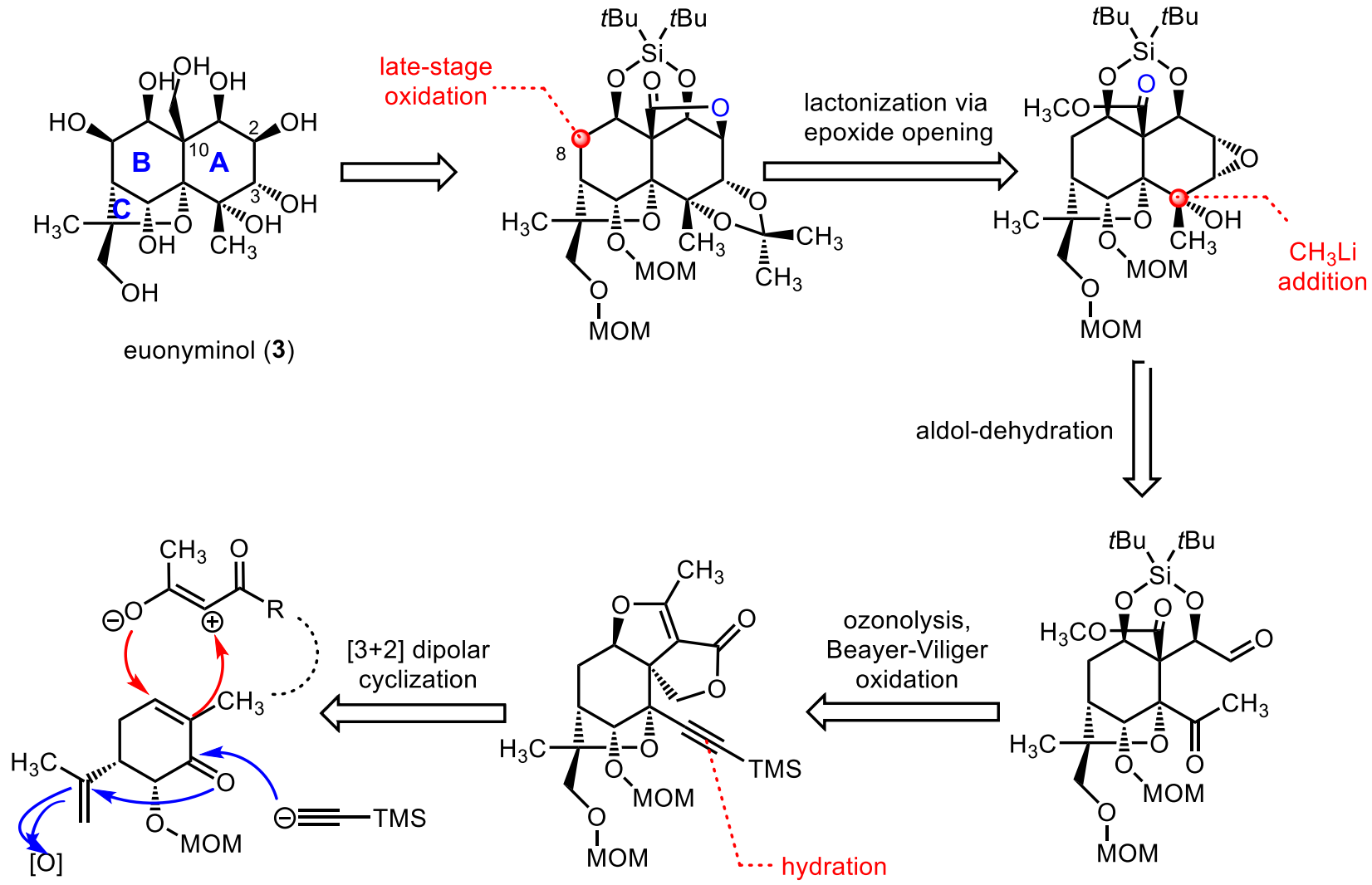
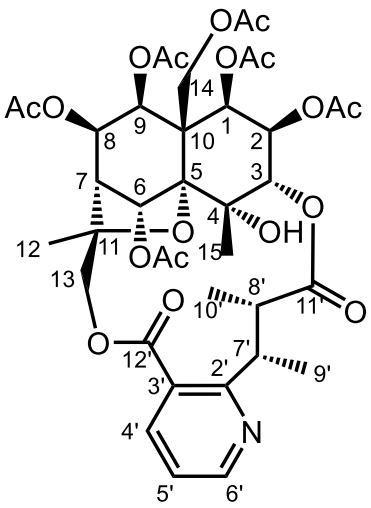
Enantioselective Synthesis of Euonyminol

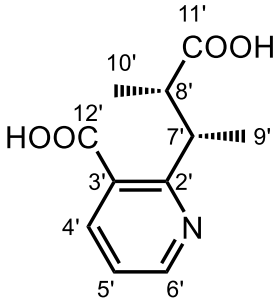
Martin Tomanik, Zhi Xu, and Seth B. Herzon*



DOI: 10.1021/jacs.0c12998.

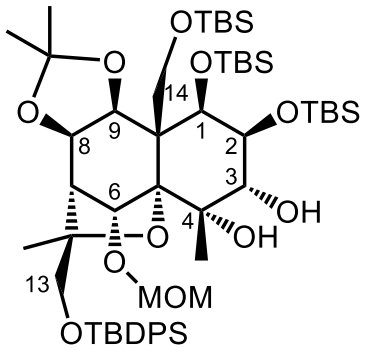


euonymine (1)



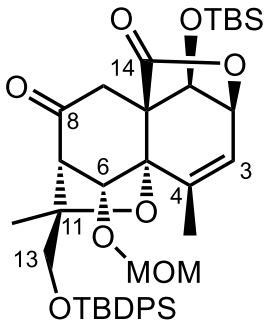
evoninic acid (**4**)

macro-lactonization



5

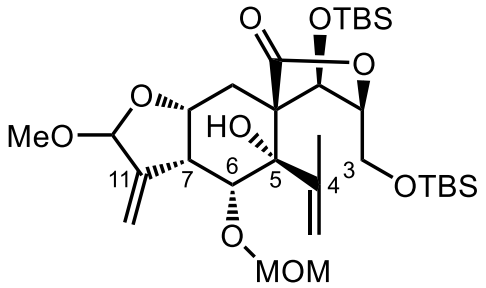
AB-ring functionalization



6

etherification

ring-closing metathesis



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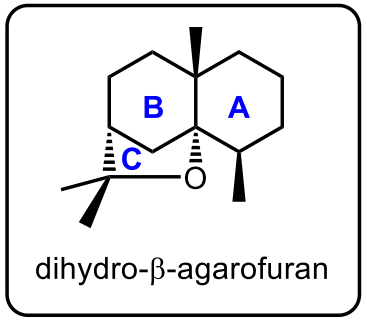
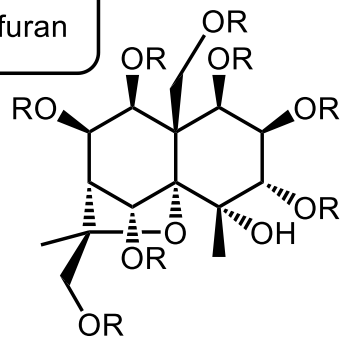


dihydro-β-agarofuran

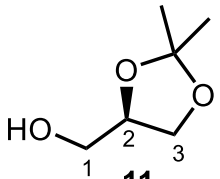
acetylation



euonyminol octaacetate(2): R = Ac

NaOMe
MeOH

euonyminol(3): R = H



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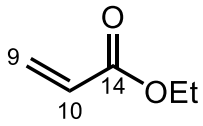
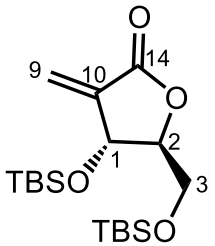


Morita-Baylis-Hillman reaction



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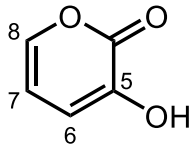
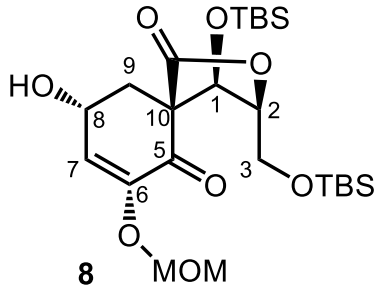


9

Diels-Alder reaction



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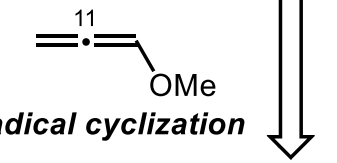
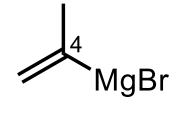
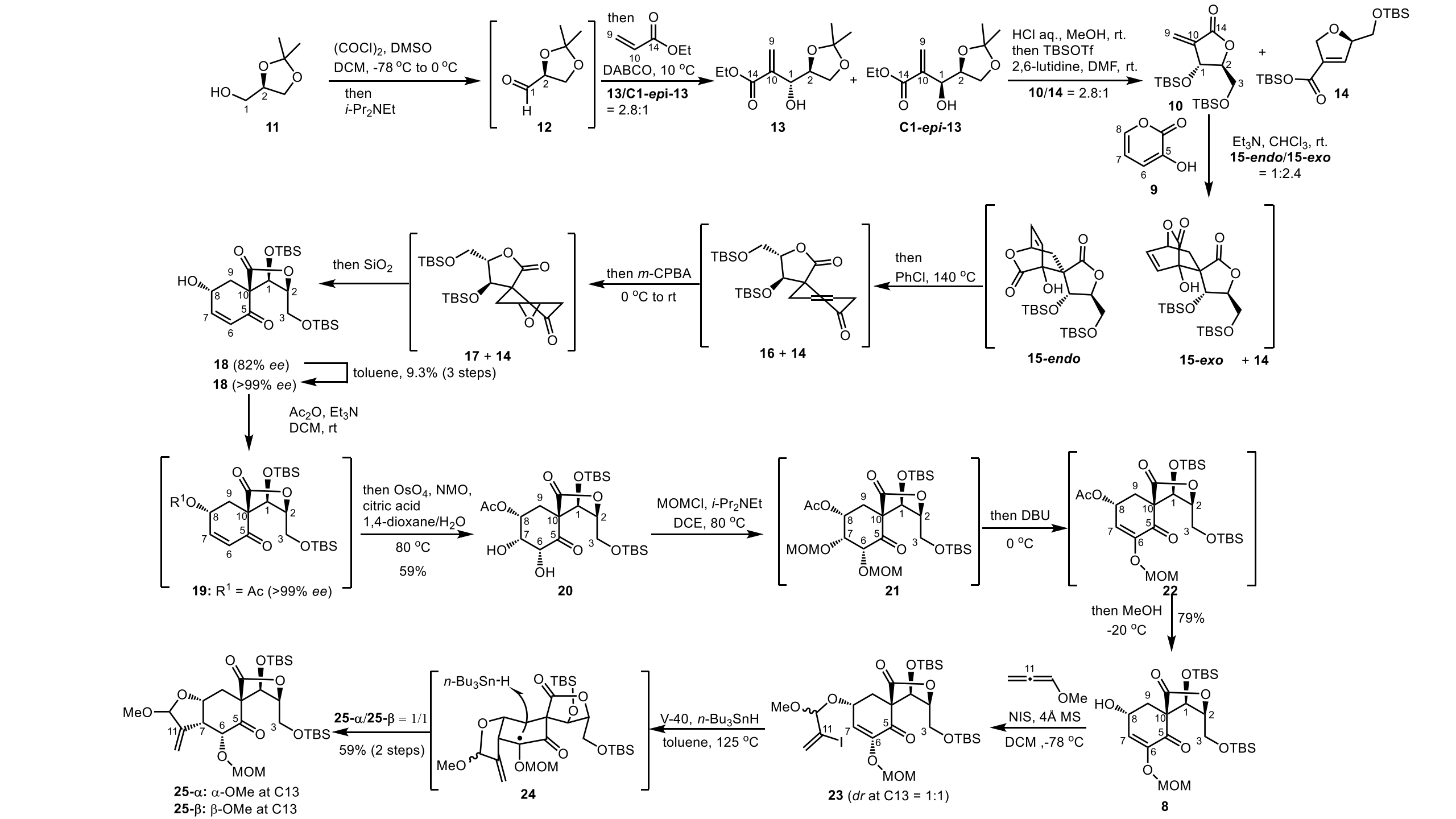


radical cyclization




11
(COCl)2, DMSO
DCM, -78 °C to 0 °C
then
i-Pr2NEt
12
then
DABCO, 10 °C
13/C1-epi-13
= 2.8:1
13
C1-epi-13
HCl aq., MeOH, rt.
then TBSOTf
2,6-lutidine, DMF, rt.
10/14 = 2.8:1
10
14
9
Et3N, CHCl3, rt.
15-endo/15-exo
= 1:2.4
15-endo
15-exo + 14
then
PhCl, 140 °C
16 + 14
then m-CPBA
0 °C to rt
17 + 14
then SiO2
18 (82% ee)
18 (>99% ee)
toluene, 9.3% (3 steps)
Ac2O, Et3N
DCM, rt
19: R1 = Ac (>99% ee)
then OsO4, NMO,
citric acid
1,4-dioxane/H2O
80 °C
59%
20
MOMCl, i-Pr2NEt
DCE, 80 °C
21
then DBU
0 °C
22
then MeOH
-20 °C
79%
8
NIS, 4Å MS
DCM ,-78 °C
23 (dr at C13 = 1:1)
V-40, n-Bu3SnH
toluene, 125 °C
24
25-α/25-β = 1/1
59% (2 steps)
25-α: α-OMe at C13
25-β: β-OMe at C13

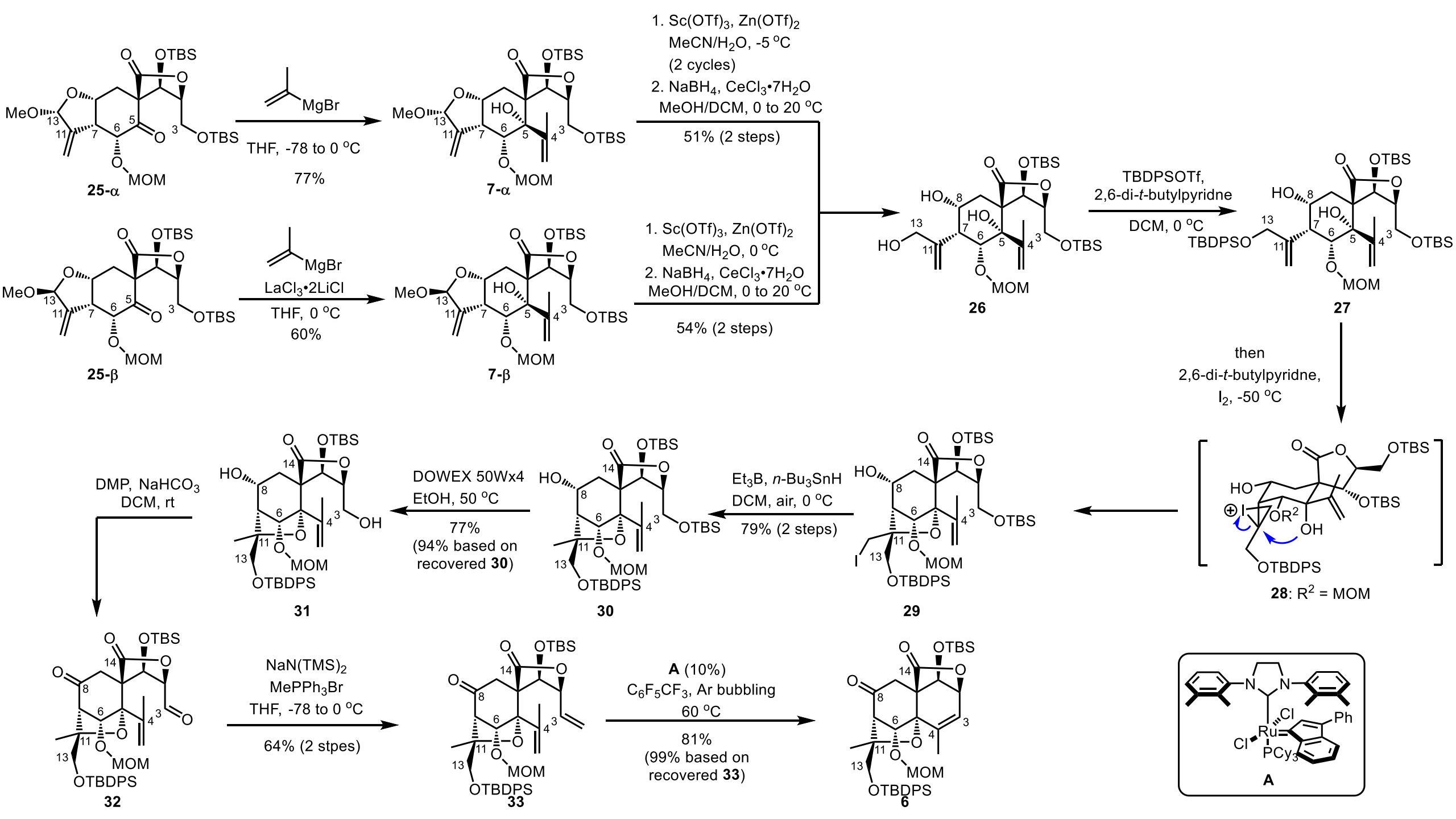
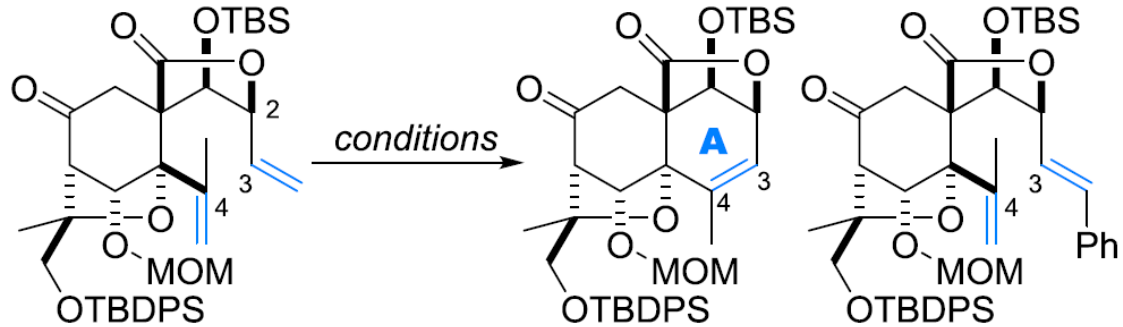

25-α
MgBr
THF, -78 to 0 °C
77%
7-α
1. Sc(OTf)3, Zn(OTf)2
MeCN/H2O, -5 °C
(2 cycles)
2. NaBH4, CeCl3•7H2O
MeOH/DCM, 0 to 20 °C
51% (2 steps)
25-β
MgBr
LaCl3•2LiCl
THF, 0 °C
60%
7-β
1. Sc(OTf)3, Zn(OTf)2
MeCN/H2O, 0 °C
2. NaBH4, CeCl3•7H2O
MeOH/DCM, 0 to 20 °C
54% (2 steps)
26
TBDPSOTf,
2,6-di-t-butylpyridine
DCM, 0 °C
27
then
2,6-di-t-butylpyridne,
I2, -50 °C
28: R2 = MOM
Et3B, n-Bu3SnH
DCM, air, 0 °C
79% (2 steps)
29
DOWEX 50Wx4
EtOH, 50 °C
77%
(94% based on
recovered 30)
30
DMP, NaHCO3
DCM, rt
31
NaN(TMS)2
MePPh3Br
THF, -78 to 0 °C
64% (2 stpes)
32
A (10%)
C6F5CF3, Ar bubbling
60 °C
81%
(99% based on
recovered 33)
33
6
A

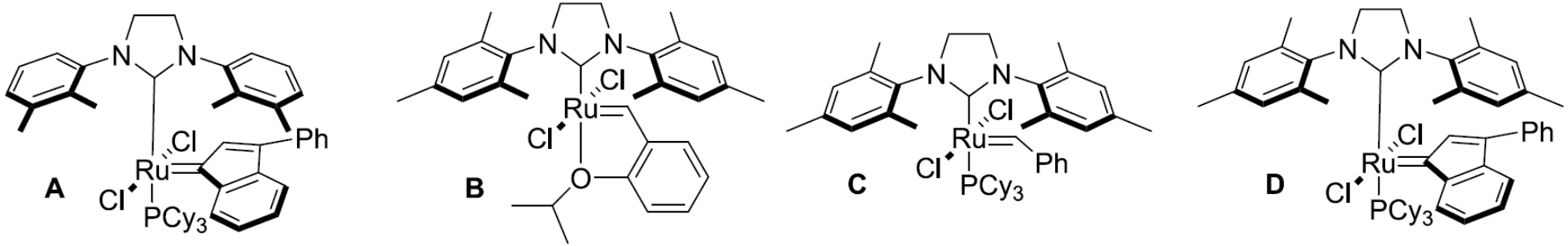
Table 1. Investigation of the A-Ring Formation

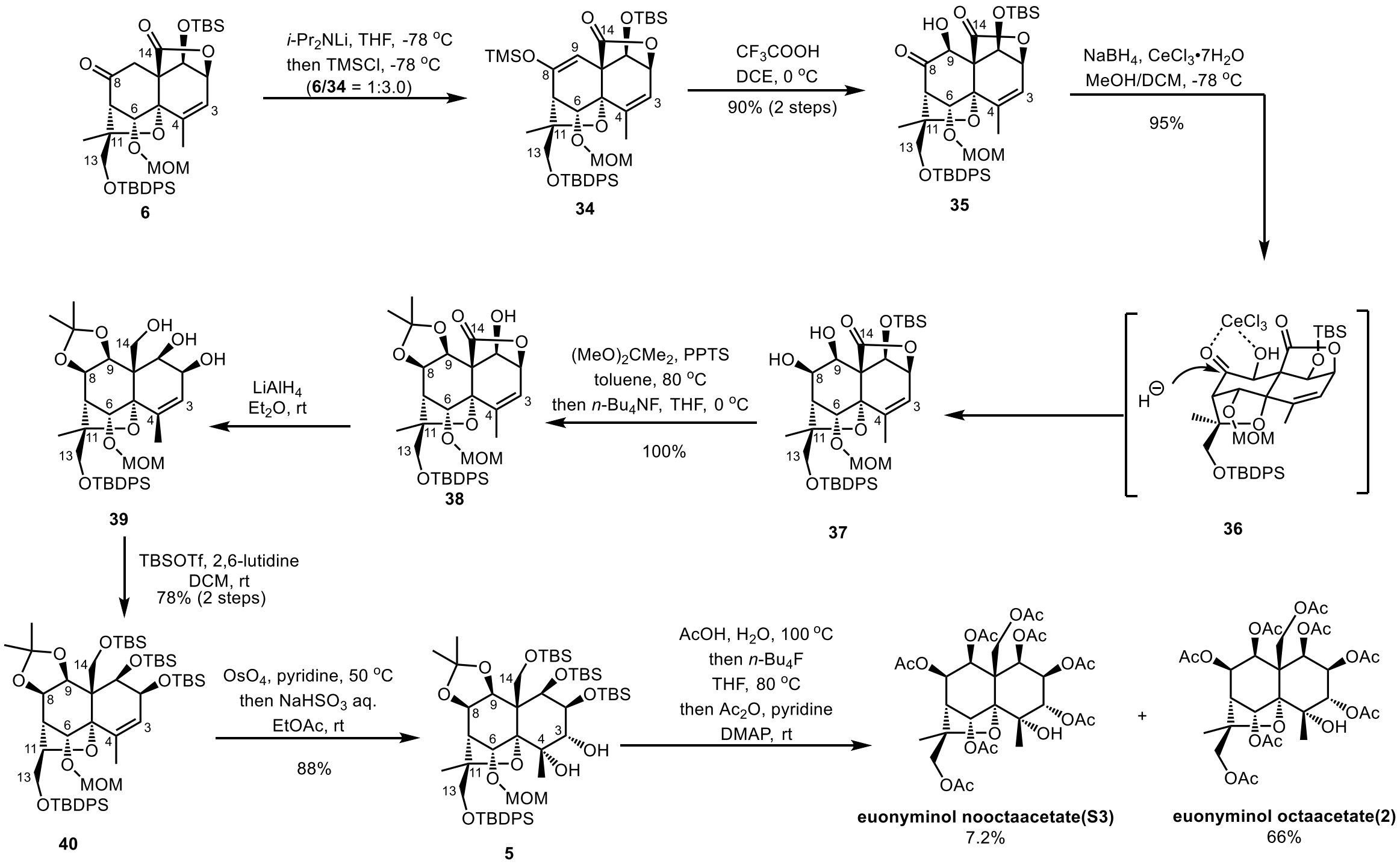


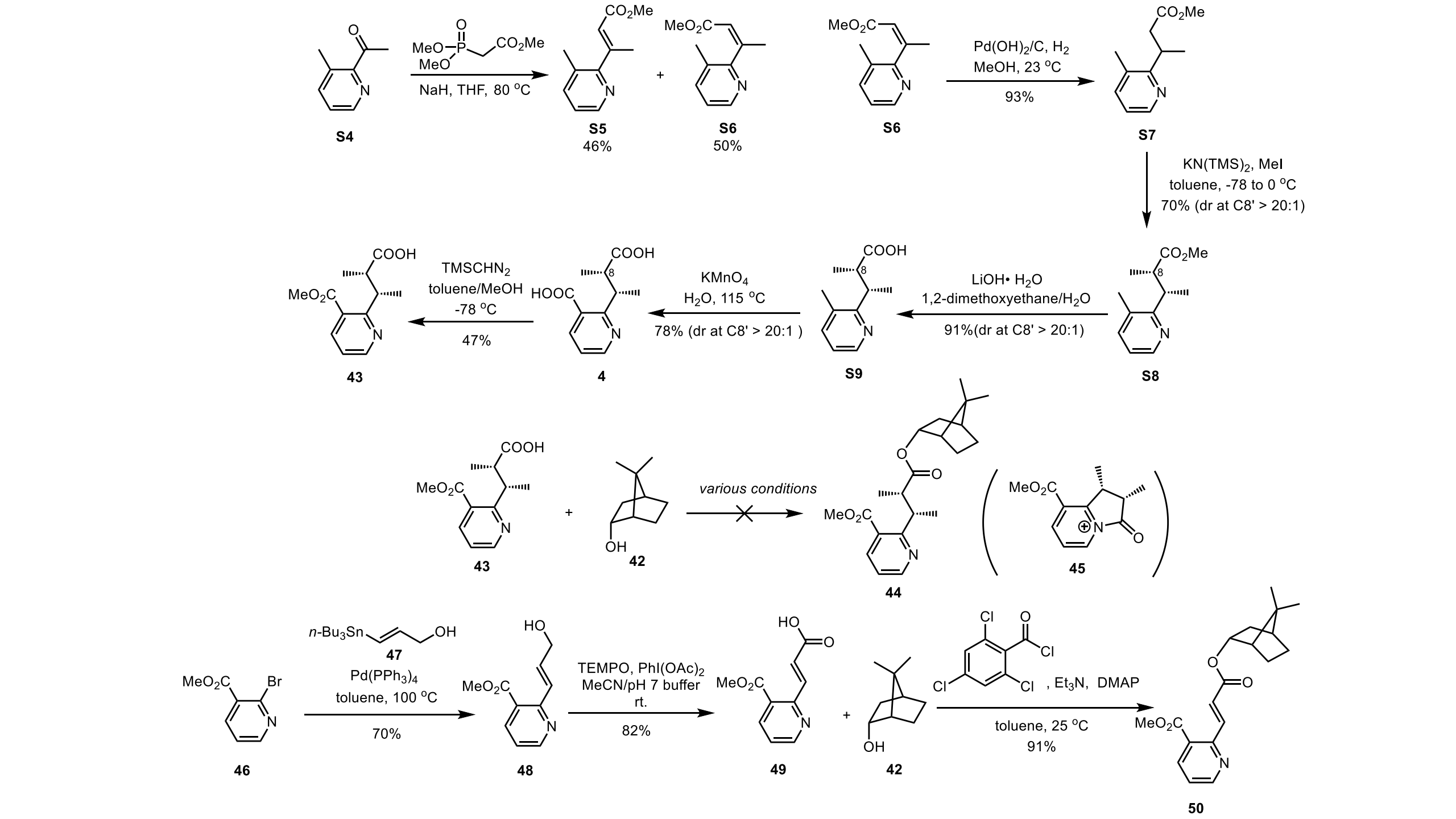
33 **6** **41**

entry	conditions	results
1[a]	**B** (100 mol %), toluene, 125 °C	no reaction
2[a]	**C** (100 mol %), toluene, 125 °C	**33**/**6**/**41** = 2:1:2
3[a]	**D** (100 mol %), toluene, 125 °C	**6** (59%)
4[a]	**D** (50 mol %), $C_6F_5CF_3$, 120 °C	**6** (58%)
5[a]	**D** (50 mol %), $C_6F_5CF_3$, 80 °C	**6** (83%)
		33 (10%)
6	**A** (10 mol %), $C_6F_5CF_3$, 60 °C	**6** (81%)
		33 (18%)

[a]Diene **33** was the mixture with **C2-*epi*-33** (**33**/**C2-*epi*-33** = 10:1).




6
i-Pr2NLi, THF, -78 °C
then TMSCl, -78 °C
(6/34 = 1:3.0)
34
CF3COOH
DCE, 0 °C
90% (2 steps)
35
NaBH4, CeCl3•7H2O
MeOH/DCM, -78 °C
95%
36
(MeO)2CMe2, PPTS
toluene, 80 °C
then n-Bu4NF, THF, 0 °C
100%
38
LiAlH4
Et2O, rt
39
TBSOTf, 2,6-lutidine
DCM, rt
78% (2 steps)
40
OsO4, pyridine, 50 °C
then NaHSO3 aq.
EtOAc, rt
88%
5
AcOH, H2O, 100 °C
then n-Bu4F
THF, 80 °C
then Ac2O, pyridine
DMAP, rt
euonyminol nooctaacetate(S3)
7.2%
euonyminol octaacetate(2)
66%


S4
NaH, THF, 80 °C
S5
46%
S6
50%
Pd(OH)2/C, H2
MeOH, 23 °C
93%
S7
KN(TMS)2, MeI
toluene, -78 to 0 °C
70% (dr at C8' > 20:1)
S8
LiOH• H2O
1,2-dimethoxyethane/H2O
91%(dr at C8' > 20:1)
S9
KMnO4
H2O, 115 °C
78% (dr at C8' > 20:1)
4
TMSCHN2
toluene/MeOH
-78 °C
47%
43
various conditions
42
44
45
n-Bu3Sn
47
Pd(PPh3)4
toluene, 100 °C
70%
46
48
TEMPO, PhI(OAc)2
MeCN/pH 7 buffer
rt.
82%
49
, Et3N, DMAP
toluene, 25 °C
91%
50

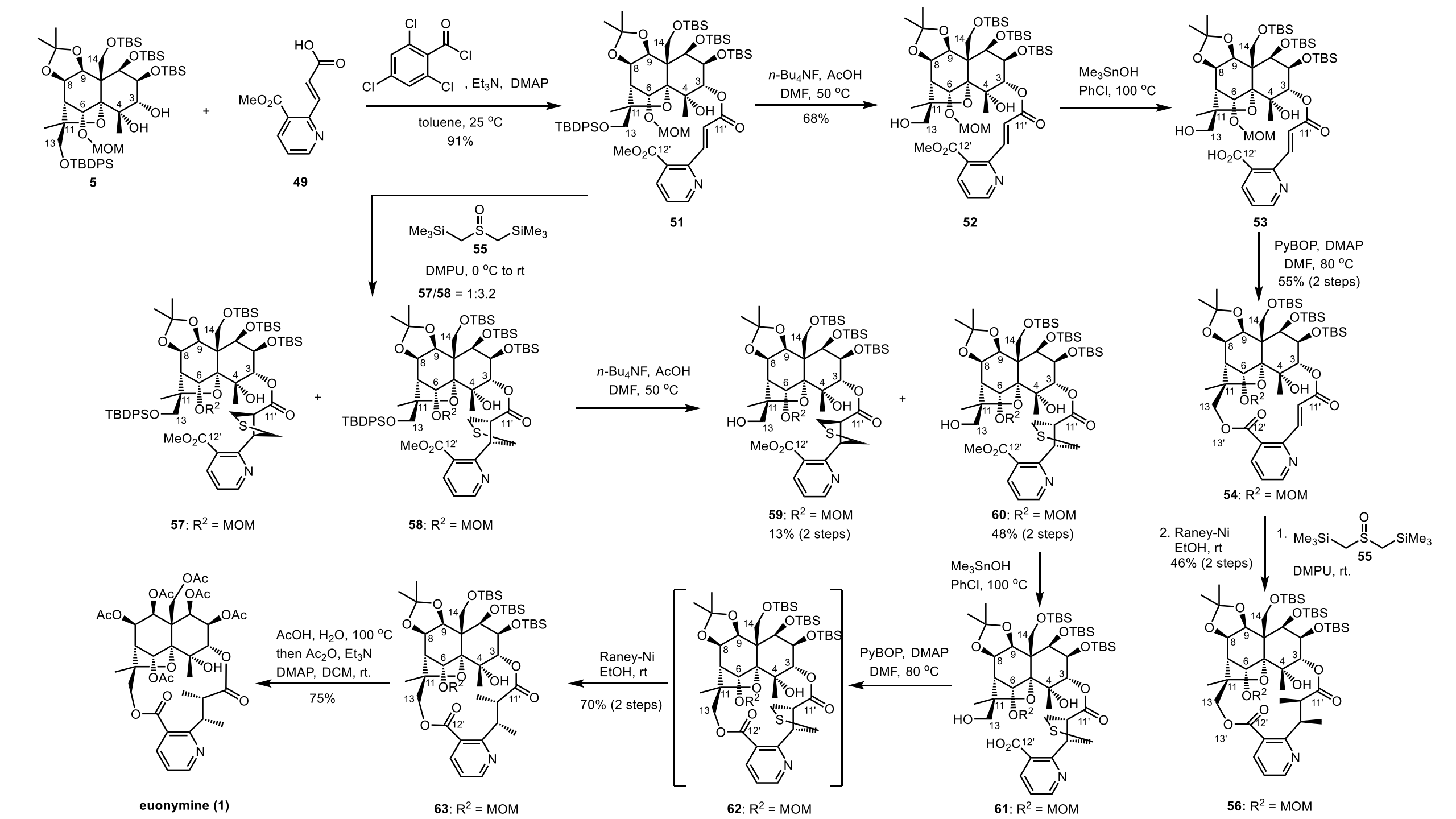
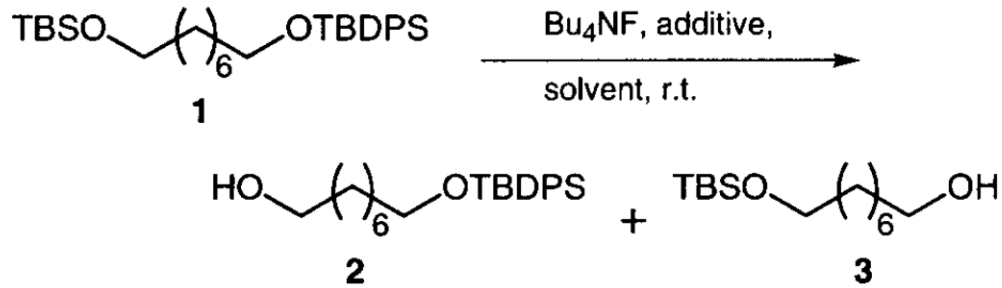
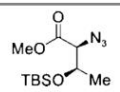
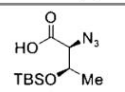
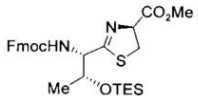
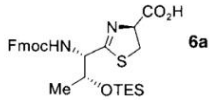
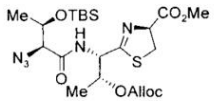
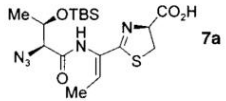
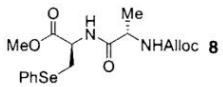
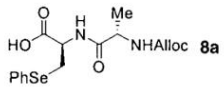
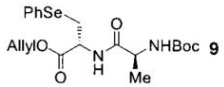
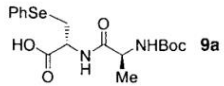
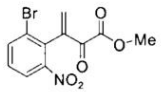
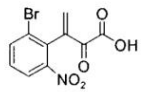
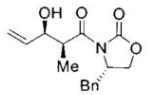
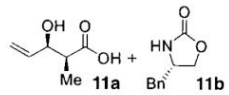
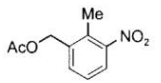
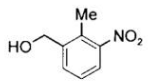
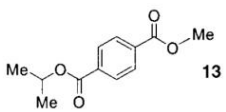
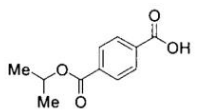
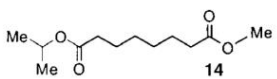
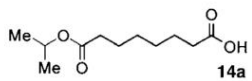
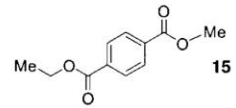
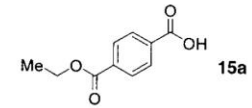
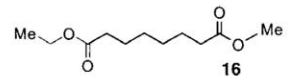
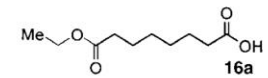
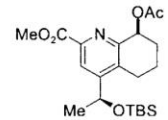
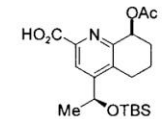
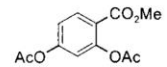
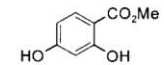
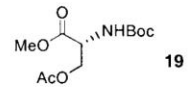
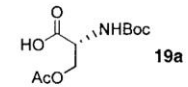
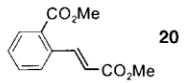
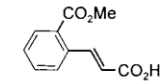
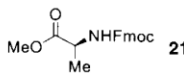
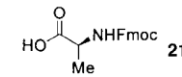

5
49
toluene, 25 °C
91%
51
n-Bu4NF, AcOH
DMF, 50 °C
68%
52
Me3SnOH
PhCl, 100 °C
53
PyBOP, DMAP
DMF, 80 °C
55% (2 steps)
54: R2 = MOM
2. Raney-Ni
EtOH, rt
46% (2 steps)
1.
55
DMPU, rt.
56: R2 = MOM
Me3SnOH
PhCl, 100 °C
61: R2 = MOM
PyBOP, DMAP
DMF, 80 °C
62: R2 = MOM
Raney-Ni
EtOH, rt
70% (2 steps)
63: R2 = MOM
AcOH, H2O, 100 °C
then Ac2O, Et3N
DMAP, DCM, rt.
75%
euonymine (1)
55
DMPU, 0 °C to rt
57/58 = 1:3.2
57: R2 = MOM
58: R2 = MOM
n-Bu4NF, AcOH
DMF, 50 °C
59: R2 = MOM
13% (2 steps)
60: R2 = MOM
48% (2 steps)

Table 1 Selective Desilylation of **1**(a)



entry	fluoride source(b)	solvent	AcOH / equiv	time / h	combined yield / %	ratio(c) **2** : **3**
1	A	THF	0	2	37	6 : 94
2	A	THF	1	17	76	2 : 98
3	A	THF	2	51(d)	43	55 : 45
4	A	THF	5	130(d)	66	>99 : <1
5	B	DMF	0	0.5	25	<1 : >99
6	B	DMF	1	13	79	<1 : >99
7	B	DMF	2	36	22	32 : 68
8	B	DMF	5	64(d)	65	97 : 3
9	A	DMF	1	14	82	<1 : >99

(a) The reaction was carried out in 0.05 M solution of **1** in the specified solvent at r.t. by using 1.0 equiv of the fluoride source. (b) A: 1M Bu_4NF in THF. B: $Bu_4NF \bullet xH_2O$. (c) Determined by ^1H NMR (270 or 300 MHz) analysis of the chromatographically pure mixture of **2** and **3**. (d) The starting material **1** remained.

Entry	Ester	Product(s)	T [°C]	t [h]	Yield [%]	Selectivity[b]
1	 **5**	 **5a**	80	3	98	–
2	 **6**	 **6a**	70	1	85	–
3	 **7**	 **7a**	80	2	88	–
4	 **8**	 **8a**	80	1	87	–
5	 **9**	 **9a**	80	2	100	–
6	 **10**	 **10a**	80	1	77	–
7	 **11**	 **11a** + **11b**	80	7	84	–
8	 **12**	 **12a**	80	2	100	–
9	 **13**	 **13a**	80	5	80	≈90:1
10	 **14**	 **14a**	80	7	82	≈10:1
11	 **15**	 **15a**	70	9	70	≈10:1
12	 **16**	 **16a**	70	10	70	≈3:1
13	 **17**	 **17a**	80	2	67	–
14	 **18**	 **18a**	80	5	100	–
15	 **19**	 **19a**	80	2	80	–
16	 **20**	 **20a**	80	9	70	≈7:1
17	 **21**	 **21a**	80	5	75	–

[a] Reactions were carried out in 1,2-DCE on a 0.04–0.15-mmol scale and worked up as described in the general procedure. Bn = benzyl; Fmoc = 9-fluorenylmethoxycarbonyl. [b] For the methyl ester.