Total Synthesis of (−)-Chromodorolide B By a Computationally-Guided Radical Addition/Cyclization/Fragmentation Cascade

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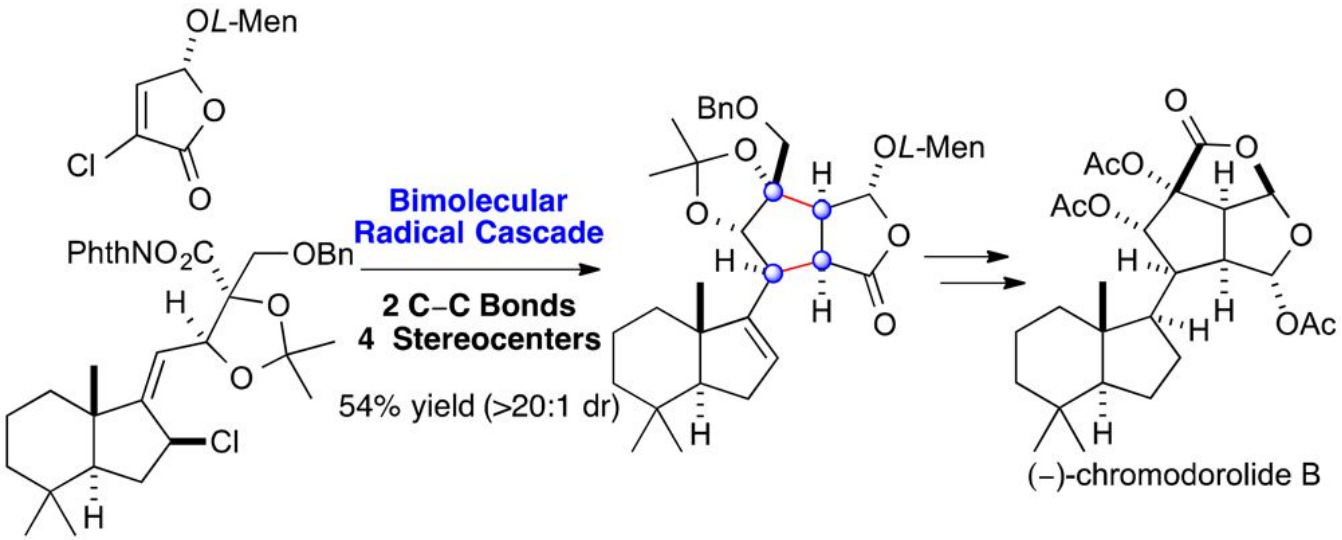
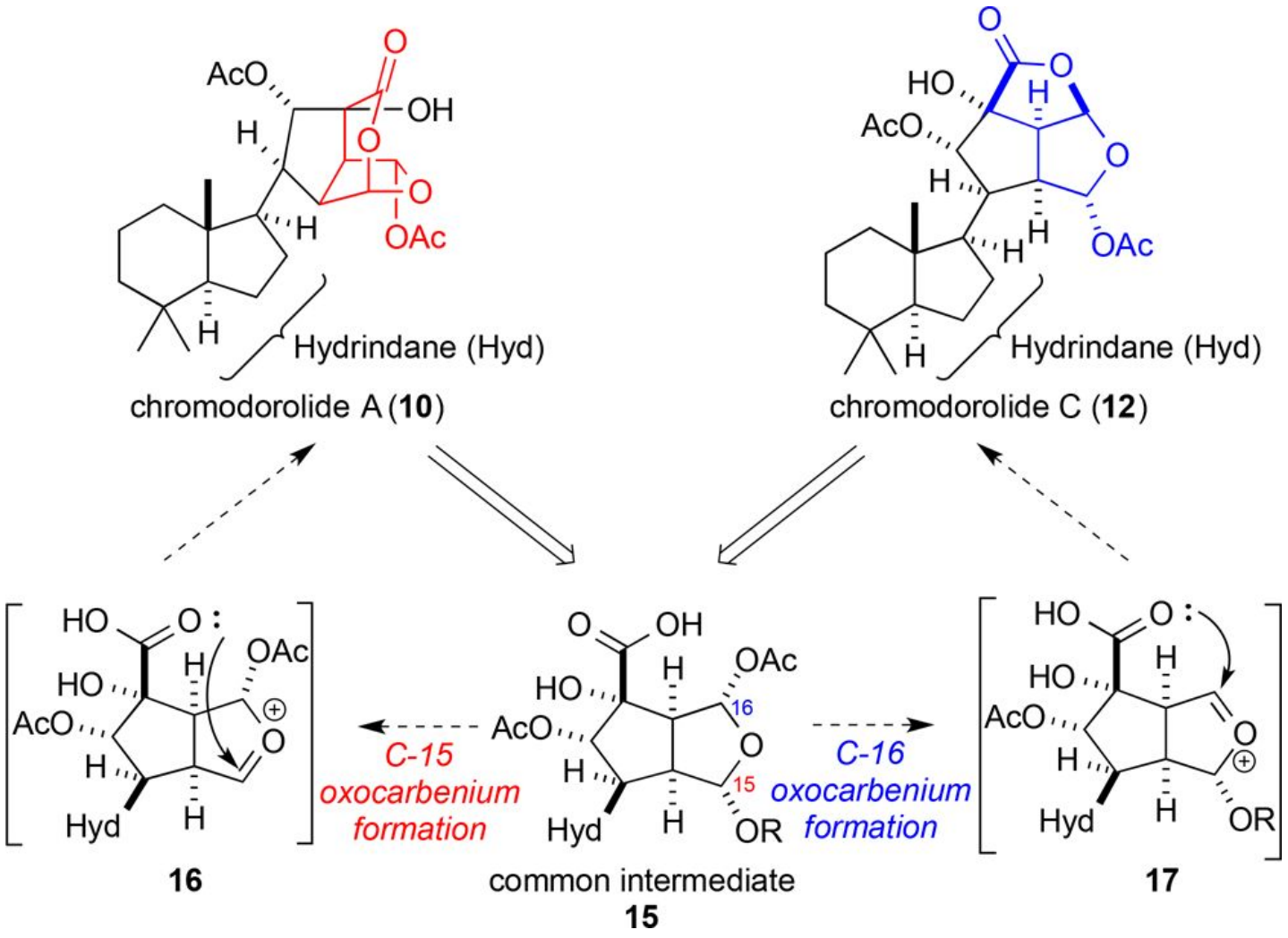
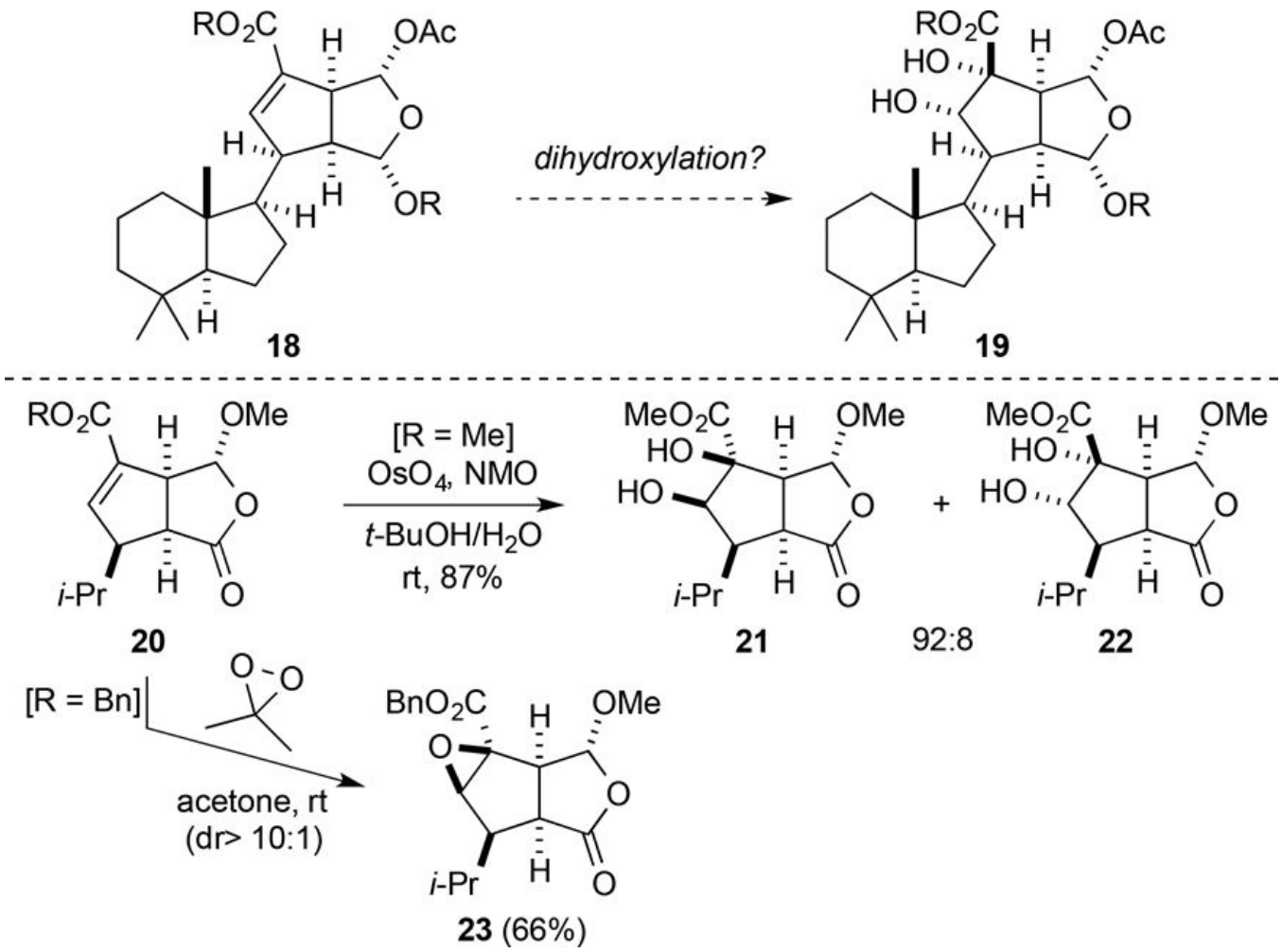
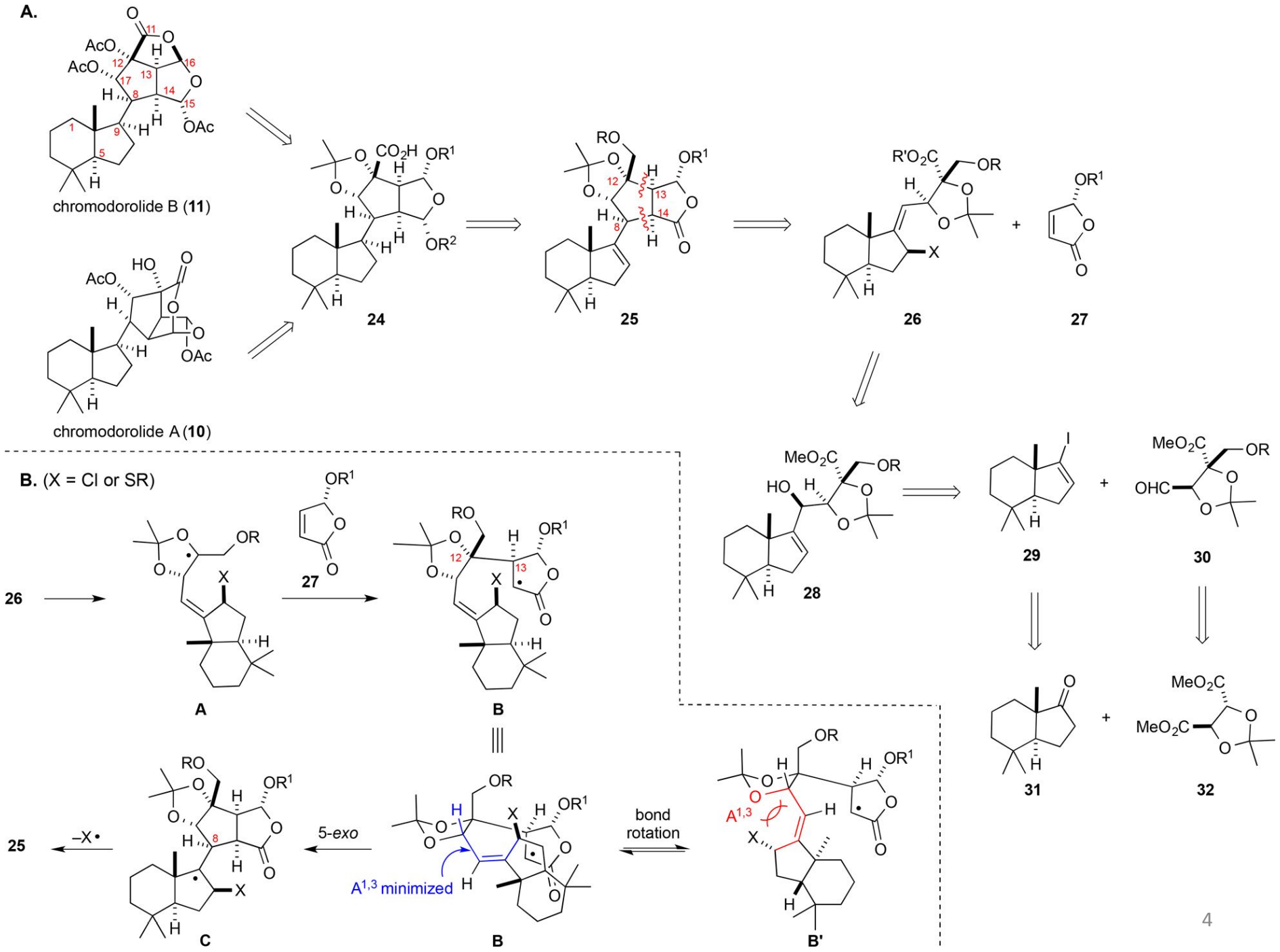
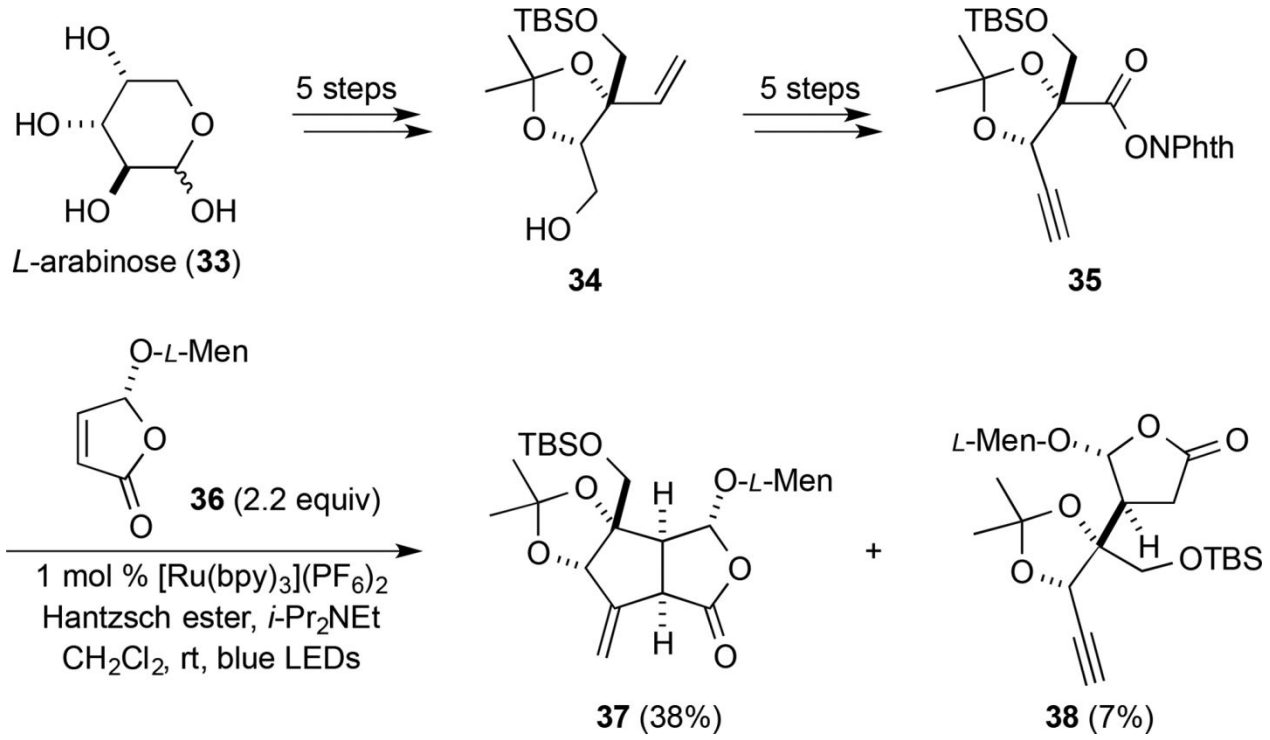


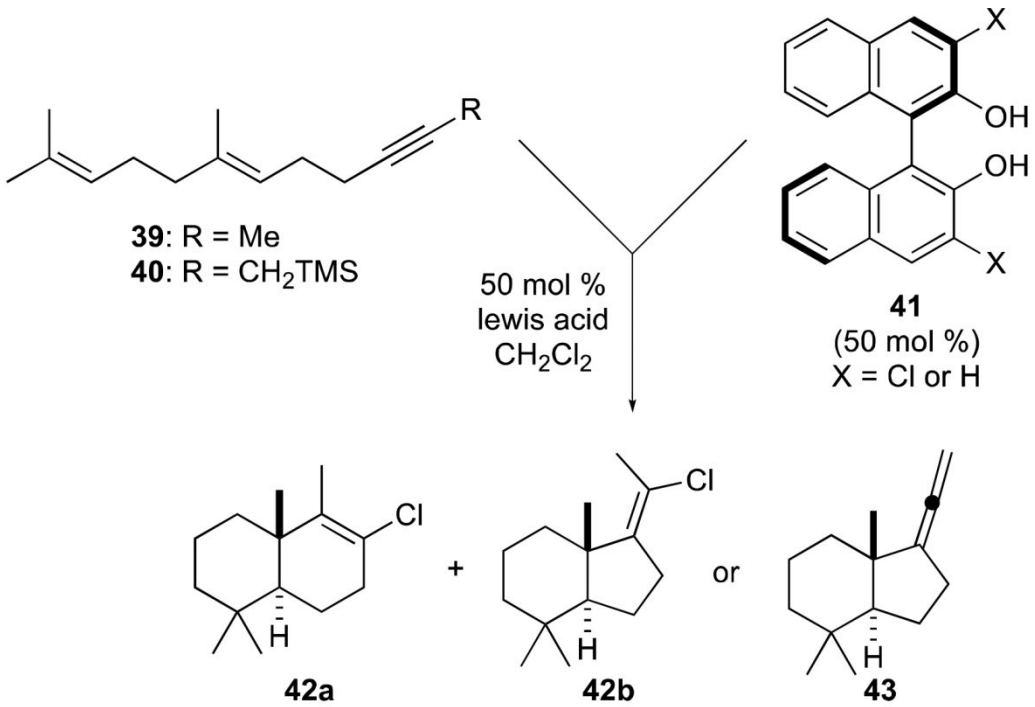
Карлинский Богдан, аспирант ИОХ РАН


AcO
OH
H
O
OAc
Hydrindane (Hyd)
chromodorolide A (10)
HO
chromodorolide C (12)
C-15
oxocarbenium
formation
C-16
oxocarbenium
formation
16
common intermediate
15
17

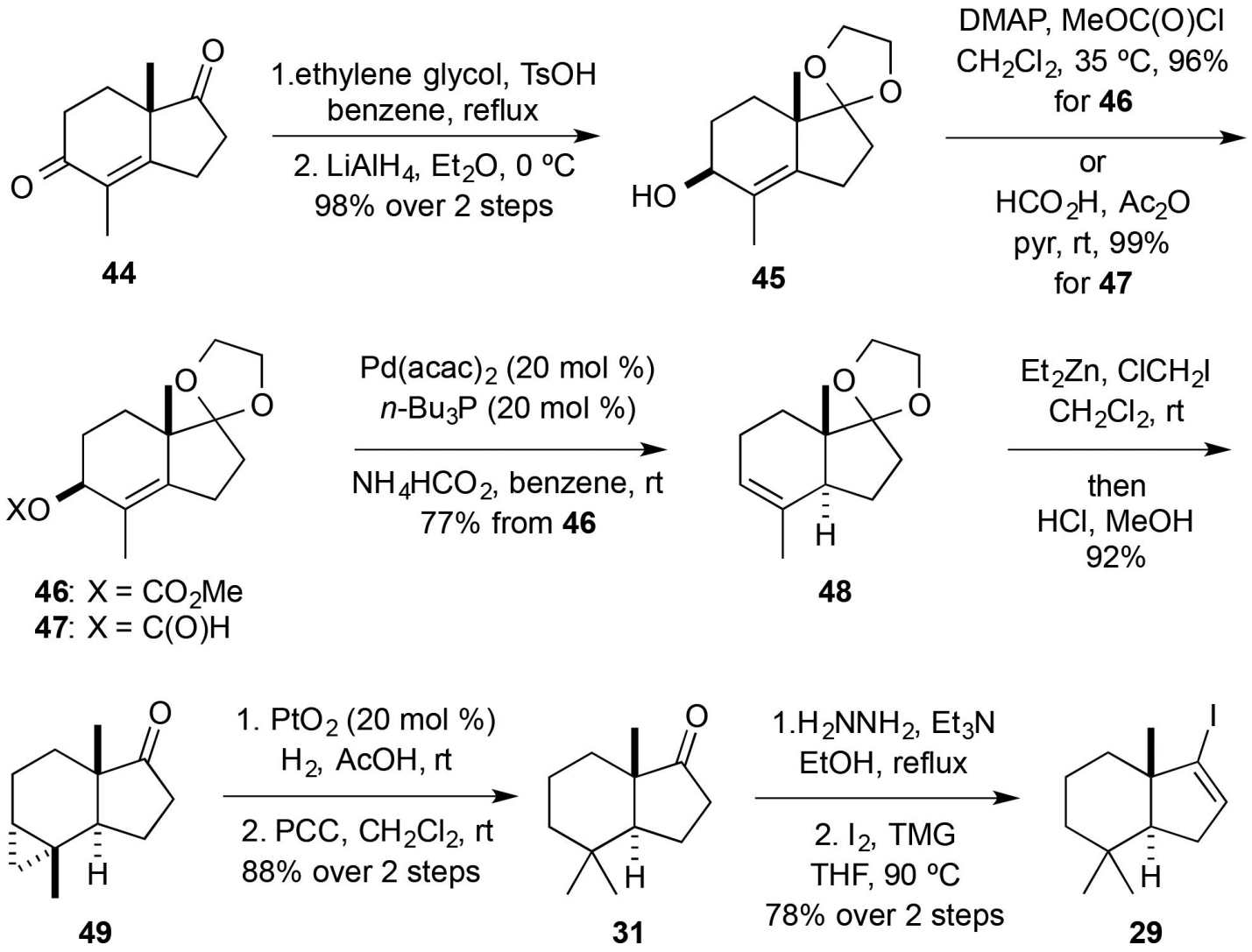

RO2C
H
OAc
O
H
H
H
OR
H
18
dihydroxylation?
RO2C
HO
HO
H
H
H
OAc
O
OR
19
RO2C
H
OMe
O
i-Pr
H
O
20
[R = Me]
OsO4, NMO
t-BuOH/H2O
rt, 87%
MeO2C
HO
HO
H
OMe
O
i-Pr
H
O
21
92:8
22
[R = Bn]
O
O
acetone, rt
(dr> 10:1)
BnO2C
O
H
OMe
O
i-Pr
H
O
23 (66%)

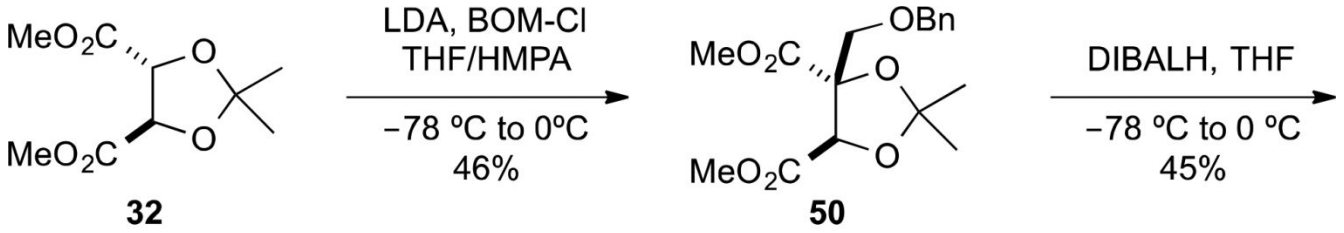

A.
chromodorolide B (11)
chromodorolide A (10)
24
25
26
27
28
29
30
31
32
B. (X = Cl or SR)
A
B
C
B'
5-exo
bond rotation
A1,3 minimized
A1,3
–X•


HO
HO
O
HO
OH
L-arabinose (33)
5 steps
TBSO
O
O
HO
34
5 steps
TBSO
O
O
O
ONPhth
35
O-L-Men
O
O
36 (2.2 equiv)
1 mol % [Ru(bpy)3](PF6)2
Hantzsch ester, i-Pr2NEt
CH2Cl2, rt, blue LEDs
TBSO
O
O
H
O-L-Men
O
H
O
37 (38%)
+
L-Men-O
O
O
O
O
H
OTBS
38 (7%)

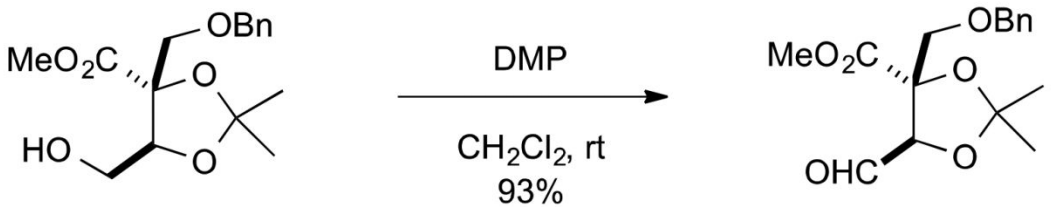


entry	Lewis acid	R	X	T (ºC)	yield[a] (ratio **42a**:**42b**)[b]	**31**, %*ee*[c]
1	$SbCl_5$	Me	Cl	−78	35% (1.0:3.0)	0%
2	$TiCl_4$	Me	Cl	−78	<5% (*ND*)	*ND*
3	$SnCl_4$	Me	Cl	−78	55% (1.0:1.5)	18%
4	$SnCl_4$	Me	Cl	−90	53% (1.0:1.1)	20%
5	$SnCl_4$	Me	Cl	−50	12% (0:1.0)	*ND*
6	$SnCl_4$	Me	H	−78	53% (1.1:1.0)	13%
7	$SnCl_4$	CH_2TMS	Cl	−78	23% (0:1.0)	*ND*

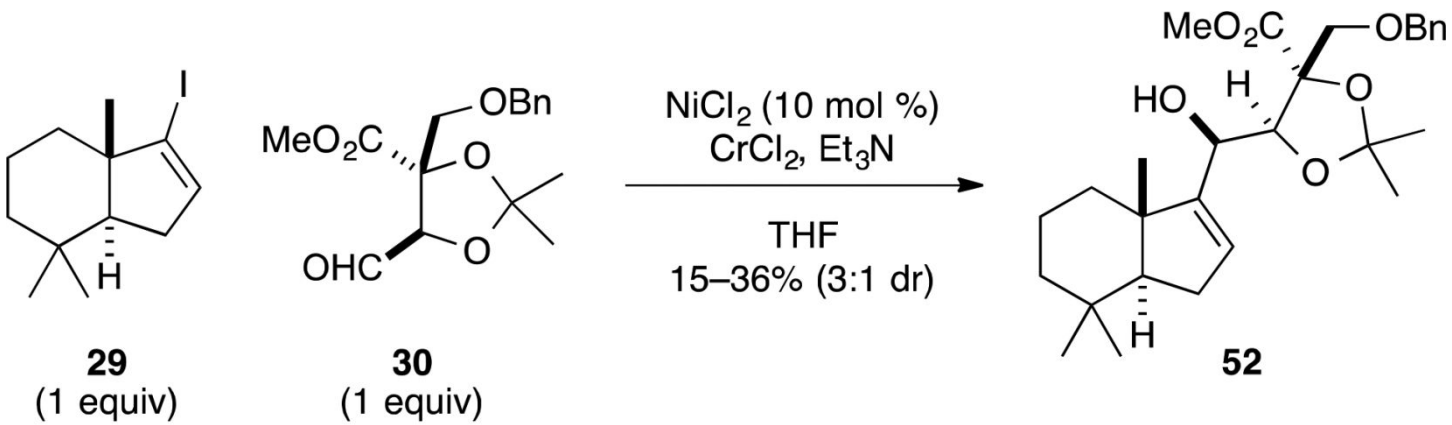

1.ethylene glycol, TsOH
benzene, reflux
2. LiAlH4, Et2O, 0 ºC
98% over 2 steps
DMAP, MeOC(O)Cl
CH2Cl2, 35 ºC, 96%
for 46
or
HCO2H, Ac2O
pyr, rt, 99%
for 47
Pd(acac)2 (20 mol %)
n-Bu3P (20 mol %)
NH4HCO2, benzene, rt
77% from 46
Et2Zn, ClCH2I
CH2Cl2, rt
then
HCl, MeOH
92%
1. PtO2 (20 mol %)
H2, AcOH, rt
2. PCC, CH2Cl2, rt
88% over 2 steps
1.H2NNH2, Et3N
EtOH, reflux
2. I2, TMG
THF, 90 ºC
78% over 2 steps
44
45
46: X = CO2Me
47: X = C(O)H
48
49
31
29



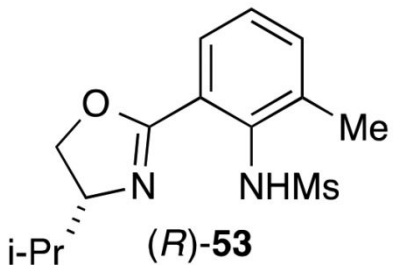
32 **50**



51 **30**



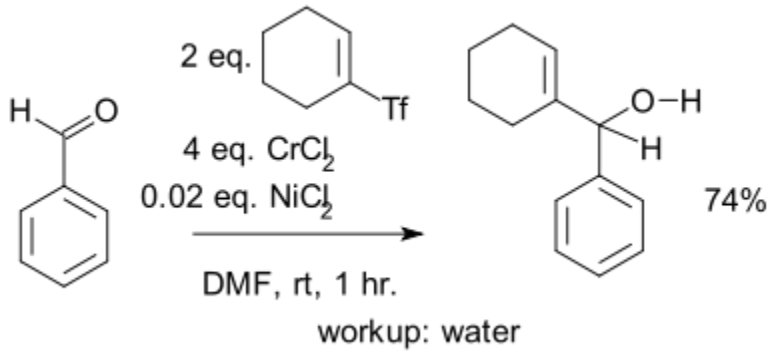
29 (1 equiv) **30** (1 equiv) **52**

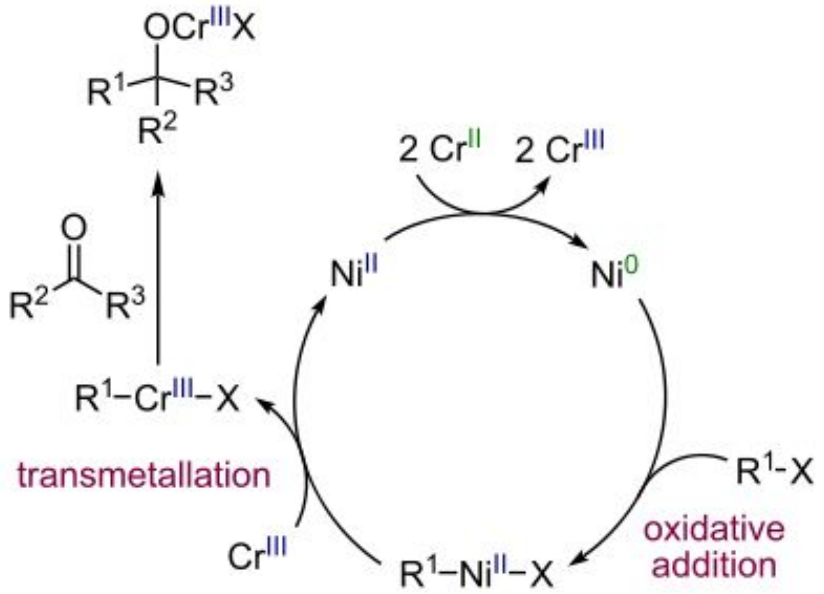


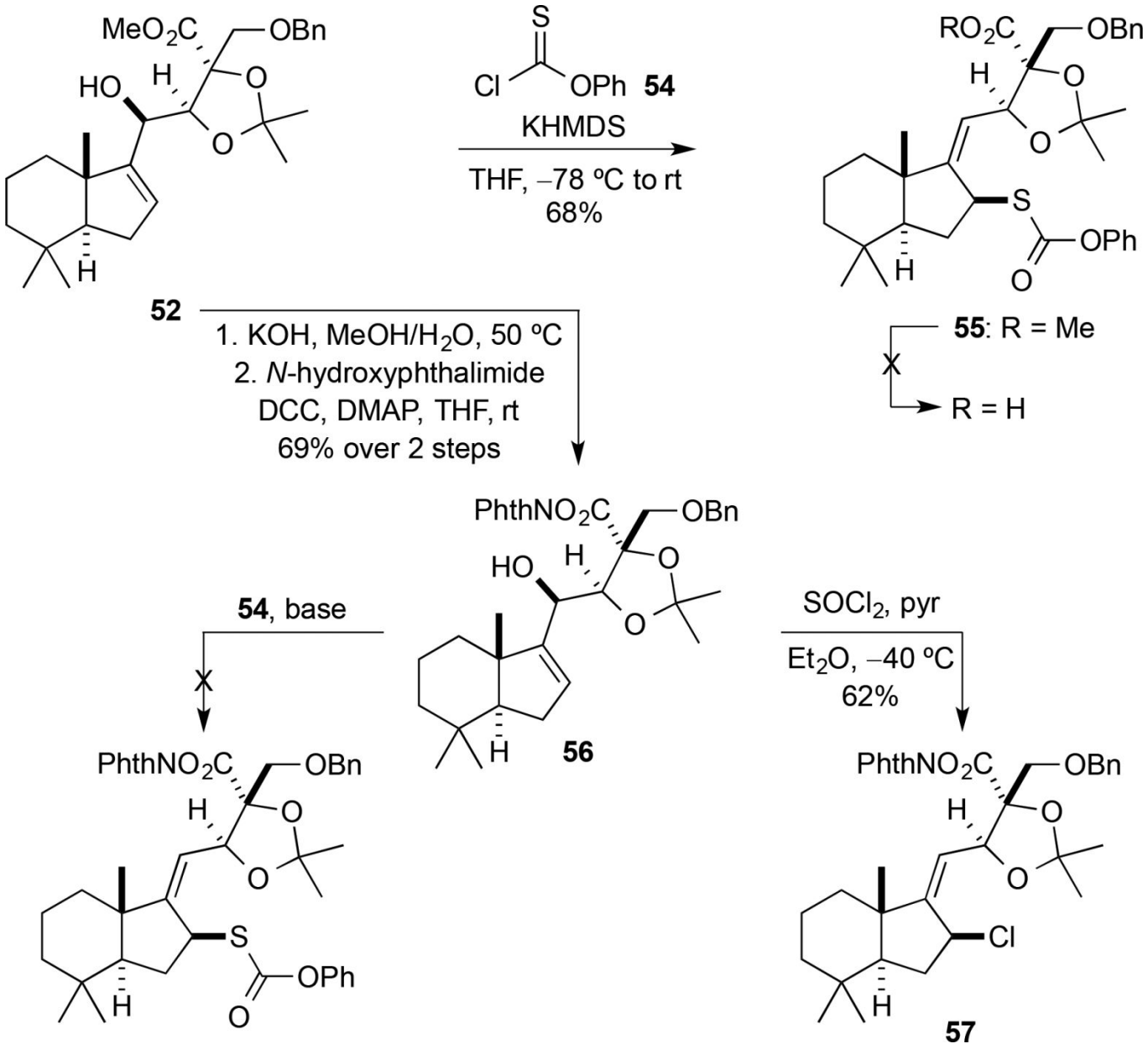
(*R*)-**53**

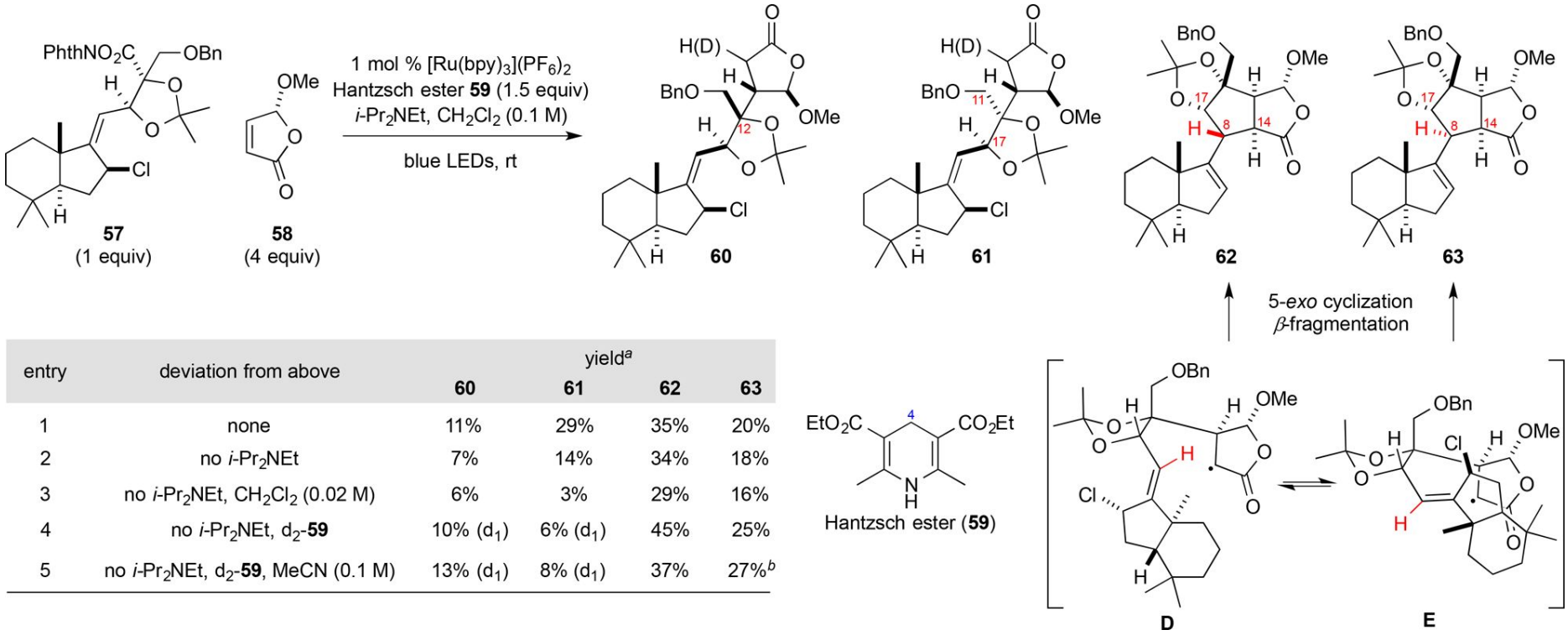
deviation from above	yield (dr)
addition of (*R*)-**53**	28% (>20:1)
addition of (*R*)-**53** **30** (1.6 equiv)	66% (>20:1)

Nozaki–Hiyama–Kishi reaction

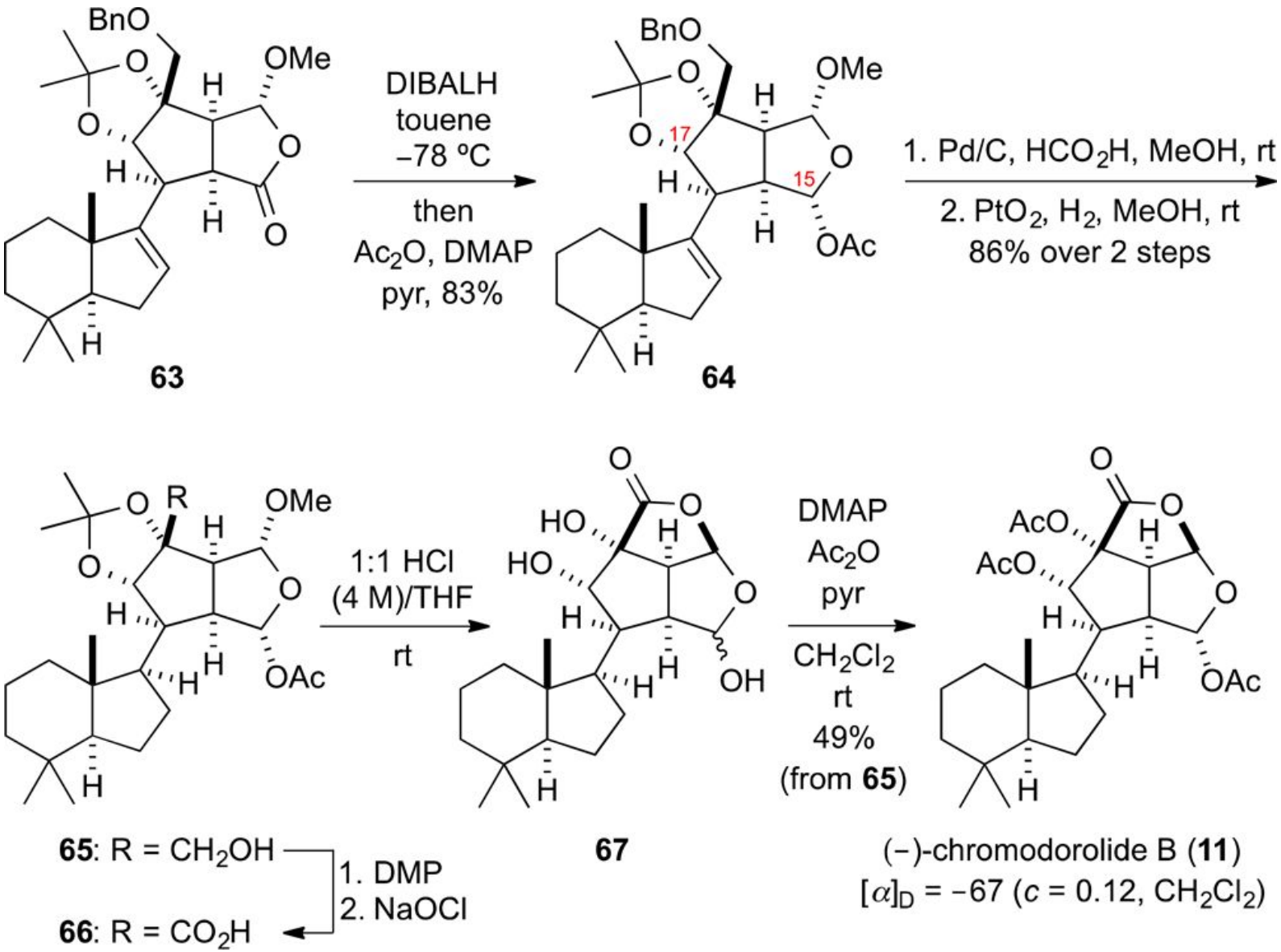


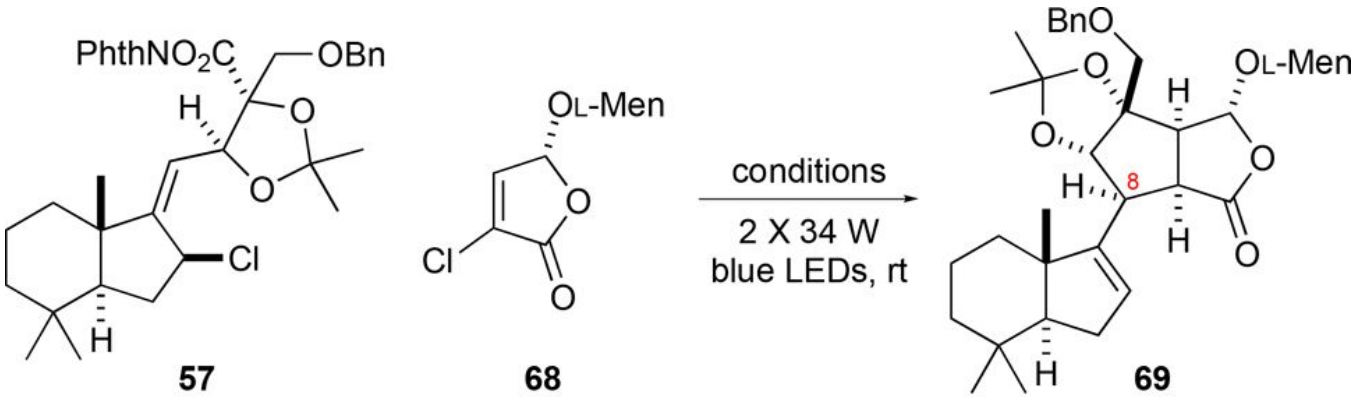



MeO2C
OBn
HO
H
O
O
H
52
S
Cl
OPh 54
KHMDS
THF, –78 ºC to rt
68%
RO2C
OBn
H
O
O
S
OPh
H
O
55: R = Me
R = H
1. KOH, MeOH/H2O, 50 ºC
2. N-hydroxyphthalimide
DCC, DMAP, THF, rt
69% over 2 steps
PhthNO2C
OBn
HO
H
O
O
H
56
54, base
SOCl2, pyr
Et2O, –40 ºC
62%
PhthNO2C
OBn
H
O
O
S
OPh
H
O
PhthNO2C
OBn
H
O
O
Cl
H
57

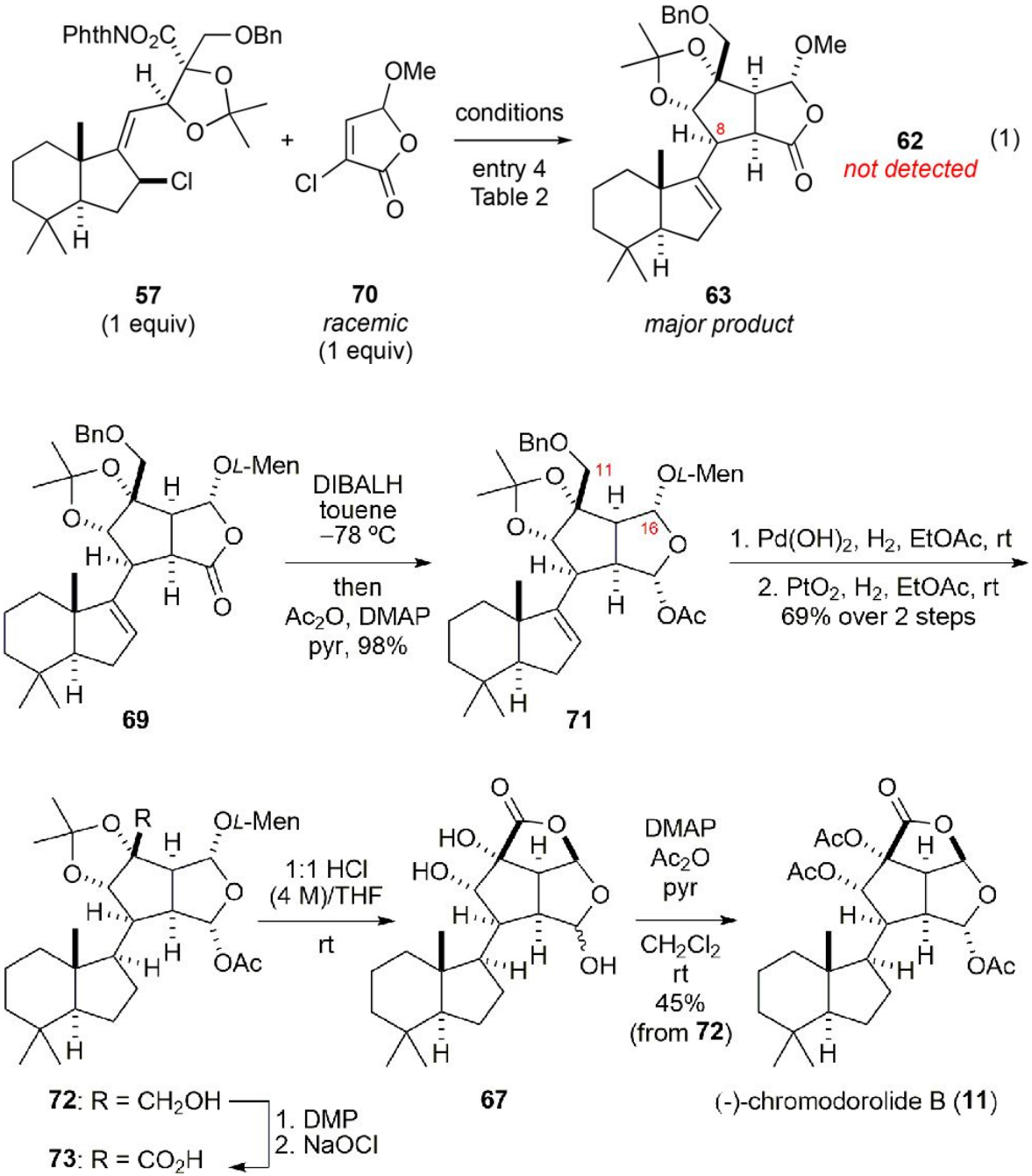


entry	deviation from above	yield[a] 60	61	62	63
1	none	11%	29%	35%	20%
2	no *i*-Pr_2NEt	7%	14%	34%	18%
3	no *i*-Pr_2NEt, CH_2Cl_2 (0.02 M)	6%	3%	29%	16%
4	no *i*-Pr_2NEt, d_2-**59**	10% (d_1)	6% (d_1)	45%	25%
5	no *i*-Pr_2NEt, d_2-**59**, MeCN (0.1 M)	13% (d_1)	8% (d_1)	37%	27%[b]


BnO
OMe
DIBALH
touene
–78 °C
then
Ac2O, DMAP
pyr, 83%
1. Pd/C, HCO2H, MeOH, rt
2. PtO2, H2, MeOH, rt
86% over 2 steps
63
64
17
15
OAc
1:1 HCl
(4 M)/THF
rt
DMAP
Ac2O
pyr
CH2Cl2
rt
49%
(from 65)
65: R = CH2OH
66: R = CO2H
1. DMP
2. NaOCl
67
(–)-chromodorolide B (11)
[α]D = –67 (c = 0.12, CH2Cl2)



entry	conditions	isolated yield
1	(a) 2 mol % $[Ru(bpy)_3](PF_6)_2$, d_2-Hantzsch ester **59**, MeCN (0.1 M) (b) 2 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, *n*-$Bu_3N$, THF (0.1 M)	41%
2	(a) 2 mol % $[Ru(bpy)_3](PF_6)_2$, d_2-Hantzsch ester **59**, MeCN (0.6 M) (b) 2 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, *n*-$Bu_3N$, THF (0.1 M)	58%
3	2 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, d_2-Hantzsch ester **59**, THF (0.6 M), then Bu_3N	56%
4	2 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, Hantzsch ester **59**, THF (0.6 M), then Bu_3N	57%
5	2 mol % 4CzIPN, Hantzsch ester **59**, THF (0.6 M), then Bu_3N	54%


PhthNO2C
OBn
H
O
O
Cl
H
57
(1 equiv)
+
OMe
O
Cl
O
70
racemic
(1 equiv)
conditions
entry 4
Table 2
BnO
O
O
OMe
H
8
H
O
O
H
63
major product
62
not detected
(1)
BnO
O
O
H
OL-Men
H
H
O
O
H
69
DIBALH
touene
–78 °C
then
Ac2O, DMAP
pyr, 98%
BnO
11
O
O
H
OL-Men
H
16
O
H
H
OAc
H
71
1. Pd(OH)2, H2, EtOAc, rt
2. PtO2, H2, EtOAc, rt
69% over 2 steps
O
R
H
OL-Men
O
O
H
H
H
OAc
H
1:1 HCl
(4 M)/THF
rt
O
HO
O
HO
H
O
H
H
OH
H
67
DMAP
Ac2O
pyr
CH2Cl2
rt
45%
(from 72)
O
AcO
O
AcO
H
O
H
H
OAc
H
(-)-chromodorolide B (11)
72: R = CH2OH
73: R = CO2H
1. DMP
2. NaOCl