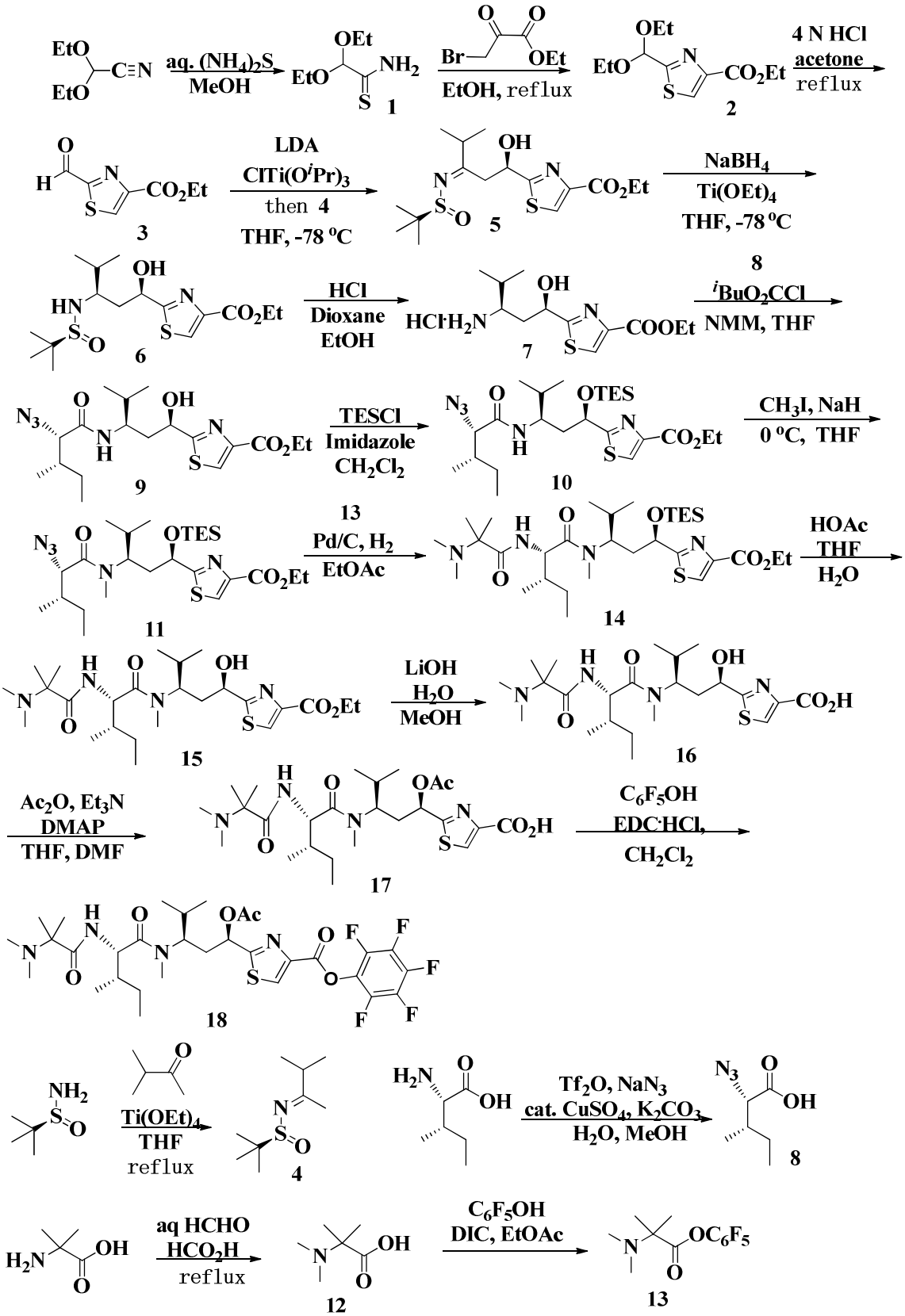

aq. (NH4)2S
MeOH
EtOH, reflux
4 N HCl
acetone
reflux
LDA
ClTi(OiPr)3
then 4
THF, -78 °C
NaBH4
Ti(OEt)4
THF, -78 °C
HCl
Dioxane
EtOH
iBuO2CCl
NMM, THF
TESCl
Imidazole
CH2Cl2
CH3I, NaH
0 °C, THF
Pd/C, H2
EtOAc
HOAc
THF
H2O
LiOH
H2O
MeOH
Ac2O, Et3N
DMAP
THF, DMF
C6F5OH
EDC·HCl,
CH2Cl2
Ti(OEt)4
THF
reflux
Tf2O, NaN3
cat. CuSO4, K2CO3
H2O, MeOH
aq HCHO
HCO2H
reflux
C6F5OH
DIC, EtOAc

Fig. 1

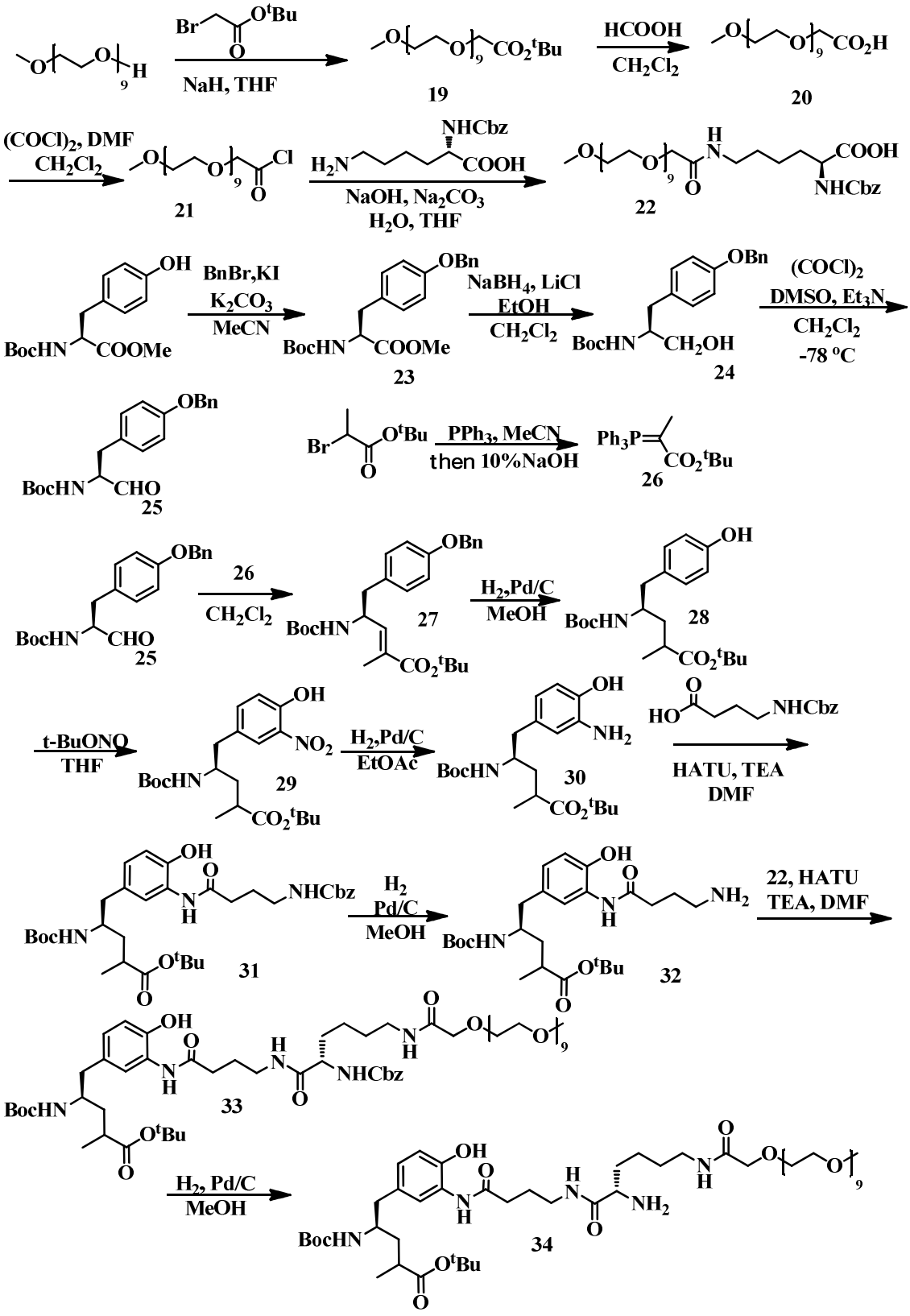

NaH, THF
19
HCOOH
CH2Cl2
20
(COCl)2, DMF
CH2Cl2
21
NaOH, Na2CO3
H2O, THF
22
BnBr,KI
K2CO3
MeCN
23
NaBH4, LiCl
EtOH
CH2Cl2
24
(COCl)2
DMSO, Et3N
CH2Cl2
-78 °C
25
PPh3, MeCN
then 10%NaOH
26
CH2Cl2
27
H2,Pd/C
MeOH
28
t-BuONO
THF
29
H2,Pd/C
EtOAc
30
HATU, TEA
DMF
31
H2
Pd/C
MeOH
32
22, HATU
TEA, DMF
33
H2, Pd/C
MeOH
34

Fig. 2

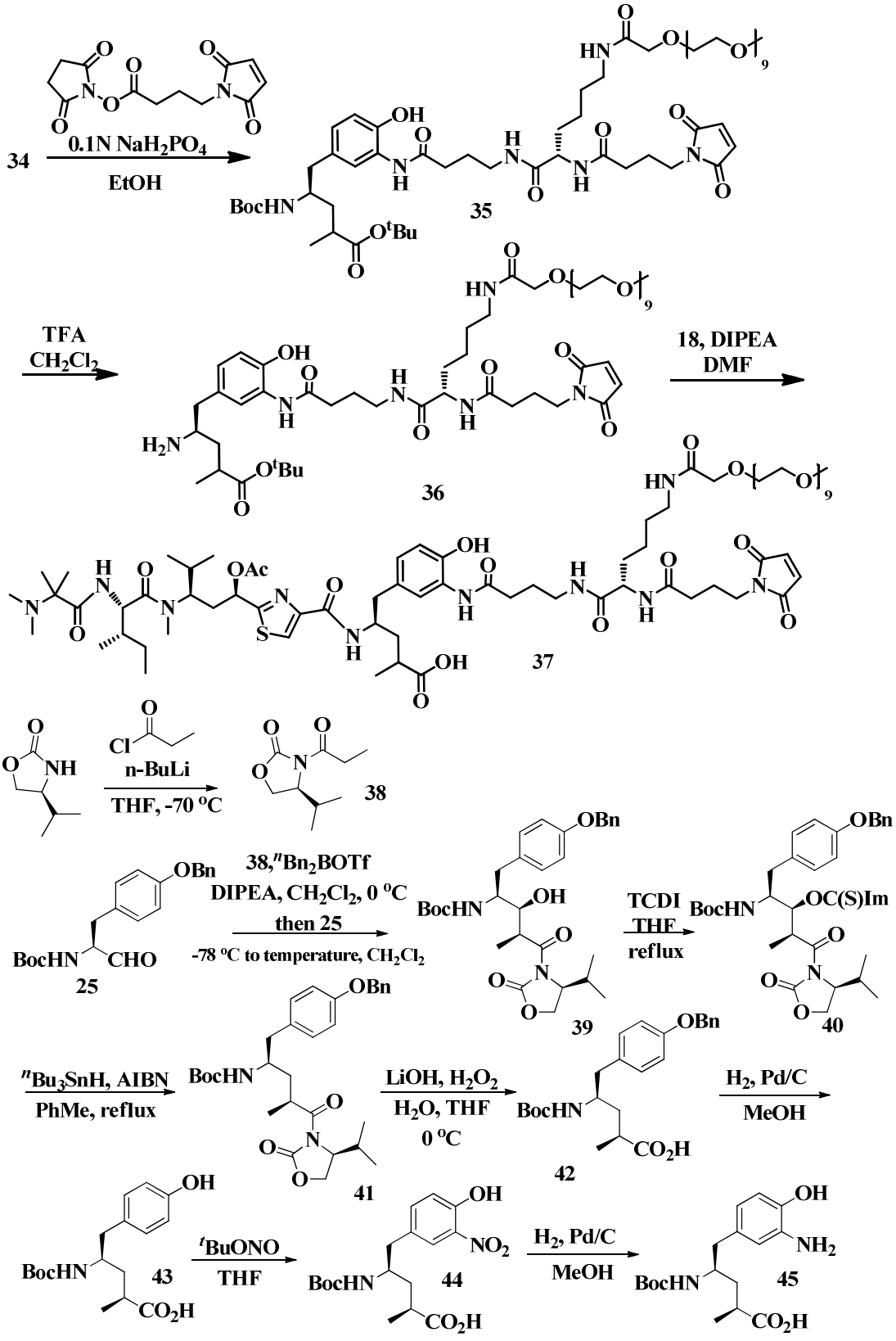

34
0.1N NaH2PO4
EtOH
35
TFA
CH2Cl2
36
18, DIPEA
DMF
37
38
n-BuLi
THF, -70 °C
38, nBn2BOTf
DIPEA, CH2Cl2, 0 °C
then 25
-78 °C to temperature, CH2Cl2
25
39
TCDI
THF
reflux
40
nBu3SnH, AIBN
PhMe, reflux
41
LiOH, H2O2
H2O, THF
0 °C
42
H2, Pd/C
MeOH
43
tBuONO
THF
44
H2, Pd/C
MeOH
45

Fig.3

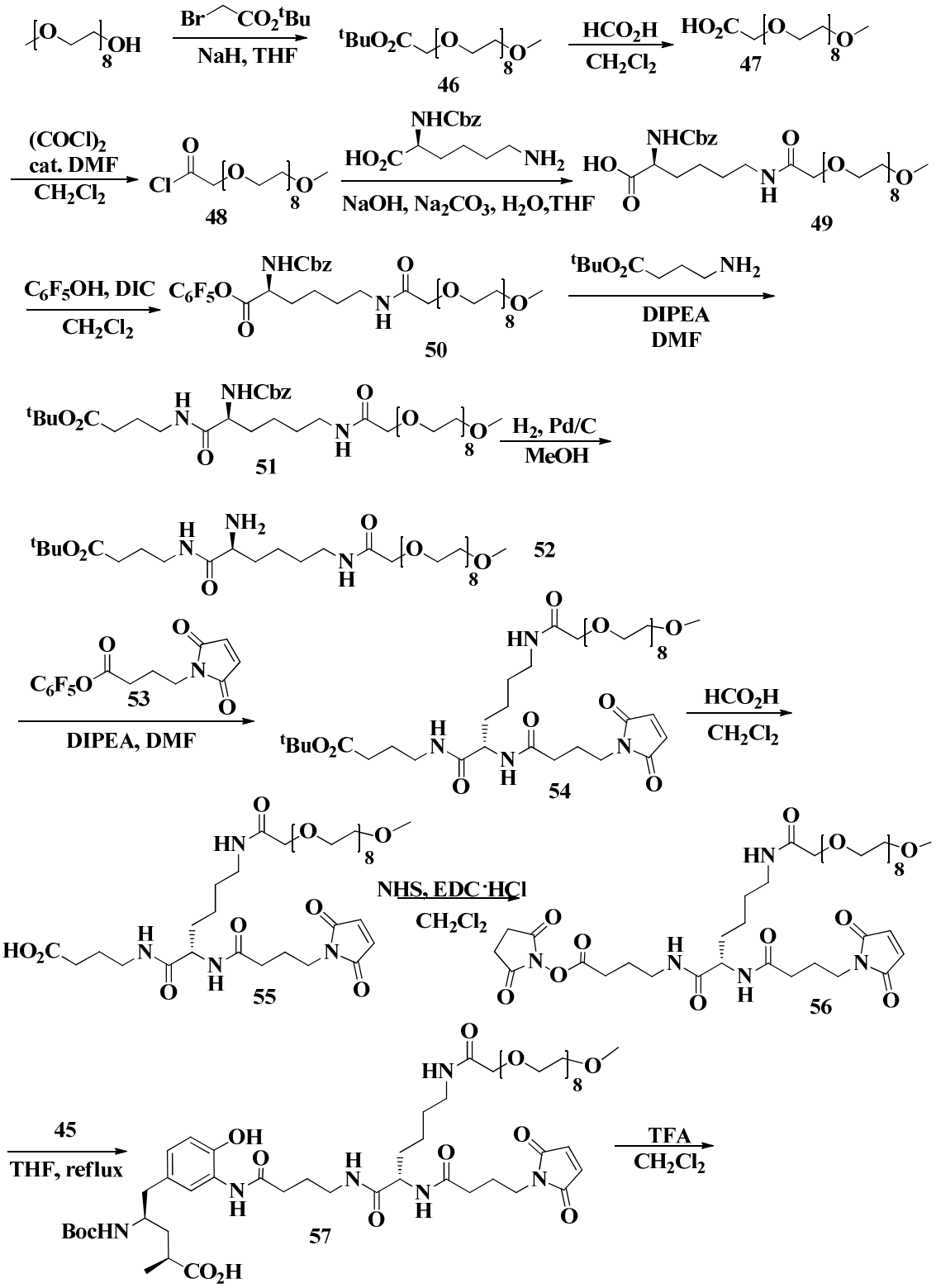

Br CO2tBu
NaH, THF
46
HCO2H
CH2Cl2
47
(COCl)2
cat. DMF
CH2Cl2
48
NHCbz
HO2C NH2
NaOH, Na2CO3, H2O,THF
49
C6F5OH, DIC
CH2Cl2
50
tBuO2C NH2
DIPEA
DMF
51
H2, Pd/C
MeOH
52
53
DIPEA, DMF
54
HCO2H
CH2Cl2
NHS, EDC·HCl
CH2Cl2
55
56
45
THF, reflux
57
TFA
CH2Cl2

Fig.4

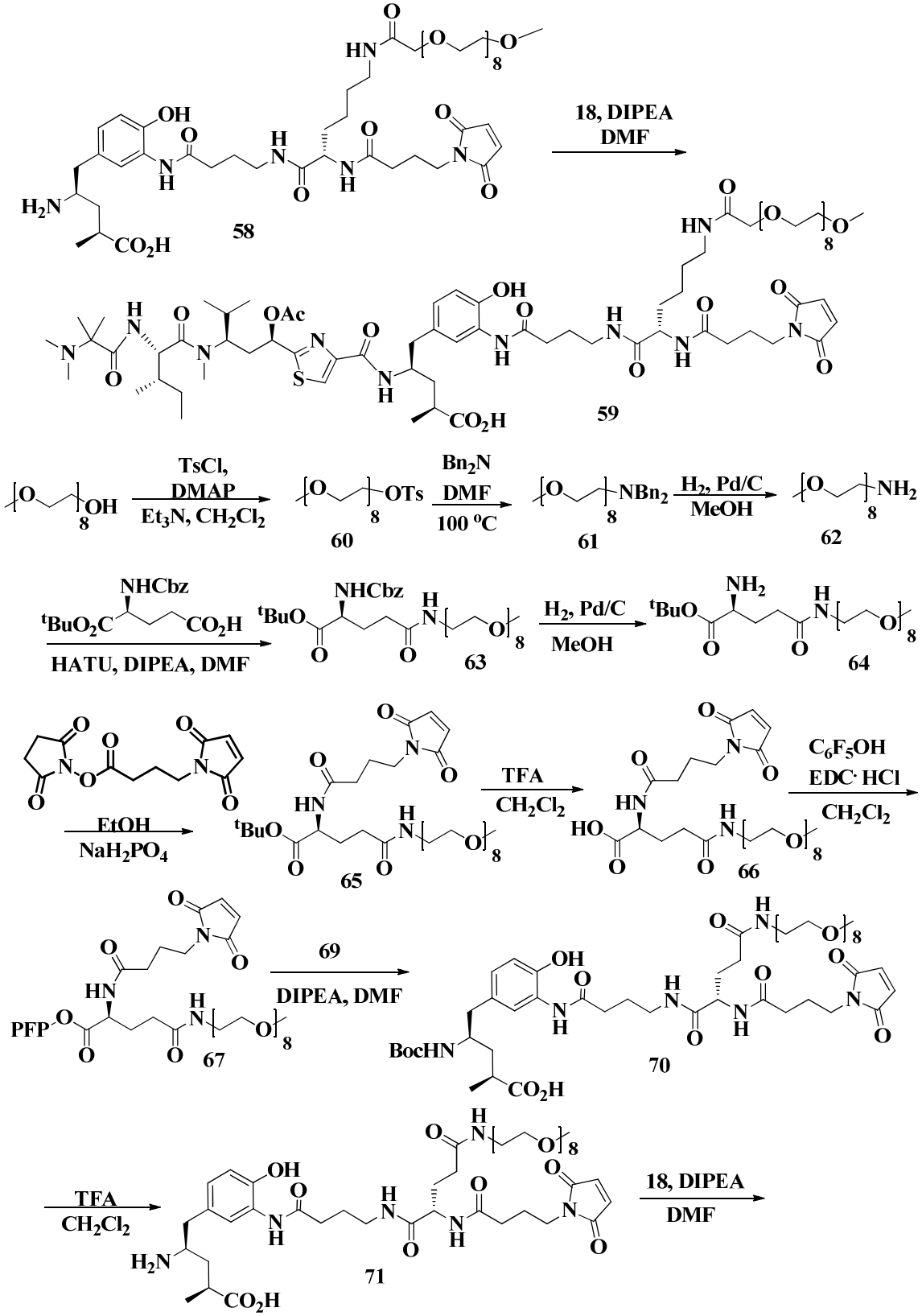

18, DIPEA
DMF
58
59
TsCl,
DMAP
Et3N, CH2Cl2
60
Bn2N
DMF
100 °C
61
H2, Pd/C
MeOH
62
HATU, DIPEA, DMF
63
H2, Pd/C
MeOH
64
EtOH
NaH2PO4
65
TFA
CH2Cl2
66
C6F5OH
EDC· HCl
CH2Cl2
67
69
DIPEA, DMF
70
TFA
CH2Cl2
71
18, DIPEA
DMF

Fig. 5

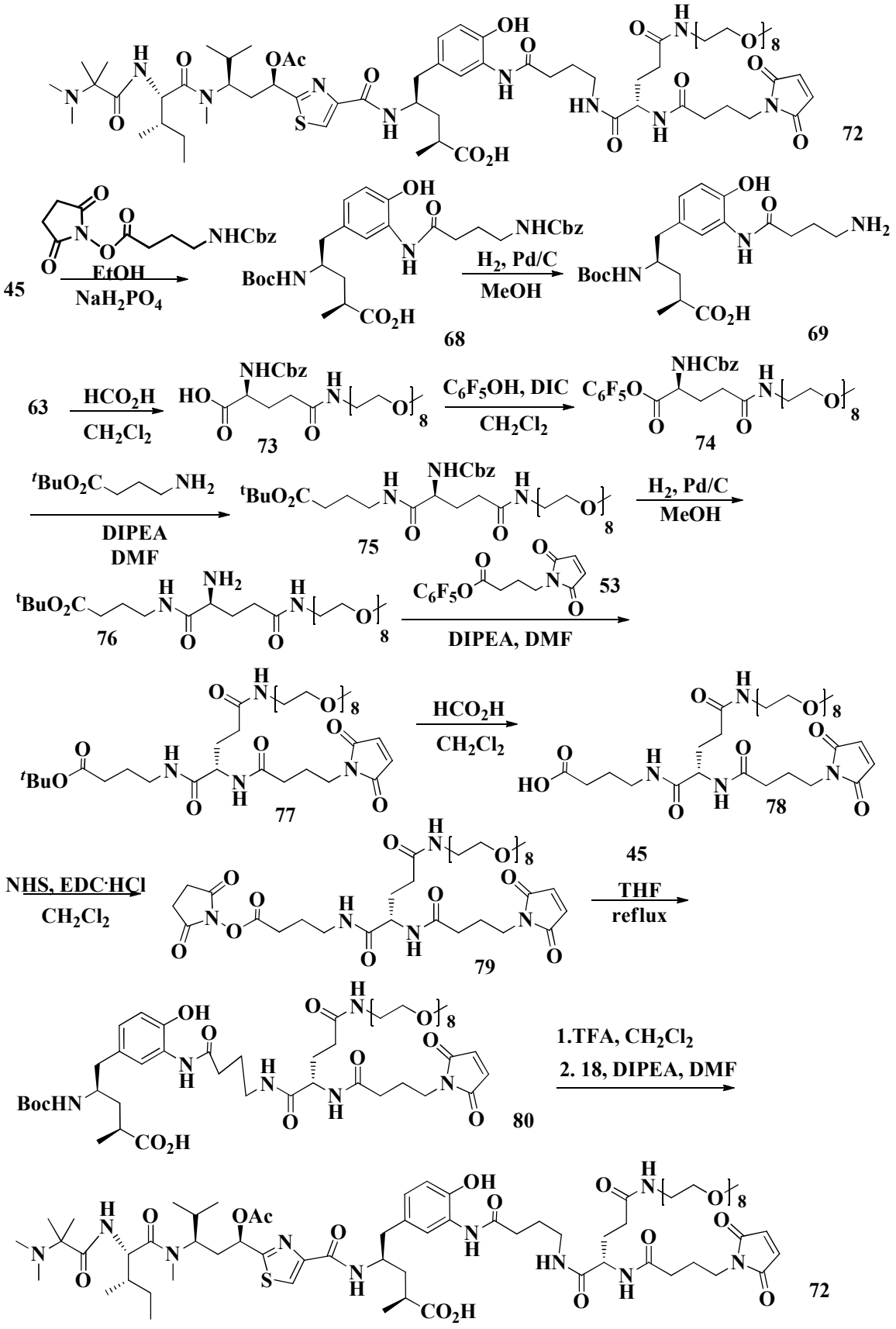

72
45
EtOH
NaH2PO4
68
H2, Pd/C
MeOH
69
63
HCO2H
CH2Cl2
73
C6F5OH, DIC
CH2Cl2
74
DIPEA
DMF
75
H2, Pd/C
MeOH
76
53
DIPEA, DMF
HCO2H
CH2Cl2
77
78
NHS, EDC·HCl
CH2Cl2
79
45
THF
reflux
80
1.TFA, CH2Cl2
2. 18, DIPEA, DMF
72

Fig. 6

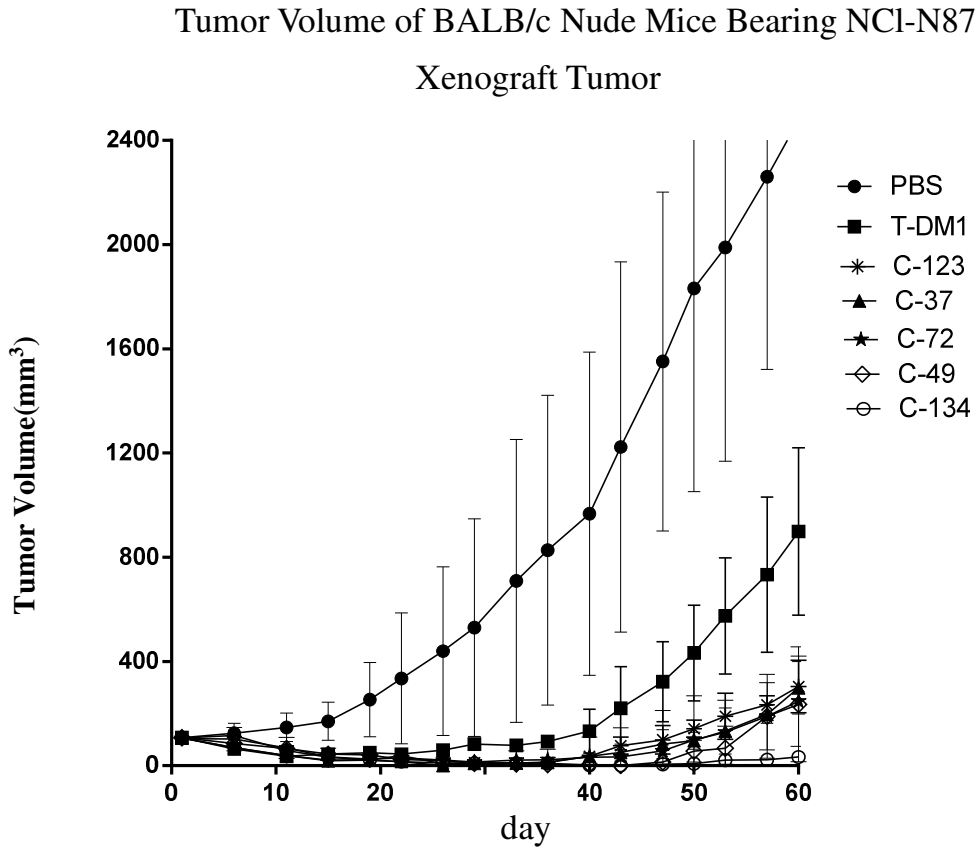

Tumor Volume of BALB/c Nude Mice Bearing NCl-N87 Xenograft Tumor
Tumor Volume(mm3)
2400
2000
1600
1200
800
400
0
0
10
20
40
50
60
day
PBS
T-DM1
C-123
C-37
C-72
C-49
C-134

Fig. 7

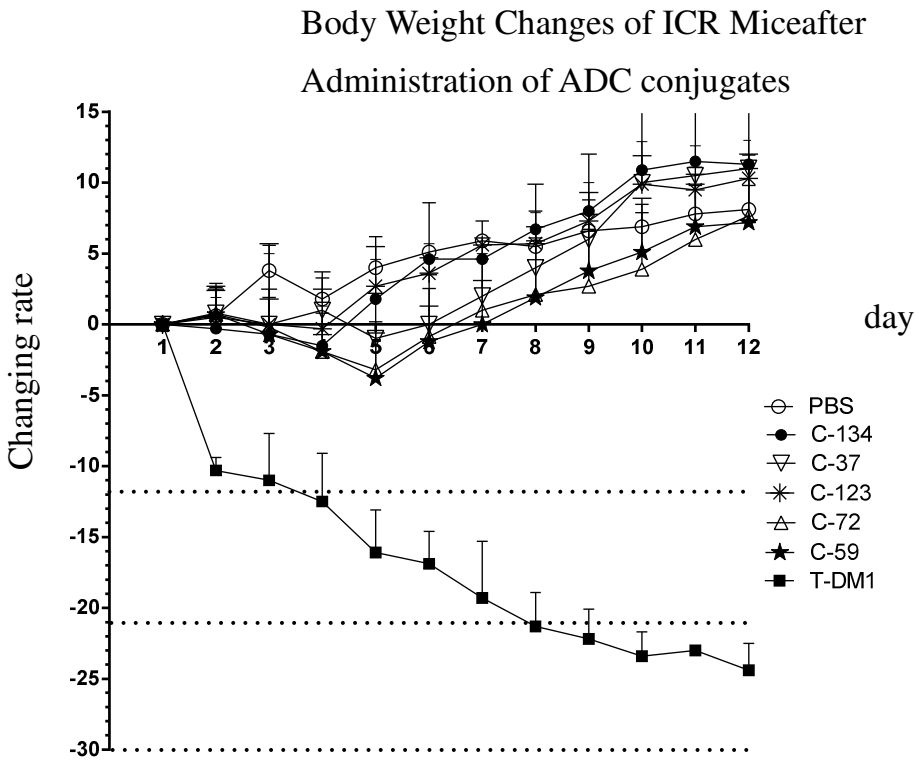

Body Weight Changes of ICR Miceafter
Administration of ADC conjugates
Changing rate
day
15
10
5
0
-5
-10
-15
-20
-25
-30
1
2
3
5
6
7
8
9
10
11
12
PBS
C-134
C-37
C-123
C-72
C-59
T-DM1

Fig. 8