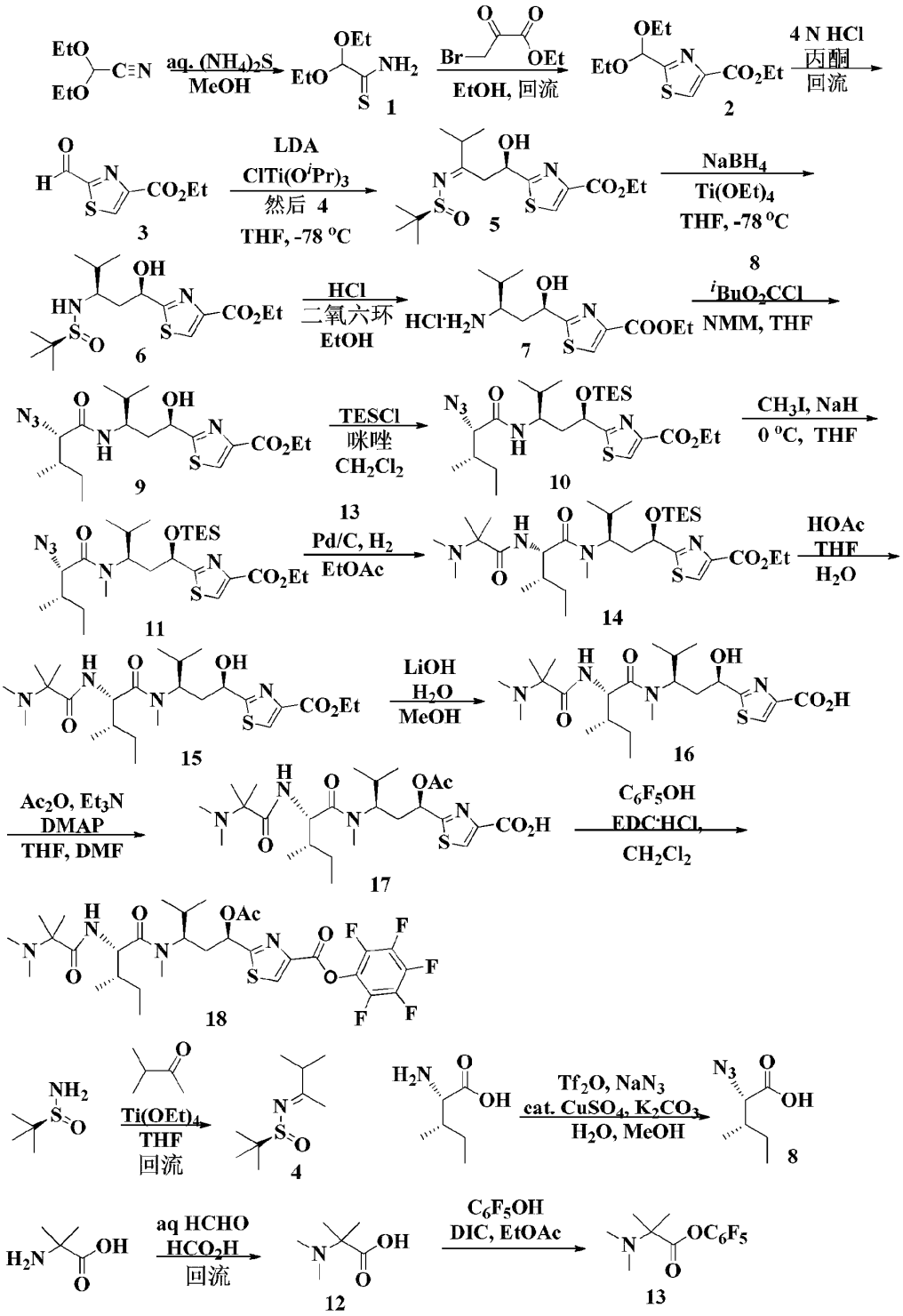

aq. (NH4)2S
MeOH
EtOH, 回流
4 N HCl
丙酮
回流
LDA
ClTi(OiPr)3
然后 4
THF, -78 °C
NaBH4
Ti(OEt)4
THF, -78 °C
HCl
二氧六环
EtOH
iBuO2CCl
NMM, THF
TESCl
咪唑
CH2Cl2
CH3I, NaH
0 °C, THF
Pd/C, H2
EtOAc
HOAc
THF
H2O
LiOH
H2O
MeOH
Ac2O, Et3N
DMAP
THF, DMF
C6F5OH
EDC·HCl,
CH2Cl2
Ti(OEt)4
THF
回流
Tf2O, NaN3
cat. CuSO4, K2CO3
H2O, MeOH
aq HCHO
HCO2H
回流
C6F5OH
DIC, EtOAc

图 1

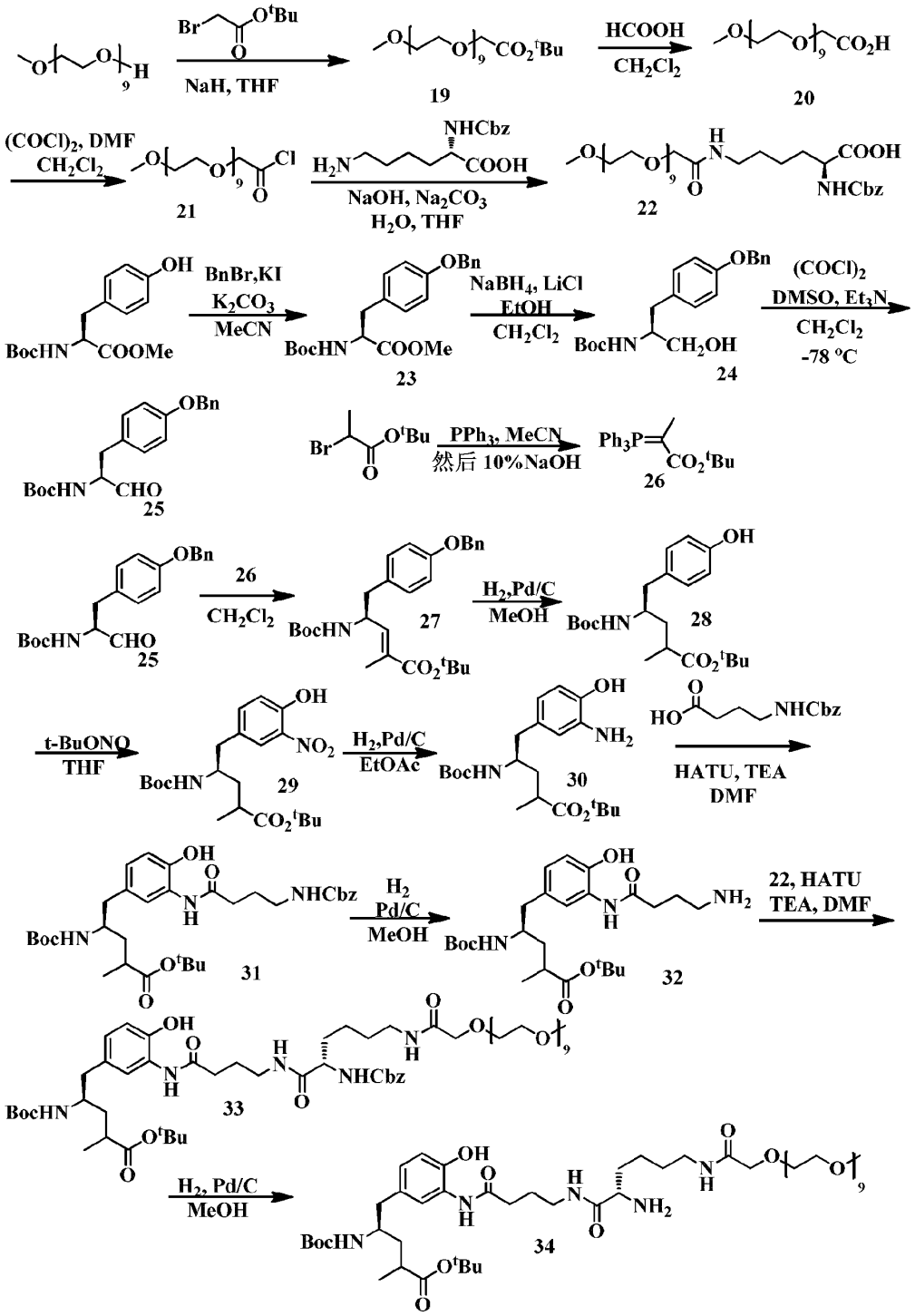

NaH, THF
HCOOH
CH2Cl2
(COCl)2, DMF
CH2Cl2
NaOH, Na2CO3
H2O, THF
BnBr,KI
K2CO3
MeCN
NaBH4, LiCl
EtOH
CH2Cl2
(COCl)2
DMSO, Et3N
CH2Cl2
-78 °C
PPh3, MeCN
然后 10%NaOH
t-BuONO
THF
H2,Pd/C
EtOAc
HATU, TEA
DMF
H2
Pd/C
MeOH
22, HATU
TEA, DMF
H2, Pd/C
MeOH

图 2

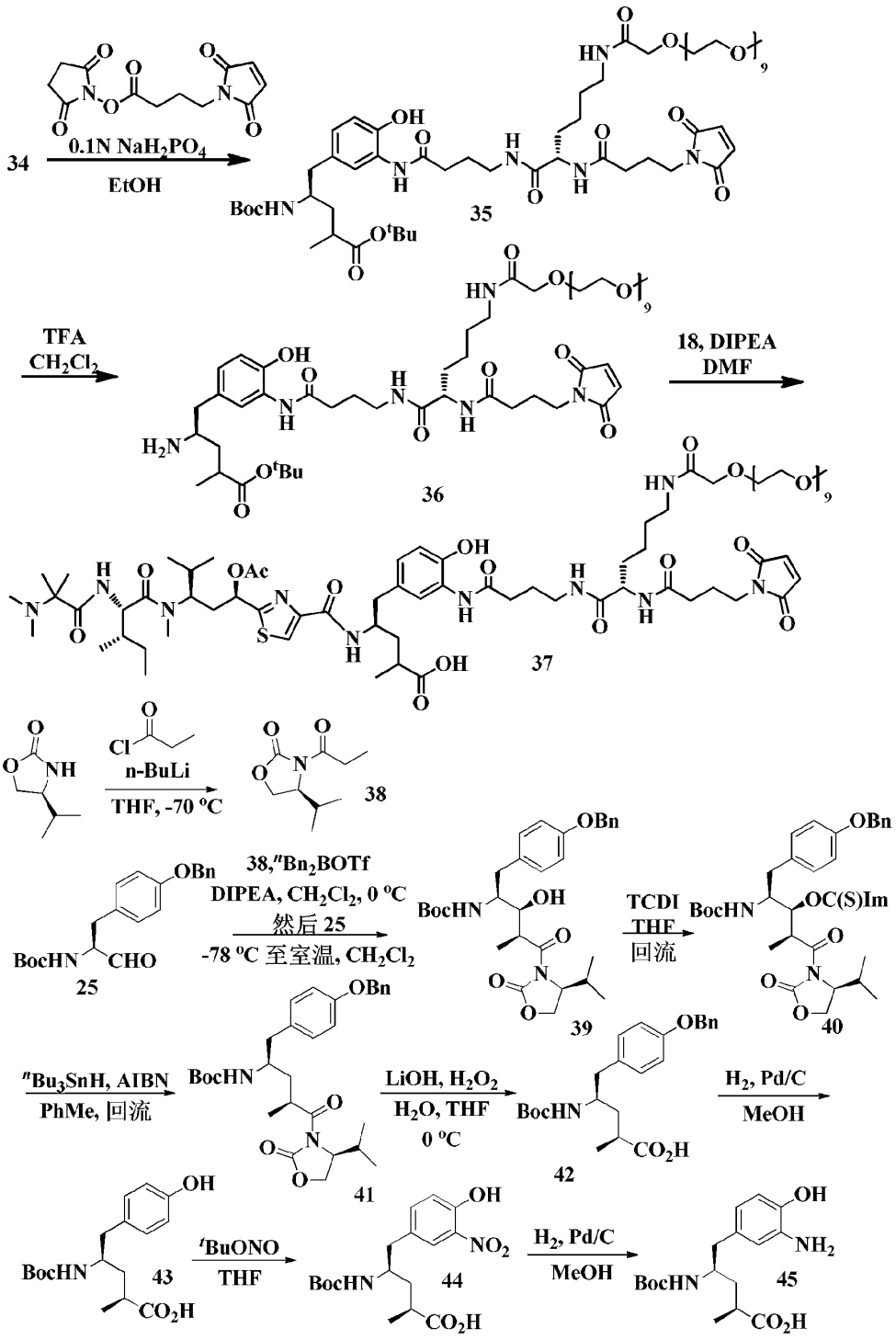

34
0.1N NaH2PO4
EtOH
35
TFA
CH2Cl2
36
18, DIPEA
DMF
37
n-BuLi
THF, -70 °C
38
38, nBu2BOTf
DIPEA, CH2Cl2, 0 °C
然后 25
-78 °C 至室温, CH2Cl2
25
39
TCDI
THF
回流
40
nBu3SnH, AIBN
PhMe, 回流
41
LiOH, H2O2
H2O, THF
0 °C
42
H2, Pd/C
MeOH
43
tBuONO
THF
44
H2, Pd/C
MeOH
45

图 3

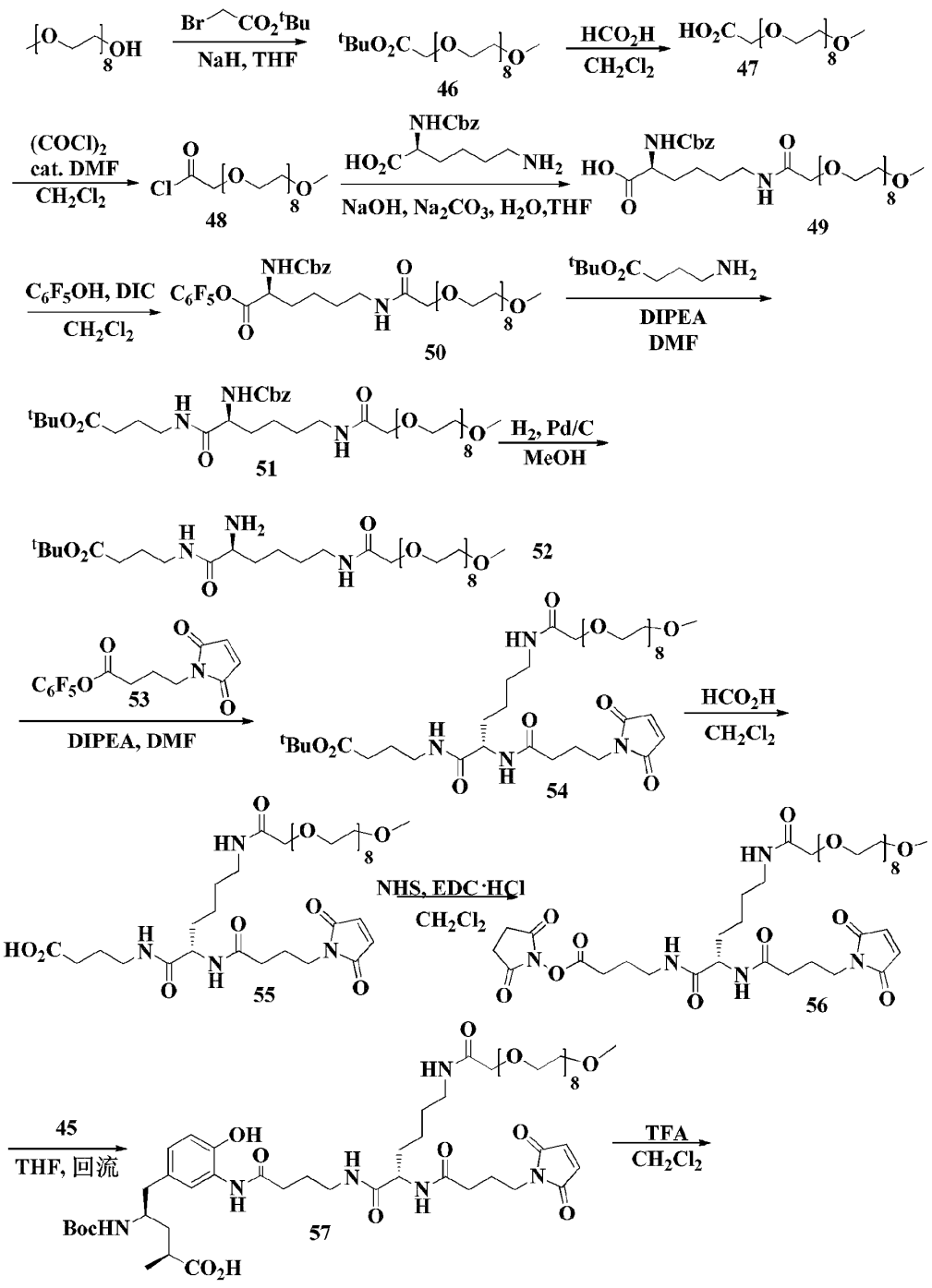

Br CO2tBu
NaH, THF
HCO2H
CH2Cl2
46
47
(COCl)2
cat. DMF
CH2Cl2
48
NaOH, Na2CO3, H2O,THF
49
C6F5OH, DIC
CH2Cl2
50
DIPEA
DMF
H2, Pd/C
MeOH
51
52
53
DIPEA, DMF
54
55
NHS, EDC·HCl
CH2Cl2
56
45
THF, 回流
57
TFA
CH2Cl2

图 4

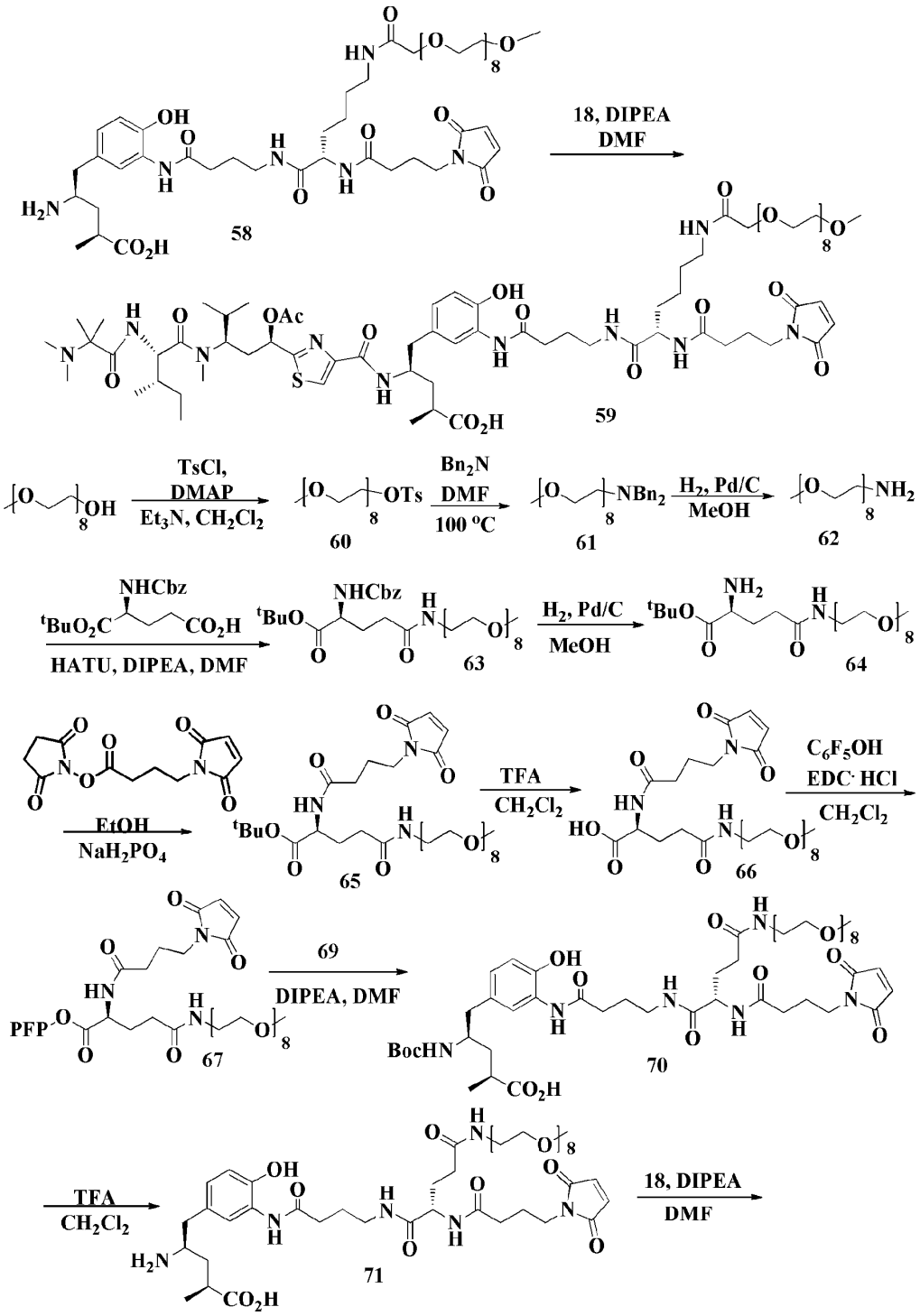

18, DIPEA
DMF
58
59
TsCl,
DMAP
Et3N, CH2Cl2
60
Bn2N
DMF
100 °C
61
H2, Pd/C
MeOH
62
HATU, DIPEA, DMF
63
H2, Pd/C
MeOH
64
EtOH
NaH2PO4
65
TFA
CH2Cl2
66
C6F5OH
EDC· HCl
CH2Cl2
67
69
DIPEA, DMF
70
TFA
CH2Cl2
71
18, DIPEA
DMF

图 5

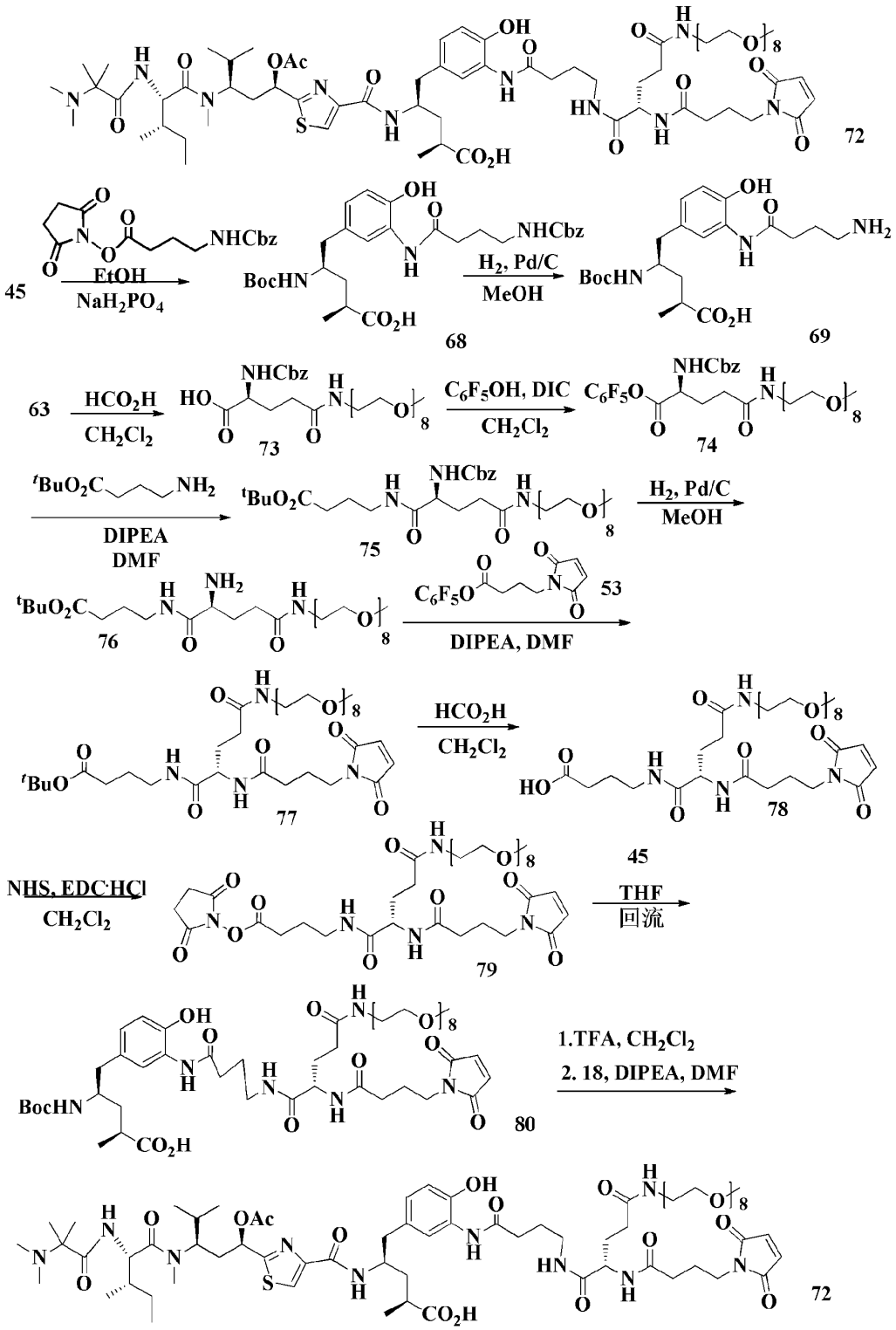

72
45
EtOH
NaH2PO4
NHCbz
BocHN
CO2H
68
H2, Pd/C
MeOH
NH2
69
63
HCO2H
CH2Cl2
73
C6F5OH, DIC
CH2Cl2
74
tBuO2C
NH2
DIPEA
DMF
75
76
C6F5O
53
DIPEA, DMF
tBuO
77
78
NHS, EDC·HCl
79
THF
回流
80
1.TFA, CH2Cl2
2. 18, DIPEA, DMF

图 6

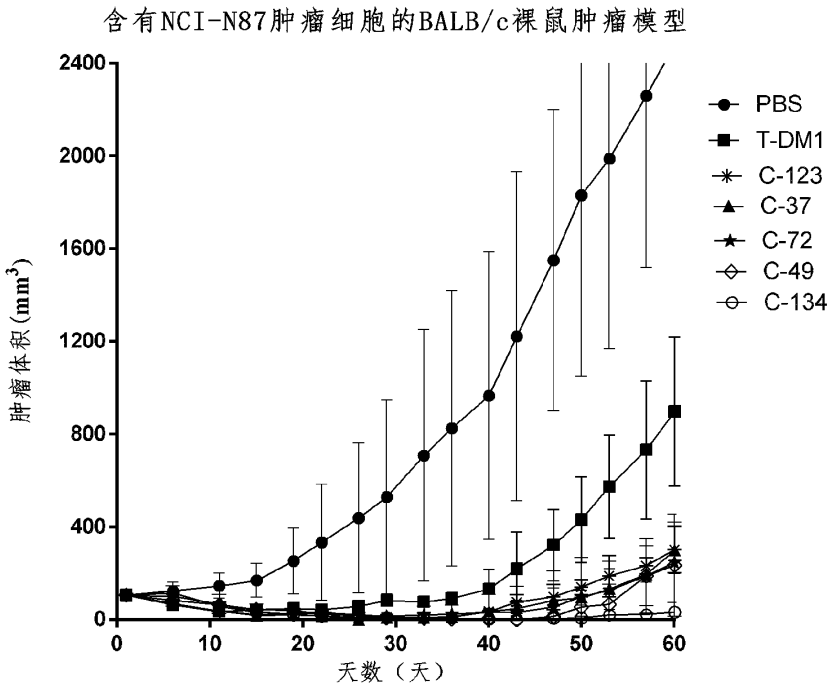

含有NCI-N87肿瘤细胞的BALB/c裸鼠肿瘤模型
肿瘤体积(mm3)
2400
2000
1600
1200
800
400
0
0
10
20
30
40
50
60
天数（天）
PBS
T-DM1
C-123
C-37
C-72
C-49
C-134

图 7

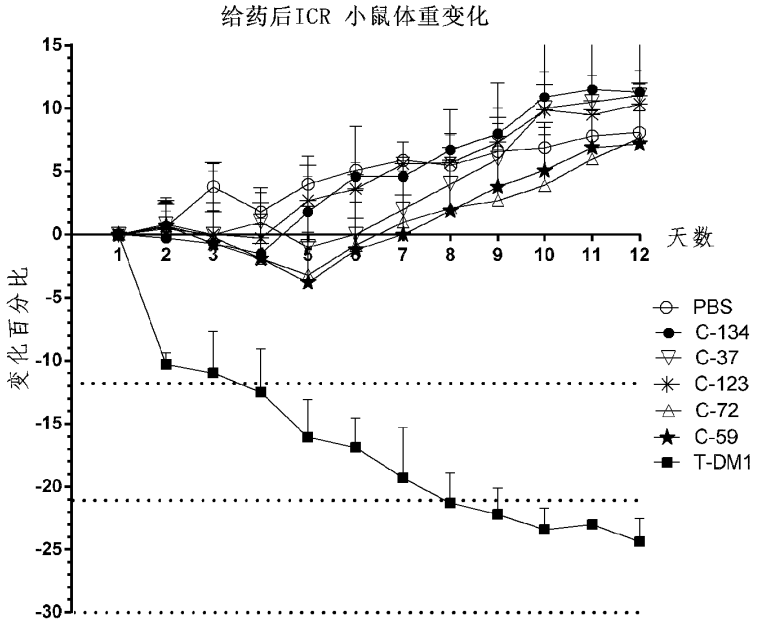

给药后ICR 小鼠体重变化
变化百分比
15
10
5
0
-5
-10
-15
-20
-25
-30
1
2
3
5
6
7
8
9
10
11
12
天数
PBS
C-134
C-37
C-123
C-72
C-59
T-DM1

图 8