FIGURES

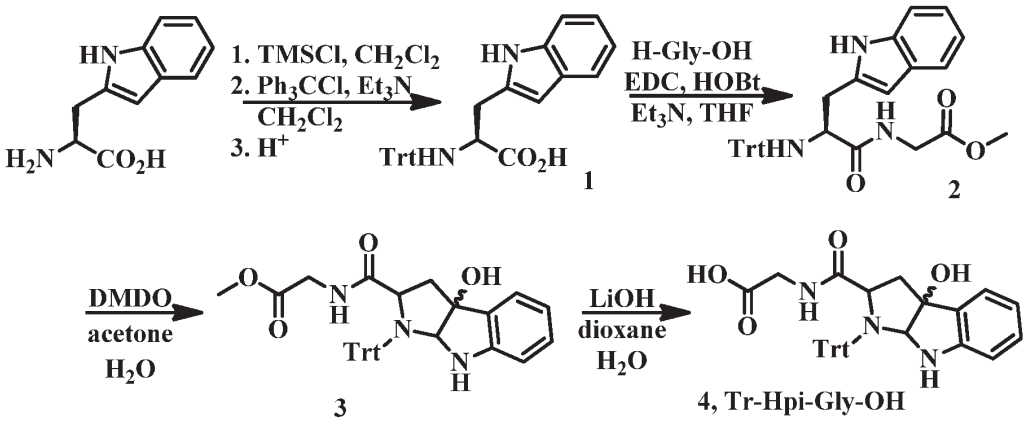

Fig 1.

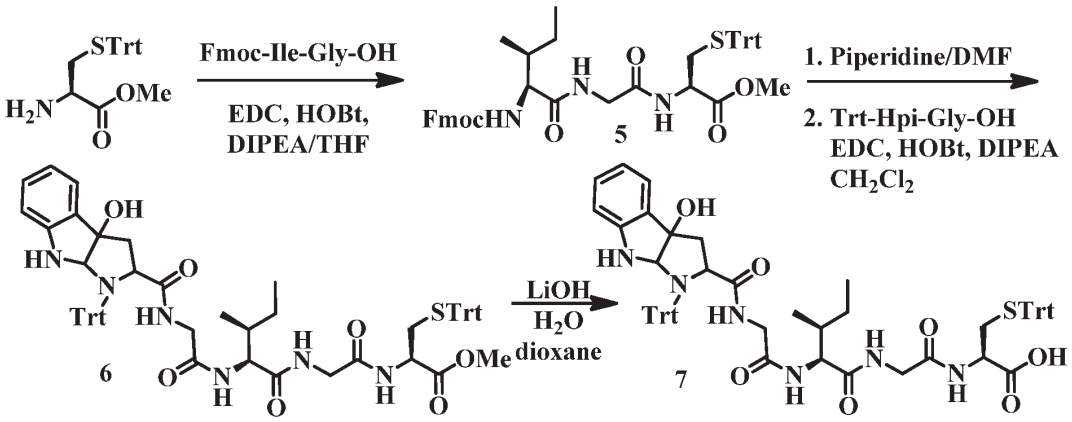

Fig 2.

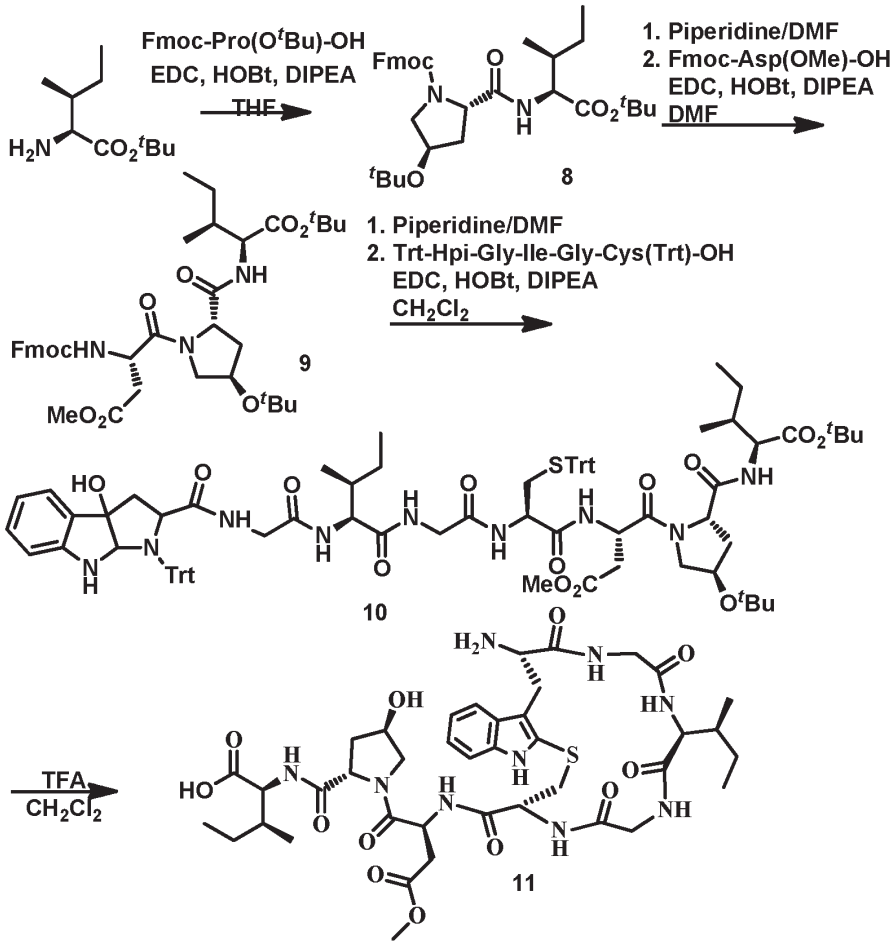
Fmoc-Pro(O^{t}Bu)-OH
EDC, HOBt, DIPEA
THF
1. Piperidine/DMF
2. Fmoc-Asp(OMe)-OH
EDC, HOBt, DIPEA
DMF
8
1. Piperidine/DMF
2. Trt-Hpi-Gly-Ile-Gly-Cys(Trt)-OH
EDC, HOBt, DIPEA
CH_2Cl_2
9
10
TFA
CH_2Cl_2
11

Fig 3.

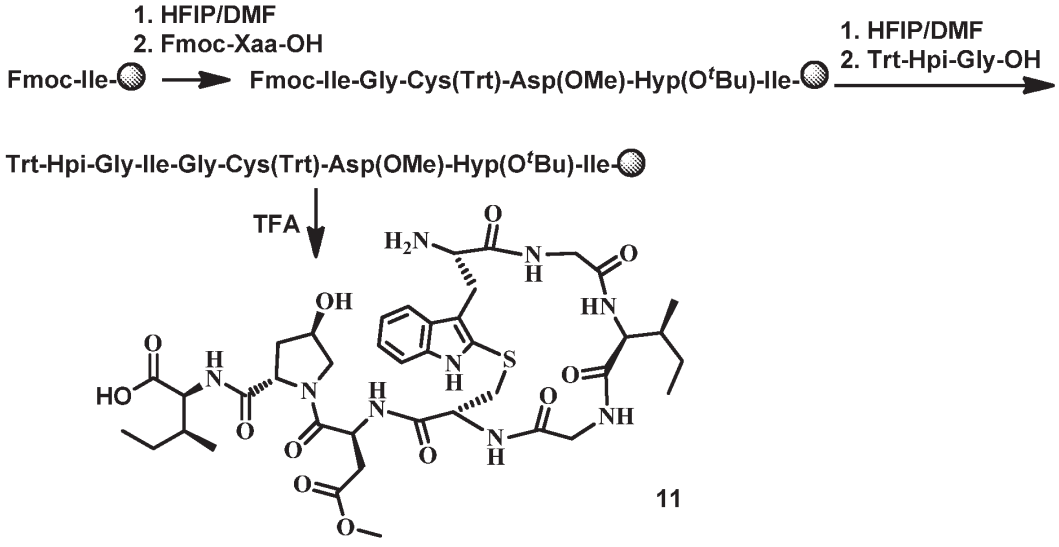
1. HFIP/DMF
2. Fmoc-Xaa-OH
Fmoc-Ile-
Fmoc-Ile-Gly-Cys(Trt)-Asp(OMe)-Hyp(O^{t}Bu)-Ile-
1. HFIP/DMF
2. Trt-Hpi-Gly-OH
Trt-Hpi-Gly-Ile-Gly-Cys(Trt)-Asp(OMe)-Hyp(O^{t}Bu)-Ile-
TFA
11

Fig 4.

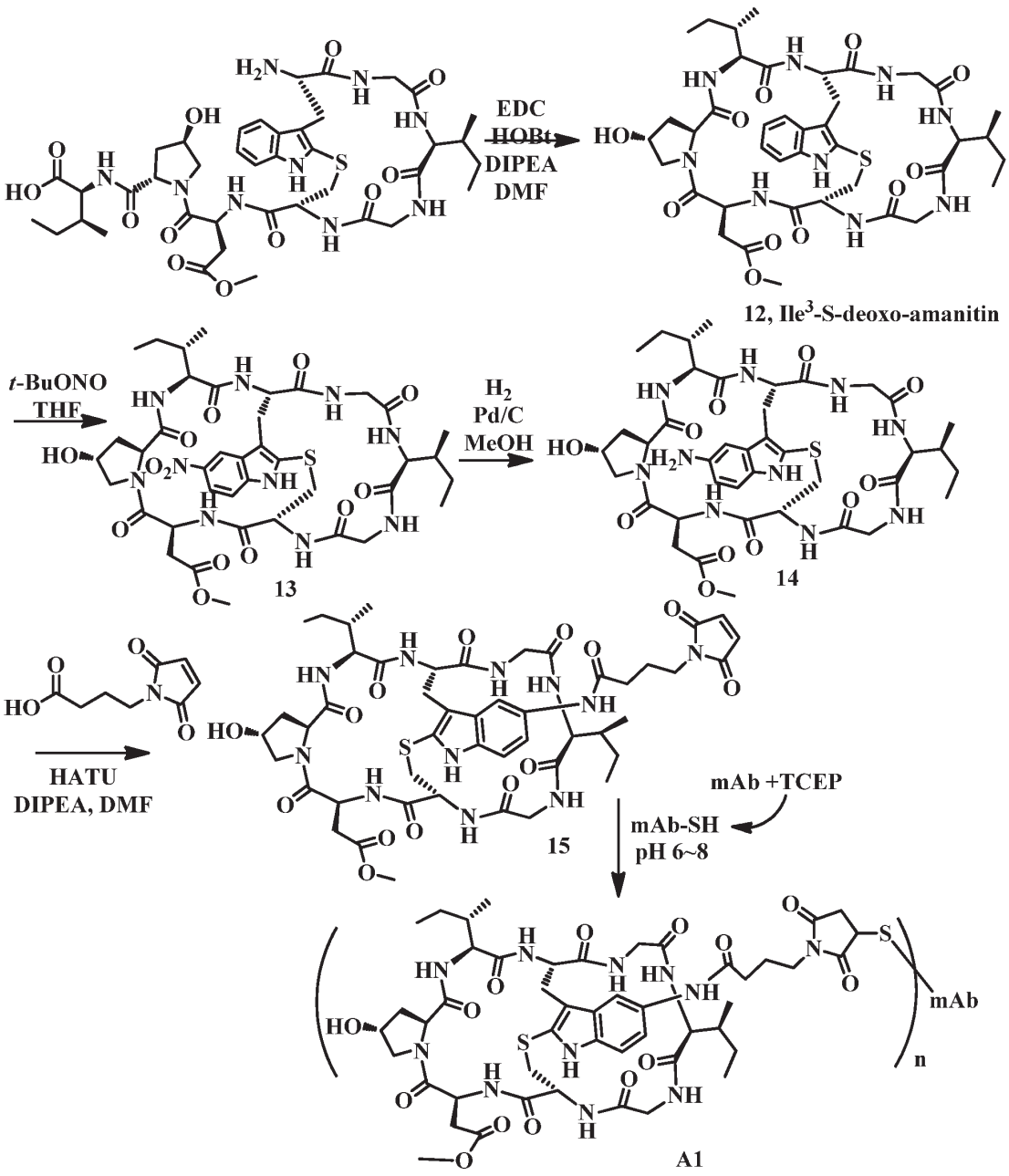
EDC
HOBt
DIPEA
DMF
12, Ile3-S-deoxo-amanitin
t-BuONO
THF
H2
Pd/C
MeOH
13
14
HATU
DIPEA, DMF
15
mAb +TCEP
mAb-SH
pH 6~8
mAb
n
A1

Fig 5.

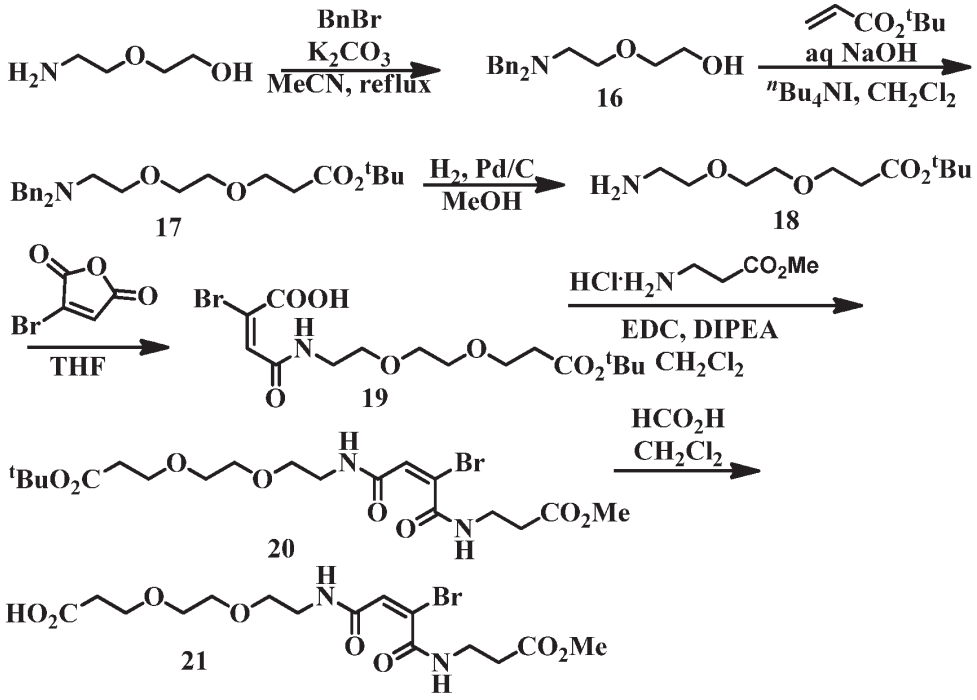
BnBr
K2CO3
MeCN, reflux
16
aq NaOH
nBu4NI, CH2Cl2
17
H2, Pd/C
MeOH
18
THF
19
HCl·H2N
CO2Me
EDC, DIPEA
CH2Cl2
HCO2H
CH2Cl2
20
21

Fig 6.

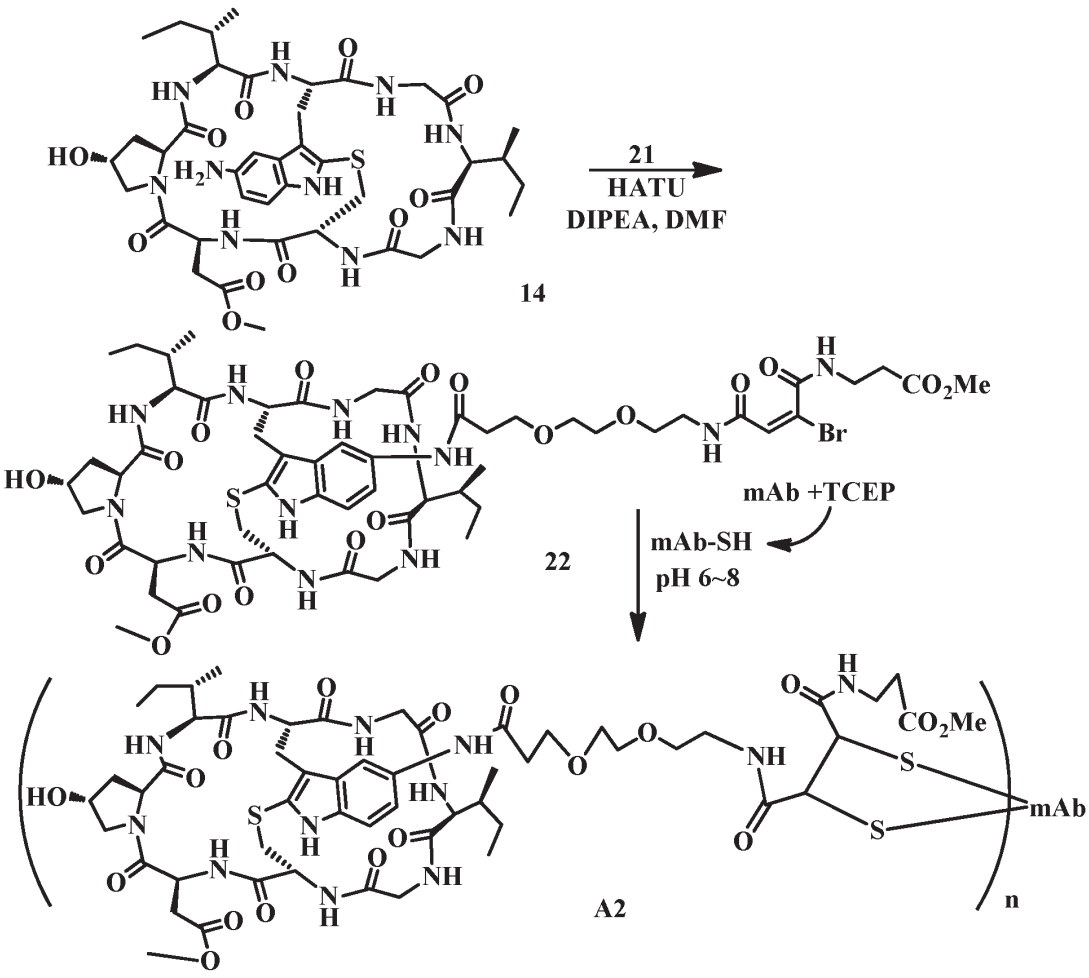

Fig 7.

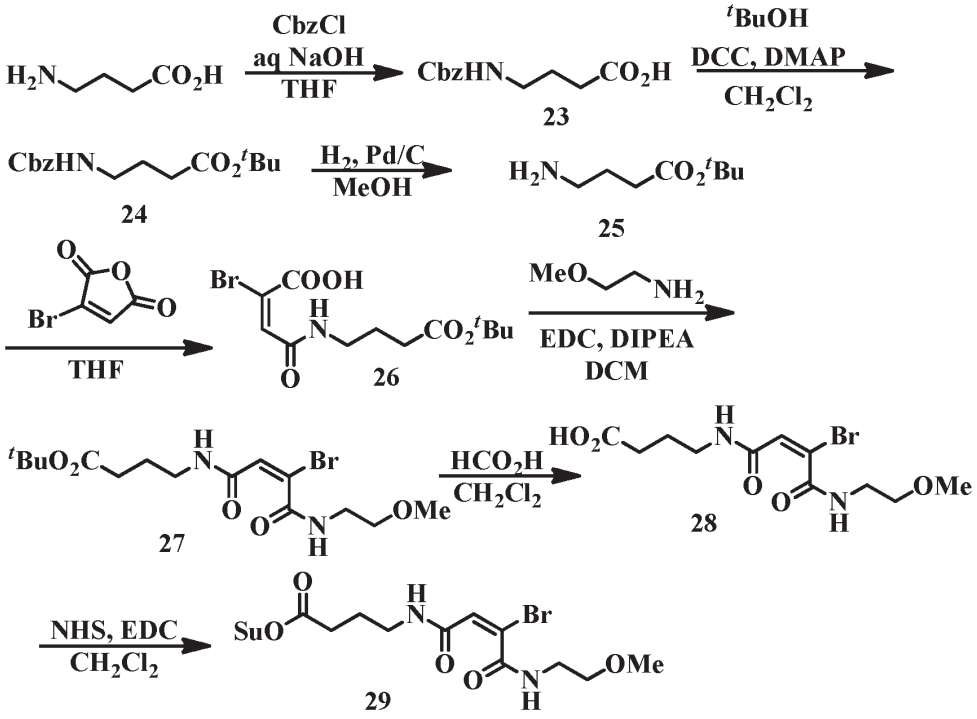
CbzCl
aq NaOH
THF
tBuOH
DCC, DMAP
CH2Cl2
23
H2, Pd/C
MeOH
24
25
THF
26
EDC, DIPEA
DCM
HCO2H
CH2Cl2
27
28
NHS, EDC
CH2Cl2
29

Fig 8.

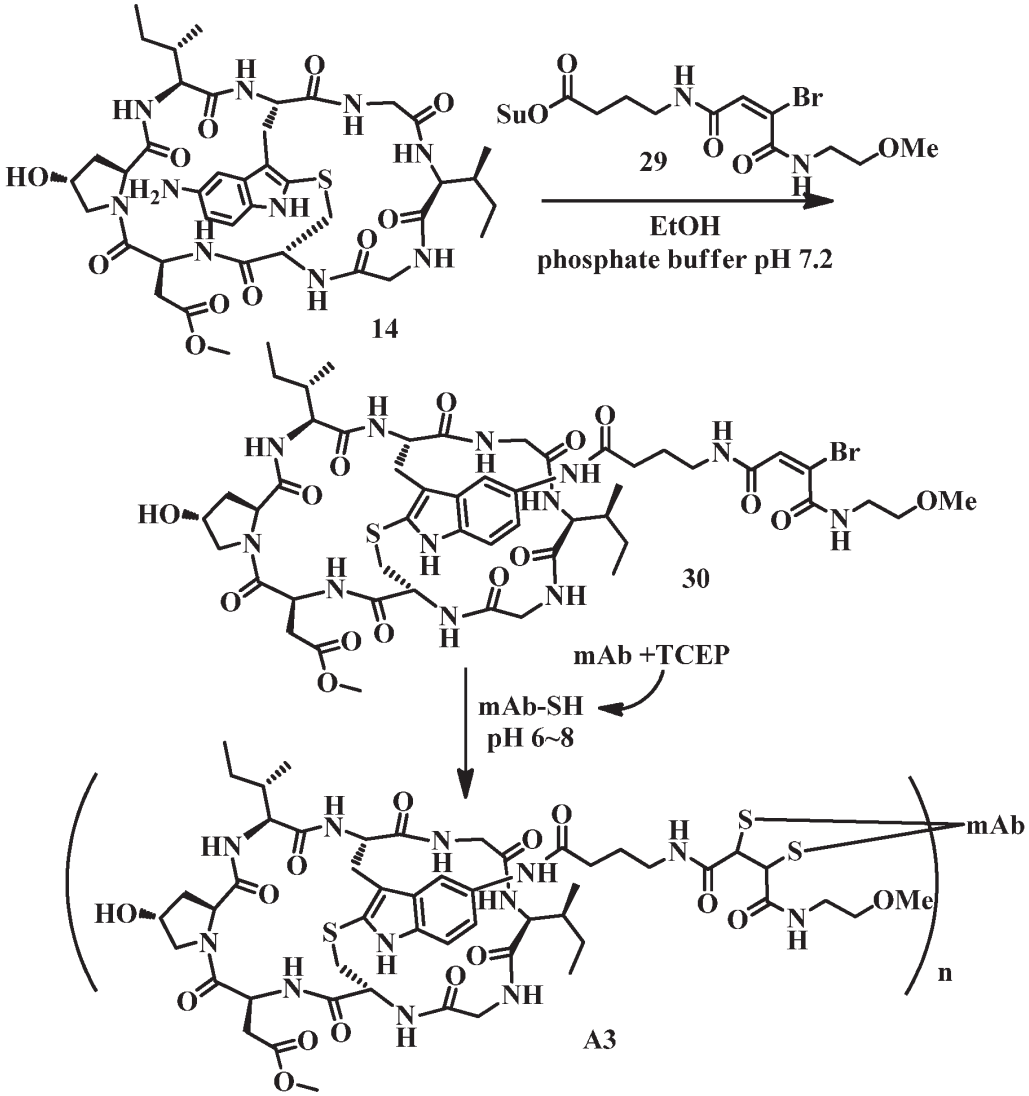
SuO
29
Br
OMe
EtOH
phosphate buffer pH 7.2
14
30
mAb +TCEP
mAb-SH
pH 6~8
mAb
n
A3

Fig 9.

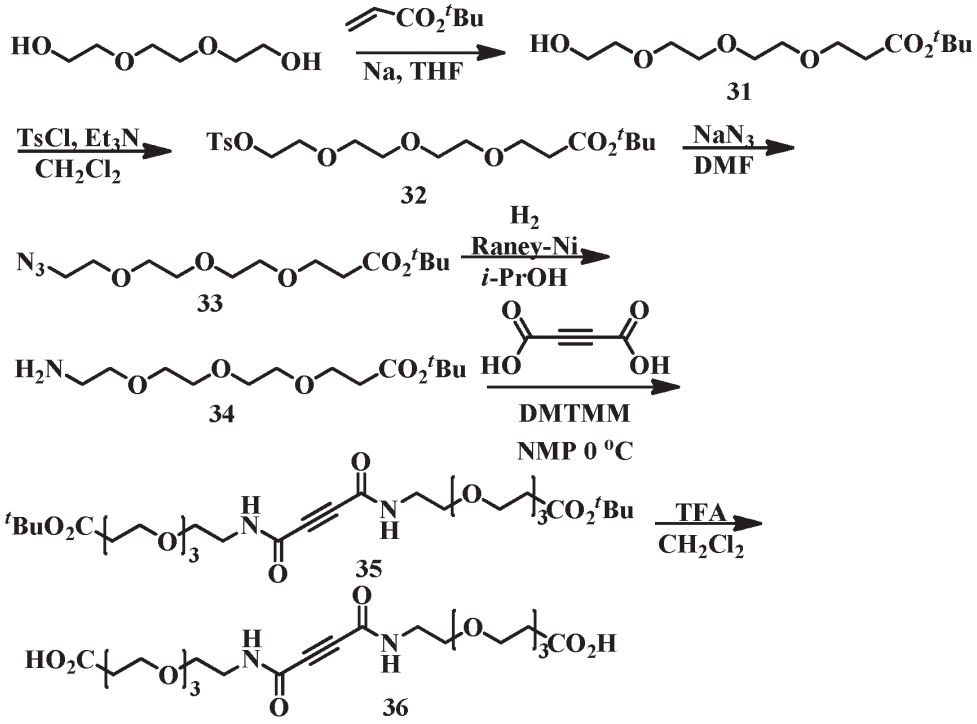
HO
O
O
OH
CO2tBu
Na, THF
HO
O
O
O
CO2tBu
31
TsCl, Et3N
CH2Cl2
TsO
O
O
O
CO2tBu
32
NaN3
DMF
N3
O
O
O
CO2tBu
33
H2
Raney-Ni
i-PrOH
H2N
O
O
O
CO2tBu
34
O
O
HO
OH
DMTMM
NMP 0 °C
tBuO2C
O3
H
N
O
N
H
O
3CO2tBu
35
TFA
CH2Cl2
HO2C
O3
H
N
O
N
H
O
3CO2H
36

Fig 10.

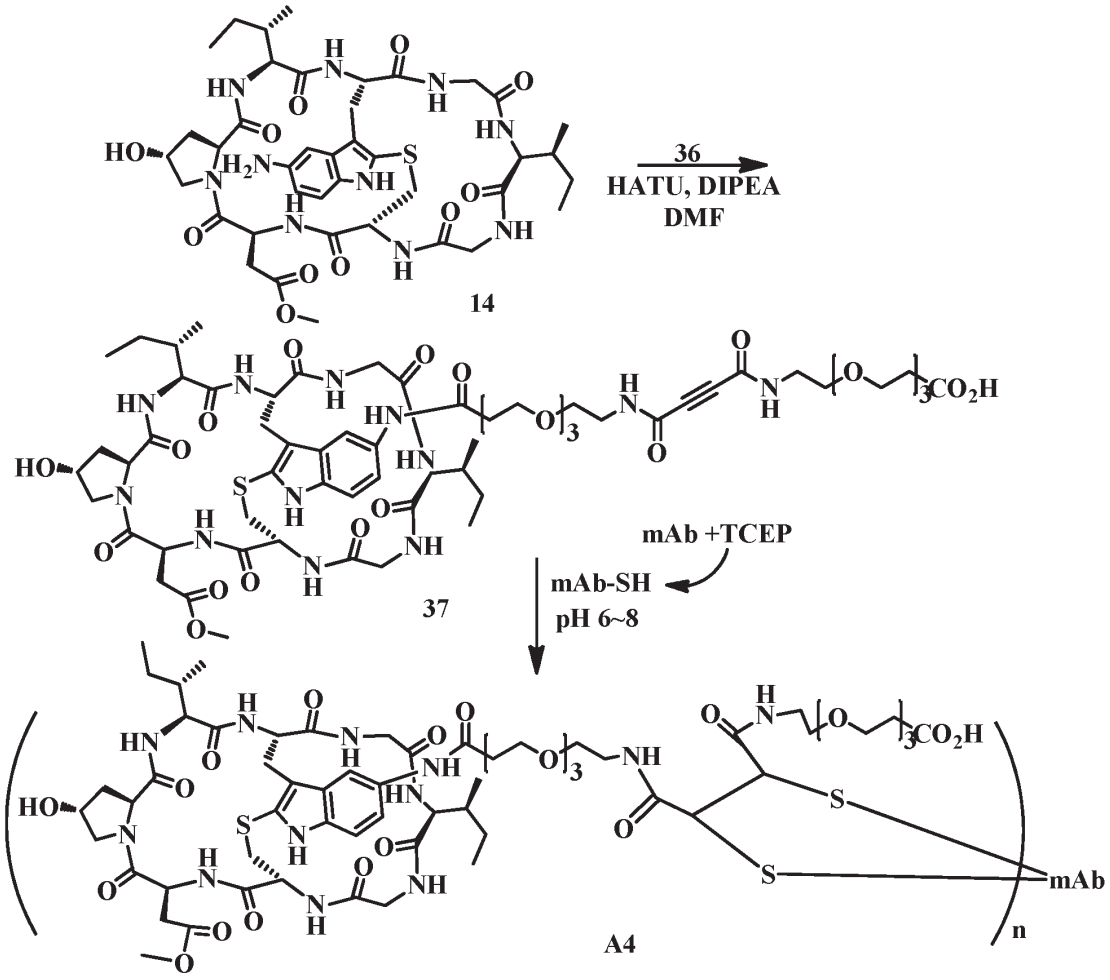
36
HATU, DIPEA
DMF
14
mAb +TCEP
mAb-SH
pH 6~8
37
A4
mAb
n

Fig 11.

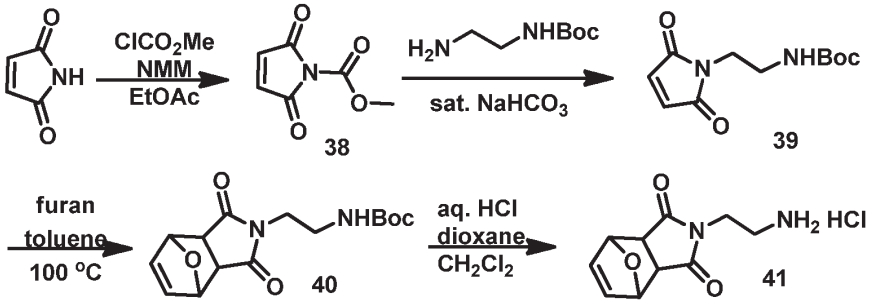
ClCO2Me
NMM
EtOAc
38
H2N
NHBoc
sat. NaHCO3
39
furan
toluene
100 °C
40
aq. HCl
dioxane
CH2Cl2
NH2 HCl
41

Fig 12.

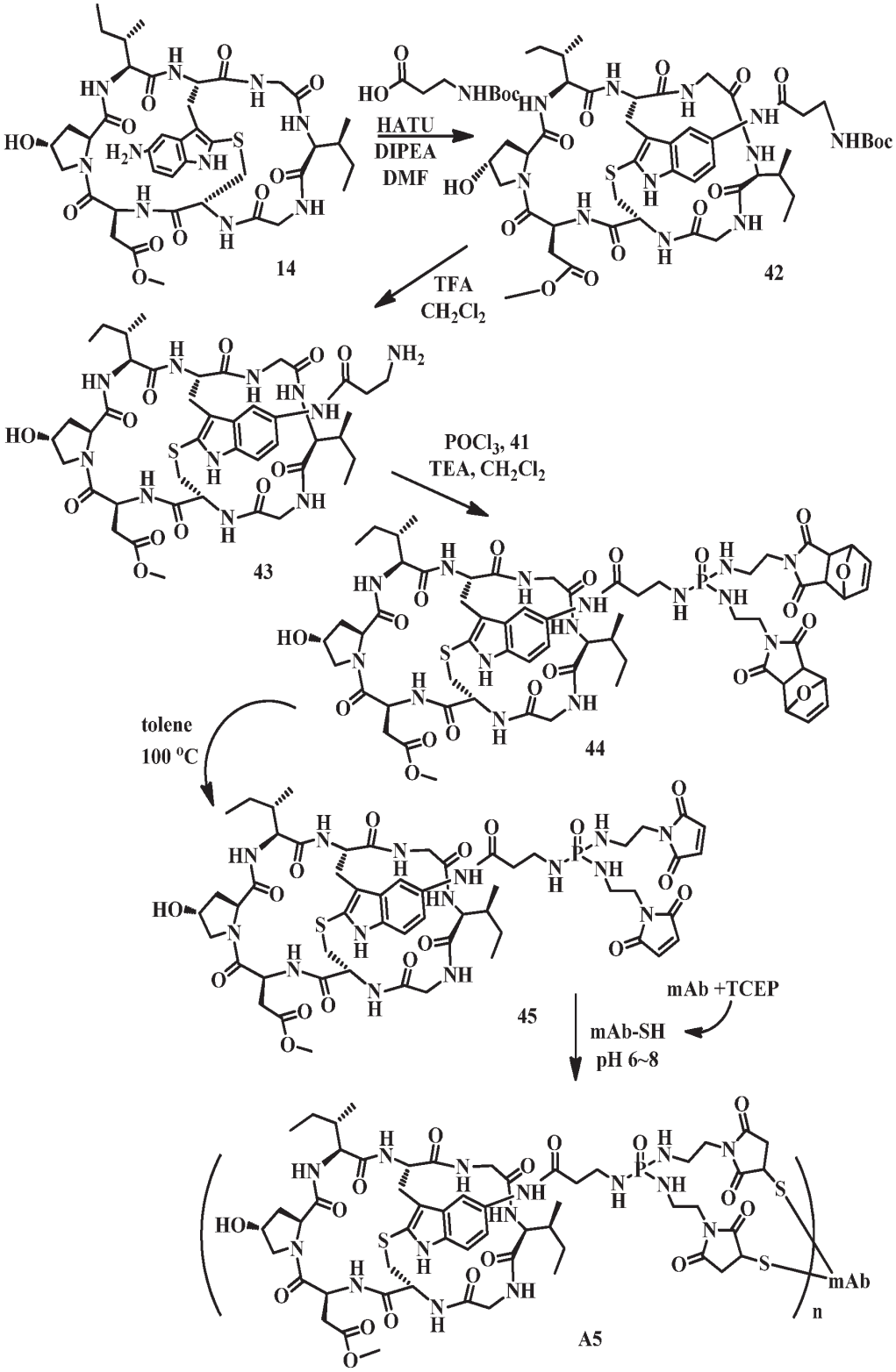
HATU
DIPEA
DMF
14
42
TFA
CH_2Cl_2
43
$POCl_3$, 41
TEA, CH_2Cl_2
44
tolene
100 °C
45
mAb +TCEP
mAb-SH
pH 6~8
A5
mAb
n

Fig 13.

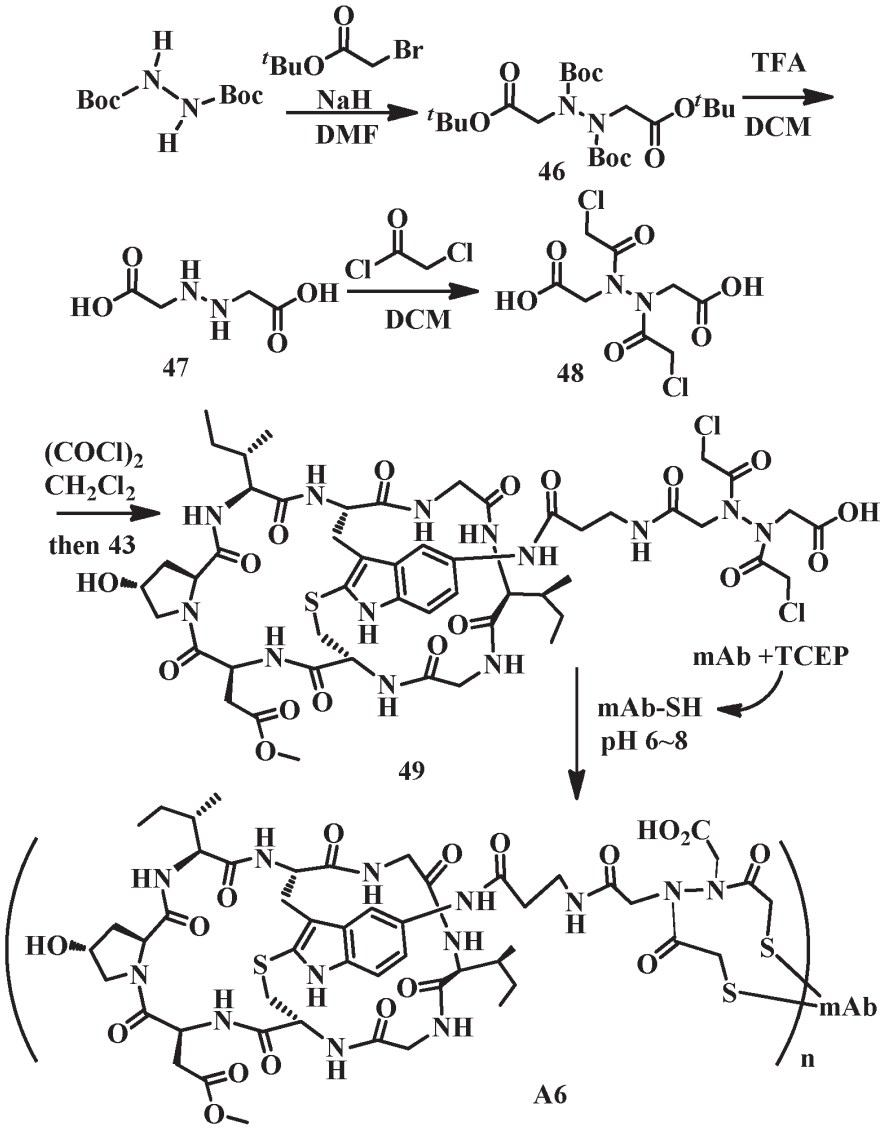
NaH
DMF
TFA
DCM
46
47
48
DCM
(COCl)2
CH2Cl2
then 43
mAb +TCEP
mAb-SH
pH 6~8
49
A6
mAb
n

Fig 14.

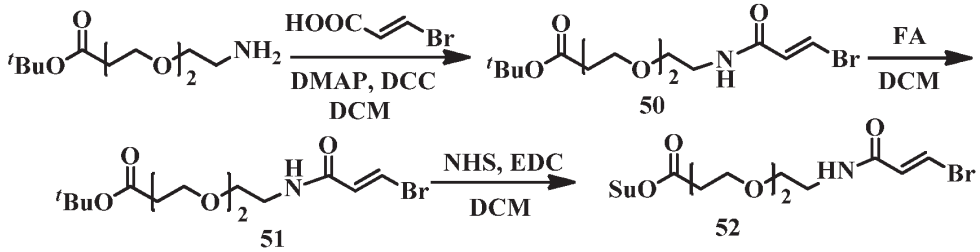
DMAP, DCC
DCM
50
FA
DCM
NHS, EDC
DCM
51
52

Fig 15.

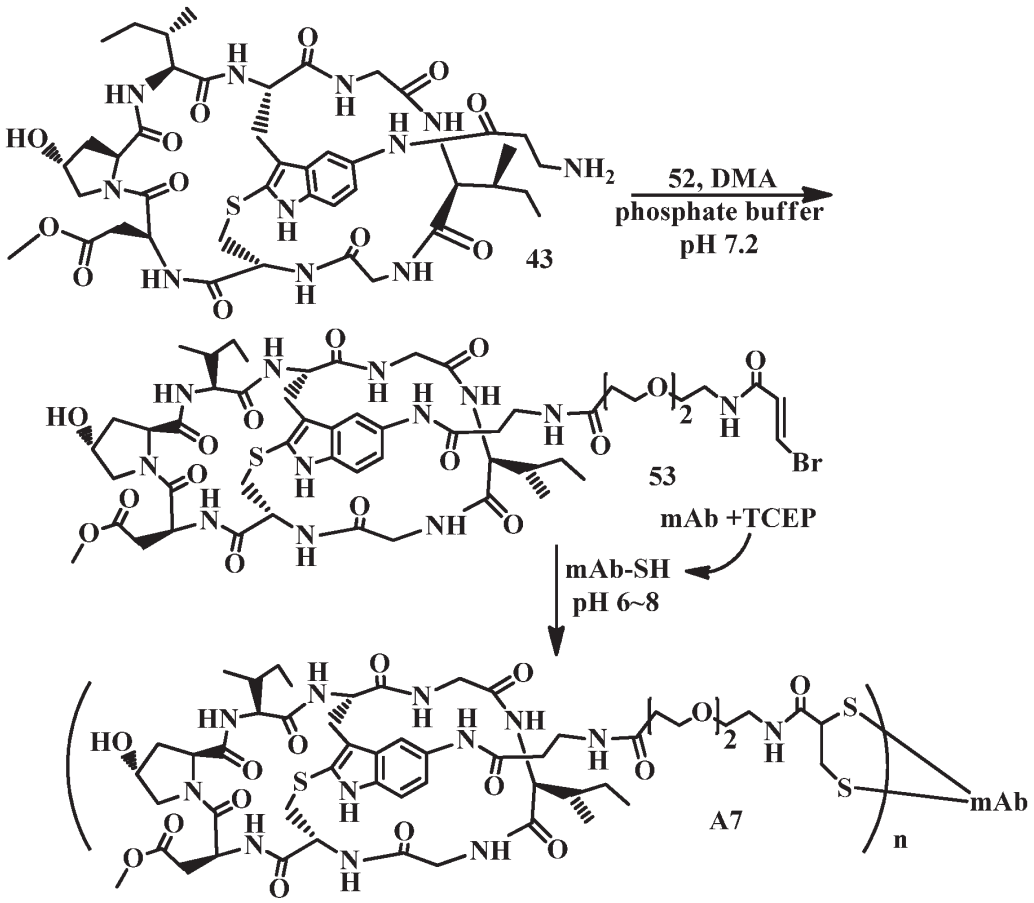
52, DMA
phosphate buffer
pH 7.2
43
53
mAb +TCEP
mAb-SH
pH 6~8
A7
n
mAb

Fig 16.

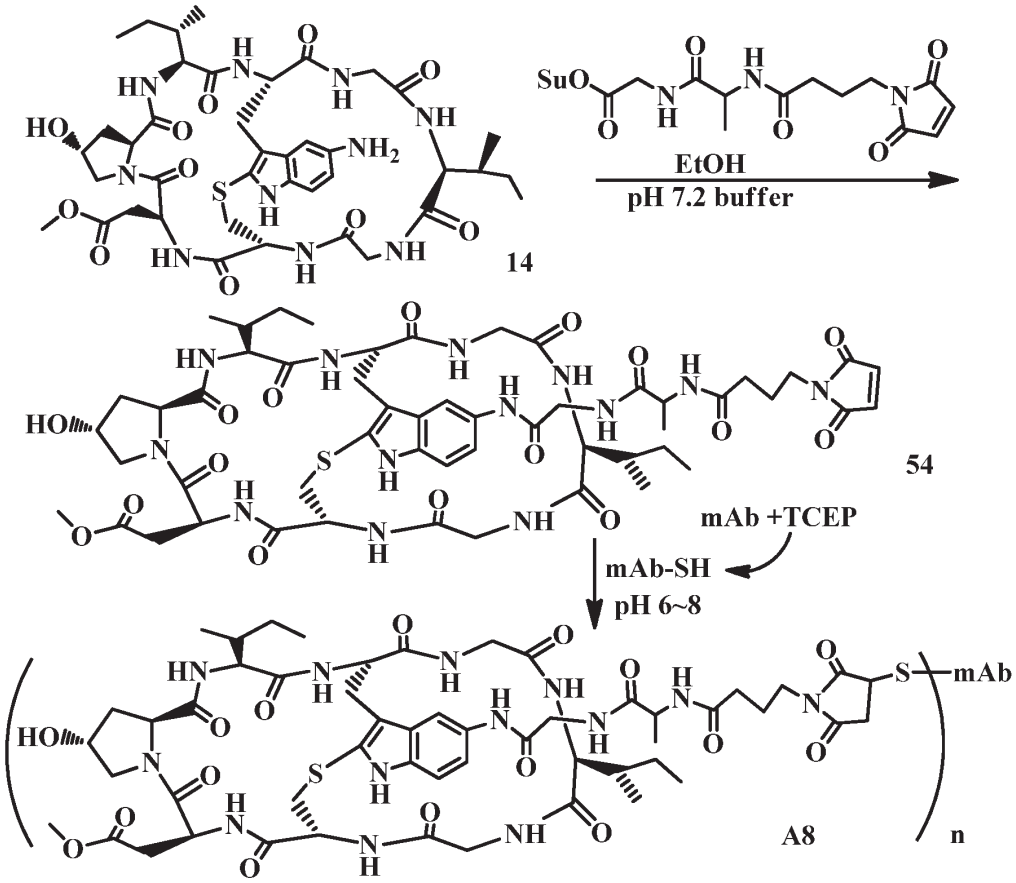
SuO
EtOH
pH 7.2 buffer
14
54
mAb +TCEP
mAb-SH
pH 6~8
mAb
A8
n

Fig 17.

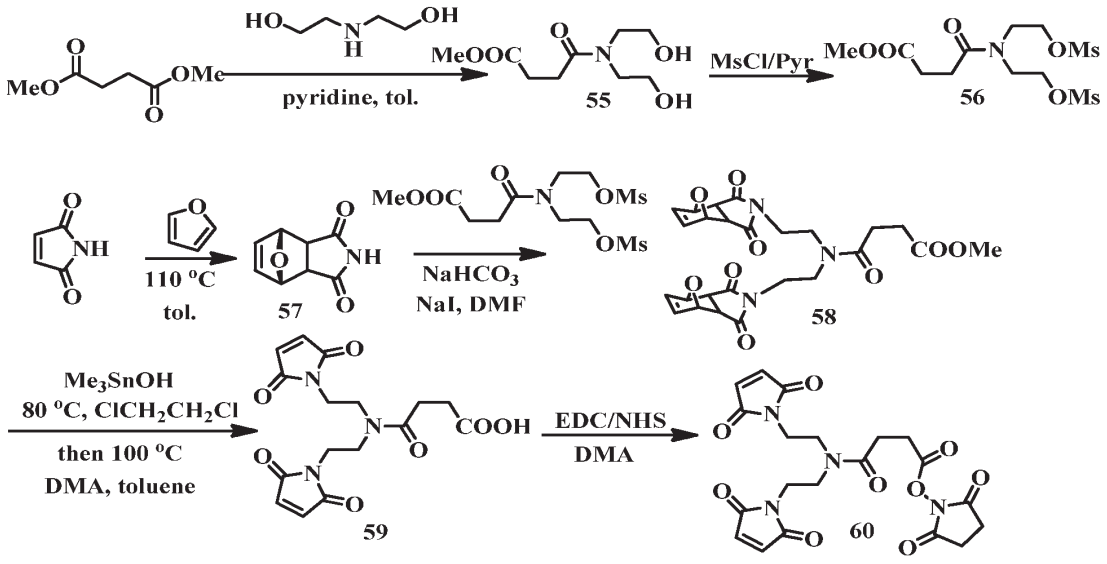
pyridine, tol.
55
MsCl/Pyr
56
110 °C
tol.
57
NaHCO3
NaI, DMF
58
Me3SnOH
80 °C, ClCH2CH2Cl
then 100 °C
DMA, toluene
59
EDC/NHS
DMA
60

Fig 18.

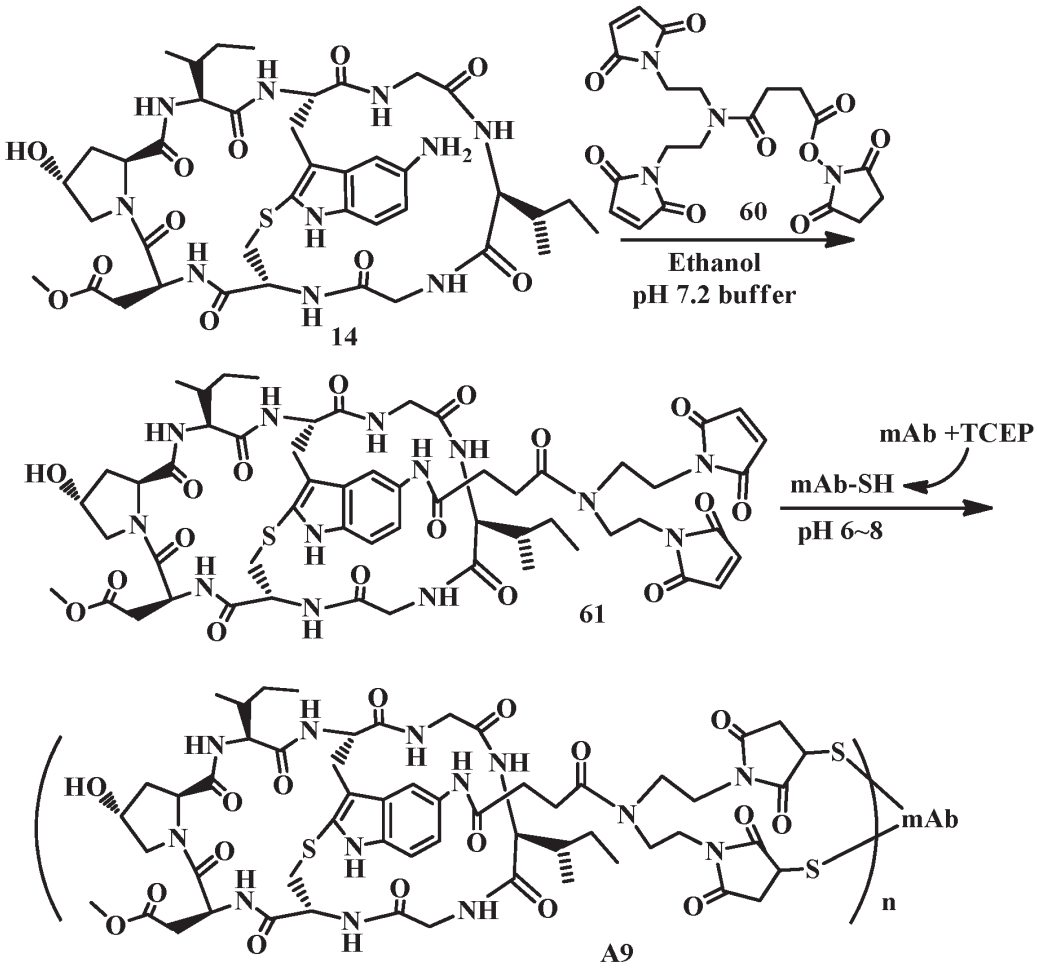

Fig 19.

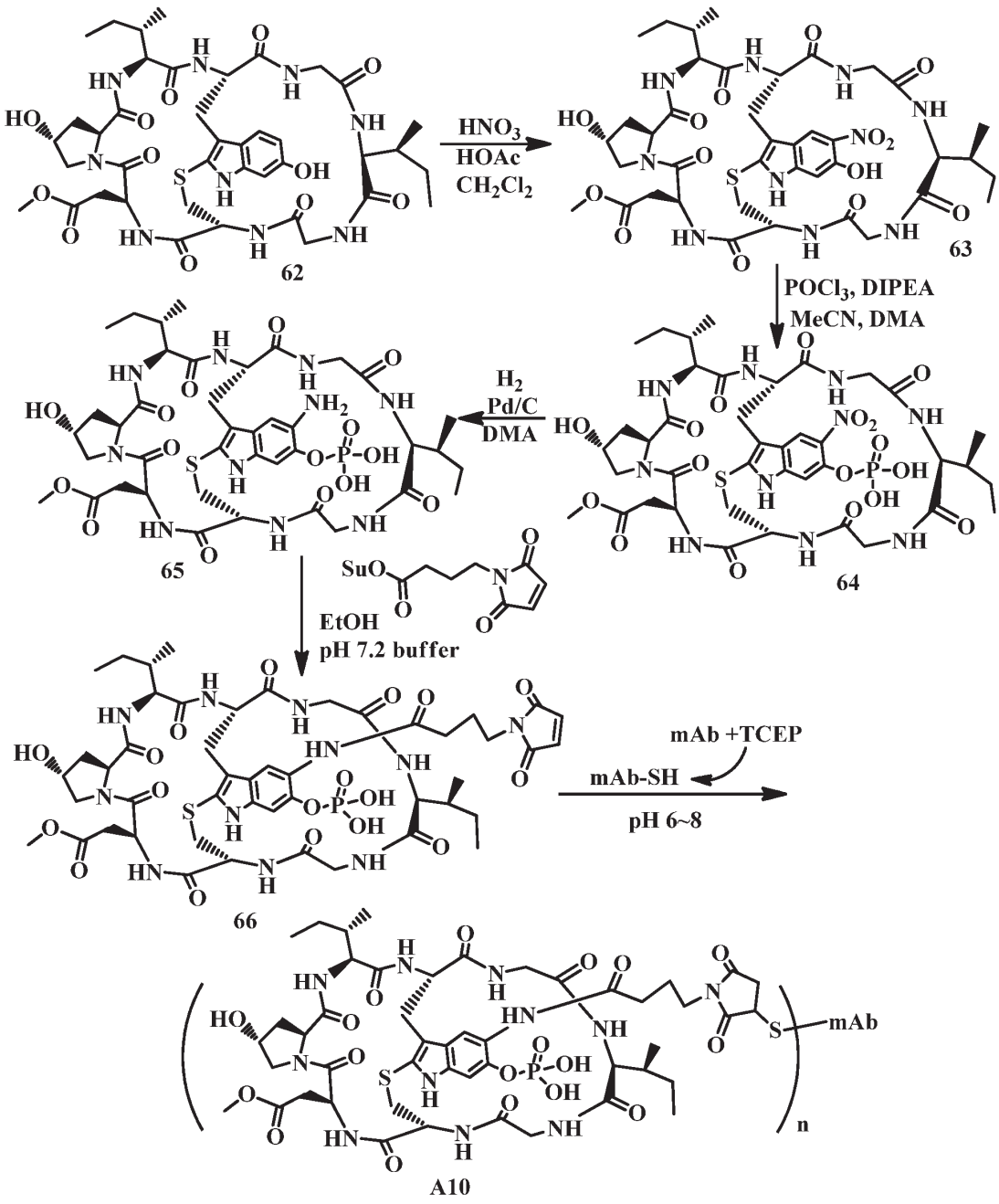
HNO3
HOAc
CH2Cl2
62
63
POCl3, DIPEA
MeCN, DMA
H2
Pd/C
DMA
64
65
SuO
EtOH
pH 7.2 buffer
66
mAb +TCEP
mAb-SH
pH 6~8
A10
mAb
n

Fig 20.

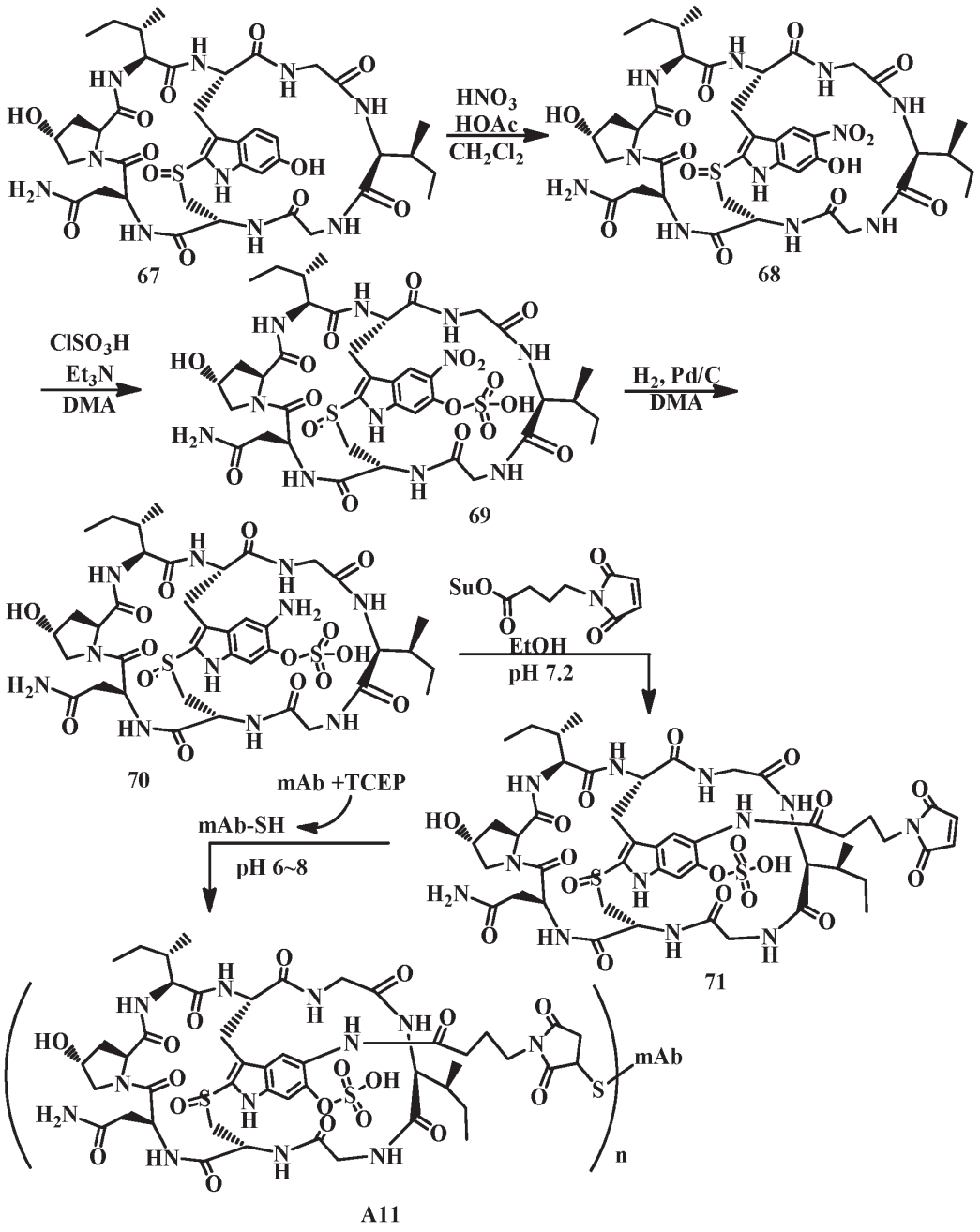
HNO3
HOAc
CH2Cl2
67
68
ClSO3H
Et3N
DMA
H2, Pd/C
DMA
69
70
SuO
EtOH
pH 7.2
mAb +TCEP
mAb-SH
pH 6~8
71
mAb
n
A11

Fig 21.

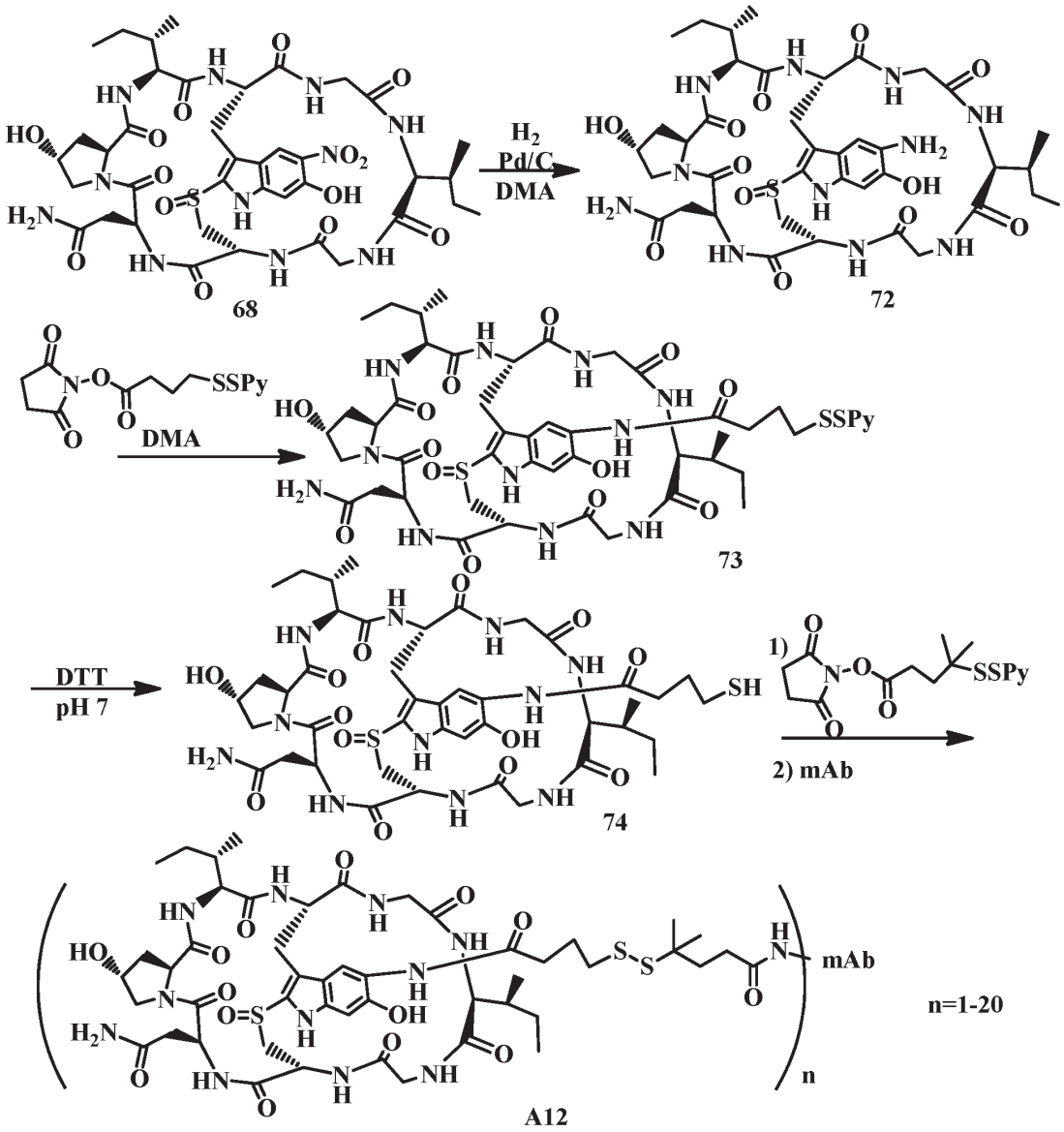

Fig 22.

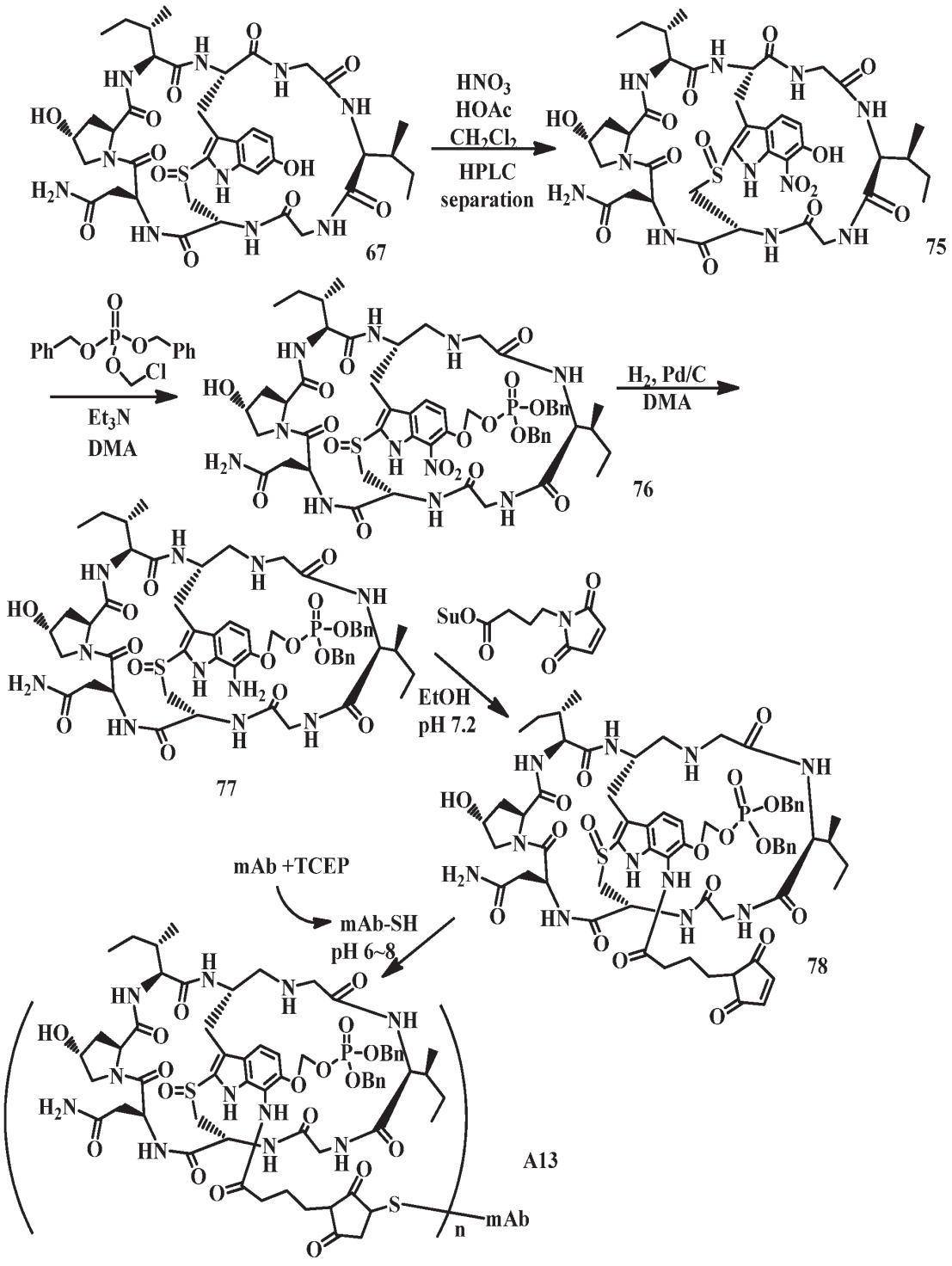
HNO3
HOAc
CH2Cl2
HPLC
separation
67
75
Et3N
DMA
H2, Pd/C
DMA
76
77
SuO
EtOH
pH 7.2
78
mAb +TCEP
mAb-SH
pH 6~8
A13
mAb
n

Fig 23.

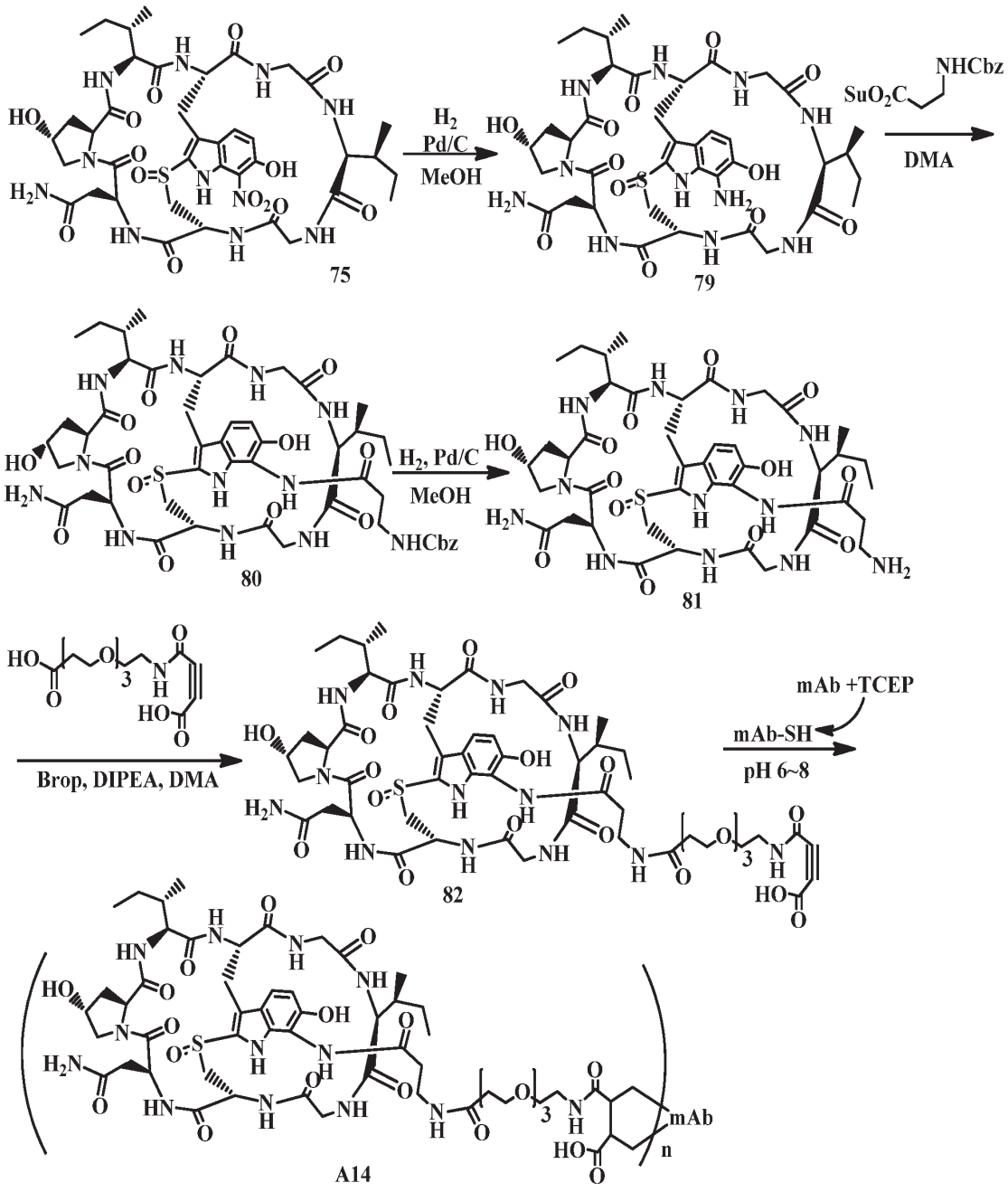
H2
Pd/C
MeOH
SuO2C
NHCbz
DMA
75
79
H2, Pd/C
MeOH
80
81
Brop, DIPEA, DMA
mAb +TCEP
mAb-SH
pH 6~8
82
A14
mAb
n

Fig 24.

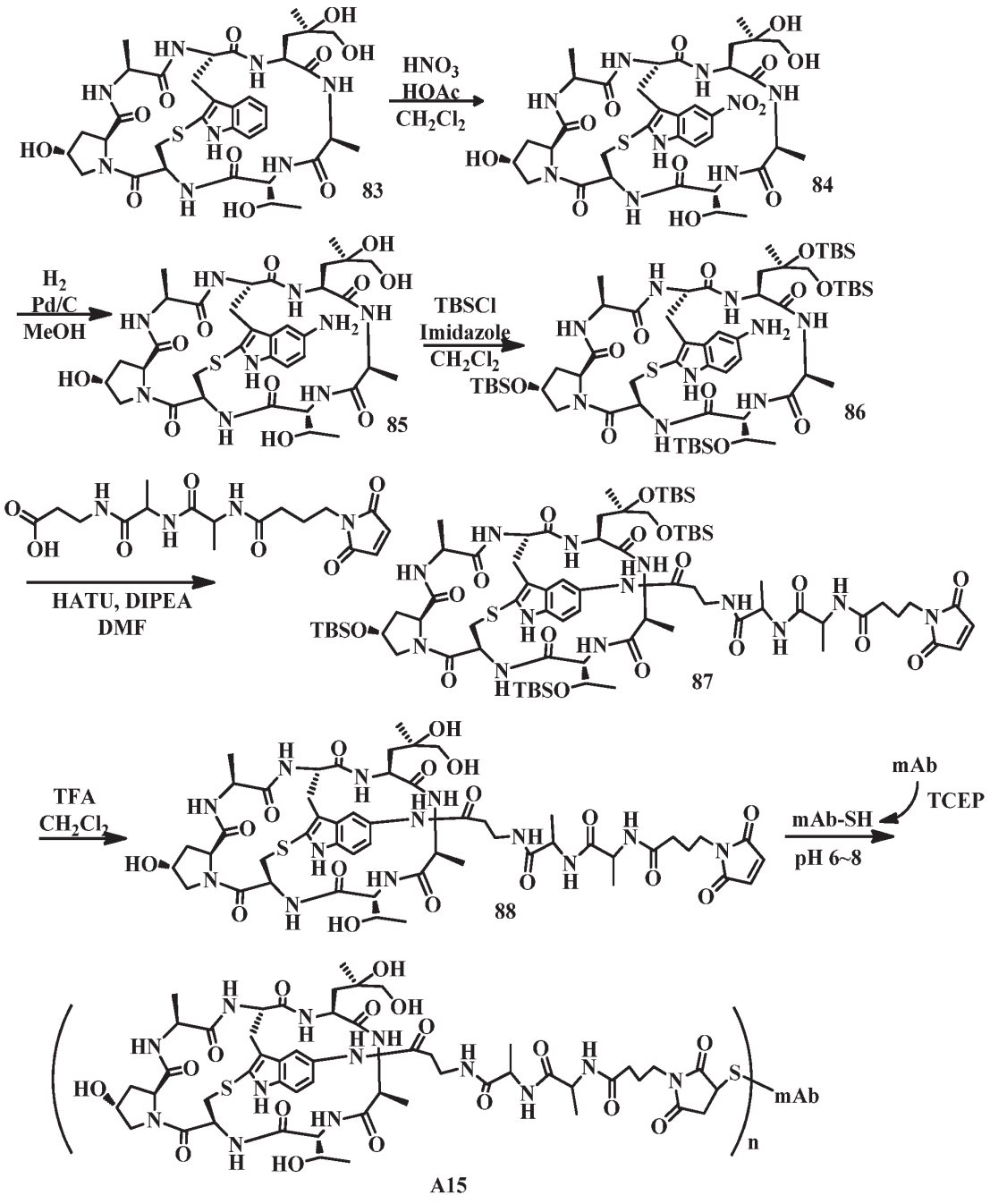
HNO3
HOAc
CH2Cl2
H2
Pd/C
MeOH
TBSCl
Imidazole
CH2Cl2
HATU, DIPEA
DMF
TFA
CH2Cl2
mAb
TCEP
mAb-SH
pH 6~8
83
84
85
86
87
88
A15

Fig 25.

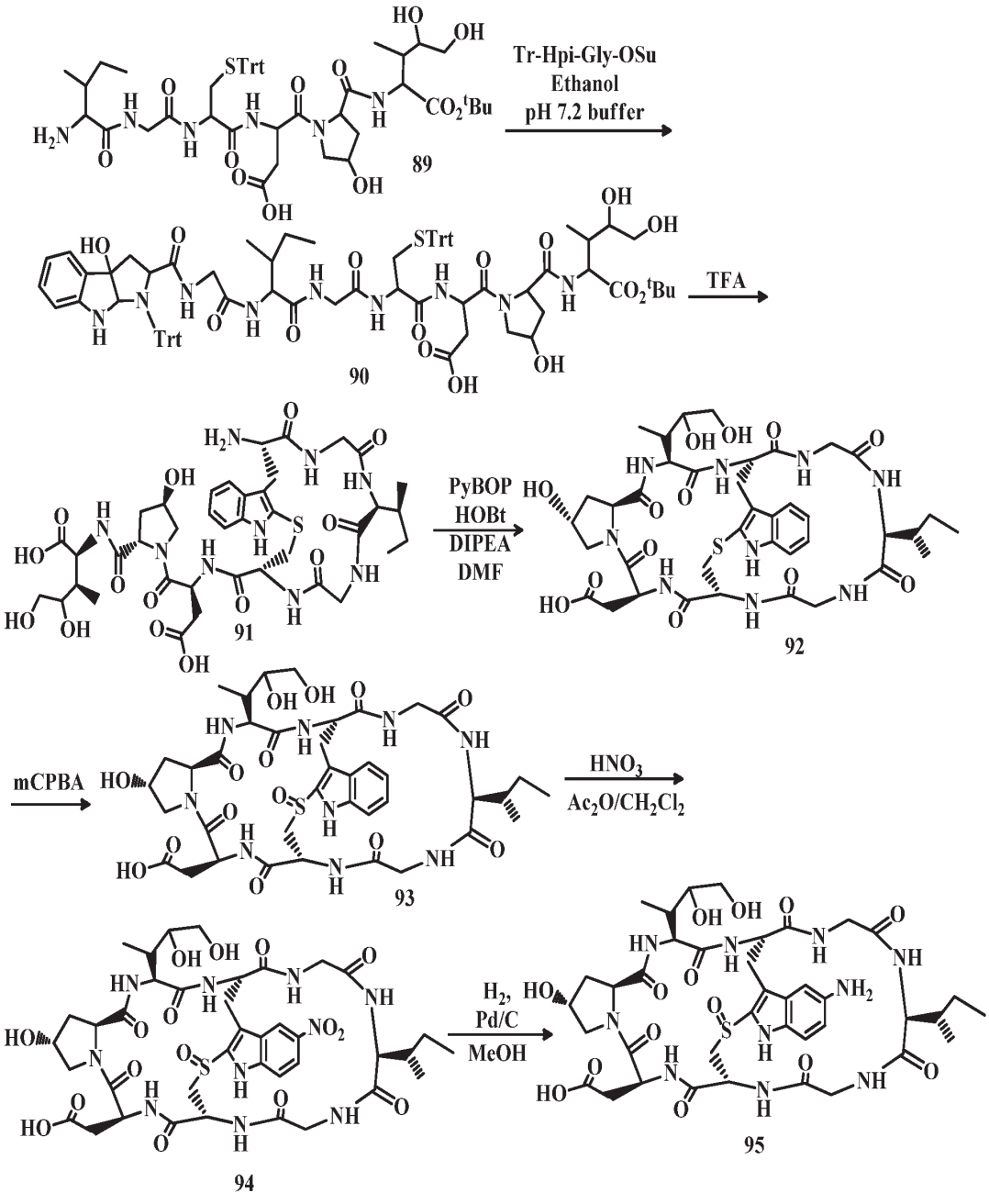
Tr-Hpi-Gly-OSu
Ethanol
pH 7.2 buffer
89
TFA
90
PyBOP
HOBt
DIPEA
DMF
91
92
mCPBA
93
HNO3
Ac2O/CH2Cl2
H2, Pd/C
MeOH
94
95

Fig 26.

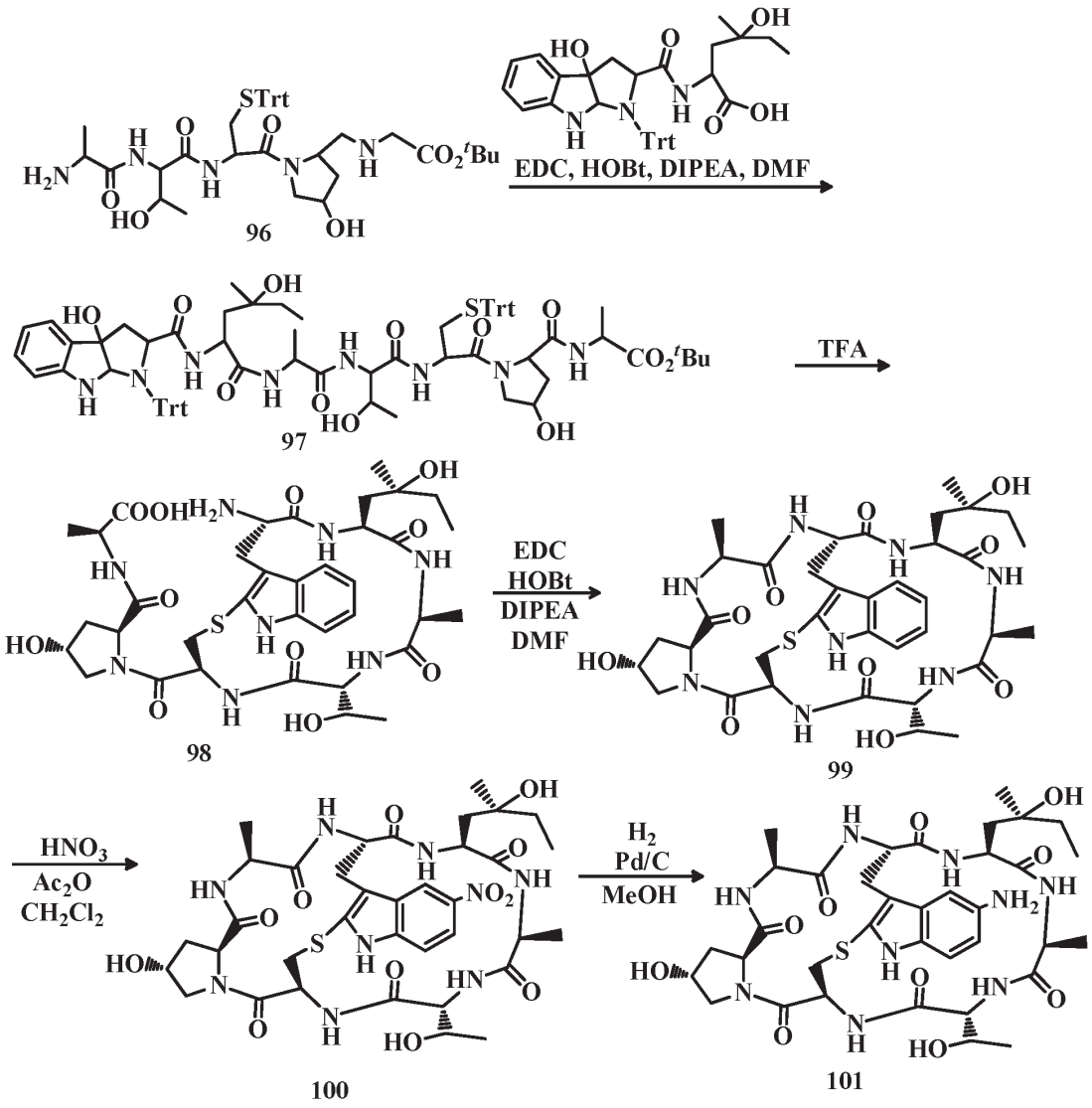
EDC, HOBt, DIPEA, DMF
TFA
EDC
HOBt
DIPEA
DMF
HNO3
Ac2O
CH2Cl2
H2
Pd/C
MeOH
96
97
98
99
100
101

Fig 27.

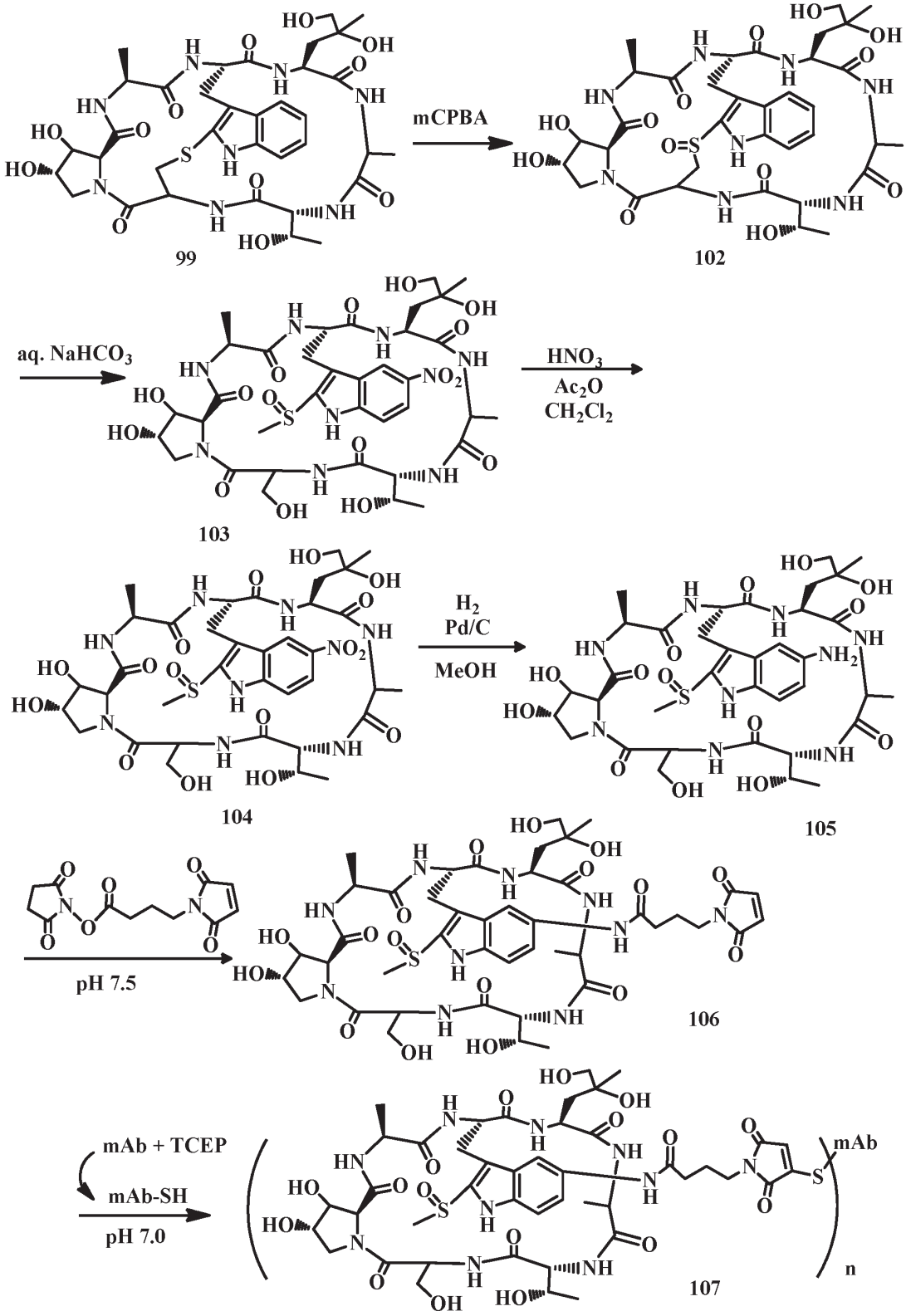
mCPBA
99
102
aq. NaHCO3
HNO3
Ac2O
CH2Cl2
103
H2
Pd/C
MeOH
104
105
pH 7.5
106
mAb + TCEP
mAb-SH
pH 7.0
mAb
n
107

Fig 28.

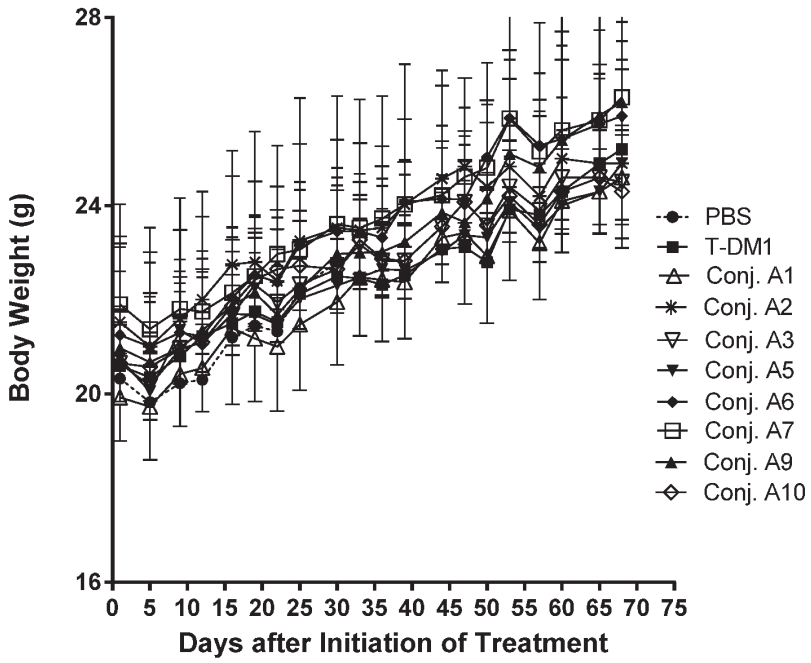

Figure 29

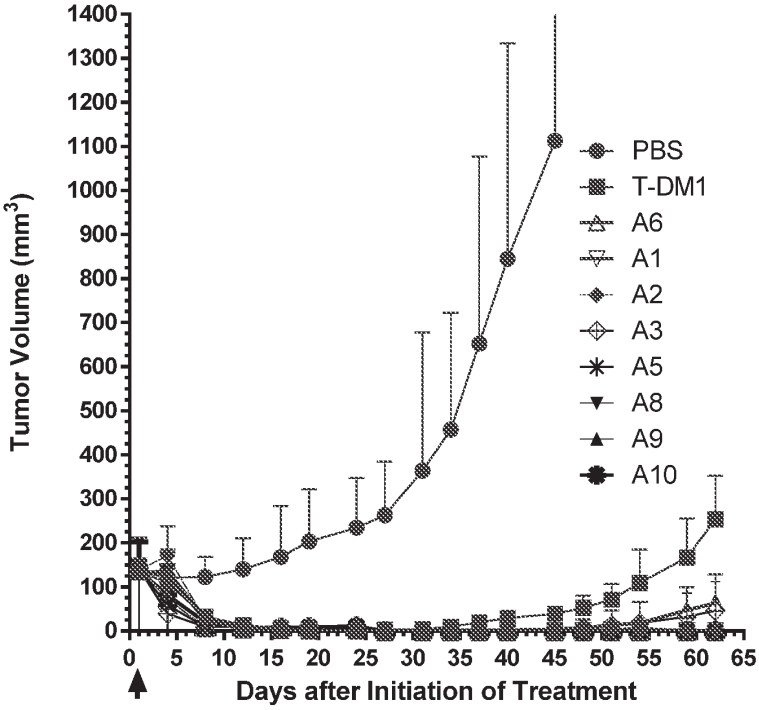

Figure 30