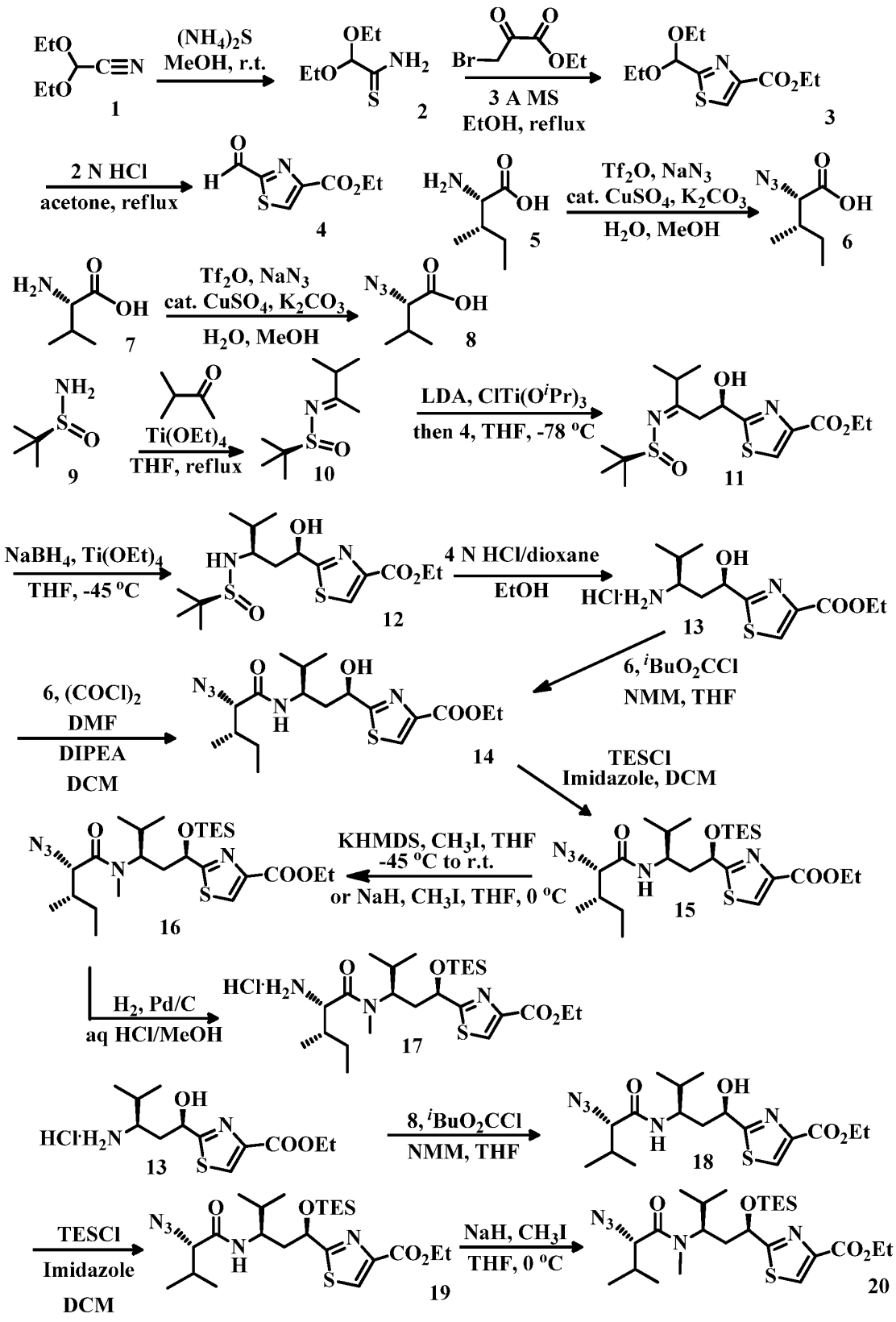

(NH4)2S
MeOH, r.t.
3 A MS
EtOH, reflux
2 N HCl
acetone, reflux
Tf2O, NaN3
cat. CuSO4, K2CO3
H2O, MeOH
Ti(OEt)4
THF, reflux
LDA, ClTi(OiPr)3
then 4, THF, -78 °C
NaBH4, Ti(OEt)4
THF, -45 °C
4 N HCl/dioxane
EtOH
6, iBuO2CCl
NMM, THF
6, (COCl)2
DMF
DIPEA
DCM
TESCl
Imidazole, DCM
KHMDS, CH3I, THF
-45 °C to r.t.
or NaH, CH3I, THF, 0 °C
H2, Pd/C
aq HCl/MeOH
8, iBuO2CCl
NMM, THF
TESCl
Imidazole
DCM
NaH, CH3I
THF, 0 °C

Fig. 1.

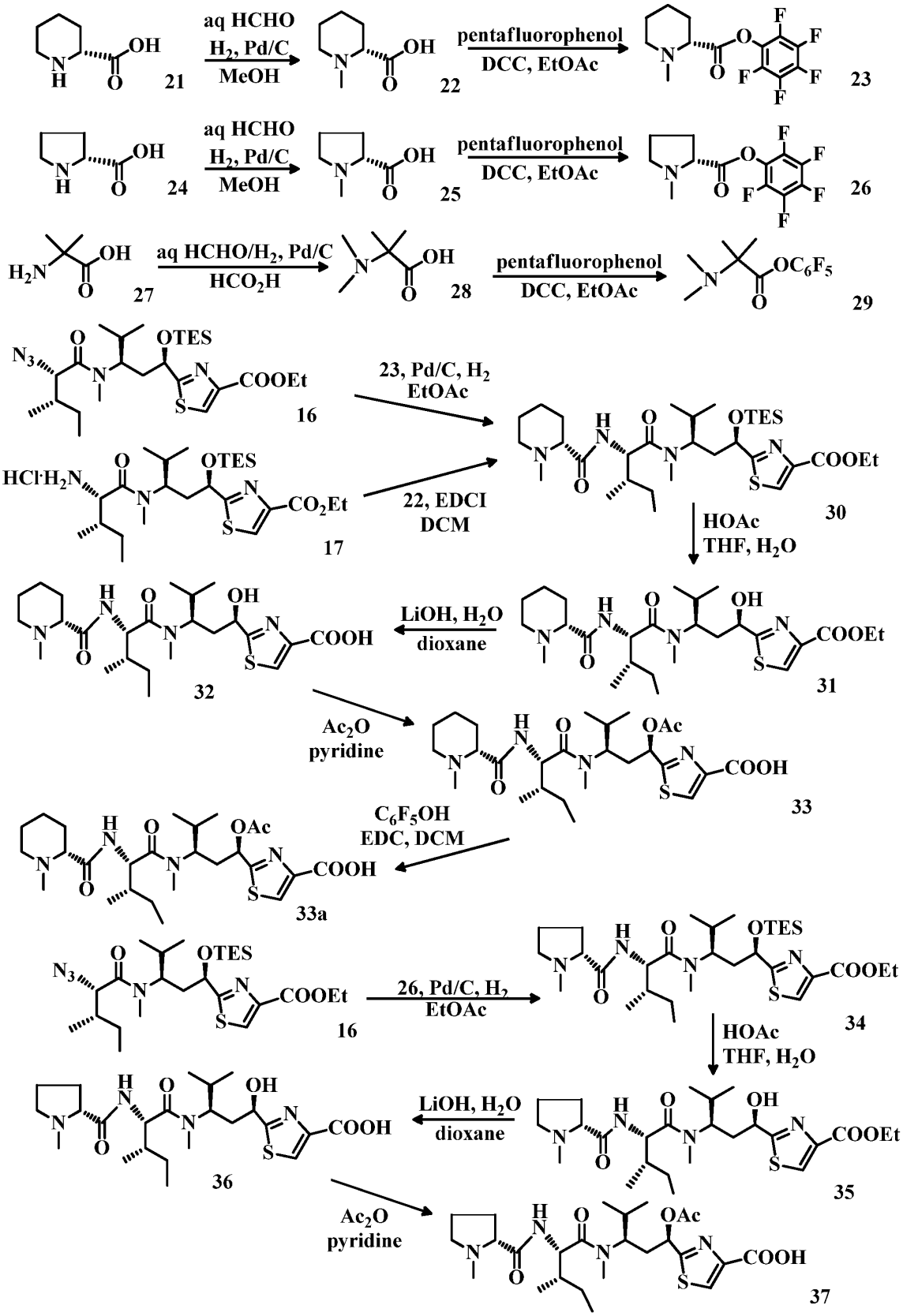

aq HCHO
H2, Pd/C
MeOH
pentafluorophenol
DCC, EtOAc
21
22
23
24
25
26
aq HCHO/H2, Pd/C
HCO2H
27
28
29
OTES
COOEt
16
23, Pd/C, H2
EtOAc
HCl·H2N
CO2Et
17
22, EDCI
DCM
30
HOAc
THF, H2O
LiOH, H2O
dioxane
COOH
31
32
Ac2O
pyridine
OAc
33
C6F5OH
EDC, DCM
33a
26, Pd/C, H2
EtOAc
34
35
36
37

Fig. 2

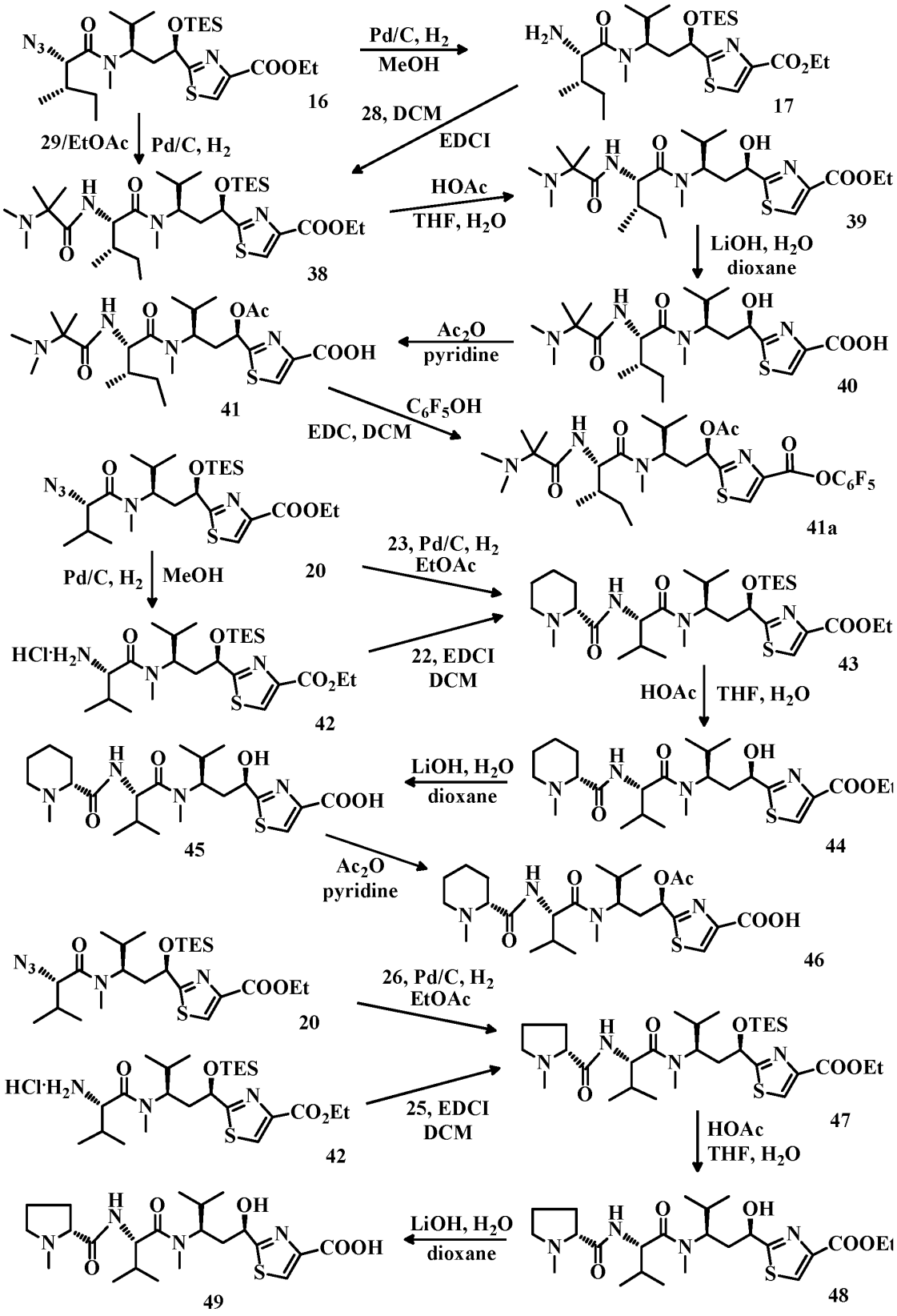

Pd/C, H2
MeOH
16
17
28, DCM
EDCI
29/EtOAc
Pd/C, H2
HOAc
THF, H2O
38
39
LiOH, H2O
dioxane
Ac2O
pyridine
41
40
C6F5OH
EDC, DCM
41a
20
23, Pd/C, H2
EtOAc
Pd/C, H2
MeOH
22, EDCI
DCM
42
43
HOAc
THF, H2O
LiOH, H2O
dioxane
45
44
Ac2O
pyridine
46
20
26, Pd/C, H2
EtOAc
25, EDCI
DCM
42
47
HOAc
THF, H2O
LiOH, H2O
dioxane
49
48

Fig. 3.

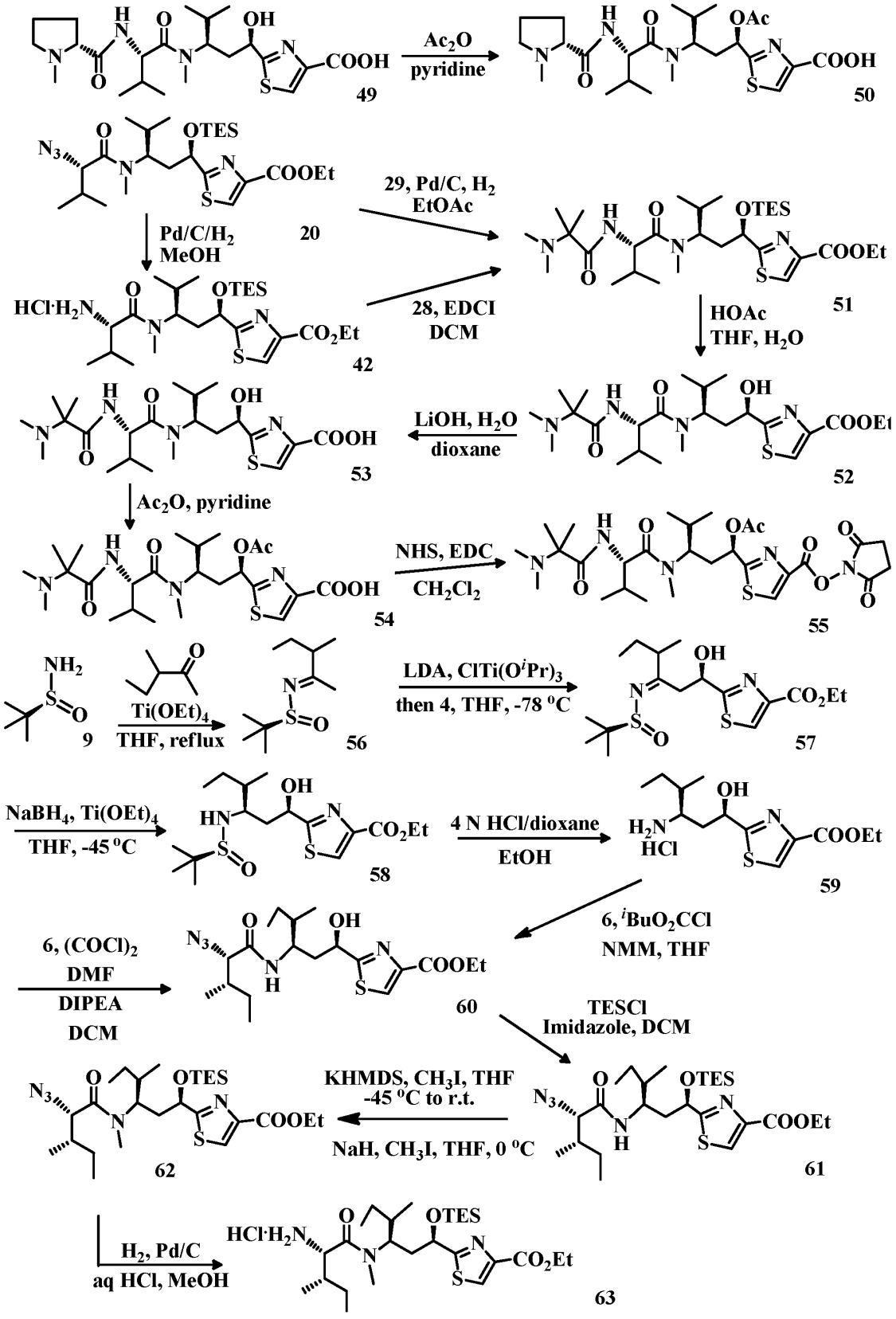

Ac2O
pyridine
49
50
OTES
N3
COOEt
20
Pd/C/H2
MeOH
29, Pd/C, H2
EtOAc
HCl·H2N
CO2Et
42
28, EDCI
DCM
51
HOAc
THF, H2O
LiOH, H2O
dioxane
53
52
Ac2O, pyridine
NHS, EDC
CH2Cl2
54
55
NH2
9
Ti(OEt)4
THF, reflux
56
LDA, ClTi(OiPr)3
then 4, THF, -78 °C
57
NaBH4, Ti(OEt)4
THF, -45 °C
58
4 N HCl/dioxane
EtOH
H2N
HCl
59
6, (COCl)2
DMF
DIPEA
DCM
60
6, iBuO2CCl
NMM, THF
TESCl
Imidazole, DCM
KHMDS, CH3I, THF
-45 °C to r.t.
NaH, CH3I, THF, 0 °C
62
61
H2, Pd/C
aq HCl, MeOH
63

Fig.4.

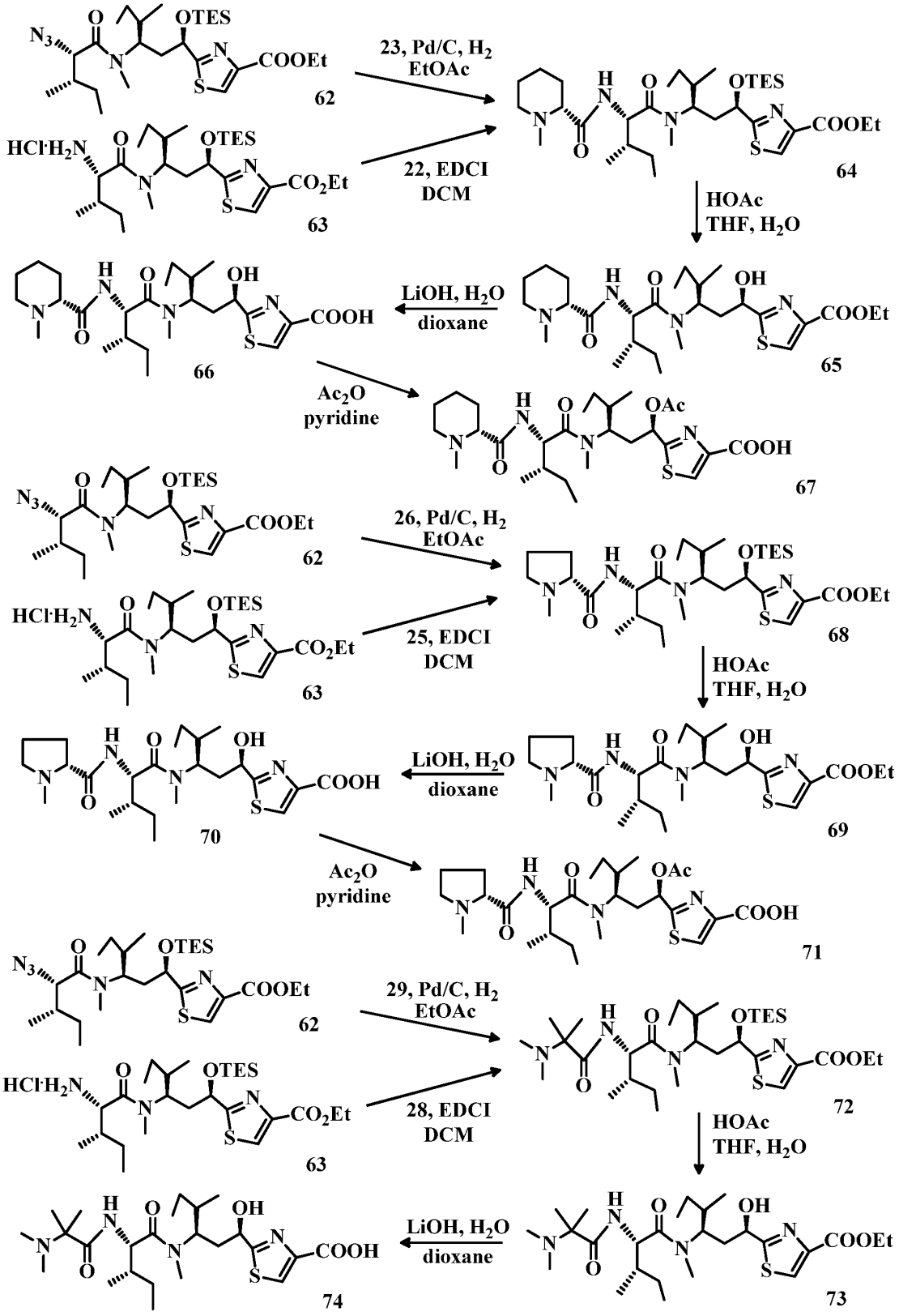

23, Pd/C, H2
EtOAc
22, EDCI
DCM
HOAc
THF, H2O
LiOH, H2O
dioxane
Ac2O
pyridine
26, Pd/C, H2
EtOAc
25, EDCI
DCM
HOAc
THF, H2O
LiOH, H2O
dioxane
Ac2O
pyridine
29, Pd/C, H2
EtOAc
28, EDCI
DCM
HOAc
THF, H2O
LiOH, H2O
dioxane

Fig. 5.

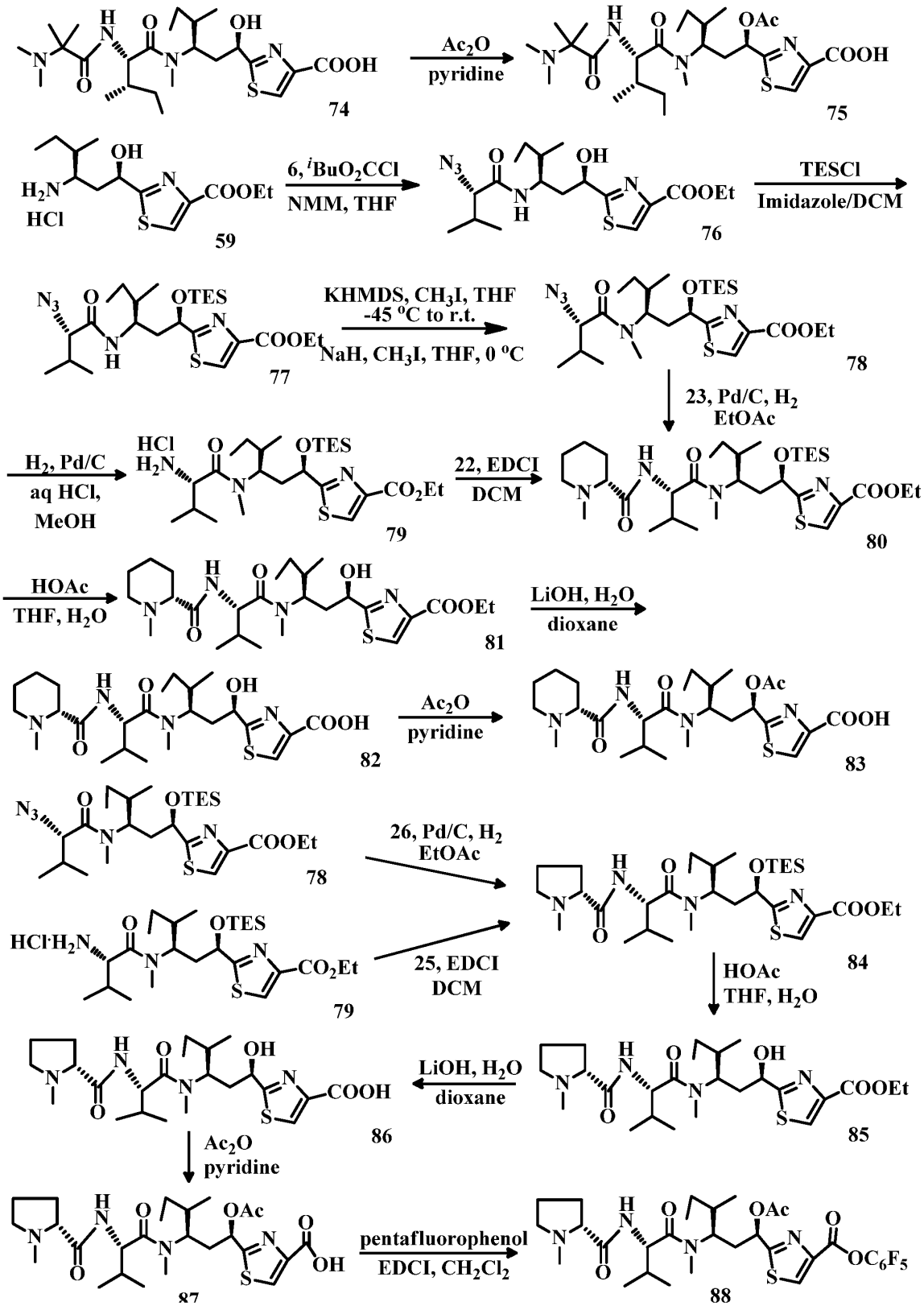

Ac2O
pyridine
74
75
6, iBuO2CCl
NMM, THF
59
76
TESCl
Imidazole/DCM
KHMDS, CH3I, THF
-45 °C to r.t.
NaH, CH3I, THF, 0 °C
77
78
23, Pd/C, H2
EtOAc
H2, Pd/C
aq HCl,
MeOH
22, EDCI
DCM
79
80
HOAc
THF, H2O
81
LiOH, H2O
dioxane
82
83
26, Pd/C, H2
EtOAc
25, EDCI
DCM
84
85
86
87
88
pentafluorophenol
EDCI, CH2Cl2

Fig. 6.

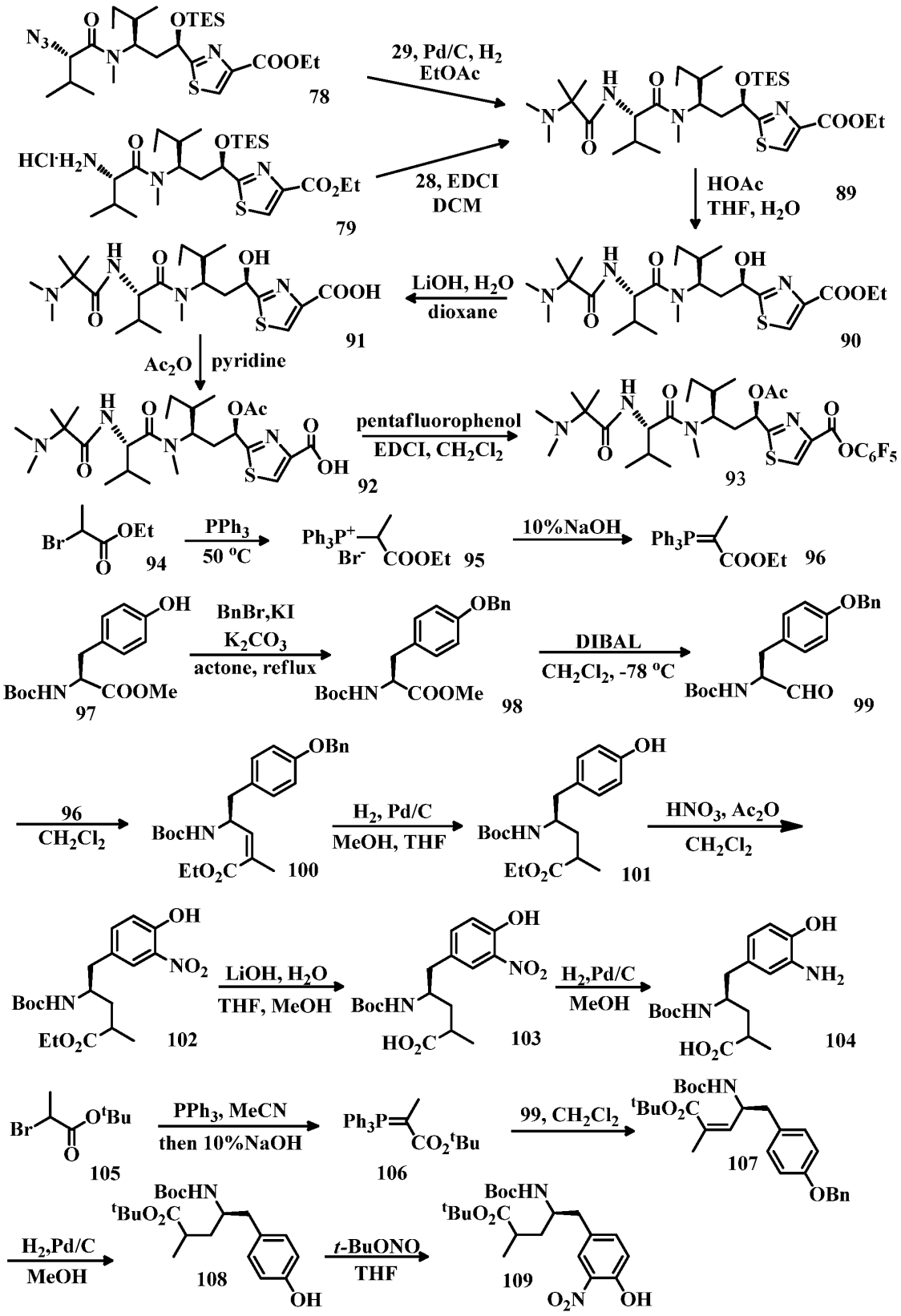

29, Pd/C, H2
EtOAc
28, EDCI
DCM
HOAc
THF, H2O
LiOH, H2O
dioxane
Ac2O
pyridine
pentafluorophenol
EDCI, CH2Cl2
PPh3
50 °C
10%NaOH
BnBr,KI
K2CO3
actone, reflux
DIBAL
CH2Cl2, -78 °C
96
CH2Cl2
H2, Pd/C
MeOH, THF
HNO3, Ac2O
CH2Cl2
LiOH, H2O
THF, MeOH
H2,Pd/C
MeOH
PPh3, MeCN
then 10%NaOH
99, CH2Cl2
H2,Pd/C
MeOH
t-BuONO
THF

Fig. 7.

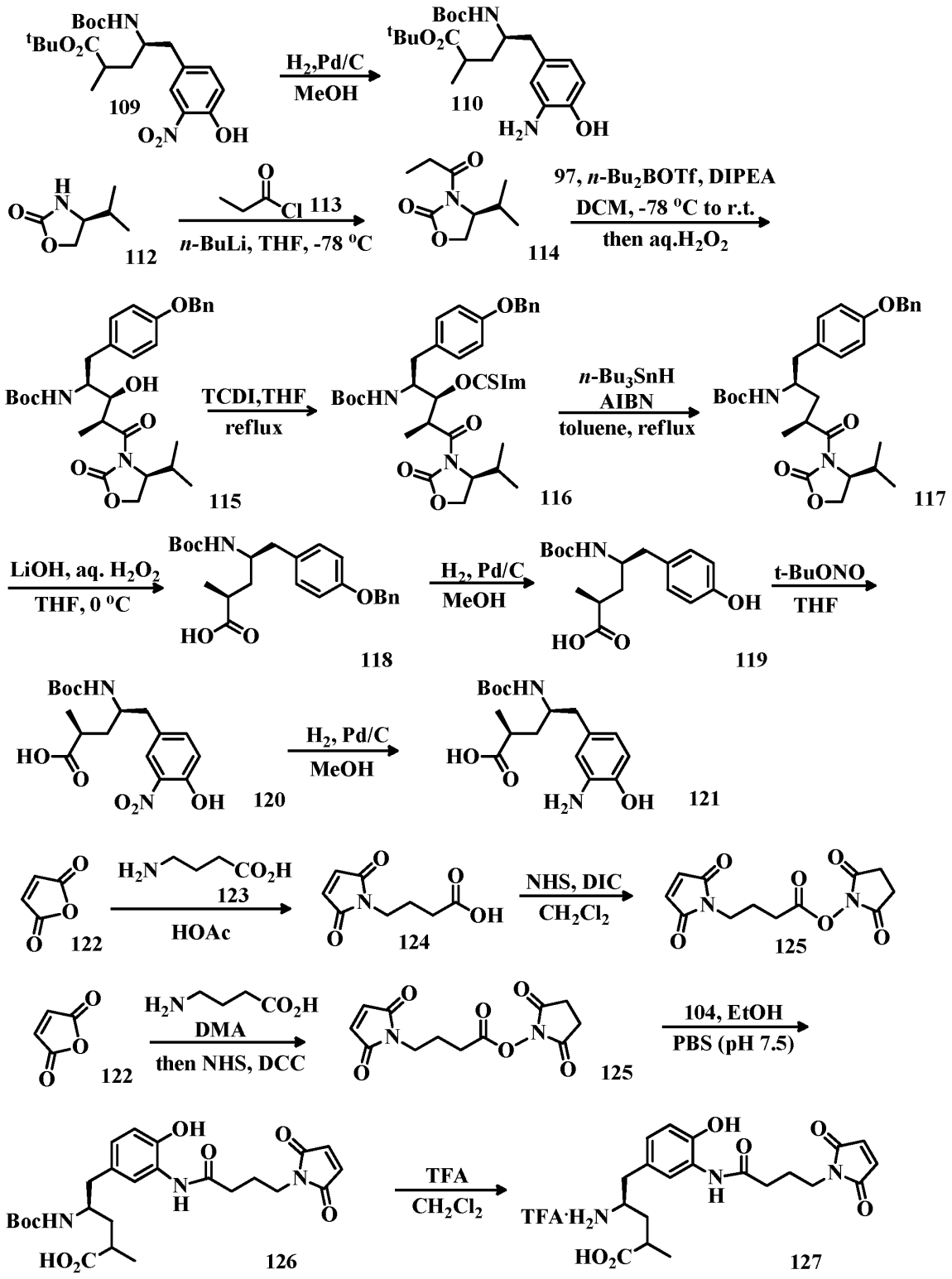

BocHN
tBuO2C
109
H2,Pd/C
MeOH
110
H2N
OH
112
113
n-BuLi, THF, -78 °C
114
97, n-Bu2BOTf, DIPEA
DCM, -78 °C to r.t.
then aq.H2O2
OBn
BocHN
OH
TCDI,THF
reflux
OCSIm
n-Bu3SnH
AIBN
toluene, reflux
115
116
117
LiOH, aq. H2O2
THF, 0 °C
118
H2, Pd/C
MeOH
119
t-BuONO
THF
HO
O2N
120
121
122
H2N
CO2H
123
HOAc
124
NHS, DIC
CH2Cl2
125
DMA
then NHS, DCC
104, EtOH
PBS (pH 7.5)
TFA
CH2Cl2
HO2C
126
TFA·H2N
127

Fig. 8.

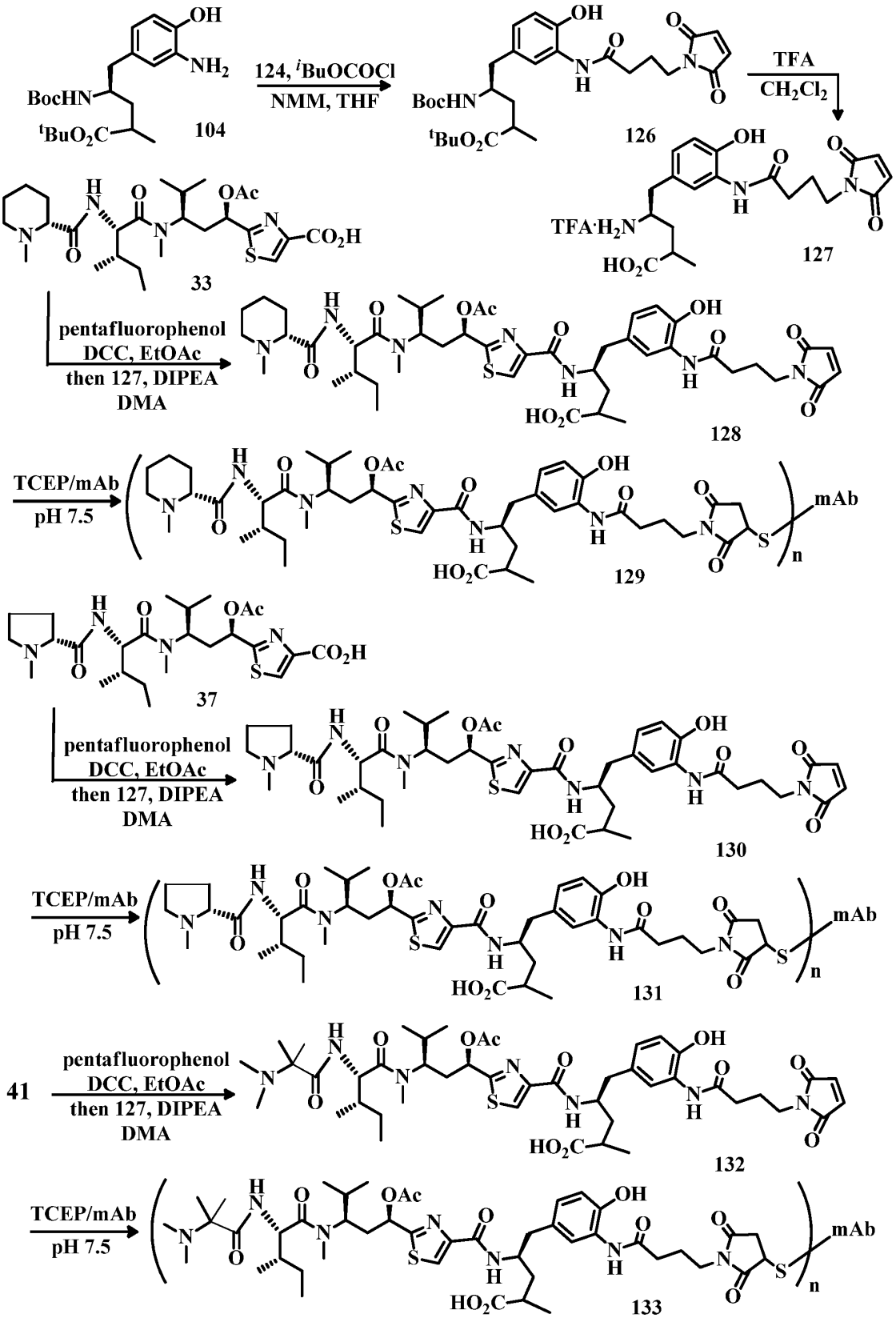

OH
NH2
BocHN
tBuO2C
104
124, iBuOCOCl
NMM, THF
126
TFA
CH2Cl2
TFA·H2N
HO2C
127
OAc
CO2H
33
pentafluorophenol
DCC, EtOAc
then 127, DIPEA
DMA
128
TCEP/mAb
pH 7.5
mAb
n
129
37
130
131
41
132
133

Fig. 9.

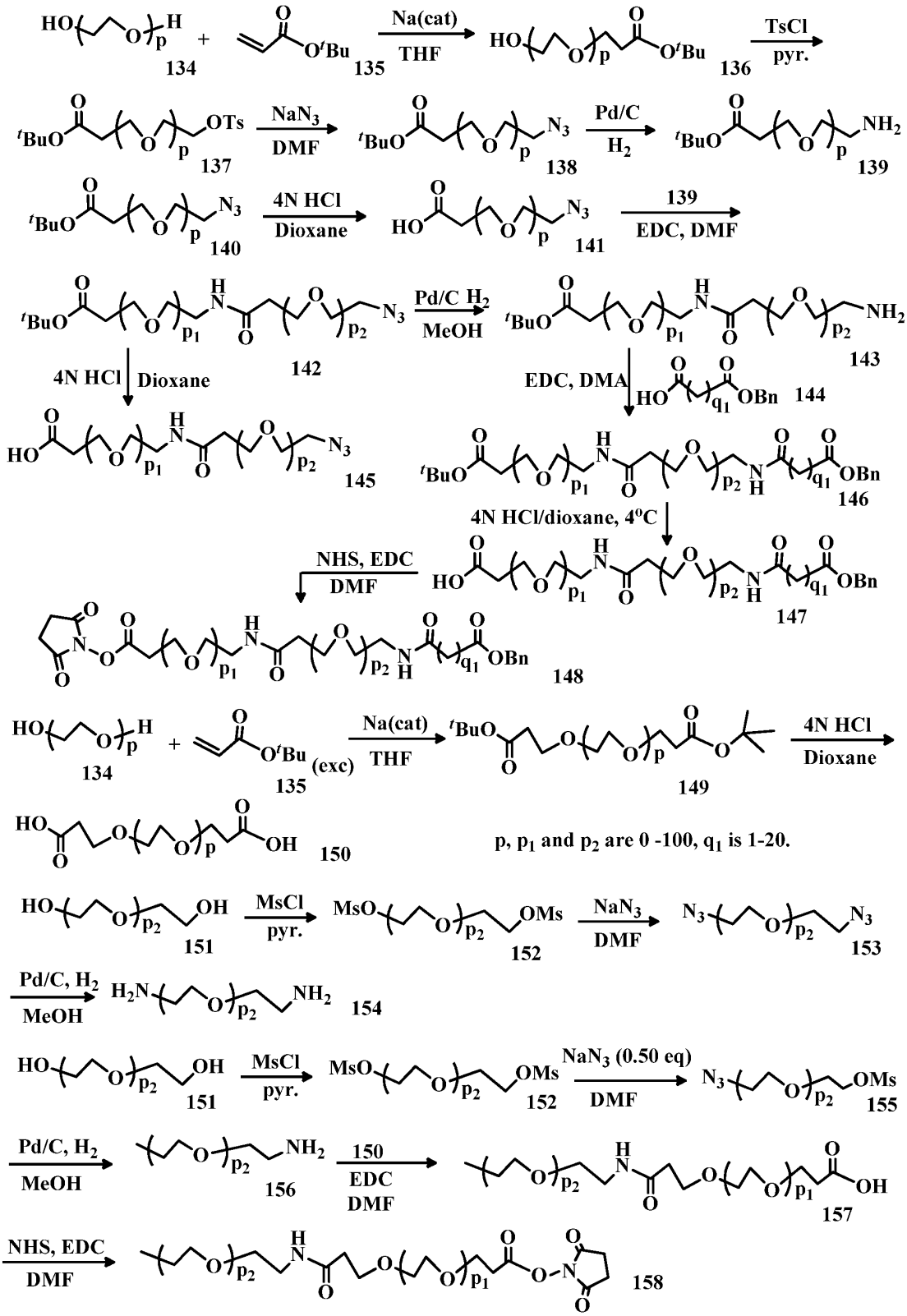

Na(cat)
THF
TsCl
pyr.
NaN3
DMF
Pd/C
H2
4N HCl
Dioxane
139
EDC, DMF
Pd/C H2
MeOH
EDC, DMA
4N HCl/dioxane, 4°C
NHS, EDC
DMF
(exc)
MsCl
pyr.
NaN3 (0.50 eq)
Pd/C, H2
MeOH
150
EDC
DMF
p, p1 and p2 are 0 -100, q1 is 1-20.

Fig. 10

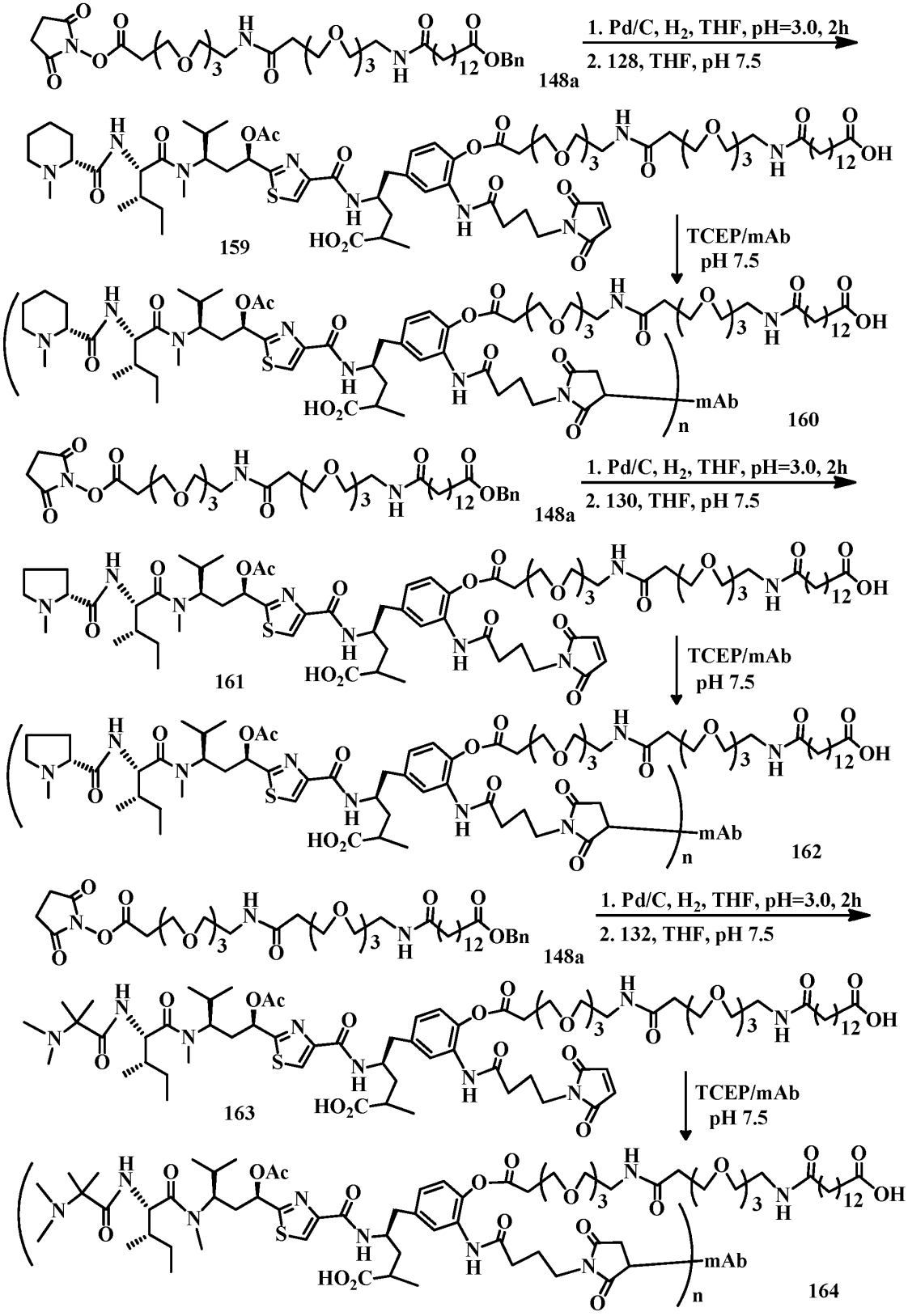

1. Pd/C, H2, THF, pH=3.0, 2h
2. 128, THF, pH 7.5
148a
159
TCEP/mAb
pH 7.5
160
mAb
n
1. Pd/C, H2, THF, pH=3.0, 2h
2. 130, THF, pH 7.5
148a
161
TCEP/mAb
pH 7.5
162
mAb
n
1. Pd/C, H2, THF, pH=3.0, 2h
2. 132, THF, pH 7.5
148a
163
TCEP/mAb
pH 7.5
164
mAb
n

Fig. 11

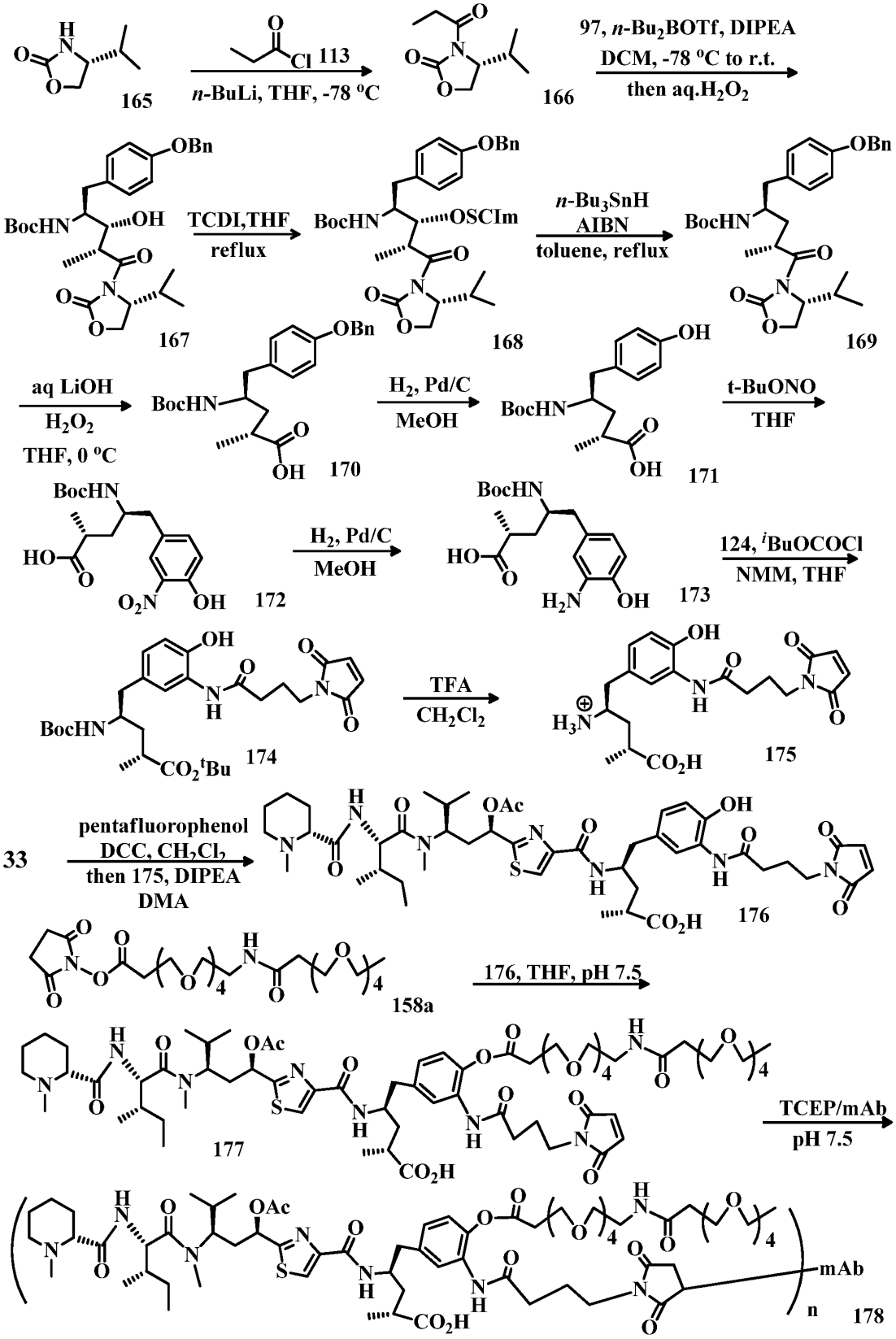

165
113
n-BuLi, THF, -78 °C
166
97, n-Bu2BOTf, DIPEA
DCM, -78 °C to r.t.
then aq.H2O2
167
TCDI,THF
reflux
168
n-Bu3SnH
AIBN
toluene, reflux
169
aq LiOH
H2O2
THF, 0 °C
170
H2, Pd/C
MeOH
171
t-BuONO
THF
172
H2, Pd/C
MeOH
173
124, iBuOCOCl
NMM, THF
174
TFA
CH2Cl2
175
33
pentafluorophenol
DCC, CH2Cl2
then 175, DIPEA
DMA
176
158a
176, THF, pH 7.5
177
TCEP/mAb
pH 7.5
178
mAb
n

Fig. 12.

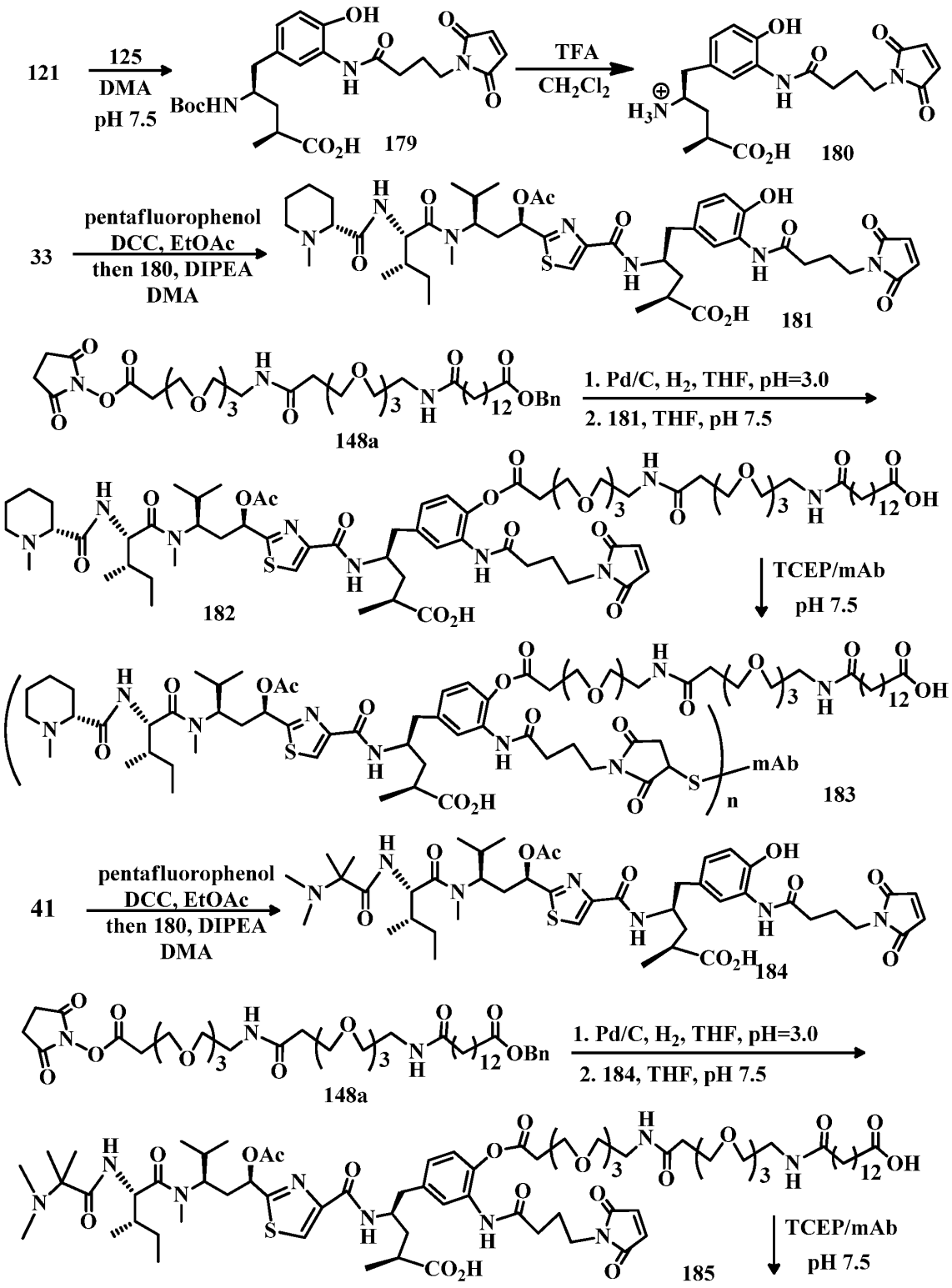

121
125
DMA
pH 7.5
BocHN
CO2H
179
TFA
CH2Cl2
H3N
180
33
pentafluorophenol
DCC, EtOAc
then 180, DIPEA
DMA
181
148a
1. Pd/C, H2, THF, pH=3.0
2. 181, THF, pH 7.5
182
TCEP/mAb
pH 7.5
mAb
n
183
41
184
185

Fig. 13.

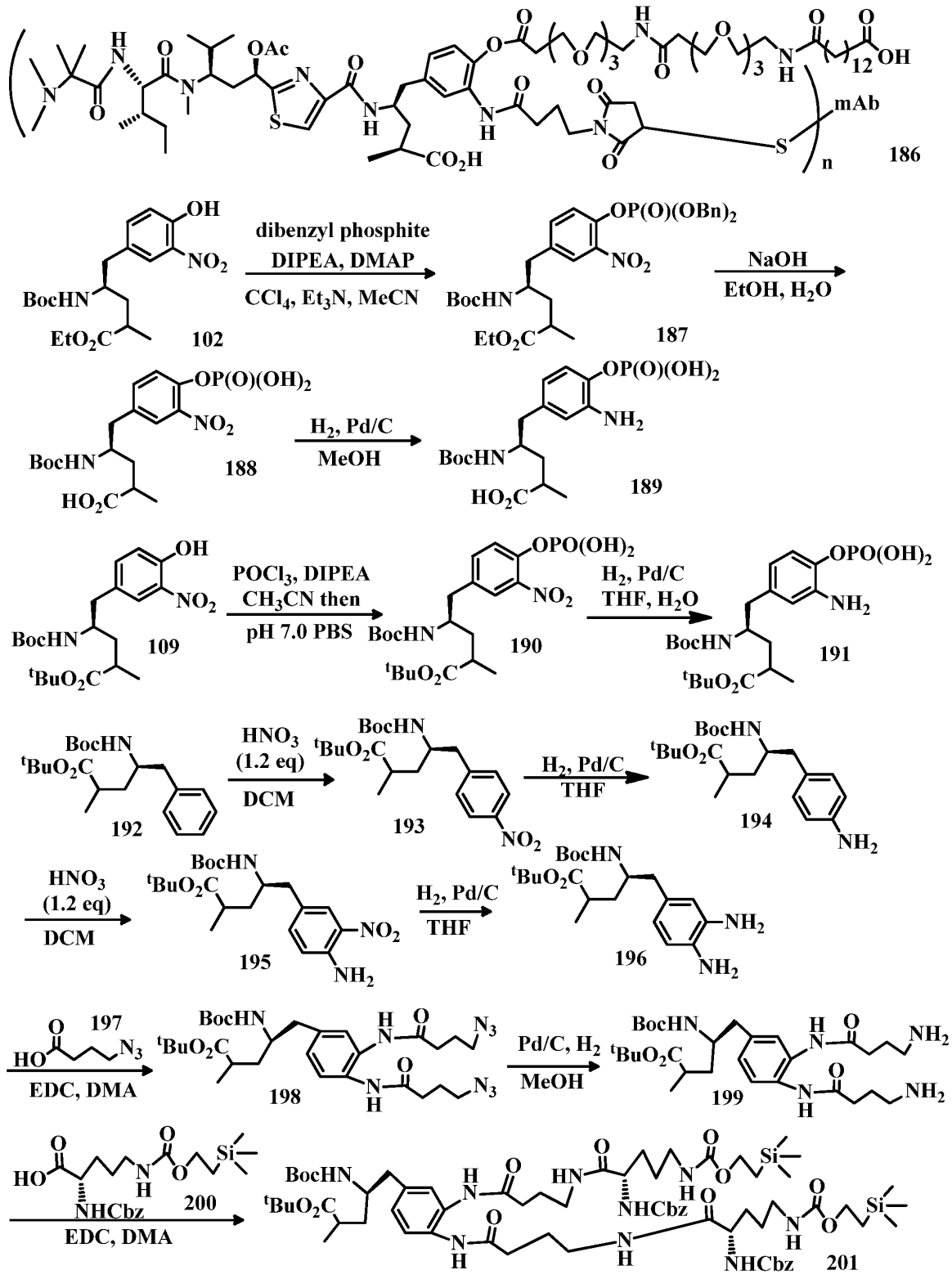

dibenzyl phosphite
DIPEA, DMAP
CCl4, Et3N, MeCN
NaOH
EtOH, H2O
H2, Pd/C
MeOH
POCl3, DIPEA
CH3CN then
pH 7.0 PBS
H2, Pd/C
THF, H2O
HNO3
(1.2 eq)
DCM
H2, Pd/C
THF
HNO3
(1.2 eq)
DCM
H2, Pd/C
THF
EDC, DMA
Pd/C, H2
MeOH
EDC, DMA
mAb
102
187
188
189
109
190
191
192
193
194
195
196
197
198
199
200
201
186

Fig. 14.

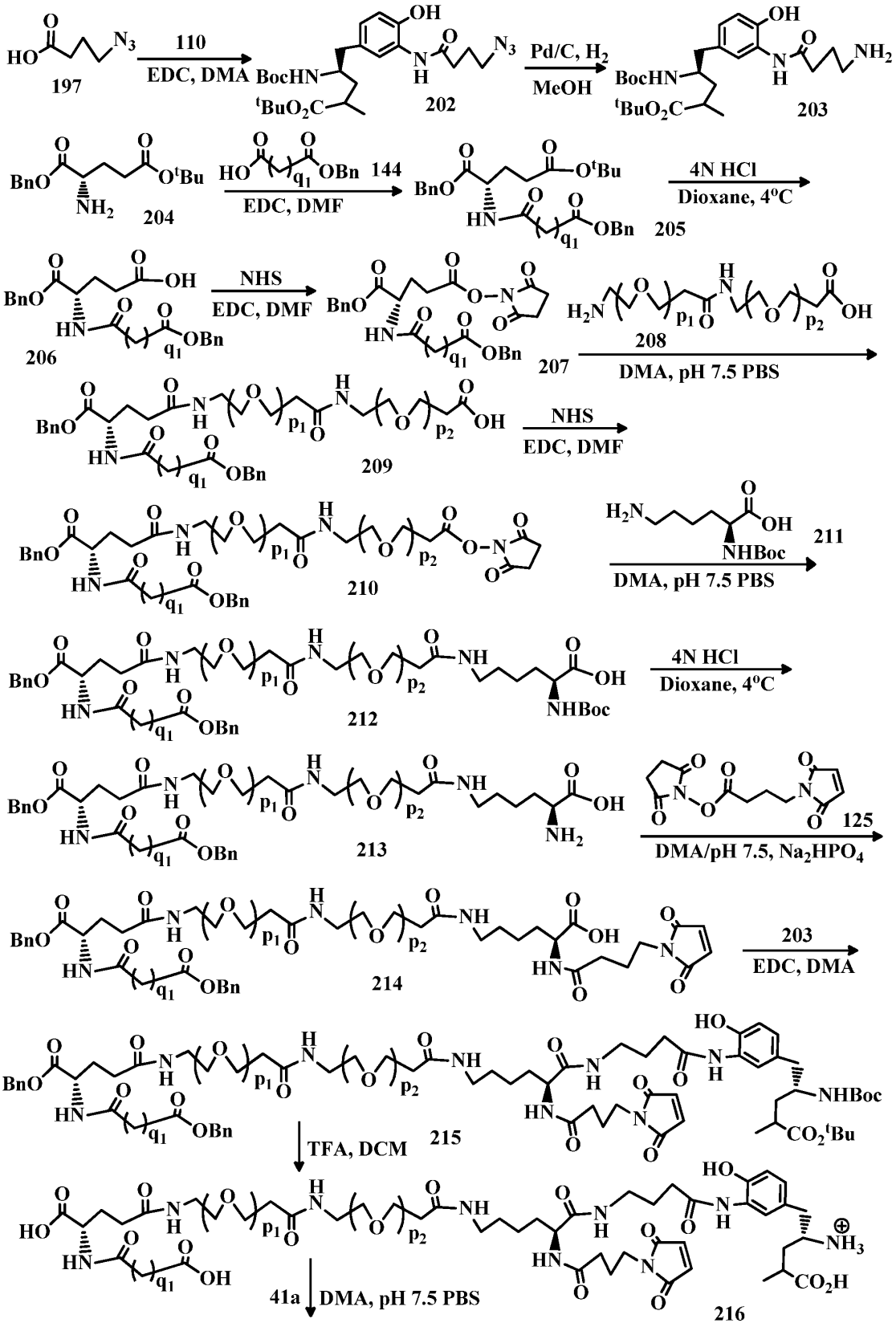

197
110
EDC, DMA
202
Pd/C, H2
MeOH
203
204
144
EDC, DMF
205
4N HCl
Dioxane, 4°C
206
NHS
EDC, DMF
207
208
DMA, pH 7.5 PBS
209
NHS
EDC, DMF
210
211
DMA, pH 7.5 PBS
212
4N HCl
Dioxane, 4°C
213
125
DMA/pH 7.5, Na2HPO4
214
203
EDC, DMA
215
TFA, DCM
41a
DMA, pH 7.5 PBS
216

Fig. 15.

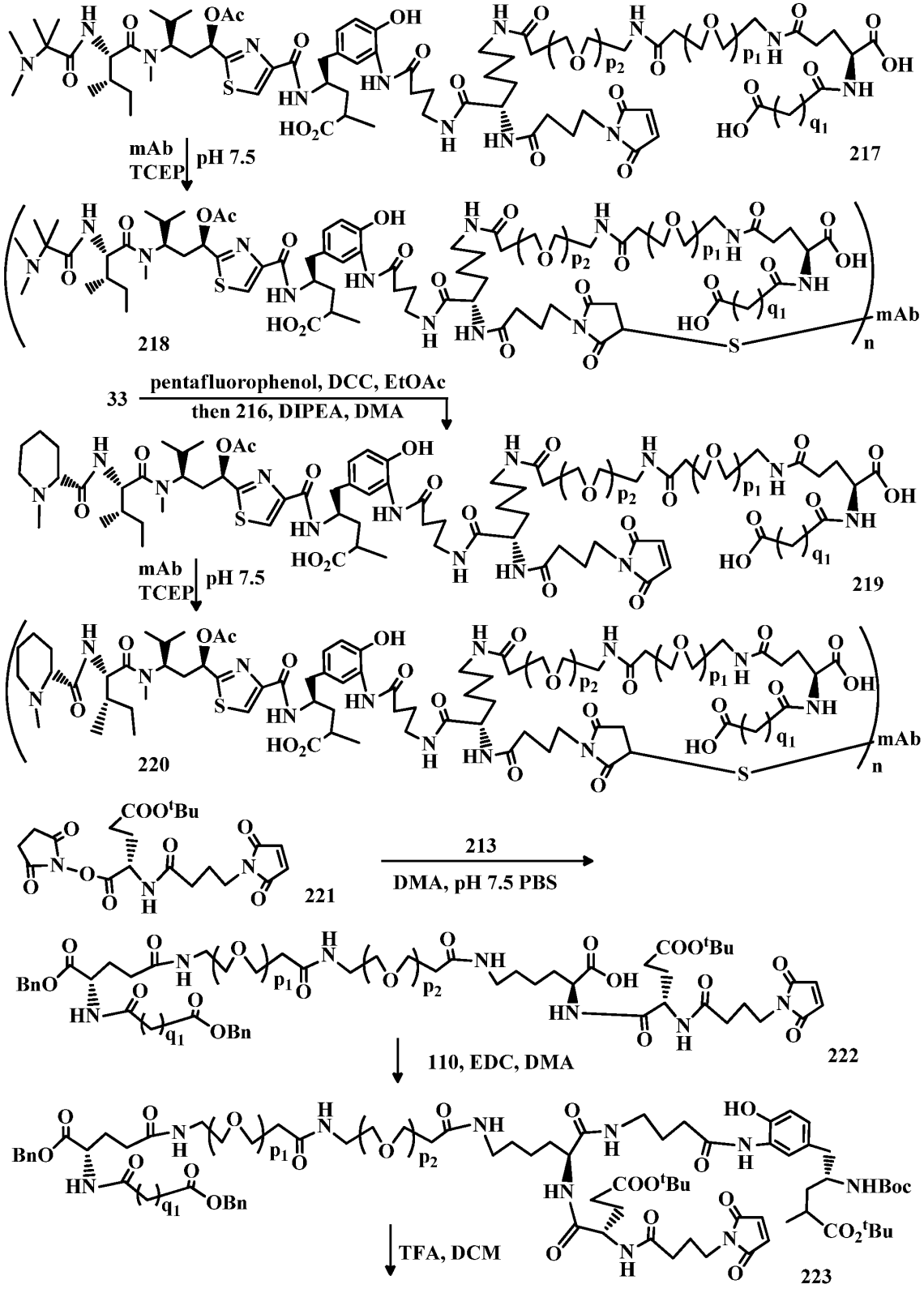

mAb
TCEP
pH 7.5
217
218
33
pentafluorophenol, DCC, EtOAc
then 216, DIPEA, DMA
219
220
221
213
DMA, pH 7.5 PBS
222
110, EDC, DMA
TFA, DCM
223

Fig. 16

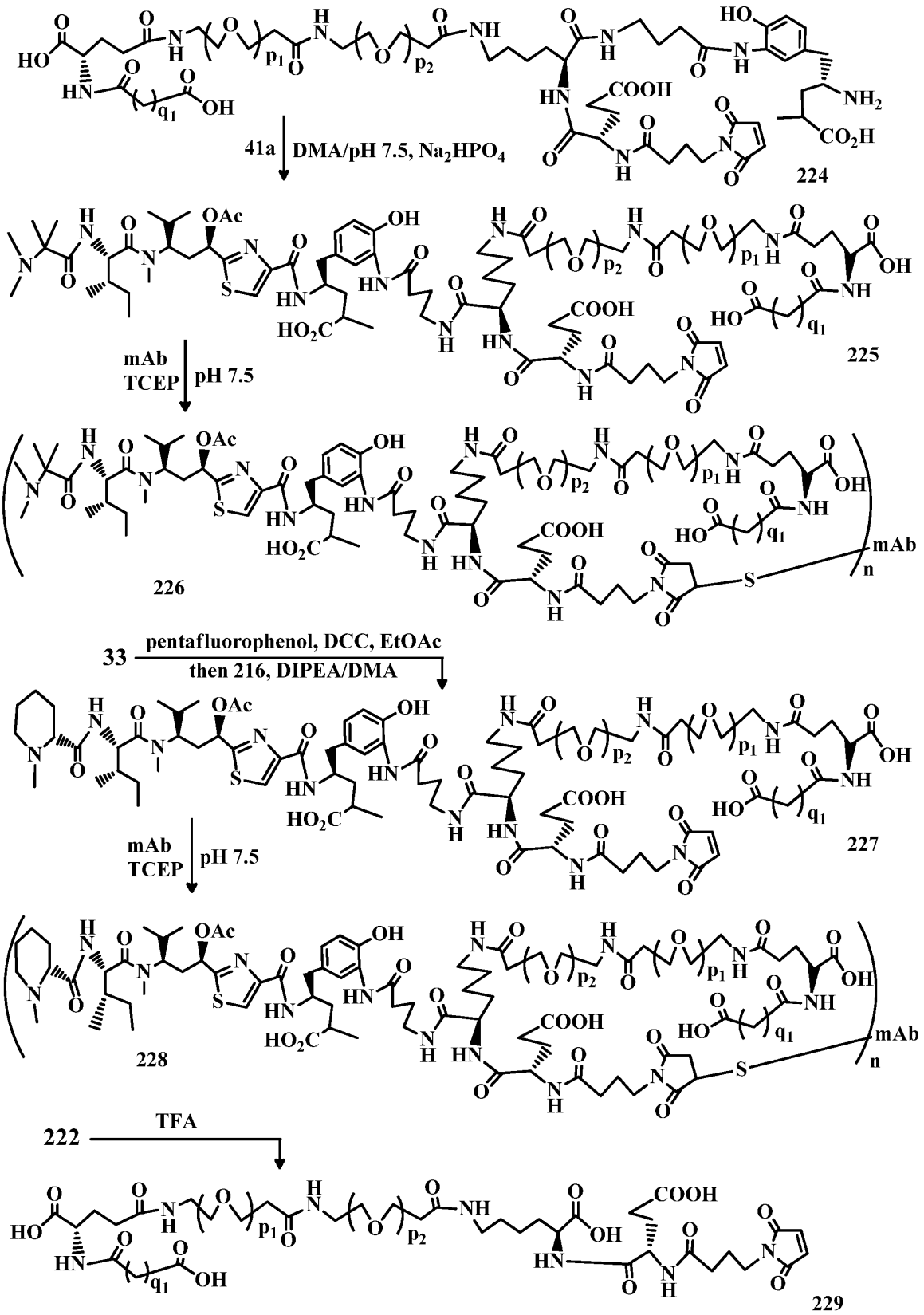

41a
DMA/pH 7.5, Na2HPO4
224
mAb
TCEP
pH 7.5
225
226
33
pentafluorophenol, DCC, EtOAc
then 216, DIPEA/DMA
227
228
222
TFA
229

Fig. 17

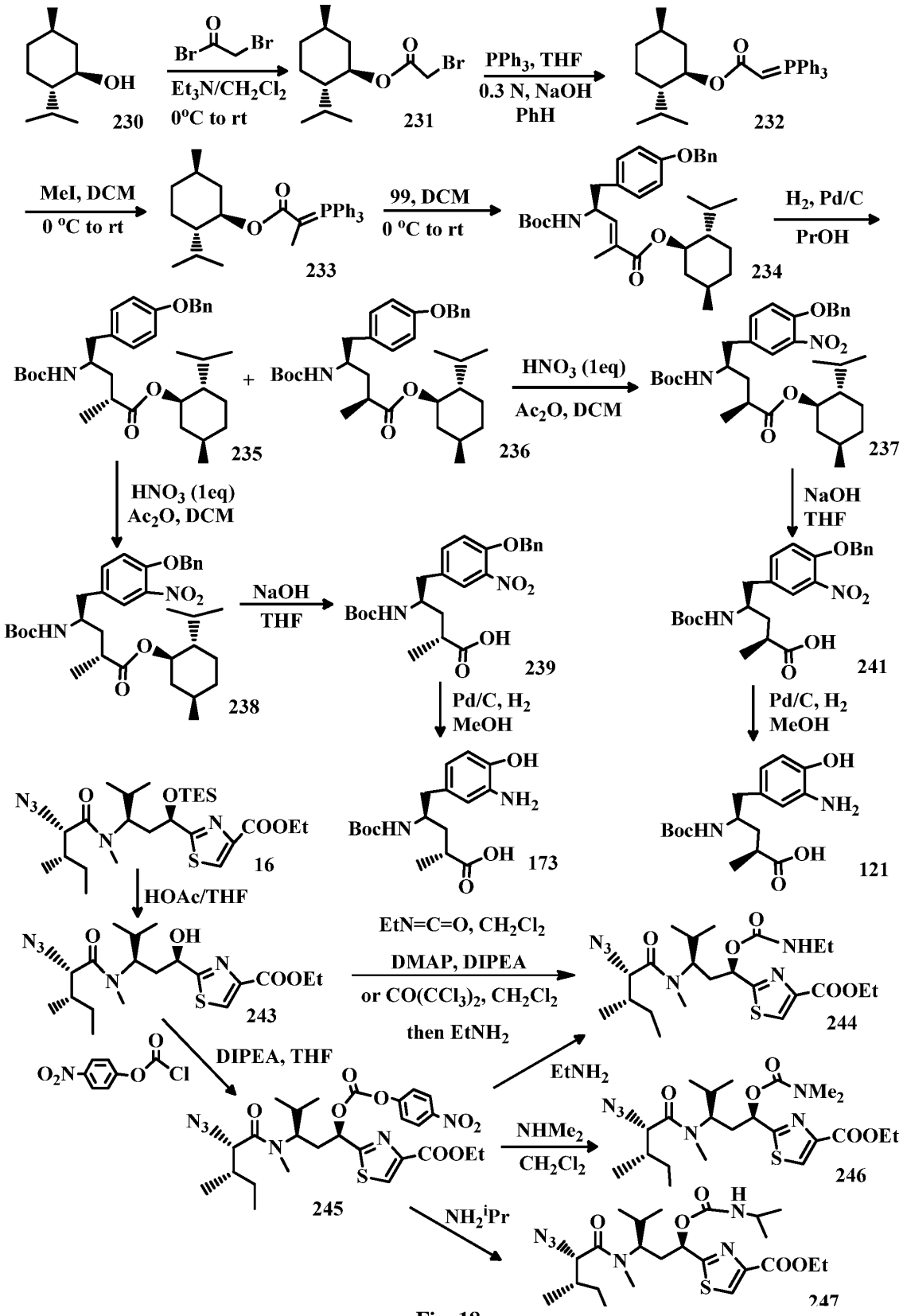

230
231
232
233
234
235
236
237
238
239
241
16
173
121
243
244
245
246
247
Br
Et3N/CH2Cl2
0°C to rt
PPh3, THF
0.3 N, NaOH
PhH
MeI, DCM
0 °C to rt
99, DCM
0 °C to rt
H2, Pd/C
PrOH
HNO3 (1eq)
Ac2O, DCM
NaOH
THF
Pd/C, H2
MeOH
HOAc/THF
DIPEA, THF
EtN=C=O, CH2Cl2
DMAP, DIPEA
or CO(CCl3)2, CH2Cl2
then EtNH2
EtNH2
NHMe2
CH2Cl2
NH2iPr
BocHN
OBn
NO2
OTES
COOEt
OH
NHEt
NMe2

Fig. 18.

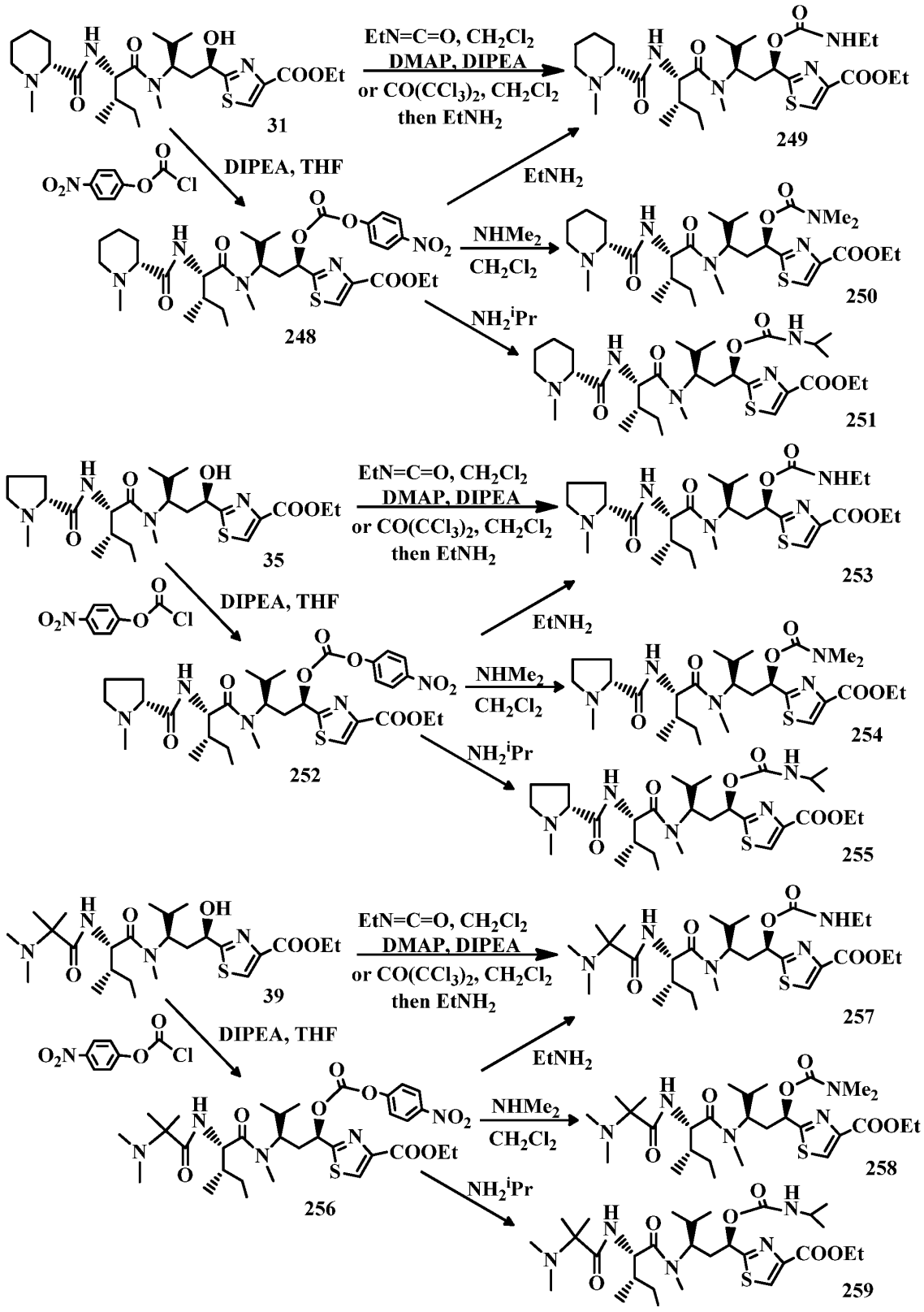

EtN=C=O, CH2Cl2
DMAP, DIPEA
or CO(CCl3)2, CH2Cl2
then EtNH2
DIPEA, THF
EtNH2
NHMe2
CH2Cl2
NH2iPr
31
248
249
250
251
35
252
253
254
255
39
256
257
258
259

Fig. 19.

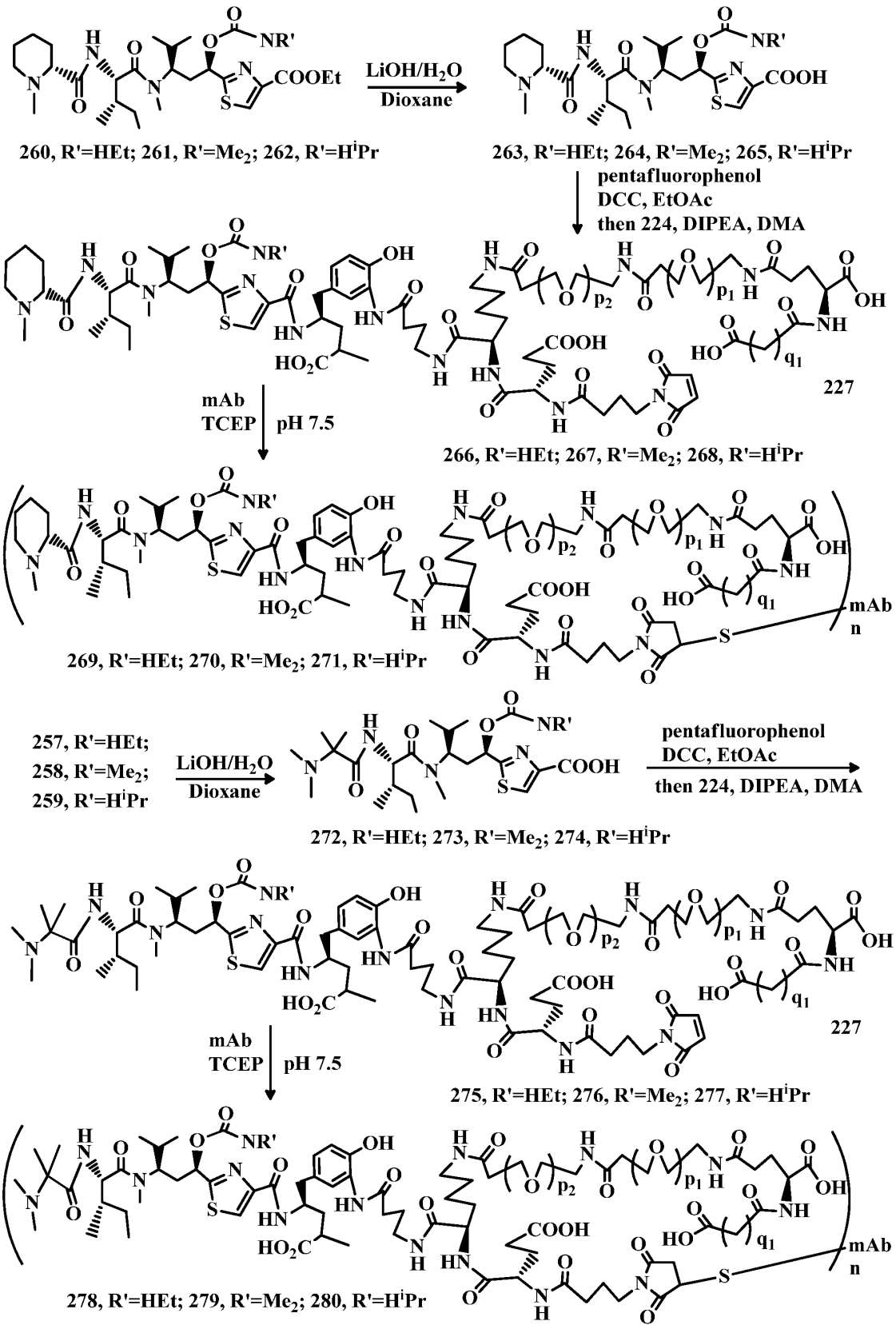

LiOH/H2O
Dioxane
260, R'=HEt; 261, R'=Me2; 262, R'=HiPr
263, R'=HEt; 264, R'=Me2; 265, R'=HiPr
pentafluorophenol
DCC, EtOAc
then 224, DIPEA, DMA
227
mAb
TCEP
pH 7.5
266, R'=HEt; 267, R'=Me2; 268, R'=HiPr
269, R'=HEt; 270, R'=Me2; 271, R'=HiPr
257, R'=HEt;
258, R'=Me2;
259, R'=HiPr
LiOH/H2O
Dioxane
pentafluorophenol
DCC, EtOAc
then 224, DIPEA, DMA
272, R'=HEt; 273, R'=Me2; 274, R'=HiPr
227
mAb
TCEP
pH 7.5
275, R'=HEt; 276, R'=Me2; 277, R'=HiPr
278, R'=HEt; 279, R'=Me2; 280, R'=HiPr

Fig. 20.

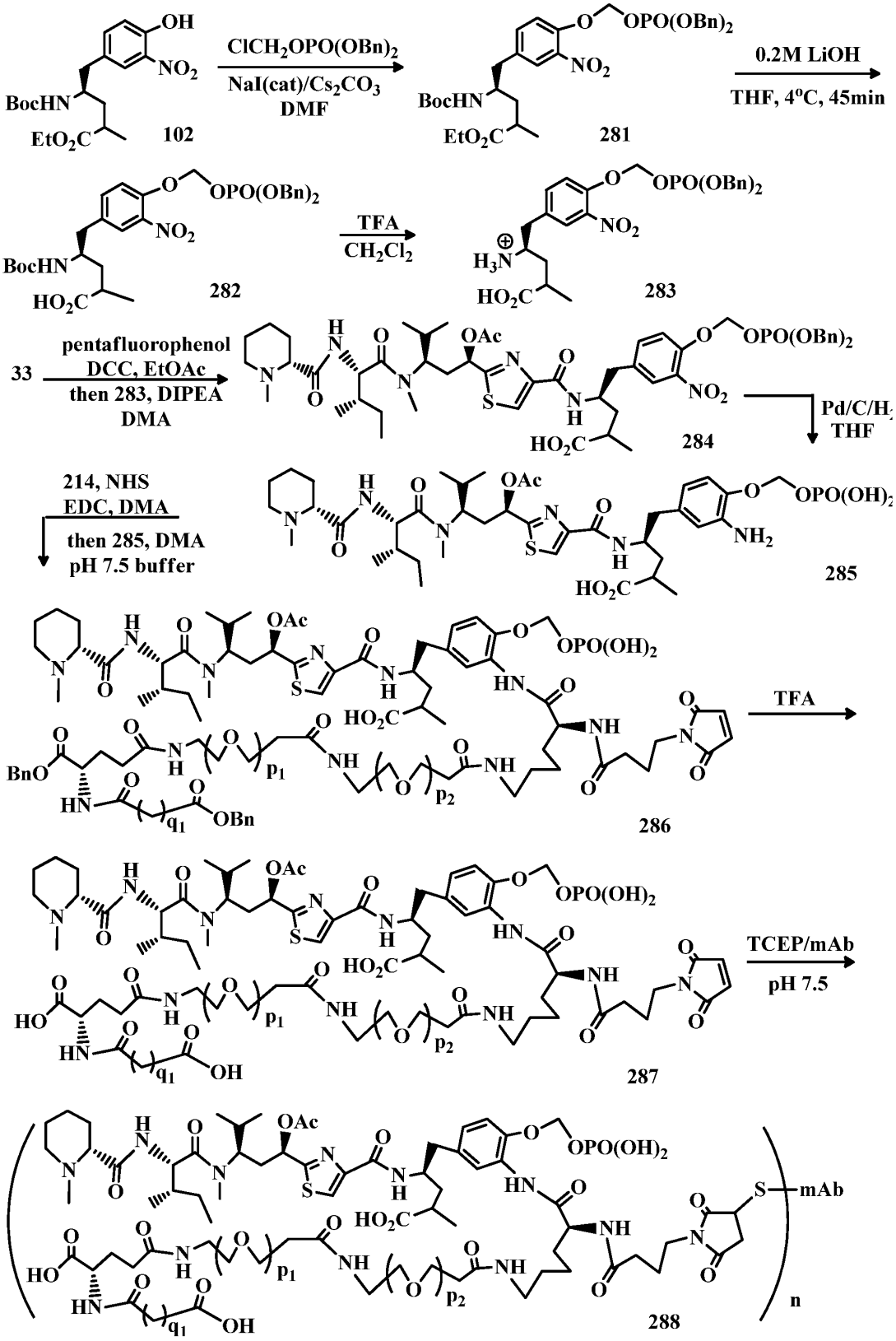

ClCH2OPO(OBn)2
NaI(cat)/Cs2CO3
DMF
0.2M LiOH
THF, 4°C, 45min
TFA
CH2Cl2
pentafluorophenol
DCC, EtOAc
then 283, DIPEA
DMA
33
Pd/C/H2
THF
214, NHS
EDC, DMA
then 285, DMA
pH 7.5 buffer
TFA
TCEP/mAb
pH 7.5
102
281
282
283
284
285
286
287
288
mAb
n

Fig. 21.

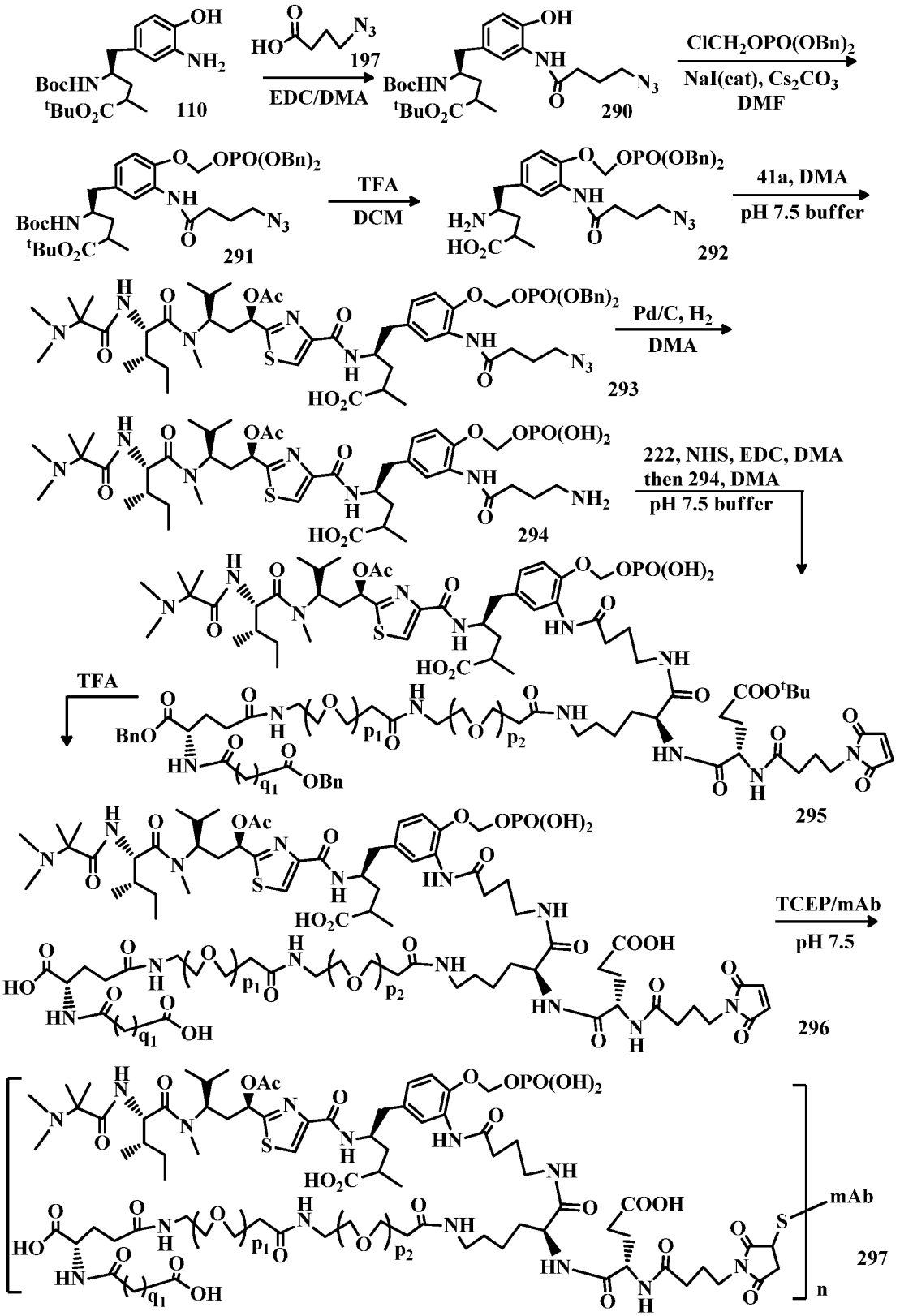

110
197
EDC/DMA
290
ClCH2OPO(OBn)2
NaI(cat), Cs2CO3
DMF
291
TFA
DCM
292
41a, DMA
pH 7.5 buffer
293
Pd/C, H2
DMA
294
222, NHS, EDC, DMA
then 294, DMA
pH 7.5 buffer
295
TFA
296
TCEP/mAb
pH 7.5
297
mAb
n

Fig. 22.

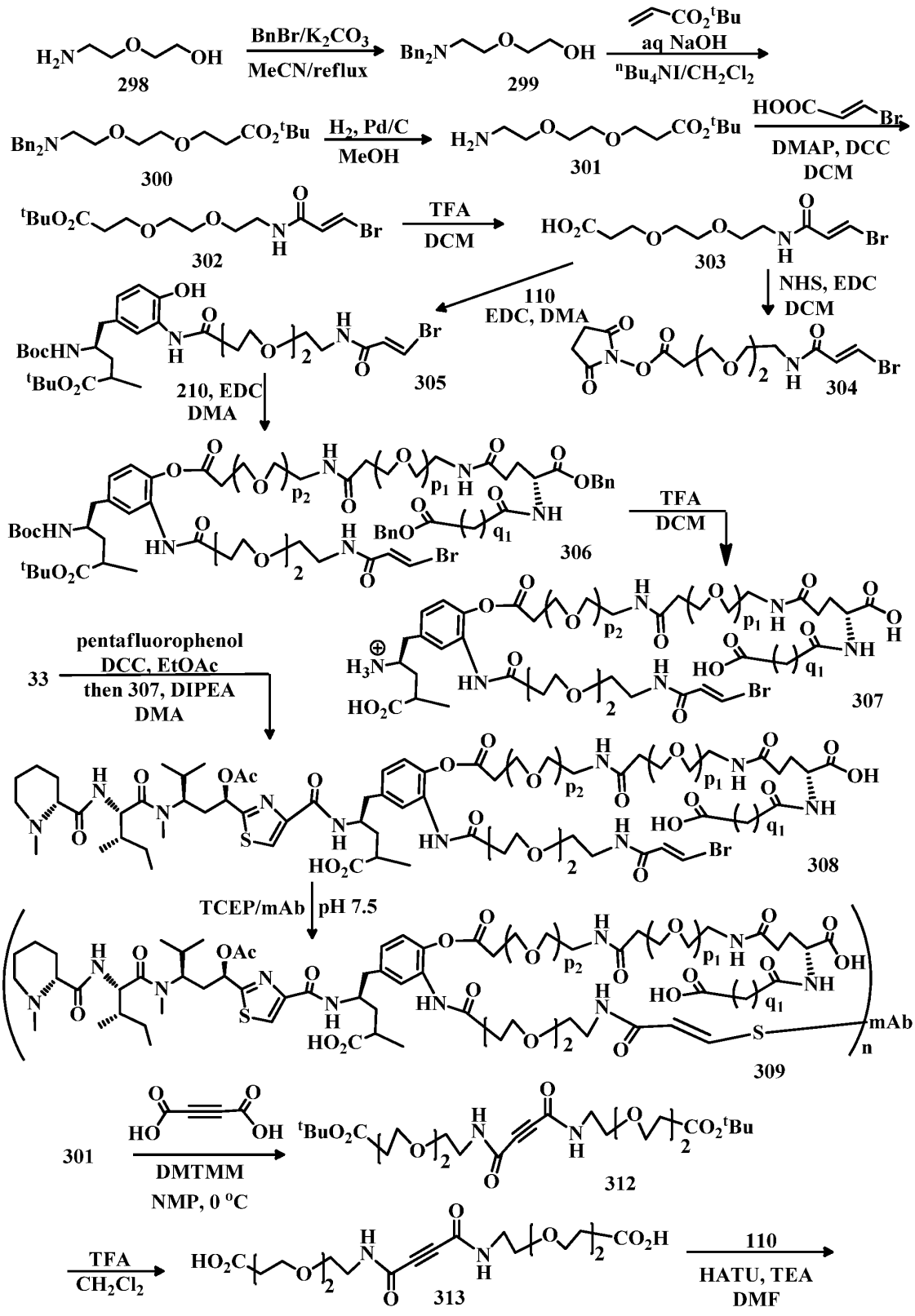

BnBr/K2CO3
MeCN/reflux
aq NaOH
nBu4NI/CH2Cl2
H2, Pd/C
MeOH
DMAP, DCC
DCM
TFA
DCM
NHS, EDC
DCM
110
EDC, DMA
210, EDC
DMA
TFA
DCM
pentafluorophenol
DCC, EtOAc
then 307, DIPEA
DMA
33
TCEP/mAb pH 7.5
DMTMM
NMP, 0 °C
301
TFA
CH2Cl2
110
HATU, TEA
DMF
298
299
300
301
302
303
304
305
306
307
308
309
312
313

Fig. 23

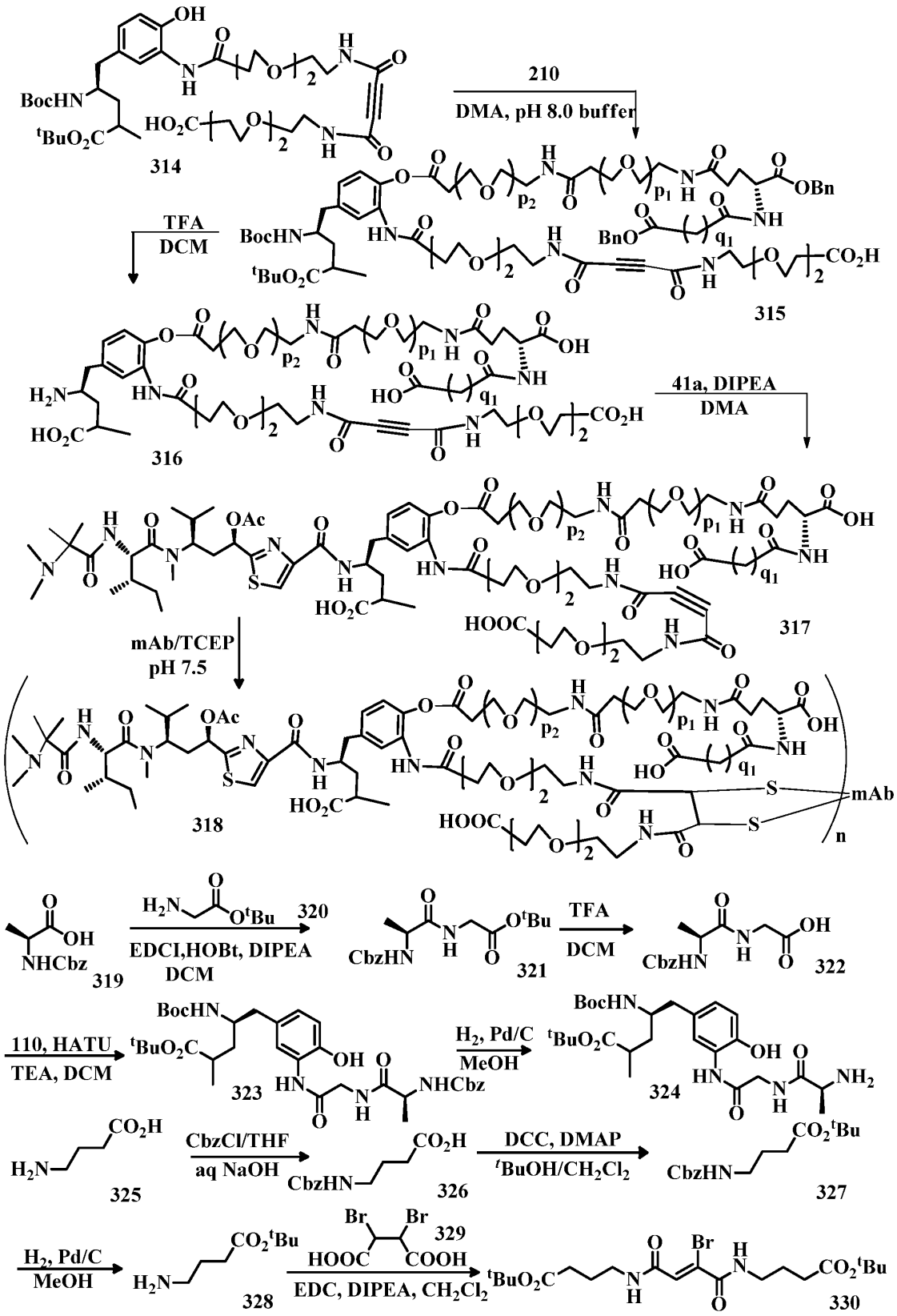

210
DMA, pH 8.0 buffer
314
TFA
DCM
315
316
41a, DIPEA
DMA
317
mAb/TCEP
pH 7.5
318
319
320
EDCI,HOBt, DIPEA
DCM
321
TFA
DCM
322
110, HATU
TEA, DCM
323
H2, Pd/C
MeOH
324
325
CbzCl/THF
aq NaOH
326
DCC, DMAP
tBuOH/CH2Cl2
327
H2, Pd/C
MeOH
328
329
EDC, DIPEA, CH2Cl2
330

Fig. 24.

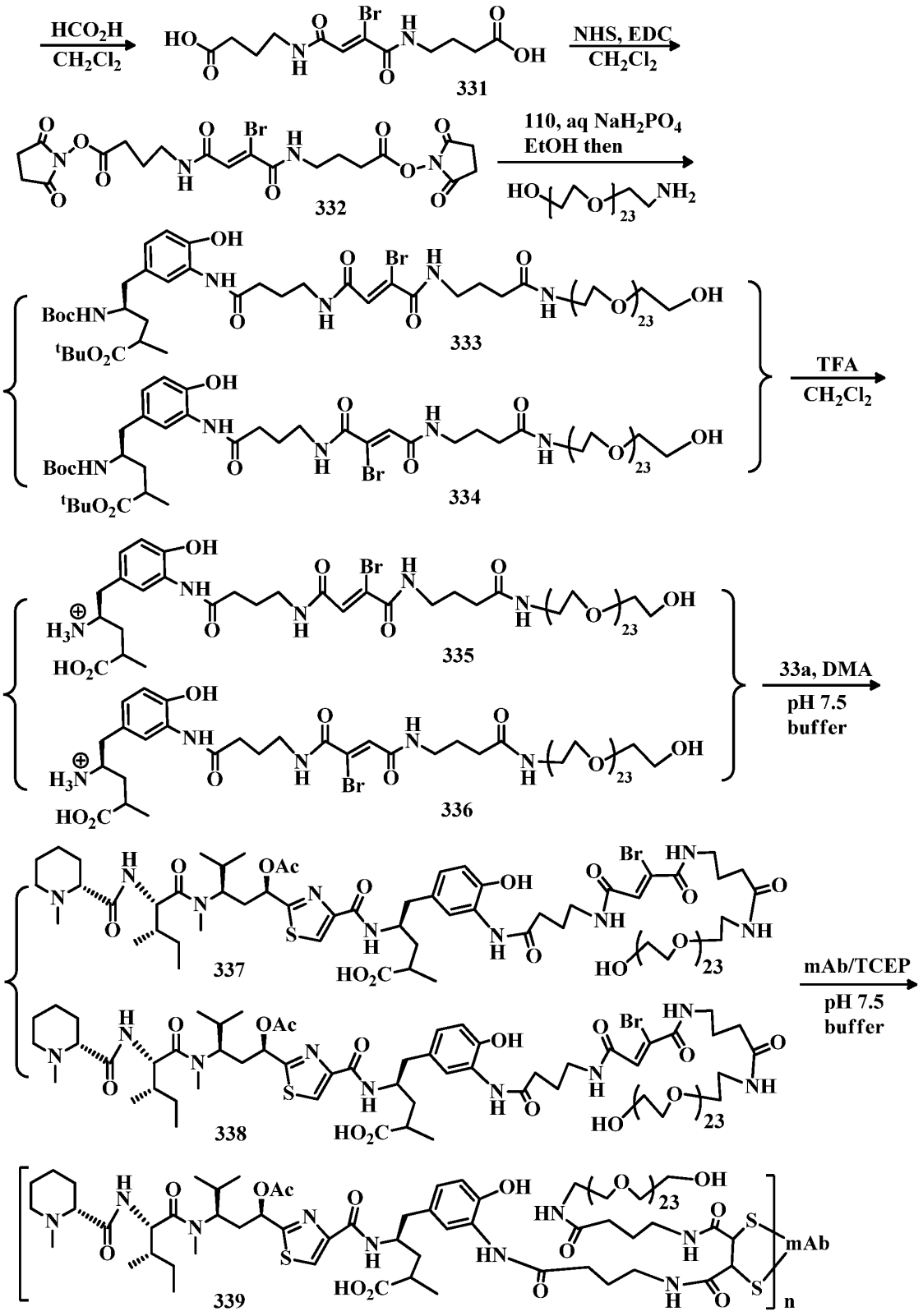

HCO2H
CH2Cl2
NHS, EDC
CH2Cl2
331
110, aq NaH2PO4
EtOH then
332
333
334
TFA
CH2Cl2
335
336
33a, DMA
pH 7.5
buffer
337
338
mAb/TCEP
pH 7.5
buffer
339
mAb
n

Fig. 25

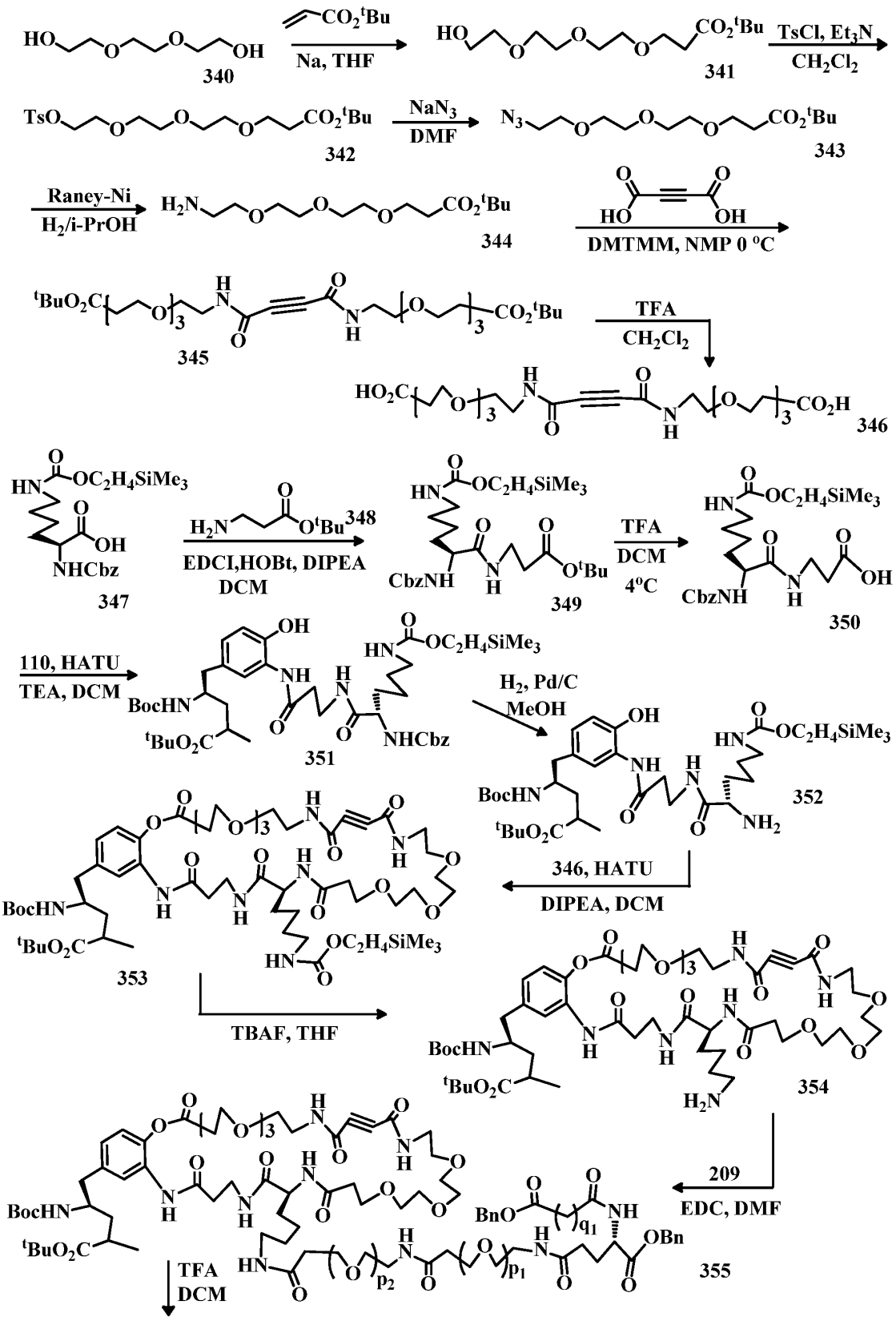

340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
Na, THF
TsCl, Et3N
CH2Cl2
NaN3
DMF
Raney-Ni
H2/i-PrOH
DMTMM, NMP 0 °C
TFA
CH2Cl2
EDCI,HOBt, DIPEA
DCM
TFA
DCM
4°C
110, HATU
TEA, DCM
H2, Pd/C
MeOH
346, HATU
DIPEA, DCM
TBAF, THF
209
EDC, DMF
TFA
DCM

Fig. 26

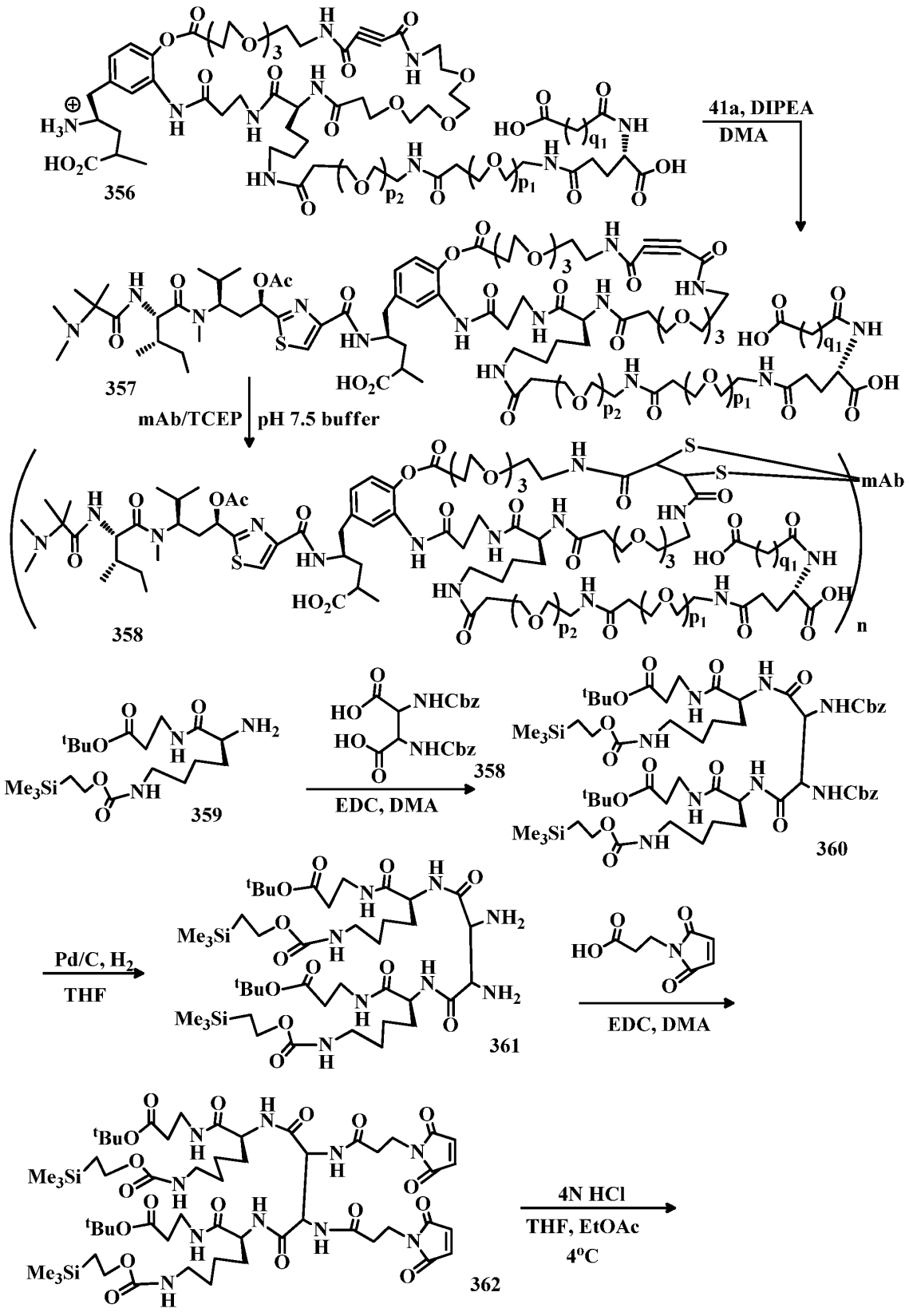

41a, DIPEA
DMA
356
357
mAb/TCEP
pH 7.5 buffer
358
mAb
n
359
EDC, DMA
360
Pd/C, H2
THF
361
EDC, DMA
362
4N HCl
THF, EtOAc
4°C

Fig. 27

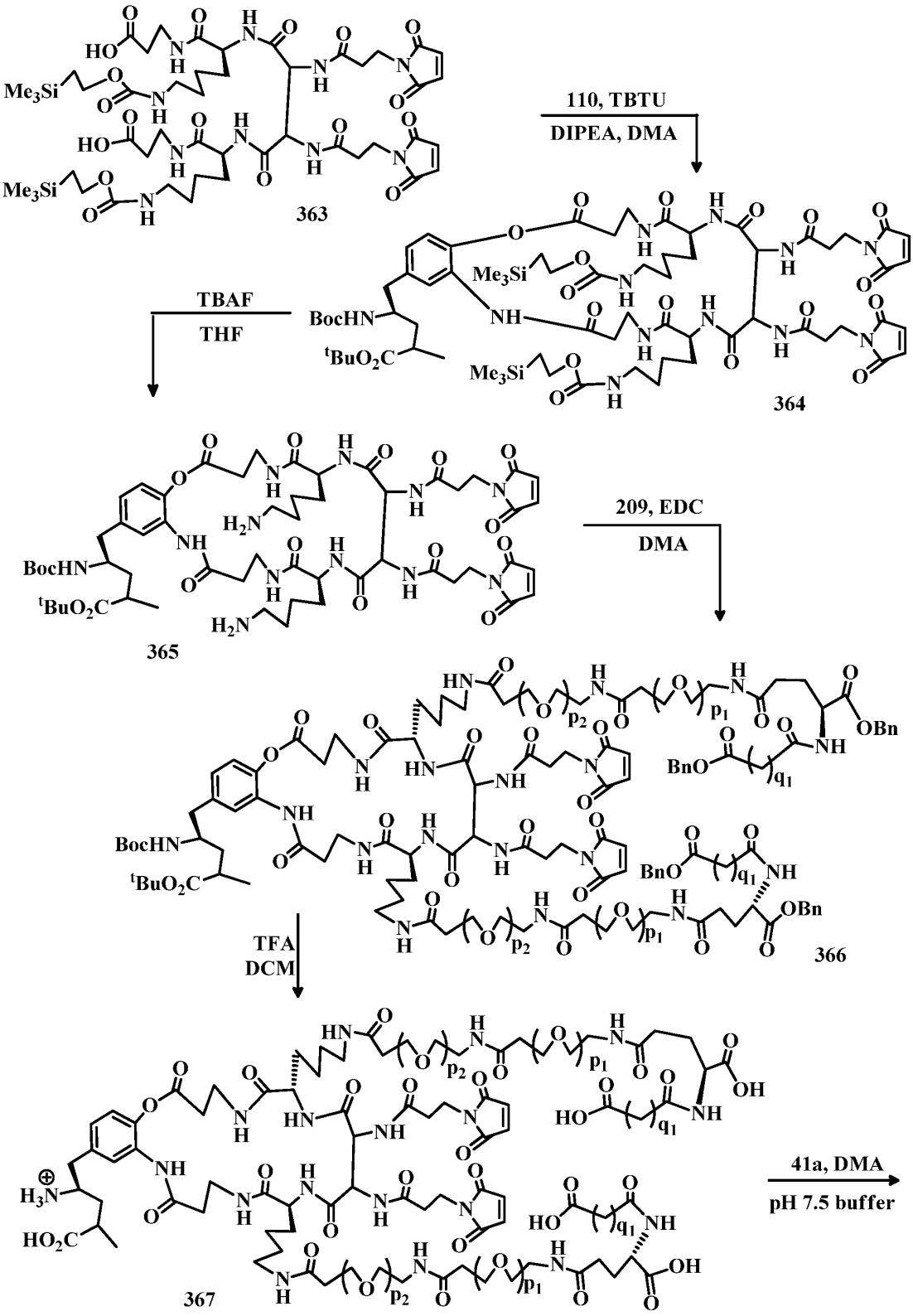

110, TBTU
DIPEA, DMA
363
364
TBAF
THF
209, EDC
DMA
365
366
TFA
DCM
367
41a, DMA
pH 7.5 buffer

Fig. 28

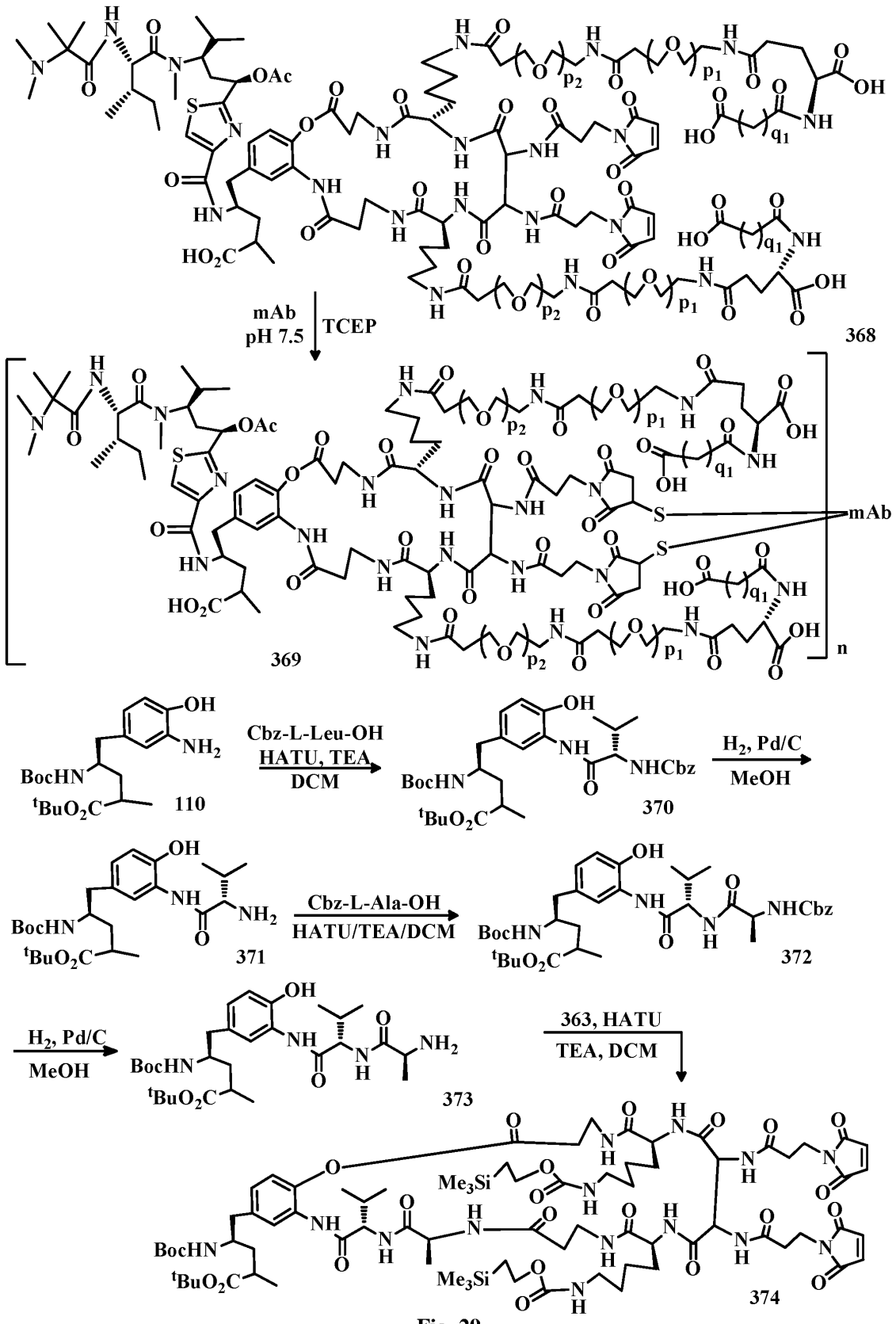

mAb
pH 7.5
TCEP
368
369
mAb
n
Cbz-L-Leu-OH
HATU, TEA
DCM
110
370
H2, Pd/C
MeOH
Cbz-L-Ala-OH
HATU/TEA/DCM
371
372
H2, Pd/C
MeOH
373
363, HATU
TEA, DCM
374

Fig. 29

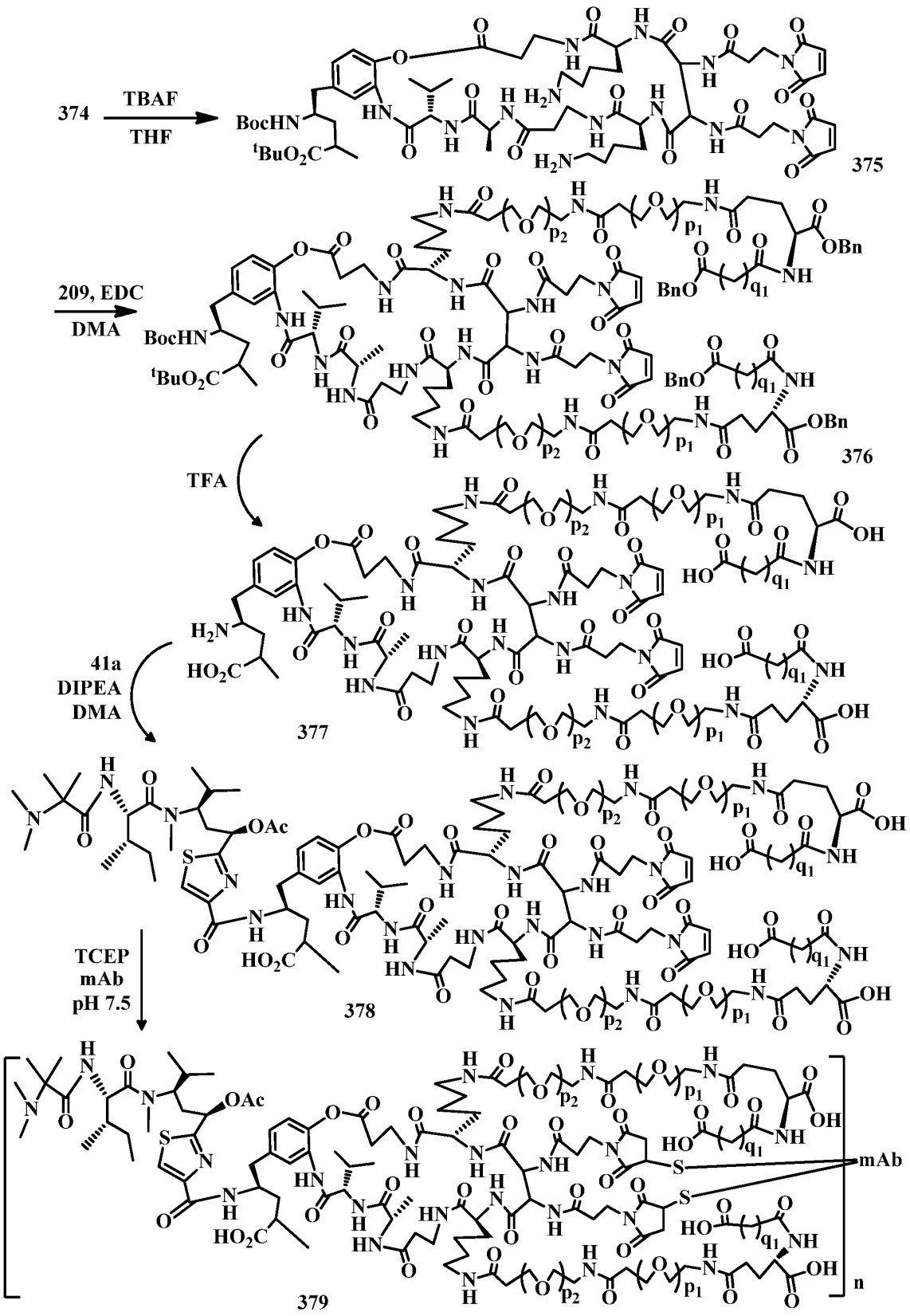

374
TBAF
THF
375
209, EDC
DMA
376
TFA
41a
DIPEA
DMA
377
TCEP
mAb
pH 7.5
378
379
mAb
n

Fig. 30.

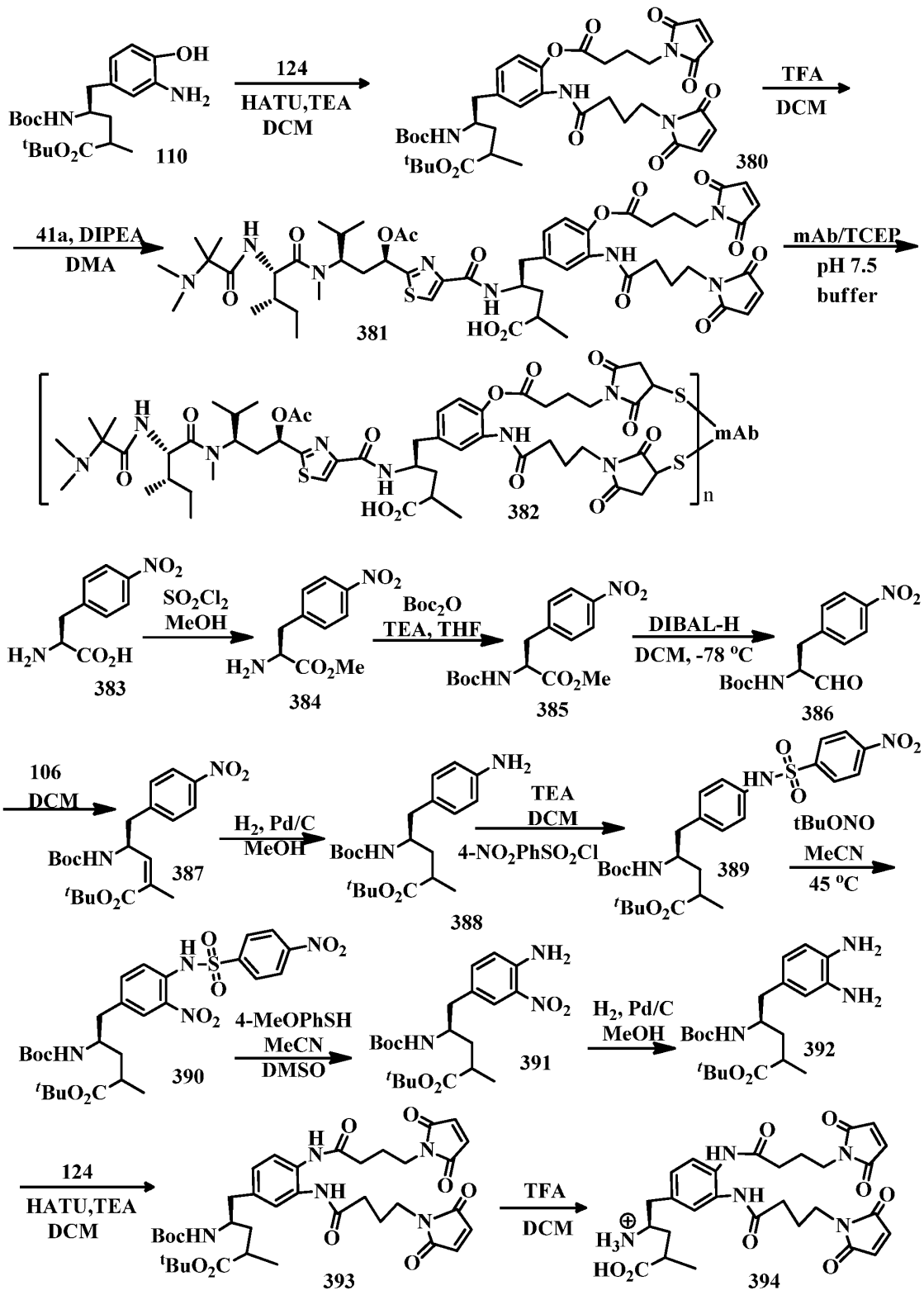

124
HATU,TEA
DCM
TFA
DCM
110
380
41a, DIPEA
DMA
mAb/TCEP
pH 7.5
buffer
381
382
mAb
SO2Cl2
MeOH
Boc2O
TEA, THF
DIBAL-H
DCM, -78 °C
383
384
385
386
106
DCM
H2, Pd/C
MeOH
TEA
DCM
4-NO2PhSO2Cl
tBuONO
MeCN
45 °C
387
388
389
4-MeOPhSH
MeCN
DMSO
H2, Pd/C
MeOH
390
391
392
124
HATU,TEA
DCM
TFA
DCM
393
394

Fig. 31

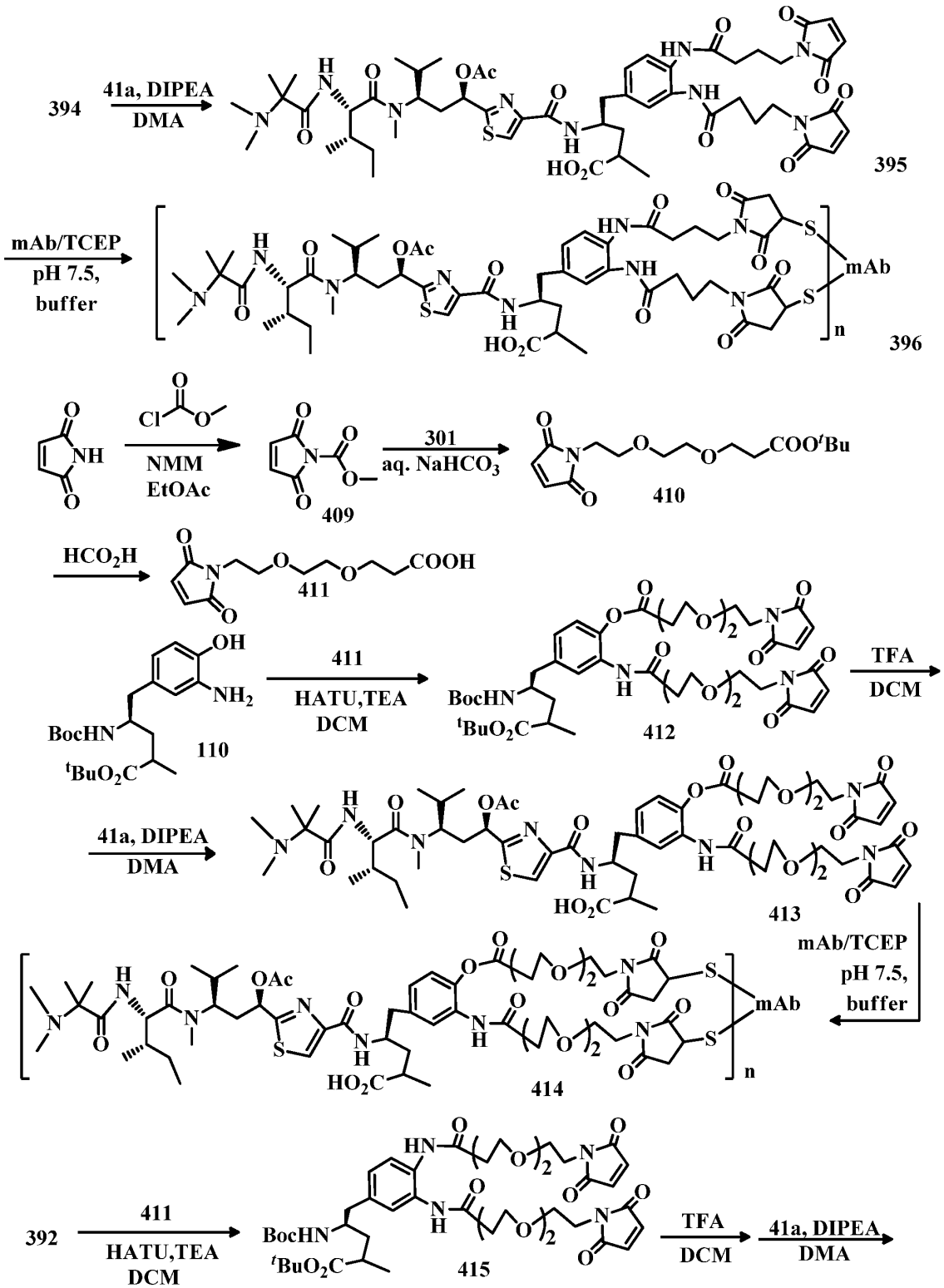

394
41a, DIPEA
DMA
395
mAb/TCEP
pH 7.5,
buffer
mAb
n
396
NMM
EtOAc
409
301
aq. NaHCO3
410
HCO2H
411
110
411
HATU,TEA
DCM
412
TFA
DCM
41a, DIPEA
DMA
413
mAb/TCEP
pH 7.5,
buffer
414
392
411
HATU,TEA
DCM
415
TFA
DCM
41a, DIPEA
DMA

Fig. 32.

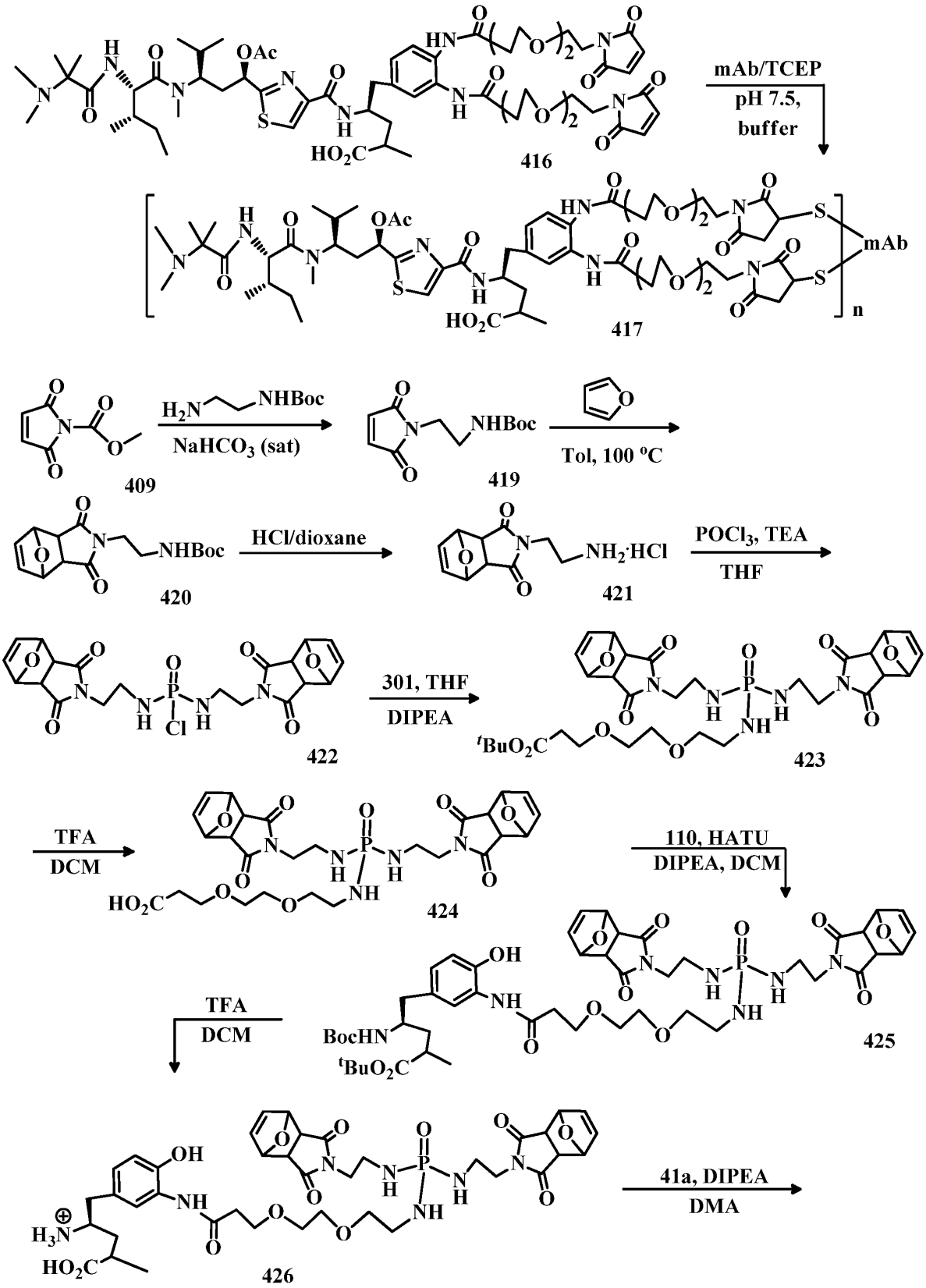

mAb/TCEP
pH 7.5,
buffer
416
417
mAb
n
409
H_2N NHBoc
$NaHCO_3$ (sat)
419
Tol, 100 °C
420
HCl/dioxane
421
$POCl_3$, TEA
THF
422
301, THF
DIPEA
423
TFA
DCM
424
110, HATU
DIPEA, DCM
425
426
41a, DIPEA
DMA

Fig. 33.

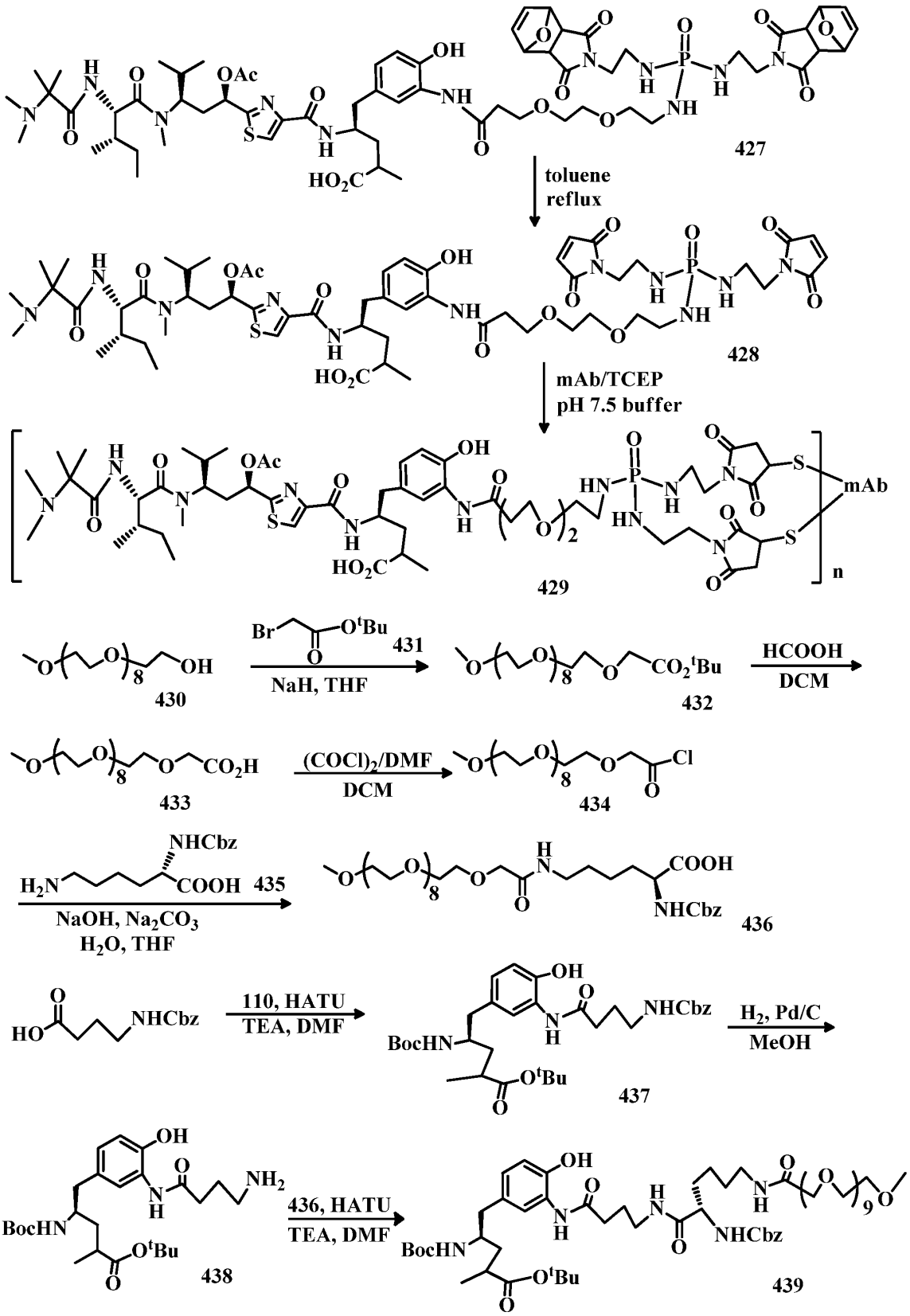

427
toluene
reflux
428
mAb/TCEP
pH 7.5 buffer
429
n
mAb
430
Br
O^tBu
431
NaH, THF
432
HCOOH
DCM
433
(COCl)2/DMF
DCM
434
NHCbz
H2N
COOH
435
NaOH, Na2CO3
H2O, THF
436
HO
NHCbz
110, HATU
TEA, DMF
BocHN
O^tBu
437
H2, Pd/C
MeOH
438
436, HATU
TEA, DMF
439

Fig. 34

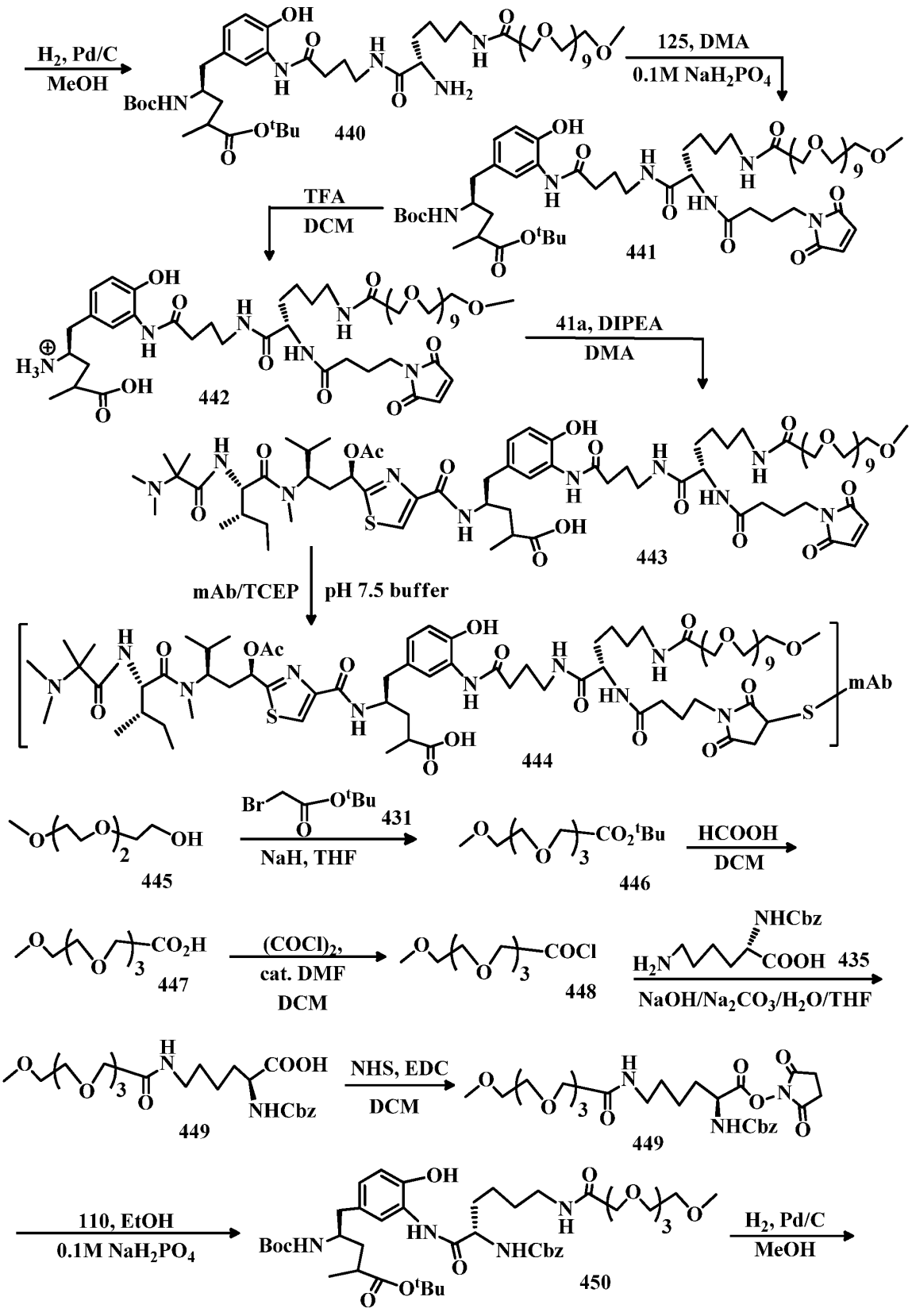

H2, Pd/C
MeOH
440
125, DMA
0.1M NaH2PO4
441
TFA
DCM
442
41a, DIPEA
DMA
443
mAb/TCEP
pH 7.5 buffer
444
mAb
445
Br
O
OtBu
431
NaH, THF
446
HCOOH
DCM
447
(COCl)2,
cat. DMF
DCM
448
NHCbz
H2N
COOH
435
NaOH/Na2CO3/H2O/THF
449
NHS, EDC
DCM
449
110, EtOH
0.1M NaH2PO4
450
H2, Pd/C
MeOH

Fig. 35

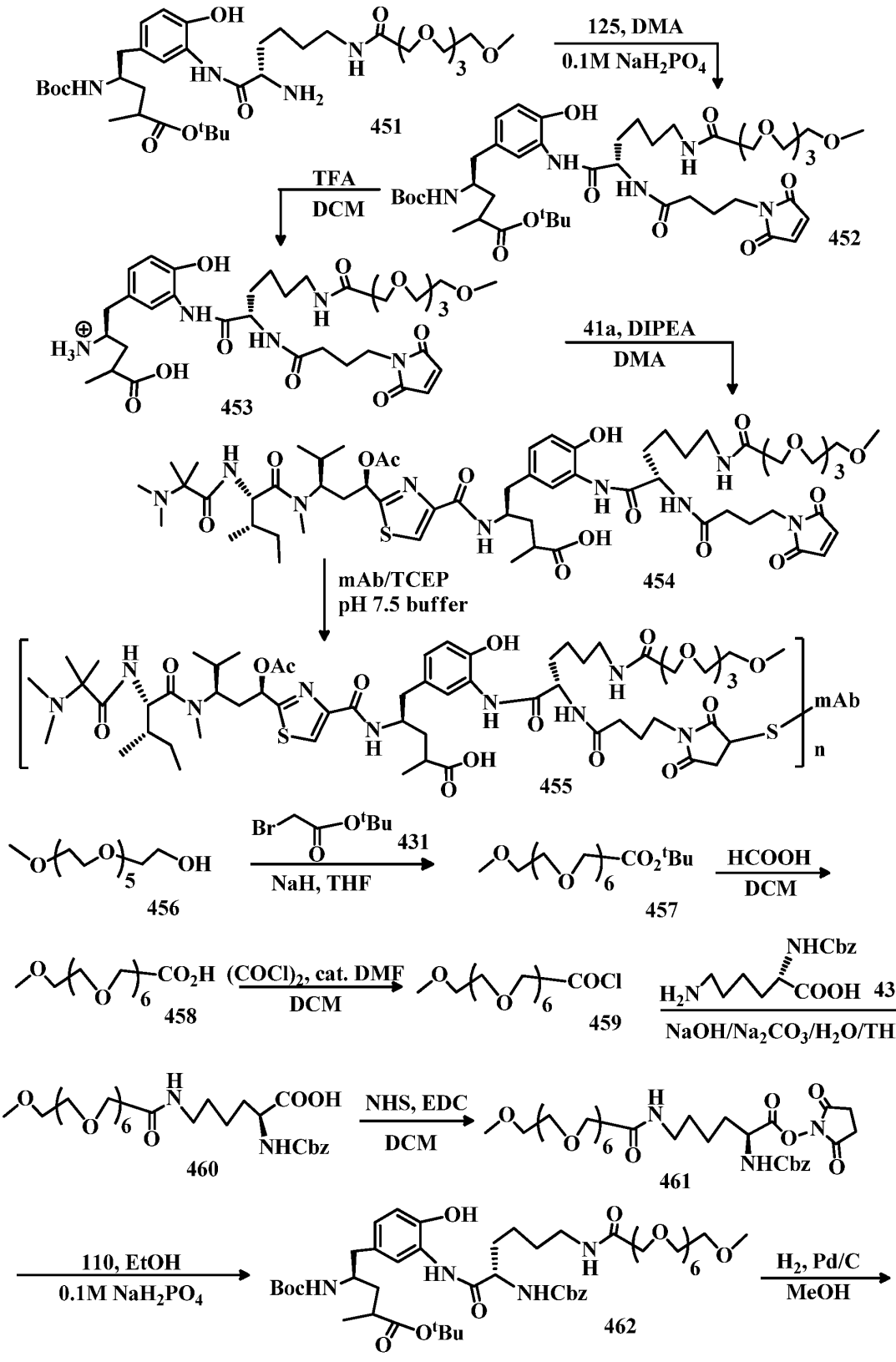

125, DMA
0.1M NaH2PO4
451
452
TFA
DCM
453
41a, DIPEA
DMA
454
mAb/TCEP
pH 7.5 buffer
455
431
NaH, THF
456
457
HCOOH
DCM
458
(COCl)2, cat. DMF
DCM
459
435
NaOH/Na2CO3/H2O/THF
460
NHS, EDC
DCM
461
110, EtOH
0.1M NaH2PO4
462
H2, Pd/C
MeOH

Fig.36.

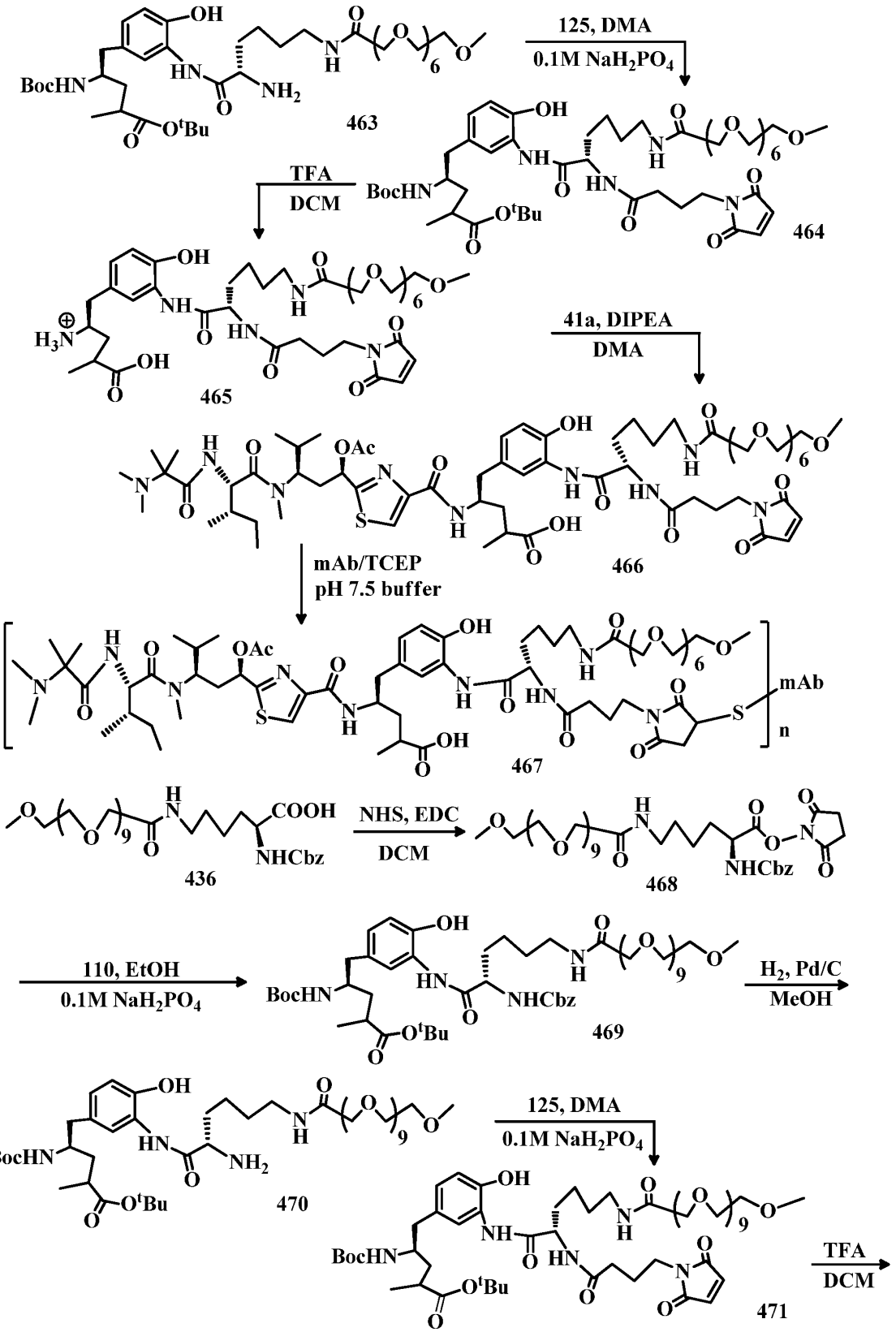

125, DMA
0.1M NaH2PO4
463
464
TFA
DCM
465
41a, DIPEA
DMA
466
mAb/TCEP
pH 7.5 buffer
467
436
NHS, EDC
DCM
468
110, EtOH
0.1M NaH2PO4
469
H2, Pd/C
MeOH
470
125, DMA
0.1M NaH2PO4
471
TFA
DCM

Fig. 37

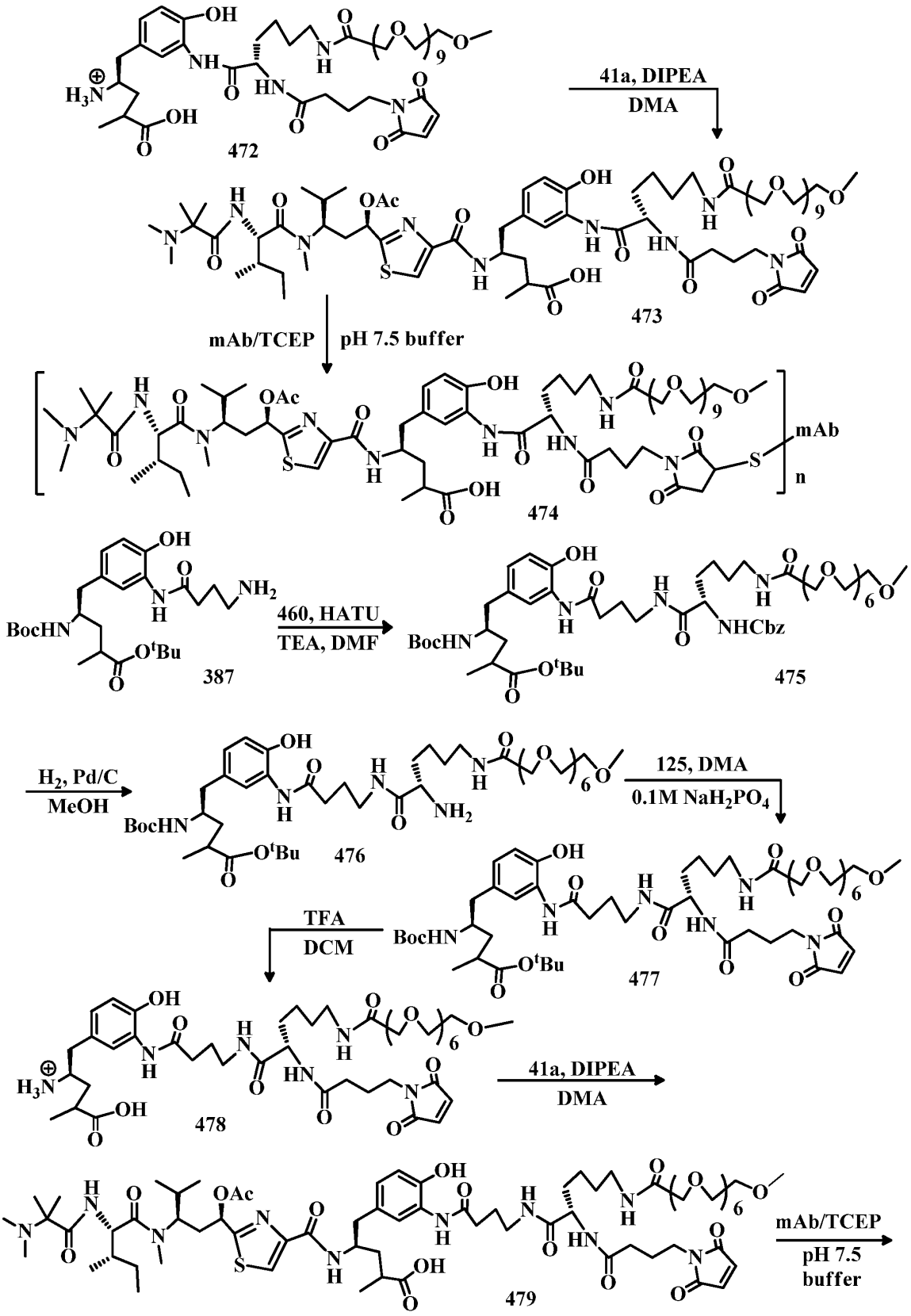

41a, DIPEA
DMA
472
473
mAb/TCEP
pH 7.5 buffer
474
460, HATU
TEA, DMF
387
475
H2, Pd/C
MeOH
476
125, DMA
0.1M NaH2PO4
TFA
DCM
477
478
41a, DIPEA
DMA
479
mAb/TCEP
pH 7.5
buffer

Fig. 38

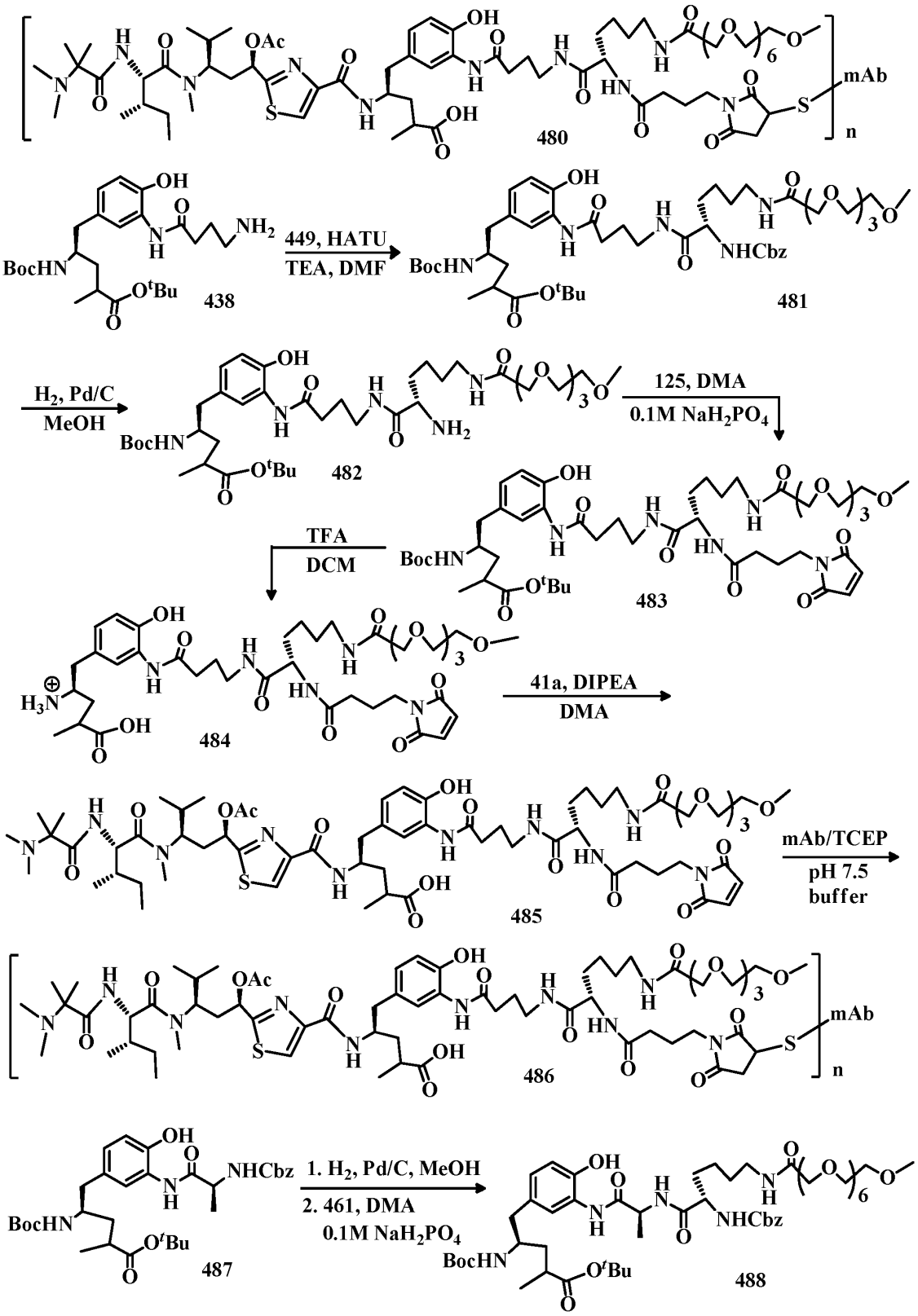

480
438
449, HATU
TEA, DMF
481
H2, Pd/C
MeOH
482
125, DMA
0.1M NaH2PO4
TFA
DCM
483
484
41a, DIPEA
DMA
485
mAb/TCEP
pH 7.5
buffer
486
487
1. H2, Pd/C, MeOH
2. 461, DMA
0.1M NaH2PO4
488

Fig. 39

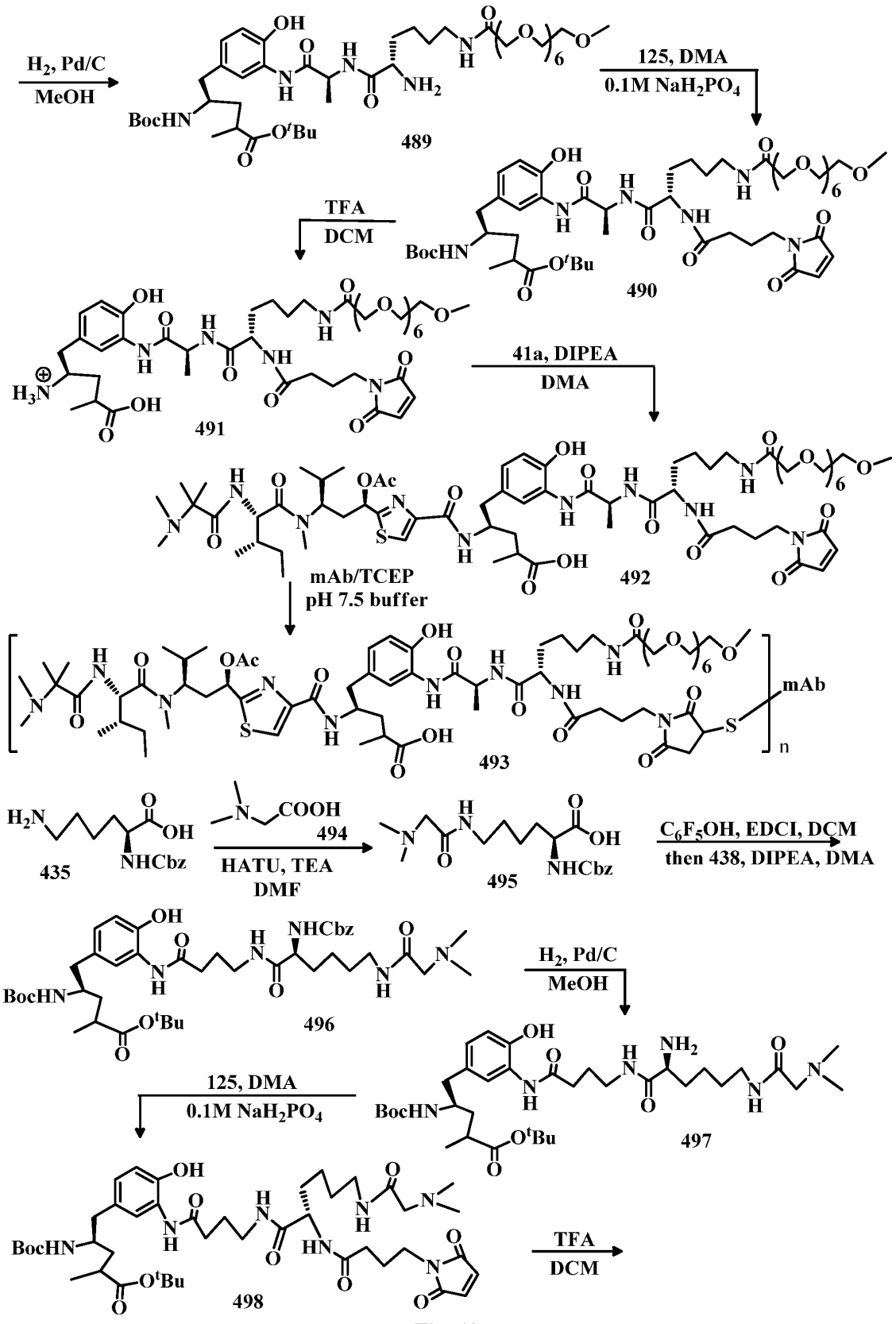

H2, Pd/C
MeOH
125, DMA
0.1M NaH2PO4
TFA
DCM
41a, DIPEA
DMA
mAb/TCEP
pH 7.5 buffer
HATU, TEA
DMF
C6F5OH, EDCI, DCM
then 438, DIPEA, DMA
125, DMA
0.1M NaH2PO4
TFA
DCM
489
490
491
492
493
494
495
496
497
498
435
mAb

Fig. 40

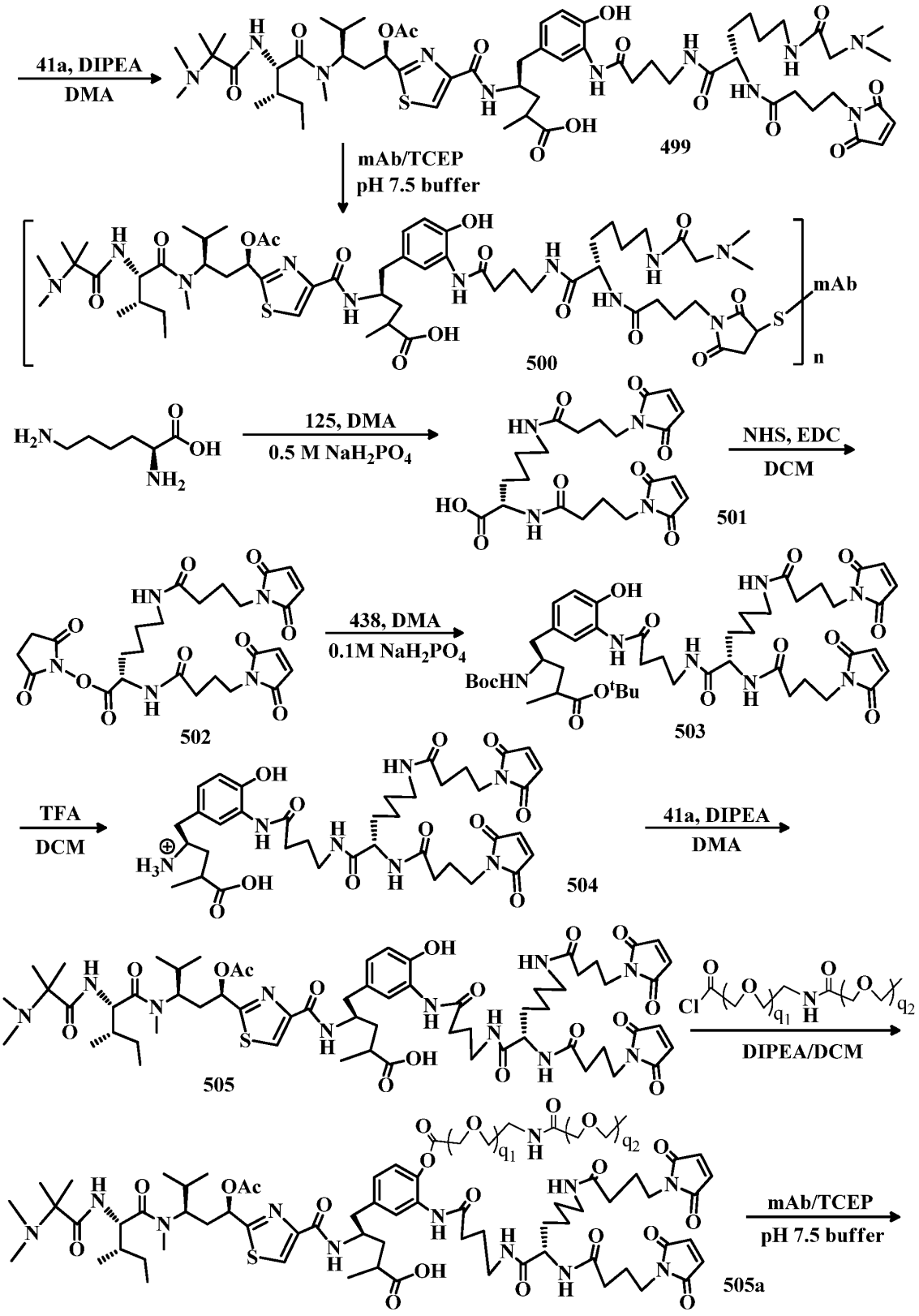

41a, DIPEA
DMA
499
mAb/TCEP
pH 7.5 buffer
mAb
n
500
125, DMA
0.5 M NaH2PO4
NHS, EDC
DCM
501
438, DMA
0.1M NaH2PO4
502
503
TFA
DCM
504
41a, DIPEA
DMA
505
DIPEA/DCM
mAb/TCEP
pH 7.5 buffer
505a

Fig. 41

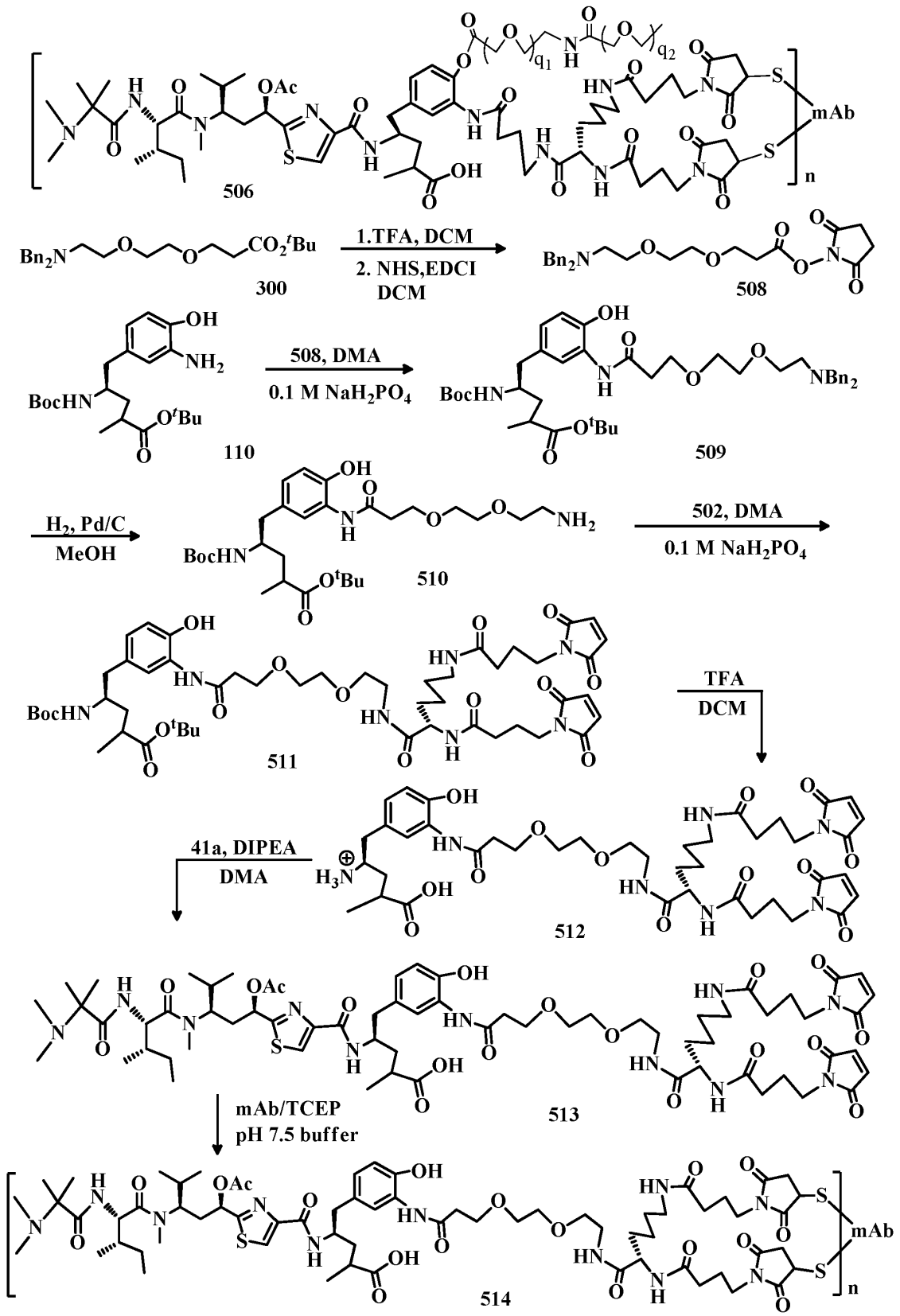

506
1.TFA, DCM
2. NHS,EDCI
DCM
300
508
508, DMA
0.1 M NaH2PO4
110
509
H2, Pd/C
MeOH
510
502, DMA
0.1 M NaH2PO4
511
TFA
DCM
41a, DIPEA
DMA
512
513
mAb/TCEP
pH 7.5 buffer
514

Fig. 42

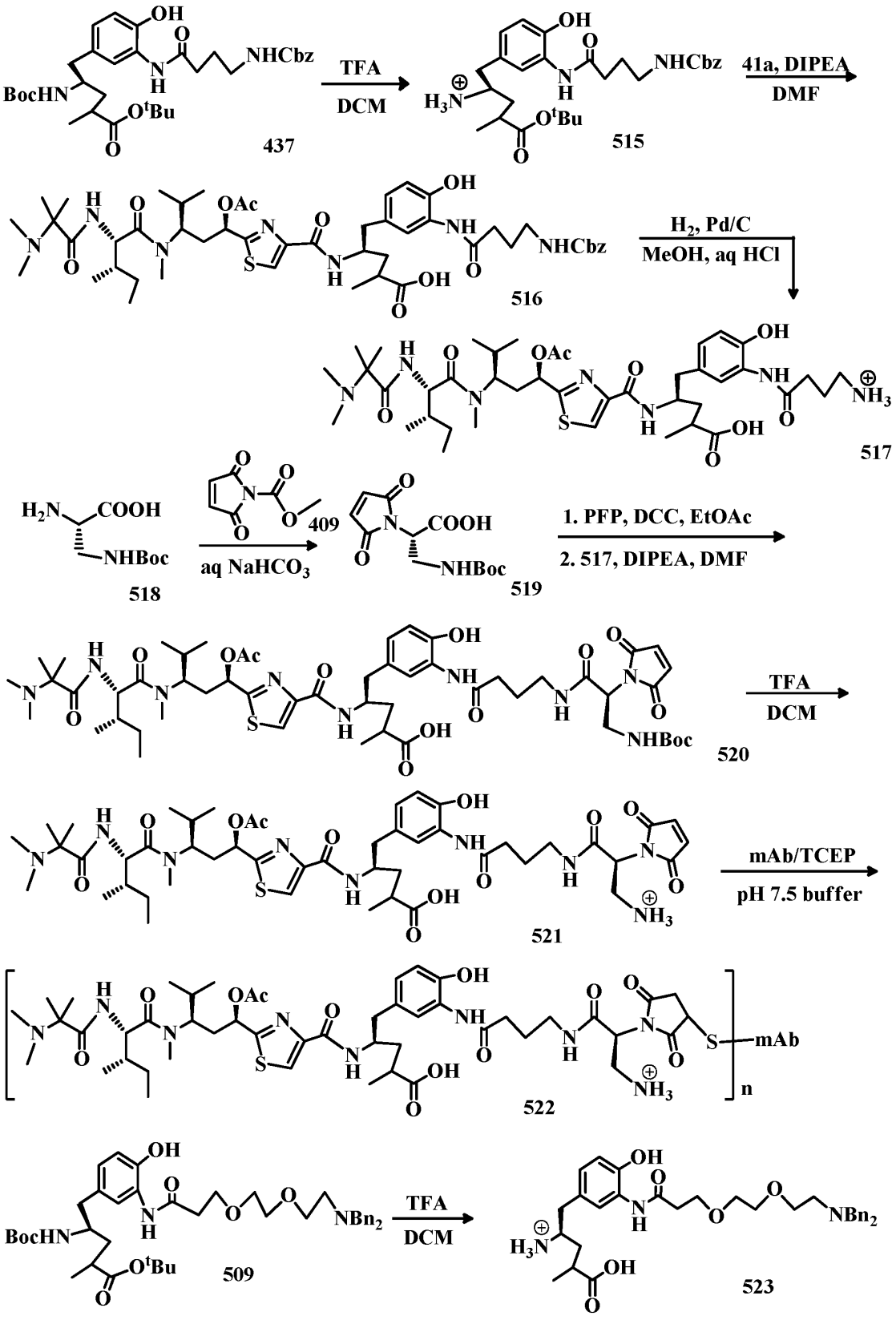

TFA
DCM
41a, DIPEA
DMF
437
515
516
H_2, Pd/C
MeOH, aq HCl
517
409
aq $NaHCO_3$
518
519
1. PFP, DCC, EtOAc
2. 517, DIPEA, DMF
520
521
mAb/TCEP
pH 7.5 buffer
522
509
523

Fig. 43

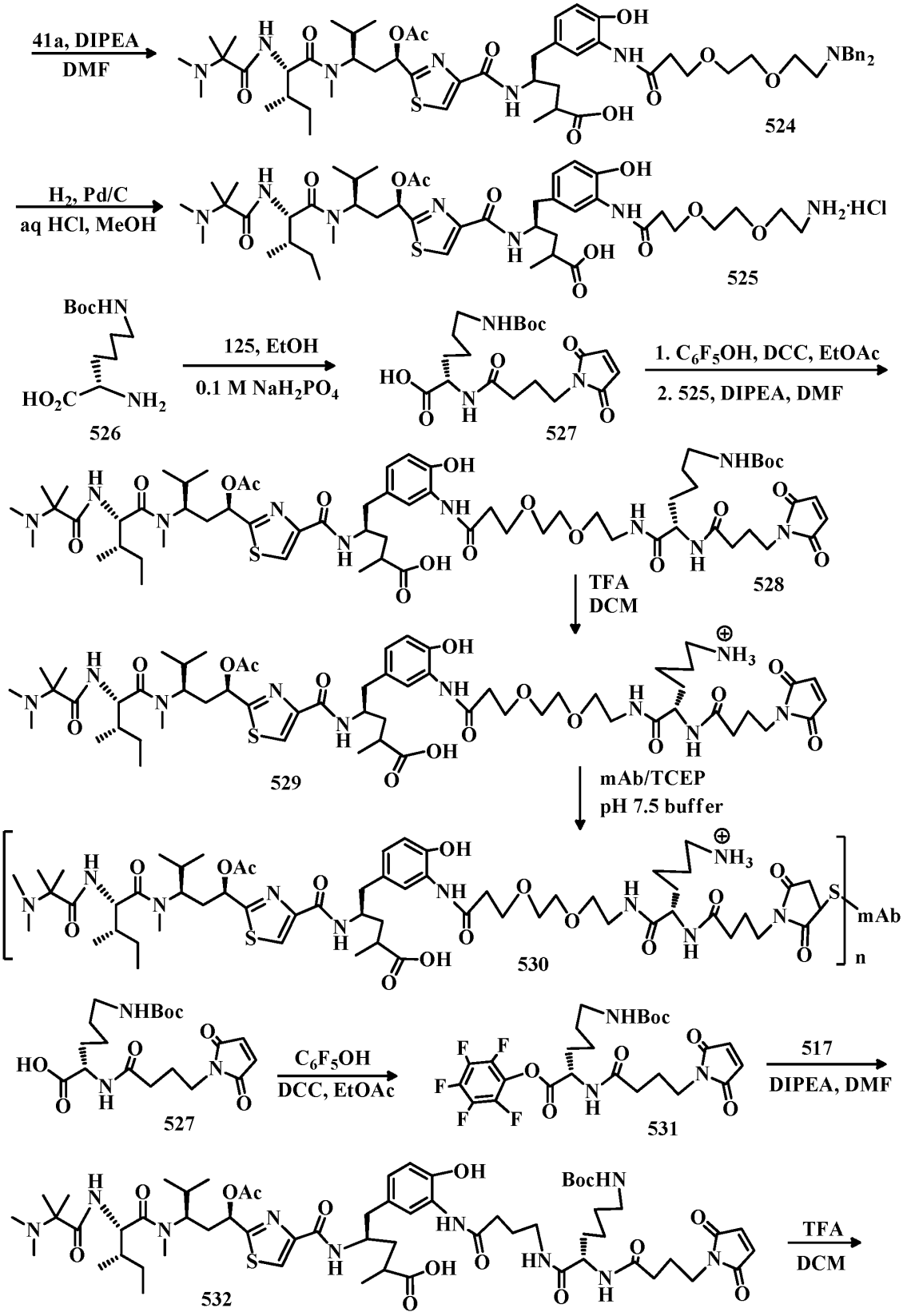

41a, DIPEA
DMF
524
H2, Pd/C
aq HCl, MeOH
525
BocHN
HO2C
NH2
526
125, EtOH
0.1 M NaH2PO4
527
1. C6F5OH, DCC, EtOAc
2. 525, DIPEA, DMF
528
TFA
DCM
529
mAb/TCEP
pH 7.5 buffer
530
mAb
n
C6F5OH
DCC, EtOAc
531
517
DIPEA, DMF
532

Fig. 44

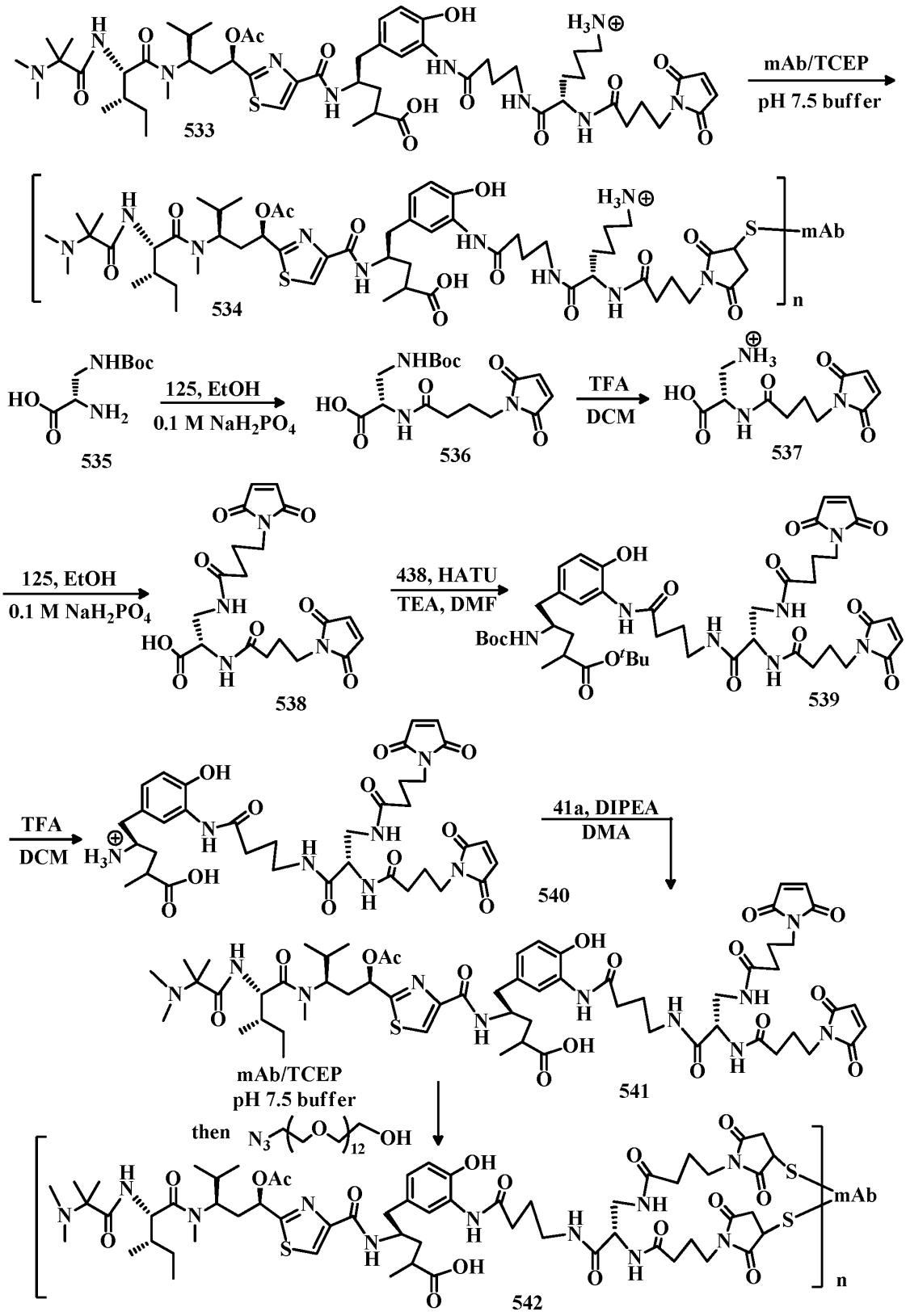

533
mAb/TCEP
pH 7.5 buffer
534
535
125, EtOH
0.1 M NaH2PO4
536
TFA
DCM
537
125, EtOH
0.1 M NaH2PO4
538
438, HATU
TEA, DMF
539
TFA
DCM
540
41a, DIPEA
DMA
mAb/TCEP
pH 7.5 buffer
then
541
542

Fig. 45

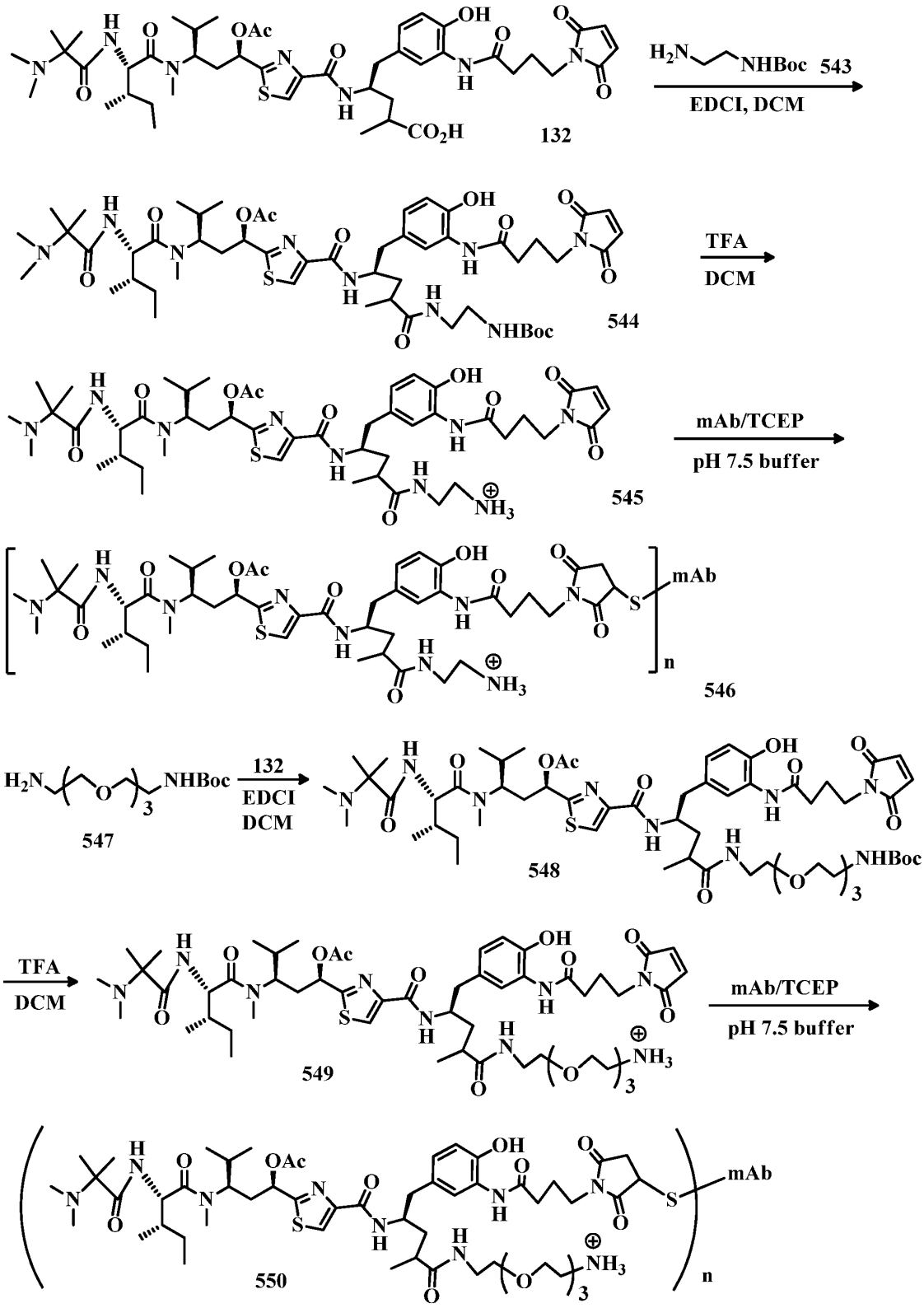

OAc
OH
CO_2H
132
H_2N
NHBoc
543
EDCI, DCM
544
TFA
DCM
545
mAb/TCEP
pH 7.5 buffer
mAb
n
546
547
132
EDCI
DCM
548
549
550

Fig. 46

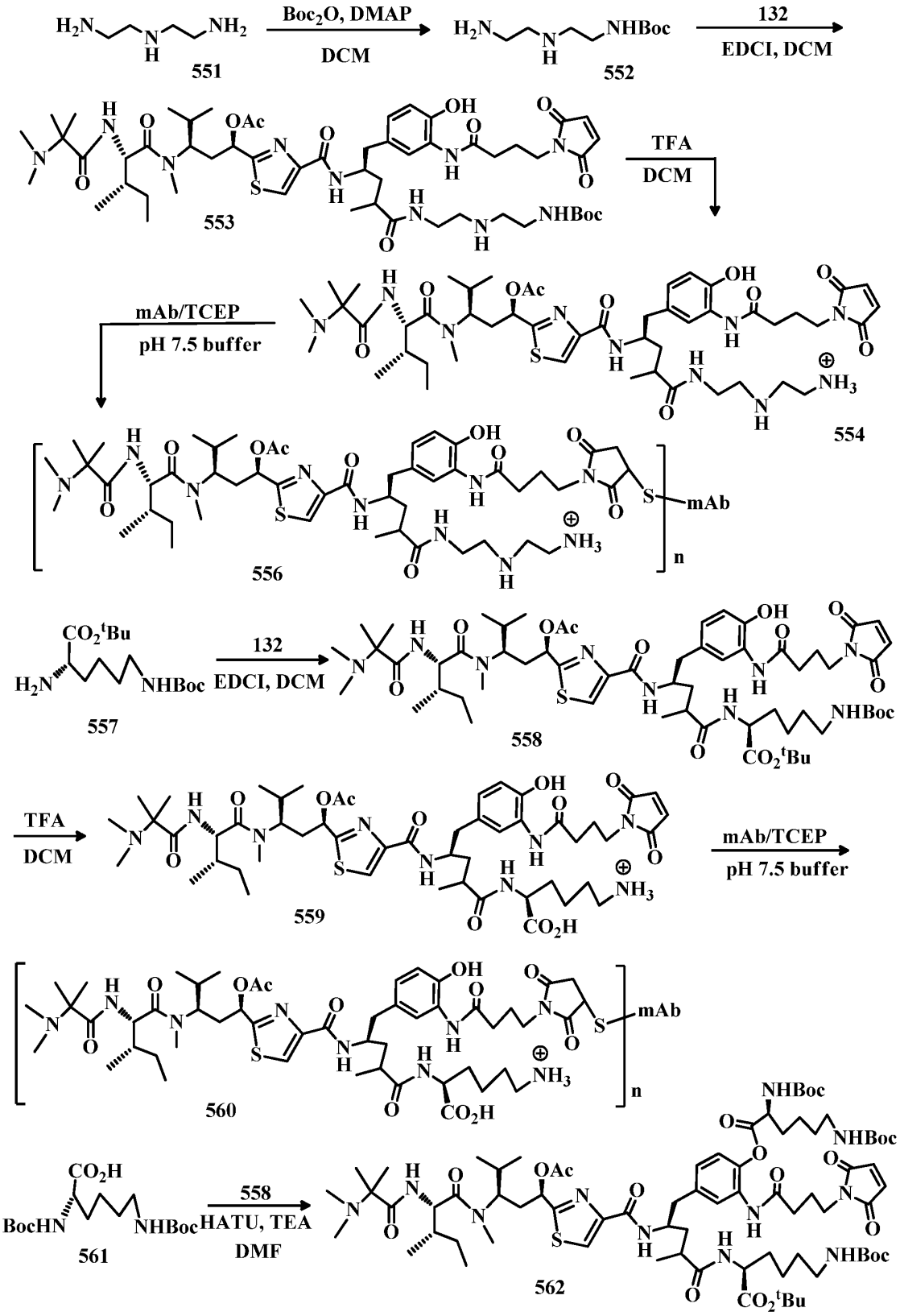

Boc2O, DMAP
DCM
132
EDCI, DCM
551
552
553
TFA
DCM
mAb/TCEP
pH 7.5 buffer
554
556
mAb
n
557
559
560
561
558
HATU, TEA
DMF
562

Fig. 47

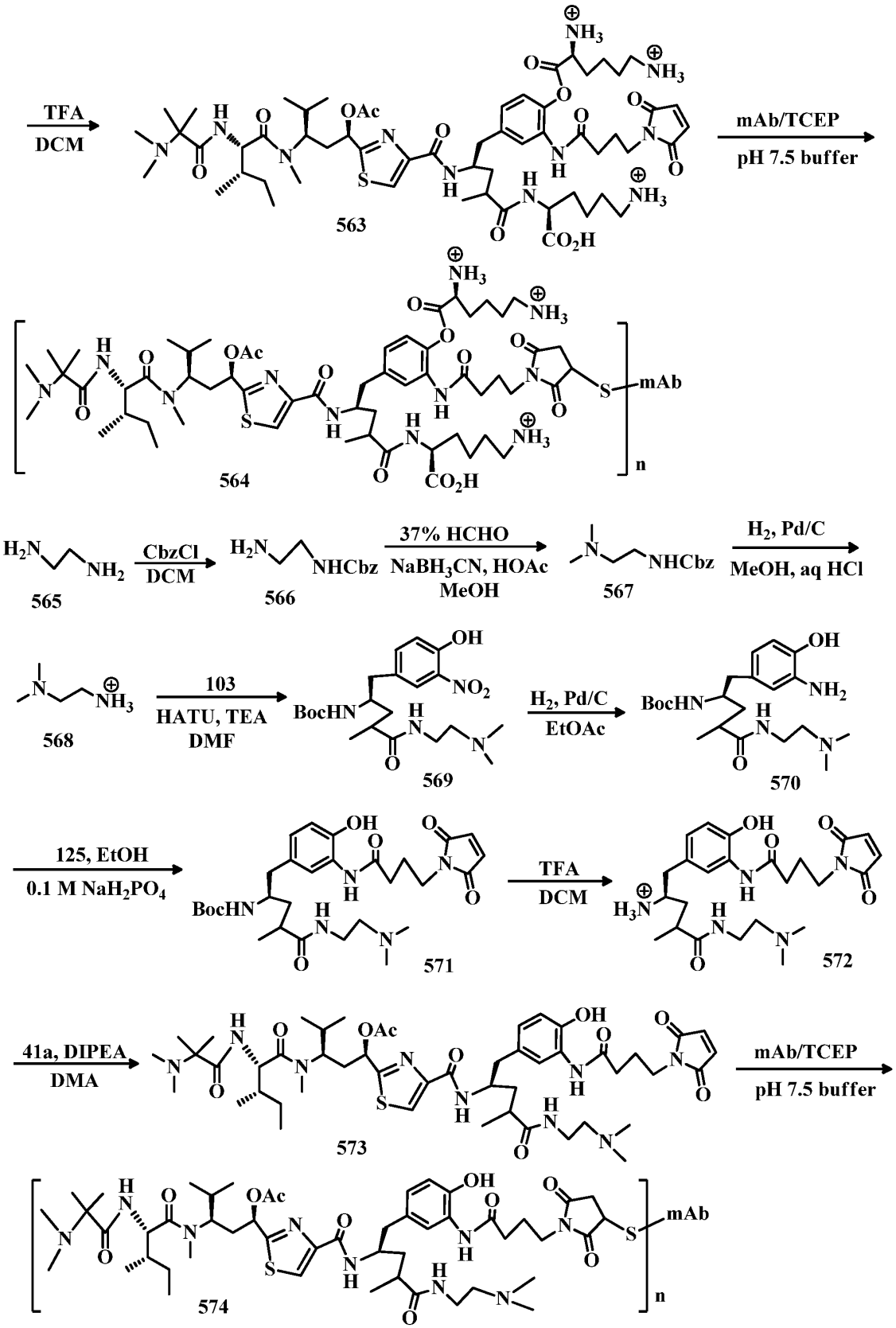

TFA
DCM
563
mAb/TCEP
pH 7.5 buffer
564
mAb
n
CbzCl
DCM
565
566
37% HCHO
NaBH3CN, HOAc
MeOH
567
H2, Pd/C
MeOH, aq HCl
568
103
HATU, TEA
DMF
569
H2, Pd/C
EtOAc
570
125, EtOH
0.1 M NaH2PO4
571
TFA
DCM
572
41a, DIPEA
DMA
573
mAb/TCEP
pH 7.5 buffer
574
mAb
n

Fig. 48.

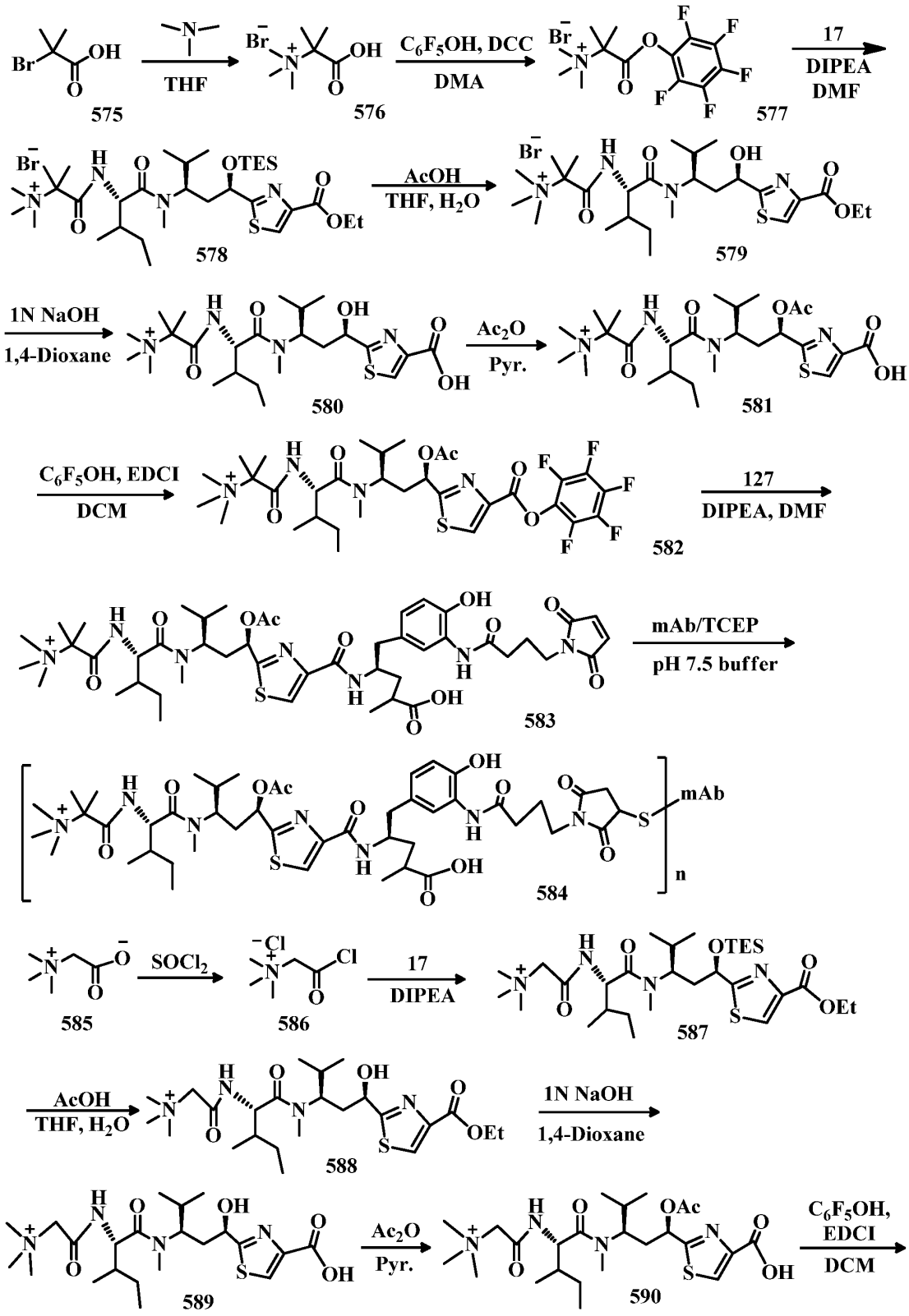

THF
C6F5OH, DCC
DMA
17
DIPEA
DMF
AcOH
THF, H2O
1N NaOH
1,4-Dioxane
Ac2O
Pyr.
C6F5OH, EDCI
DCM
127
DIPEA, DMF
mAb/TCEP
pH 7.5 buffer
SOCl2
17
DIPEA
AcOH
THF, H2O
1N NaOH
1,4-Dioxane
Ac2O
Pyr.
C6F5OH,
EDCI
DCM

Fig. 49.

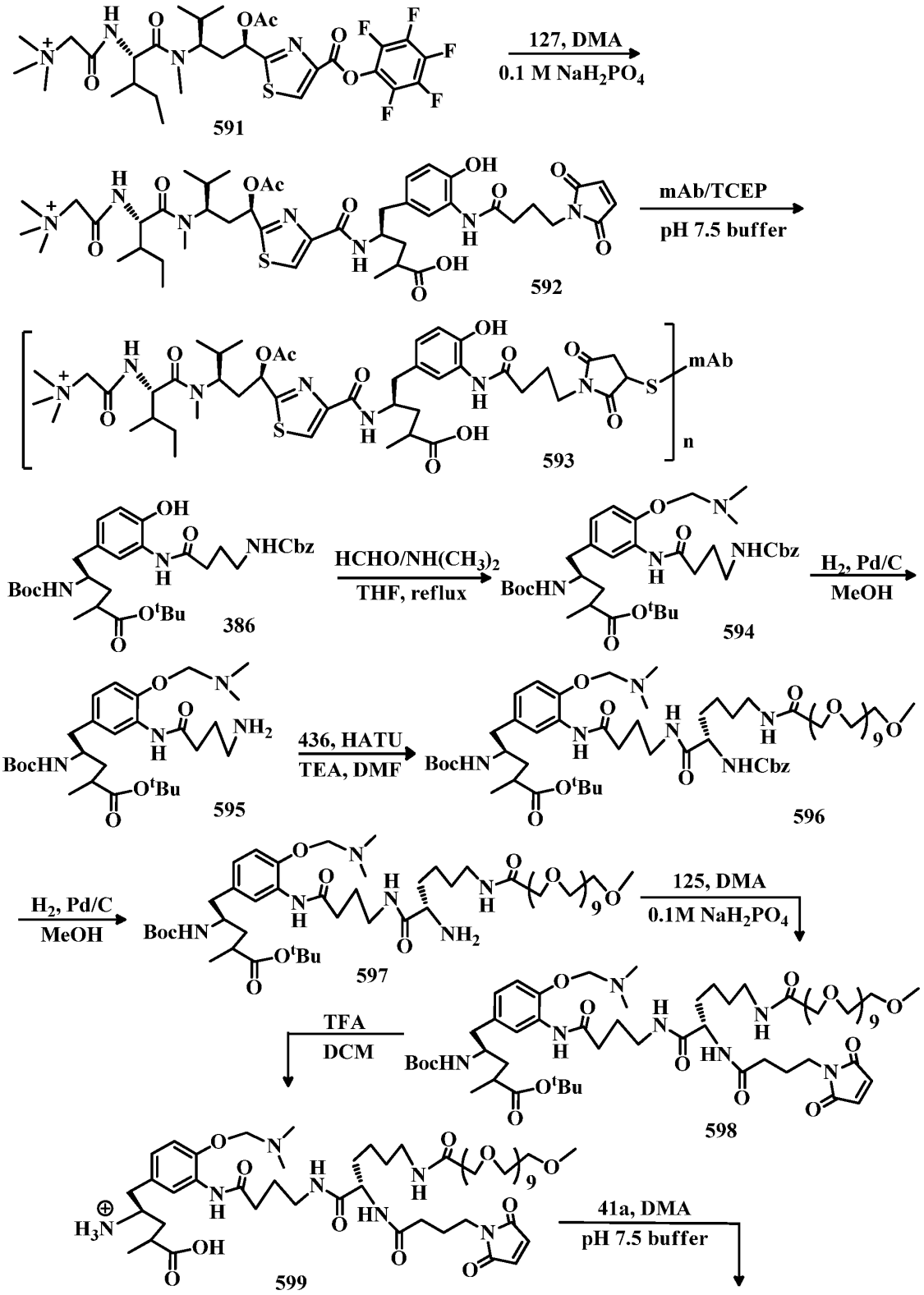

127, DMA
0.1 M NaH2PO4
591
mAb/TCEP
pH 7.5 buffer
592
593
mAb
n
386
HCHO/NH(CH3)2
THF, reflux
594
H2, Pd/C
MeOH
595
436, HATU
TEA, DMF
596
H2, Pd/C
MeOH
597
125, DMA
0.1M NaH2PO4
TFA
DCM
598
599
41a, DMA
pH 7.5 buffer

Fig. 50.

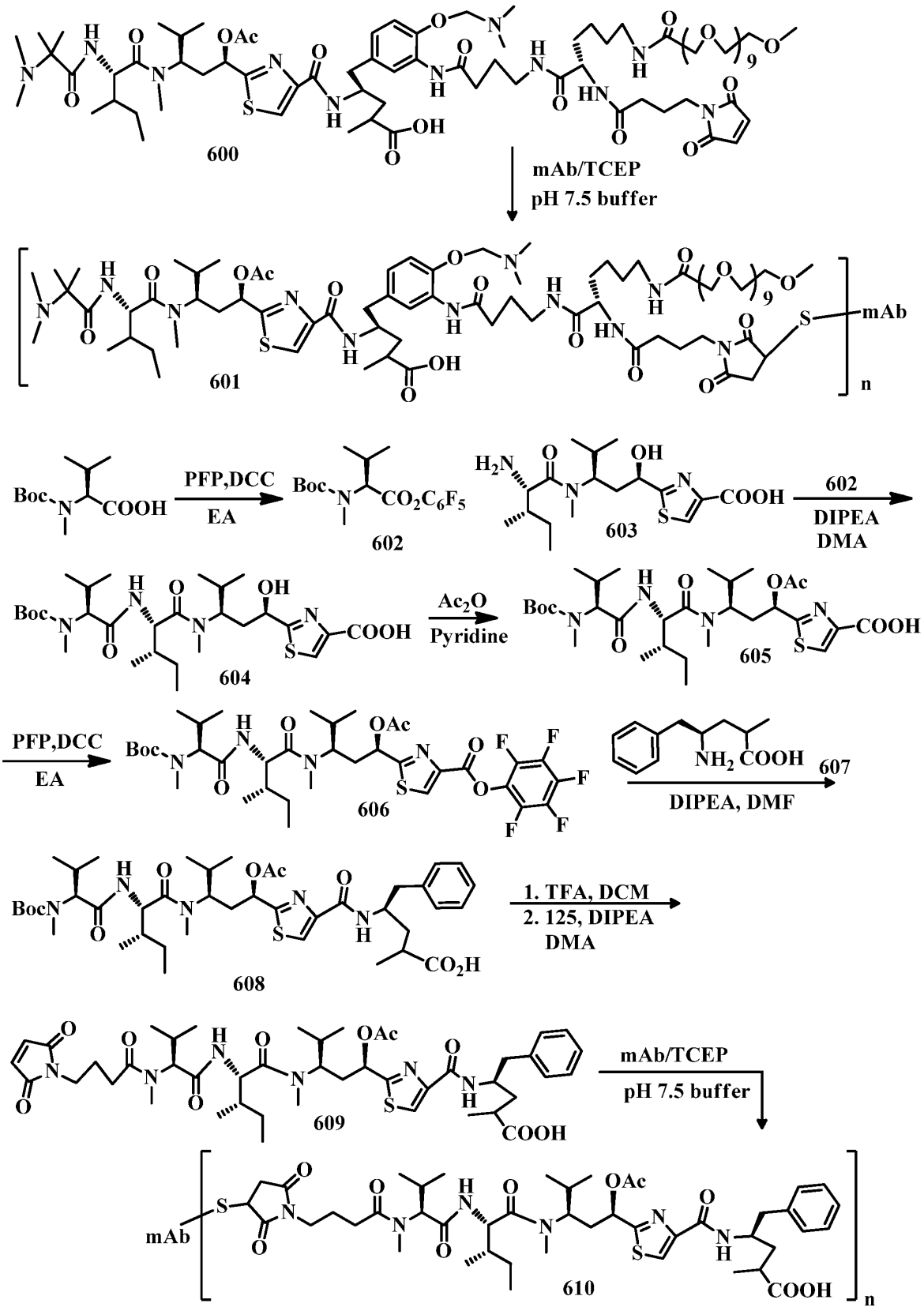

600
mAb/TCEP
pH 7.5 buffer
601
PFP,DCC
EA
602
603
DIPEA
DMA
604
Ac2O
Pyridine
605
PFP,DCC
EA
606
607
DIPEA, DMF
608
1. TFA, DCM
2. 125, DIPEA
DMA
609
mAb/TCEP
pH 7.5 buffer
610

Fig. 51

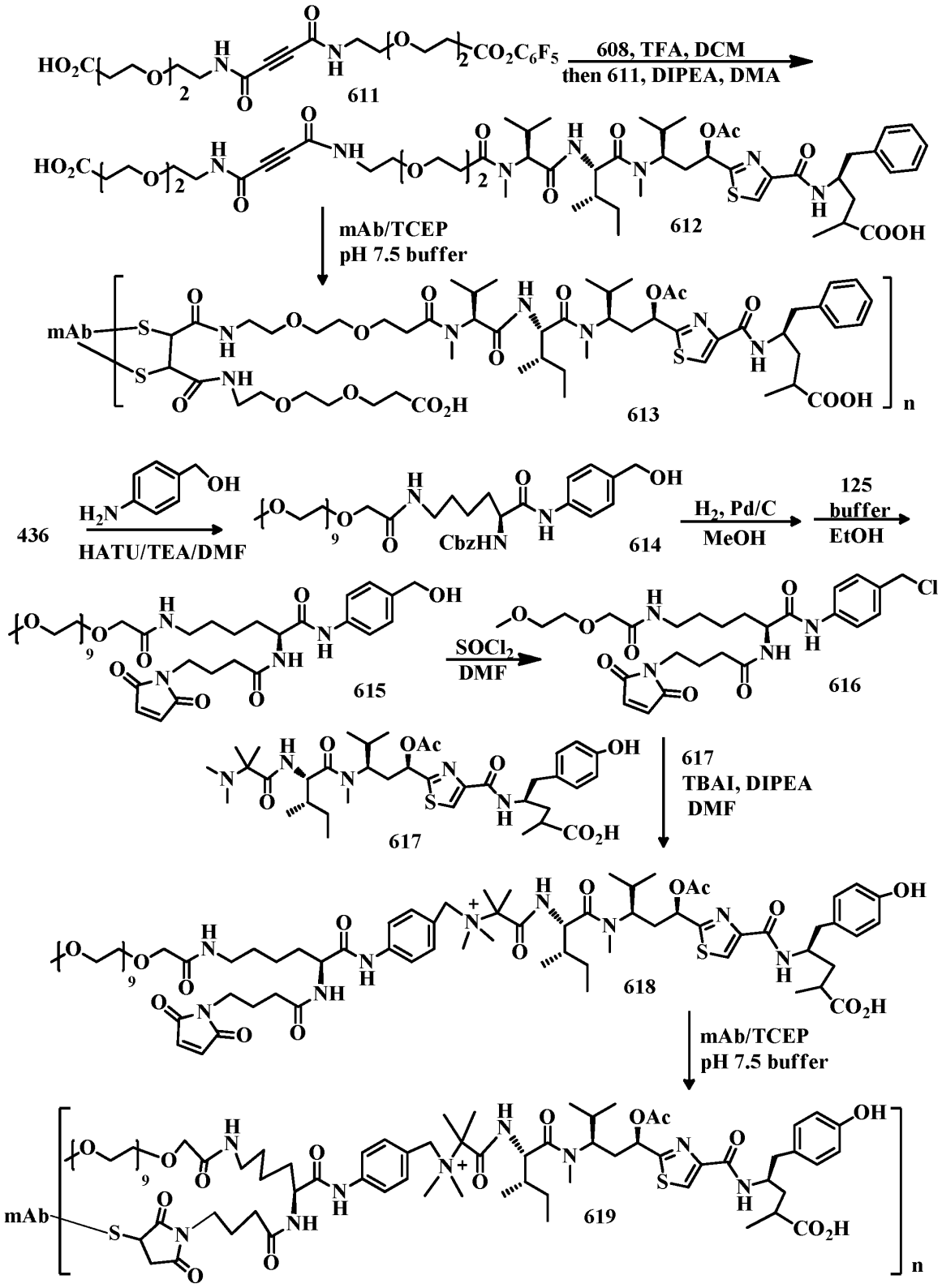

608, TFA, DCM
then 611, DIPEA, DMA
611
612
mAb/TCEP
pH 7.5 buffer
613
436
HATU/TEA/DMF
614
H2, Pd/C
MeOH
125
buffer
EtOH
615
SOCl2
DMF
616
617
TBAI, DIPEA
DMF
618
mAb/TCEP
pH 7.5 buffer
619

Fig. 52

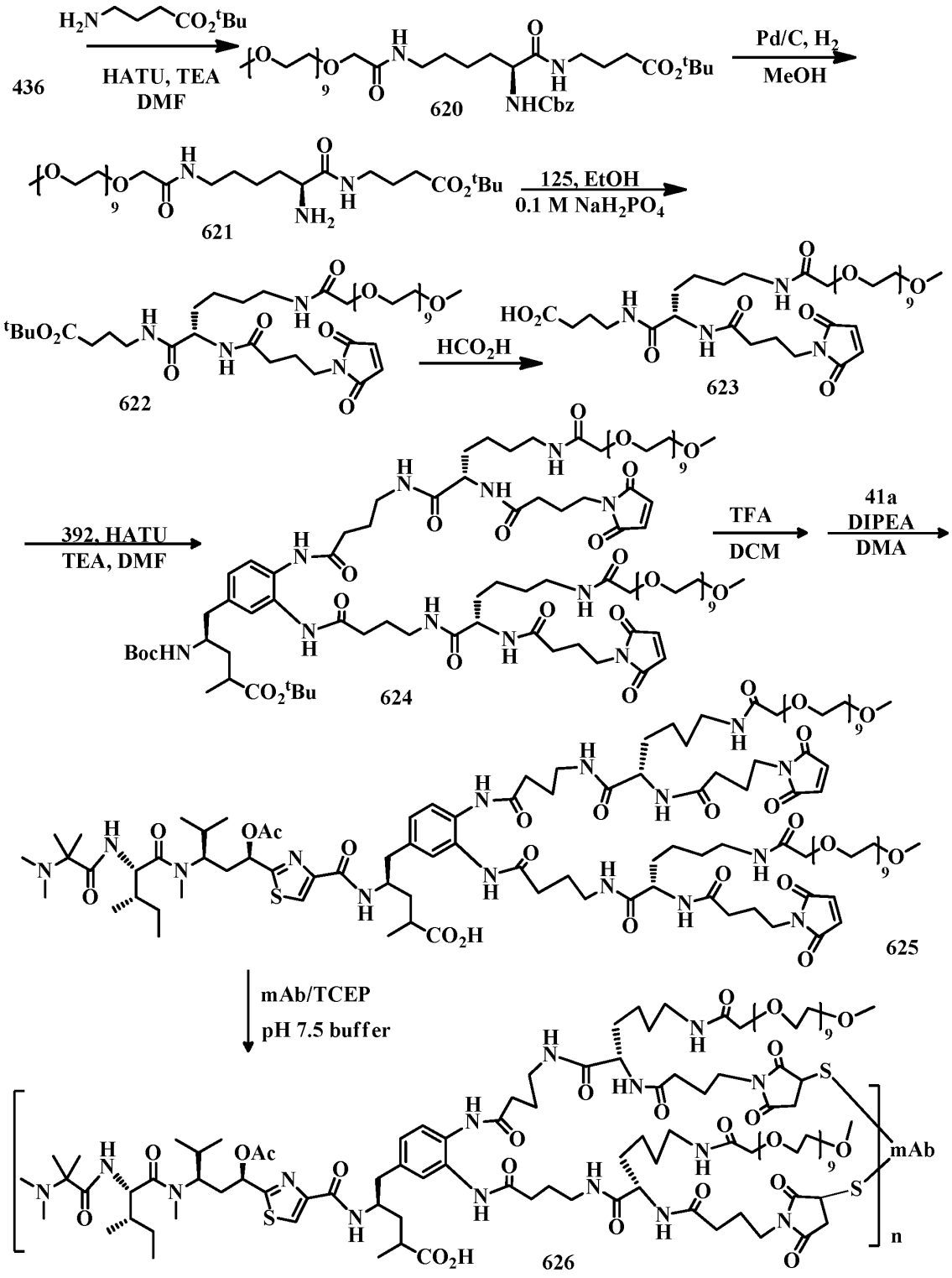

436
HATU, TEA
DMF
620
NHCbz
Pd/C, H2
MeOH
621
125, EtOH
0.1 M NaH2PO4
622
HCO2H
623
392, HATU
TEA, DMF
624
BocHN
TFA
DCM
41a
DIPEA
DMA
625
mAb/TCEP
pH 7.5 buffer
626
mAb
n

Fig. 53

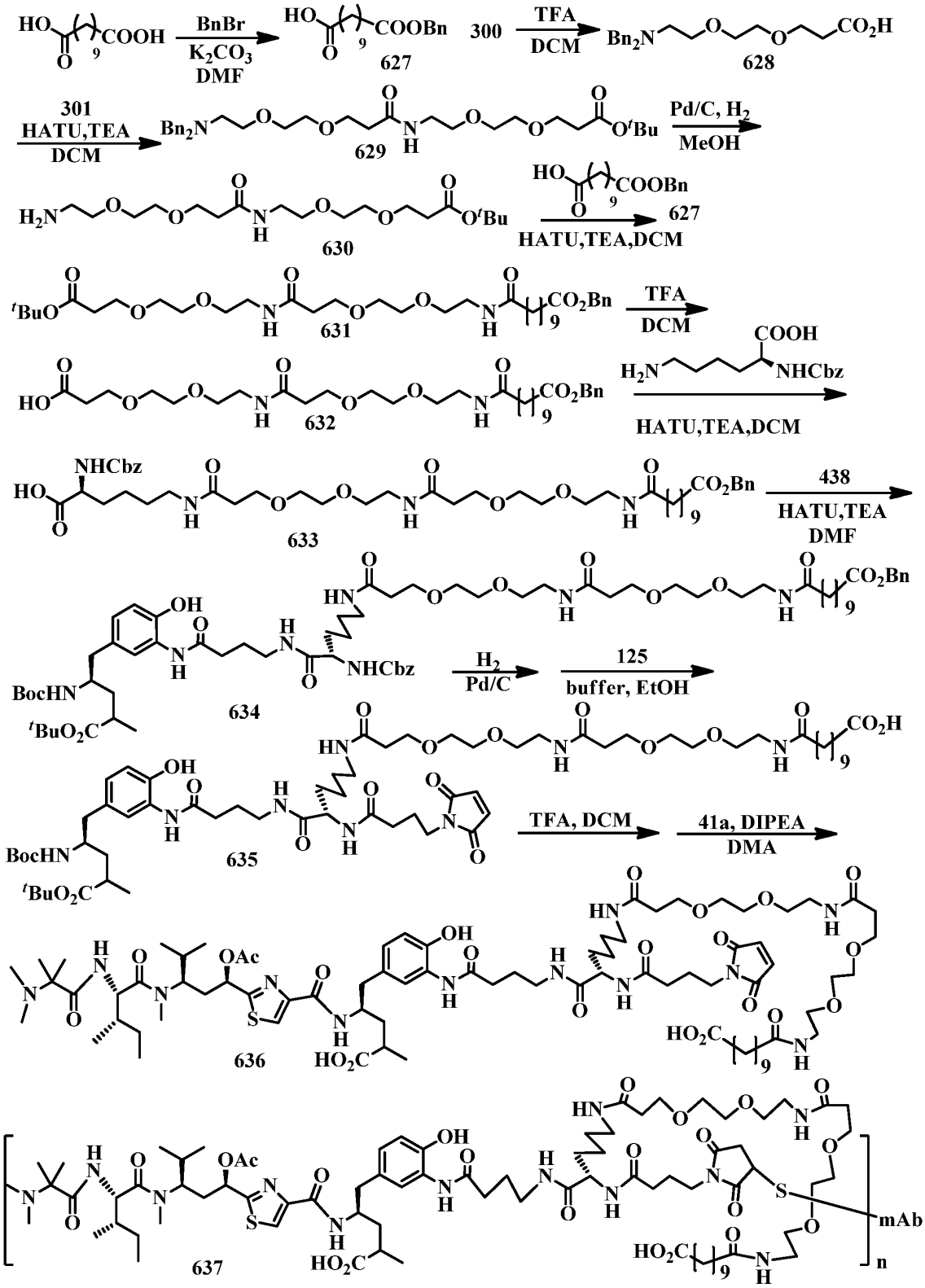

BnBr
K2CO3
DMF
627
300
TFA
DCM
628
301
HATU,TEA
DCM
629
Pd/C, H2
MeOH
630
HATU,TEA,DCM
631
TFA
DCM
632
HATU,TEA,DCM
633
438
HATU,TEA
DMF
634
H2
Pd/C
125
buffer, EtOH
635
TFA, DCM
41a, DIPEA
DMA
636
637
mAb

Fig. 54

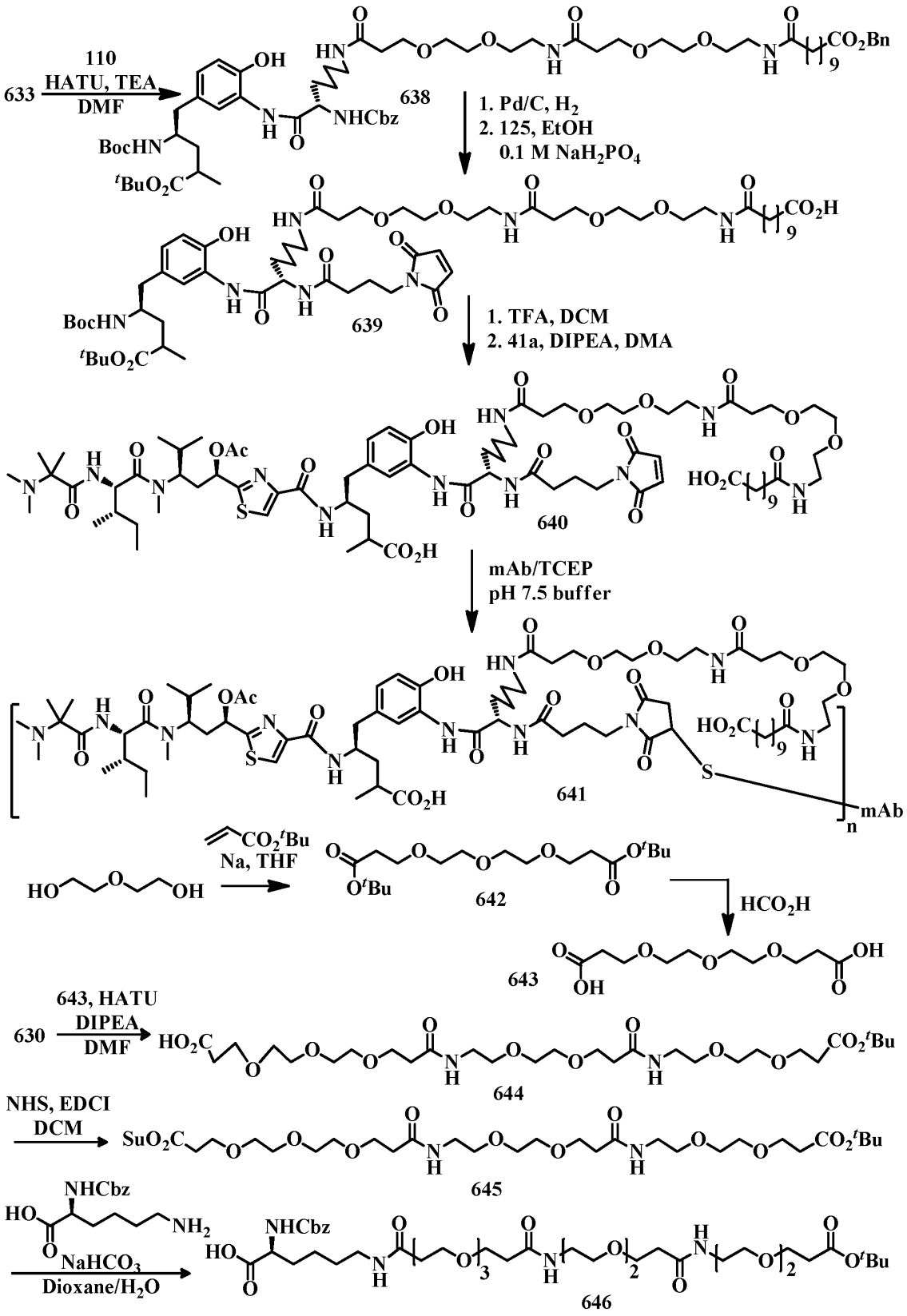

110
HATU, TEA
DMF
633
638
1. Pd/C, H2
2. 125, EtOH
0.1 M NaH2PO4
639
1. TFA, DCM
2. 41a, DIPEA, DMA
640
mAb/TCEP
pH 7.5 buffer
641
mAb
Na, THF
642
HCO2H
643
643, HATU
DIPEA
DMF
630
644
NHS, EDCI
DCM
645
NaHCO3
Dioxane/H2O
646

Fig. 55

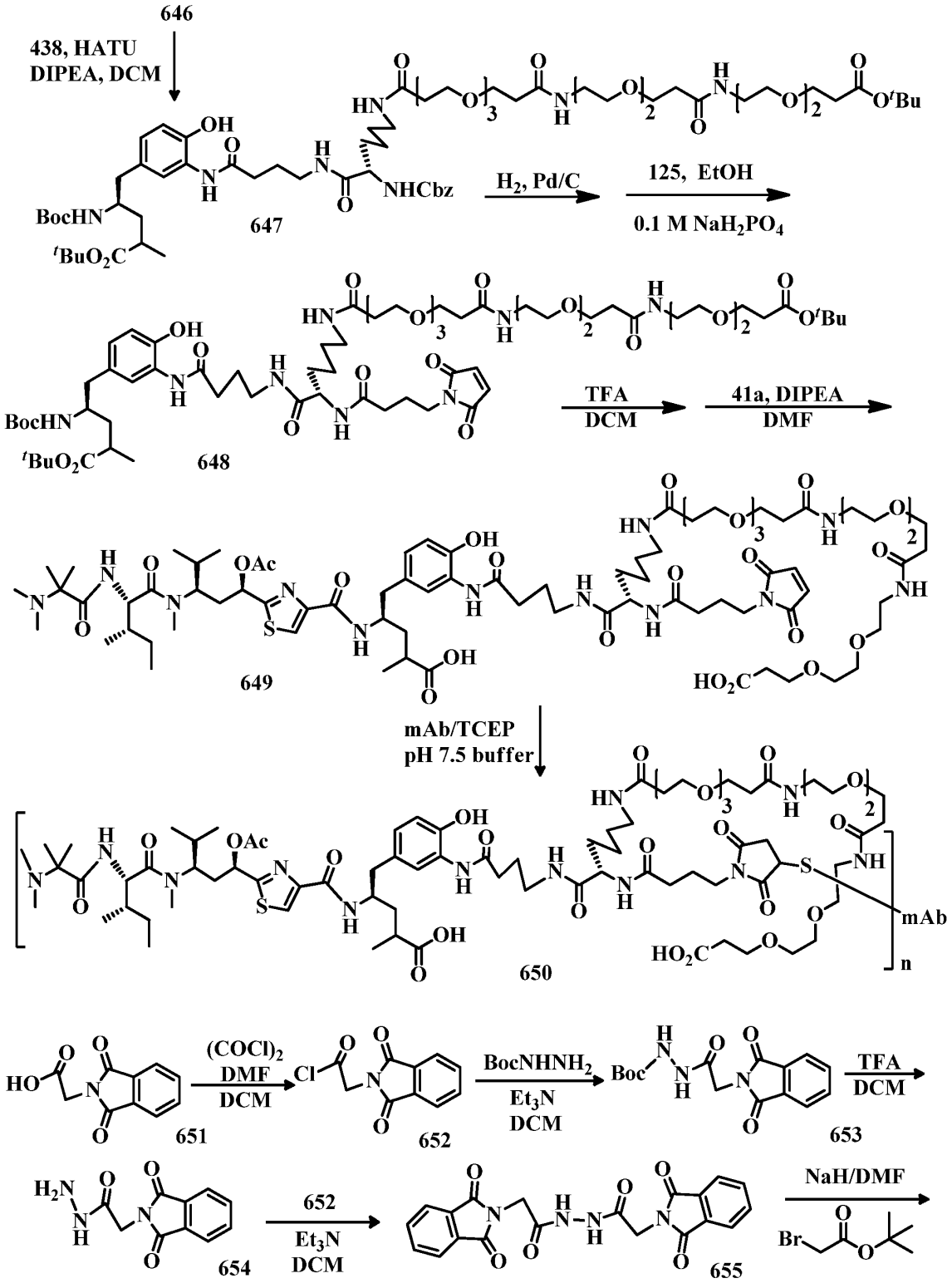

646
438, HATU
DIPEA, DCM
647
H2, Pd/C
125, EtOH
0.1 M NaH2PO4
648
TFA
DCM
41a, DIPEA
DMF
649
mAb/TCEP
pH 7.5 buffer
650
mAb
n
651
(COCl)2
DMF
DCM
652
BocNHNH2
Et3N
DCM
653
TFA
DCM
654
652
Et3N
DCM
655
NaH/DMF

Fig. 56

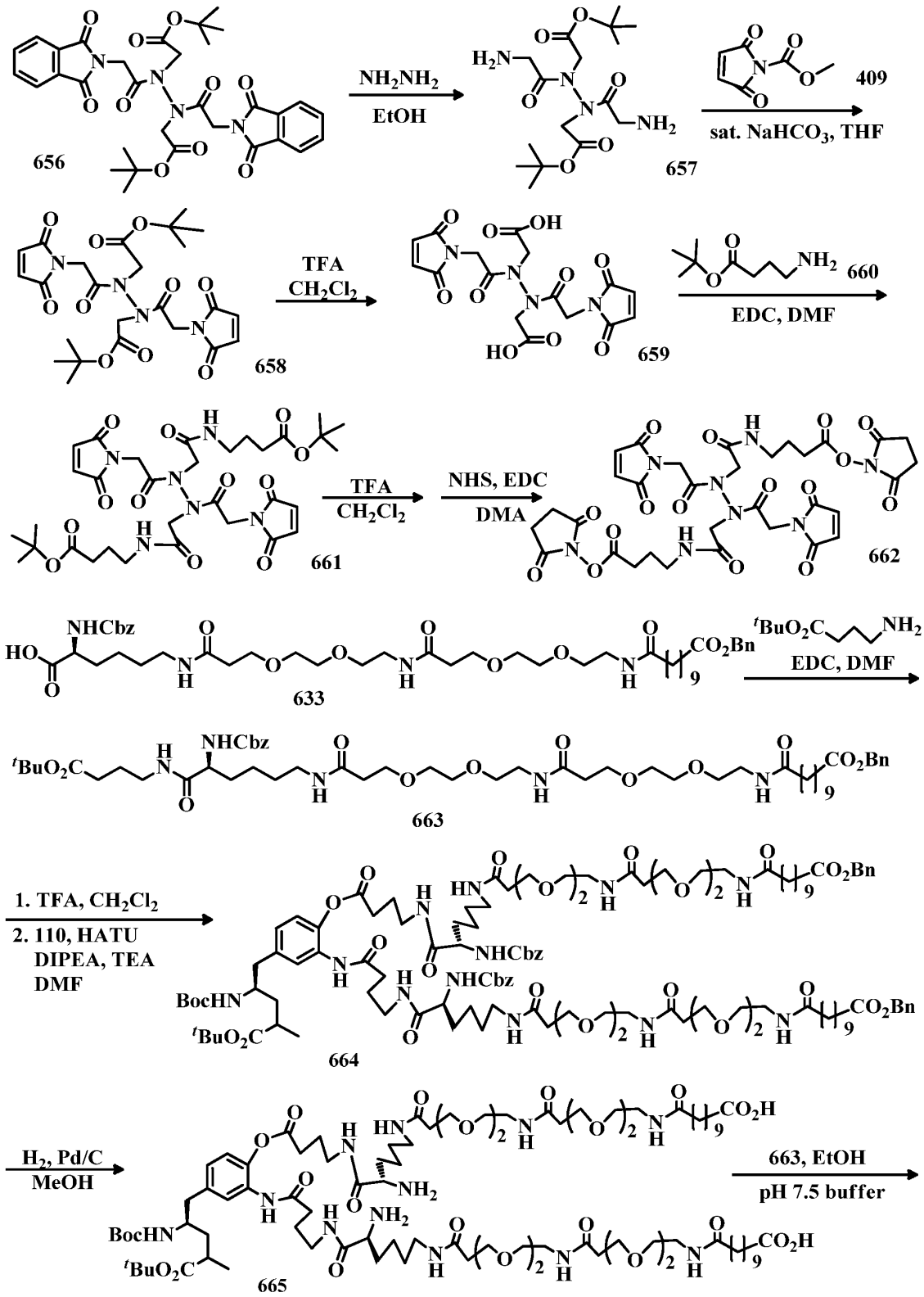

656
NH_2NH_2
EtOH
657
409
sat. $NaHCO_3$, THF
658
TFA
CH_2Cl_2
659
660
EDC, DMF
661
TFA
CH_2Cl_2
NHS, EDC
DMA
662
633
$^tBuO_2C$
NH_2
EDC, DMF
663
1. TFA, CH_2Cl_2
2. 110, HATU
DIPEA, TEA
DMF
664
H_2, Pd/C
MeOH
665
663, EtOH
pH 7.5 buffer

Fig. 57

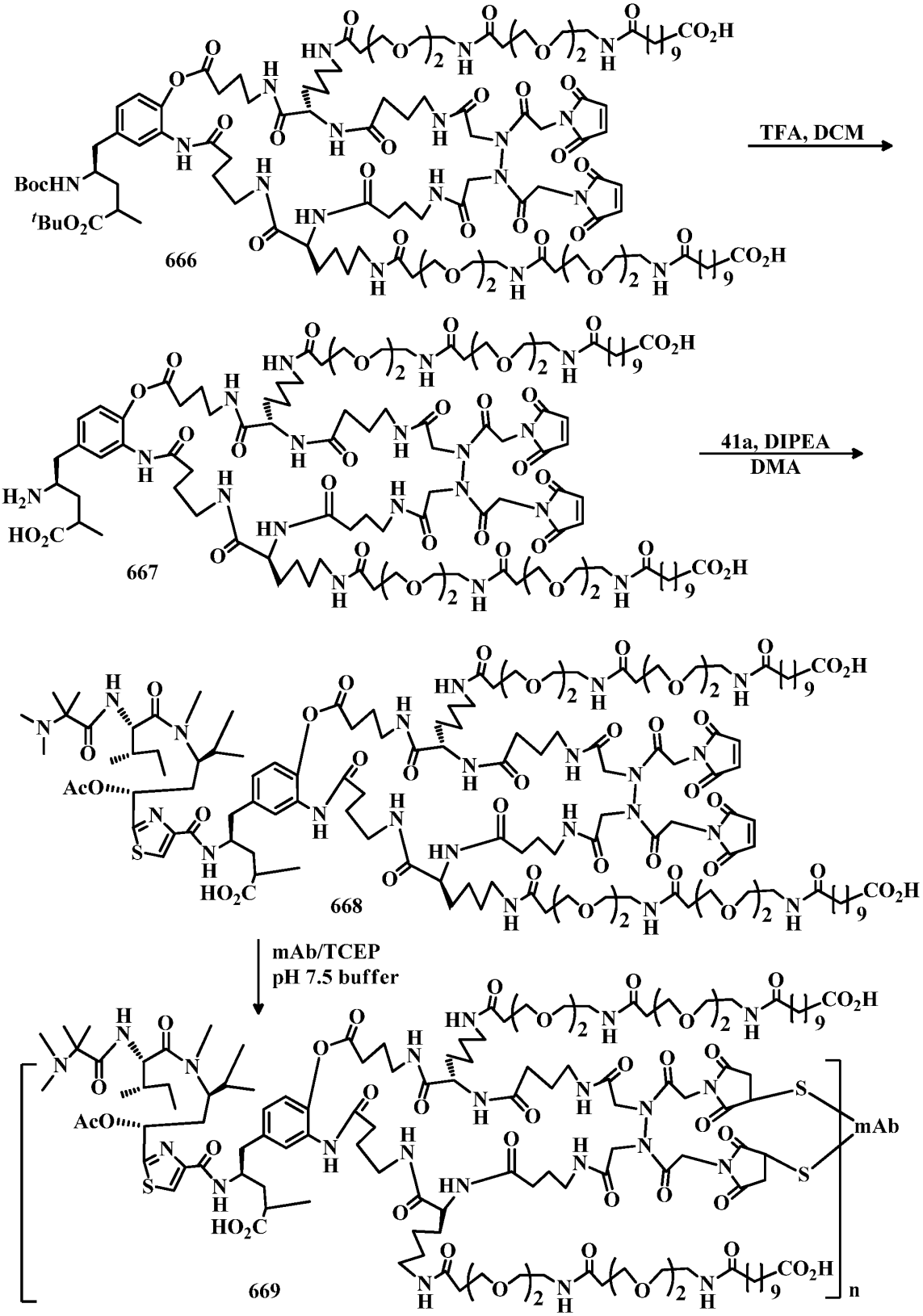


Fig. 58

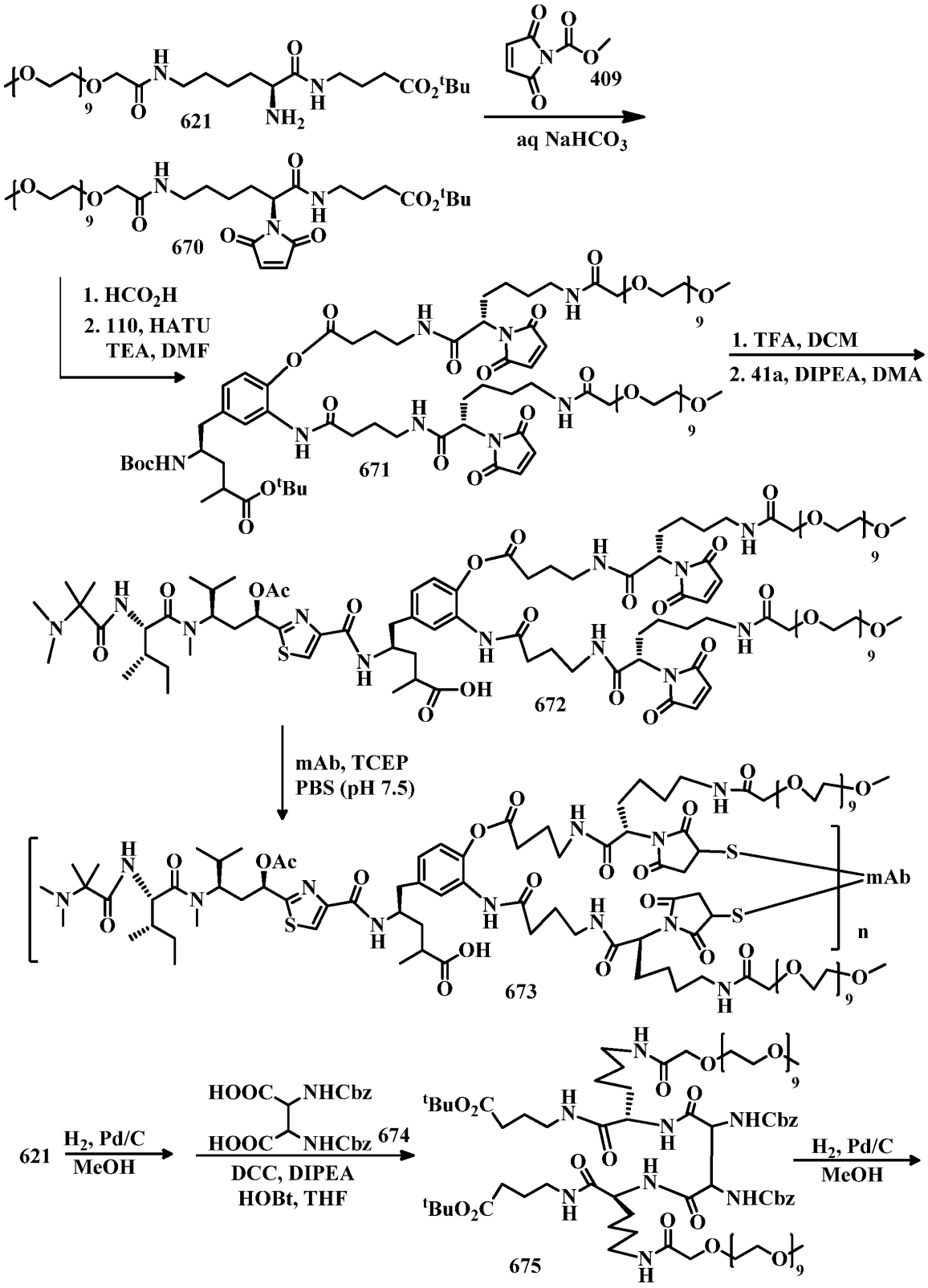

621
409
aq NaHCO3
670
1. HCO2H
2. 110, HATU
TEA, DMF
671
1. TFA, DCM
2. 41a, DIPEA, DMA
672
mAb, TCEP
PBS (pH 7.5)
673
mAb
n
621
H2, Pd/C
MeOH
HOOC NHCbz
HOOC NHCbz
674
DCC, DIPEA
HOBt, THF
675
H2, Pd/C
MeOH

Fig. 59

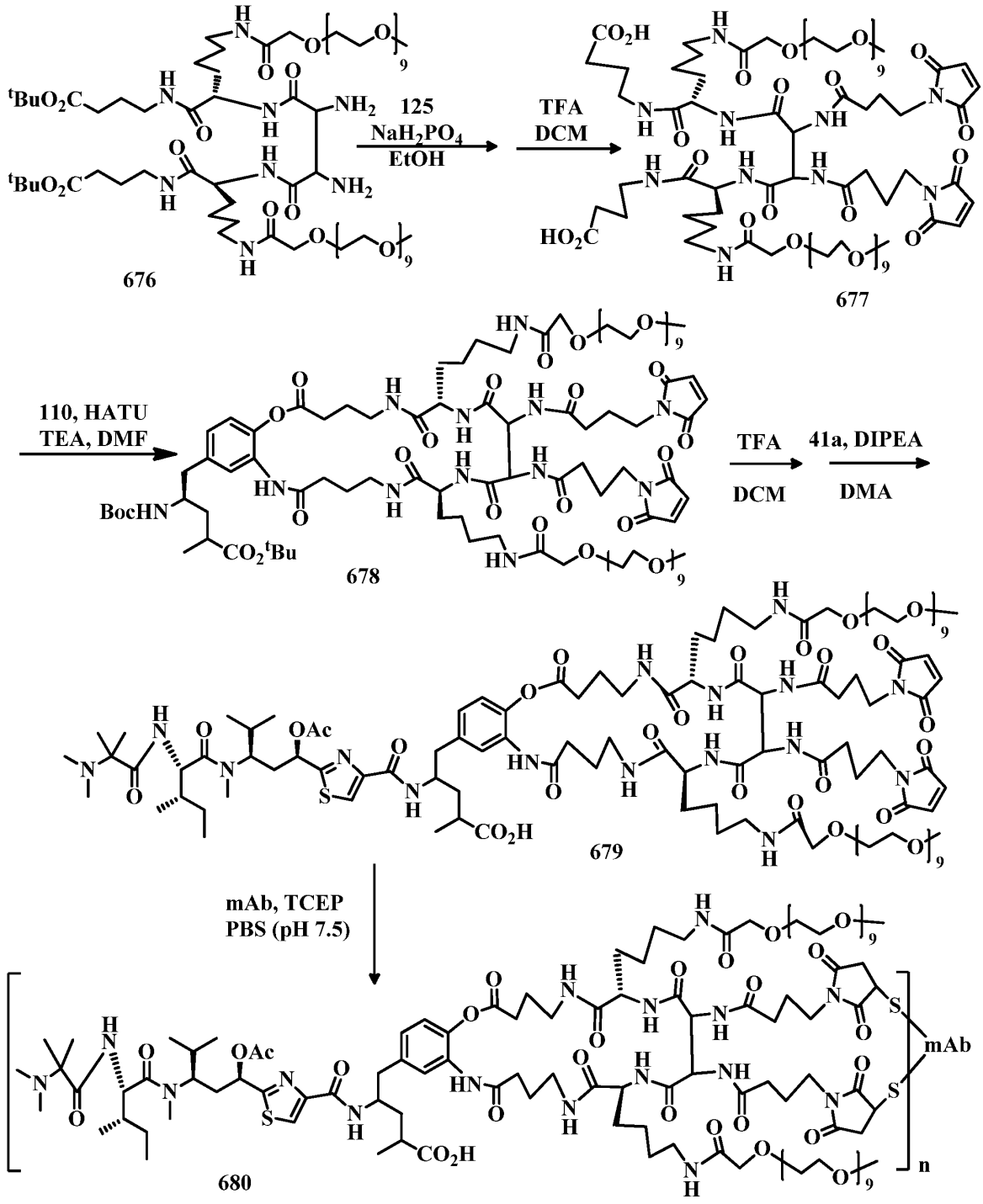

125
NaH_2PO_4
EtOH
TFA
DCM
676
677
110, HATU
TEA, DMF
678
TFA
DCM
41a, DIPEA
DMA
679
mAb, TCEP
PBS (pH 7.5)
680
mAb
n

Fig. 60

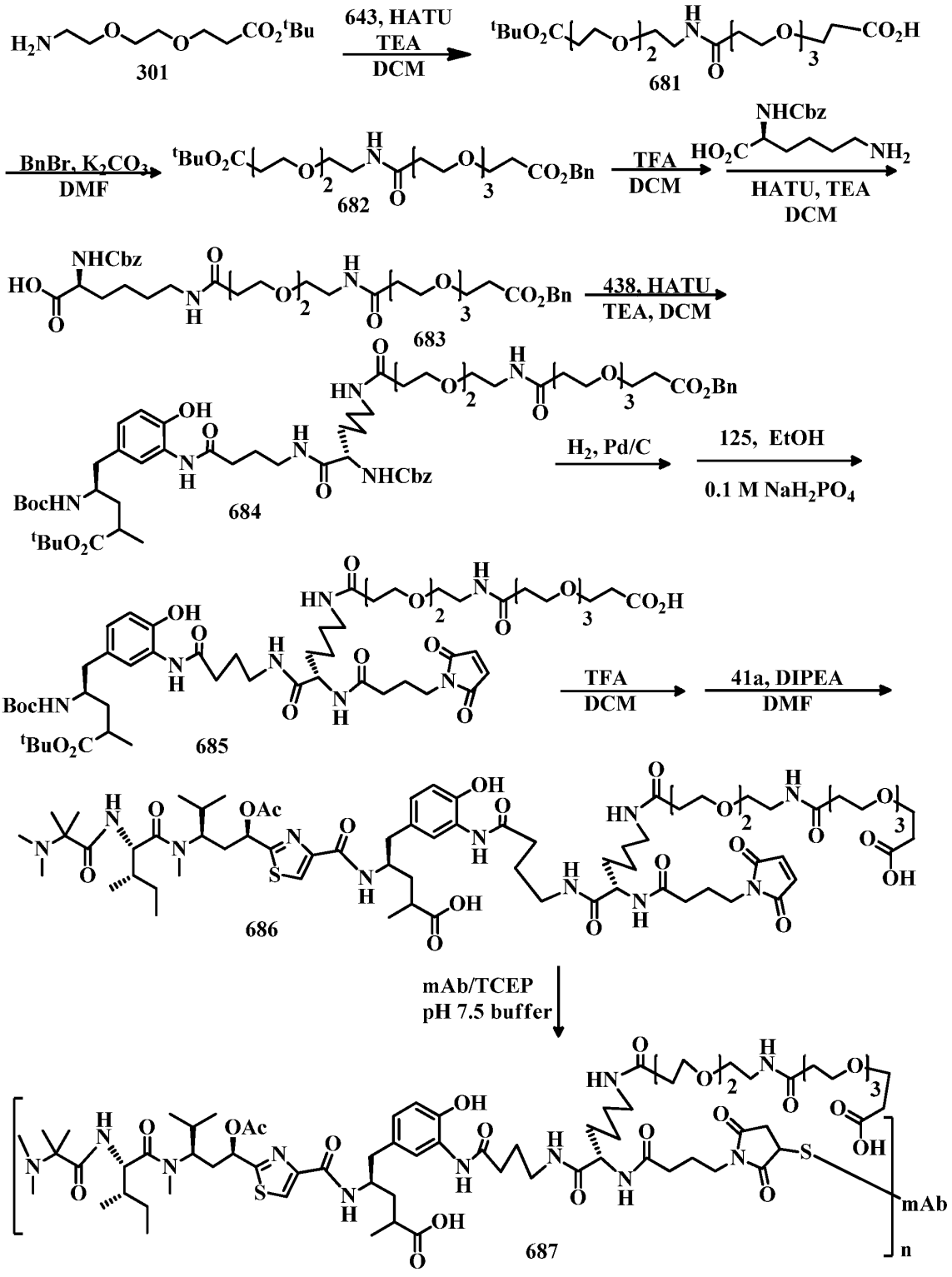

643, HATU
TEA
DCM
301
681
BnBr, K2CO3
DMF
682
TFA
DCM
HATU, TEA
DCM
438, HATU
TEA, DCM
683
H2, Pd/C
125, EtOH
0.1 M NaH2PO4
684
TFA
DCM
41a, DIPEA
DMF
685
686
mAb/TCEP
pH 7.5 buffer
687
mAb
n

Fig. 61

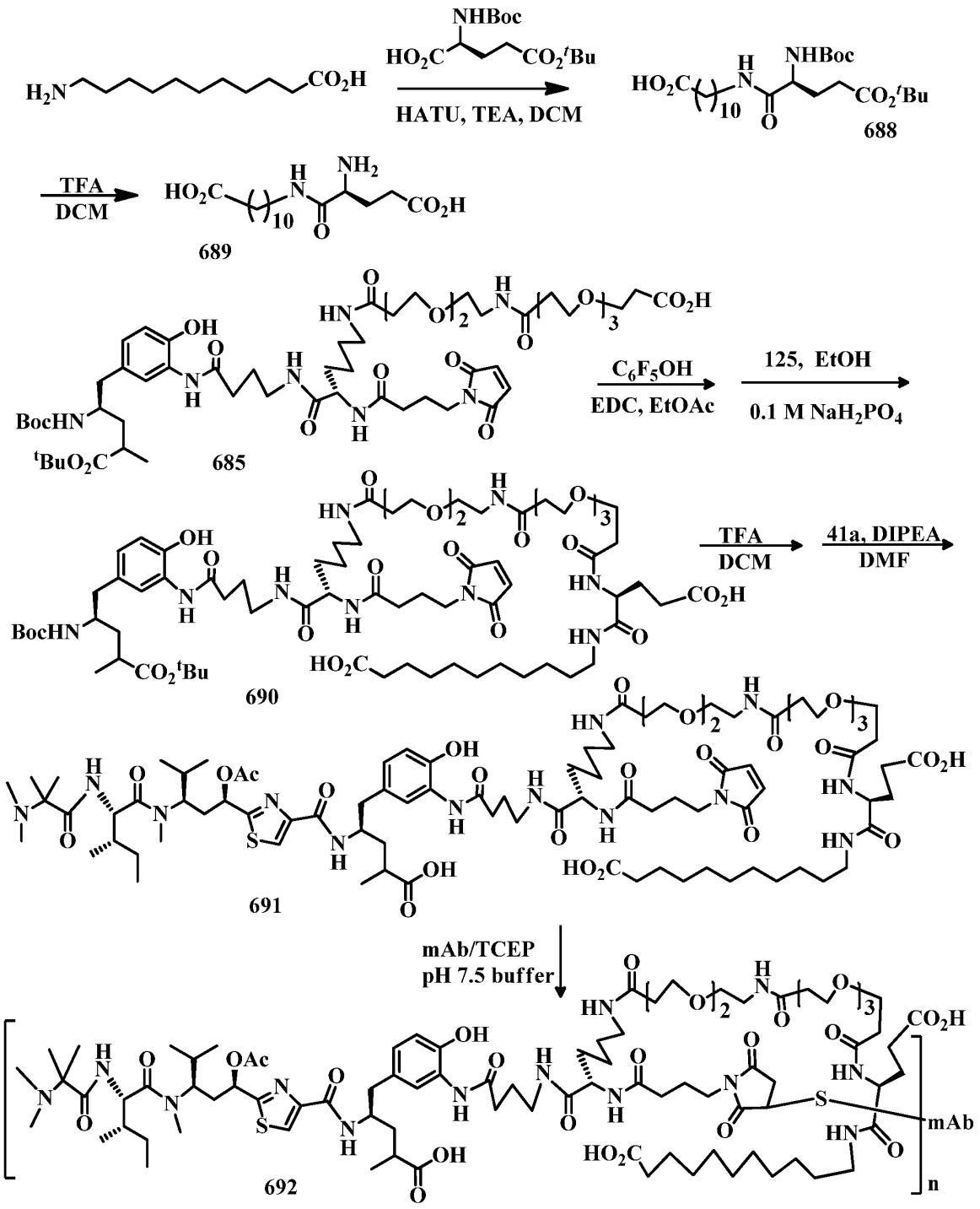

HATU, TEA, DCM
688
TFA
DCM
689
685
C6F5OH
EDC, EtOAc
125, EtOH
0.1 M NaH2PO4
690
TFA
DCM
41a, DIPEA
DMF
691
mAb/TCEP
pH 7.5 buffer
692
mAb
n

Fig. 62

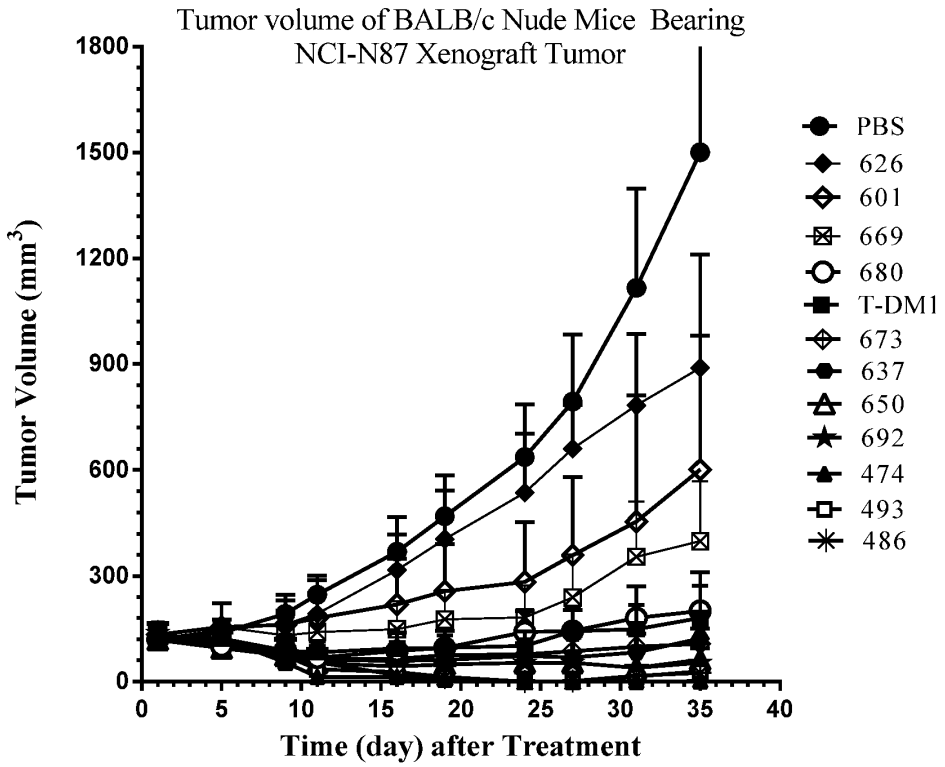

Tumor volume of BALB/c Nude Mice Bearing
NCI-N87 Xenograft Tumor
Tumor Volume (mm3)
1800
1500
1200
900
600
300
0
0
5
10
15
20
25
30
35
40
Time (day) after Treatment
PBS
626
601
669
680
T-DM1
673
637
650
692
474
493
486

Fig. 63.

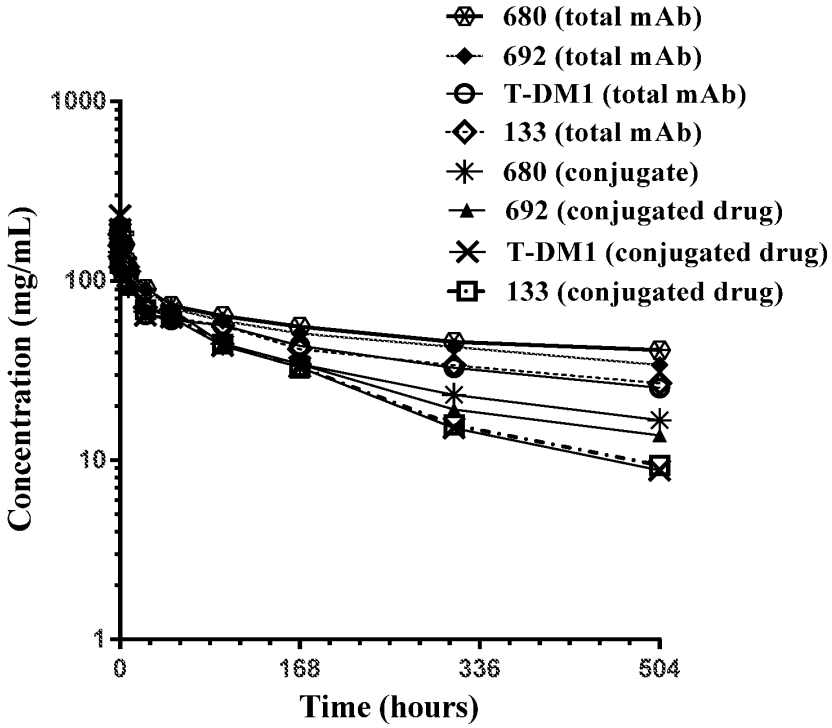

680 (total mAb)
692 (total mAb)
T-DM1 (total mAb)
133 (total mAb)
680 (conjugate)
692 (conjugated drug)
T-DM1 (conjugated drug)
133 (conjugated drug)
Concentration (mg/mL)
1000
100
10
1
0
168
336
504
Time (hours)

Fig. 64