FIG.1

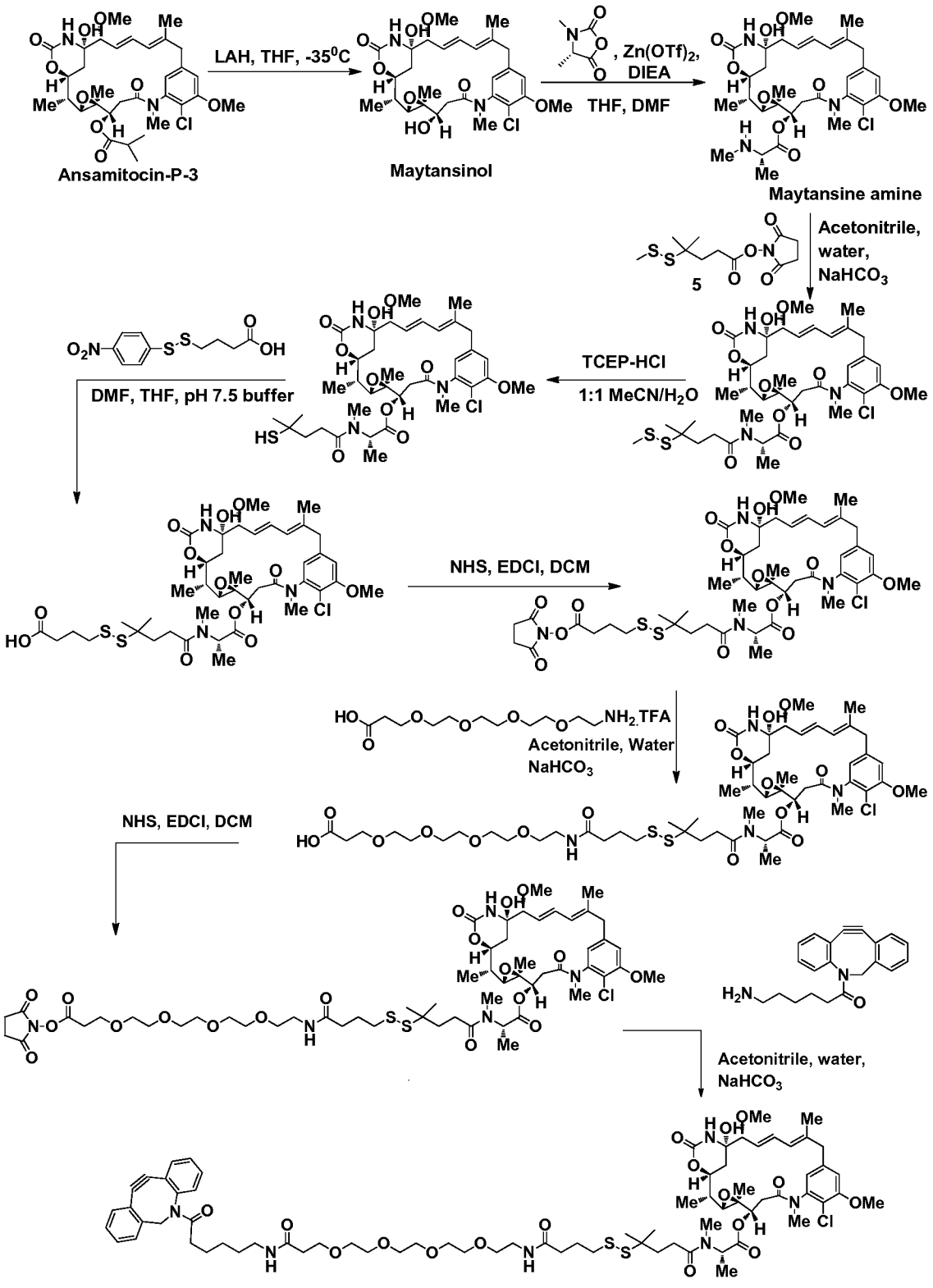

LAH, THF, -35°C
, Zn(OTf)2, DIEA
THF, DMF
Ansamitocin-P-3
Maytansinol
Maytansine amine
Acetonitrile, water, NaHCO3
5
TCEP-HCl
1:1 MeCN/H2O
DMF, THF, pH 7.5 buffer
NHS, EDCI, DCM
NH2.TFA
Acetonitrile, Water
NaHCO3
NHS, EDCI, DCM
Acetonitrile, water, NaHCO3

FIG.2

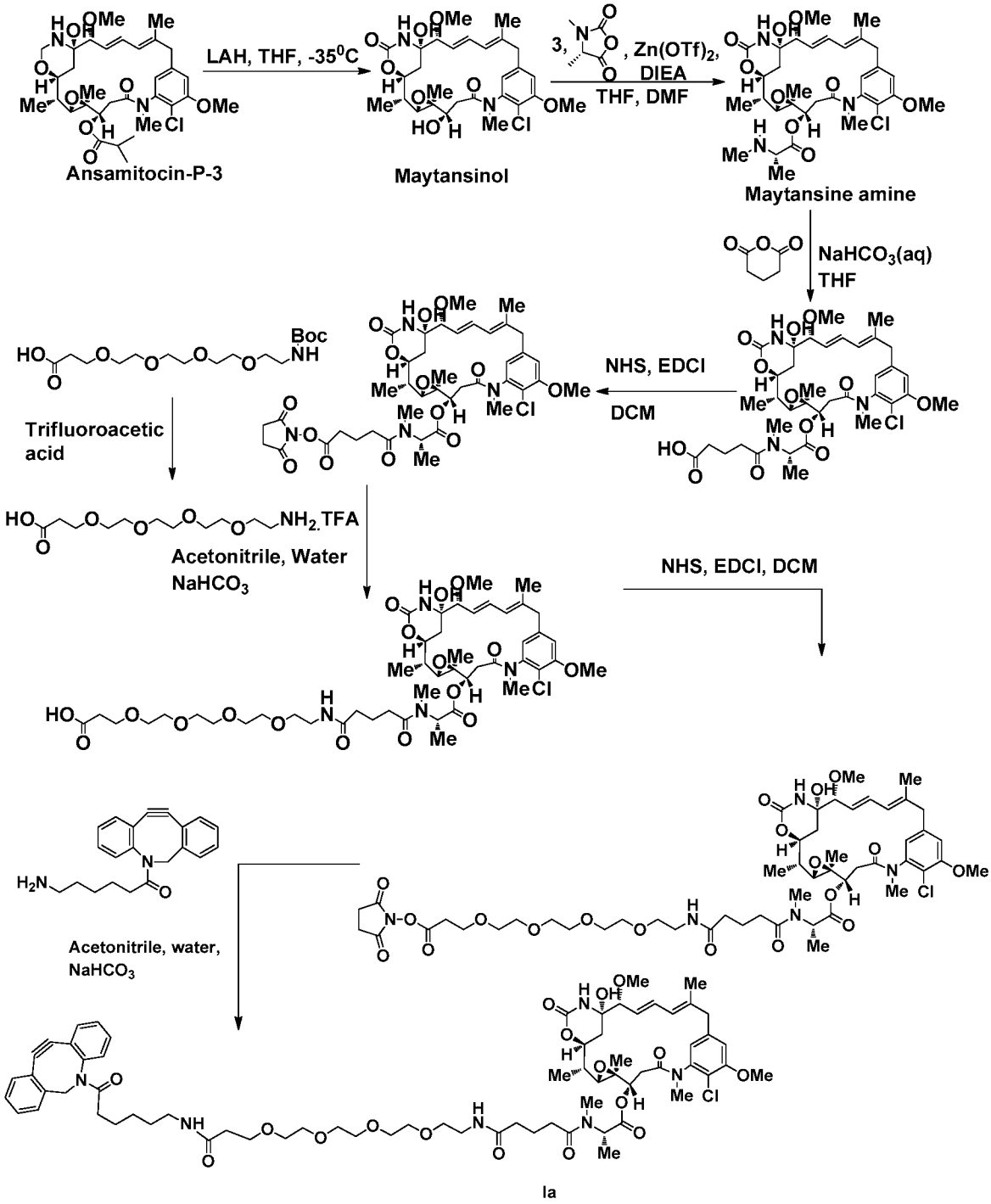

LAH, THF, -35°C
Ansamitocin-P-3
Maytansinol
3, , Zn(OTf)2, DIEA
THF, DMF
Maytansine amine
NaHCO3(aq)
THF
NHS, EDCI
DCM
Boc
NH
HO
Trifluoroacetic acid
NH2.TFA
Acetonitrile, Water
NaHCO3
NHS, EDCI, DCM
H2N
Acetonitrile, water,
NaHCO3
Ia

FIG.3

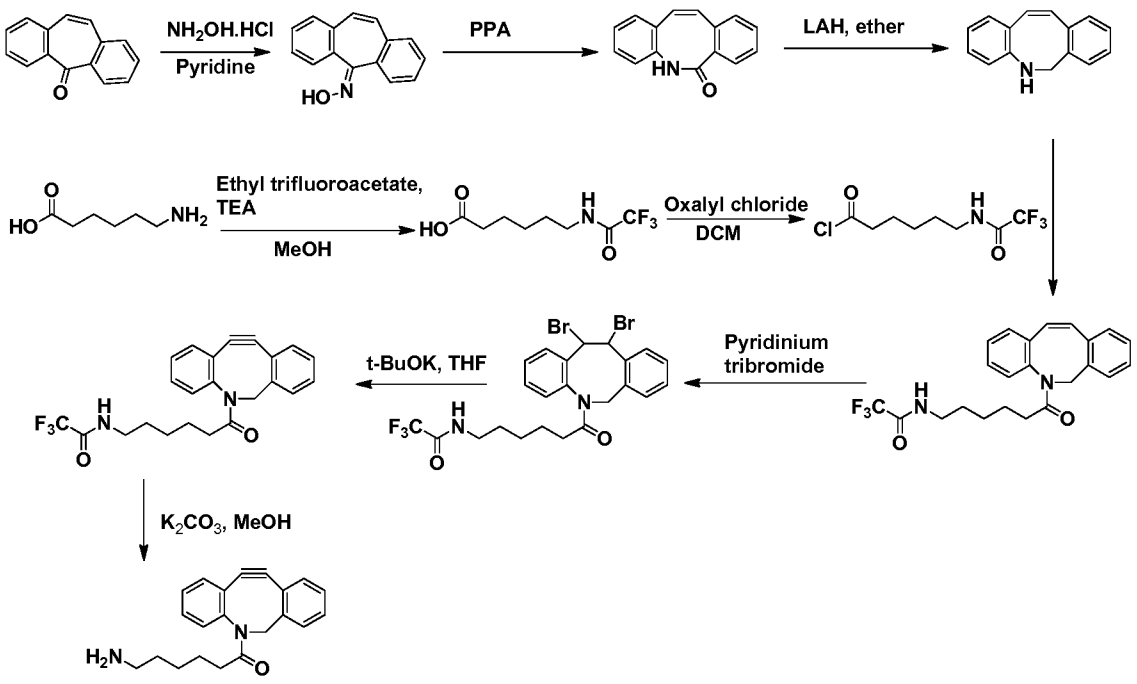

NH2OH.HCl
Pyridine
PPA
LAH, ether
Ethyl trifluoroacetate,
TEA
MeOH
Oxalyl chloride
DCM
Pyridinium
tribromide
t-BuOK, THF
K2CO3, MeOH

FIG.4

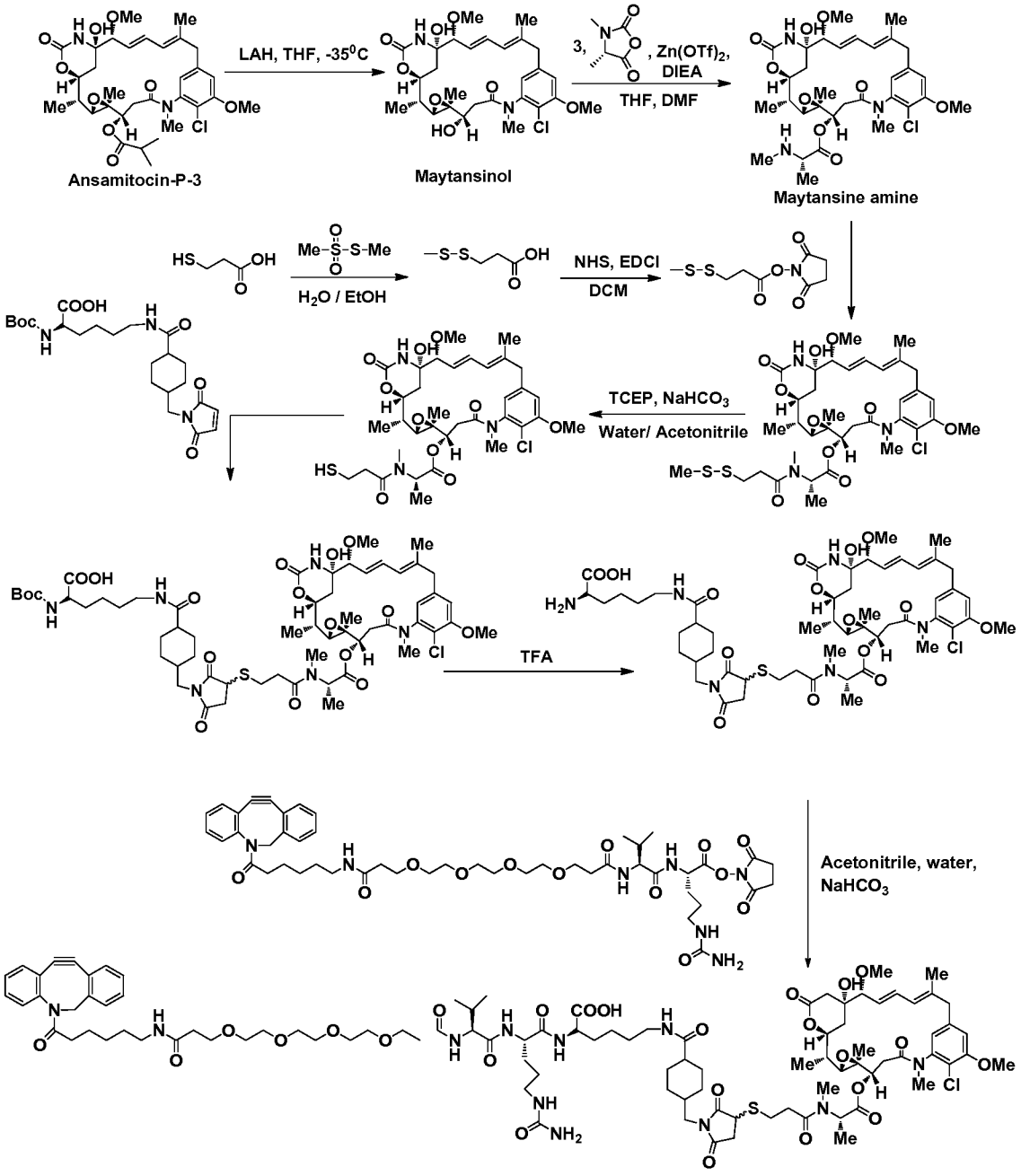

LAH, THF, -35°C
Ansamitocin-P-3
Maytansinol
3, , Zn(OTf)2, DIEA
THF, DMF
Maytansine amine
NHS, EDCI
DCM
H2O / EtOH
TCEP, NaHCO3
Water/ Acetonitrile
TFA
Acetonitrile, water, NaHCO3

FIG.5

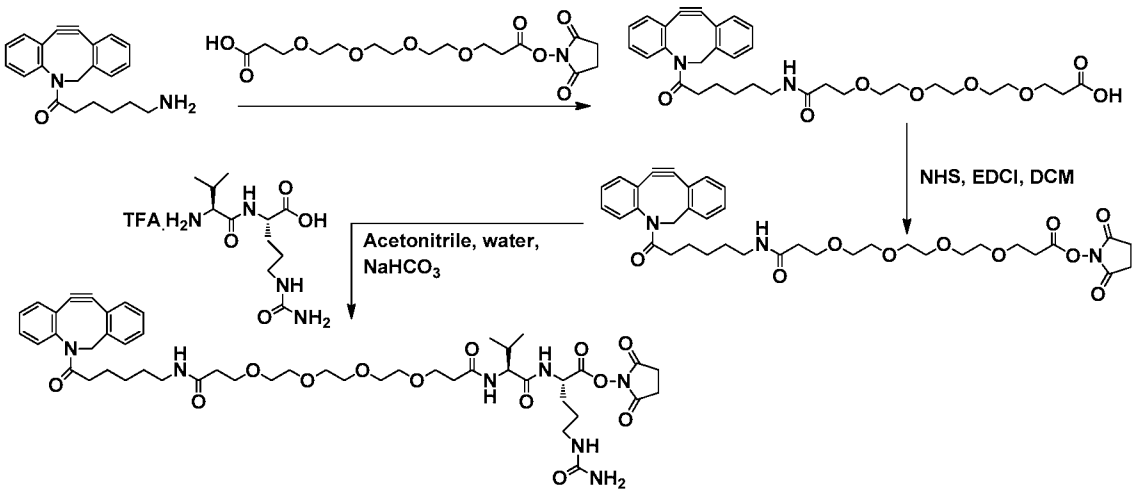


FIG.6A

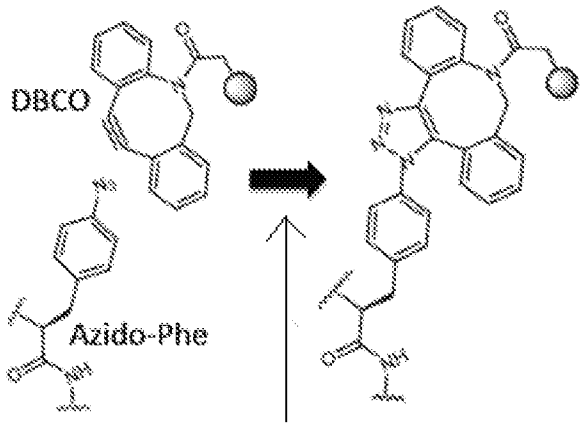


FIG.6B

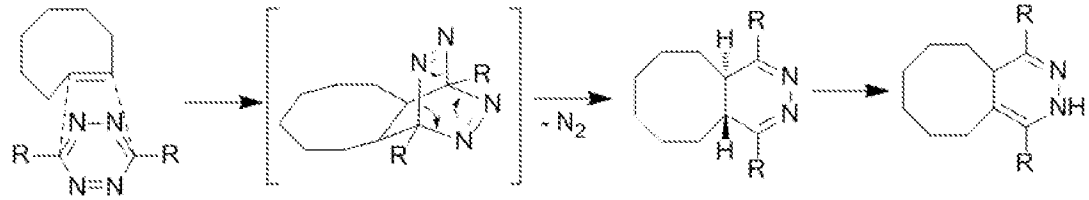


FIG.7

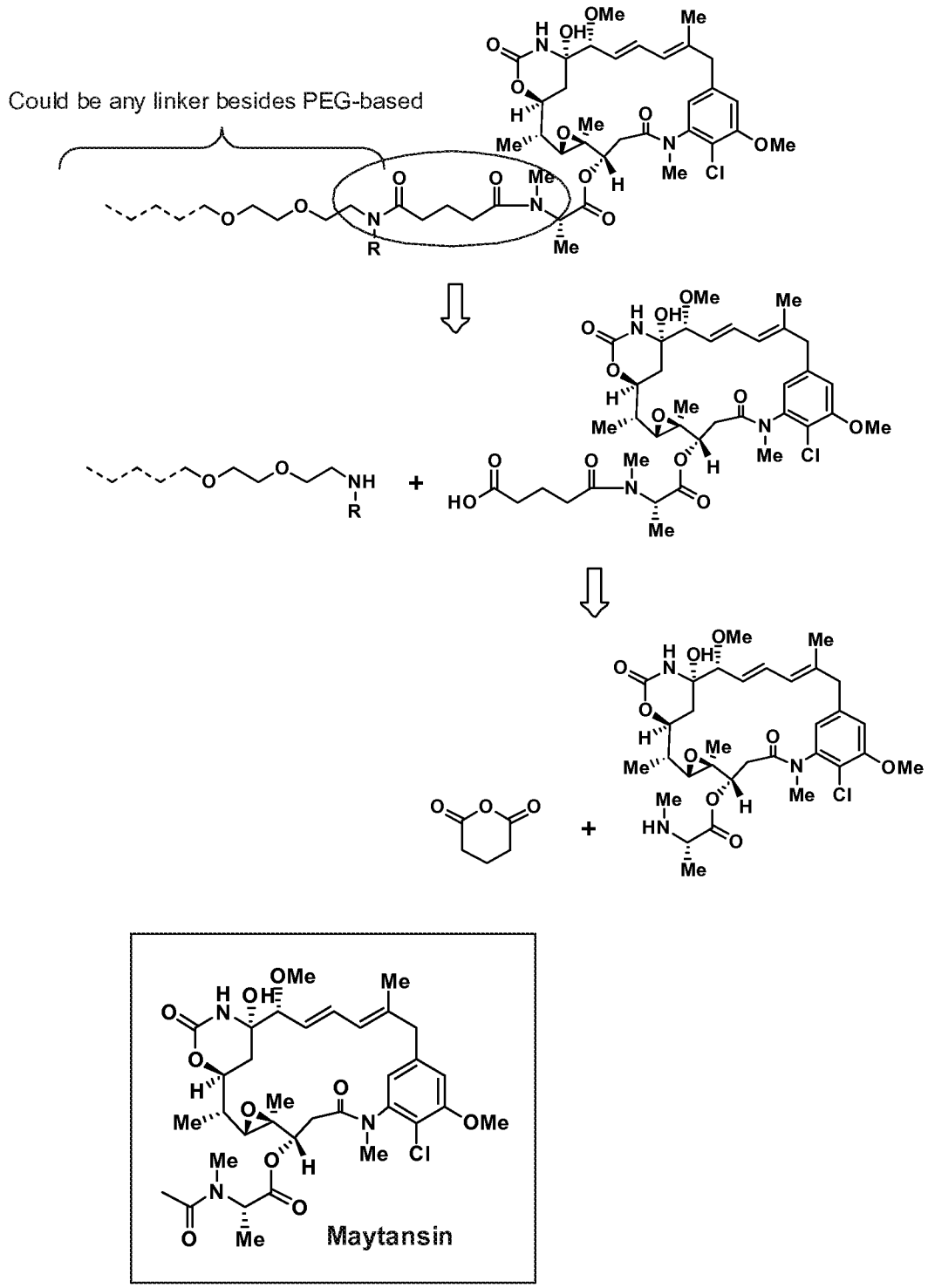


FIG.8

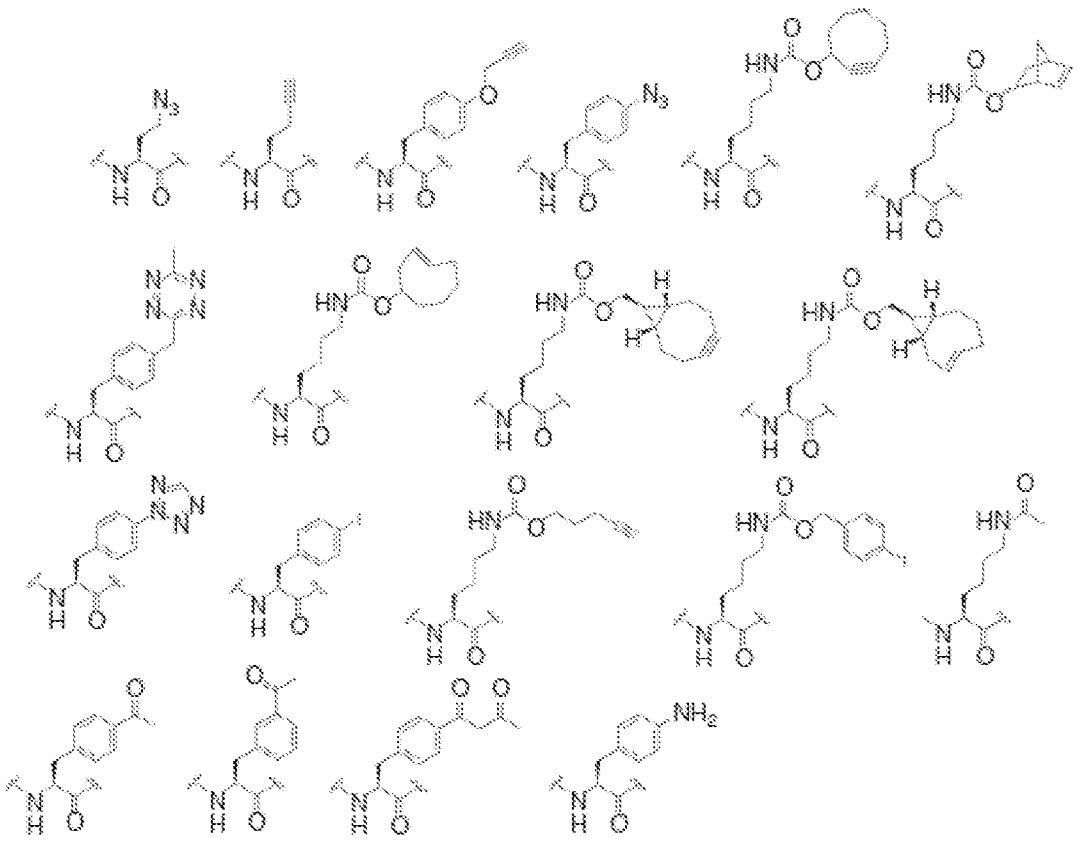
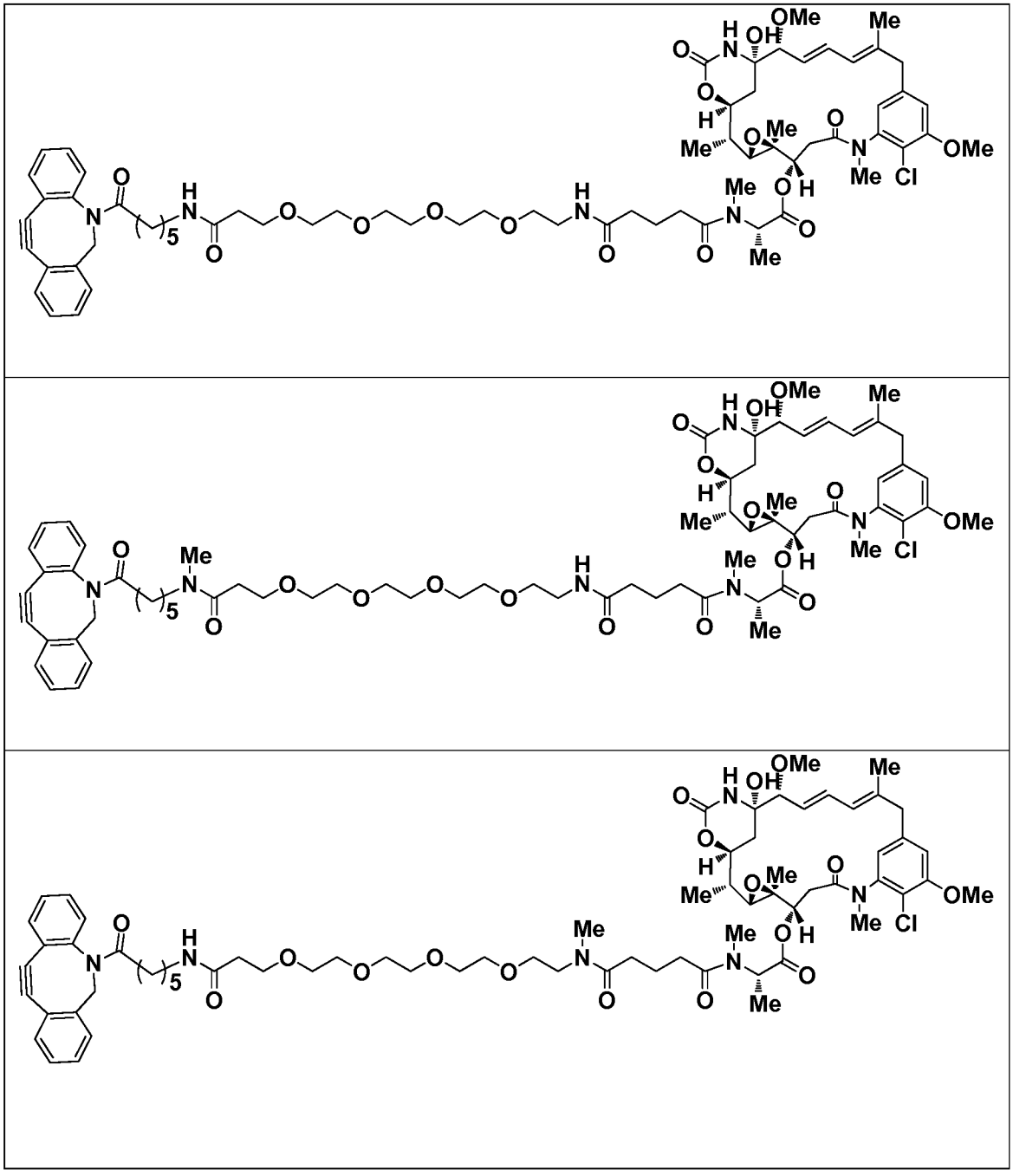


FIG.9A



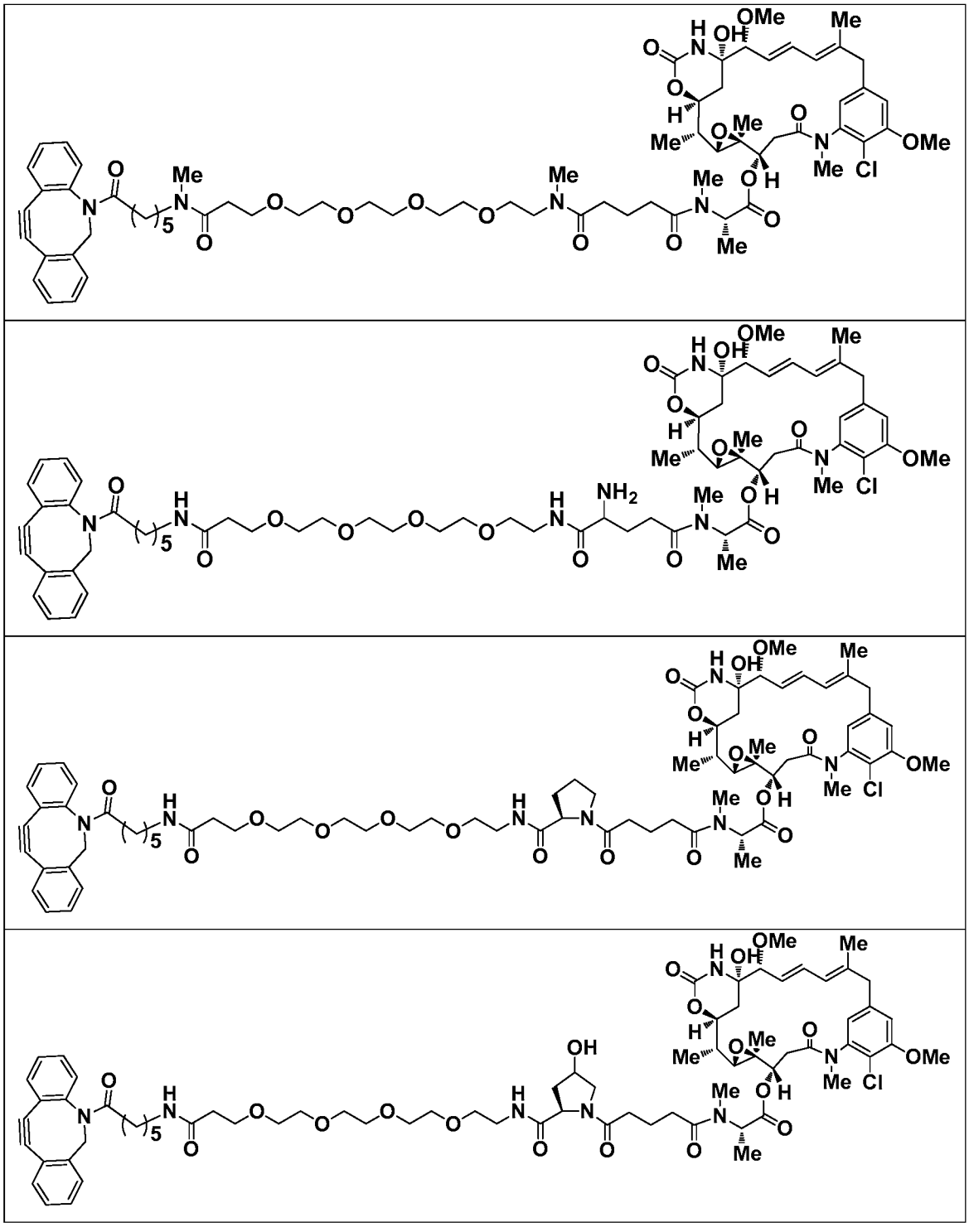
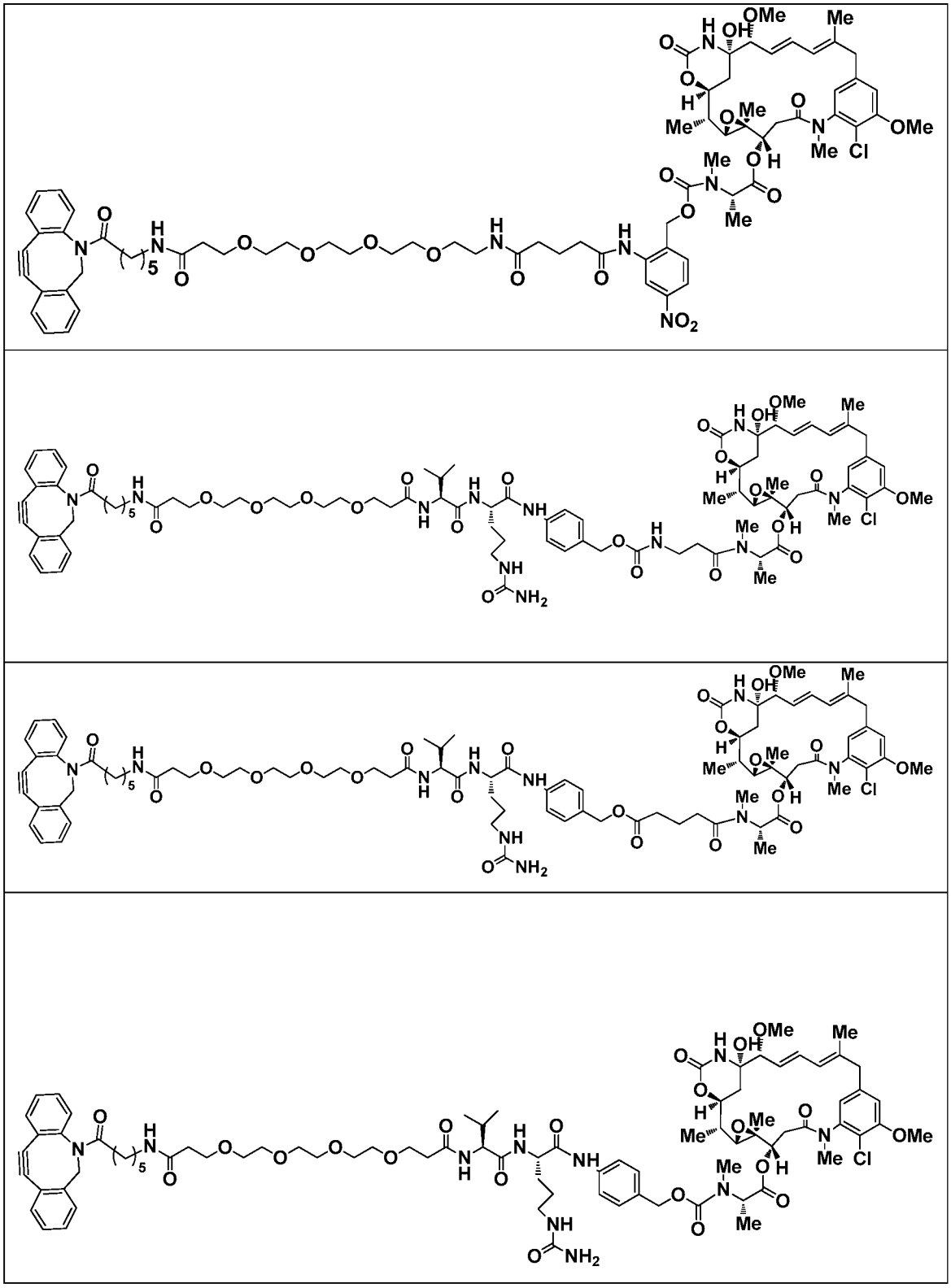


FIG.9B



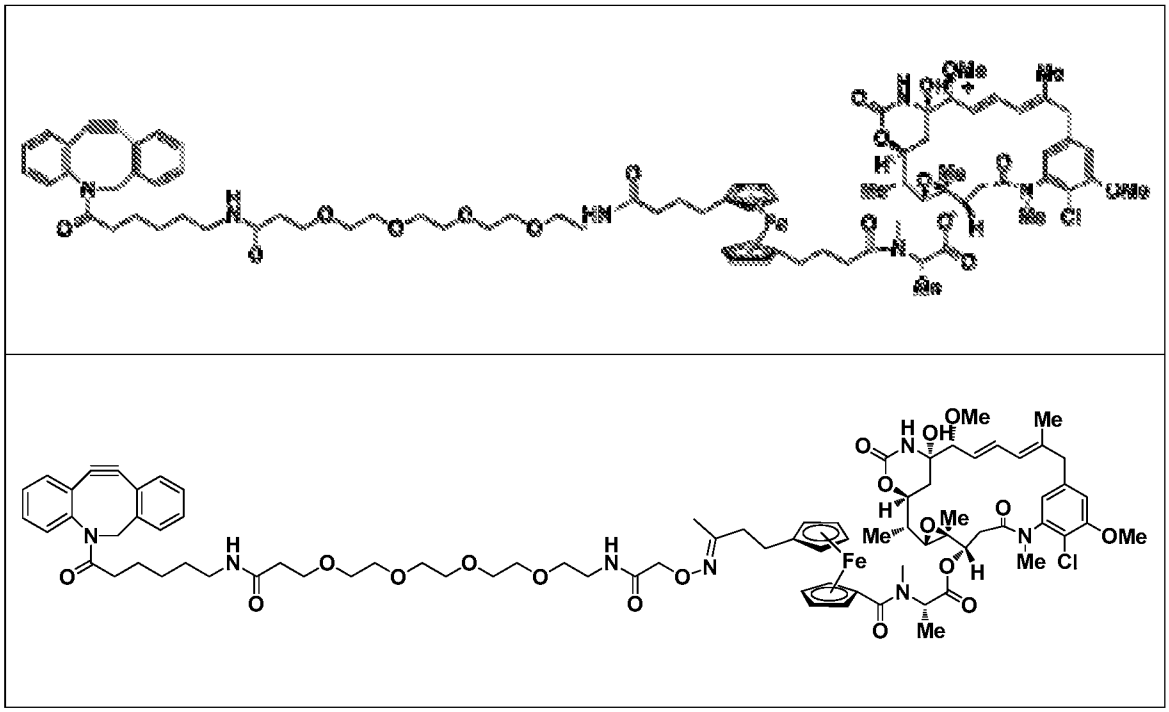


FIG.9C

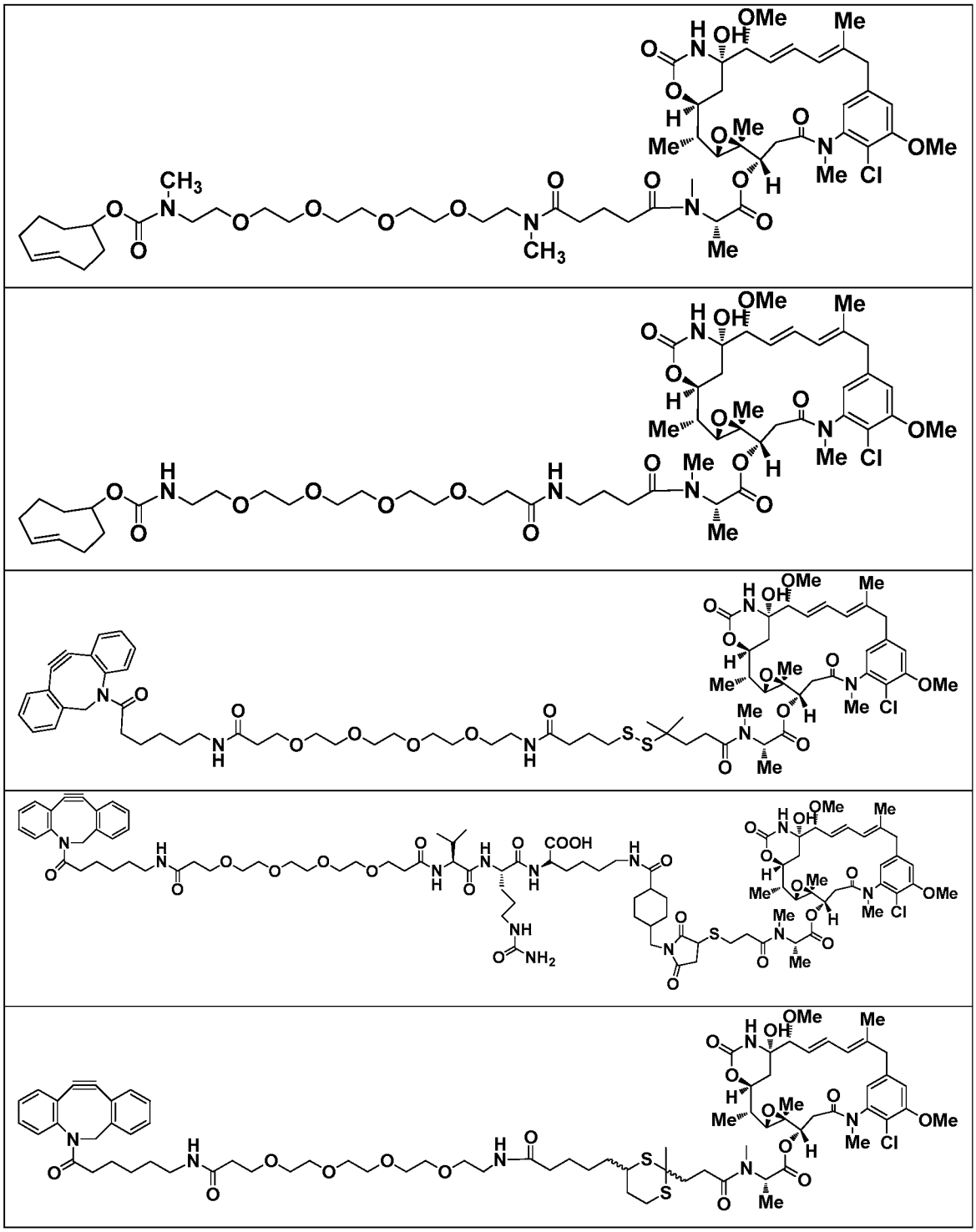


FIG.10

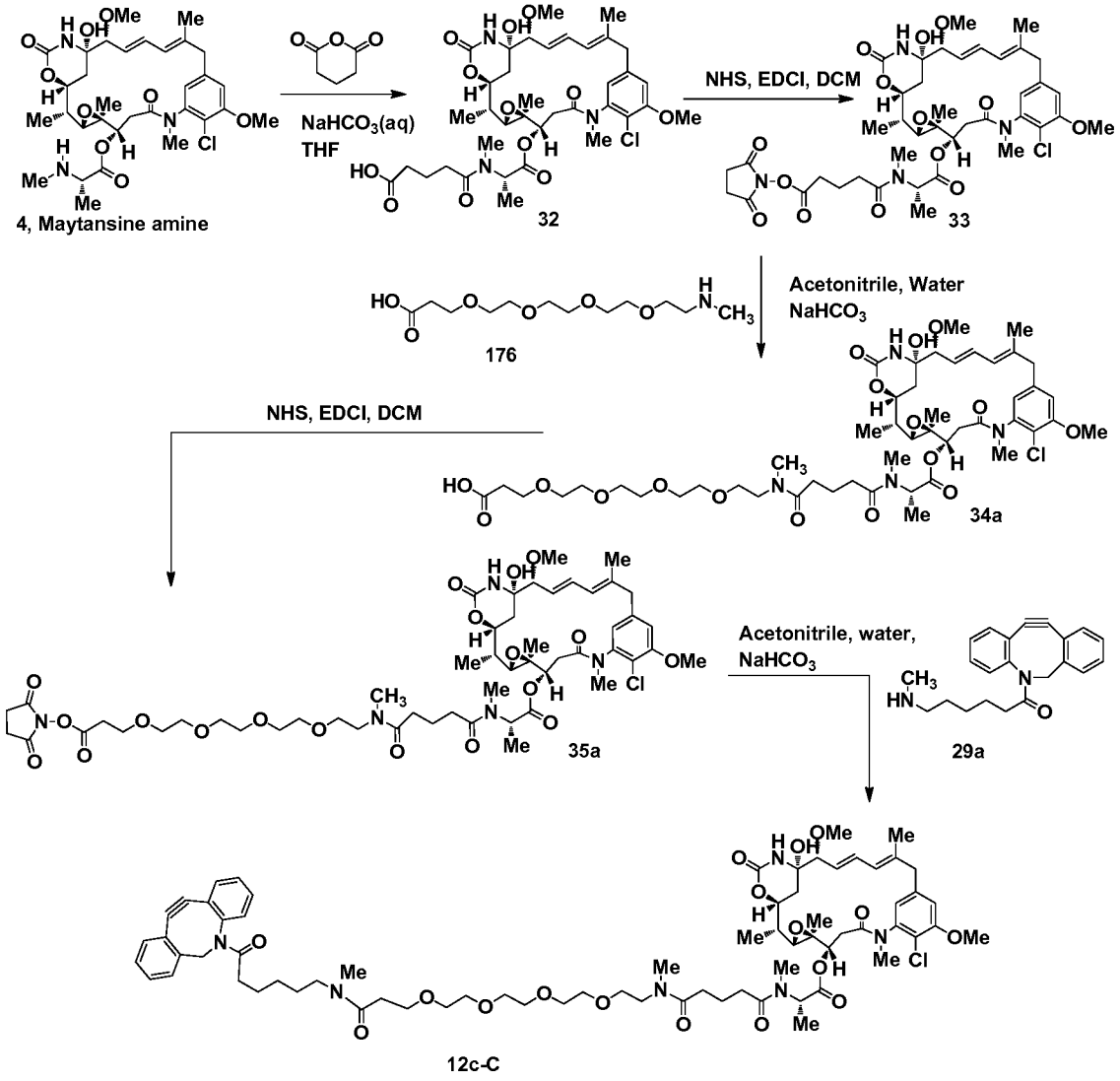

4, Maytansine amine
NaHCO3(aq)
THF
32
NHS, EDCI, DCM
33
176
Acetonitrile, Water
NaHCO3
34a
NHS, EDCI, DCM
35a
Acetonitrile, water,
NaHCO3
29a
12c-C

FIG.11

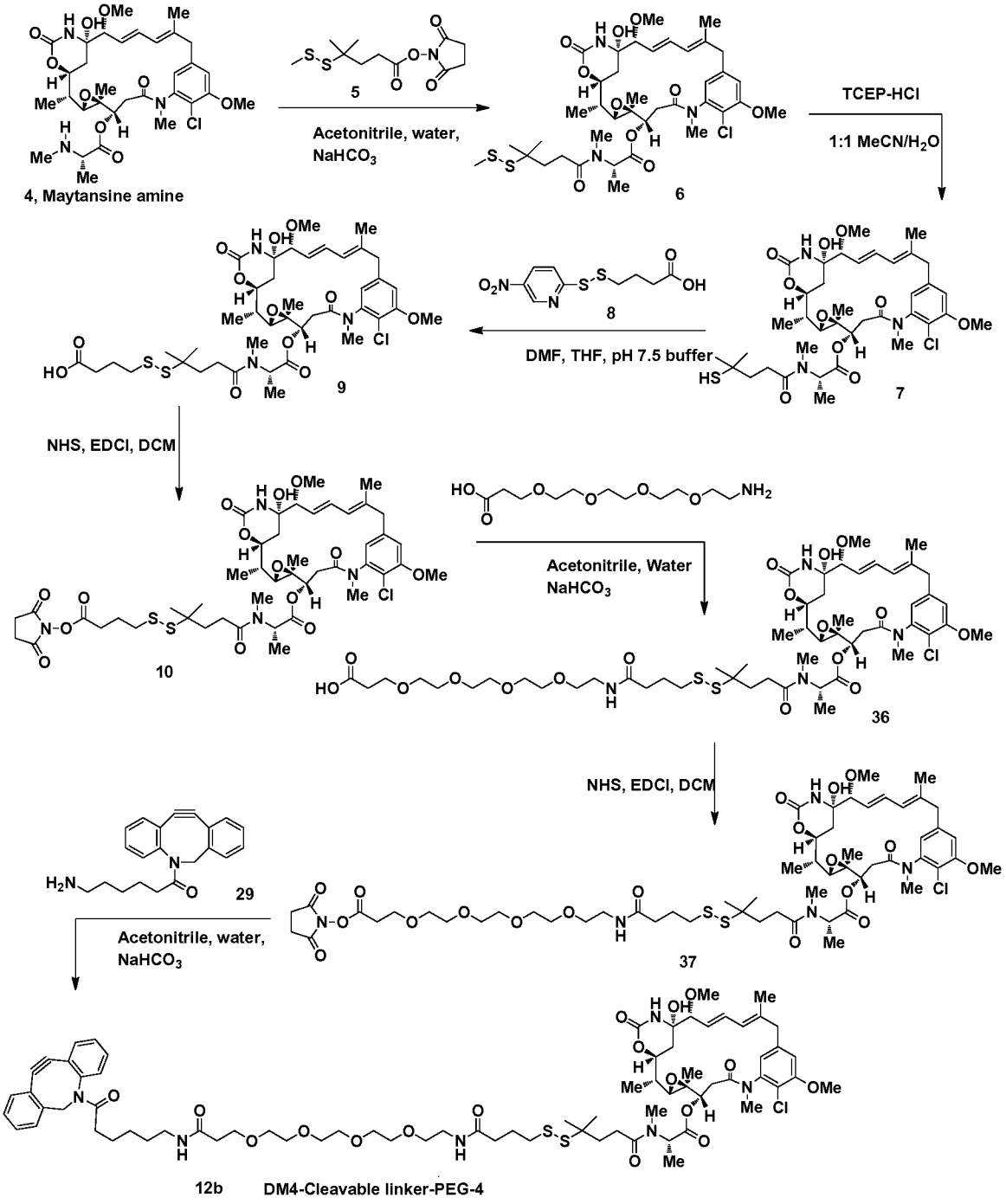

4, Maytansine amine
5
Acetonitrile, water, NaHCO3
6
TCEP-HCl
1:1 MeCN/H2O
7
8
DMF, THF, pH 7.5 buffer
9
NHS, EDCI, DCM
10
Acetonitrile, Water NaHCO3
36
NHS, EDCI, DCM
29
Acetonitrile, water, NaHCO3
37
12b DM4-Cleavable linker-PEG-4

FIG.12

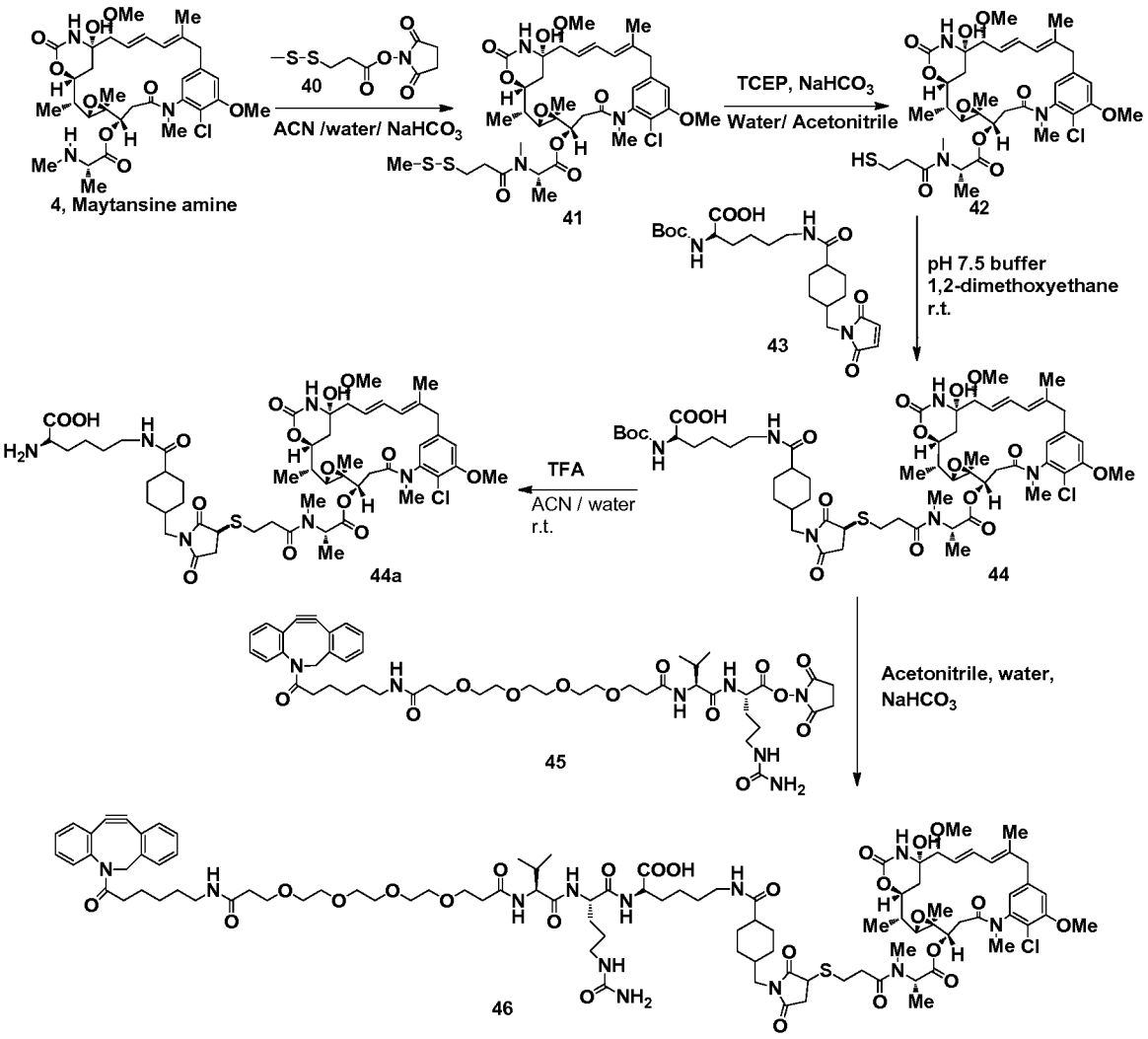

4, Maytansine amine
40
ACN /water/ NaHCO3
41
TCEP, NaHCO3
Water/ Acetonitrile
42
43
pH 7.5 buffer
1,2-dimethoxyethane
r.t.
44
TFA
ACN / water
r.t.
44a
45
Acetonitrile, water,
NaHCO3
46

FIG.13

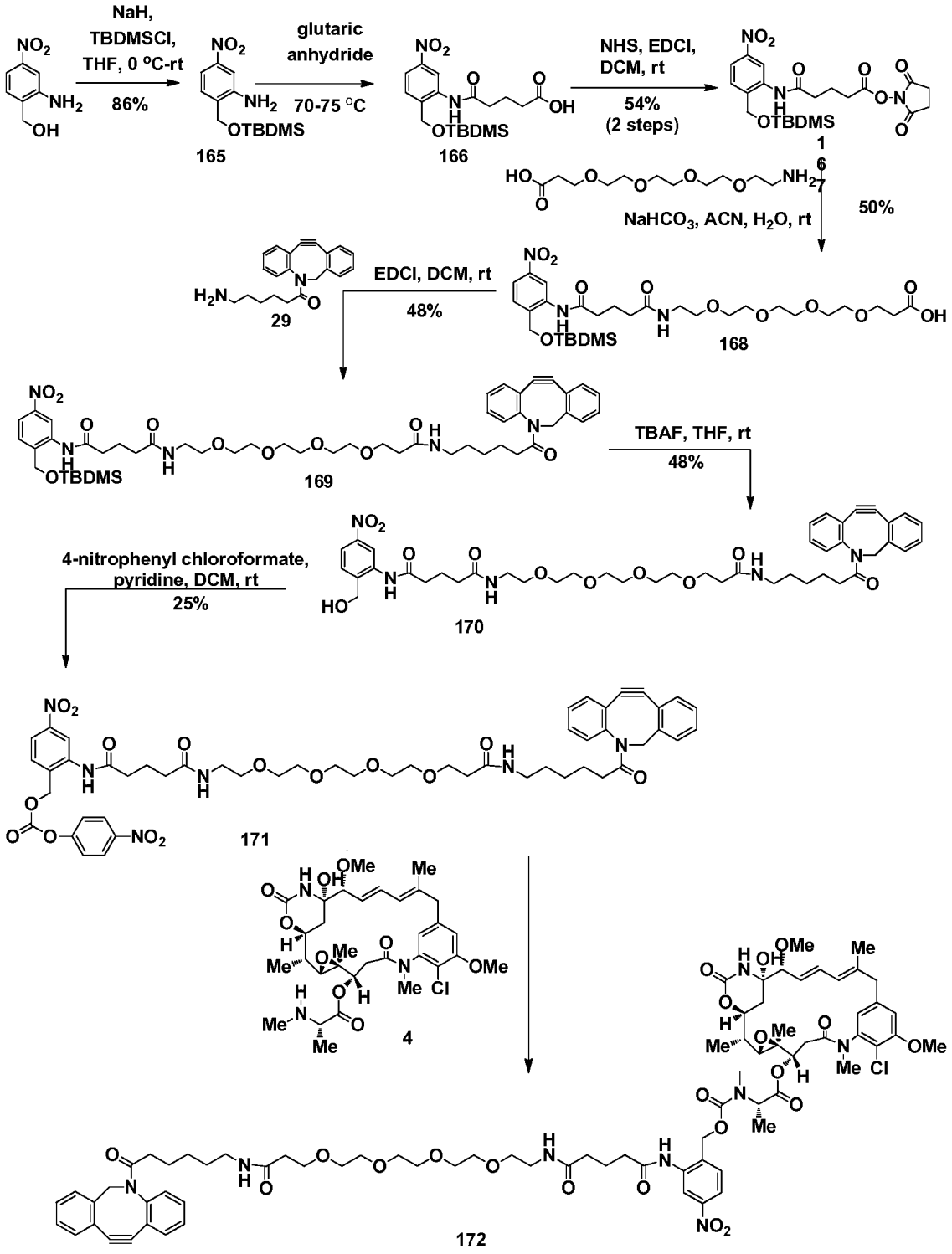

NaH,
TBDMSCl,
THF, 0 °C-rt
86%
glutaric
anhydride
70-75 °C
NHS, EDCI,
DCM, rt
54%
(2 steps)
165
166
167
NaHCO3, ACN, H2O, rt
50%
EDCI, DCM, rt
48%
29
168
169
TBAF, THF, rt
48%
4-nitrophenyl chloroformate,
pyridine, DCM, rt
25%
170
171
4
172

FIG.14

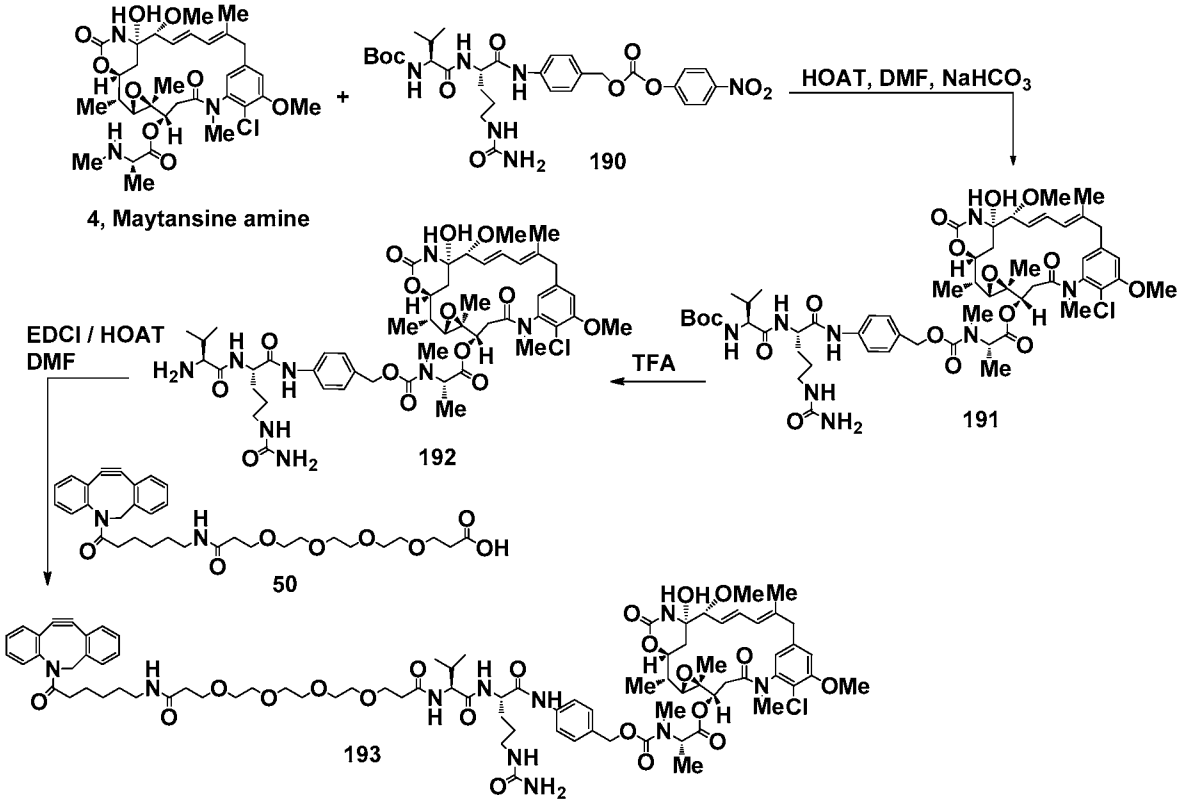

4, Maytansine amine
190
HOAT, DMF, NaHCO3
191
TFA
192
EDCI / HOAT
DMF
50
193

FIG.15

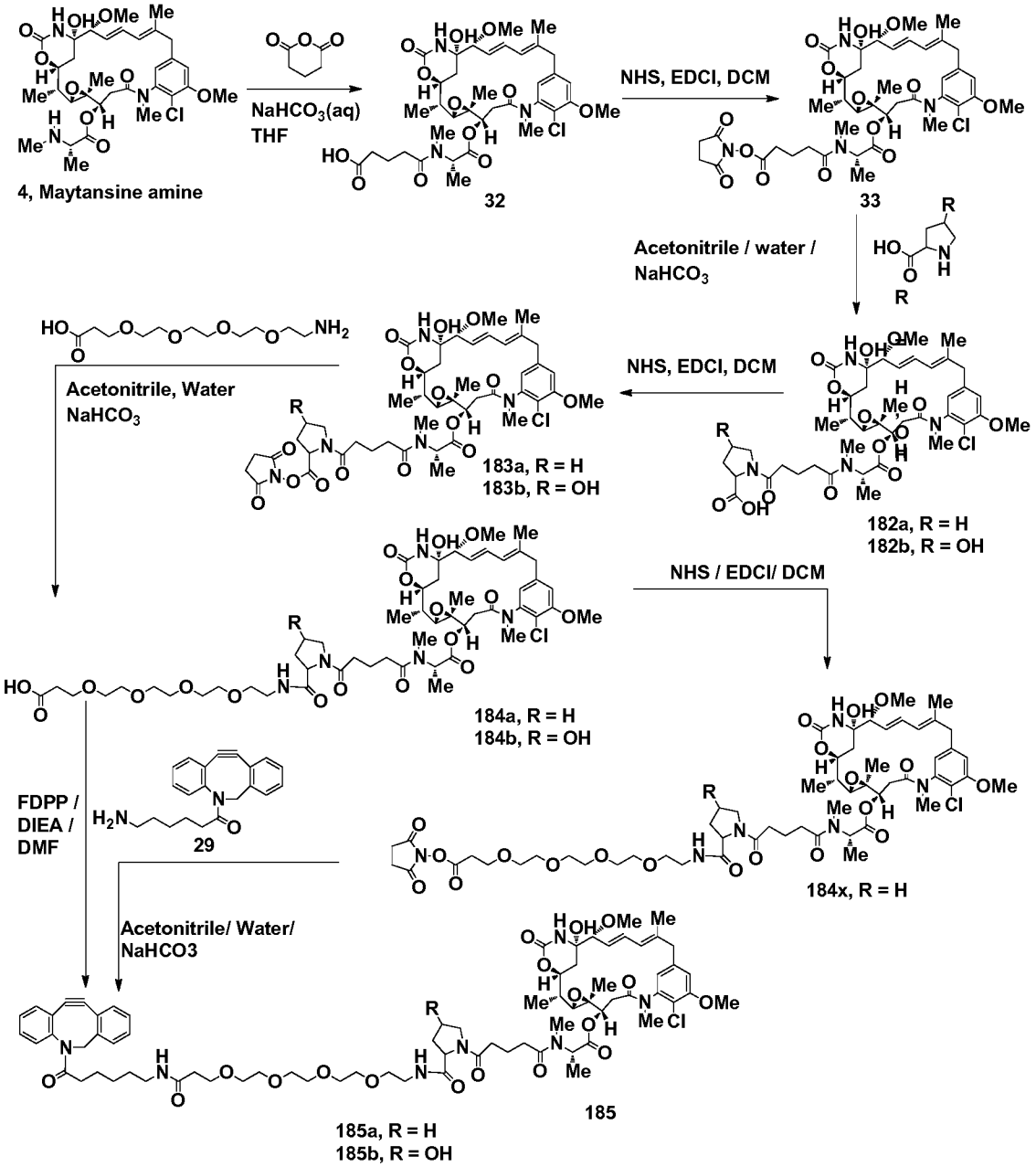

4, Maytansine amine
NaHCO3(aq)
THF
32
NHS, EDCI, DCM
33
Acetonitrile / water /
NaHCO3
182a, R = H
182b, R = OH
NHS, EDCI, DCM
183a, R = H
183b, R = OH
Acetonitrile, Water
NaHCO3
184a, R = H
184b, R = OH
NHS / EDCI/ DCM
184x, R = H
FDPP /
DIEA /
DMF
29
Acetonitrile/ Water/
NaHCO3
185
185a, R = H
185b, R = OH

FIG.16

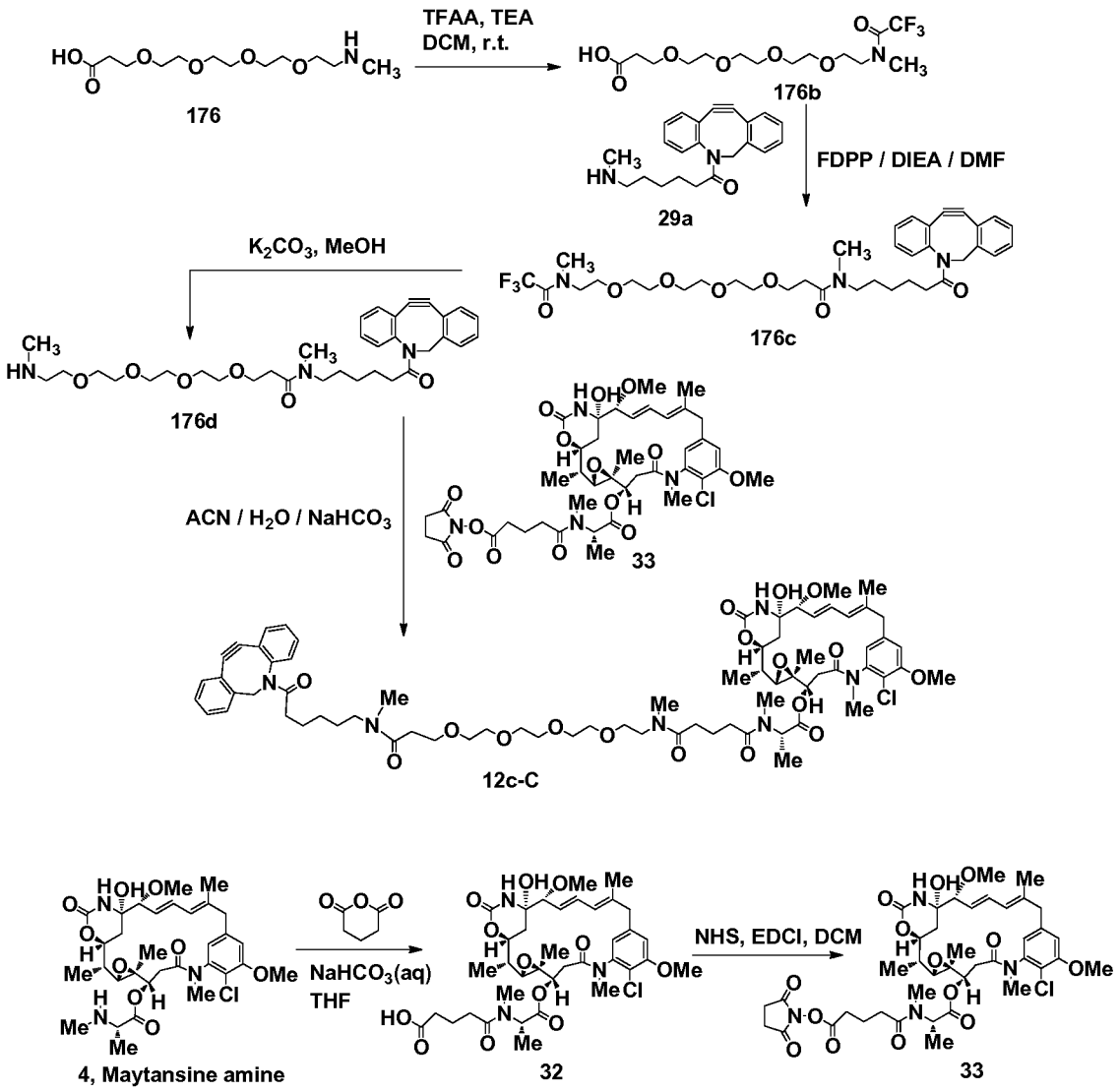

TFAA, TEA
DCM, r.t.
176
176b
29a
FDPP / DIEA / DMF
K2CO3, MeOH
176c
176d
ACN / H2O / NaHCO3
33
12c-C
4, Maytansine amine
NaHCO3(aq)
THF
32
NHS, EDCI, DCM
33

FIG.17

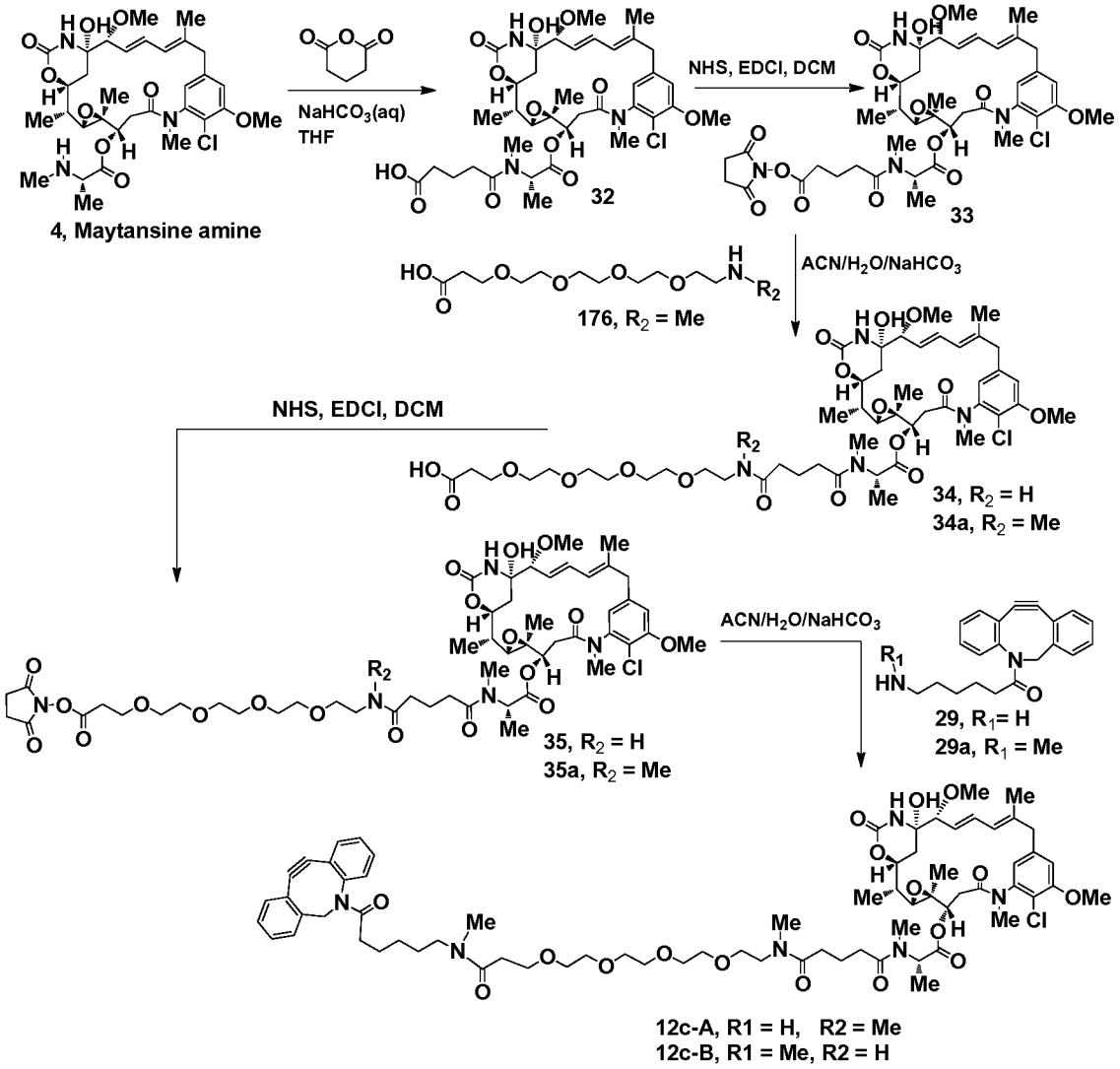

4, Maytansine amine
NaHCO3(aq)
THF
32
NHS, EDCI, DCM
33
ACN/H2O/NaHCO3
176, R2 = Me
NHS, EDCI, DCM
34, R2 = H
34a, R2 = Me
35, R2 = H
35a, R2 = Me
ACN/H2O/NaHCO3
29, R1= H
29a, R1 = Me
12c-A, R1 = H, R2 = Me
12c-B, R1 = Me, R2 = H

FIG.18

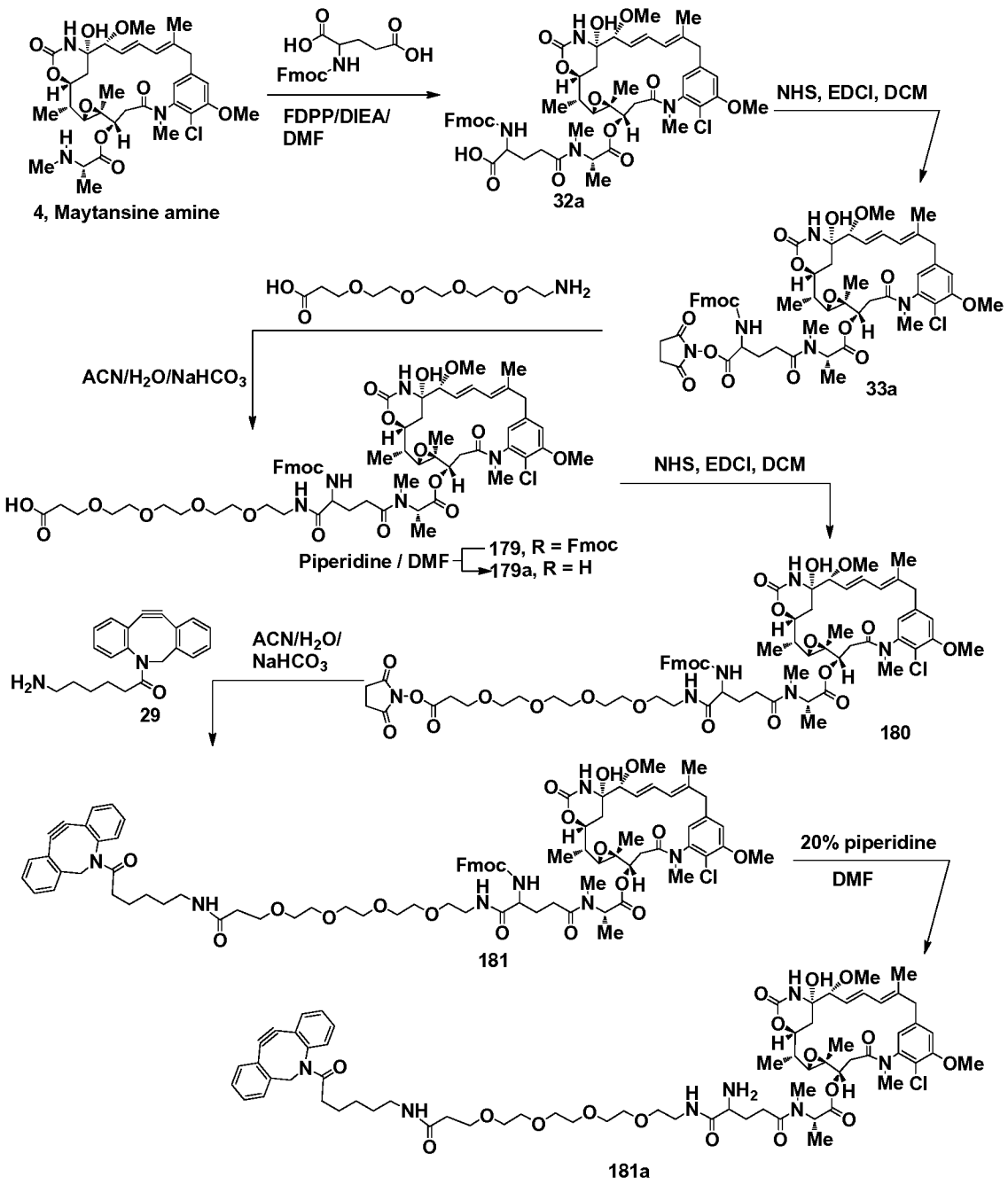

4, Maytansine amine
FDPP/DIEA/
DMF
32a
NHS, EDCI, DCM
33a
ACN/H2O/NaHCO3
Piperidine / DMF
179, R = Fmoc
179a, R = H
NHS, EDCI, DCM
180
29
ACN/H2O/
NaHCO3
181
20% piperidine
DMF
181a

FIG.19

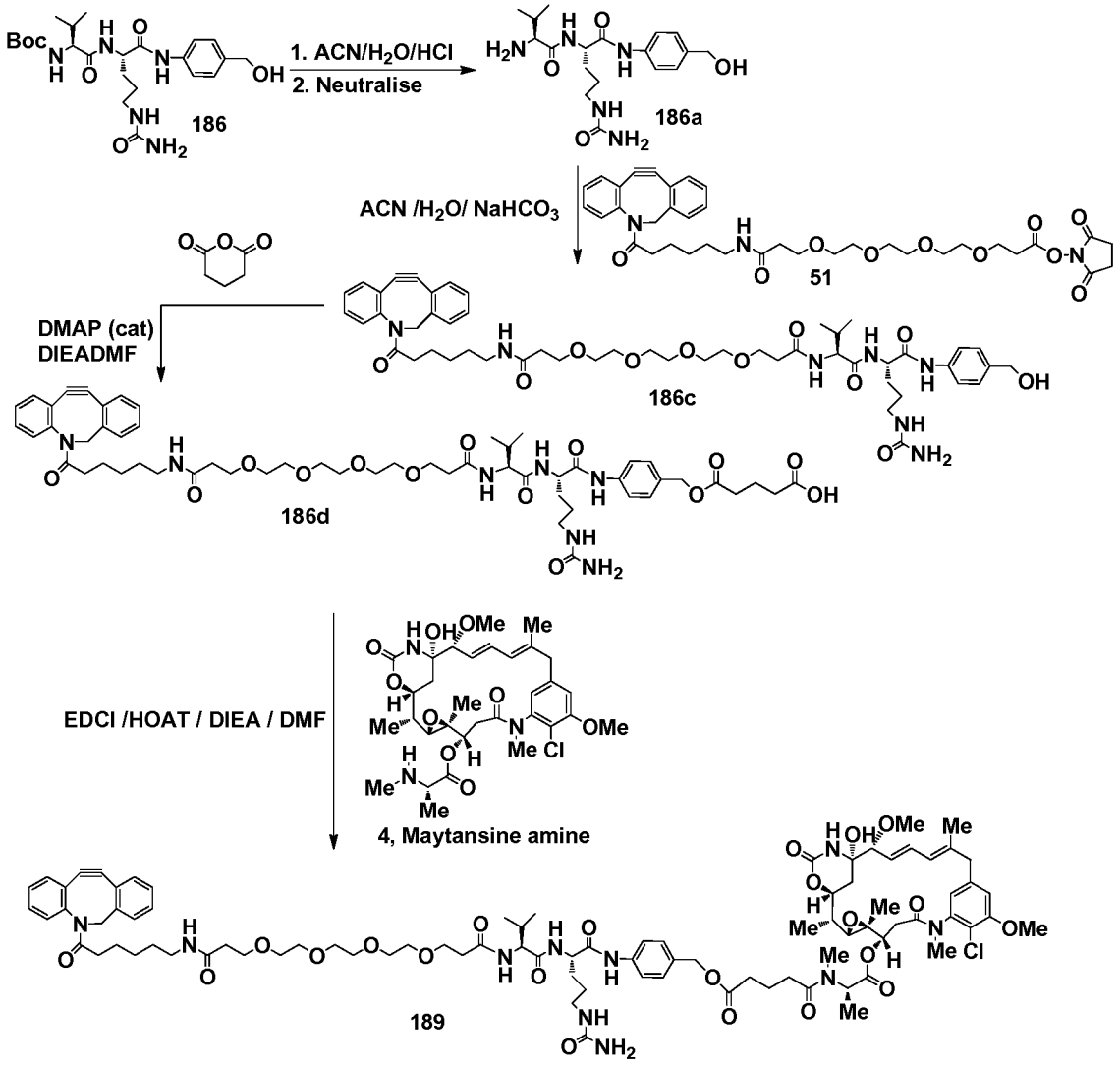

1. ACN/H2O/HCl
2. Neutralise
186
186a
ACN /H2O/ NaHCO3
51
DMAP (cat)
DIEADMF
186c
186d
EDCI /HOAT / DIEA / DMF
4, Maytansine amine
189

FIG.20

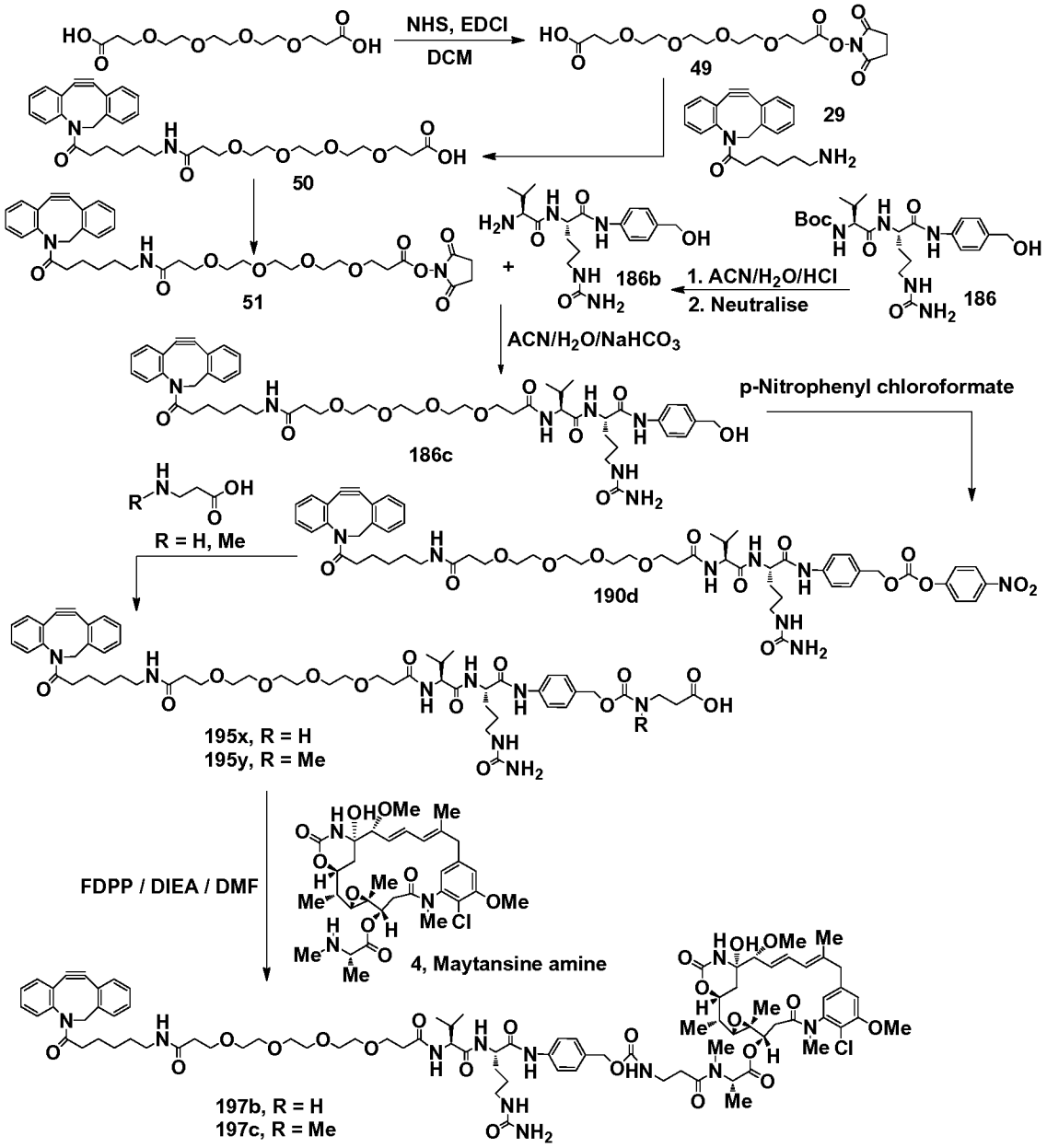

NHS, EDCI
DCM
49
29
50
51
186b
1. ACN/H2O/HCl
2. Neutralise
186
ACN/H2O/NaHCO3
186c
p-Nitrophenyl chloroformate
R = H, Me
190d
195x, R = H
195y, R = Me
FDPP / DIEA / DMF
4, Maytansine amine
197b, R = H
197c, R = Me

FIG.21

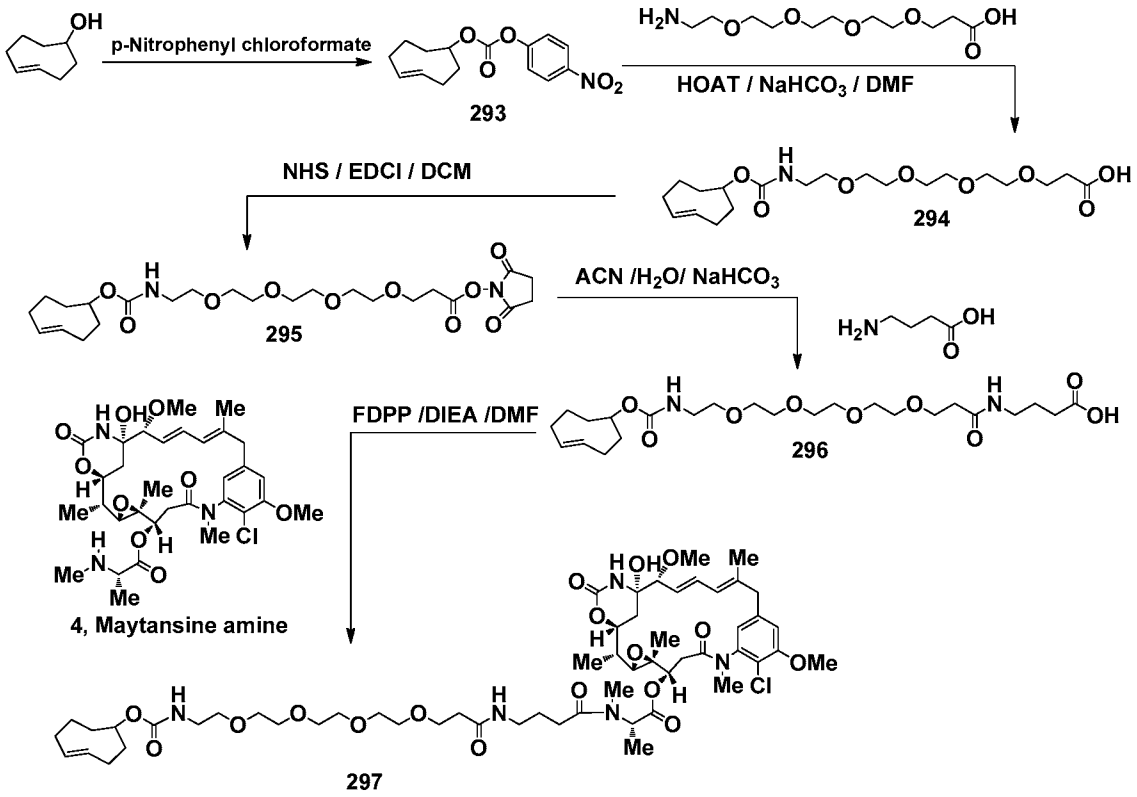

p-Nitrophenyl chloroformate
293
HOAT / NaHCO3 / DMF
294
NHS / EDCI / DCM
295
ACN /H2O/ NaHCO3
296
FDPP /DIEA /DMF
4, Maytansine amine
297

FIG.22

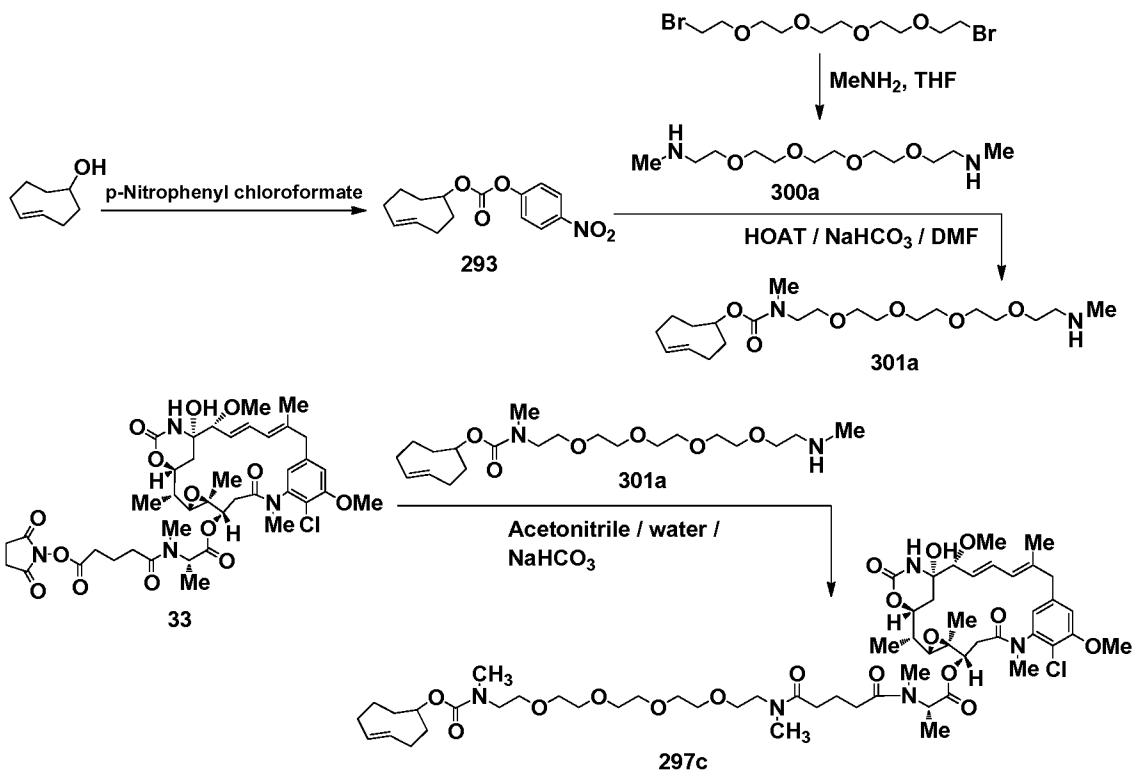

MeNH2, THF
300a
p-Nitrophenyl chloroformate
293
HOAT / NaHCO3 / DMF
301a
33
Acetonitrile / water /
NaHCO3
297c

FIG.23

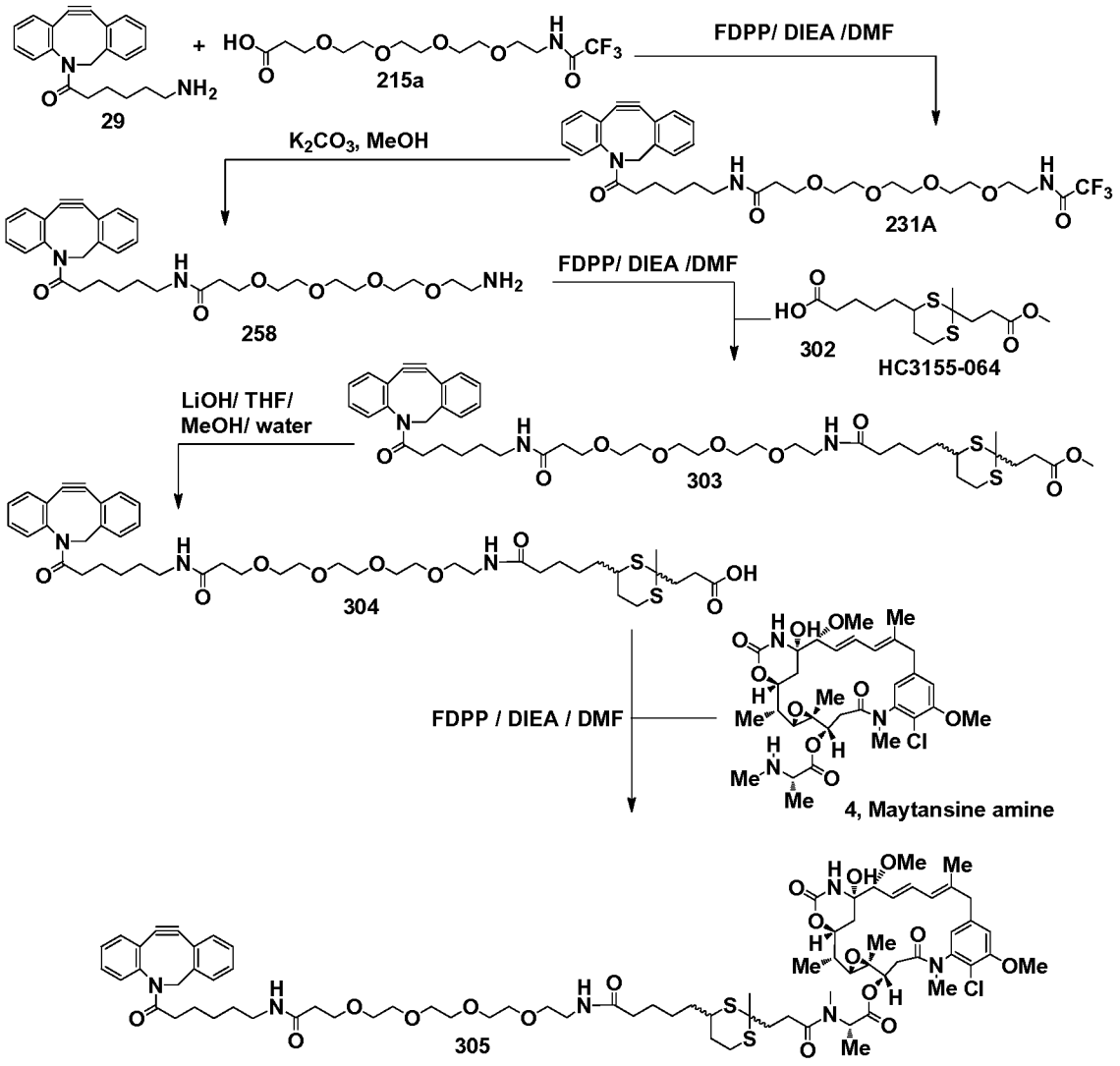

29
215a
FDPP/ DIEA /DMF
231A
K_2CO_3, MeOH
258
FDPP/ DIEA /DMF
302
HC3155-064
LiOH/ THF/
MeOH/ water
303
304
FDPP / DIEA / DMF
4, Maytansine amine
305

FIG.24

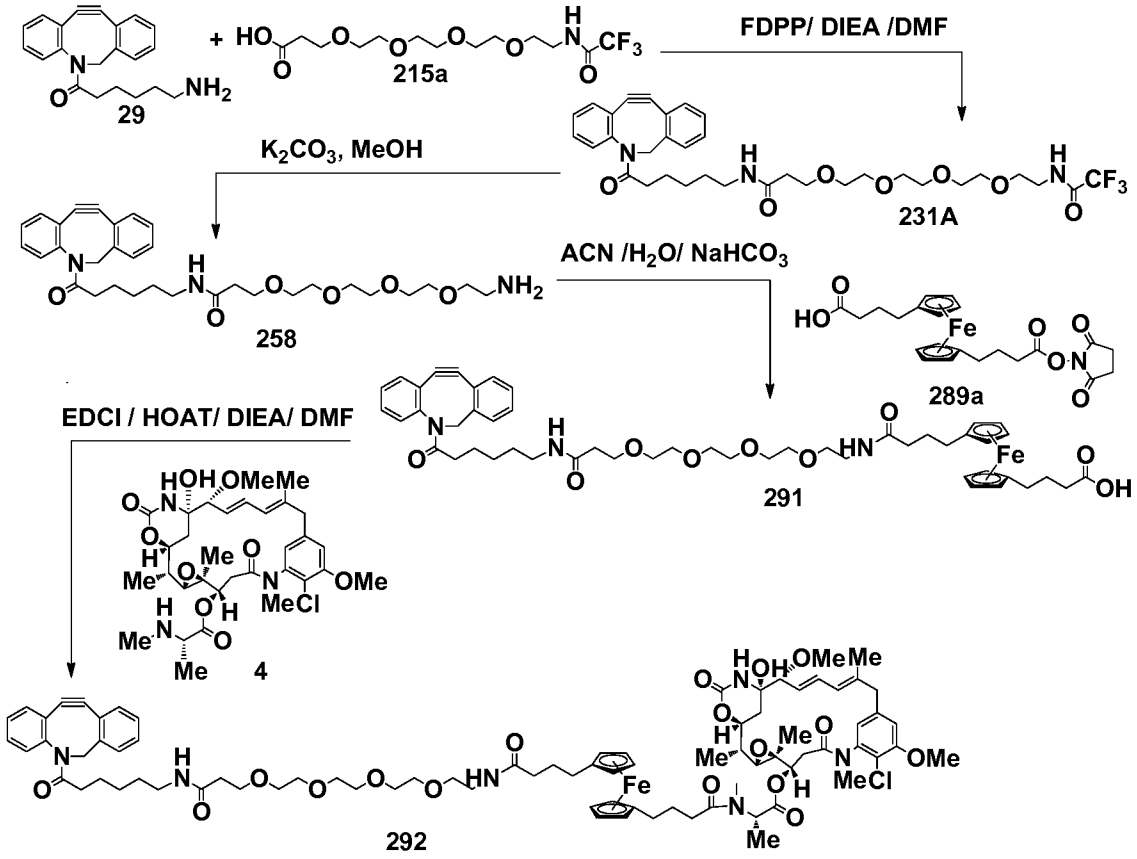
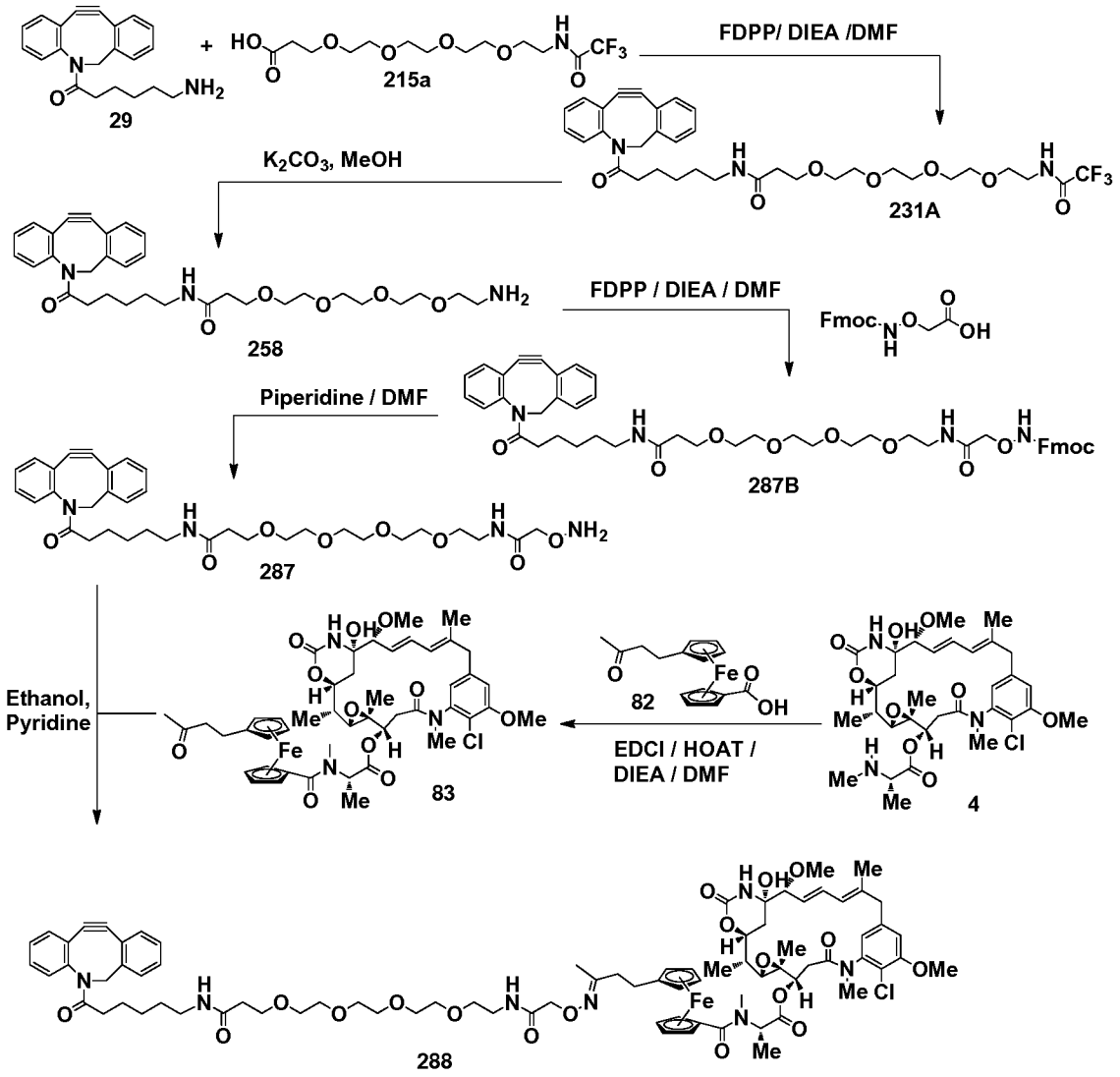

29
215a
FDPP/ DIEA /DMF
231A
K_2CO_3, MeOH
258
ACN /H_2O/ $NaHCO_3$
289a
291
EDCI / HOAT/ DIEA/ DMF
4
292

FIG.25


29
215a
FDPP/ DIEA /DMF
231A
K_2CO_3, MeOH
258
FDPP / DIEA / DMF
Fmoc
287B
Piperidine / DMF
287
Ethanol, Pyridine
83
82
EDCI / HOAT / DIEA / DMF
4
288