Fused Ring Inhibitors of Hepatitis C

Inventors: Leping Li and Min Zhong

Statement of Related Applications

[0001] This application claims the benefit of U.S. provisional applications 61/164,342 filed on March 27, 2009 and 61/214,883 filed on April 28, 2009.

Field of the Invention

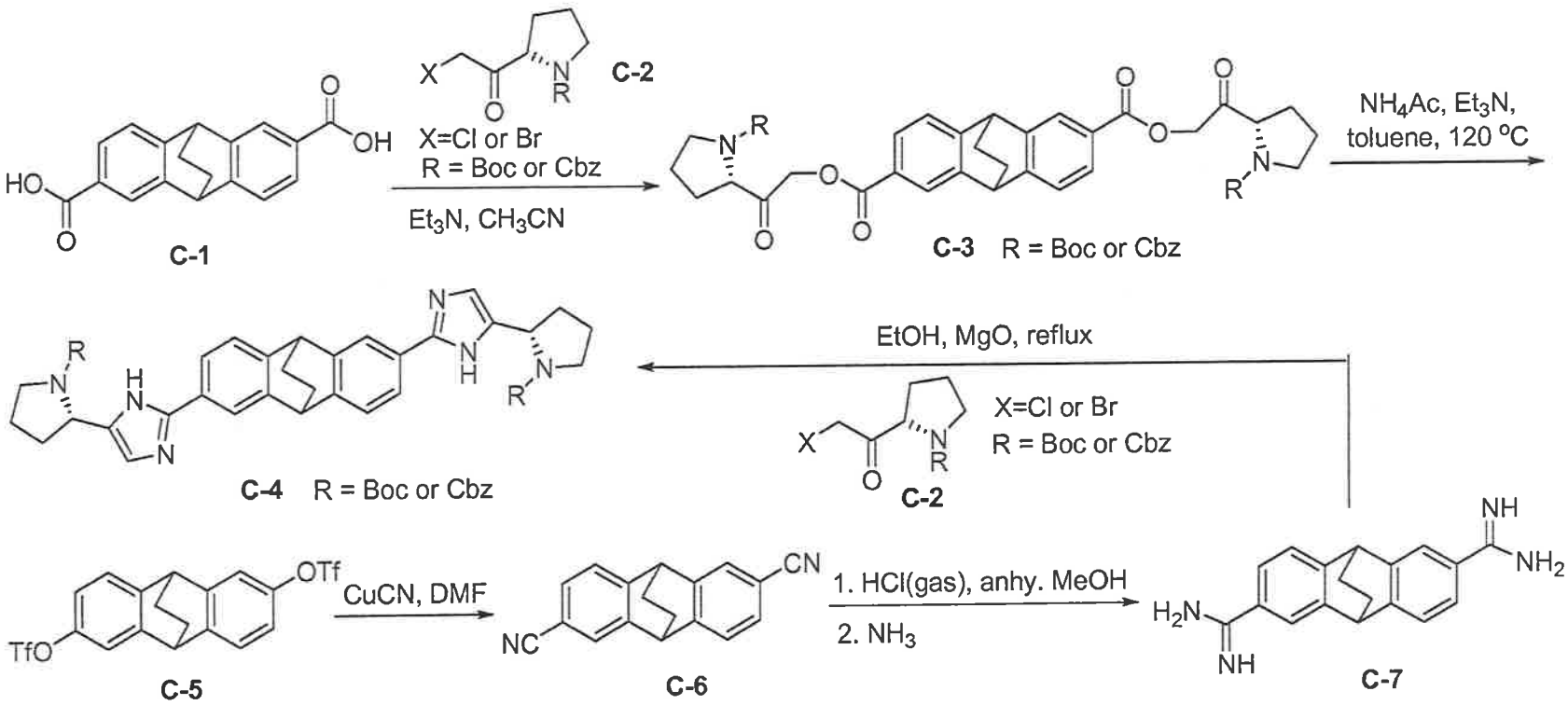
[0002] The invention relates to compounds useful for inhibiting hepatitis C virus ("HCV") replication, particularly functions of the non-structural 5A ("NS5A") protein of HCV.

Background of the Invention

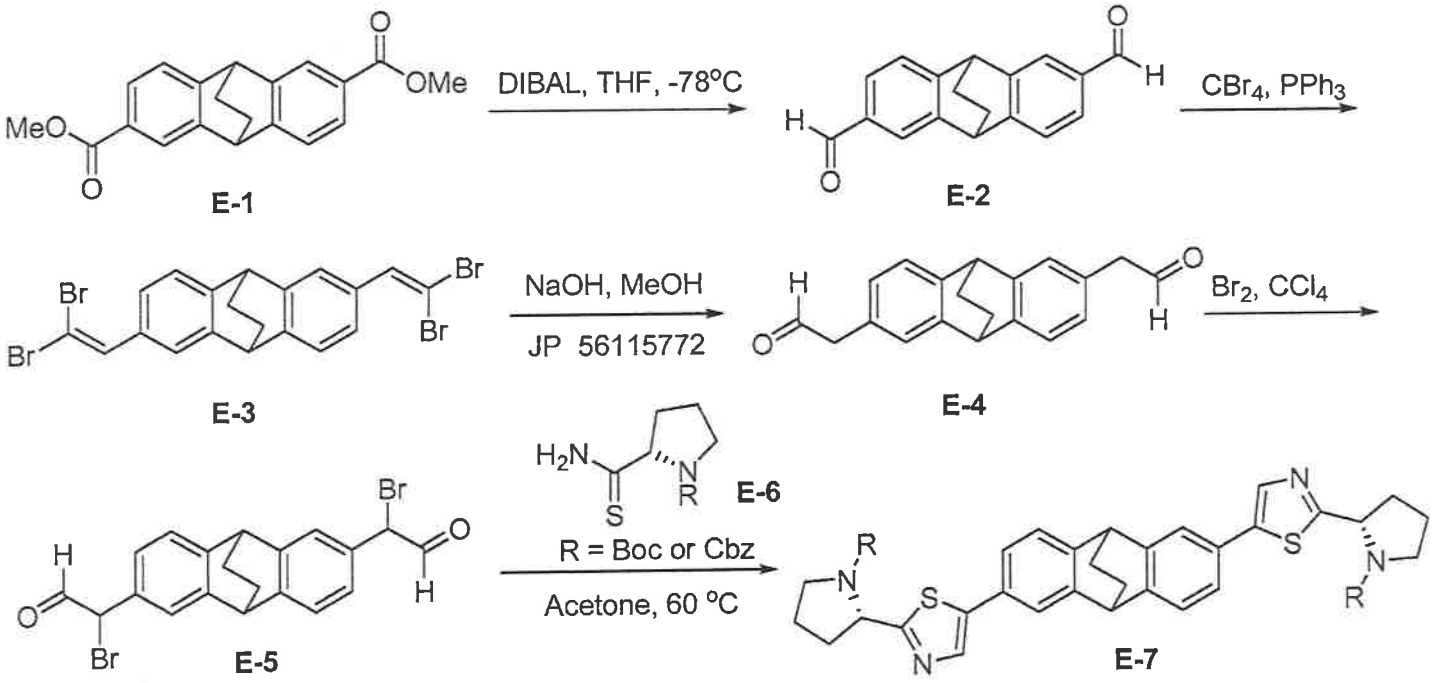
[0003] HCV is a single-stranded RNA virus that is a member of the *Flaviviridae* family. The virus shows extensive genetic heterogeneity as there are currently seven identified genotypes and more than 50 identified subtypes. In HCV infected cells, viral RNA is translated into a polyprotein that is cleaved into ten individual proteins. At the amino terminus are structural proteins: the core (C) protein and the envelope glycoproteins, E1 and E2, and p7, an integral membrane protein that follows E1 and E2. Additionally, there are six non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B, which play a functional role in the HCV lifecycle. (*see,* for example, Lindenbach, B.D. and Rice, C.M. *Nature.* 436:933-938, 2005).

[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

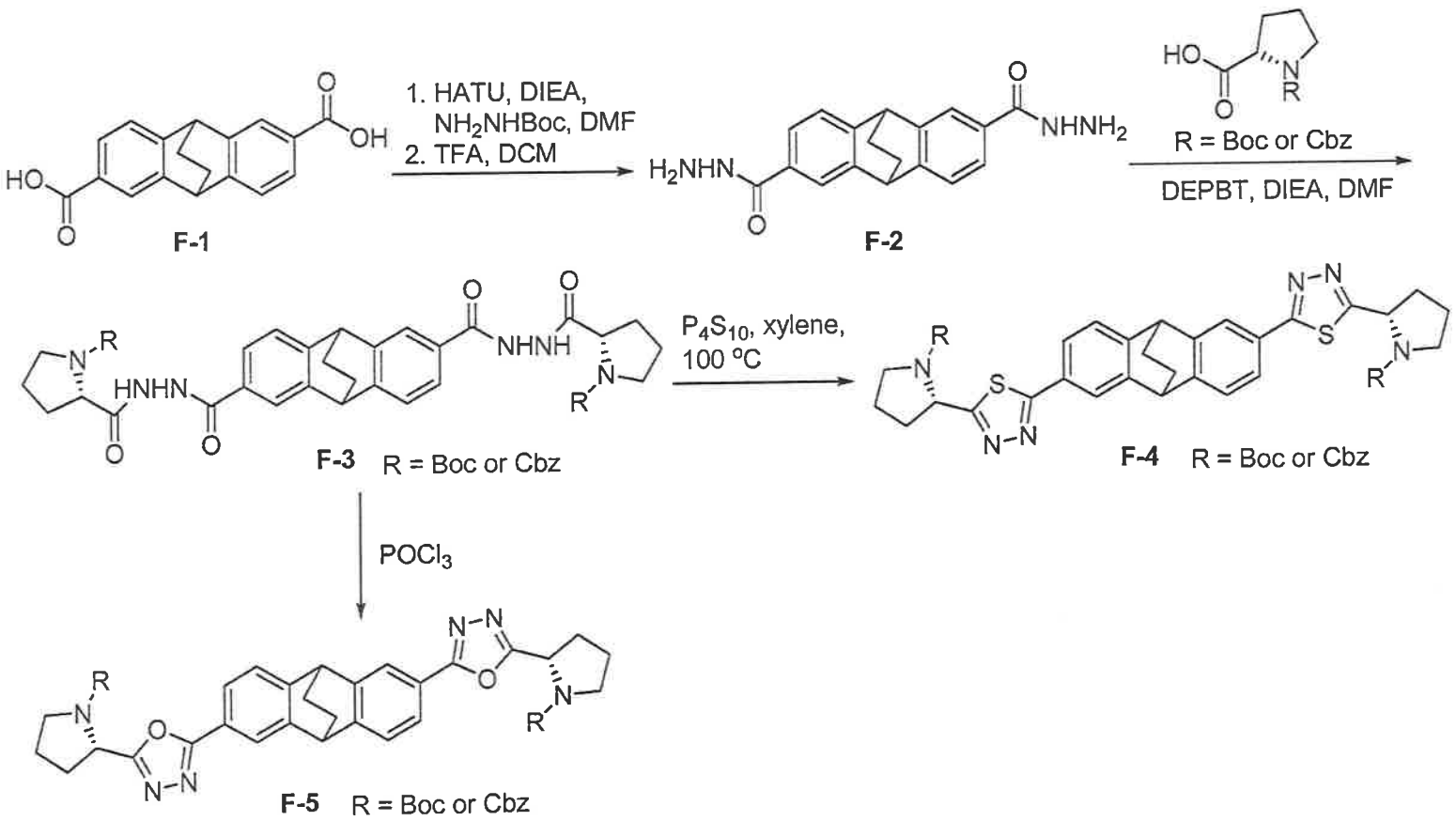
[0005] The present standard of care treatment regimen for HCV infection involves interferon-alpha, alone or in combination with ribavirin. The treatment is cumbersome and sometimes has debilitating and severe side effects and many patients do not durably respond to treatment. New and effective methods of treating HCV infection are urgently needed.


C-1
C-2
X=Cl or Br
R = Boc or Cbz
Et3N, CH3CN
C-3 R = Boc or Cbz
NH4Ac, Et3N,
toluene, 120 °C
C-4 R = Boc or Cbz
EtOH, MgO, reflux
X=Cl or Br
R = Boc or Cbz
C-2
C-5
CuCN, DMF
C-6
1. HCl(gas), anhy. MeOH
2. NH3
C-7

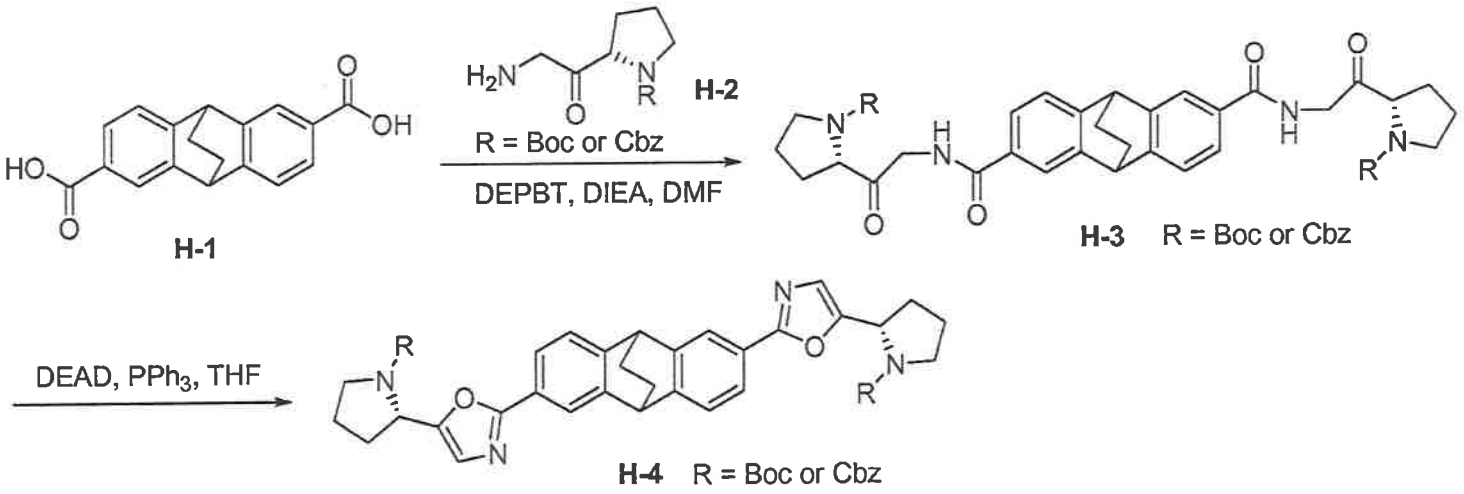
Scheme C


MeO
O
OMe
O
E-1
DIBAL, THF, -78°C
H
O
O
E-2
CBr4, PPh3
Br
Br
Br
Br
E-3
NaOH, MeOH
JP 56115772
H
O
O
H
E-4
Br2, CCl4
H2N
N
R
S
E-6
Br
H
O
O
H
Br
E-5
R = Boc or Cbz
Acetone, 60 °C
R
N
S
N
N
S
N
R
E-7

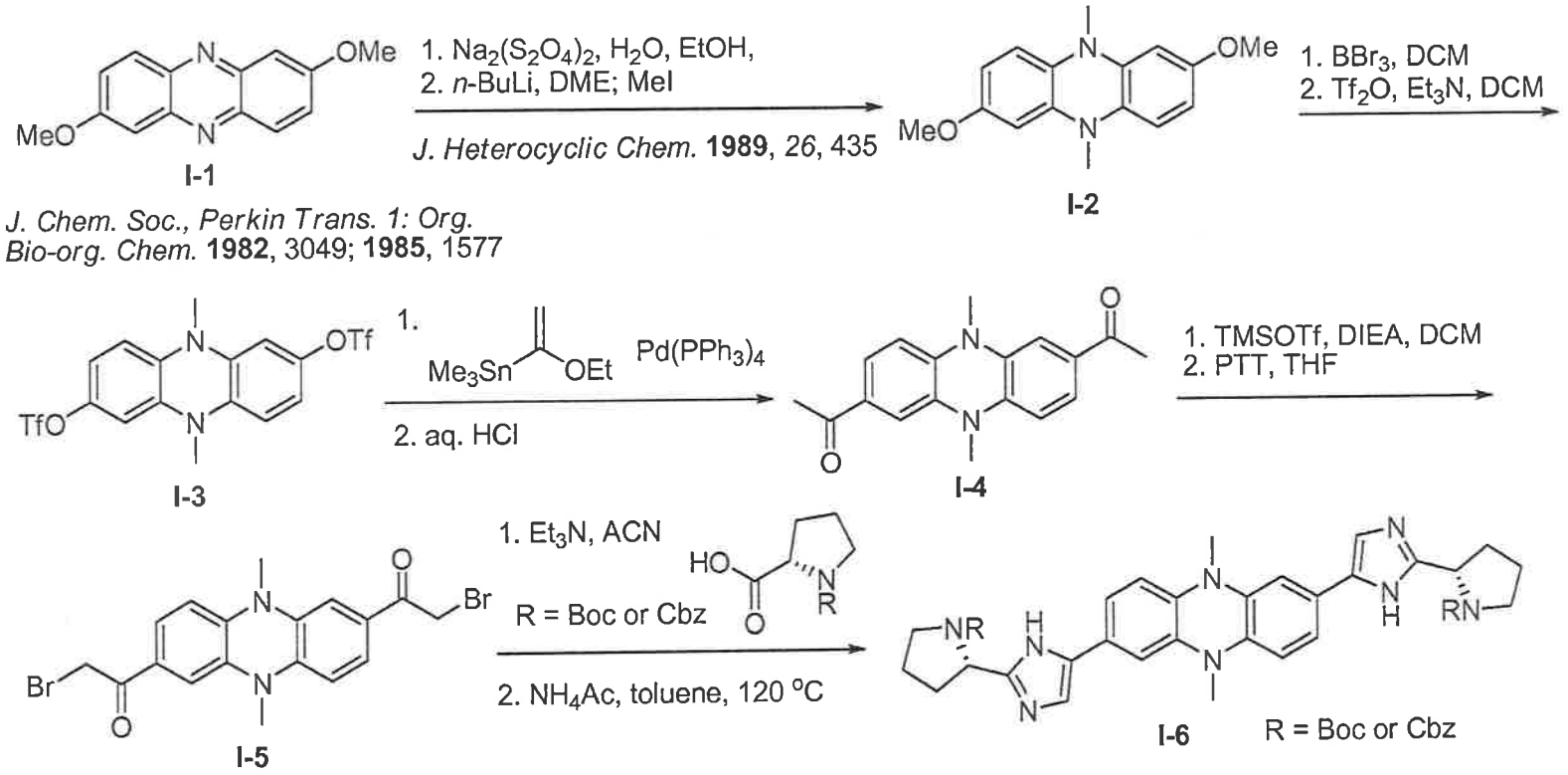
Scheme E


1. HATU, DIEA,
NH2NHBoc, DMF
2. TFA, DCM
F-1
F-2
R = Boc or Cbz
DEPBT, DIEA, DMF
P4S10, xylene,
100 °C
F-3 R = Boc or Cbz
F-4 R = Boc or Cbz
POCl3
F-5 R = Boc or Cbz

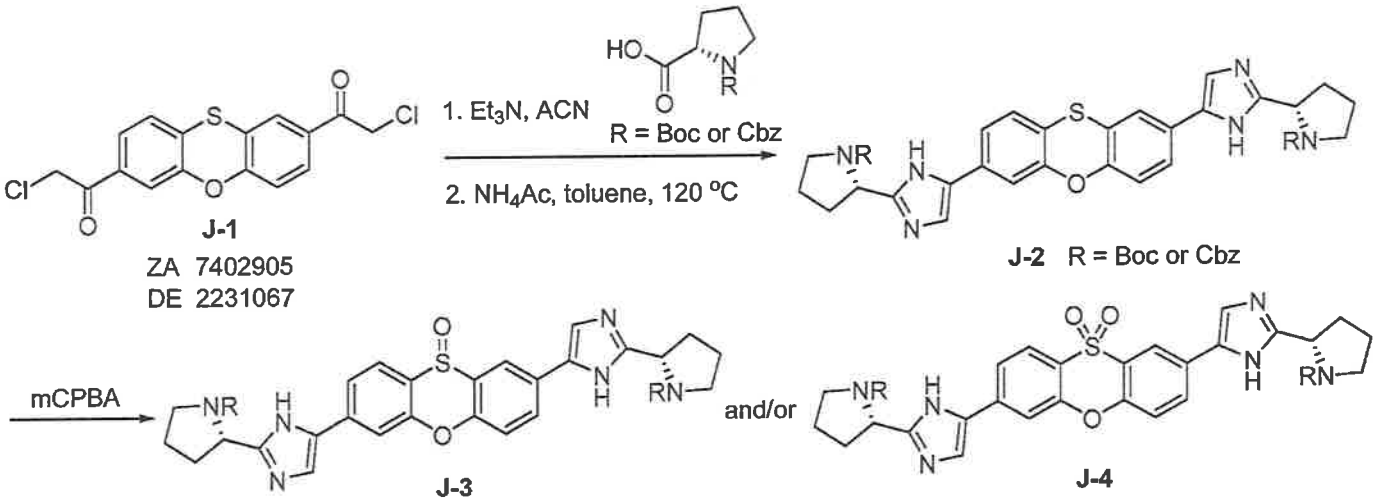
Scheme F


H-1
H-2
R = Boc or Cbz
DEPBT, DIEA, DMF
H-3 R = Boc or Cbz
DEAD, PPh3, THF
H-4 R = Boc or Cbz

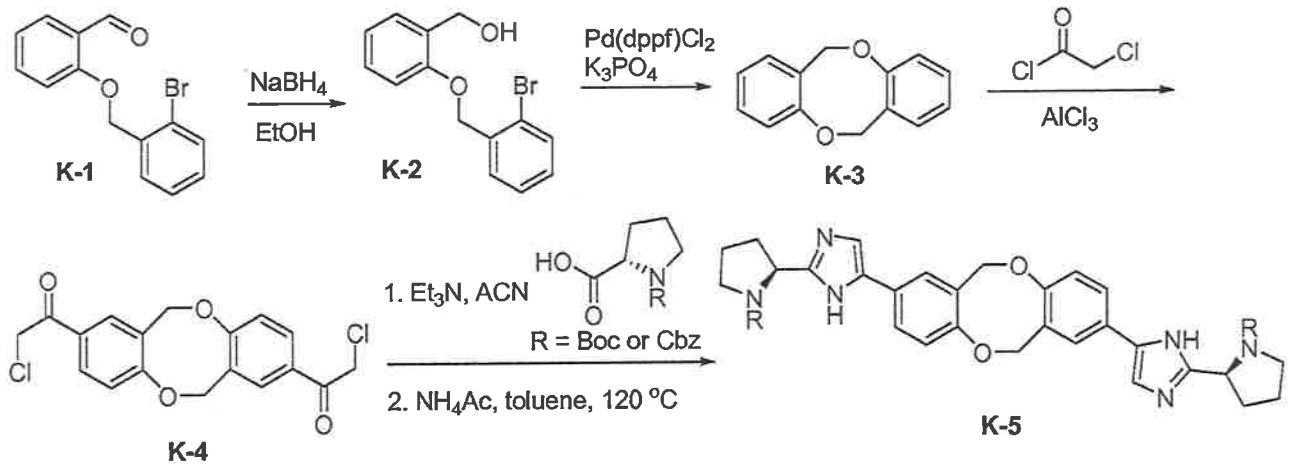
Scheme H


OMe
MeO
N
N
I-1
1. $Na_2(S_2O_4)_2$, H_2O, EtOH,
2. *n*-BuLi, DME; MeI
J. Heterocyclic Chem. **1989**, *26*, 435
OMe
MeO
N
N
I-2
1. BBr_3, DCM
2. Tf_2O, Et_3N, DCM
J. Chem. Soc., Perkin Trans. 1: Org.
Bio-org. Chem. **1982**, 3049; **1985**, 1577
OTf
TfO
N
N
I-3
1.
Me_3Sn
OEt
$Pd(PPh_3)_4$
2. aq. HCl
O
O
N
N
I-4
1. TMSOTf, DIEA, DCM
2. PTT, THF
Br
Br
O
O
N
N
I-5
1. Et_3N, ACN
HO
O
N
R
R = Boc or Cbz
2. NH_4Ac, toluene, 120 °C
NR
RN
N
H
N
H
N
N
I-6
R = Boc or Cbz

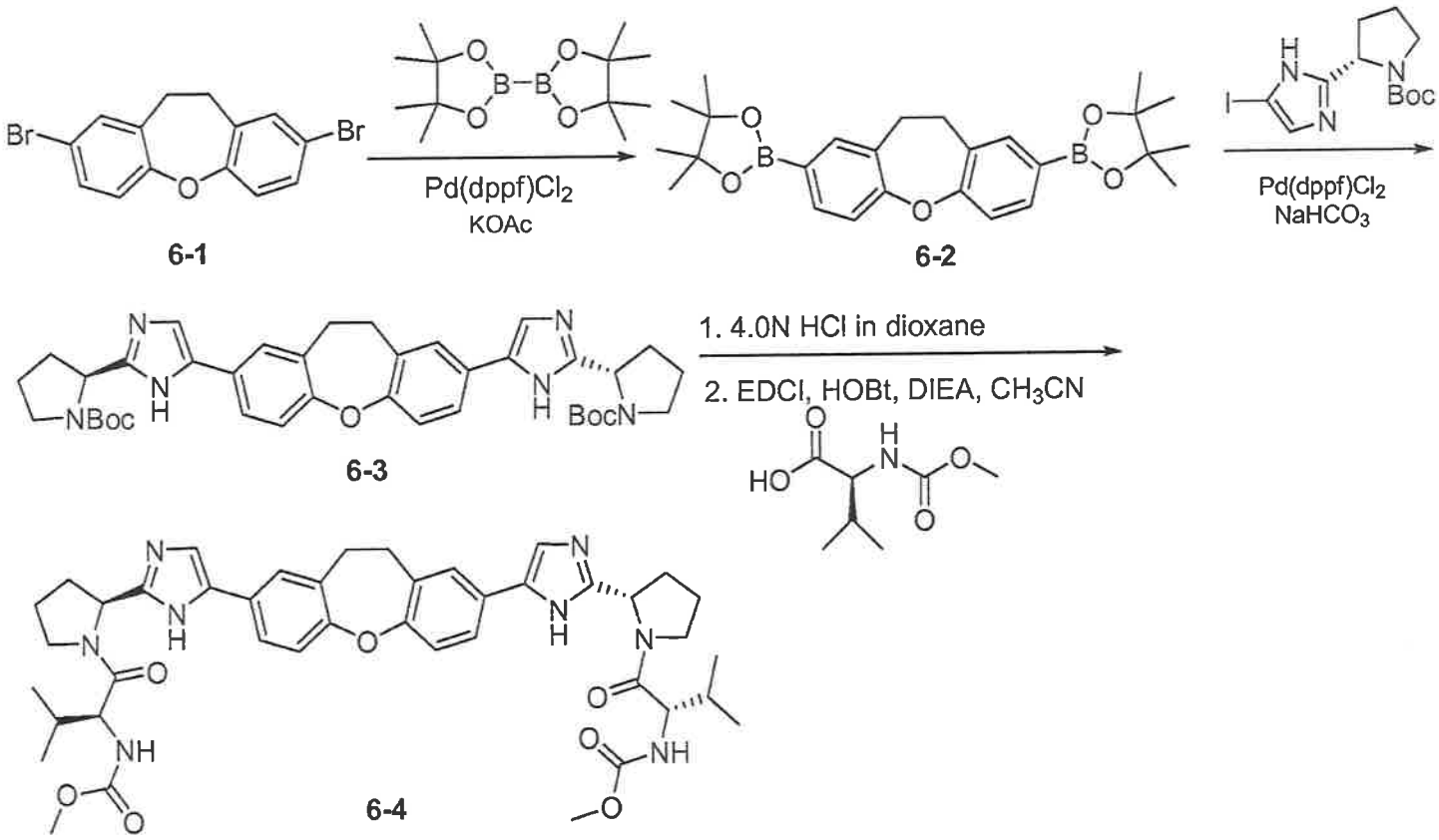
Scheme I


1. Et3N, ACN
2. NH4Ac, toluene, 120 °C
R = Boc or Cbz
J-1
ZA 7402905
DE 2231067
J-2 R = Boc or Cbz
mCPBA
J-3
and/or
J-4

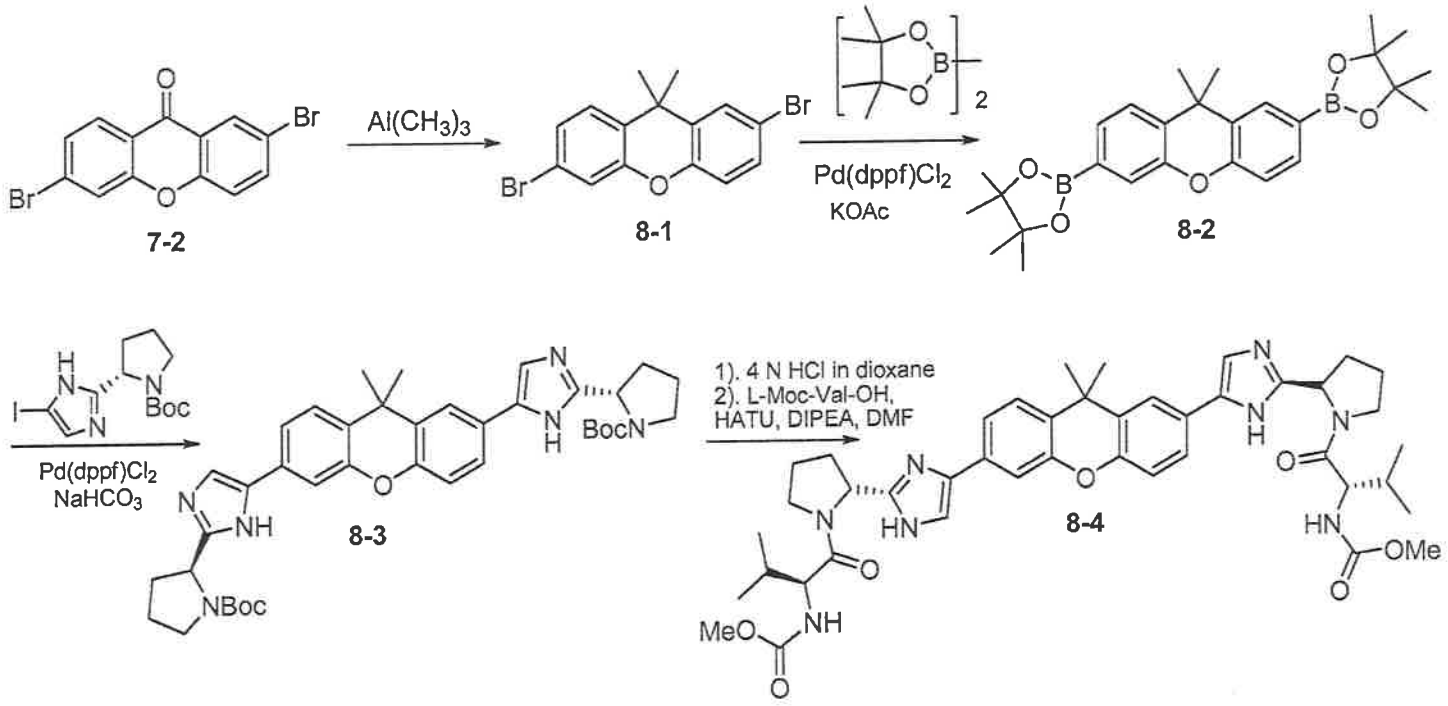
Scheme J


K-1
NaBH4
EtOH
K-2
Pd(dppf)Cl2
K3PO4
K-3
AlCl3
K-4
1. Et3N, ACN
R = Boc or Cbz
2. NH4Ac, toluene, 120 °C
K-5

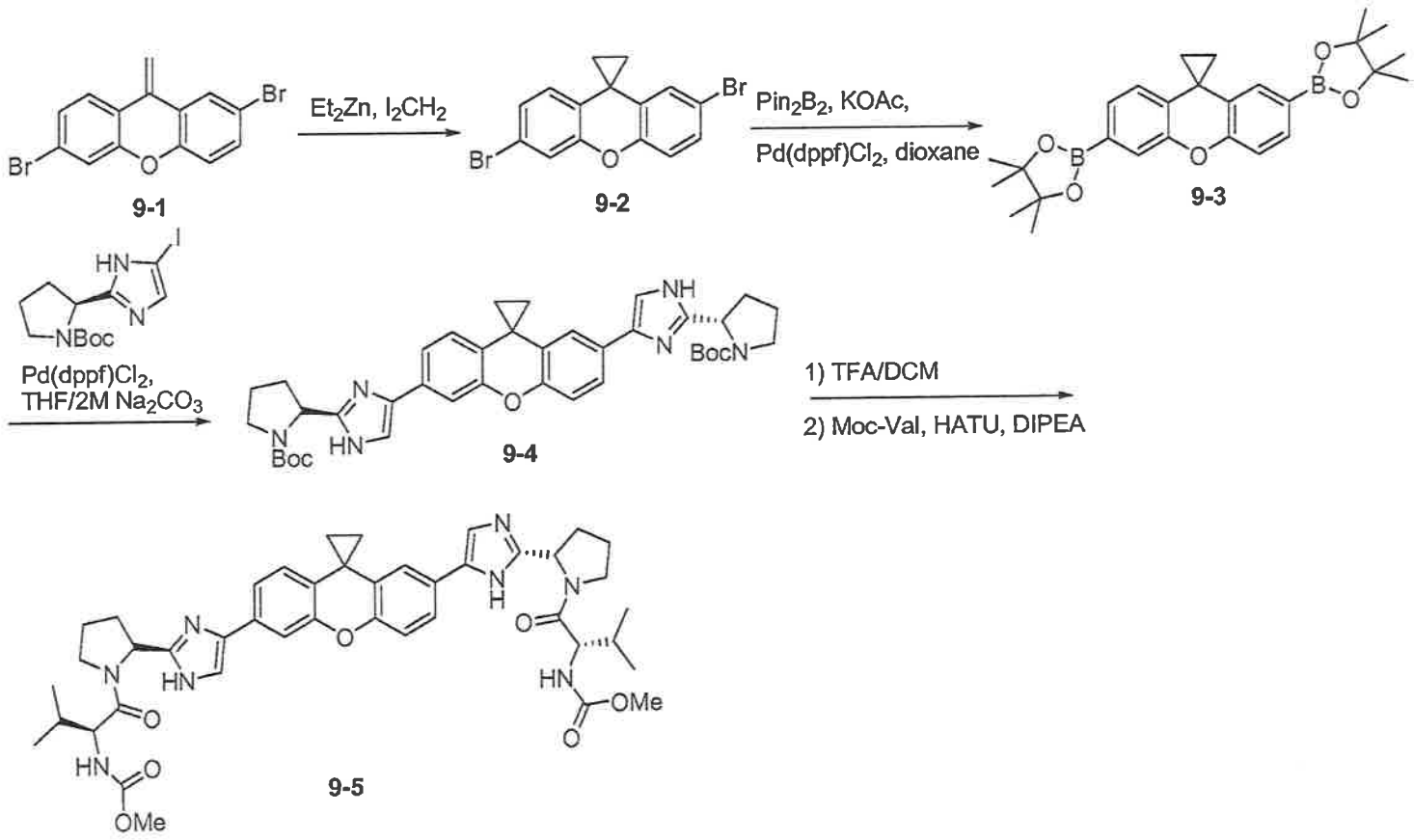
Scheme K


Br
Br
Pd(dppf)Cl2
KOAc
6-1
6-2
Pd(dppf)Cl2
NaHCO3
Boc
1. 4.0N HCl in dioxane
2. EDCI, HOBt, DIEA, CH3CN
NBoc
BocN
6-3
6-4

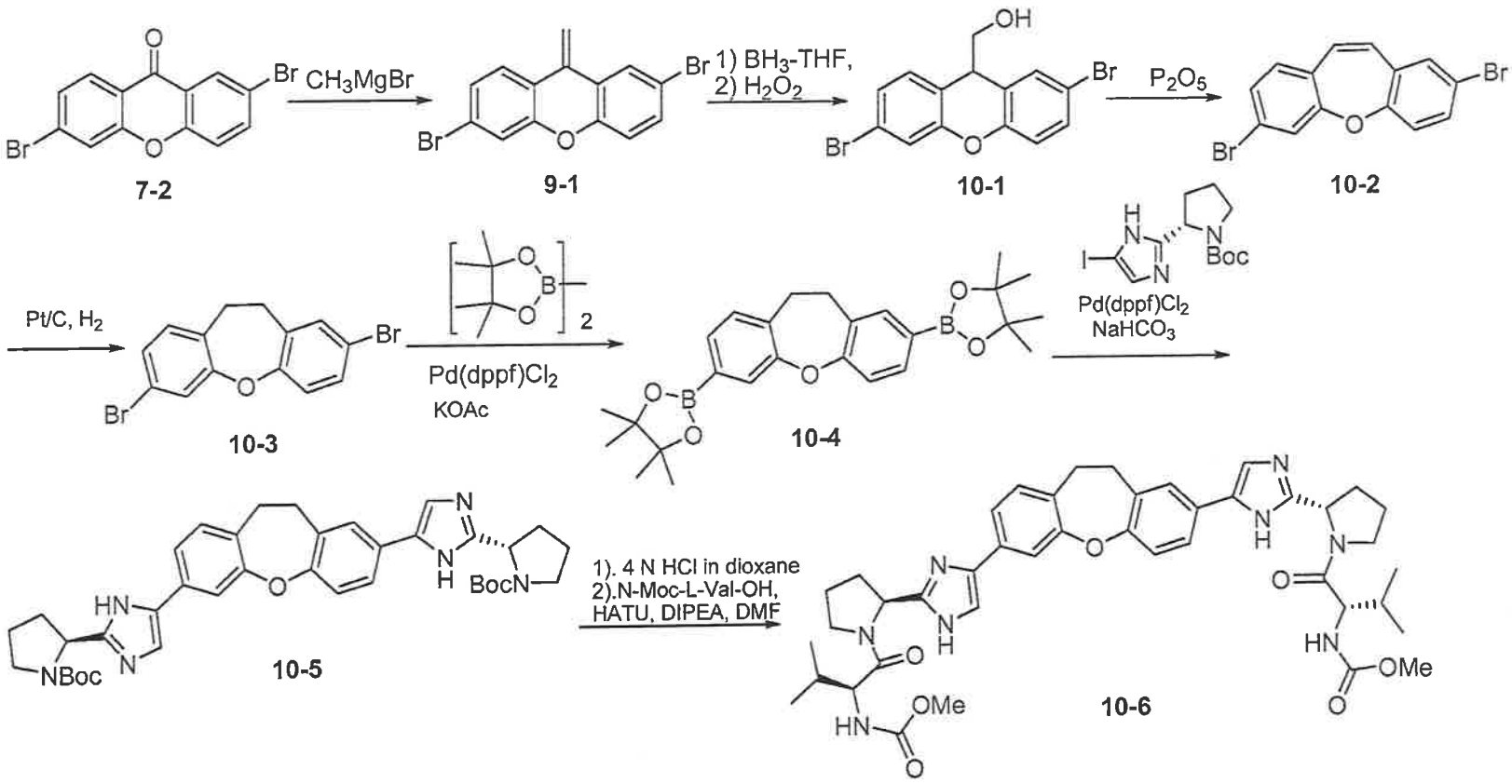
Scheme 6


Br
O
Br
7-2
Al(CH3)3
Br
Br
8-1
O
B
O
2
Pd(dppf)Cl2
KOAc
O
B
O
O
B
O
8-2
H
N
N
Boc
I
Pd(dppf)Cl2
NaHCO3
N
NH
NBoc
8-3
N
N
H
BocN
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA, DMF
N
HN
8-4
N
N
H
O
HN
OMe
O
N
O
MeO
NH
O

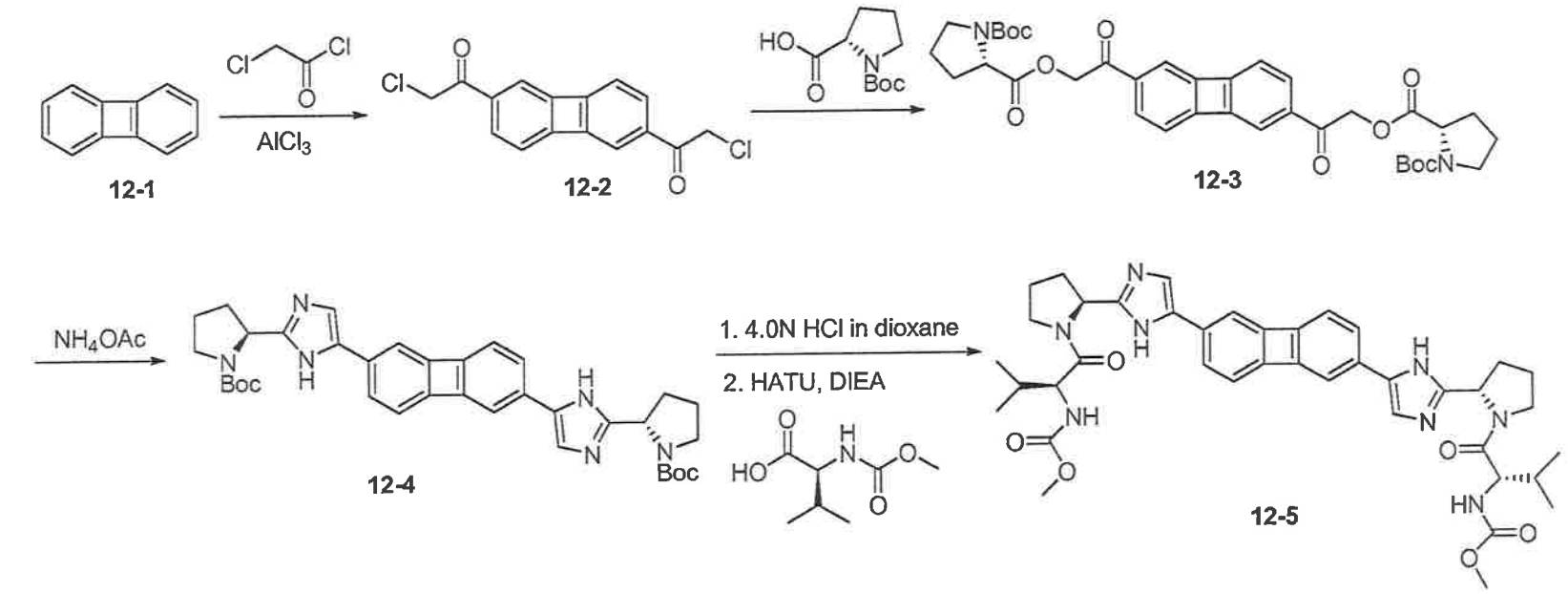
Scheme 8


Et2Zn, I2CH2
Pin2B2, KOAc,
Pd(dppf)Cl2, dioxane
9-1
9-2
9-3
Pd(dppf)Cl2,
THF/2M Na2CO3
9-4
1) TFA/DCM
2) Moc-Val, HATU, DIPEA
9-5

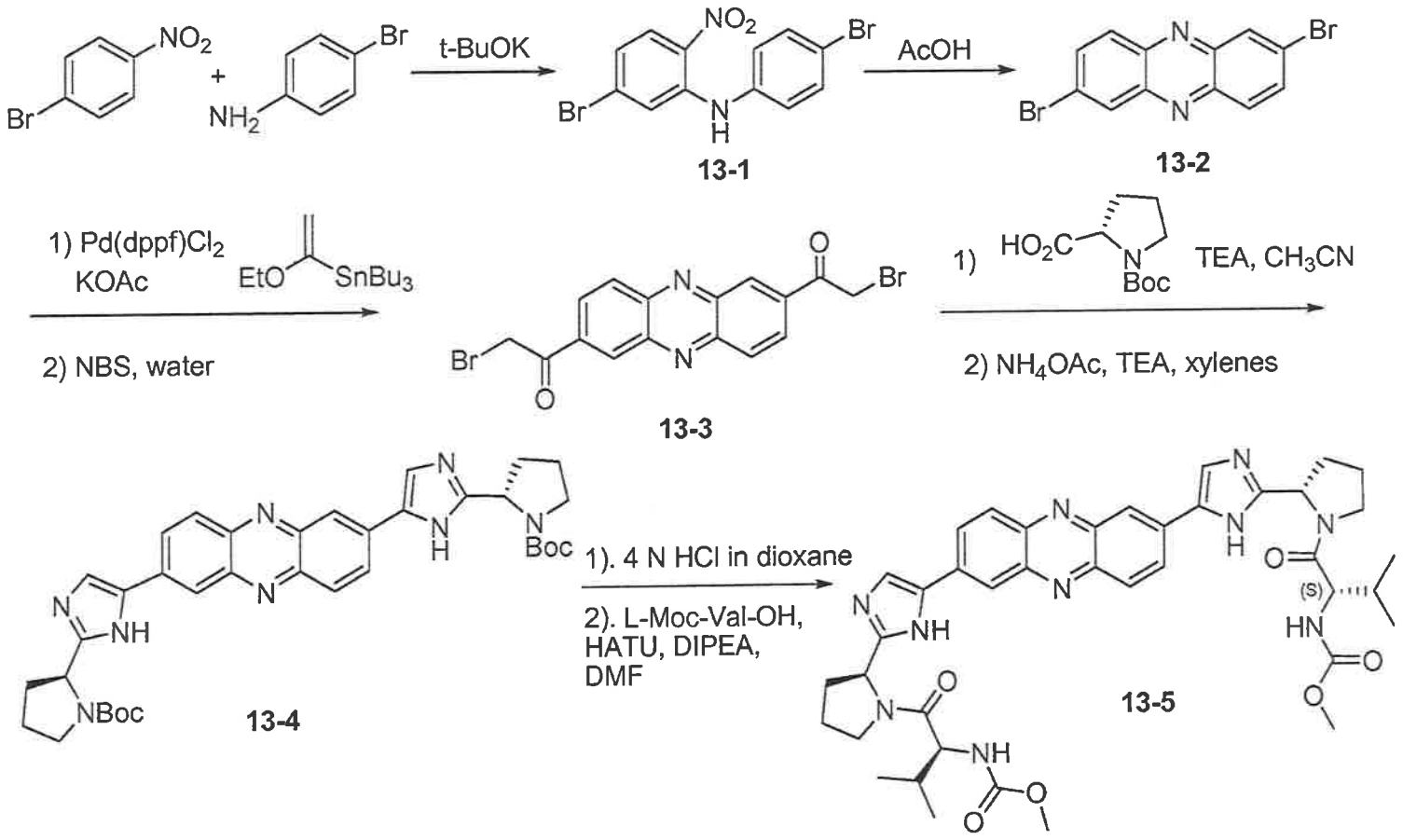
Scheme 9


7-2
9-1
10-1
10-2
10-3
10-4
10-5
10-6
CH3MgBr
1) BH3-THF,
2) H2O2
P2O5
Pt/C, H2
Pd(dppf)Cl2
KOAc
Pd(dppf)Cl2
NaHCO3
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF

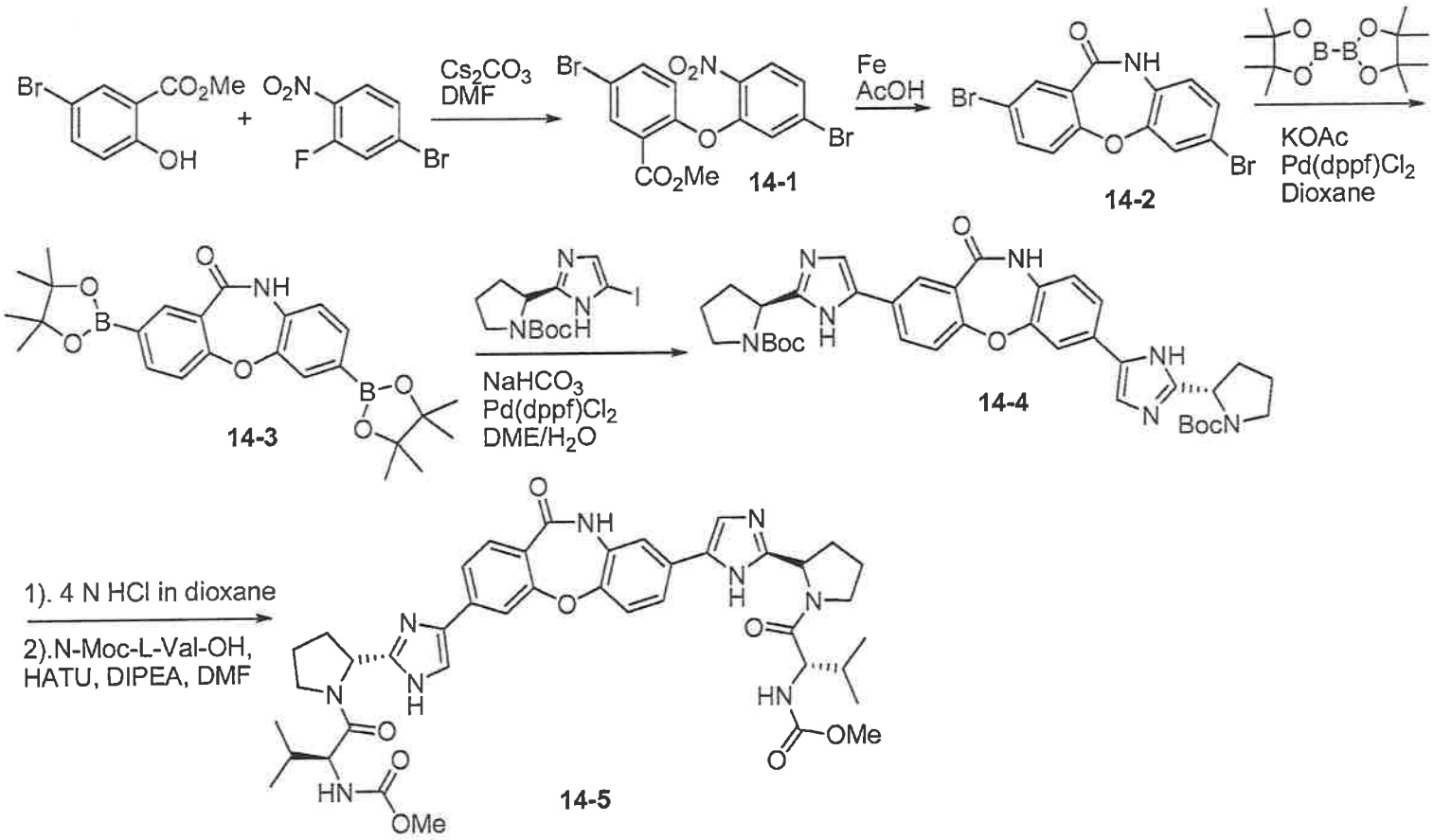
Scheme 10


12-1
AlCl3
12-2
12-3
NH4OAc
12-4
1. 4.0N HCl in dioxane
2. HATU, DIEA
12-5

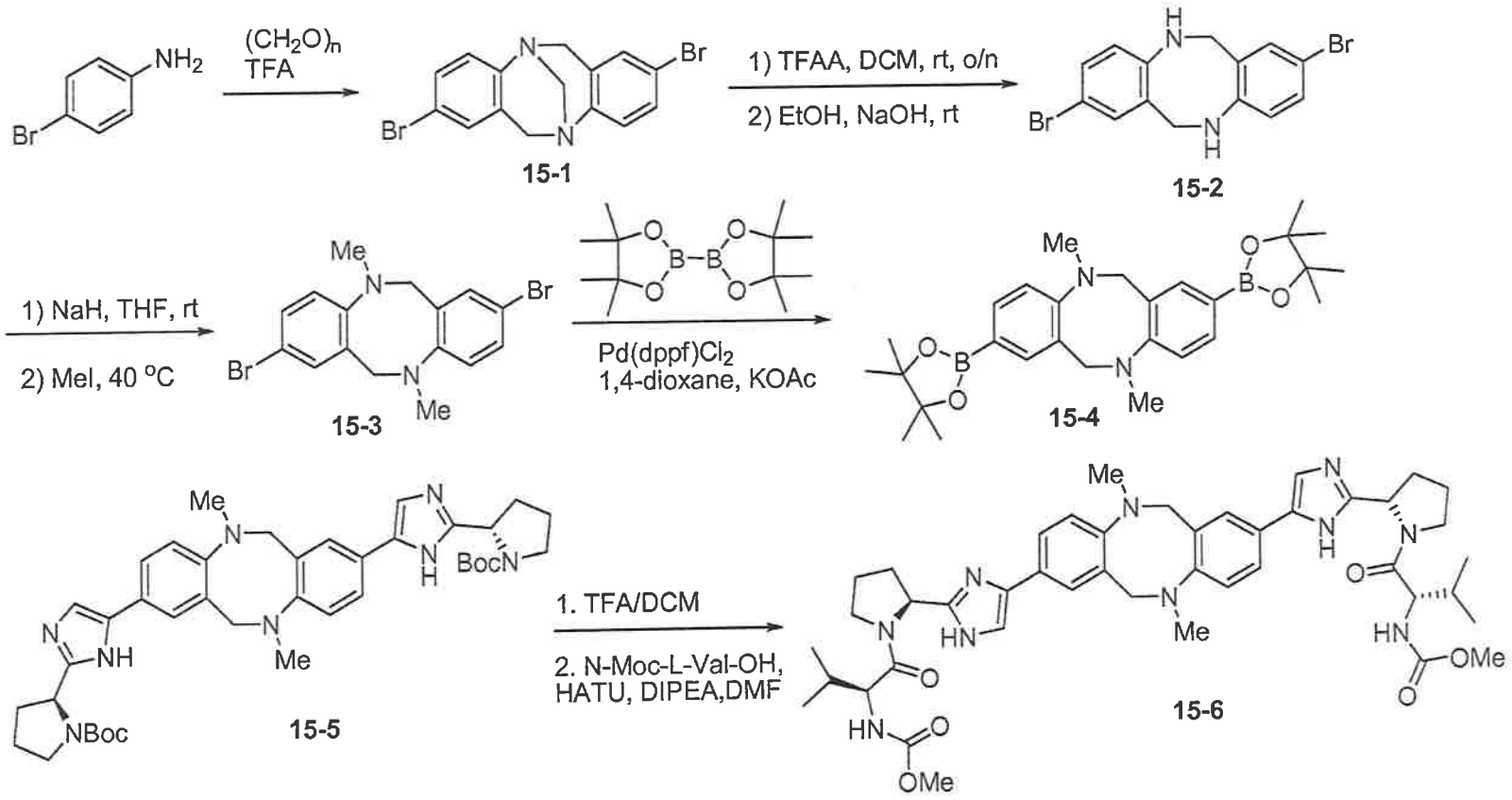
Scheme 12


NO2
Br
NH2
t-BuOK
AcOH
13-1
13-2
1) Pd(dppf)Cl2
KOAc
EtO
SnBu3
2) NBS, water
13-3
1)
HO2C
N
Boc
TEA, CH3CN
2) NH4OAc, TEA, xylenes
NBoc
13-4
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA,
DMF
13-5

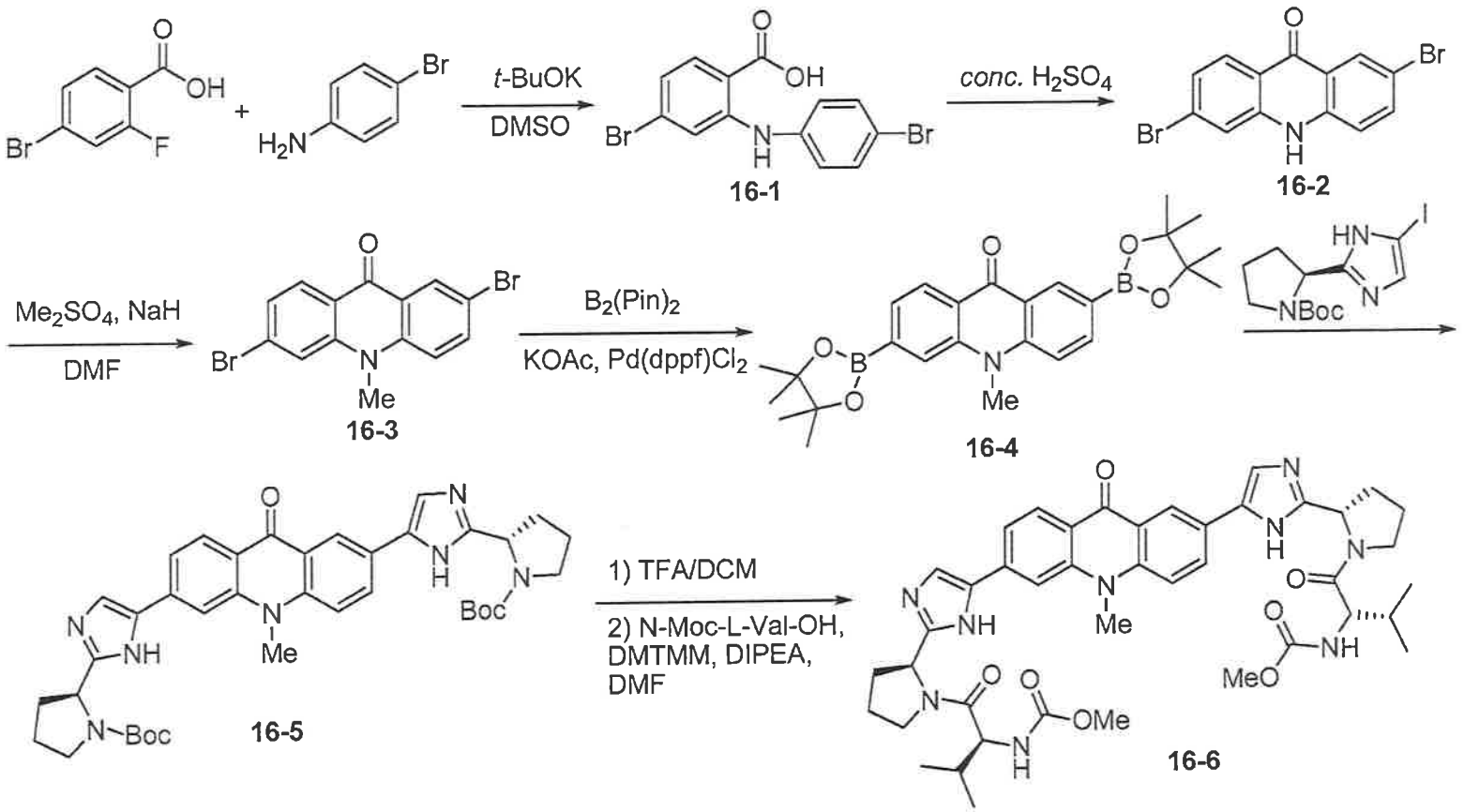
Scheme 13


Br
CO2Me
OH
+
O2N
F
Br
Cs2CO3
DMF
Br
O2N
O
Br
CO2Me
14-1
Fe
AcOH
O
NH
Br
O
Br
14-2
B-B
KOAc
Pd(dppf)Cl2
Dioxane
O
NH
B
O
O
O
B
O
O
14-3
N
I
NBocH
NaHCO3
Pd(dppf)Cl2
DME/H2O
O
NH
N
NBoc
N
H
O
NH
N
BocN
14-4
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF
O
NH
N
N
H
O
N
N
H
N
O
HN
OMe
O
N
O
HN
O
OMe
14-5

Scheme 14


(CH2O)n
TFA
1) TFAA, DCM, rt, o/n
2) EtOH, NaOH, rt
15-1
15-2
1) NaH, THF, rt
2) MeI, 40 °C
15-3
Pd(dppf)Cl2
1,4-dioxane, KOAc
15-4
1. TFA/DCM
2. N-Moc-L-Val-OH,
HATU, DIPEA,DMF
15-5
15-6

Scheme 15


t-BuOK
DMSO
conc. H2SO4
16-1
16-2
Me2SO4, NaH
DMF
16-3
B2(Pin)2
KOAc, Pd(dppf)Cl2
16-4
1) TFA/DCM
2) N-Moc-L-Val-OH,
DMTMM, DIPEA,
DMF
16-5
16-6

Scheme 16

Fused Ring Inhibitors of Hepatitis C

Inventors: Leping Li and Min Zhong

Statement of Related Applications

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Field of the Invention

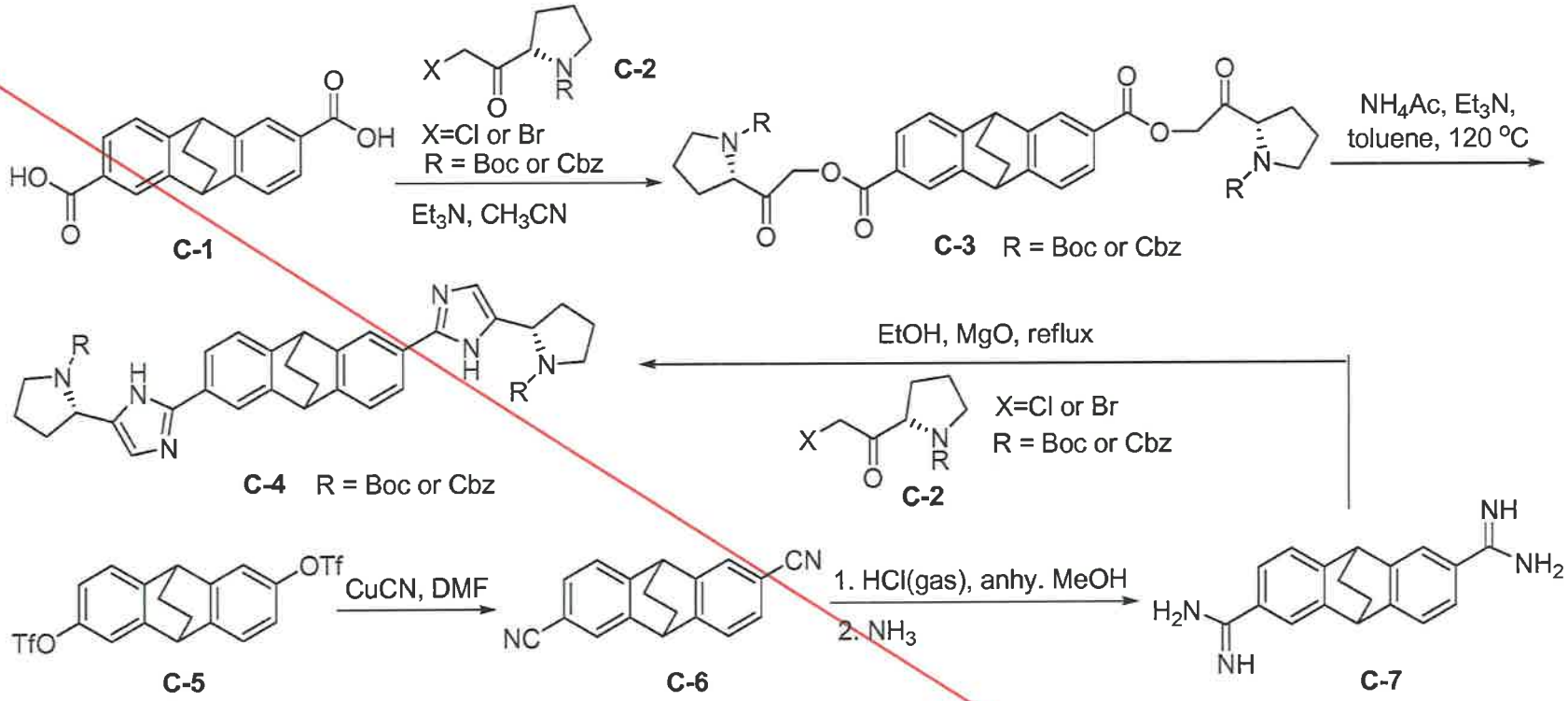
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Background of the Invention

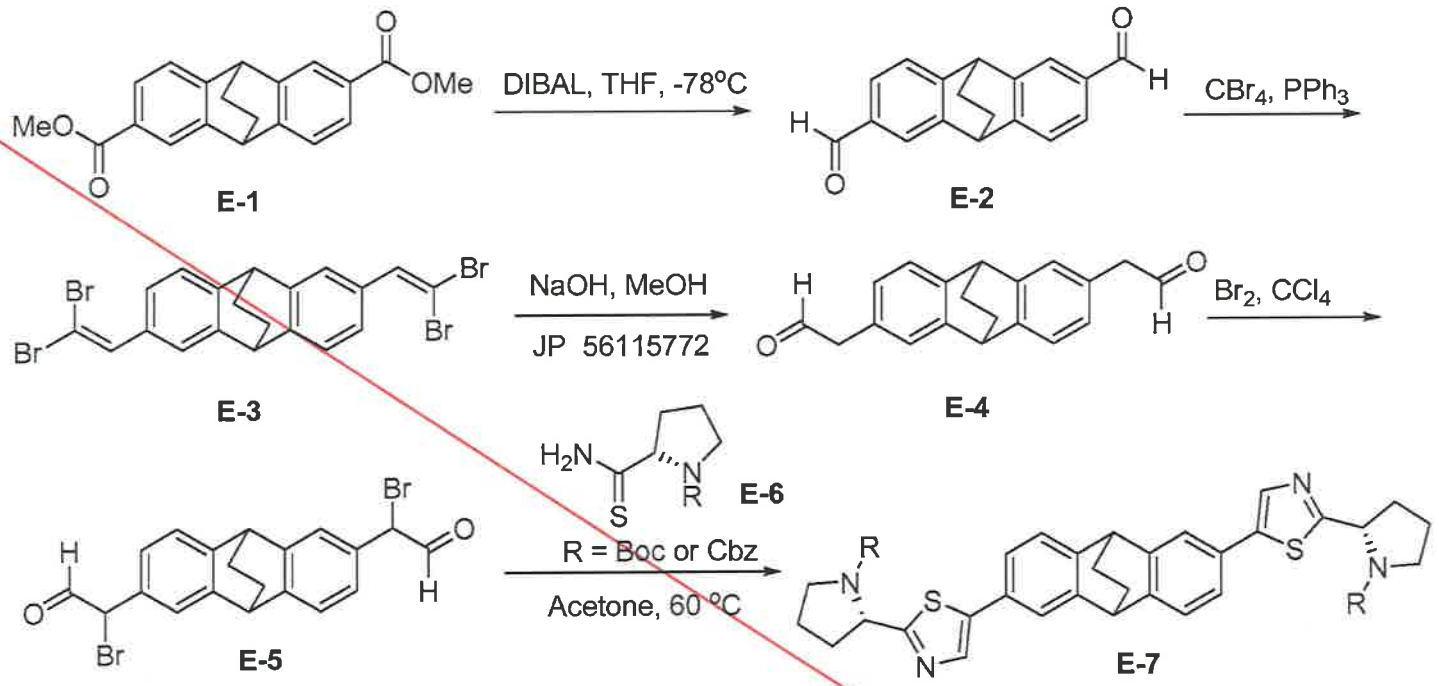
[0003] HCV is a single-stranded RNA virus that is a member of the *Flaviviridae* family. The virus shows extensive genetic heterogeneity as there are currently seven identified genotypes and more than 50 identified subtypes. In HCV infected cells, viral RNA is translated into a polyprotein that is cleaved into ten individual proteins. At the amino terminus are structural proteins: the core (C) protein and the envelope glycoproteins, E1 and E2, and p7, an integral membrane protein that follows E1 and E2. Additionally, there are six non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B, which play a functional role in the HCV lifecycle. (*see,* for example, Lindenbach, B.D. and Rice, C.M. *Nature.* 436:933-938, 2005).

[0004] Infection by HCV is a serious health issue. It is estimated that 170 million people worldwide are chronically infected with HCV. HCV infection can lead to chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

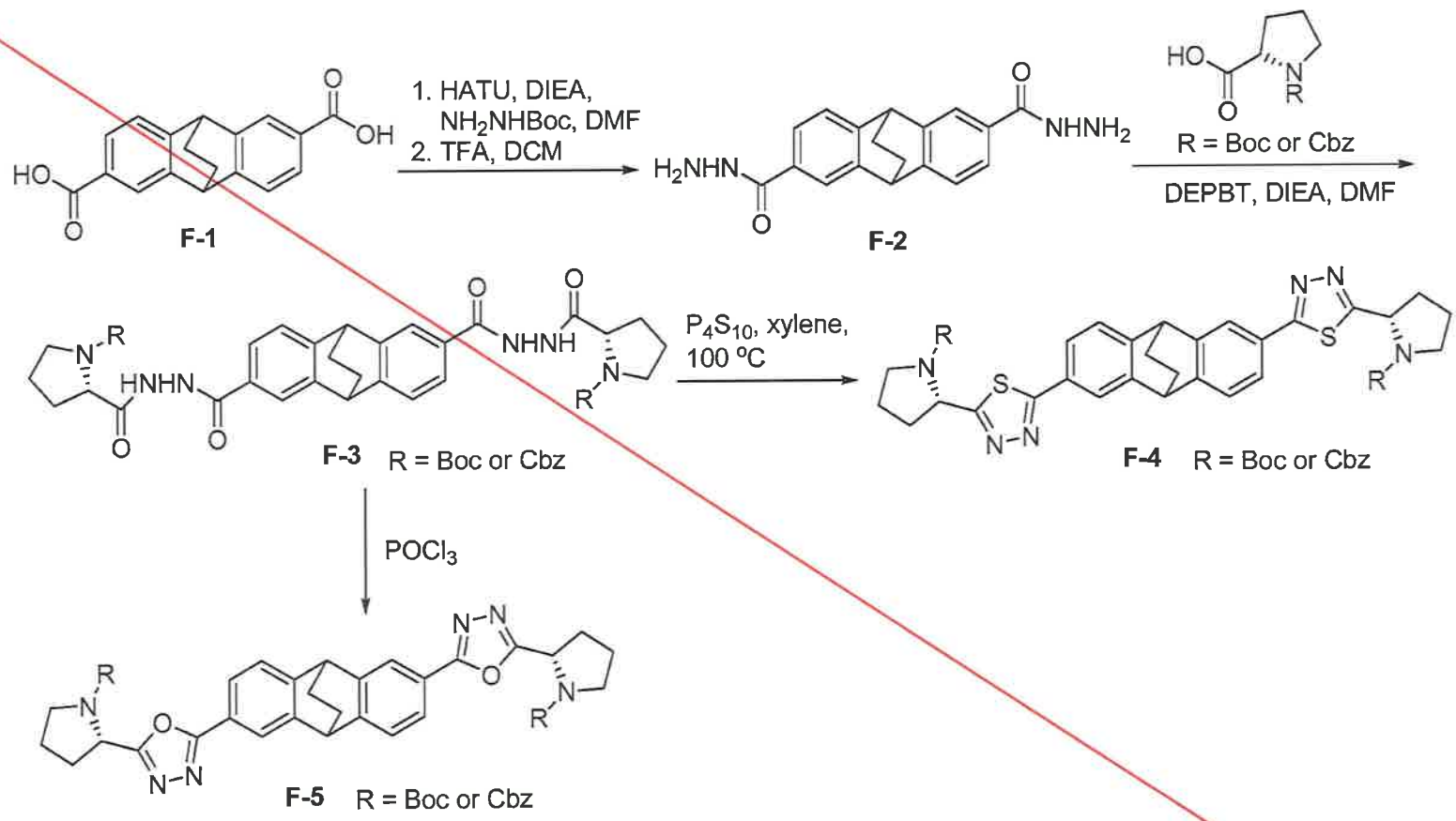
[0005] The present standard of care treatment regimen for HCV infection involves interferon-alpha, alone or in combination with ribavirin. The treatment is cumbersome and sometimes has debilitating and severe side effects and many patients do not durably respond to treatment. New and effective methods of treating HCV infection are urgently needed.


C-1
C-2
X=Cl or Br
R = Boc or Cbz
Et3N, CH3CN
C-3 R = Boc or Cbz
NH4Ac, Et3N,
toluene, 120 °C
EtOH, MgO, reflux
C-4 R = Boc or Cbz
C-2
X=Cl or Br
R = Boc or Cbz
C-5
CuCN, DMF
C-6
1. HCl(gas), anhy. MeOH
2. NH3
C-7

Scheme C


MeO
OMe
O
O
E-1
DIBAL, THF, -78°C
H
O
O
E-2
CBr4, PPh3
Br
Br
Br
Br
E-3
NaOH, MeOH
JP 56115772
H
O
O
H
E-4
Br2, CCl4
H2N
N
R
S
E-6
H
O
Br
O
H
Br
E-5
R = Boc or Cbz
Acetone, 60 °C
R
N
S
N
N
S
N
R
E-7

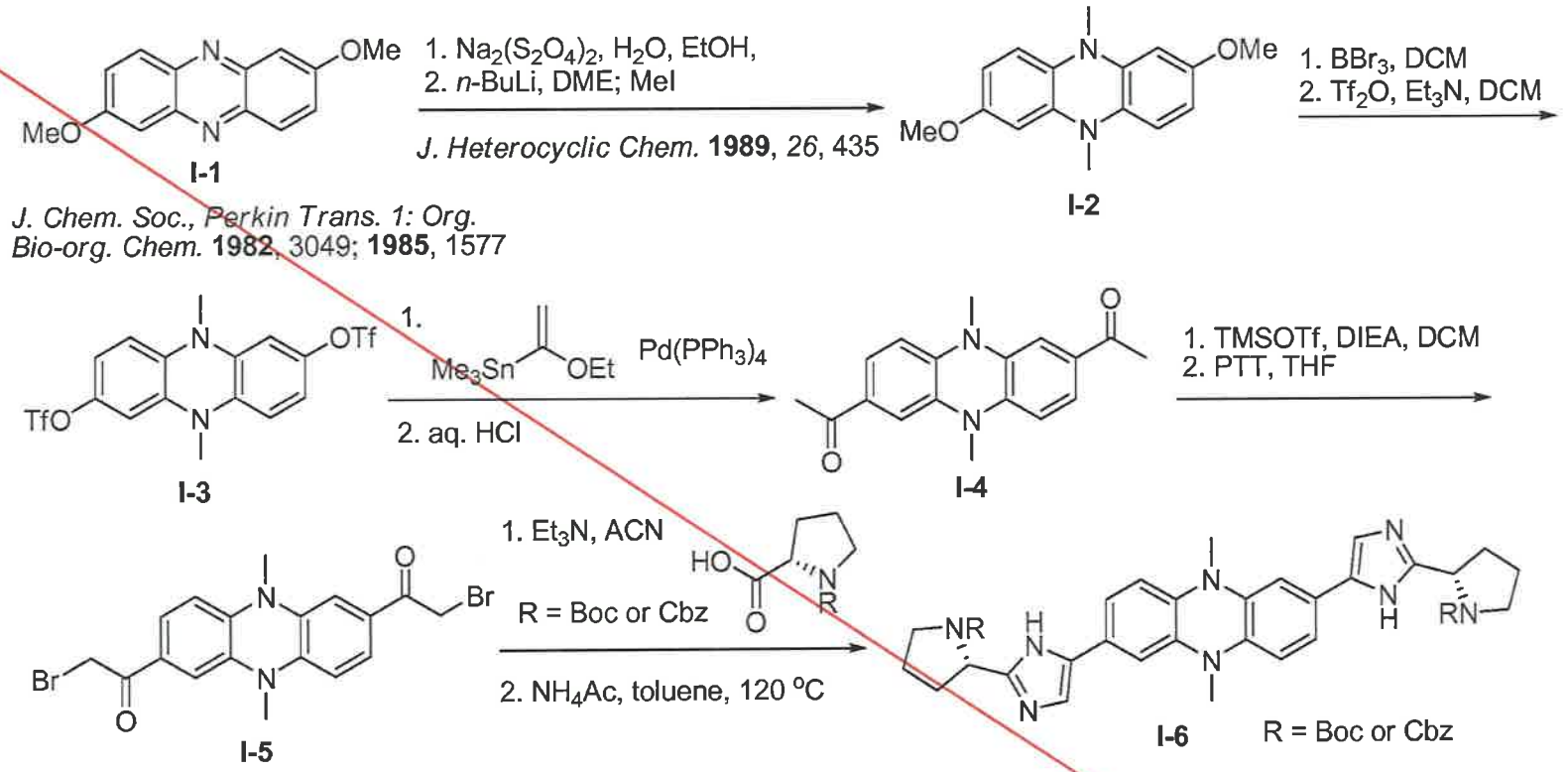
Scheme E


1. HATU, DIEA,
NH2NHBoc, DMF
2. TFA, DCM
F-1
F-2
R = Boc or Cbz
DEPBT, DIEA, DMF
F-3 R = Boc or Cbz
P4S10, xylene,
100 °C
F-4 R = Boc or Cbz
POCl3
F-5 R = Boc or Cbz

Scheme F

H-1
H-2
R = Boc or Cbz
DEPBT, DIEA, DMF
H-3 R = Boc or Cbz
DEAD, PPh3, THF
H-4 R = Boc or Cbz

Scheme H


OMe
MeO
N
N
I-1
1. $Na_2(S_2O_4)_2$, H_2O, EtOH,
2. *n*-BuLi, DME; MeI
J. Heterocyclic Chem. **1989**, *26*, 435
J. Chem. Soc., Perkin Trans. 1: Org. Bio-org. Chem. **1982**, 3049; **1985**, 1577
I-2
1. BBr_3, DCM
2. Tf_2O, Et_3N, DCM
OTf
TfO
I-3
1.
Me_3Sn
OEt
$Pd(PPh_3)_4$
2. aq. HCl
I-4
1. TMSOTf, DIEA, DCM
2. PTT, THF
Br
O
I-5
1. Et_3N, ACN
R = Boc or Cbz
2. NH_4Ac, toluene, 120 °C
HO
NR
RN
H
I-6
R = Boc or Cbz

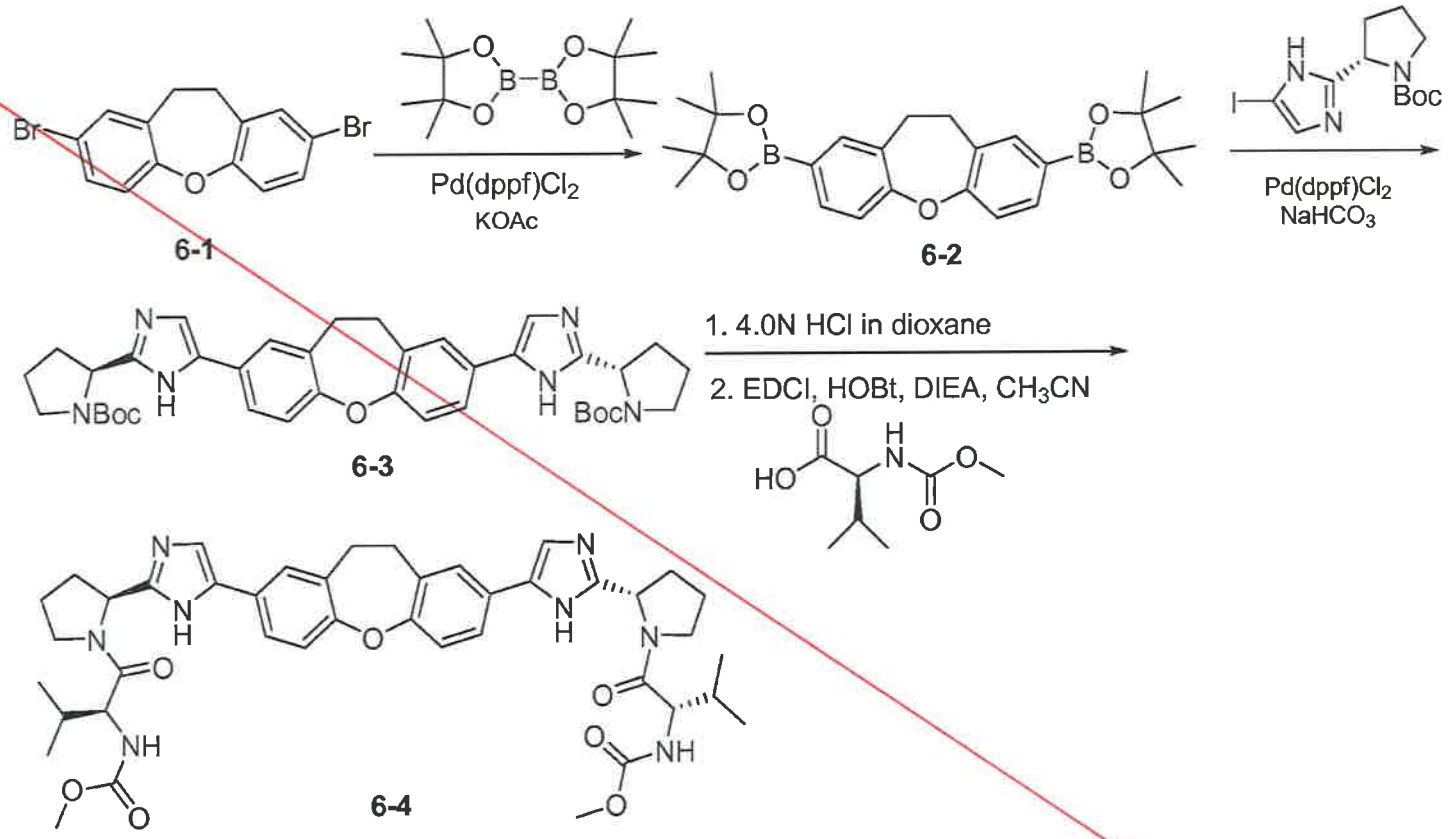
Scheme I

1. Et3N, ACN
2. NH4Ac, toluene, 120 °C
R = Boc or Cbz
J-1
J-2 R = Boc or Cbz
J-3
J-4
and/or
mCPBA
ZA 7402905
DE 2231067

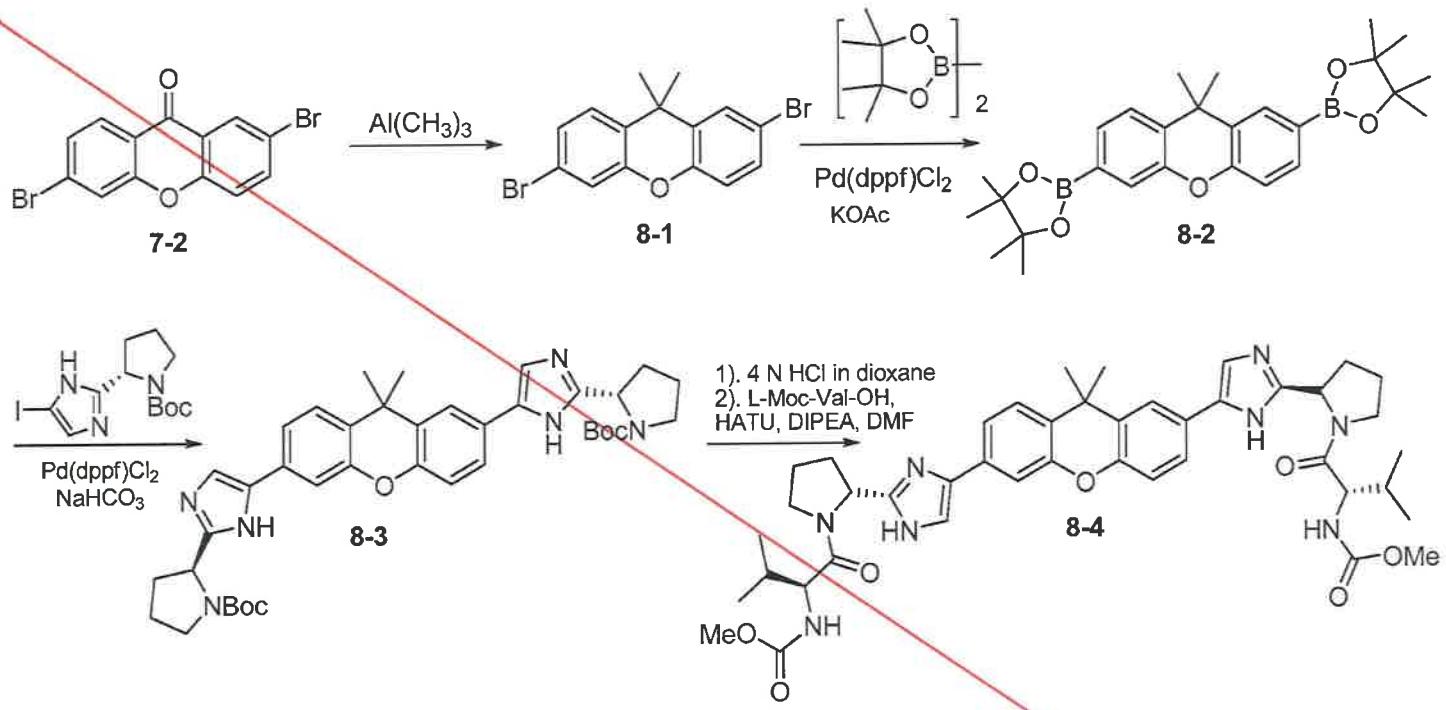
Scheme J

NaBH4
EtOH
Pd(dppf)Cl2
K3PO4
AlCl3
1. Et3N, ACN
2. NH4Ac, toluene, 120 °C
R = Boc or Cbz
K-1
K-2
K-3
K-4
K-5

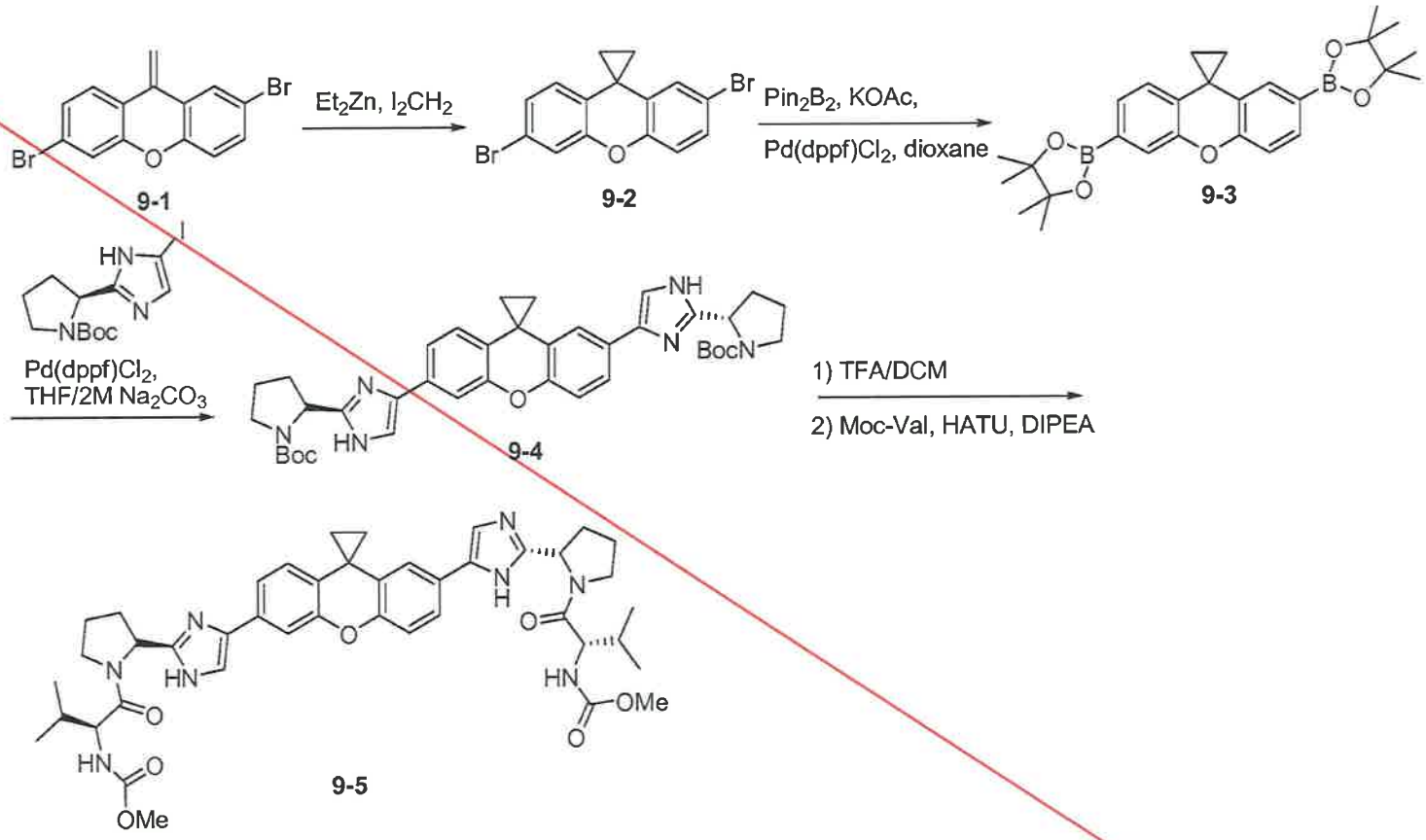
Scheme K


Br
Br
6-1
Pd(dppf)Cl2
KOAc
6-2
Pd(dppf)Cl2
NaHCO3
Boc
NBoc
BocN
6-3
1. 4.0N HCl in dioxane
2. EDCI, HOBt, DIEA, CH3CN
HO
6-4

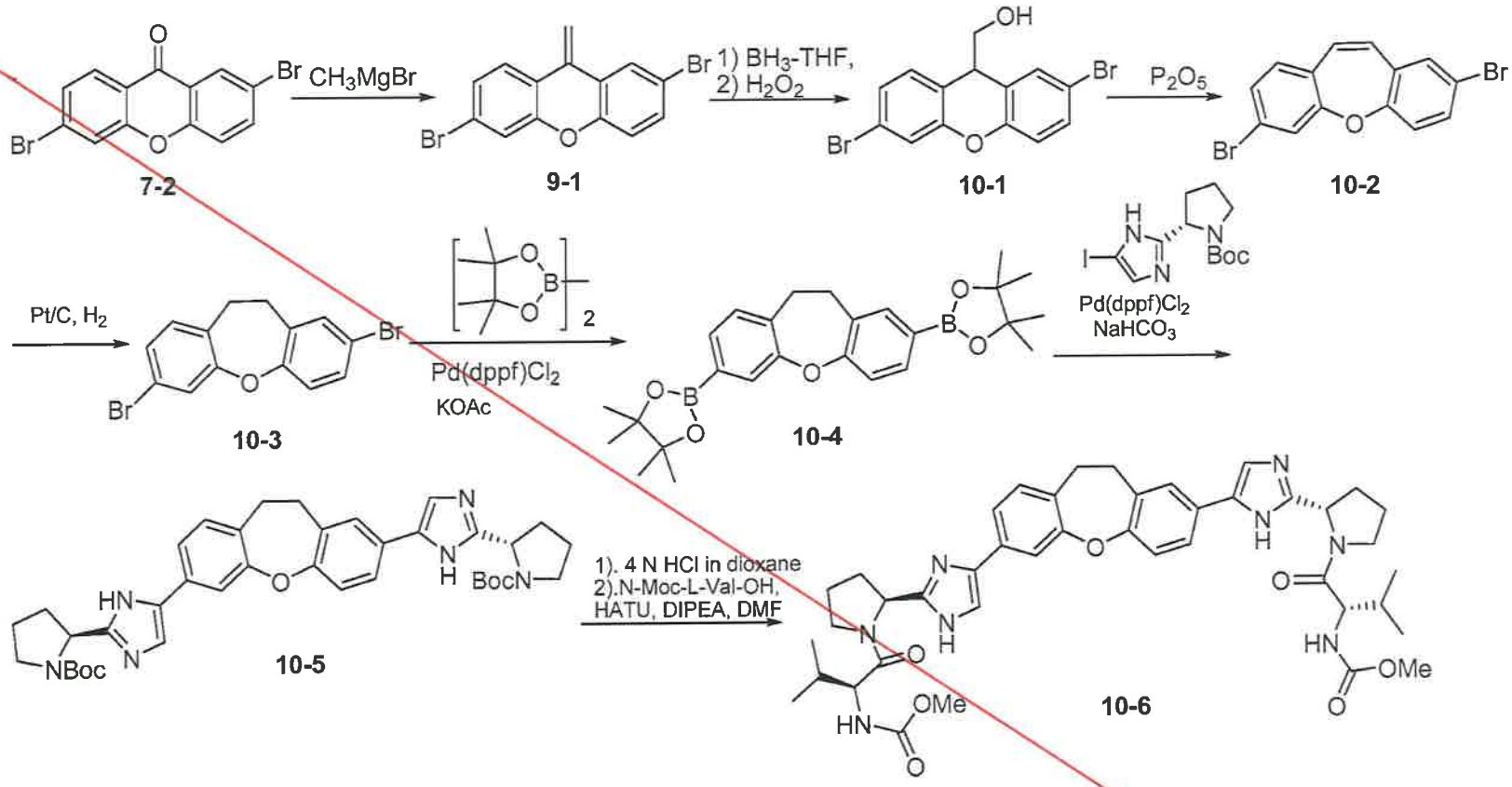
Scheme 6


Br
Br
O
7-2
Al(CH3)3
Br
8-1
Pd(dppf)Cl2
KOAc
2
8-2
Pd(dppf)Cl2
NaHCO3
8-3
NBoc
BocN
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA, DMF
8-4
HN
OMe
MeO
NH

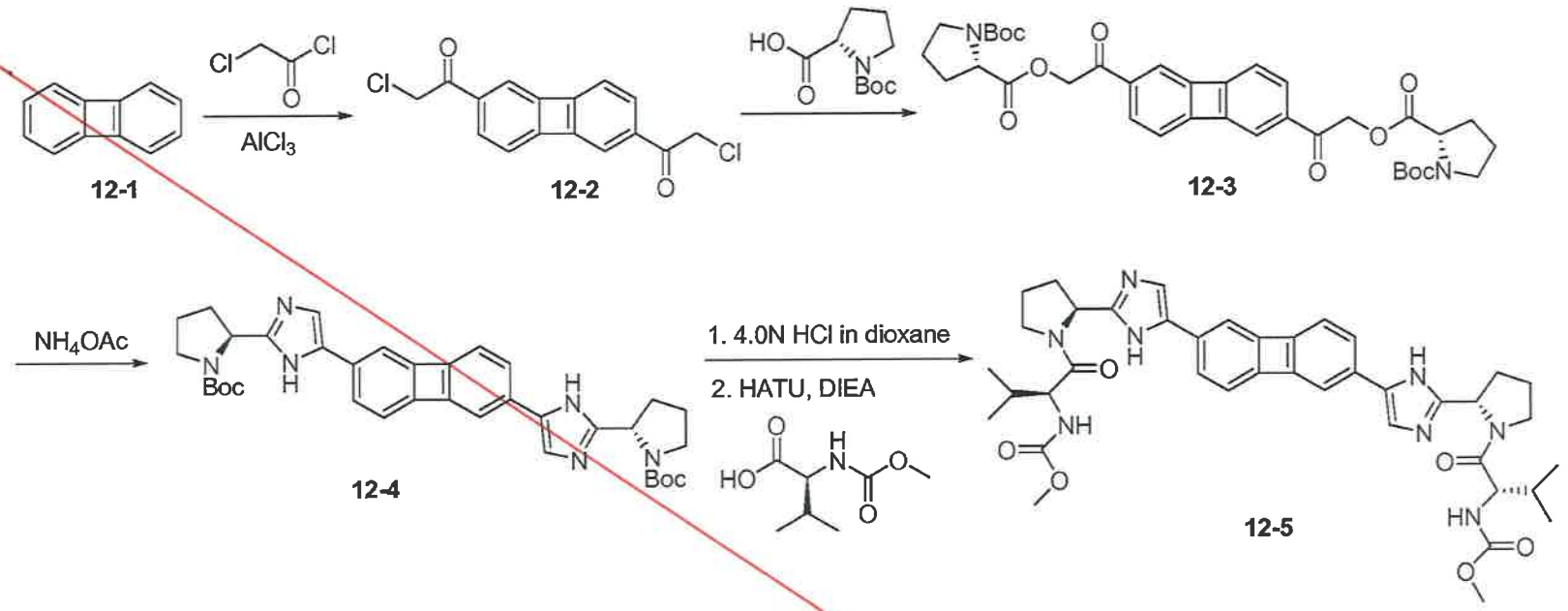
Scheme 8


Br
Br
9-1
Et2Zn, I2CH2
Br
Br
9-2
Pin2B2, KOAc,
Pd(dppf)Cl2, dioxane
O
B
O
O
B
O
9-3
HN
I
N
NBoc
Pd(dppf)Cl2,
THF/2M Na2CO3
N
HN
N
Boc
NH
N
BocN
9-4
1) TFA/DCM
2) Moc-Val, HATU, DIPEA
N
N
HN
O
HN
O
OMe
N
N
H
O
HN
OMe
O
9-5

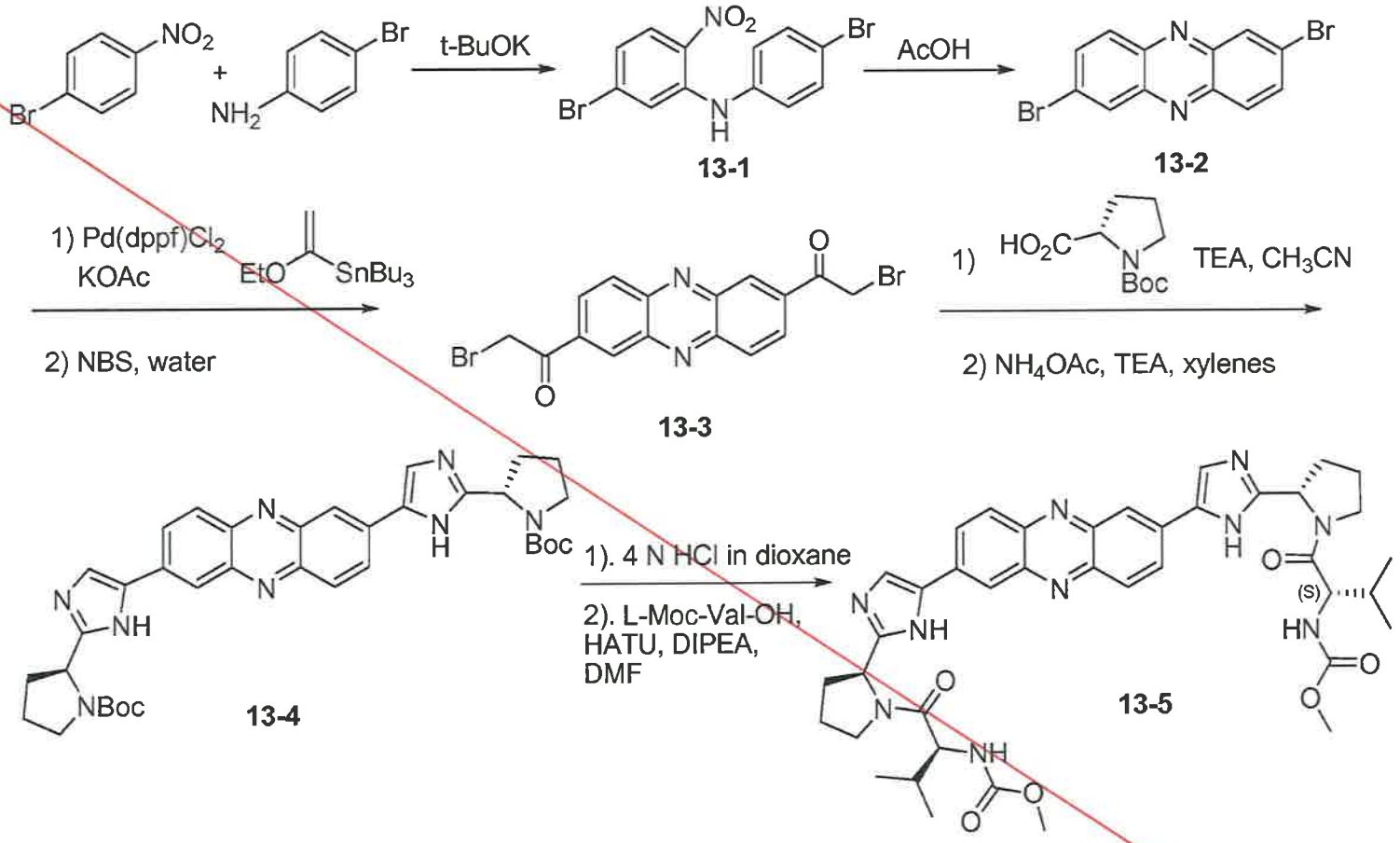
Scheme 9


7-2
9-1
10-1
10-2
10-3
10-4
10-5
10-6
CH3MgBr
1) BH3-THF,
2) H2O2
P2O5
Pt/C, H2
Pd(dppf)Cl2
KOAc
Pd(dppf)Cl2
NaHCO3
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF

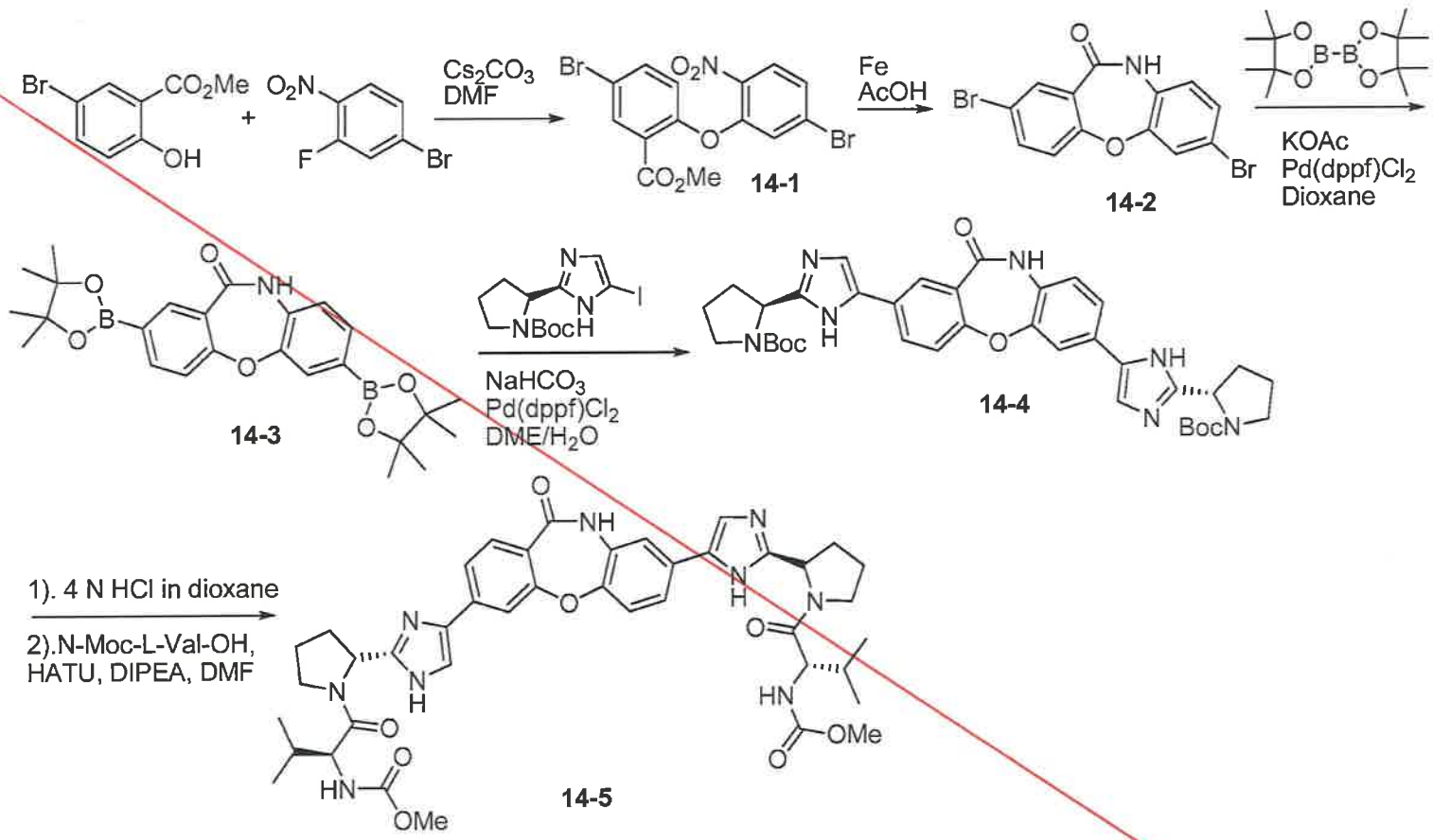
Scheme 10


12-1
AlCl3
12-2
12-3
NH4OAc
12-4
1. 4.0N HCl in dioxane
2. HATU, DIEA
12-5

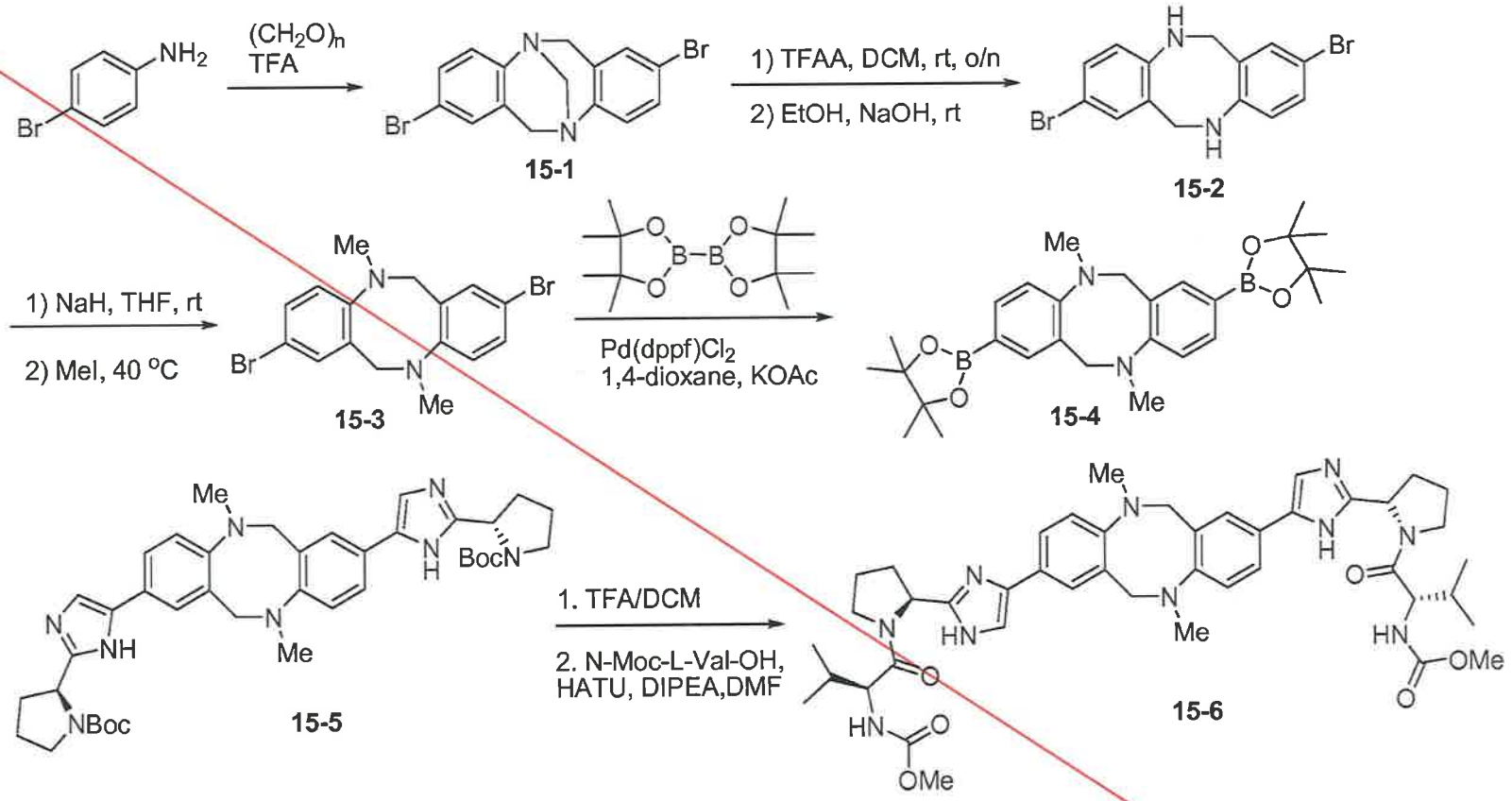
Scheme 12


NO2
Br
+
NH2
Br
t-BuOK
NO2
Br
Br
N
H
13-1
AcOH
N
Br
Br
N
13-2
1) Pd(dppf)Cl2
KOAc
EtO
SnBu3
2) NBS, water
O
Br
Br
N
N
O
13-3
1)
HO2C
N
Boc
TEA, CH3CN
2) NH4OAc, TEA, xylenes
N
N
N
H
N
Boc
N
NH
NBoc
13-4
1). 4 N HCl in dioxane
2). L-Moc-Val-OH,
HATU, DIPEA,
DMF
N
N
N
H
N
O
(S)
HN
O
O
N
NH
O
O
NH
O
O
13-5

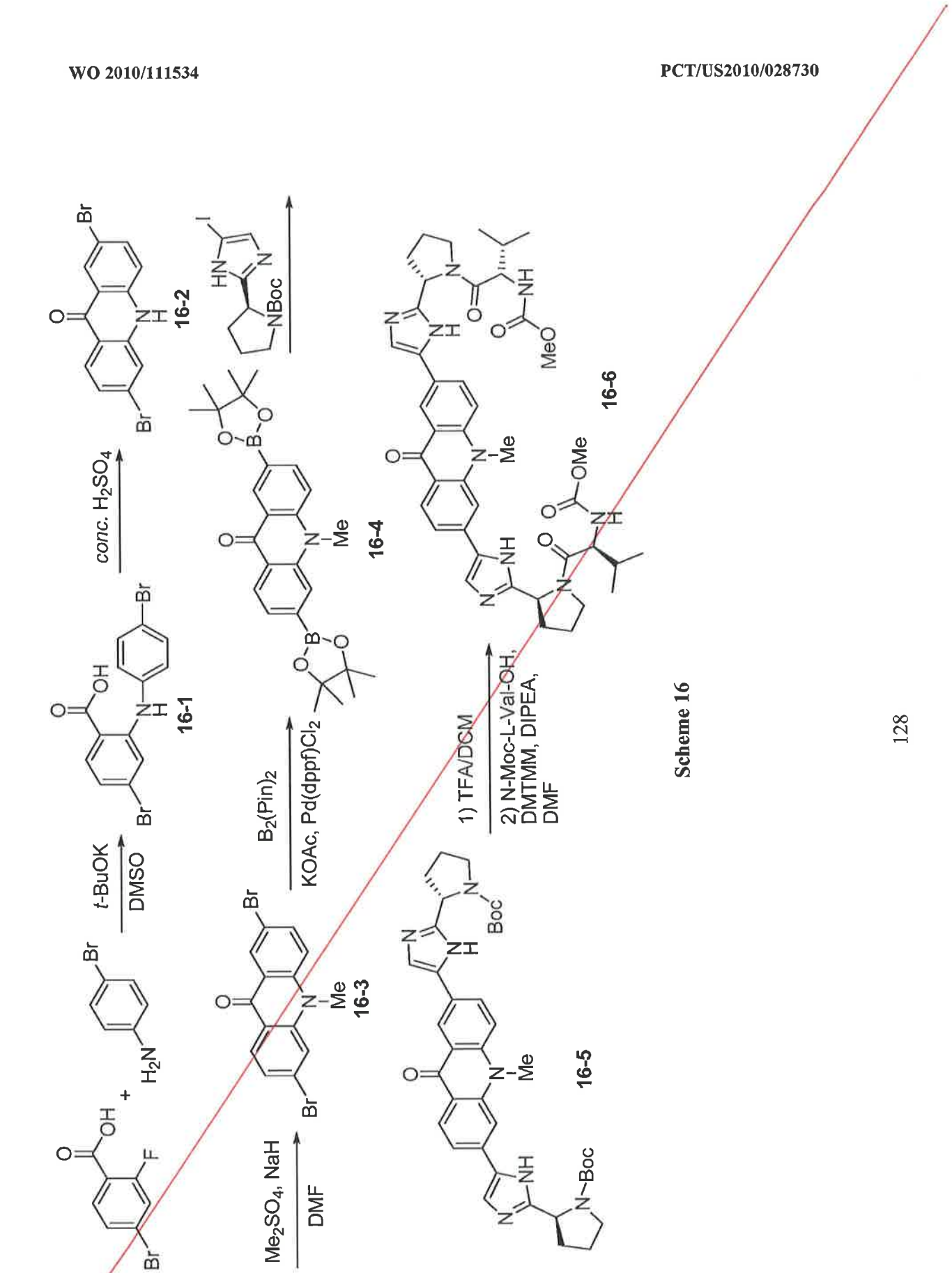
Scheme 13


Br
CO2Me
OH
O2N
F
Br
Cs2CO3
DMF
Br
O2N
O
Br
CO2Me
14-1
Fe
AcOH
O
NH
Br
O
Br
14-2
O
B-B
O
O
KOAc
Pd(dppf)Cl2
Dioxane
O
NH
O
B
O
O
B
O
O
14-3
N
NBocH
I
NaHCO3
Pd(dppf)Cl2
DME/H2O
O
NH
N
NBoc
N
H
O
NH
N
N
BocN
14-4
1). 4 N HCl in dioxane
2).N-Moc-L-Val-OH,
HATU, DIPEA, DMF
O
NH
N
N
H
O
N
N
N
H
O
HN
O
OMe
O
N
O
HN
O
OMe
14-5

Scheme 14


(CH2O)n
TFA
1) TFAA, DCM, rt, o/n
2) EtOH, NaOH, rt
15-1
15-2
1) NaH, THF, rt
2) MeI, 40 °C
15-3
Pd(dppf)Cl2
1,4-dioxane, KOAc
15-4
1. TFA/DCM
2. N-Moc-L-Val-OH,
HATU, DIPEA,DMF
15-5
15-6

Scheme 15


Br
O
OH
F
Br
+
Br
H2N
t-BuOK
DMSO
Br
O
OH
N
H
Br
16-1
conc. H2SO4
Br
O
N
H
Br
16-2
Me2SO4, NaH
DMF
Br
O
N
Me
Br
16-3
B2(Pin)2
KOAc, Pd(dppf)Cl2
O
B
O
O
B
O
N
Me
16-4
I
HN
N
NBoc
1) TFA/DCM
2) N-Moc-L-Val-OH,
DMTMM, DIPEA,
DMF
Boc
N
N
H
O
N
Me
NH
N
N-Boc
16-5
N
N
H
O
N
NH
O
MeO
O
N
Me
NH
N
O
OMe
O
NH
16-6

Scheme 16