Indole Alkaloids

International Edition: DOI: 10.1002/anie.201902004
German Edition: DOI: 10.1002/ange.201902004

A Ten-Step Total Synthesis of Speradine C

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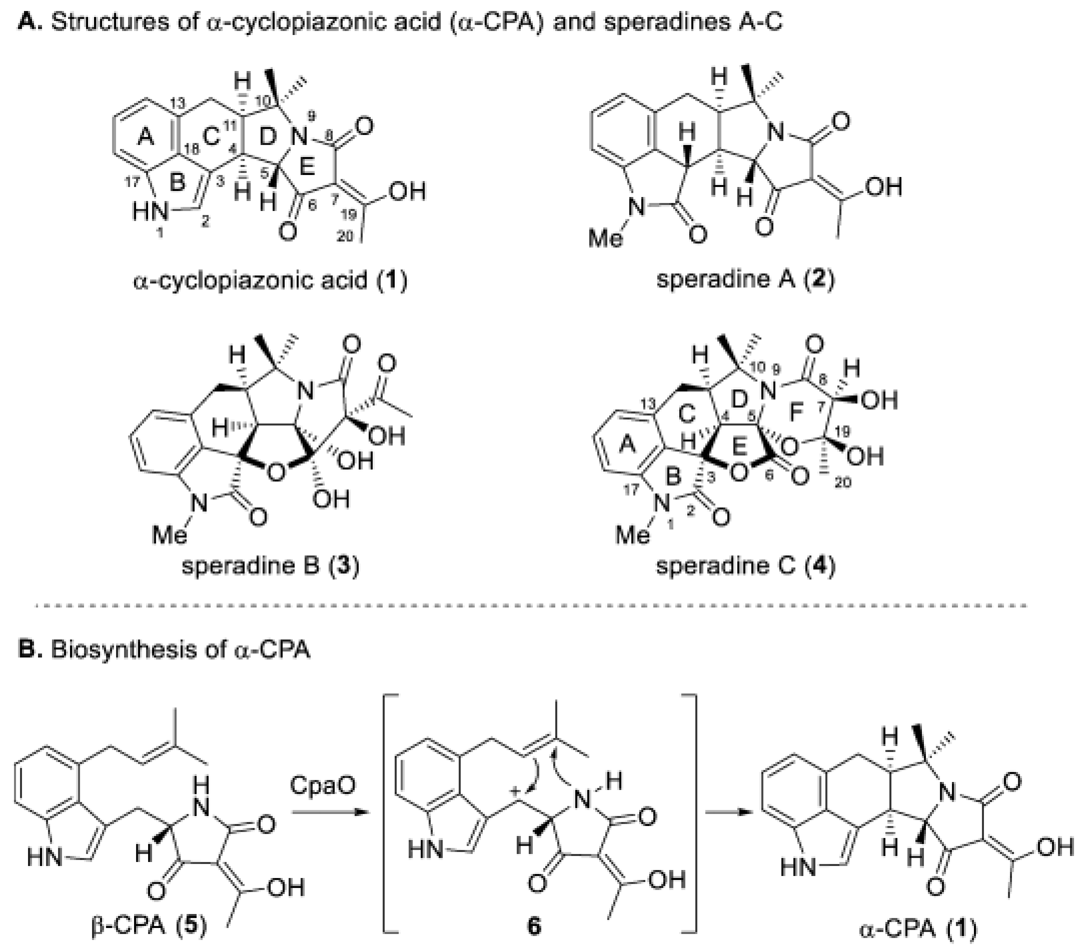
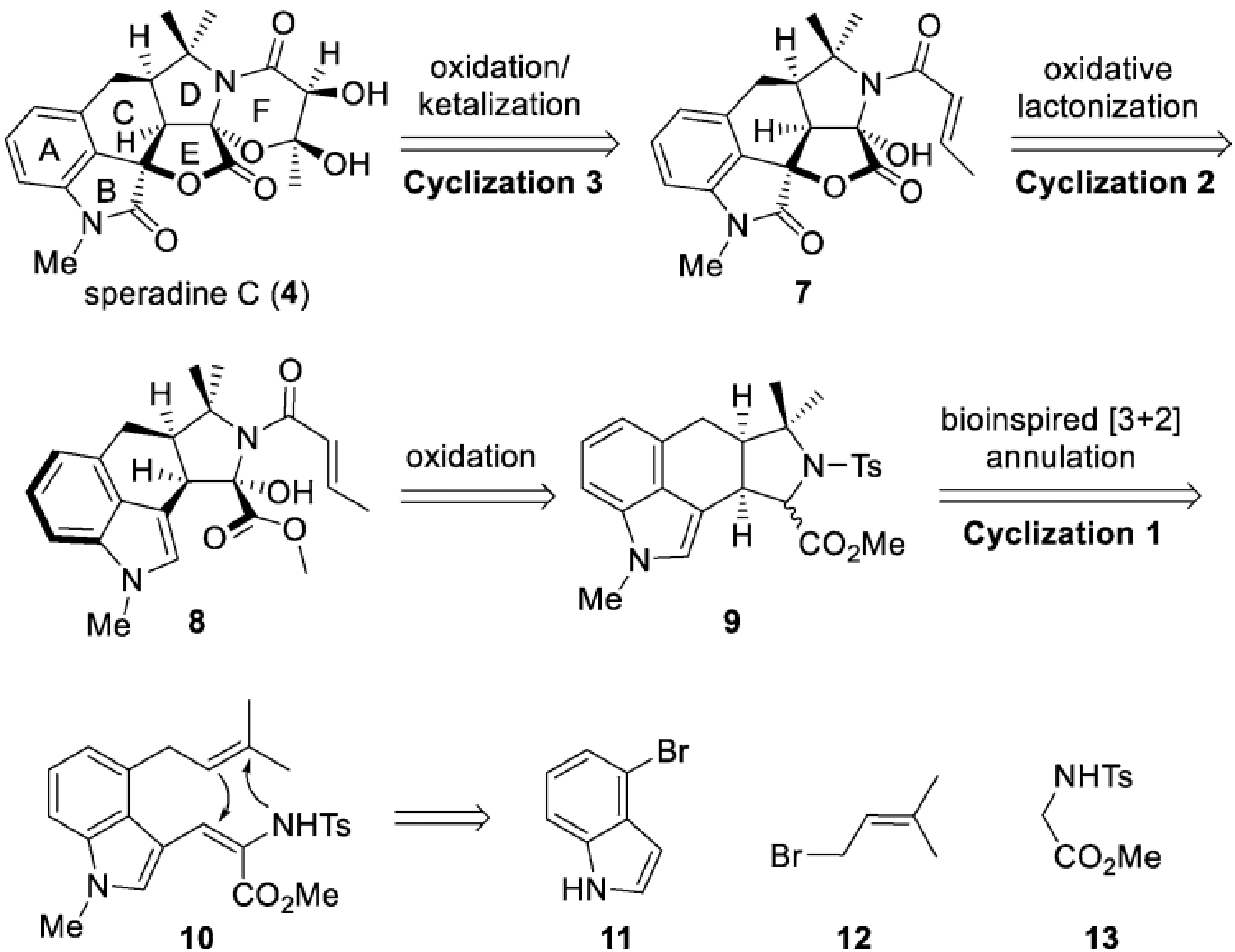
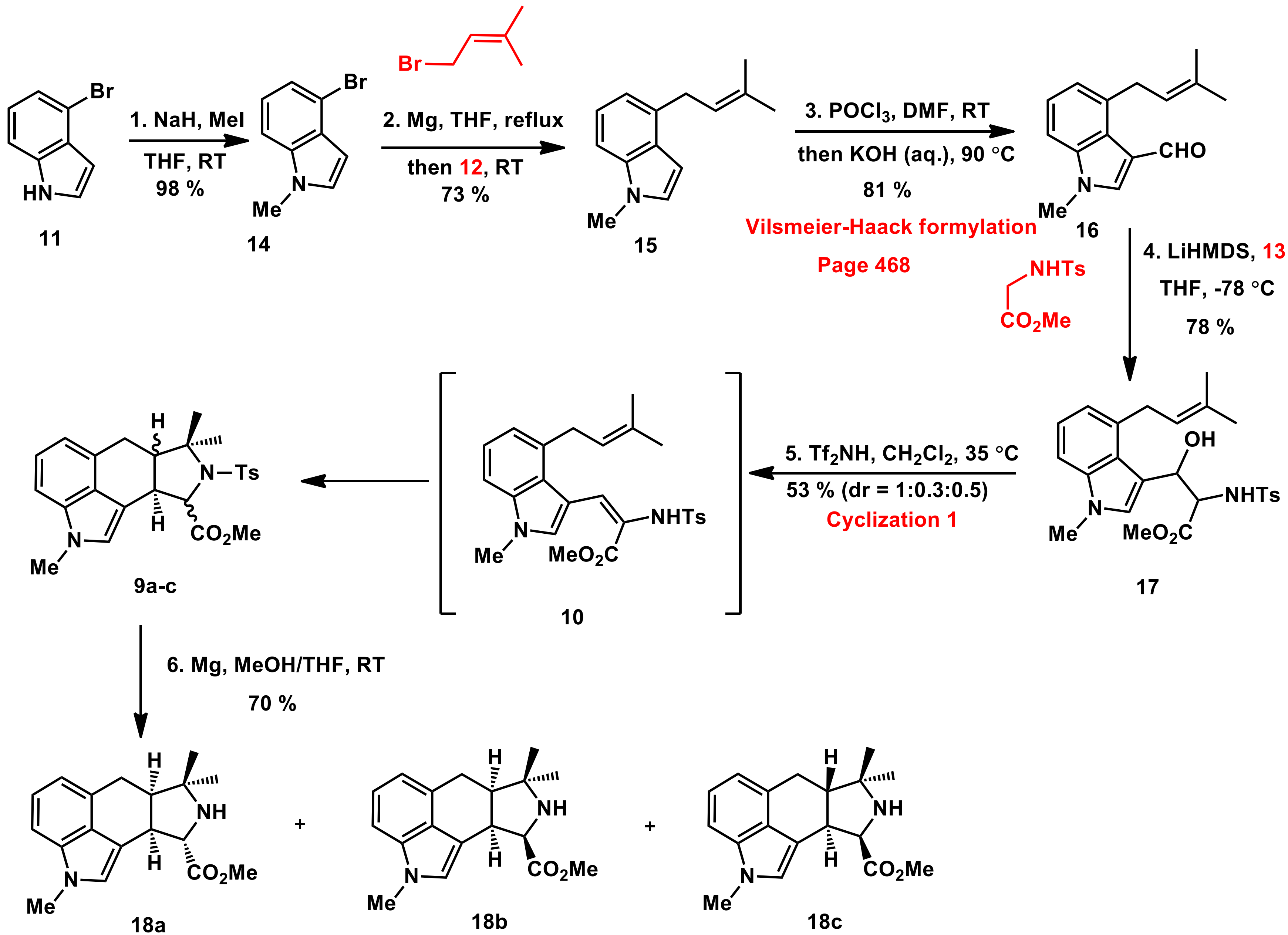


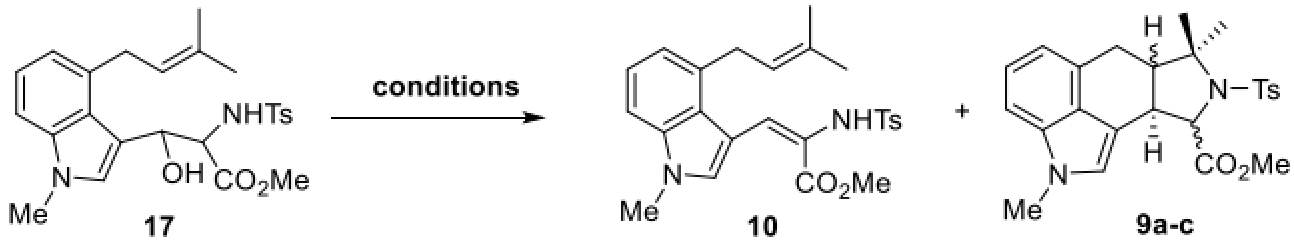
Retrosynthetic analysis of speradine C





Br
1. NaH, MeI
THF, RT
98 %
HN
11
Br
N
Me
14
Br
2. Mg, THF, reflux
then 12, RT
73 %
N
Me
15
3. POCl3, DMF, RT
then KOH (aq.), 90 °C
81 %
Vilsmeier-Haack formylation
Page 468
CHO
N
Me
16
4. LiHMDS, 13
THF, -78 °C
78 %
NHTs
CO2Me
OH
NHTs
N
Me
MeO2C
17
5. Tf2NH, CH2Cl2, 35 °C
53 % (dr = 1:0.3:0.5)
Cyclization 1
NHTs
N
Me
MeO2C
10
H
N—Ts
H
CO2Me
N
Me
9a-c
6. Mg, MeOH/THF, RT
70 %
H
NH
H
CO2Me
N
Me
18a
+
H
NH
H
CO2Me
N
Me
18b
+
H
NH
H
CO2Me
N
Me
18c

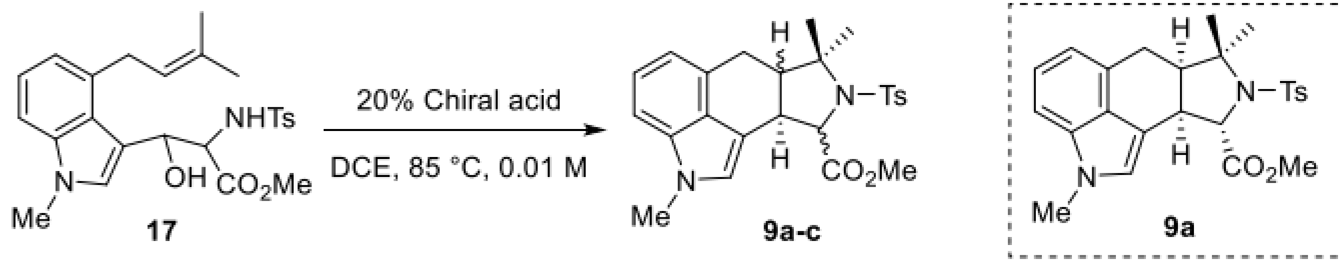
Table 2. Optimization of carboncation-initiated cascade cyclization

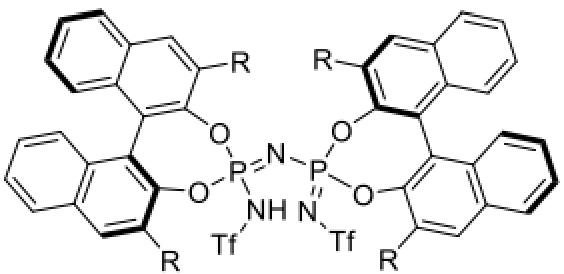


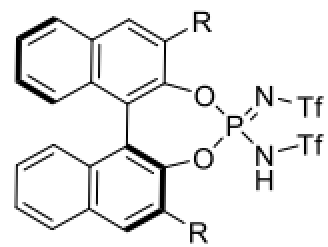
conditions	yield of **10**	yield of **9a-c**	*dr* of **9** **(a/b/c)**
$BF_3·Et_2O$ (5 equiv), DCM (0.01 M), RT	0	56%	1:0.5:0.4
$BF_3·Et_2O$ (0.2 equiv), DCM (0.01 M), RT	70%	0	/
$BF_3·Et_2O$ (1.5 equiv), DCM (0.01 M), RT	53%	trace	/
$TiCl_4$ (1.5 equiv), DCM (0.01 M), RT	56%	trace	/
Sc(OTf)3, (0.2 equiv), DCM (0.01 M), RT	65%	0	/
TfOH (0.2 equiv), DCM (0.01 M), RT	60%	0	/
TfOH (0.2 equiv), DCM (0.01 M), 40°C	33%	15%	/
TfOH (0.2 equiv), DCM (0.01 M), 84°C	25%	25%	1:0.3:0.4
Tf_2NH (0.2 equiv), DCM (0.01 M), RT	28%	30	1:0.3:0.4
Tf_2NH (0.2 equiv), DCM (0.01 M), 35°C	0	53%	1:0.27:0.51
Tf_2NH (0.2 equiv), DCE (0.02 M), 50°C	0	50%	1:0.36:0.57
Tf_2NH (0.1 equiv), DCM (0.01 M), 35°C	trace	45%	1:0.32:0.46

Note: Reaction performed on 20 mg scale of **17;** *dr* value of **9a-c** was based on ^1H NMR.

Table 3. The tested chiral Bronsted acids and results.



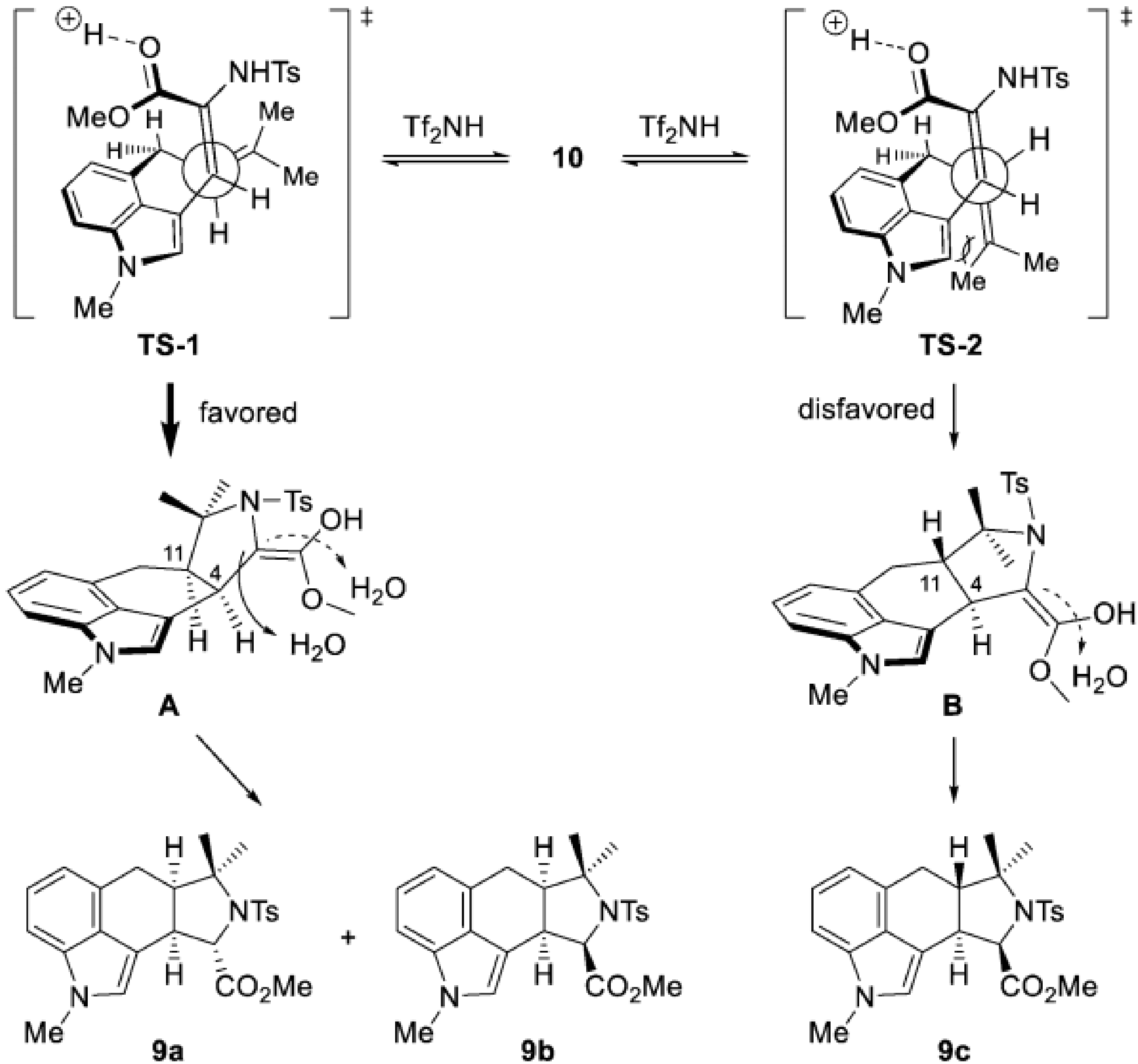




R = H : (**SPA-1**), yield = 20%, ee = 0
R = Phenyl : (**SPA-2**), yield = 0

R = 4-*t*-Bu-Phenyl : (**SPA-3**), yield = 50%, ee = 4%
R = 2-Naphthyl : (**SPA-4**), yield = 16%

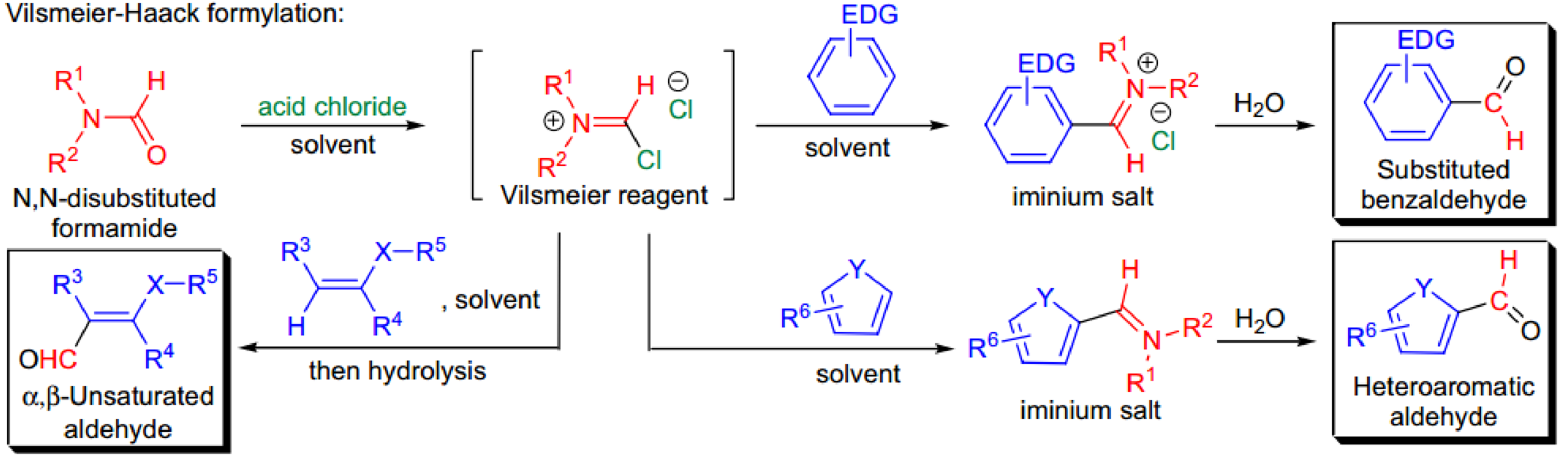
Note: The yields were based on **9a-c**; the *ee* values we tested were based on **9a**.



TS-1
Tf2NH
10
Tf2NH
TS-2
favored
disfavored
A
B
9a
9b
9c
NHTs
MeO
Me
H
N-Ts
OH
H2O
CO2Me
NTs

Vilsmeier–Haack formylation

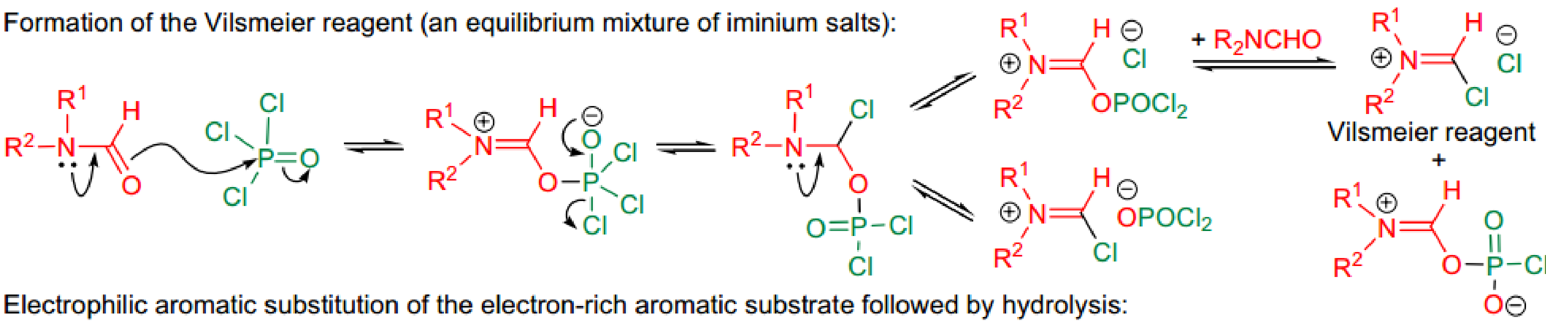
Vilsmeier-Haack formylation:



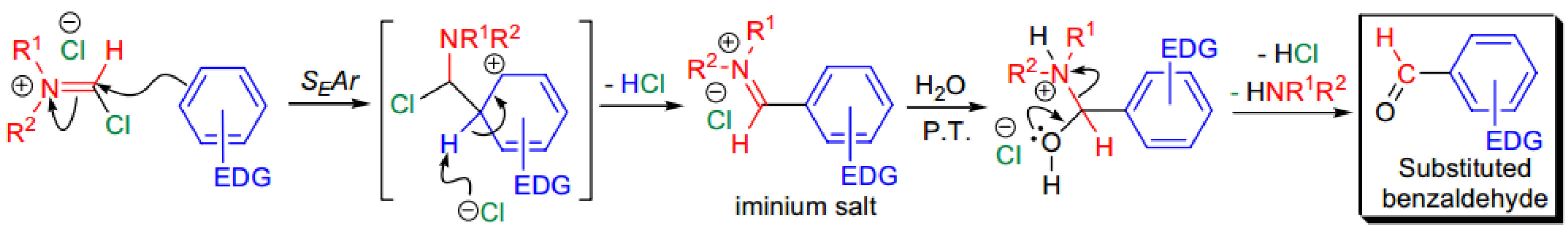
R^{1-2} = alkyl, aryl; acid chloride: $POCl_3$, $SOCl_2$, $COCl_2$, $(COCl)_2$, Ph_3PBr_2, 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, $POCl_3$;
EDG = OH, *O*-alkyl, *O*-aryl, NR_2; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH_2, CR_2; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

Mechanism: [34-41,8,42,11]

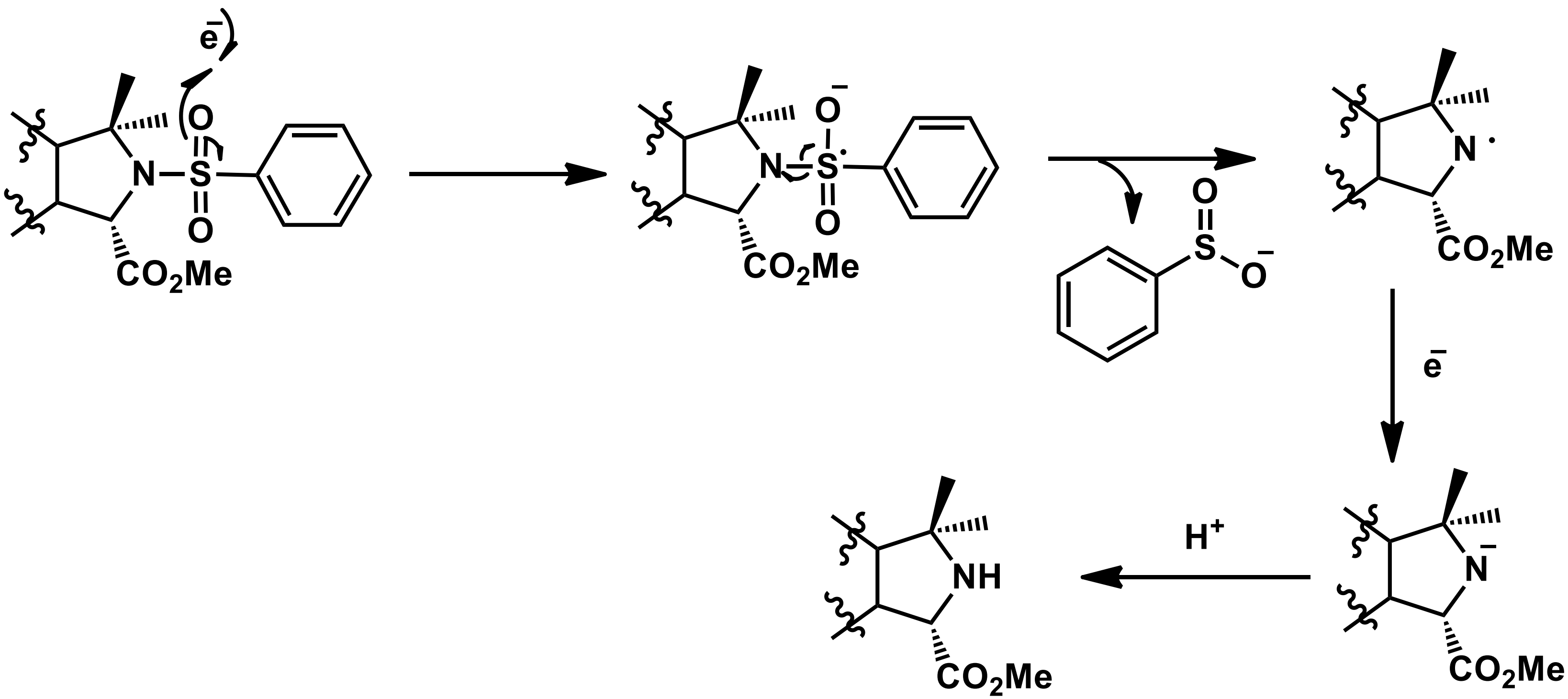
Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):

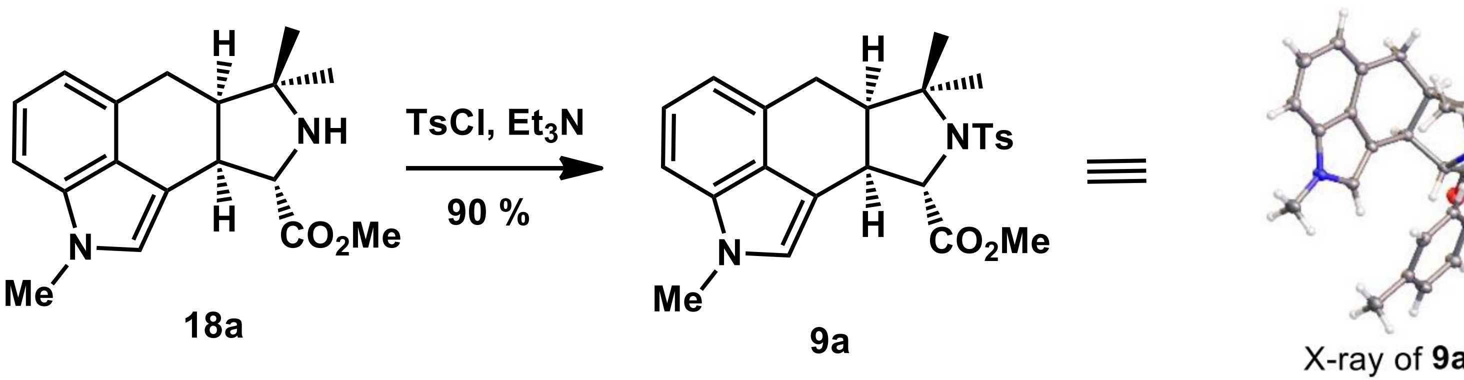


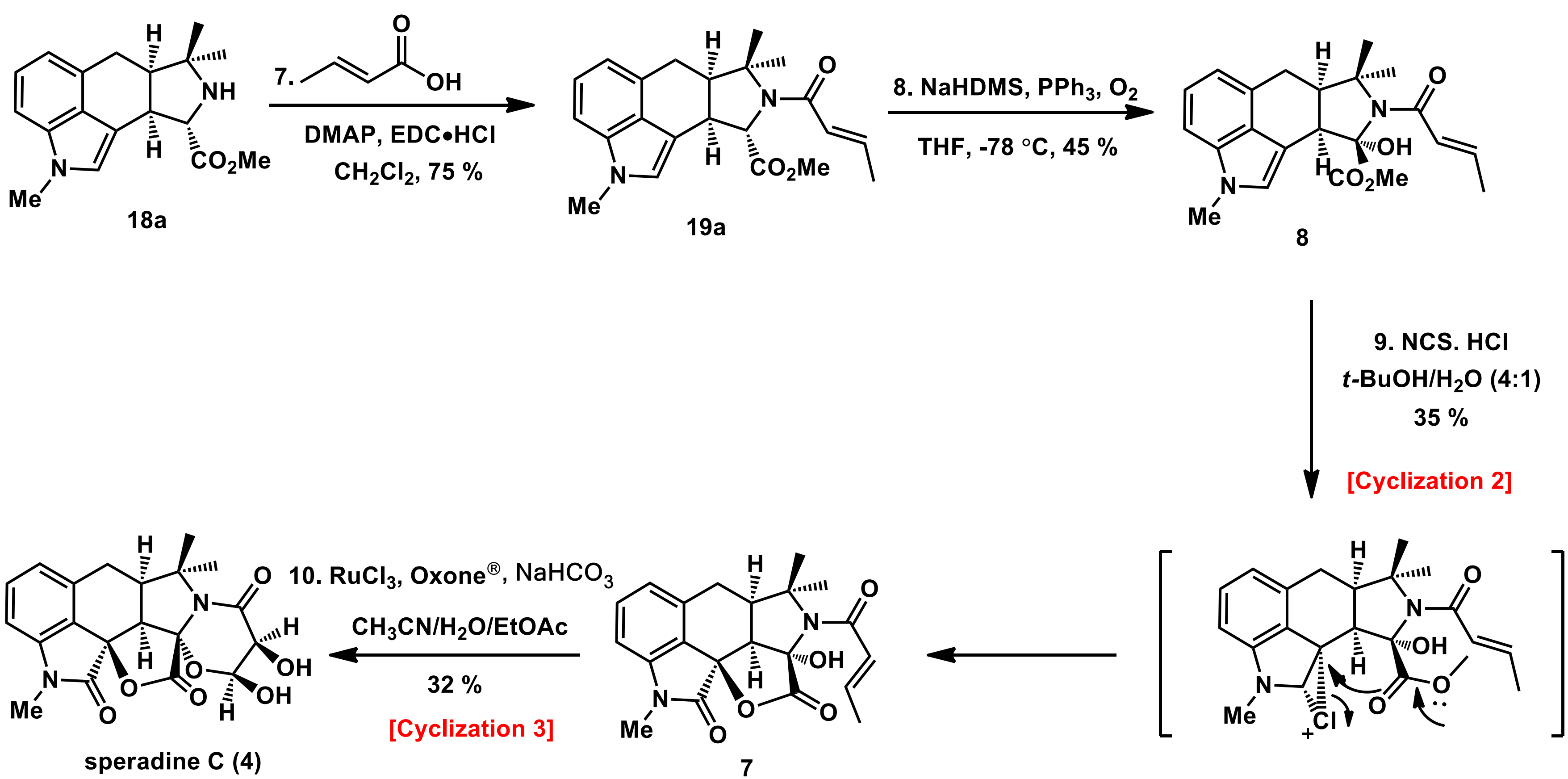
Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:

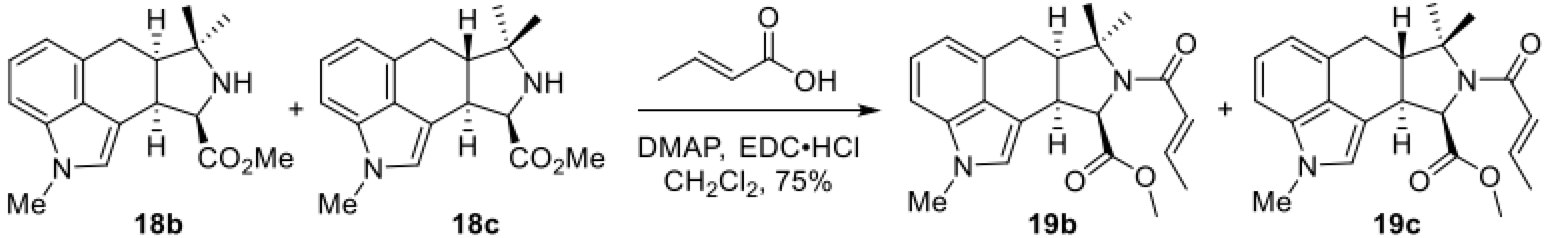


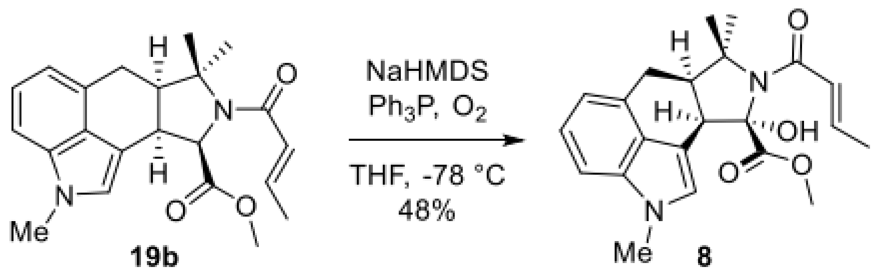
Step 6

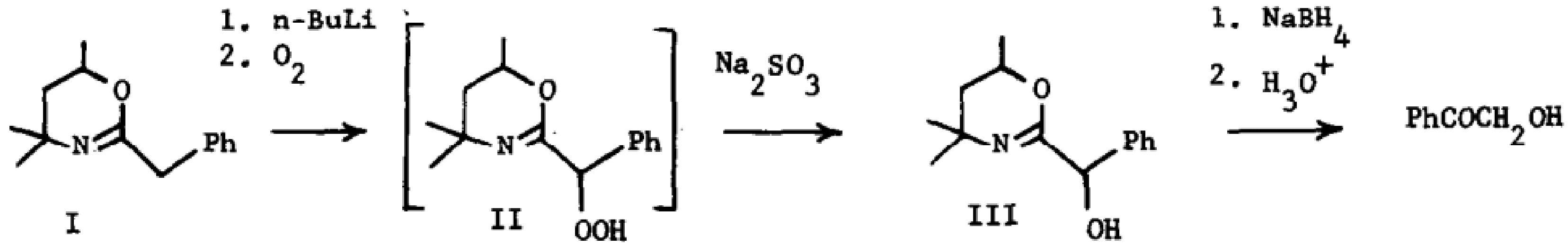



TsCl, Et_3N
90 %
18a
9a
X-ray of **9a**


7.
OH
DMAP, EDC•HCl
CH_2Cl_2, 75 %
18a
19a
8. NaHDMS, PPh_3, O_2
THF, -78 °C, 45 %
8
9. NCS. HCl
t-BuOH/H_2O (4:1)
35 %
[Cyclization 2]
7
10. $RuCl_3$, Oxone®, $NaHCO_3$
$CH_3CN/H_2O/EtOAc$
32 %
[Cyclization 3]
speradine C (4)

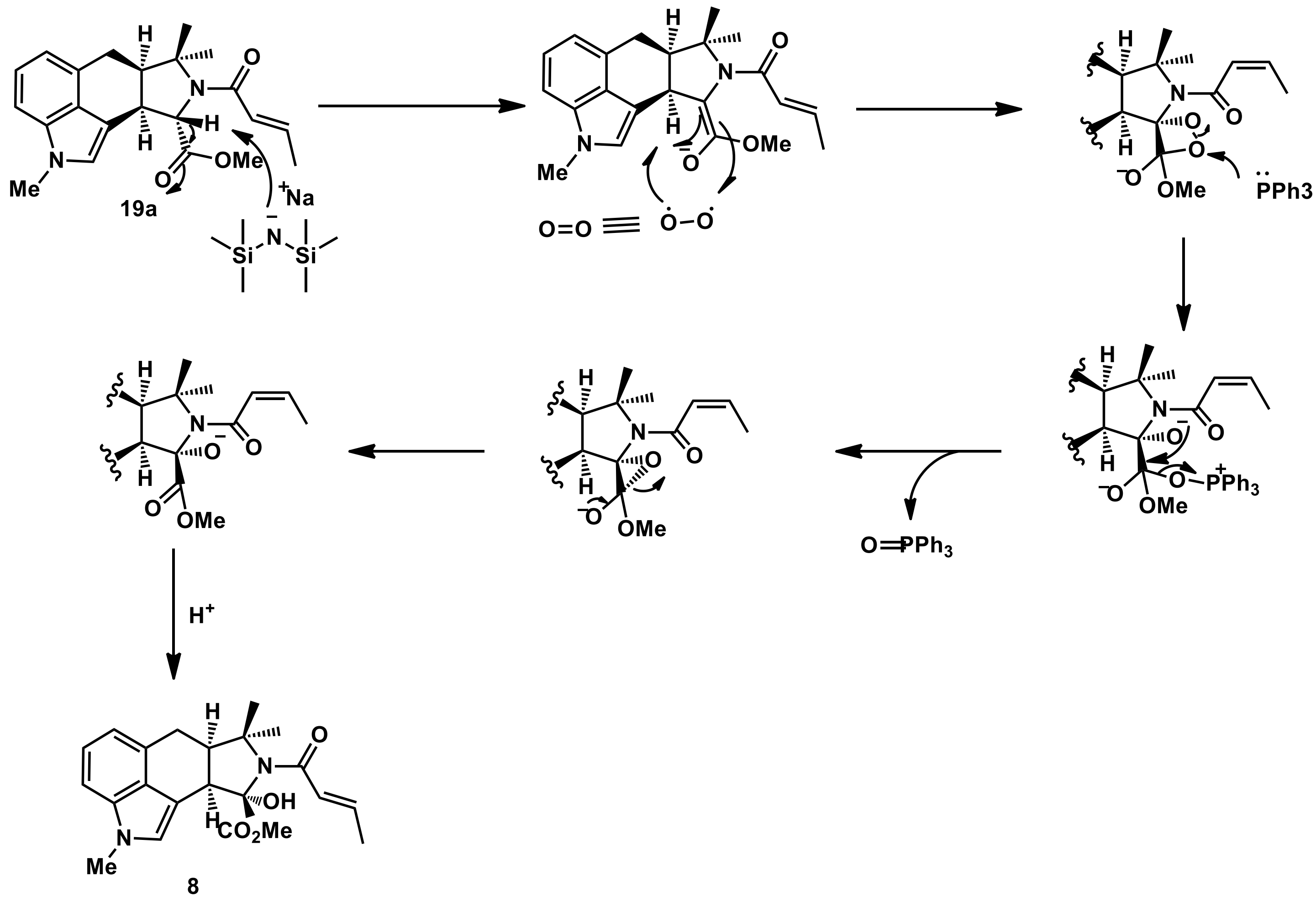

NH
CO2Me
N
Me
18b
+
NH
CO2Me
N
Me
18c
O
OH
DMAP, EDC•HCl
CH2Cl2, 75%
N
O
Me
19b
+
N
O
Me
19c


N
O
Me
19b
NaHMDS
Ph3P, O2
THF, -78 °C
48%
N
OH
O
Me
8

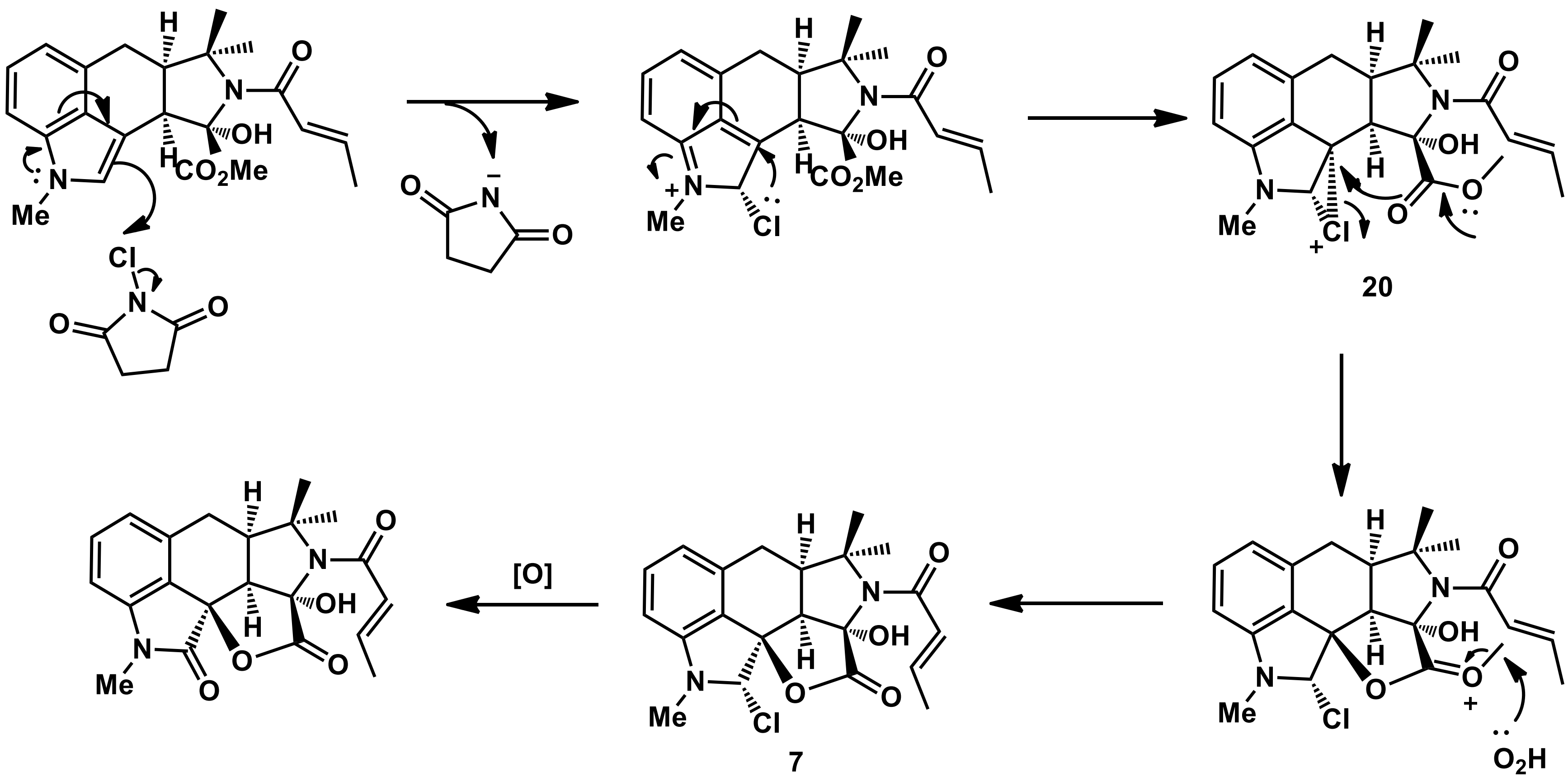


Tetrahedron Letters, 16(21), 1731–1734.

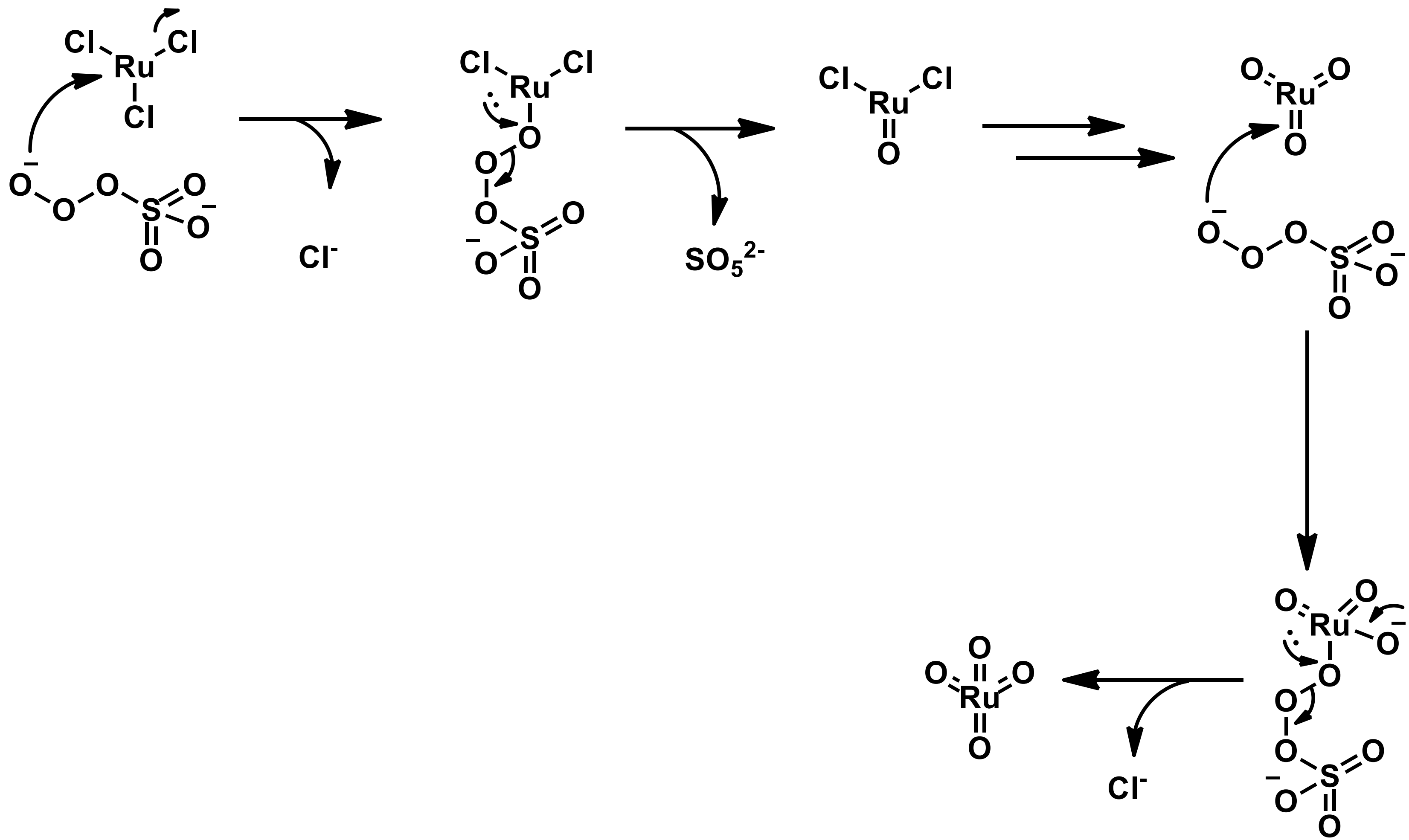
Step 8



Step 9



Step 10



Cl
Ru
Cl
Cl
O
O
O
S
O
O
O
Cl⁻
Cl
Ru
Cl
O
O
O
S
O
O
O
SO5 2-
Cl
Ru
Cl
O
O
Ru
O
O
O
O
O
S
O
O
O
O
Ru
O
O
O
O
O
O
S
O
O
O
O
Ru
O
O
O
Cl⁻

RuO_4-Catalyzed Ketohydroxylation of Olefins

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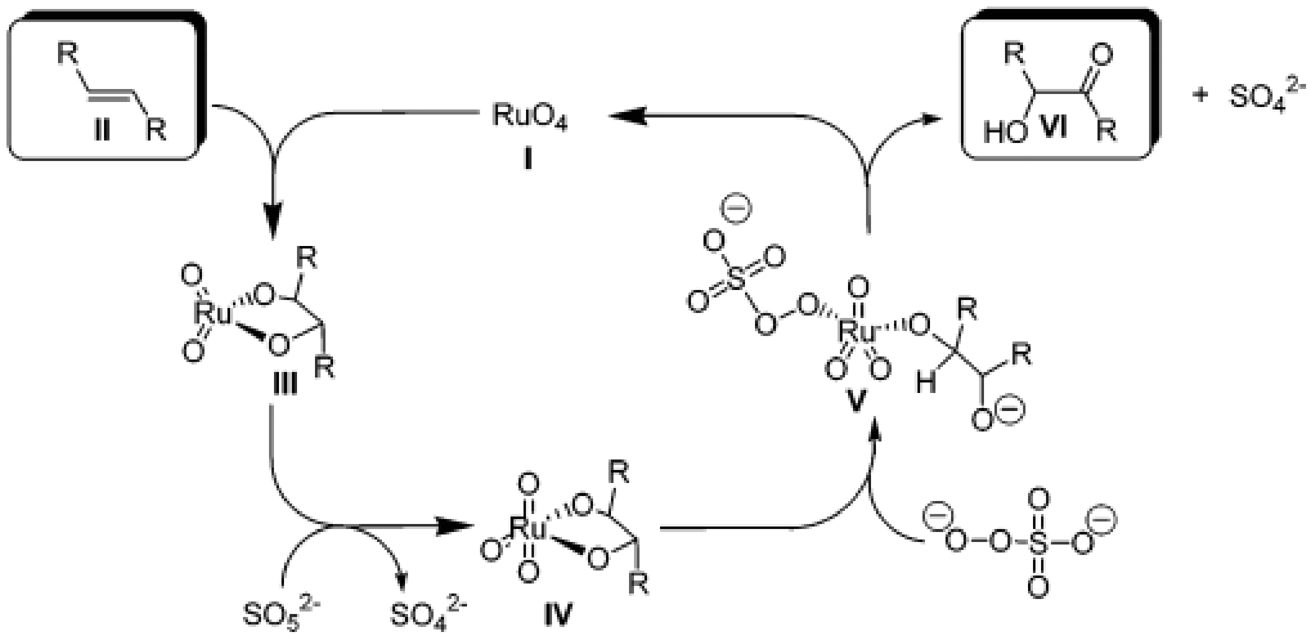
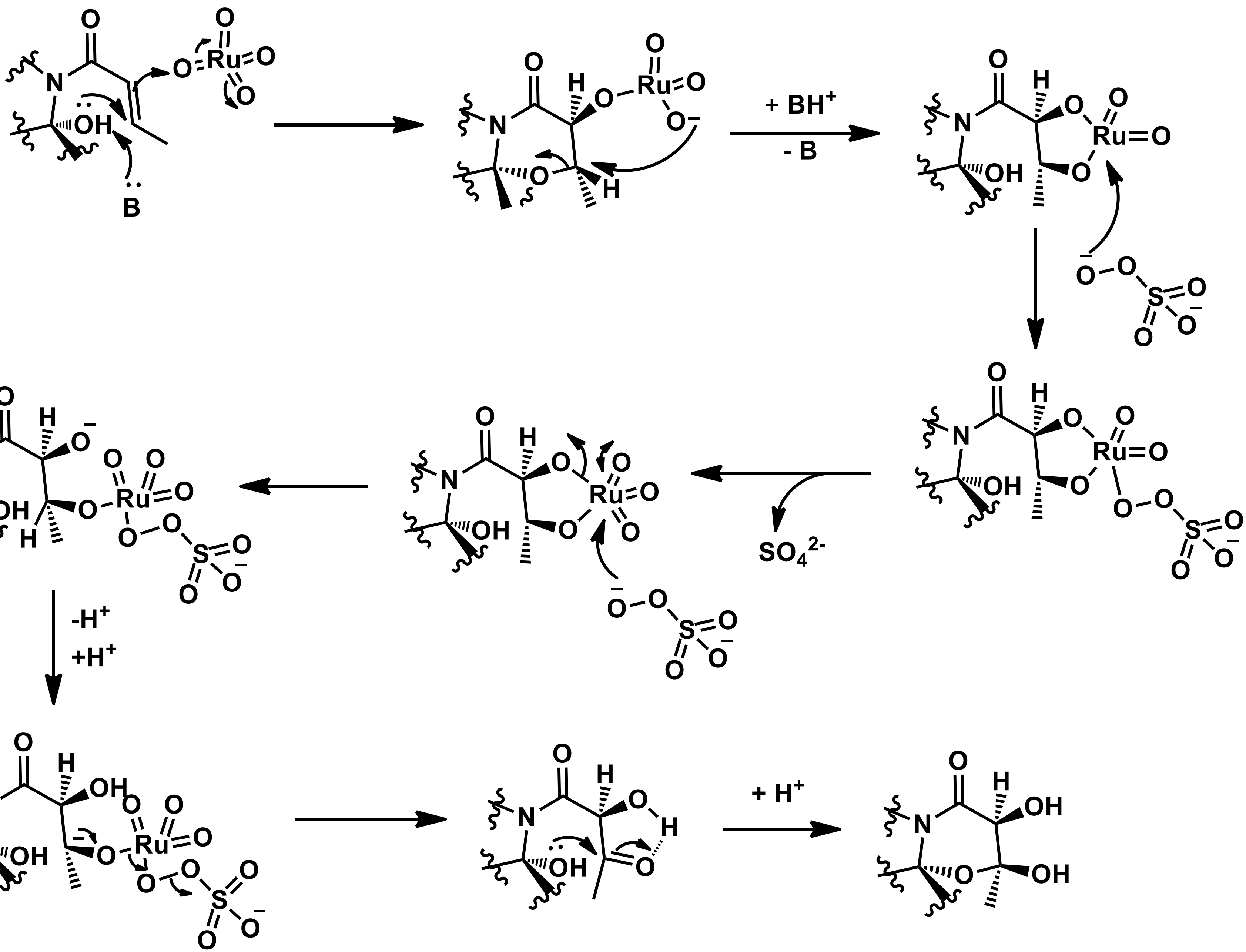
Received June 20, 2003



J. Org. Chem. **2003**, *68*, 7123-7125

Step 10



Thanks !