Total Synthesis of (±)-Communesin F via a Cycloaddition with Indol-2-one

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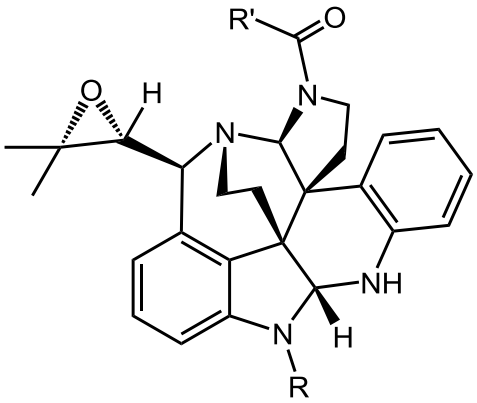
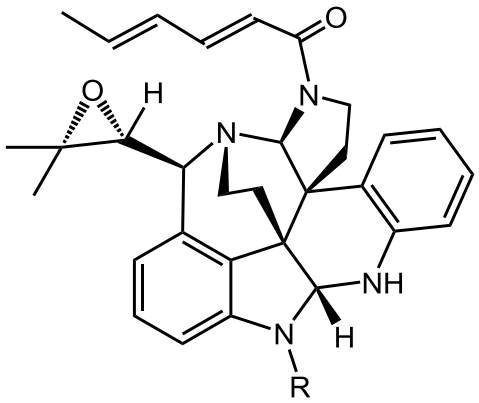
Funk, R. L. et al *J. Am. Chem. Soc.* **2012**, *134*, 16941

目录

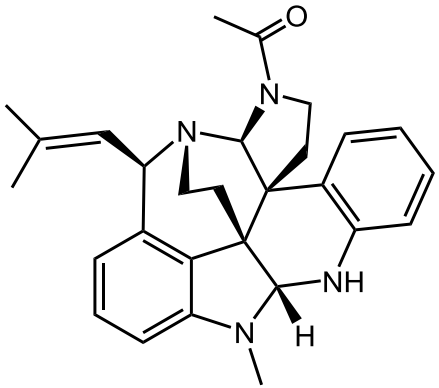
1. 简介



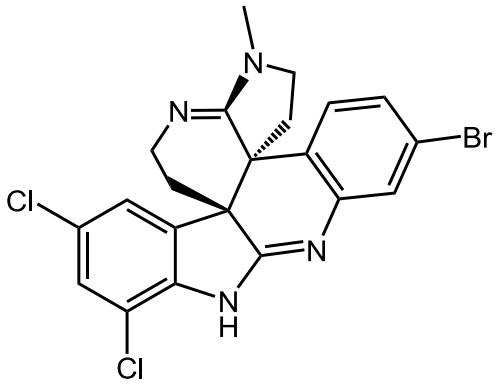
Communesin
A: R = R' = Me
E: R = H, R' = Me
G: R = Me, R' = Et
H: R = Me, R' = *n*-Pr



Communesin
B: R= Me
C: R = H
D: R = CHO

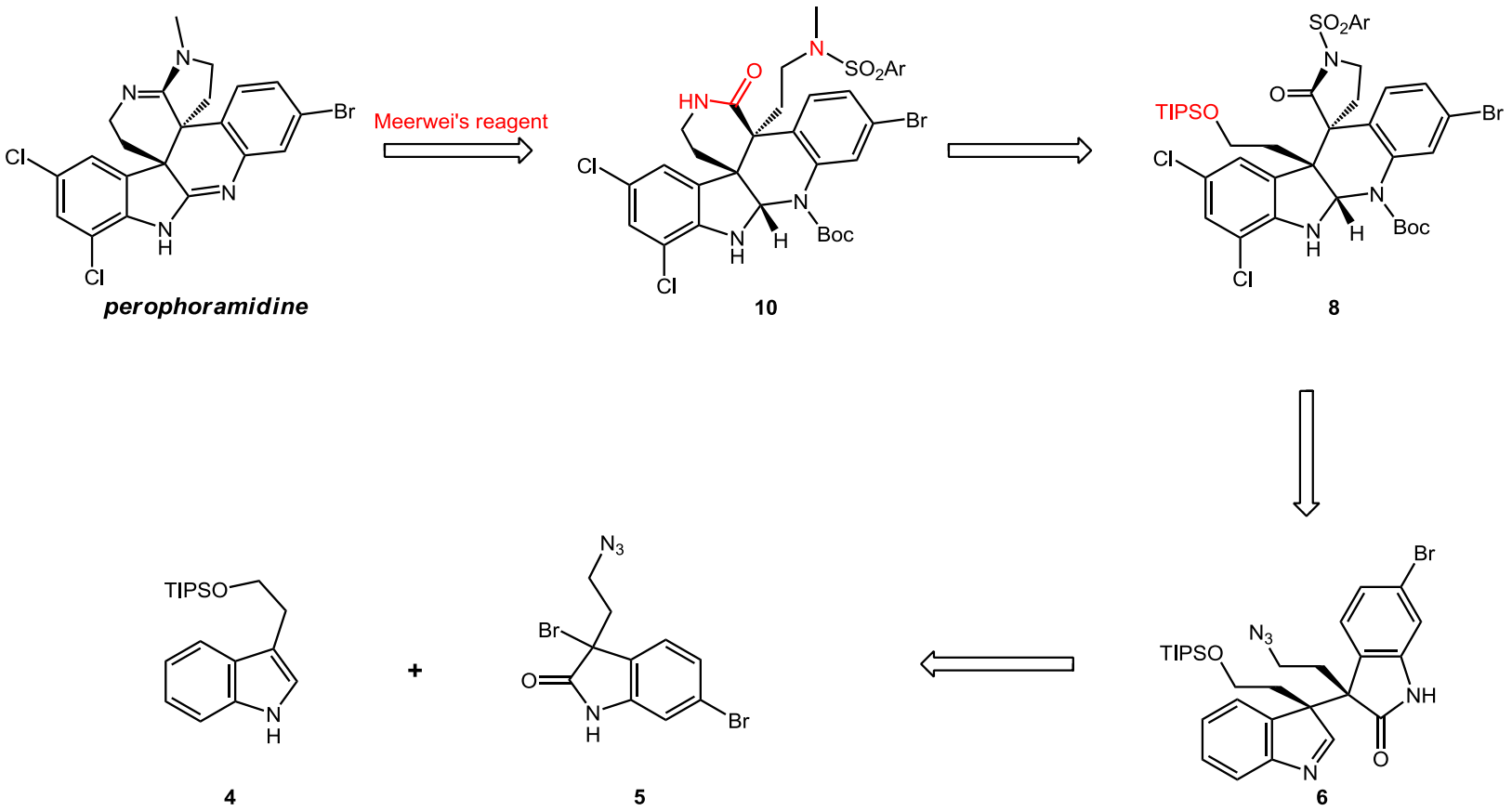


Communesin F

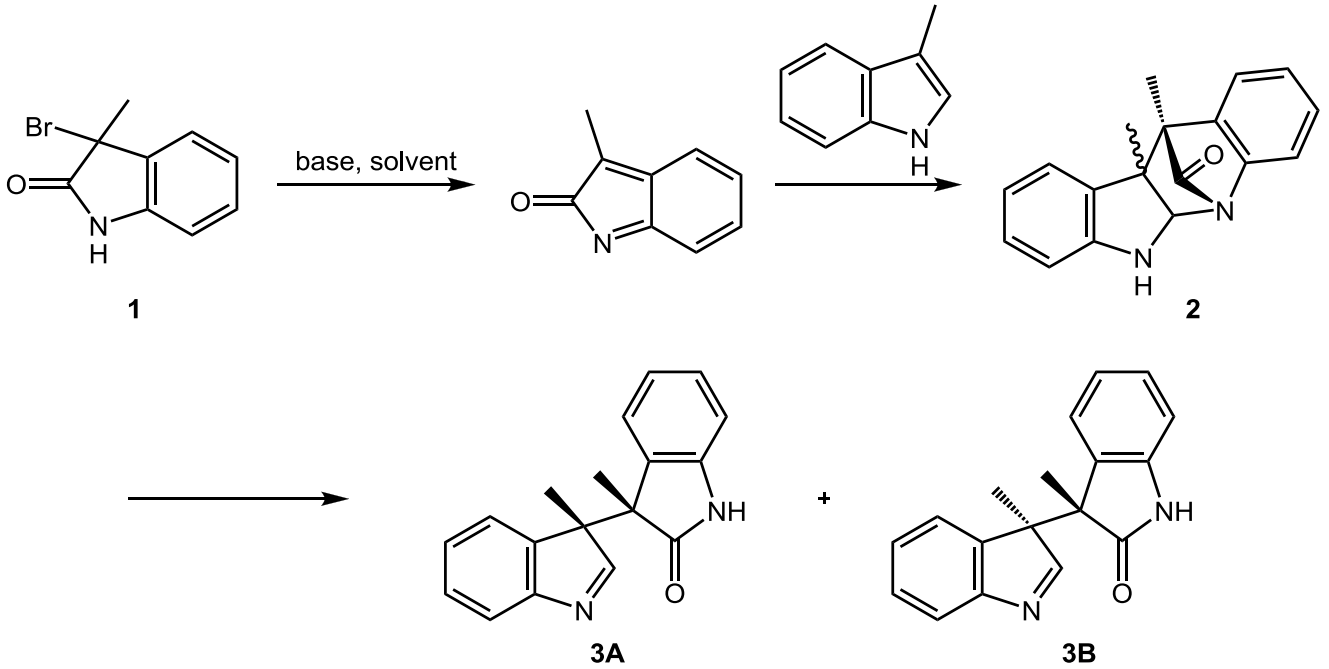


Perophoramidine

2. (±)-Perophoramidine的逆合成分析

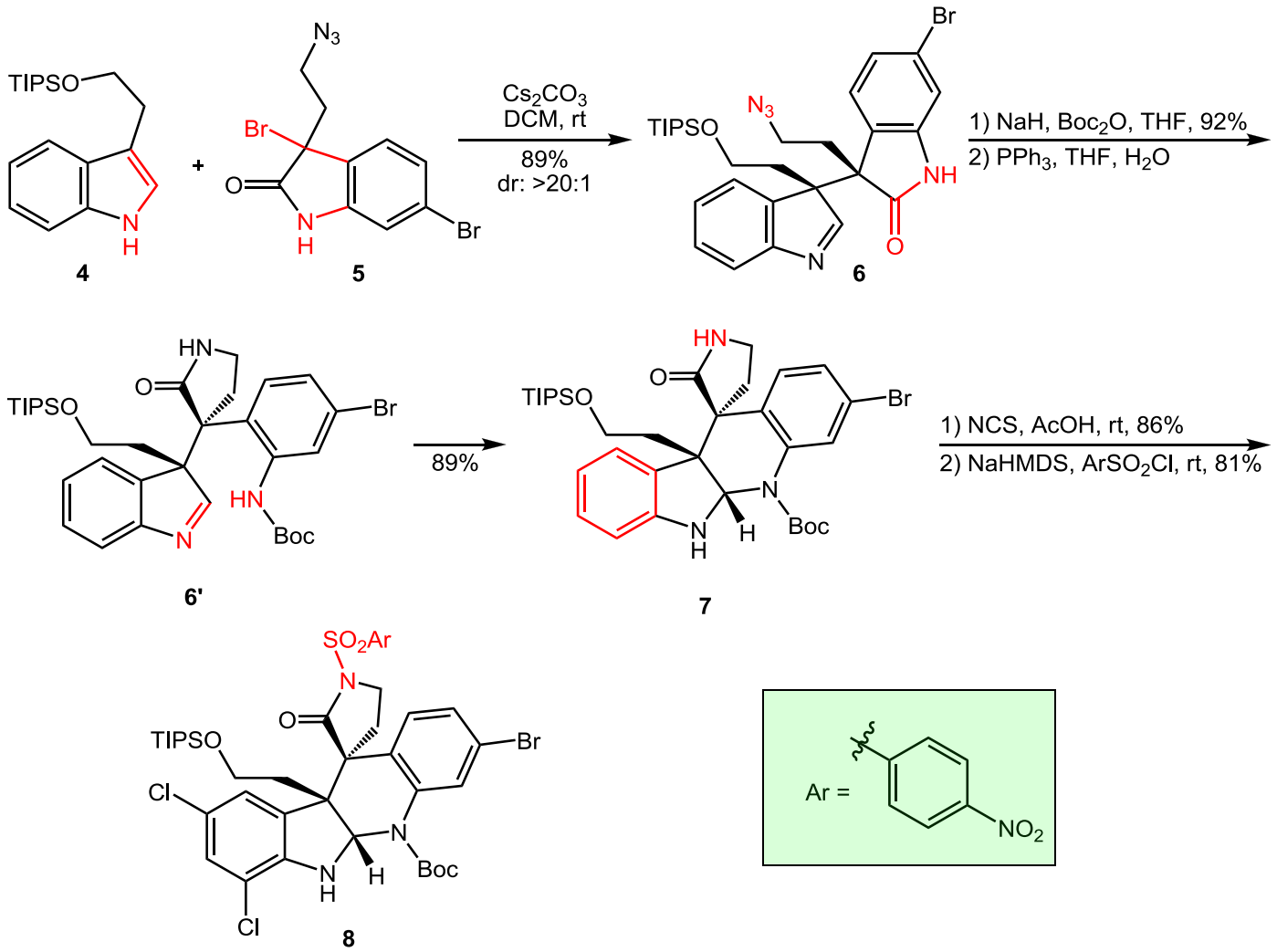


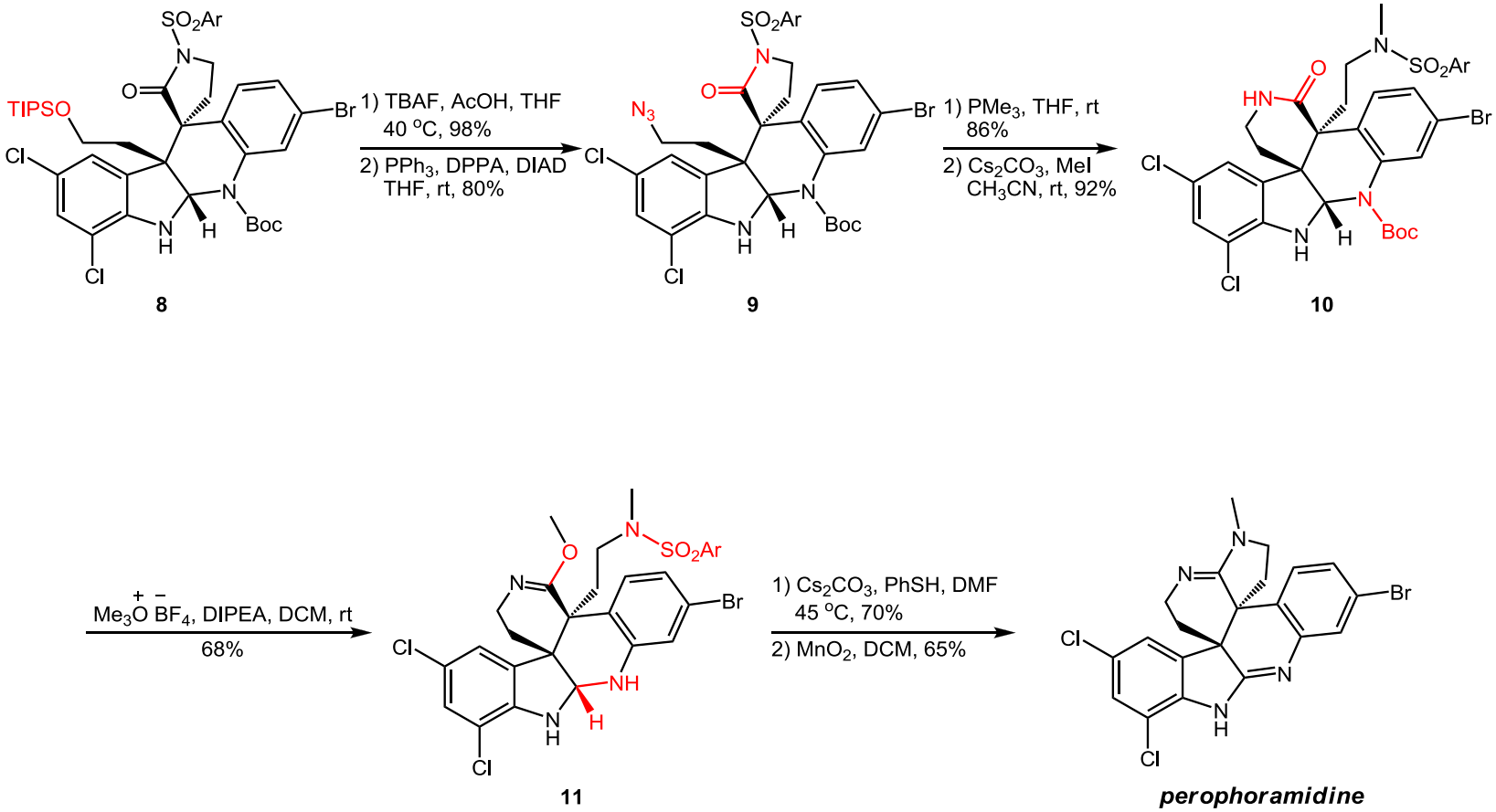
Funk, R. L. et al *J. Am. Chem. Soc.* **2004**, *126*, 5068



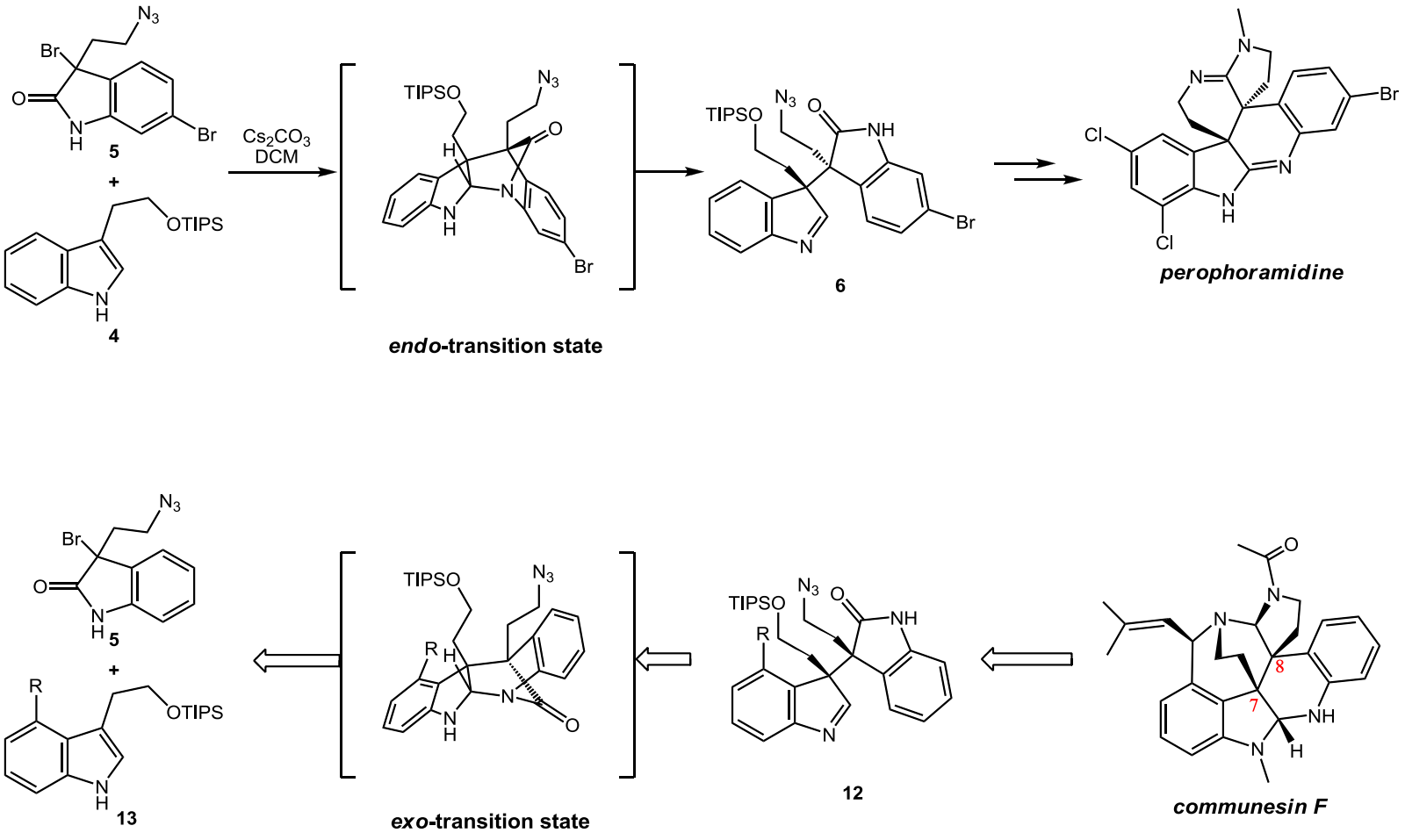
	Base	Solvent	t(h)	Yield(%)	dr(**3A**:**3B**)
1	Ag_2CO_3	THF	24	68	74:26
2	Ag_2CO_3	CH_2Cl_2	24	62	79:21
3	Cs_2CO_3	CH_3CN	12	43	89:11
4	Cs_2CO_3	CH_2Cl_2	24	76	95:5

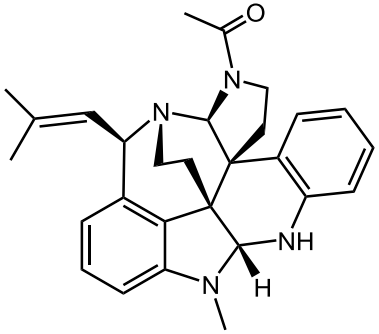
3. (±)-Perophoramidine的合成



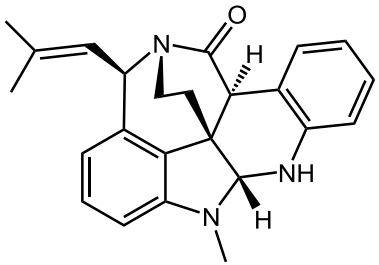

SO2Ar
TIPSO
Br
Cl
Cl
Boc
1) TBAF, AcOH, THF
40 °C, 98%
2) PPh3, DPPA, DIAD
THF, rt, 80%
N3
1) PMe3, THF, rt
86%
2) Cs2CO3, MeI
CH3CN, rt, 92%
HN
+ –
Me3O BF4, DIPEA, DCM, rt
68%
1) Cs2CO3, PhSH, DMF
45 °C, 70%
2) MnO2, DCM, 65%
8
9
10
11
perophoramidine

4. (±)-Communesin F的逆合成分析

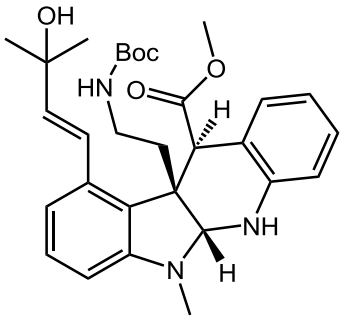




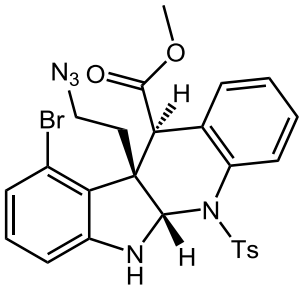
communesin F



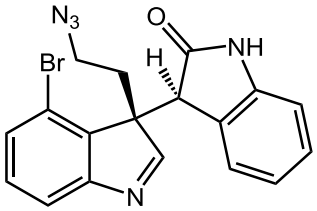
21



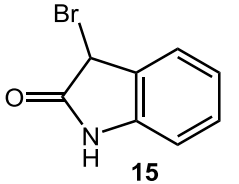
19



17



16



15

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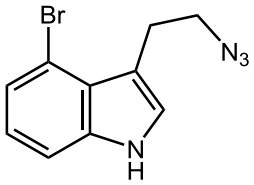
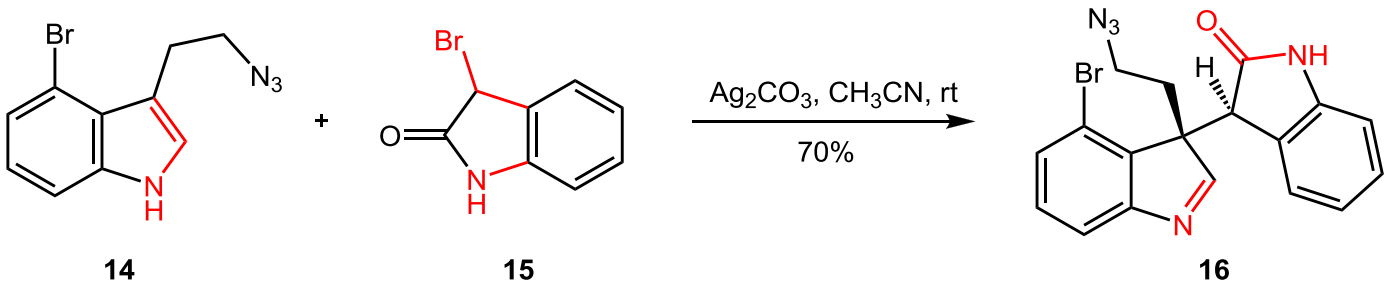
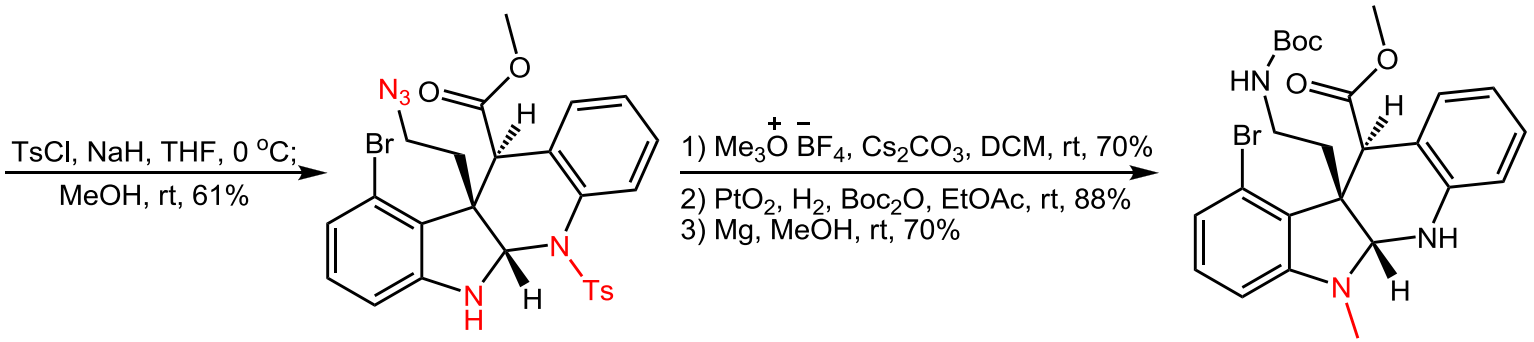


14

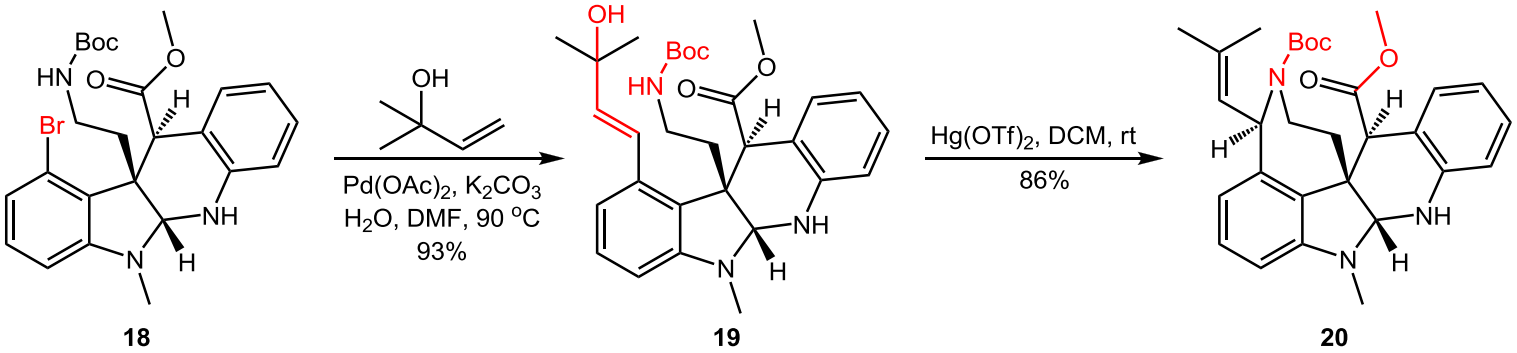
5. (±)-Communesin F的合成

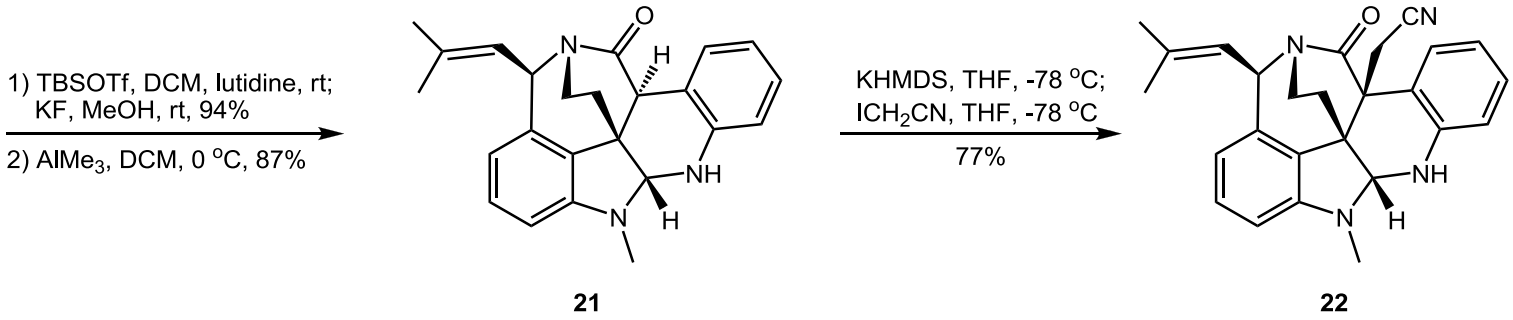


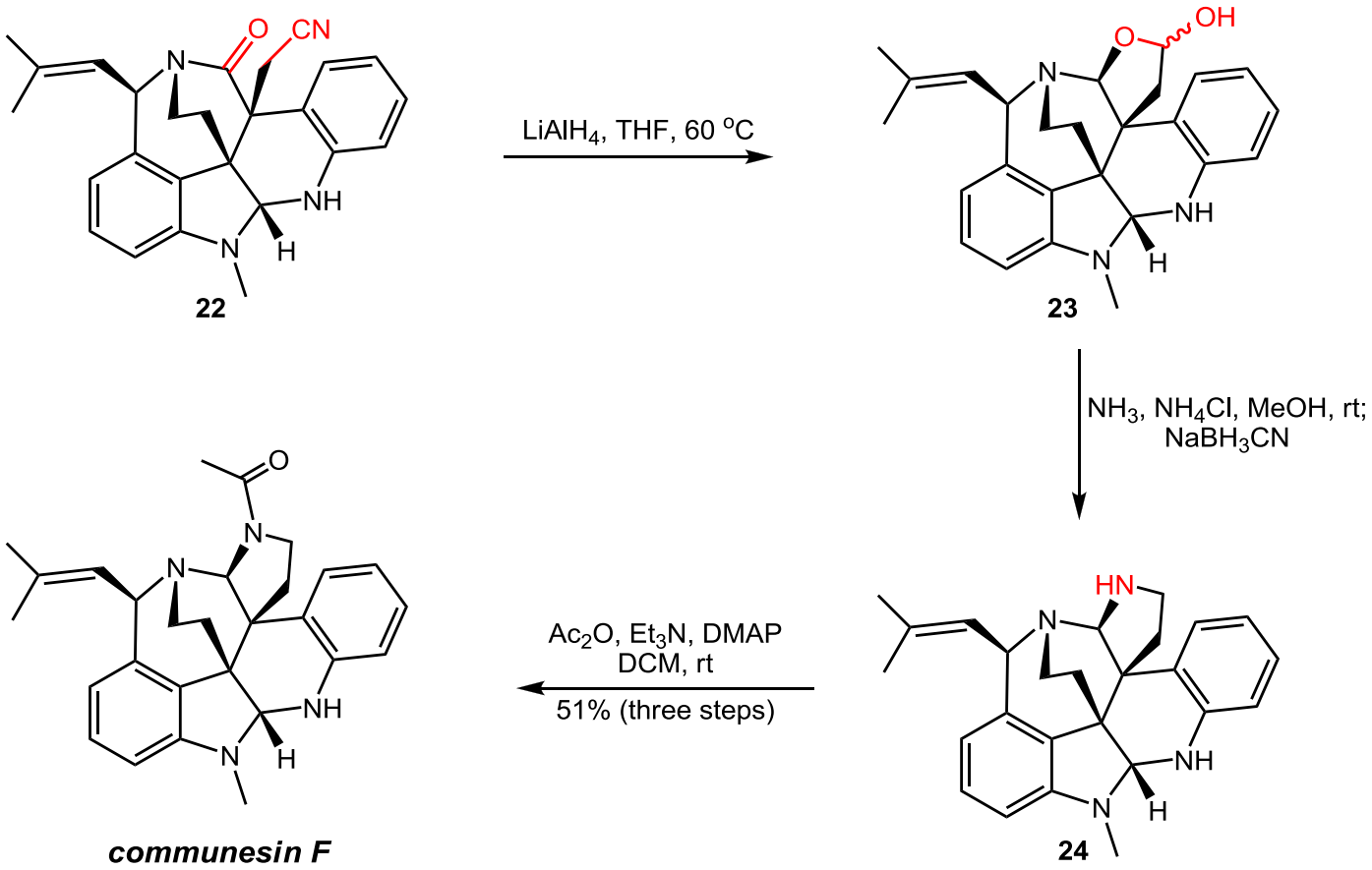
14　　15　　16



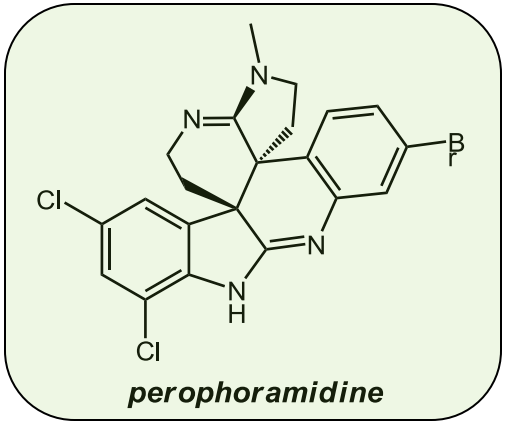
17　　18


Boc
HN
O
O
H
Br
NH
N
H
18
OH
Pd(OAc)2, K2CO3
H2O, DMF, 90 °C
93%
OH
Boc
HN
O
O
H
NH
N
H
19
Hg(OTf)2, DCM, rt
86%
Boc
N
O
O
H
H
NH
N
H
20


1) TBSOTf, DCM, lutidine, rt;
KF, MeOH, rt, 94%
2) AlMe3, DCM, 0 °C, 87%
O
N
H
NH
N
H
21
KHMDS, THF, -78 °C;
ICH2CN, THF, -78 °C
77%
O
CN
N
NH
N
H
22

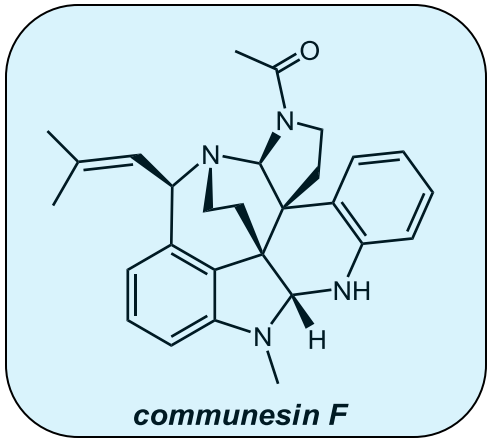

O
CN
N
NH
N
H
22
LiAlH4, THF, 60 °C
OH
O
N
NH
N
H
23
NH3, NH4Cl, MeOH, rt;
NaBH3CN
HN
N
NH
N
H
24
Ac2O, Et3N, DMAP
DCM, rt
51% (three steps)
O
N
N
NH
N
H
communesin F

6. 总结与讨论



perophoramidine

1. 12 steps, 9.7% overall yield;
2. A stereoselective cycloaddition with the parent Indol-2-one.



communesin F

1. 15 steps, 6.7% overall yield;
2. A stereoselective cycloaddition with the parent Indol-2-one;
3. An underutilized intramolecular mercuric triflate catalyzed cyclization of a carbamate with an allylic alcohol;
4. The preparation of a twisted, bridged lactam from an amino ester using trimethylaluminum.

The communesins are a group of eight architecturally intriguing natural products and are also biosynthetically and, as a consequence, structurally related to the natural product perophoramidine. In addition, communesin B is uniformly the most active of these natural products in a variety of biological assays and is moderately cytotoxic against P-388 (ED_{50} = 0.88 mM), LoVo (MIC = 3.9 mM) and KB(MIC = 8.8 mM) cells whose mechanism of action may involve the disruption of microfilaments. Accordingly, the communesins as well as perophoramidine have been the subject of numerous synthetic investigations and total syntheses of communesin A, B, F and perophoramidine have been recorded.

In summary, we have completed a concise total synthesis of (±)-communesin F in 15 linear steps from 4-bromotryptophol in an overall yield of 6.7%. Highlights of this synthesis include: (1) a stereoselective cycloaddition with the parent indol-2-one; (2) an underutilized intramolecular mercuric triflate catalyzed cyclization of a carbamate with an allylic alcohol; and (3) the preparation of a twisted, bridged lactam from an amino ester using trimethylaluminum. This total synthesis further documents the value of indol-2-one cycloadditions for the rapid construction of complex natural products that embody indolines bearing C(3) quaternary carbons. Additional applications of this methodology are underway.