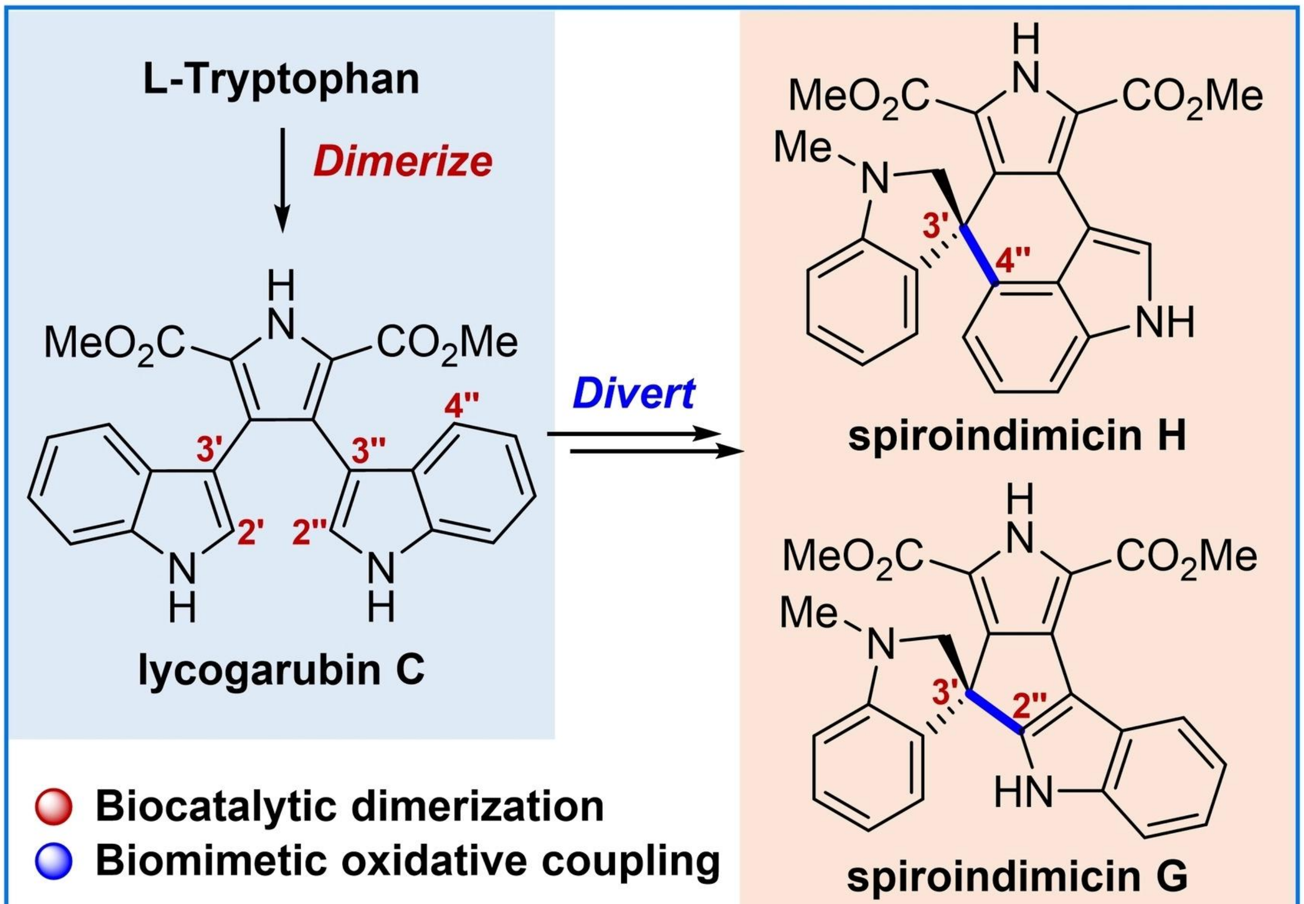
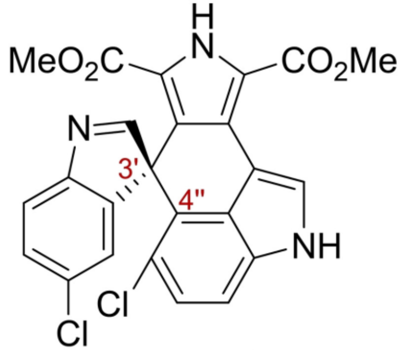
Biomimetic Total Synthesis of the Spiroindimicin Family of Natural Products

*Xikang Zheng+, Yan Li+, Mengtie Guan, Lingyue Wang, Shilong Wei, Yi-Cheng Li, Chin-Yuan Chang, and Zhengren Xu**

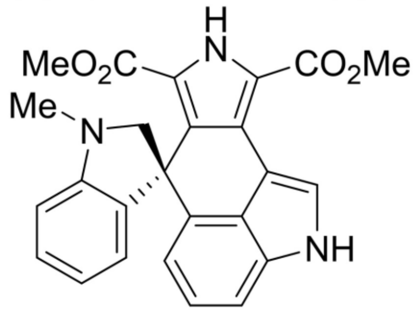


Angew. Chem. Int. Ed., **2022**, e202208802.

[5,6] spiro-ring skeleton

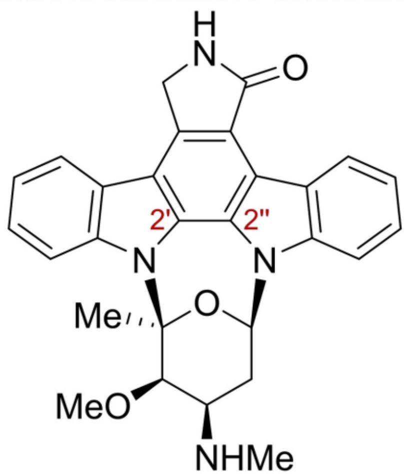


(+)-spiroindimicin A (**1**)



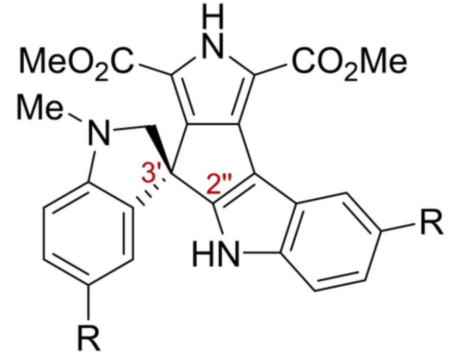
(+)-spiroindimicin H (**2**)

indolocarbazole skeleton

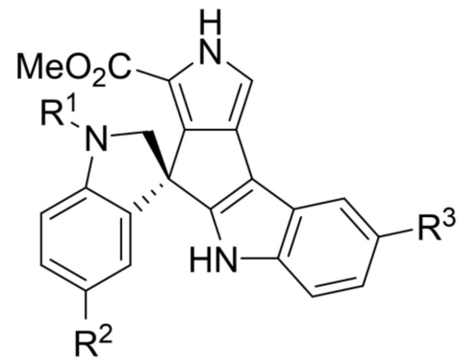


(+)-staurosporine (**9**)

[5,5] spiro-ring skeleton



(+)-spiroindimicin D (**3**): R = Cl
(+)-spiroindimicin G (**4**): R = H



(+)-spiroindimicin B (**5**):
R^1 = Me, R^2 = R^3 = Cl
(+)-spiroindimicin C (**6**):
R^1 = H, R^2 = R^3 = Cl
spiroindimicin E (**7**):
R^1 = Me, R^2 = Cl, R^3 = H
spiroindimicin F (**8**):
R^1 = Me, R^2 = H, R^3 = Cl

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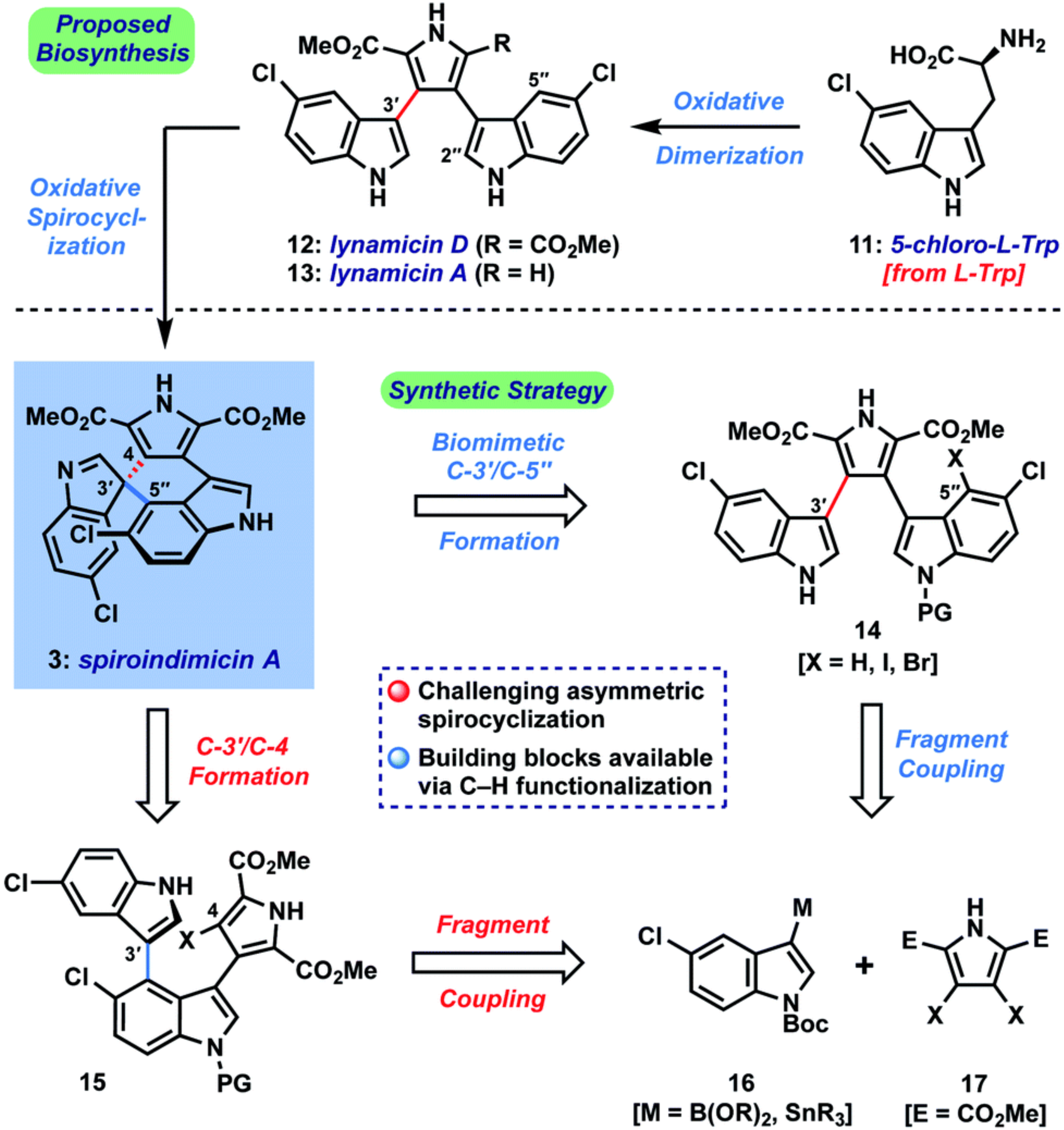
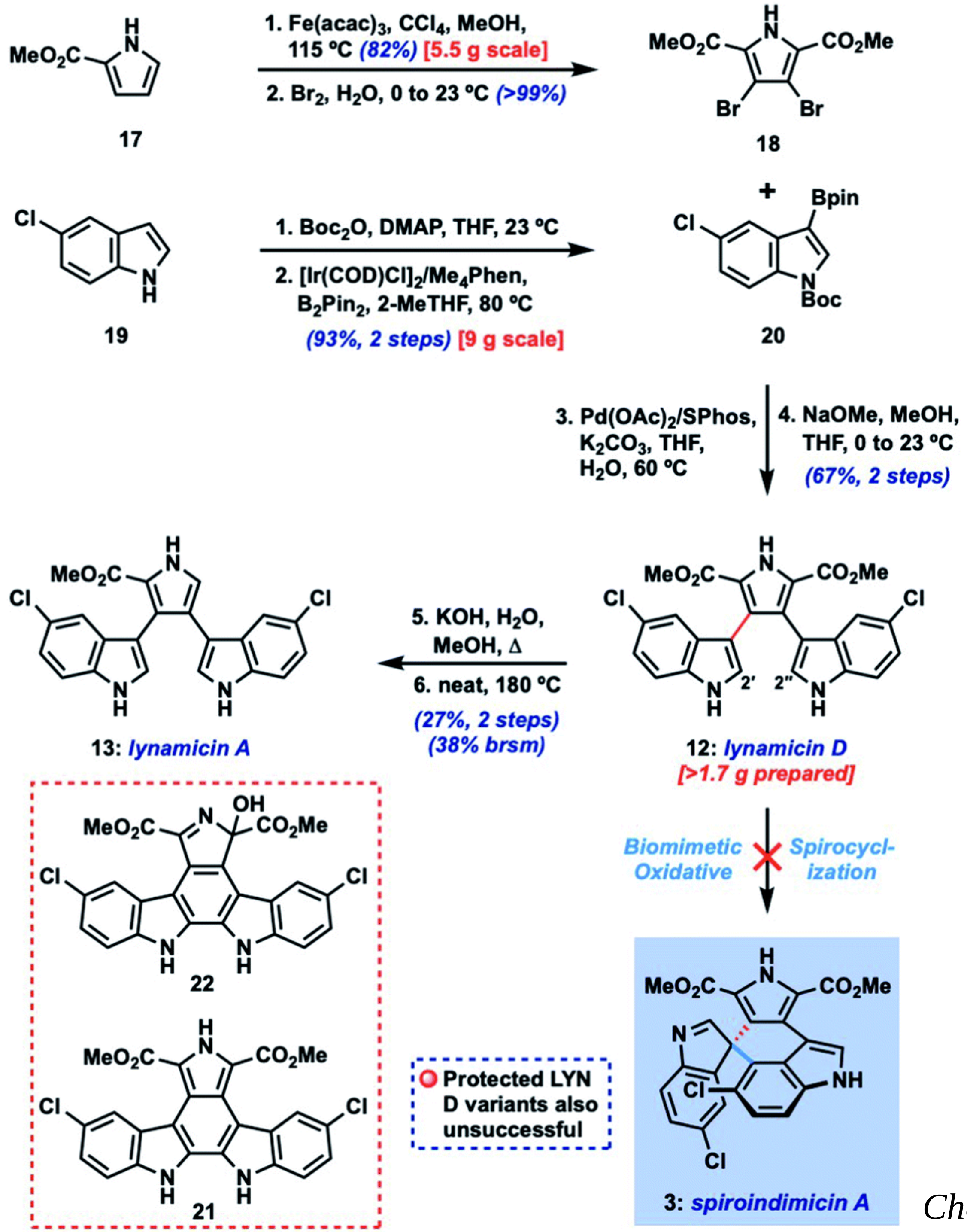
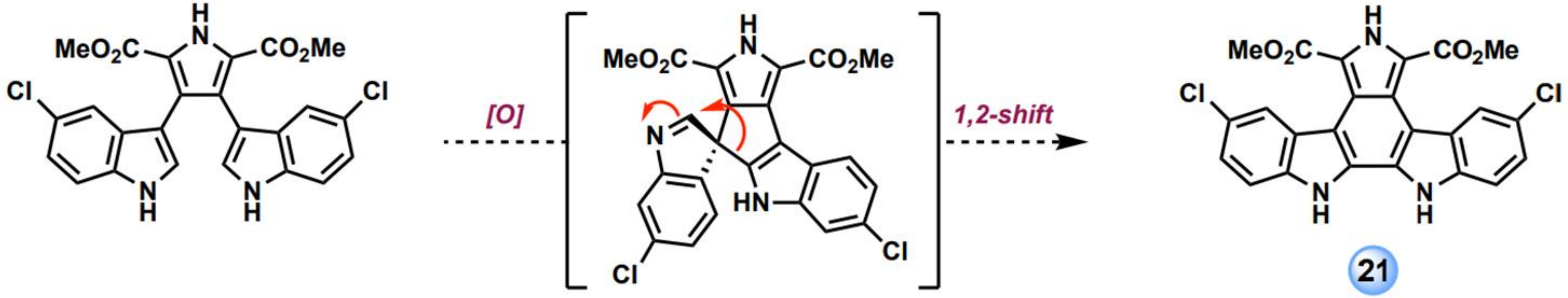


Chem. Sci., **2021**, *12*, 10388.

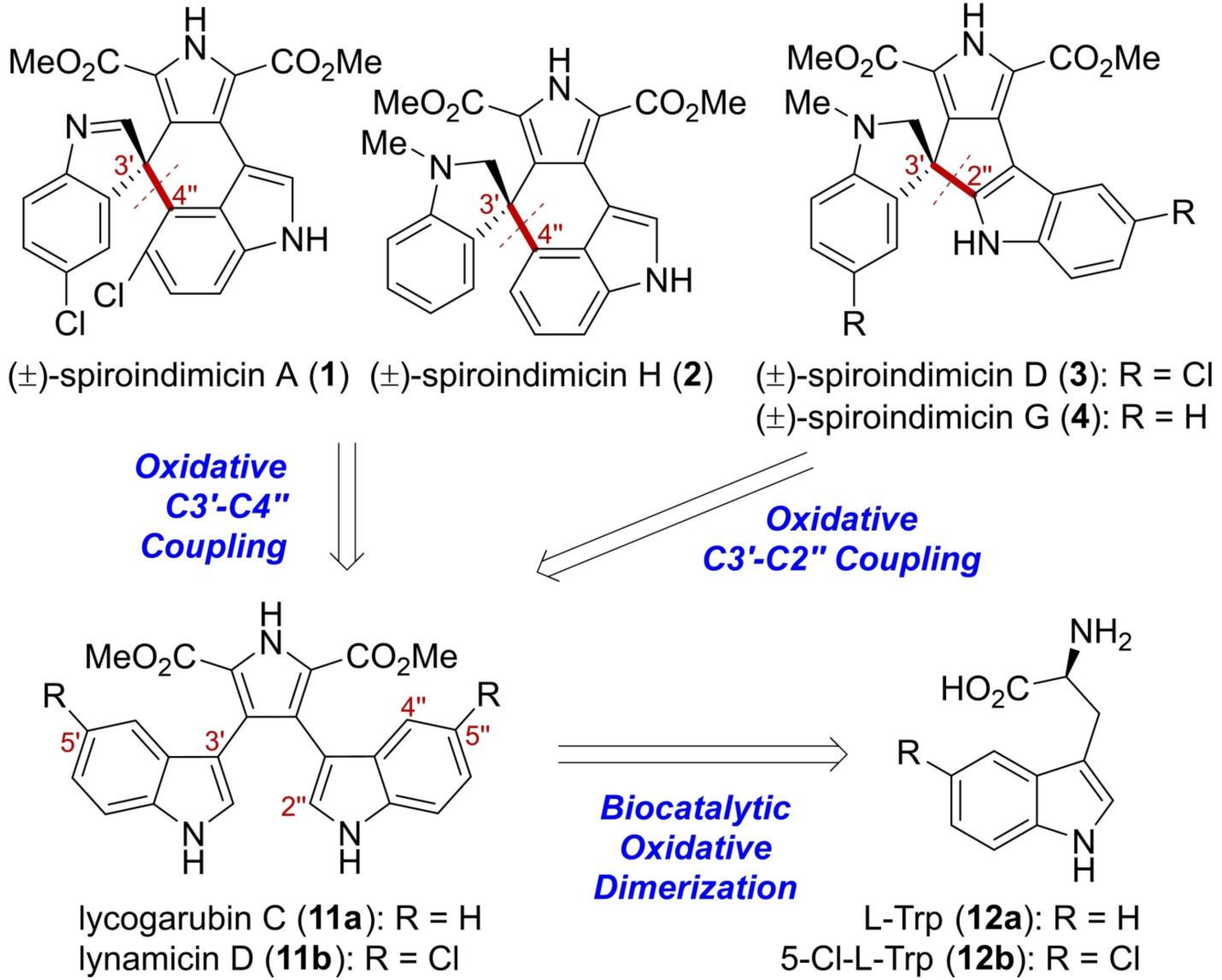


Chem. Sci., **2021**, *12*, 10388.

Possible transient spiroindolenine formation:



Chem. Sci.. **2021**, *12*, 10388.



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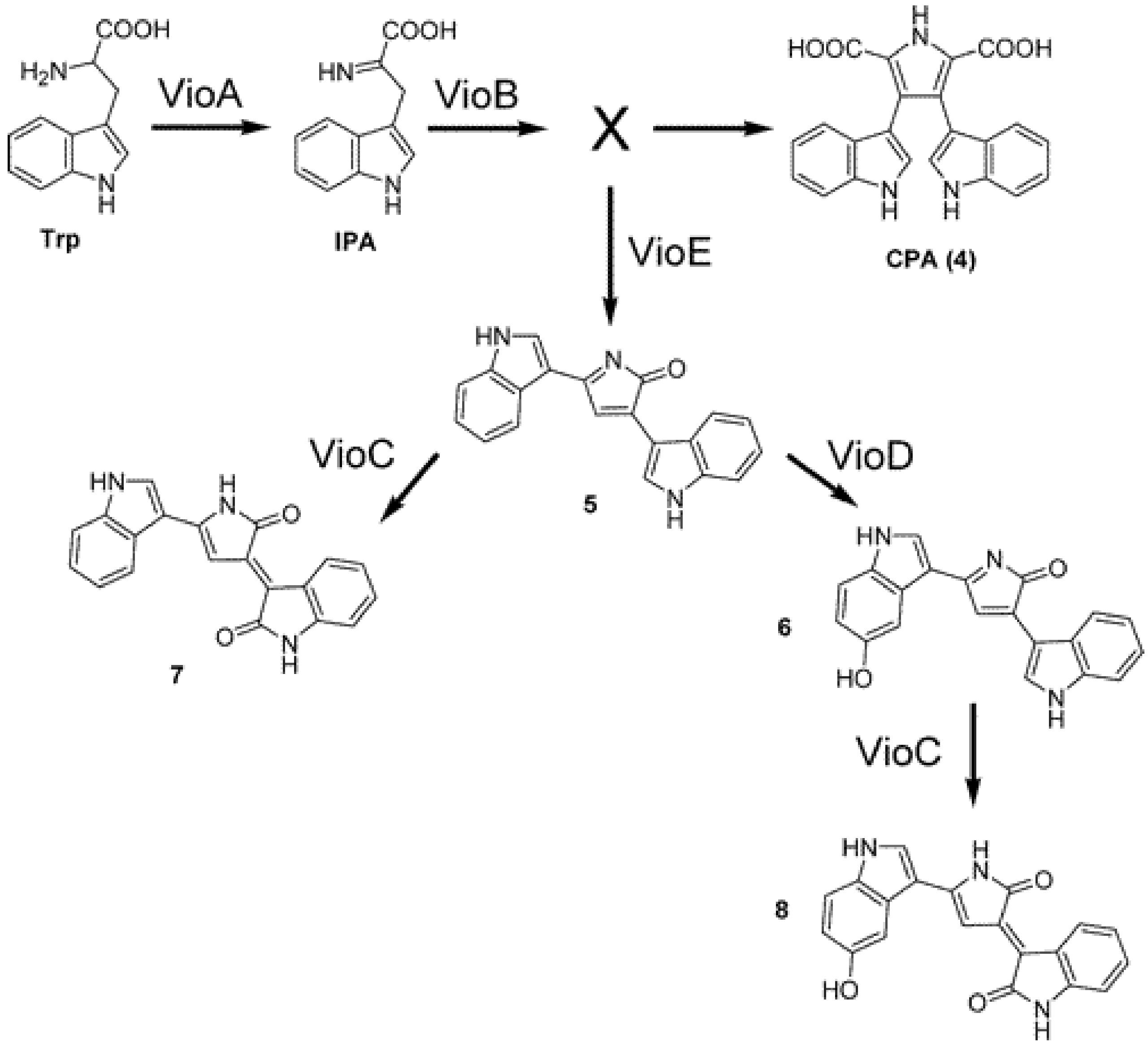
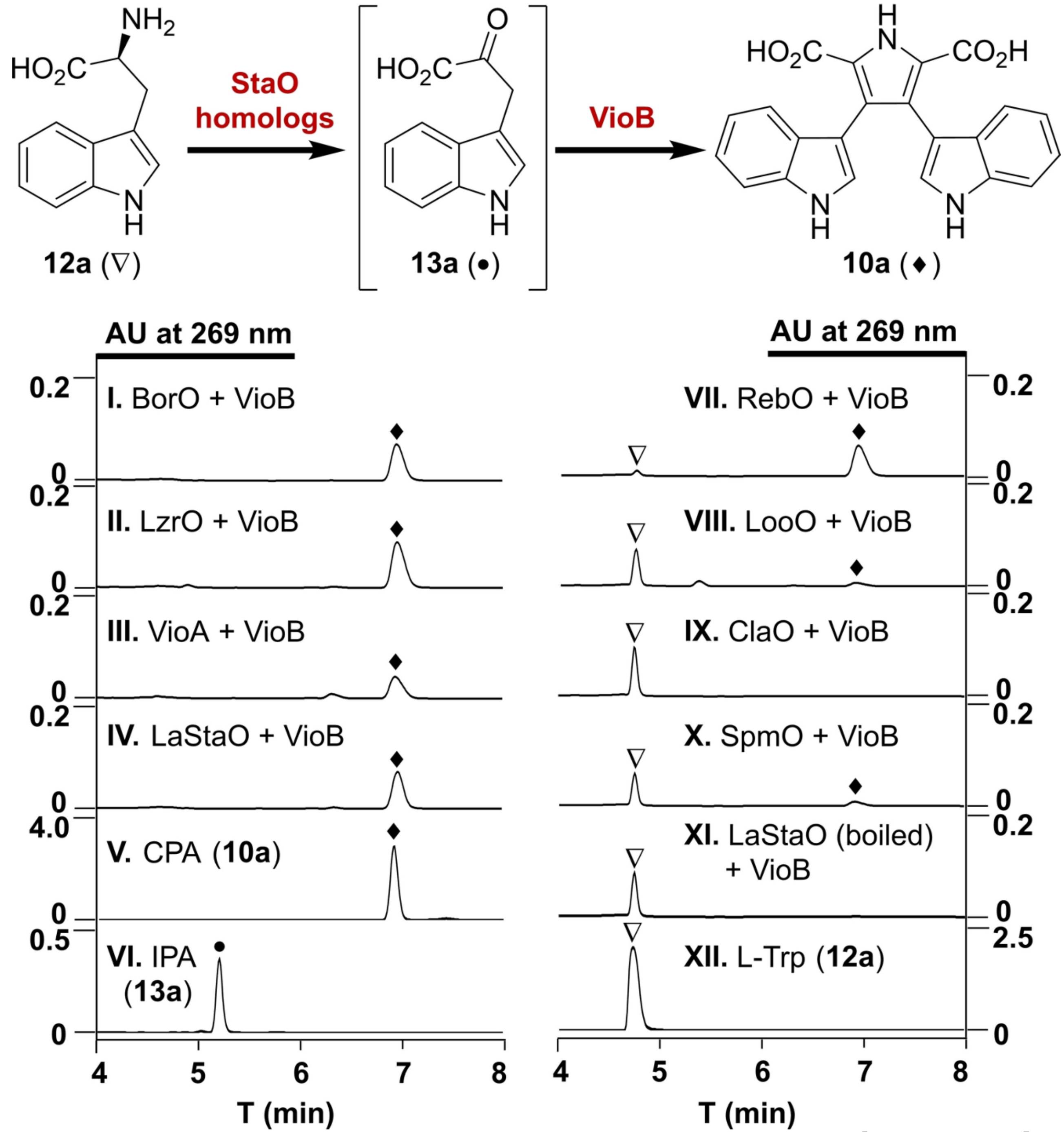
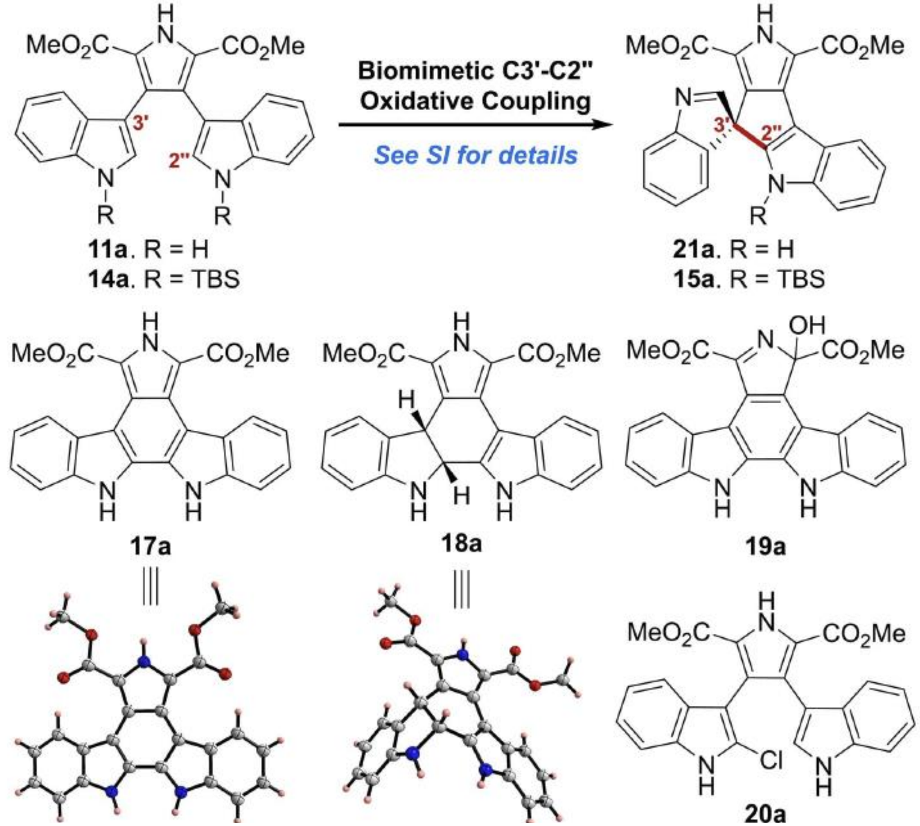


Biochemistry **2006**, *45*, 15444.



Angew. Chem. Int. Ed., **2022**, e202208802.



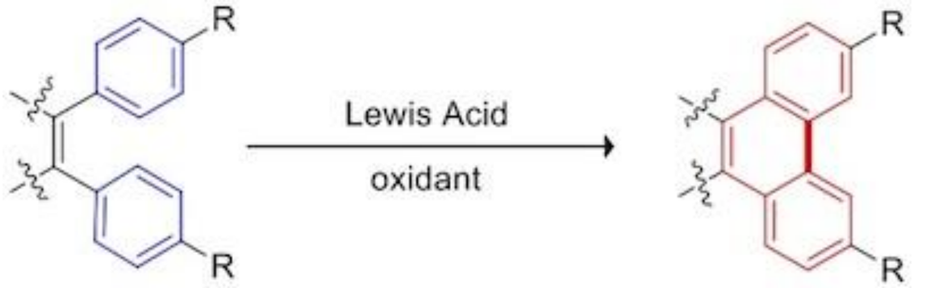
Entry	Substrate	Conditions[a]	Results
1	**11 a**	NCS, CH_2Cl_2, then pTLC	**21 a** (8 %, 9 % brsm)
2	**11 a**	NCS, CH_2Cl_2	degradation
3	**11 a**	NCS, silica gel, CH_2Cl_2	degradation
4	**11 a**	NCS, Al_2O_3, CH_2Cl_2	degradation
5	**11 a**	NBS, CH_2Cl_2	**17 a** (19 %), **18 a** (35 %)
6	**11 a**	NIS, CH_2Cl_2	No reaction
7	**11 a**	Synfluor, CH_3CN	**19 a** (67 %)
8	**14 a**	NCS, CH_2Cl_2	No reaction
9	**14 a**	NCS, silica gel, CH_2Cl_2	degradation
10	**14 a**	NCS, Al_2O_3, CH_2Cl_2	**15 a** (15 %, 43 % brsm)
11	**14 a**	NBS, Al_2O_3, CH_2Cl_2	**15 a** (trace)
12	**14 a**	NIS, Al_2O_3, CH_2Cl_2	No reaction
13	**14 a**	Synfluor, Al_2O_3, CH_2Cl_2	No reaction
14[b]	**14 a**	TCCA, Al_2O_3, CH_2Cl_2	**15 a** (35 %, 51 % brsm)

11a. R = H
14a. R = TBS

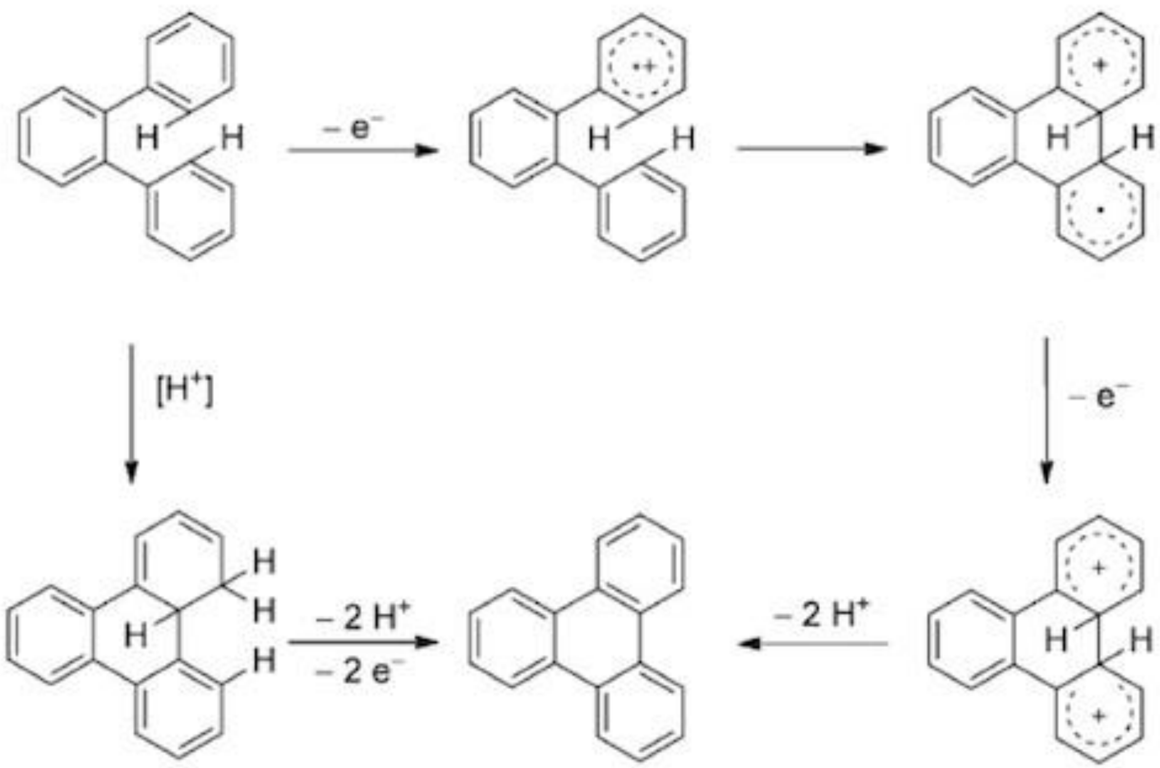
22a. R = H
16a. R = TBS

Entry	Substrate	Conditions[a]	Results[b]
1[c]	**14a**	$FeCl_3$, BTMG, CH_2Cl_2, RT	**16a** (10%, 83% brsm)
2[c]	**11a**	$FeCl_3$, BTMG, CH_2Cl_2, RT	No reaction
3	**14a**	$AgBF_4$, NIS, NaOH, CH_2Cl_2, 40 °C	**16a** (77%)
4	**11a**	$AgBF_4$, NIS, NaOH, CH_2Cl_2, 40 °C	**17a** (64%)
5[d]	**14a**	$AgBF_4$, CH_2Cl_2, 40 °C	**16a** (11%), **17a** (51%)
6	**14a**	$AgBF_4$, NaOH, CH_2Cl_2, 40 °C	**16a** (trace)
7	**14a**	NIS, CH_2Cl_2, 40 °C	No reaction
8	**14a**	NIS, NaOH, CH_2Cl_2, 40 °C	Partial deprotection
9	**14a**	$AgBF_4$, NIS, CH_2Cl_2, 40 °C	**16a** (38%)
10[e]	**14a**	$AgBF_4$, NIS, aq. HBF_4, CH_2Cl_2, 40 °C	**16a** (17%), **17a** (14%)
11	**14a**	AgOTf, NIS, NaOH, CH_2Cl_2, 40 °C	degradation
12	**14a**	$AgPF_6$, NIS, NaOH, CH_2Cl_2, 40 °C	**16a** (65%)
13	**14a**	$AgSbF_6$, NIS, NaOH, CH_2Cl_2, RT	**16a** (78%)
14[f]	**14a**	$AgSbF_6$, NIS, NaOH, CH_2Cl_2, RT	**16a** (98%)

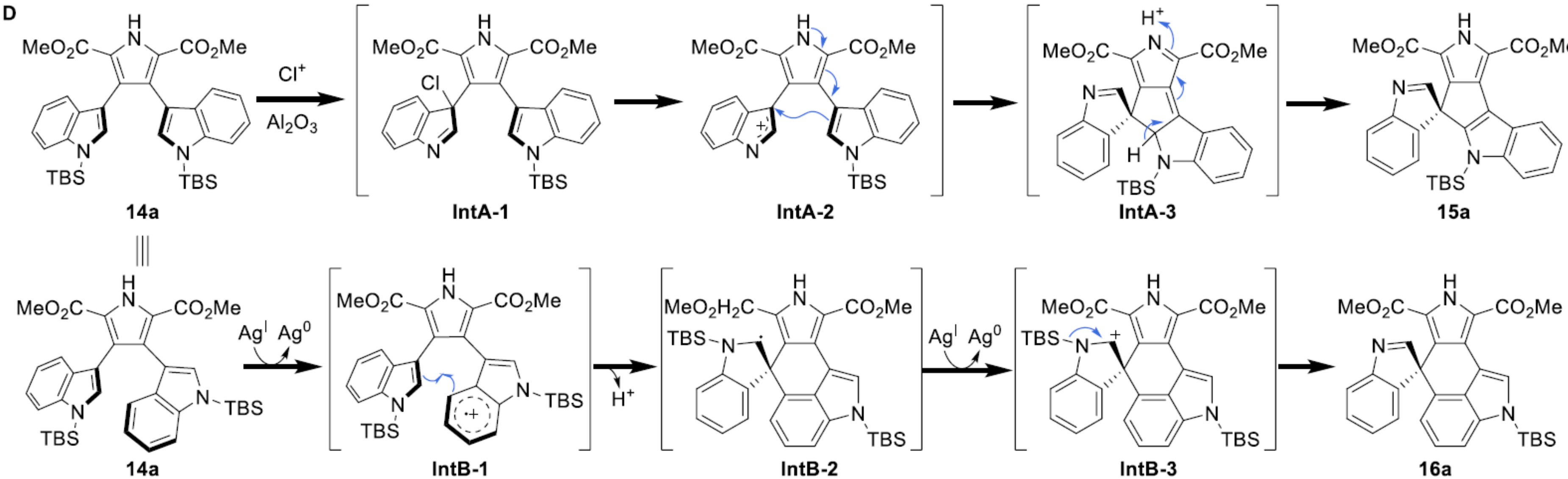
Scholl氧化偶联反应



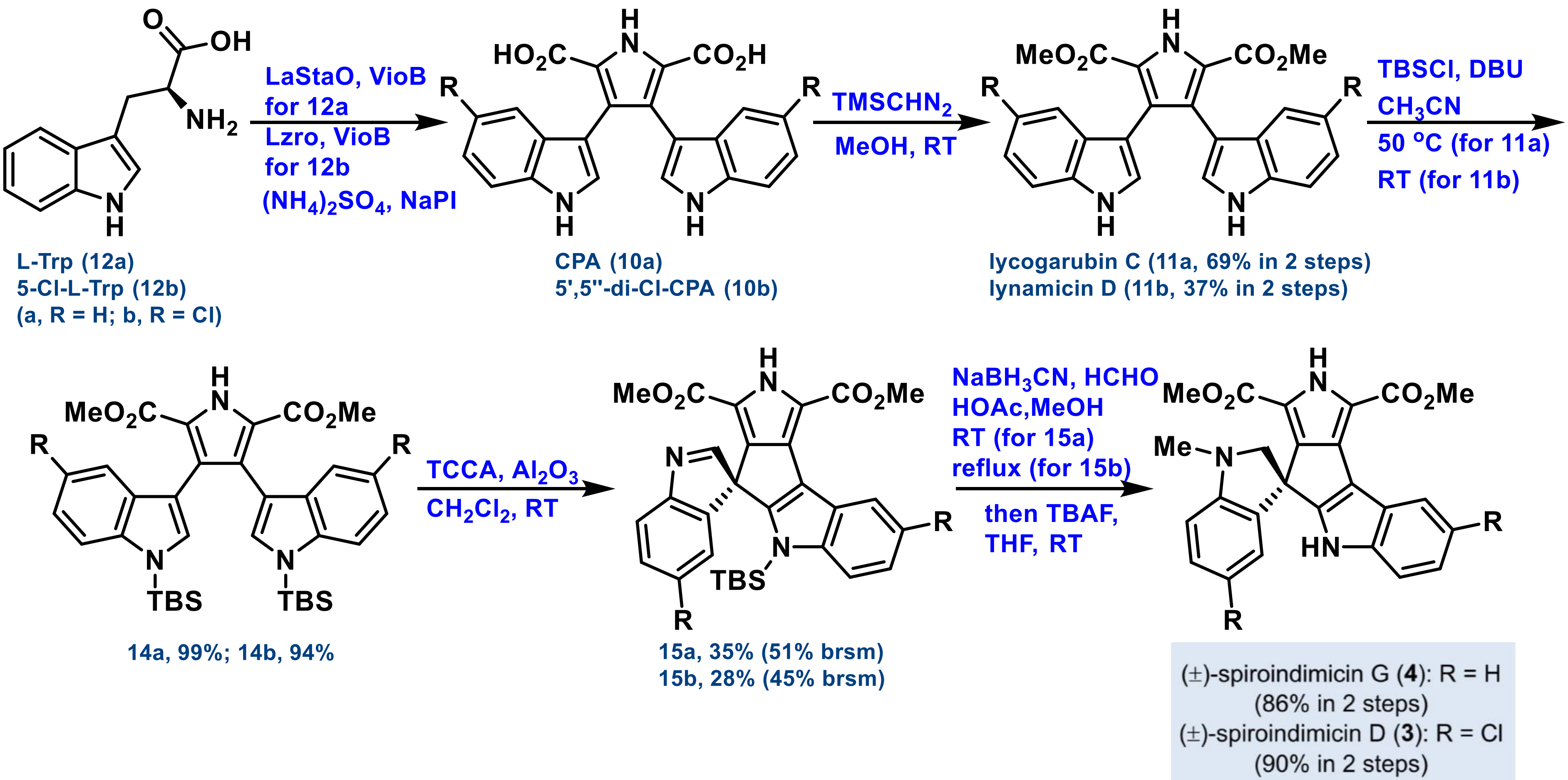
Mechanism：



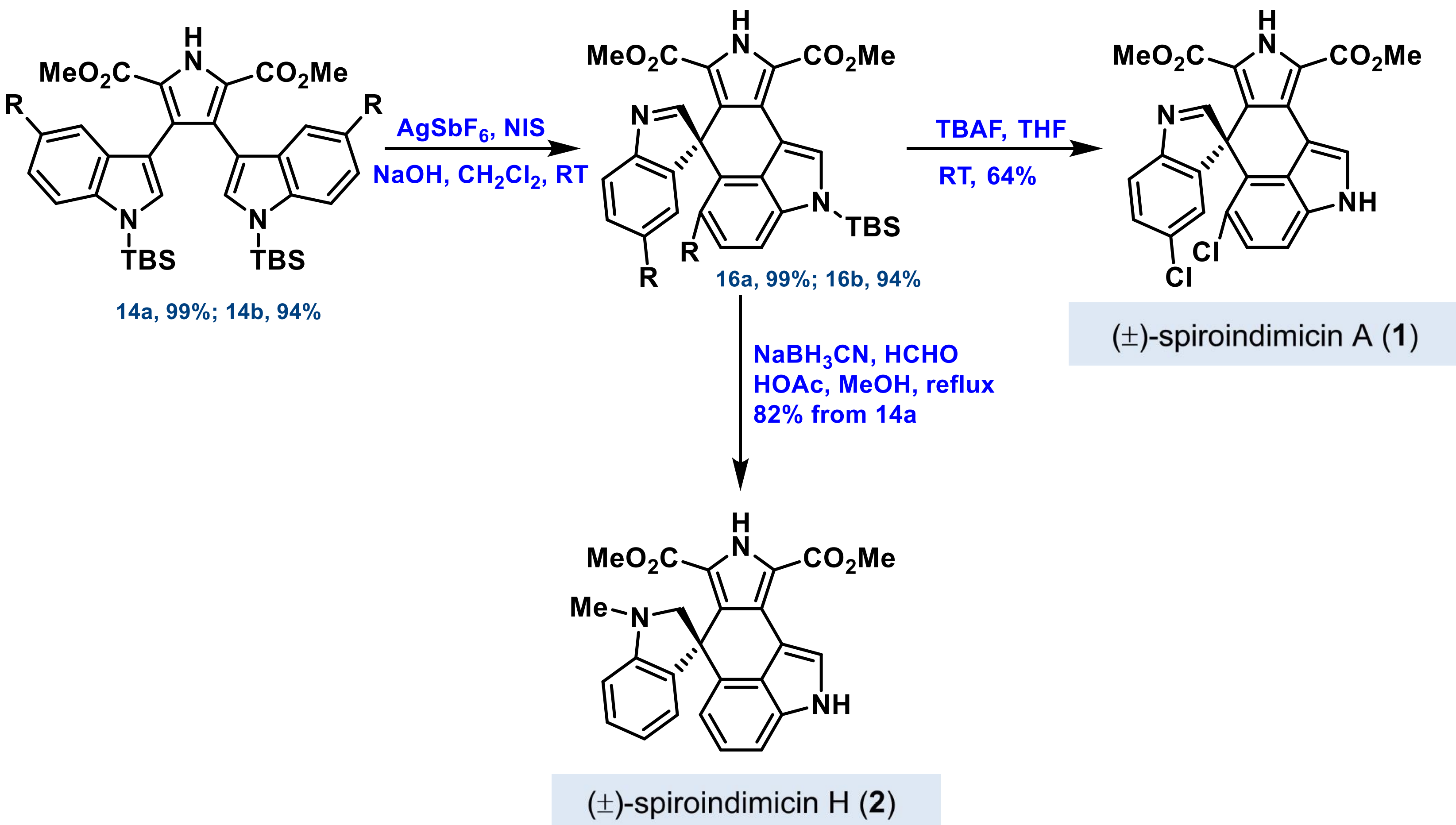
D



MeO2C
CO2Me
H
N
TBS
Cl+
Al2O3
Cl
IntA-1
IntA-2
H+
IntA-3
15a
14a
AgI
Ag0
H+
MeO2H2C
IntB-1
IntB-2
IntB-3
16a



LaStaO, VioB
for 12a
Lzro, VioB
for 12b
$(NH_4)_2SO_4$, NaPI
L-Trp (12a)
5-Cl-L-Trp (12b)
(a, R = H; b, R = Cl)
CPA (10a)
5',5''-di-Cl-CPA (10b)
$TMSCHN_2$
MeOH, RT
lycogarubin C (11a, 69% in 2 steps)
lynamicin D (11b, 37% in 2 steps)
TBSCl, DBU
CH_3CN
50 °C (for 11a)
RT (for 11b)
14a, 99%; 14b, 94%
TCCA, Al_2O_3
CH_2Cl_2, RT
15a, 35% (51% brsm)
15b, 28% (45% brsm)
$NaBH_3CN$, HCHO
HOAc,MeOH
RT (for 15a)
reflux (for 15b)
then TBAF,
THF, RT
(±)-spiroindimicin G (**4**): R = H
(86% in 2 steps)
(±)-spiroindimicin D (**3**): R = Cl
(90% in 2 steps)


MeO2C
CO2Me
R
N
TBS
14a, 99%; 14b, 94%
AgSbF6, NIS
NaOH, CH2Cl2, RT
16a, 99%; 16b, 94%
TBAF, THF
RT, 64%
NH
Cl
(±)-spiroindimicin A (1)
NaBH3CN, HCHO
HOAc, MeOH, reflux
82% from 14a
Me
(±)-spiroindimicin H (2)