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Communication

A Platform for the Synthesis of Corynantheine-Type Corynanthe Alkaloids

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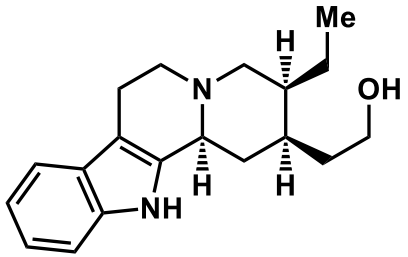
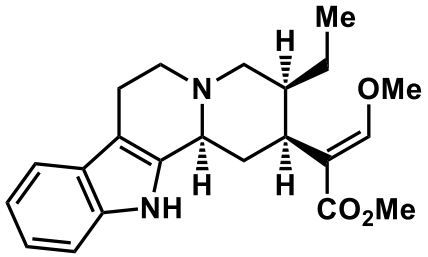
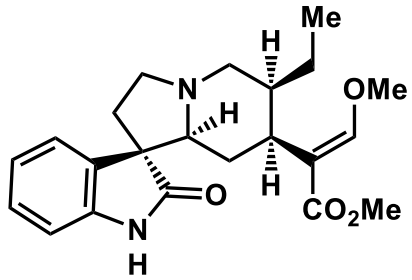


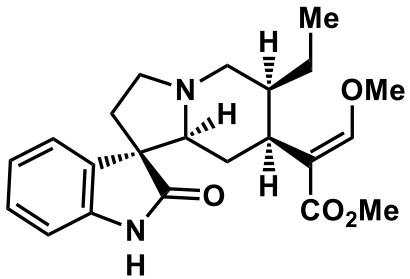
(-)-corynantheidol (1)



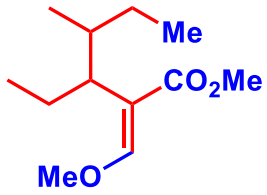
(-)-corynantheidine (2)



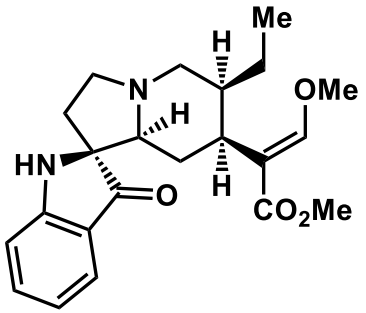
(+)-corynoxine (3)



(-)-corynoxine B (4)



corynantheine-type
Corynanthe-type carbon skeleton



(-)-corynantheidine pseudoindoxyl (5)

Figure 1. Structures of selected corynantheine-type corynanthe alkaloids.

- *enantioselective*
- *no protecting groups*
- *5 total syntheses*

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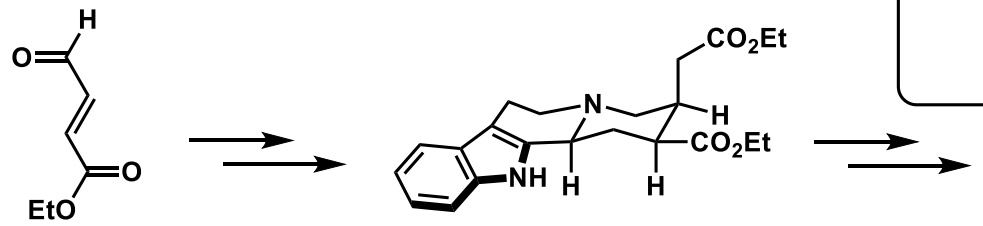
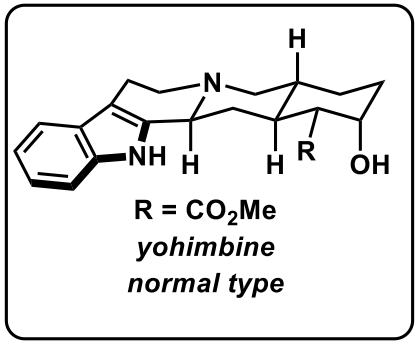
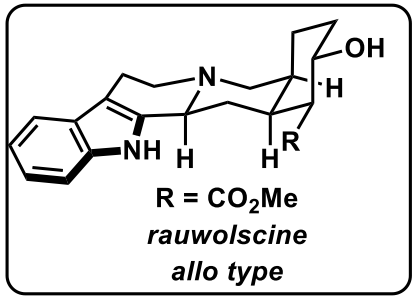
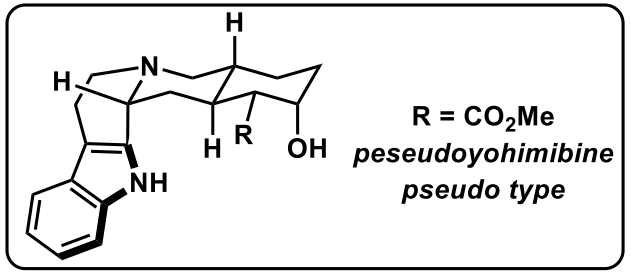
(A) Yohimbine alkaloids synthesis, Scheidt, 2020

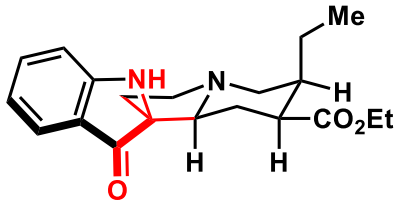






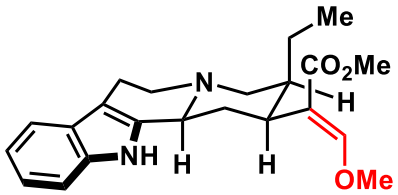


(B) Retrosynthesis of (-)-corynantheidine pseudoindoxyl (5)



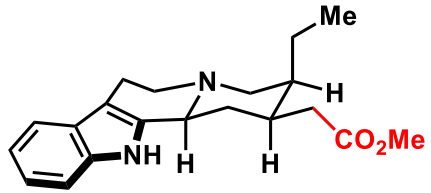
(-)-corynantheidine
pseudoindoxyl (5)

Oxidation & Rearrangement



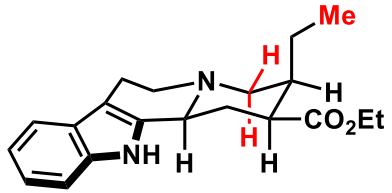
(-)-corynantheidine (2)

O-methylation Claisen reaction



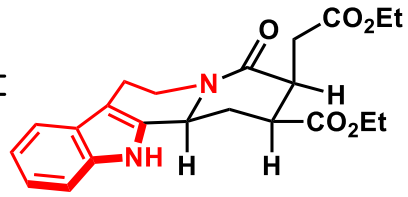
13

Homologation



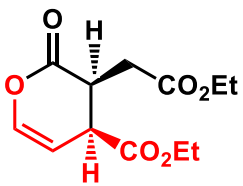
11

Selective reduction



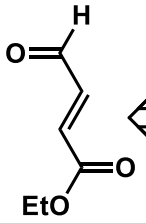
8

Amidation & Cyclization



7

NHC catalysis



6

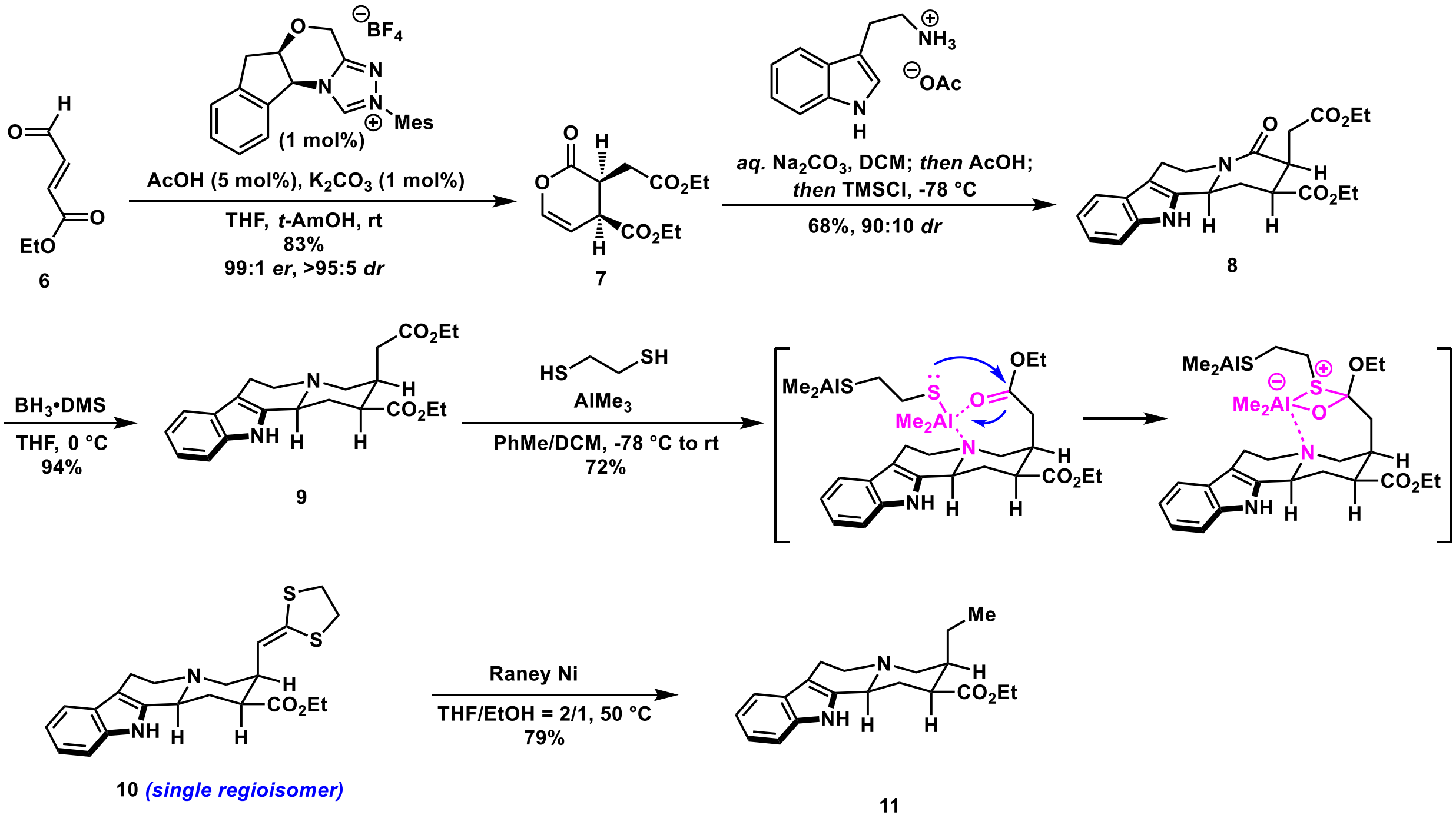
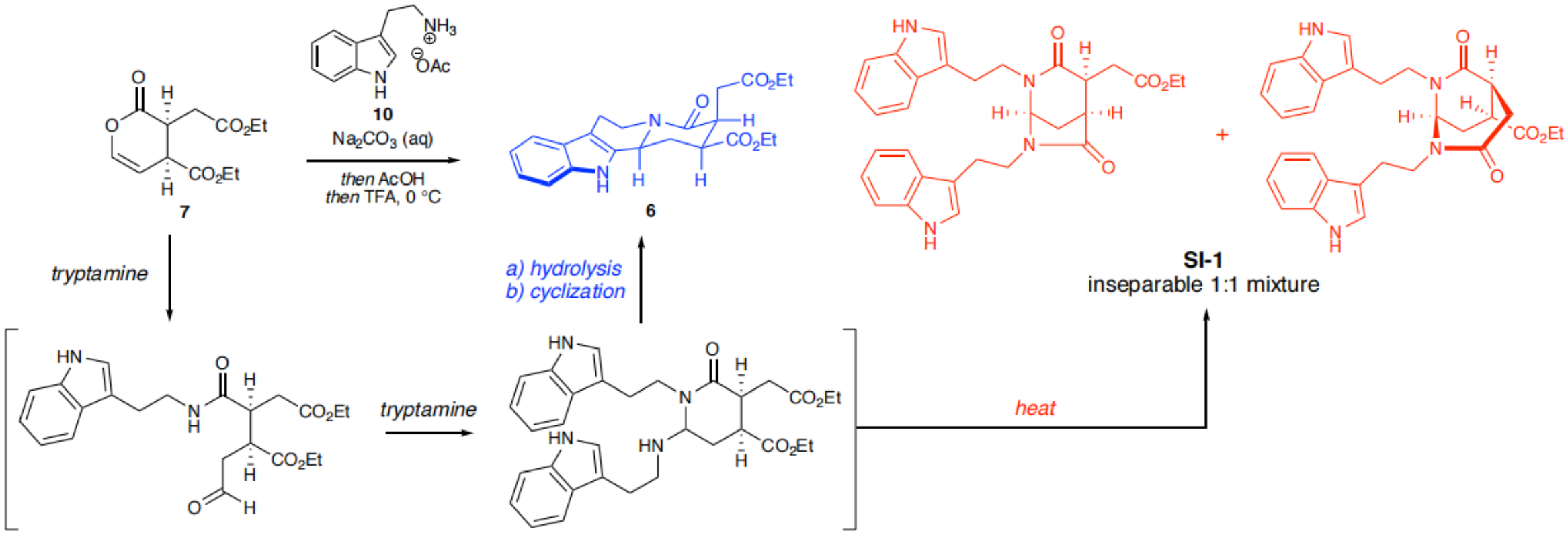
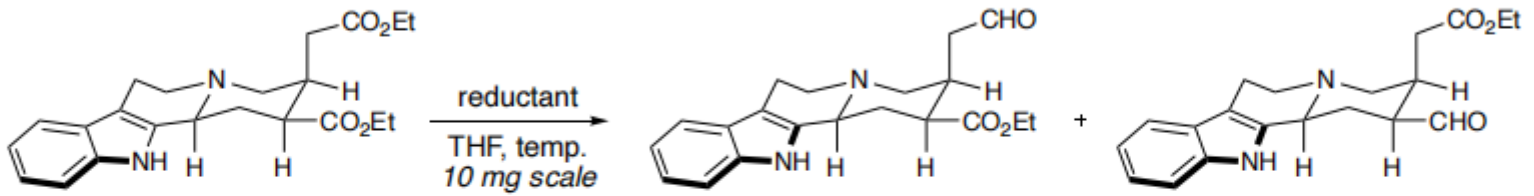

6
(1 mol%)
AcOH (5 mol%), K2CO3 (1 mol%)
THF, t-AmOH, rt
83%
99:1 er, >95:5 dr
7
aq. Na2CO3, DCM; then AcOH;
then TMSCl, -78 °C
68%, 90:10 dr
8
BH3•DMS
THF, 0 °C
94%
9
AlMe3
PhMe/DCM, -78 °C to rt
72%
Raney Ni
THF/EtOH = 2/1, 50 °C
79%
10 (single regioisomer)
11

Figure S1. One-pot amidation/cyclization sequence and production of unproductive side products **SI-1**.



J. Am. Chem. Soc., **2020**, *142*, 2187.

Table 1: Partial Reduction Reaction of **9**

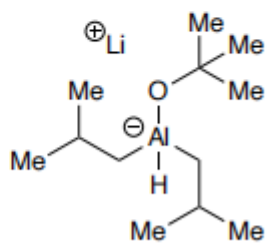


9 **I** **II**

entry	reductant	temperature (°C)	rr (**I**:**II**)
1	**A**	0	52:48
2	**A**	–20 to 0	55:45
3	**A**	–78 to 0	58:42
4	**B**	0	–[a]
5	**B**	–20 to 0	–[a]
6	**B**	–78 to 0	–[a]
7[b]	**A**	–78 to 0	52:48

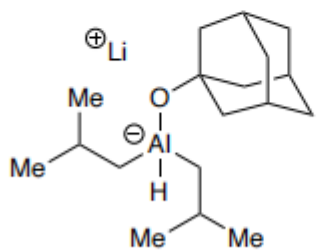
[a]significant epimerization and decomposition precluded rr determination; [b]100 mg scale

A:

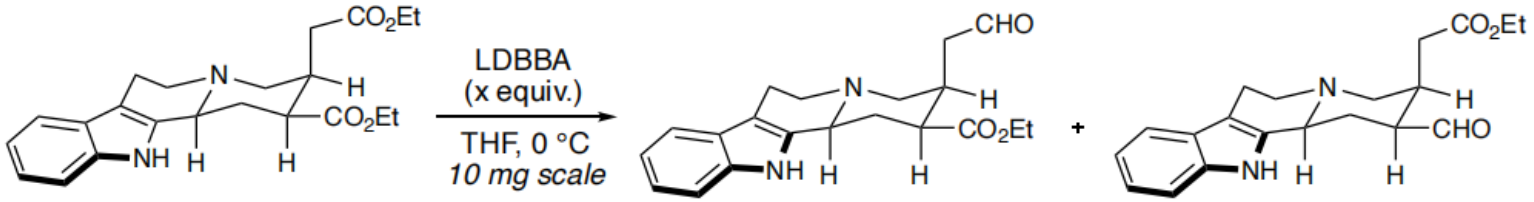


LDBBA

B:

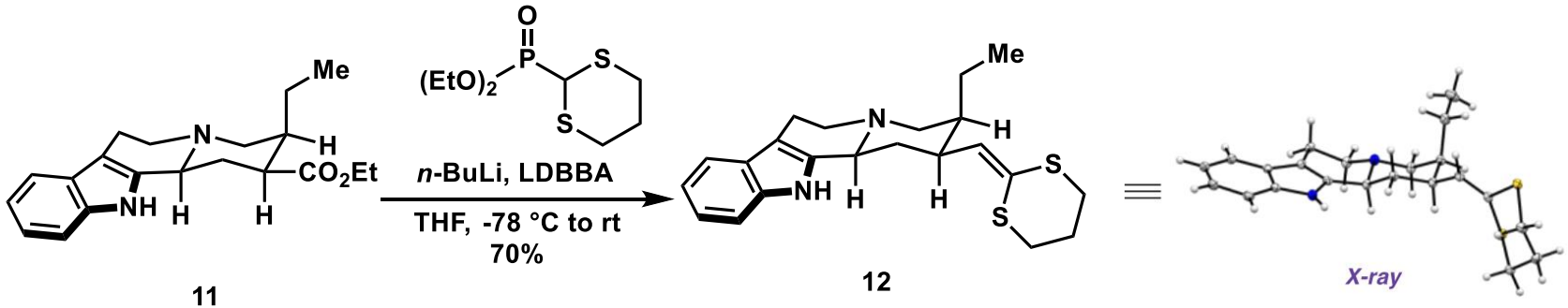


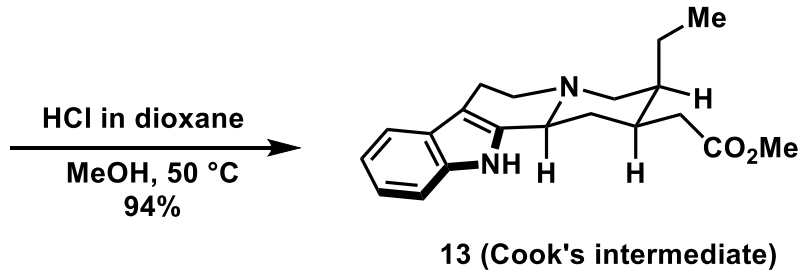
LDBAA



9 **I** **II**

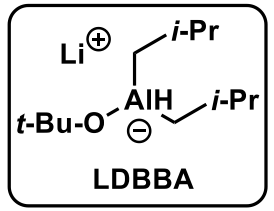
entry	additive	equiv. of LDBBA	conversion (%)	results (rr **I**:**II**)
1	–	1.1	>99	40% (58:42)
2	$Mg(OTf)_2$	1.1	0	NR
3	$Zn(OTf)_2$	1.1	0	NR
4	$Gd(OTf)_3$	1.1	0	NR
5	$Sc(OTf)_3$	1.1	0	NR
6	$La(OTf)_3$	1.1	0	NR
7	$Yb(OTf)_3$	1.1	trace	–
8	$Sm(OTf)_3$	1.1	0	NR
9	$Yb(OTf)_3$	2.1	trace	–
10	$Yb(OTf)_3$	4.1	trace	–
11	$Yb(OTf)_3$	5.1	>99	60% (58:42)
12	$Mg(OTf)_2$	5.1	>99	overreduction
13	$Zn(OTf)_2$	5.1	>99	overreduction
14	$Sc(OTf)_3$	5.1	>99	50:50
15	$Sm(OTf)_3$	5.1	>99	55:45
16	Et_2AlCl	1.1	trace	–
17	$EtAlCl_2$	1.1	trace	–

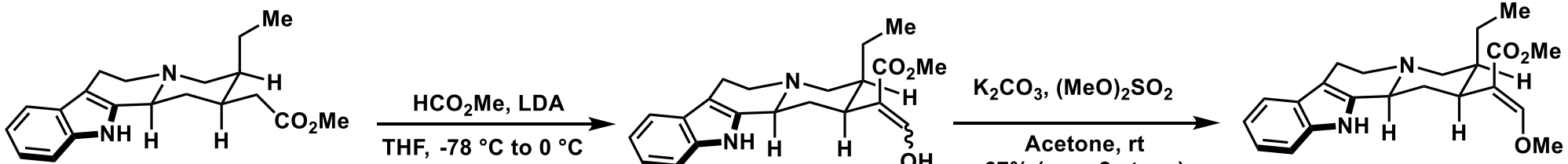


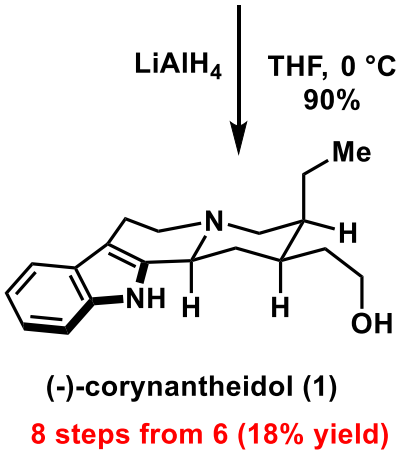


*Synthesis of Cook's intermediate **13***

Cook et al.	• 10 steps • requires protecting groups • starts with D-tryptophan
This work	• 7 steps • no protecting groups • enantioselective synthesis

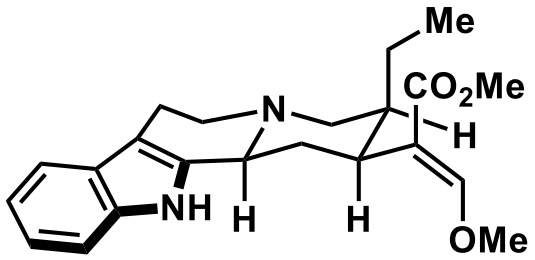






*Conditions for methylation of **14***

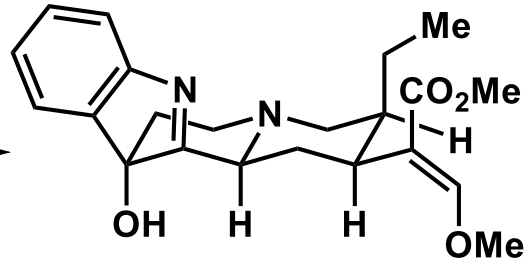
entry	reagent	base	solvent	outcome
1	$(MeO)_2SO_2$	NaOMe	benzene	20% for **2** 40% for Z-isomer
2	$TMSCHN_2$	no base	MeOH	unknown as major + **2** as minor
3	$(MeO)_2SO_2$	K_2CO_3	acetone	73% for **2** (> 20:1 E/Z)



(-)-corynantheidine (2)

oxone, H_2O, *aq*. $NaHCO_3$

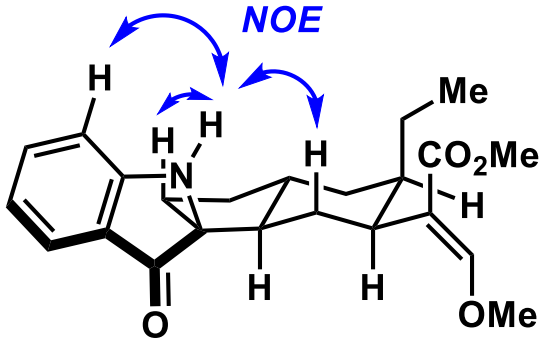
Acetone, 0 °C
36%



(+)-hydroxycorynantheidine (15)

$Sc(OTf)_3$

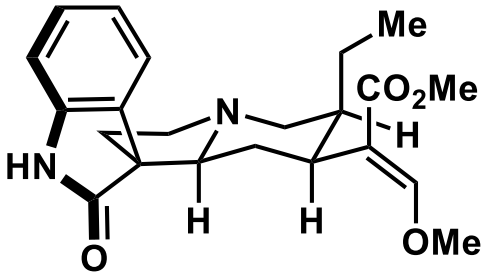
Toluene, rt
54%



(-)-corynantheidine pseudoindoxyl (5)

11 steps from 6 (3% yield)

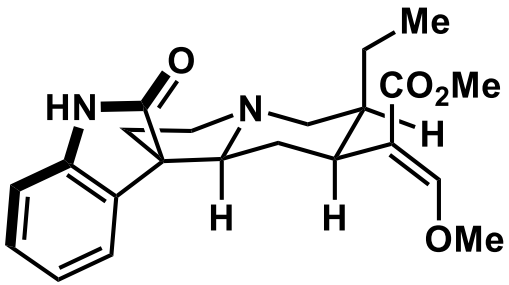
oxidants, H_2O
(NBS, TCCA, or *t*-BuOCl)



(+)-corynoxine (3)

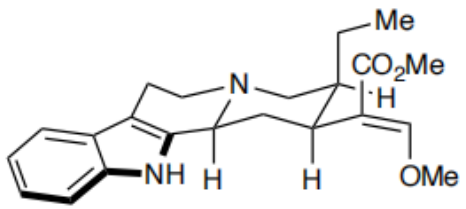
+

unfruitful direct spirooxindole formation



(-)-corynoxine B (4)

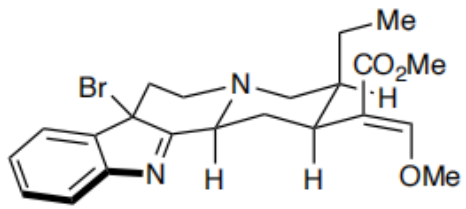
Failed route for the synthesis of (+)-corynoxine (**3**) from (-)-corynantheidine (**2**)



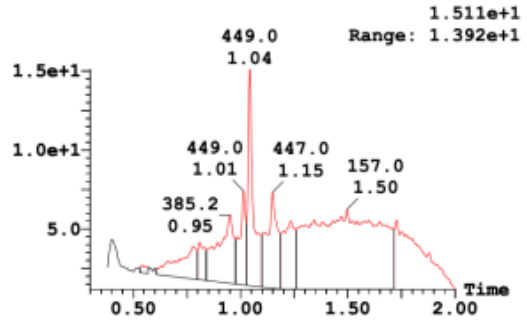
(–)-corynantheidine (**2**)

NBS

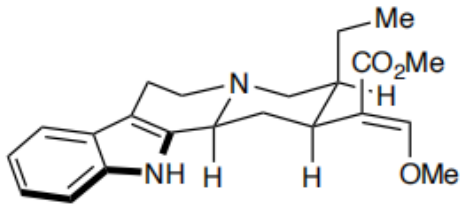
THF, H_2O



this compound mass (446 and 448 by bromide isotope) was observed, but no (+)-corynoxine (**3**) or (–)-corynoxine B (**4**)



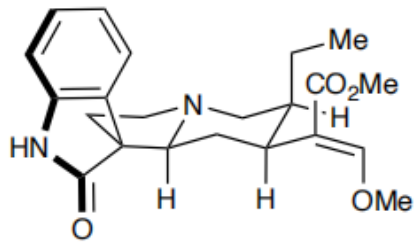
Overoxidation product mass observed as the reaction goes. (**3** or **4** was not obtained)



(–)-corynantheidine (**2**)

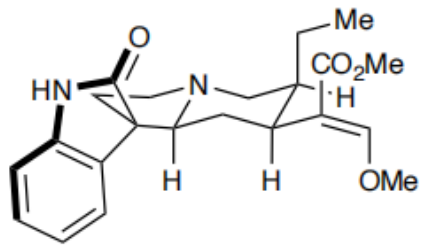
TCCA

THF, H_2O

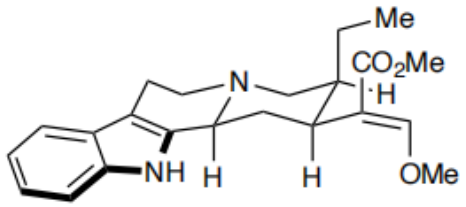


(+)-corynoxine (**3**)
isolated: 10% yield

+



(–)-corynoxine B (**4**)
not observed



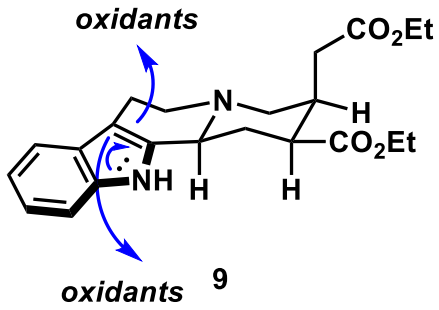
(–)-corynantheidine (**2**)

t-BuOCl, Et_3N

DCM;
then MeOH, H_2O, TFA

Messy reaction profile.
Overoxidation product mass observed as the reaction goes.
(**3** or **4** was not obtained)

A) Original plan: oxidative rearrangement reduction of 9



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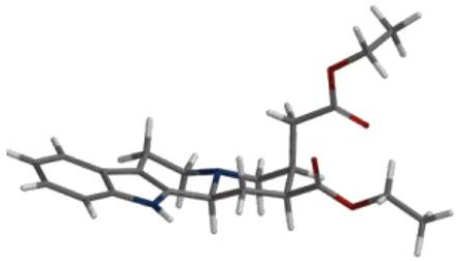
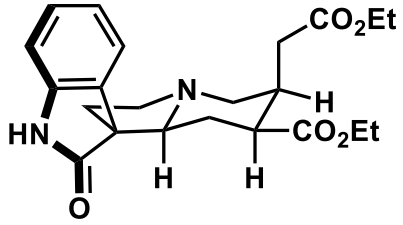


both faces are avaliable
= little selectivity

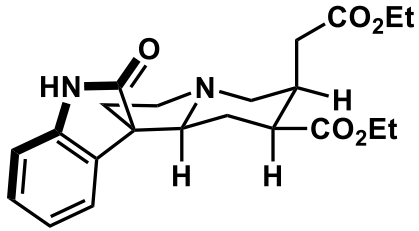
various oxidants
- low yield
- poor selectivity

up to 40:60 (17:18)



17 (*desired*)

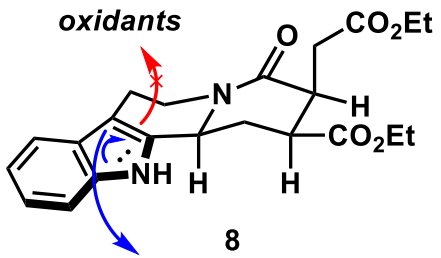
+



18 (*undesired*)

B) New route: oxidative rearrangement reaction of 8

blocked by the cup-like shape of the molecule



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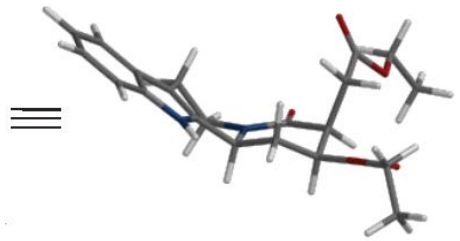
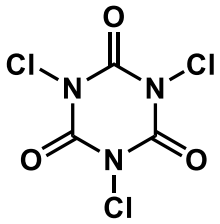
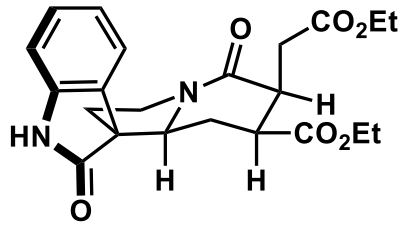


more avaliable convex face



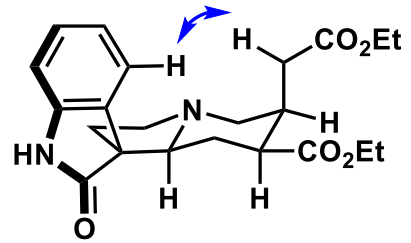
THF, H_2O, 0 °C
66%



16 (*single diastereomer*)

$NaBH_4$, I_2
THF, -20 °C
75%

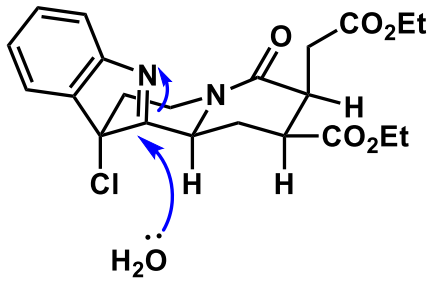
NOE

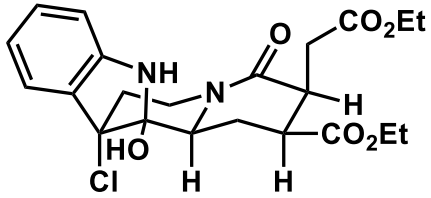


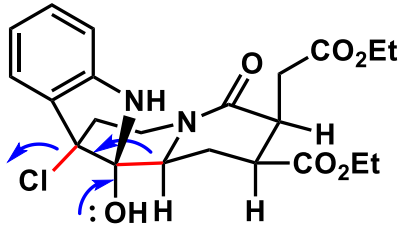
17

≡

TCCA







pinacol-type rearrangement

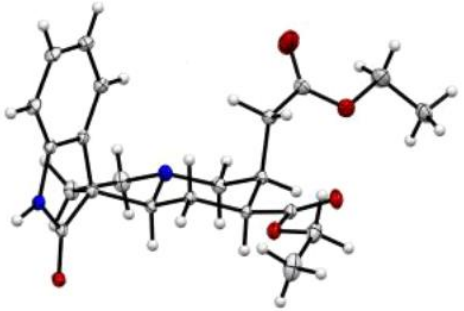
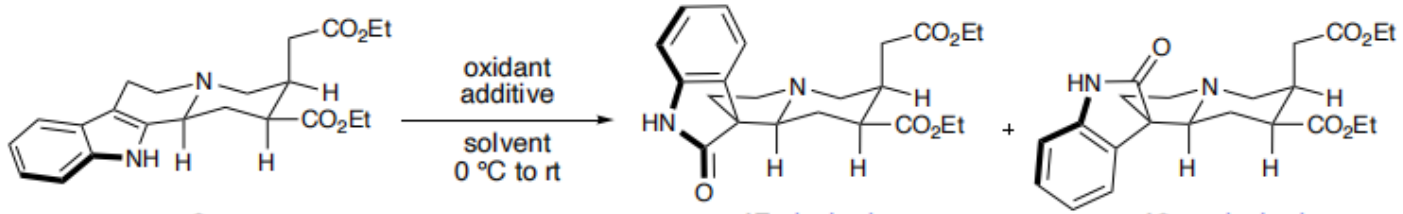
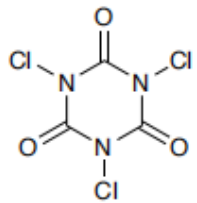


Table 3: Oxidative Rearrangement Reaction of **9**



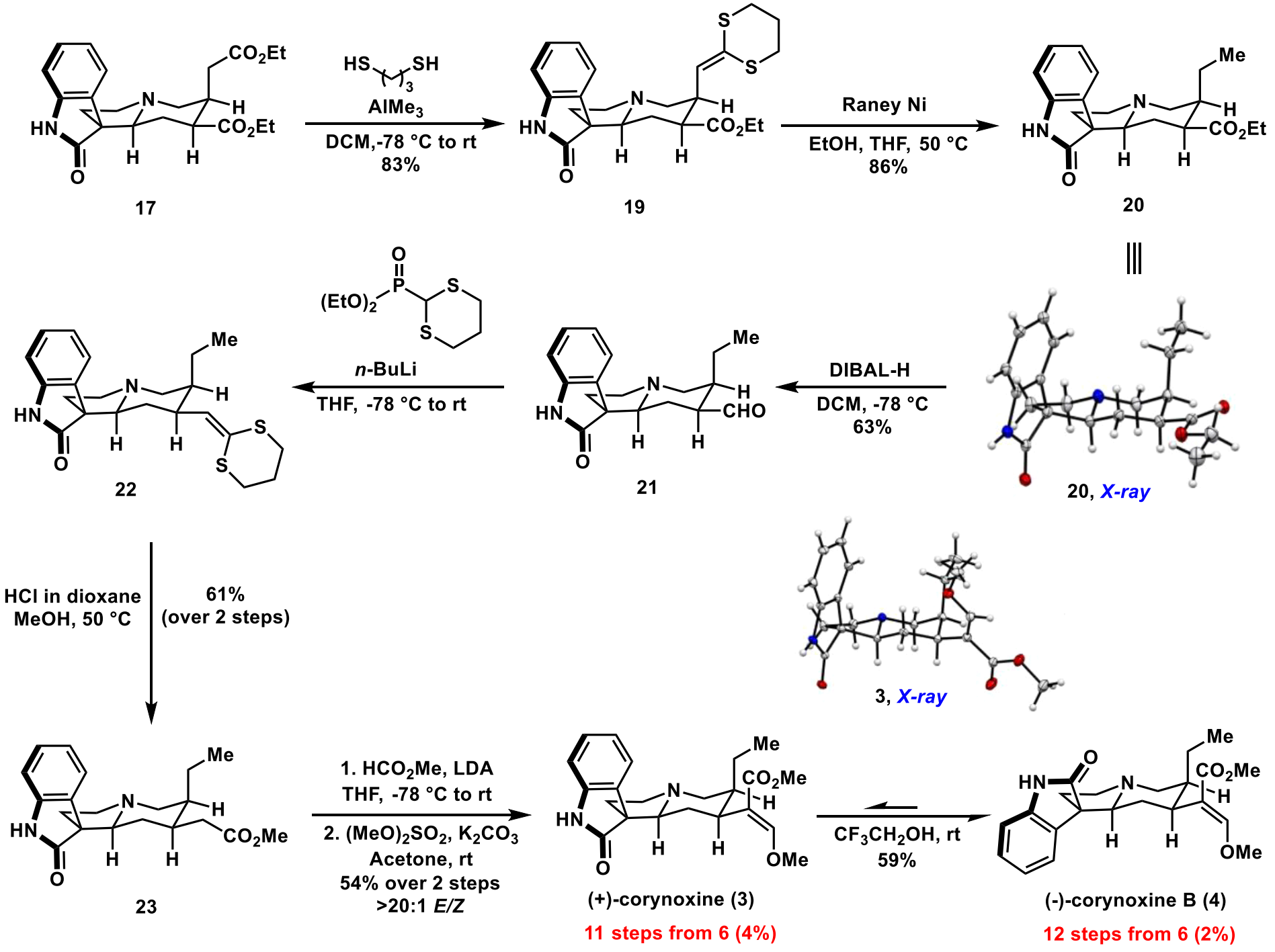
9 **17**: desired **18**: undesired

entry	solvent	oxidant	additive	combined isolated yield (**17**:**18**)
1	THF/H_2O	NBS	–	46% (31:69)[a]
2	THF/H_2O/AcOH	NBS	–	trace[c]
3	THF/H_2O/TFA	NBS	–	0%[c]
4	ACN/H_2O	NBS	–	66% (35:65)[d]
5	THF/H_2O	NBS	urea	53% (36:64)[b]
6	THF/H_2O	NBS	thiourea	0[b]
7	THF/H_2O	NIS	–	0[c]
8	THF/H_2O	NIS	phenyl phosphoric acid	0[c]
9	ACN/H_2O	Oxone	KBr	42% (49:51)[c]
10	THF/H_2O/AcOH	Oxone	KBr	0[b]
11	THF/H_2O	TCCA	–	63% (40:60)[d]



TCCA

[a]500 mg scale; [b]100 mg; [c]50 mg scale; [d]30 mg scale


17
HS SH
AlMe3
DCM,-78 °C to rt
83%
19
Raney Ni
EtOH, THF, 50 °C
86%
20
20, X-ray
DIBAL-H
DCM, -78 °C
63%
21
(EtO)2
n-BuLi
THF, -78 °C to rt
22
HCl in dioxane
MeOH, 50 °C
61%
(over 2 steps)
23
1. HCO2Me, LDA
THF, -78 °C to rt
2. (MeO)2SO2, K2CO3
Acetone, rt
54% over 2 steps
>20:1 E/Z
3, X-ray
CF3CH2OH, rt
59%
(+)-corynoxine (3)
11 steps from 6 (4%)
(-)-corynoxine B (4)
12 steps from 6 (2%)

Failed route for the synthesis of (+)-corynoxine (**3**) from **20**