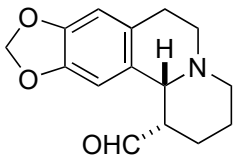
Problem Session (1)

2020.1.25 Shu Nakamura

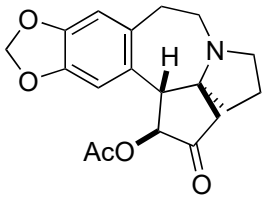
Please explain the reaction mechanism.

1



1-1 (racemic)

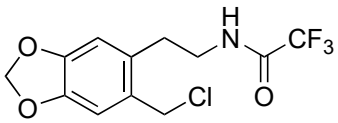
1. **1-2** (10 eq.), $KHCO_3$ (8 eq.), $CHCl_3$, 23 °C, 91%
2. **1-3** (1.9 eq.), toluene, 130 °C, 68%(brsm) (and geometrical isomer: 14%, brsm)*
3. DIBAL-H (1.5 eq.), toluene, -78 °C ; Rochelle salt aq., 55%(brsm)
4. Ac_2O (15 eq.), pyridine (20 eq.), CH_2Cl_2, 23 °C, 85%
5. Zn (4 eq.), 0.5 M NaH_2PO_4 aq./THF (3/2), 23 °C, 52%



1-4 (racemic)

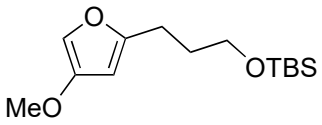
* Two isomers were isolated and only the major isomer (*E*) was used in the next step.

2.



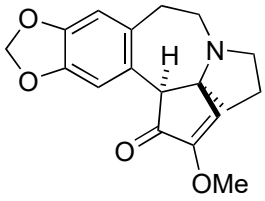
2-1

+

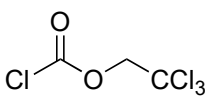


2-2 (1.2 eq.)

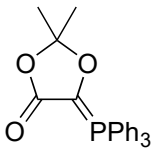
1. 2,6-lutidine (1.2 eq.), CF_3CH_2OH, 0 °C to rt, 68%
2. TBAF (3 eq.), THF, 0 °C to rt, 80%
3. Et_3N (2.5 eq.), MsCl (2 eq.) CH_2Cl_2, 0 °C to rt, 86%
4. LiOH (3 eq.), H_2O/THF, reflux, 85%
5. DDQ (1 eq.), CF_3CH_2OH, 50 °C, 60%



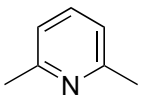
2-3 (racemic)



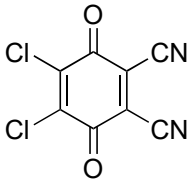
1-2



1-3



2,6-lutidine

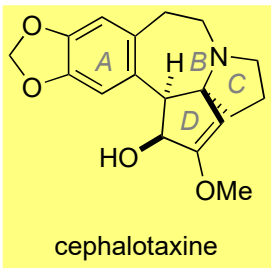


DDQ

Problem Session (1) -Answer- 2020.1.25 Shu Nakamura

Topic: Total synthesis of cephalotaxine

Introduction:



cephalotaxine

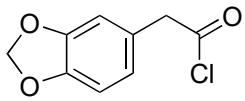
isolation
: from *Cephalotaxus drupacea* (1963)

first total synthesis
: Weinreb (1972)

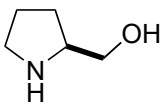
Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem*. **1963**, *28*, 2194.
Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc*. **1972**, *94*, 7172.

For more information, see:
Pérard-Viret, J.; Quteishat, L.; Alsalim, R.; Royer, J.; Dumas, F. In *The Alkaloids*; Knölker, H.-J.,Ed.; Academic Press: New York, 2017; Vol. *78*, pp. 205-352.
Abdelkafi, H.; Nay, B. *Nat. Prod. Rep.* **2012**, *29*, 845.

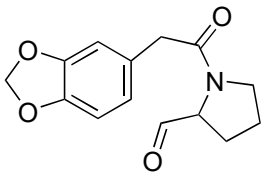
Weinreb's total synthesis of cephalotaxine: through *B*-ring closure



0-1

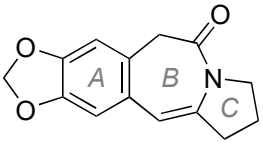


0-2



0-3

S_EAr
B-ring formation



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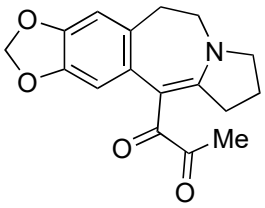
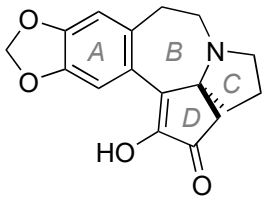


0-5

Michael addition



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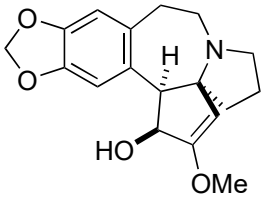

cephalotaxine

1

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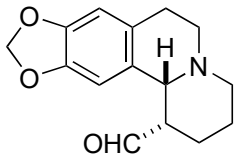
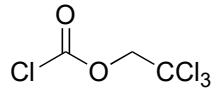
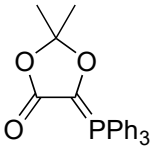


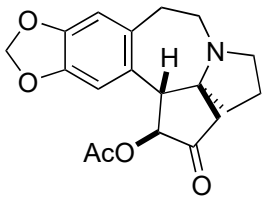
1-1 (racemic)



1-2



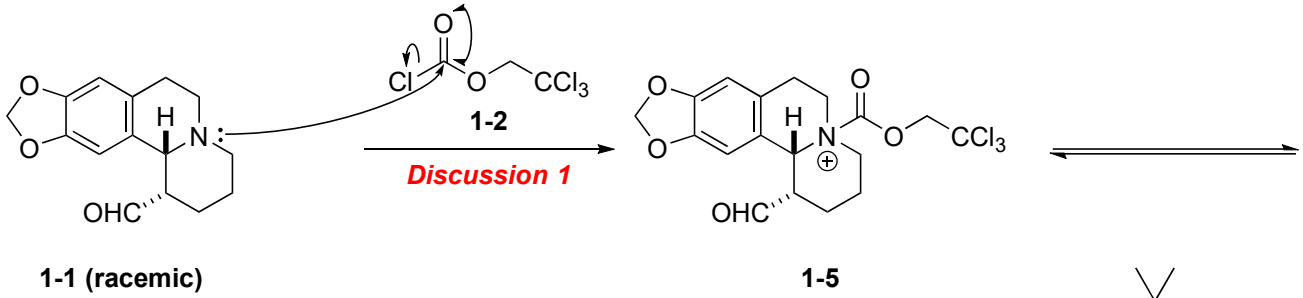
1-3



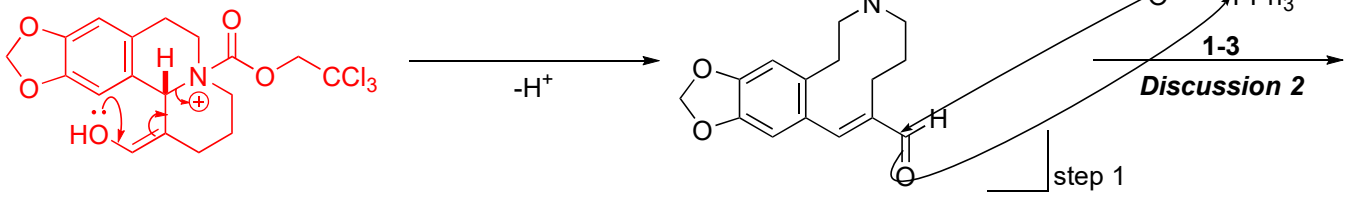
1-4 (racemic)

* Two isomers were isolated and only the major isomer (*E*) was used in the next step.

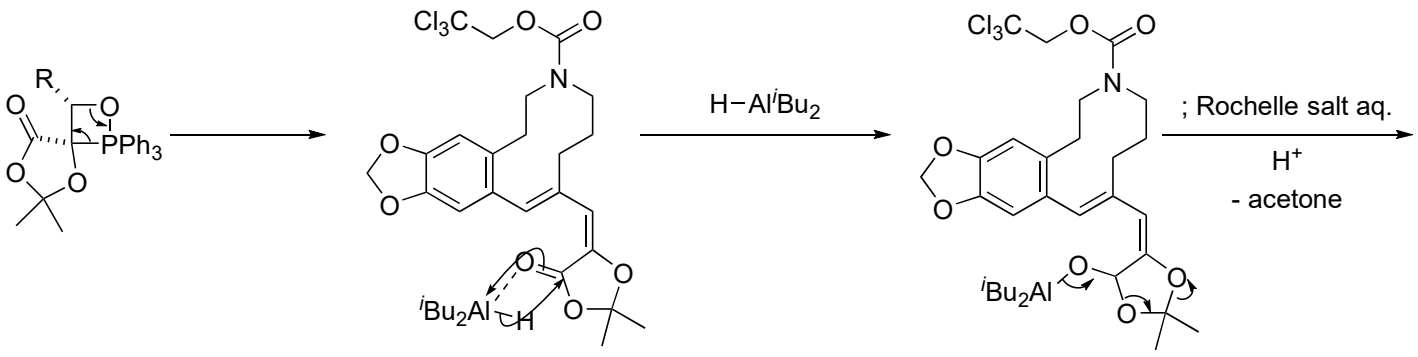
Li, W.-D. Z.; Duo, W.-G.; Zhuang, C.-H. *Org. Lett.* **2011**, *13*, 3538.



1-1 (racemic) **1-2** ***Discussion 1*** **1-5**

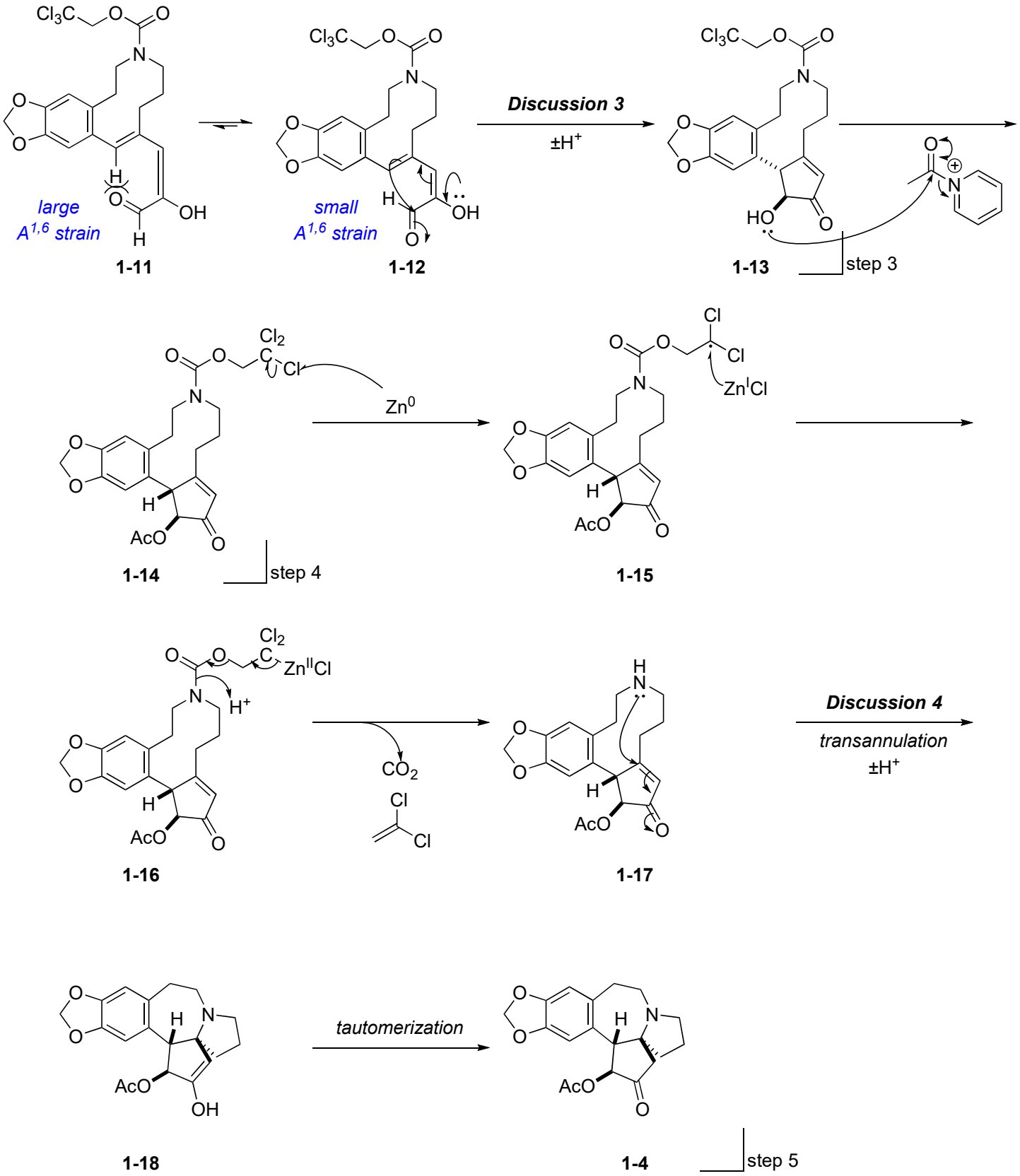


1-6 **1-3** ***Discussion 2*** **1-7**

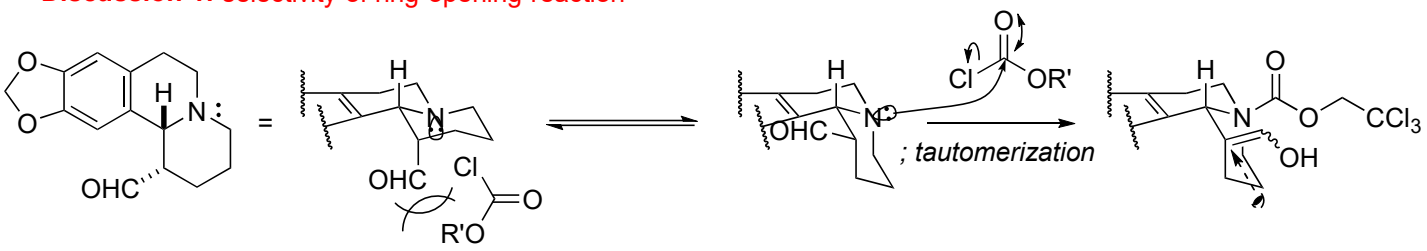


1-8 **1-9** (major) **1-10**

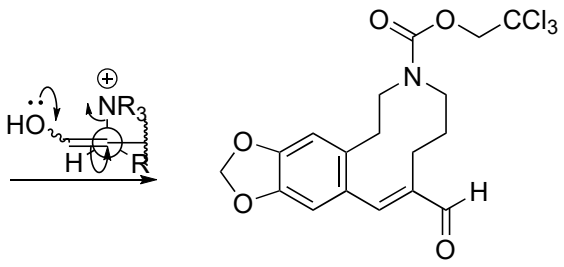
- 2 -


large
A1,6 strain
small
A1,6 strain
1-11
1-12
Discussion 3
±H+
1-13
step 3
Zn0
1-14
step 4
1-15
ZnIICl
H+
1-16
CO2
1-17
Discussion 4
transannulation
±H+
tautomerization
1-18
1-4
step 5

Discussion 1: selectivity of ring-opening reaction

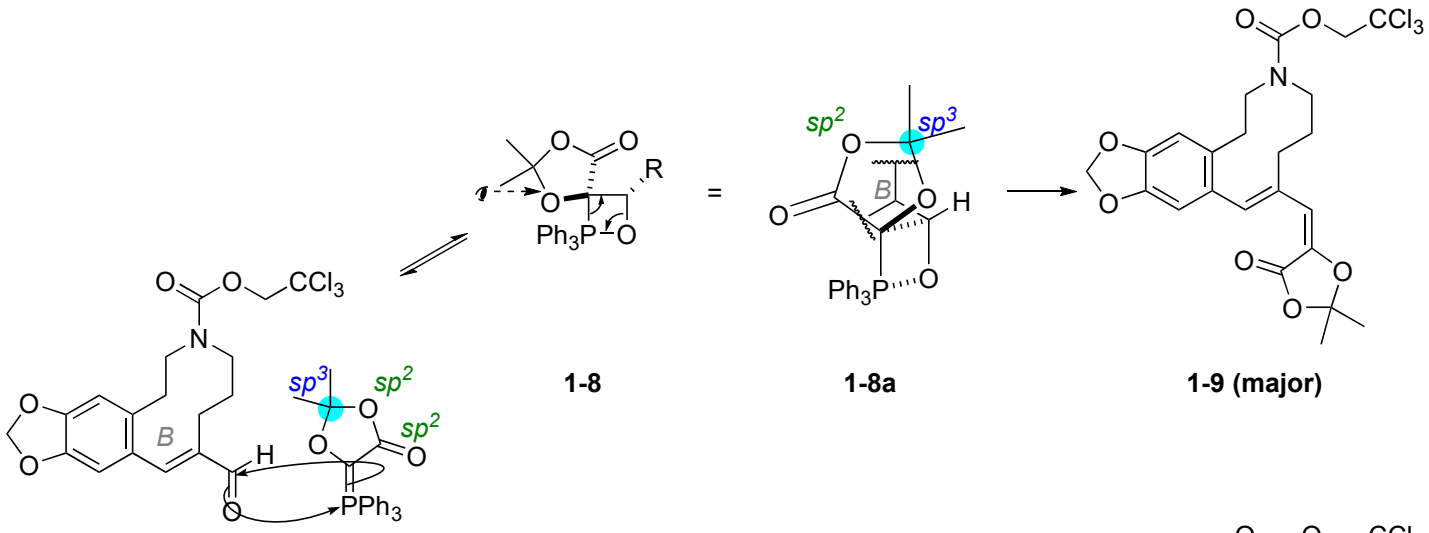


1-1 **1-1a** (R' = CH_2CCl_3) **1-1b** **1-6**



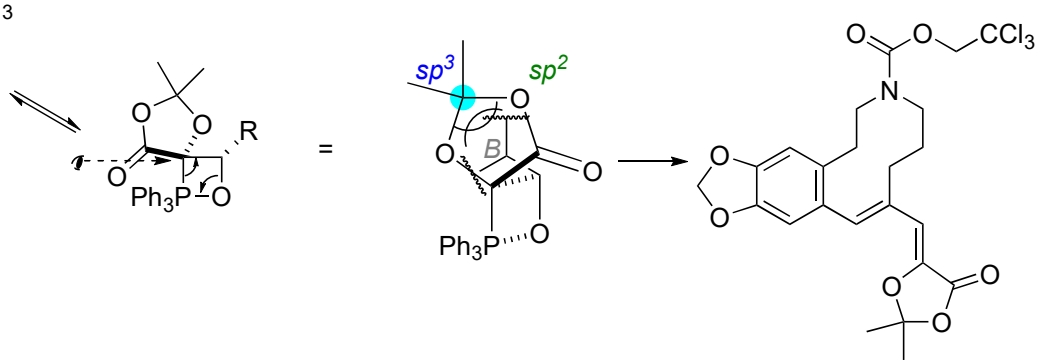
1-7

Discussion 2: selectivity of Wittig reaction



1-8 **1-8a** **1-9 (major)**

1-7 **1-3**

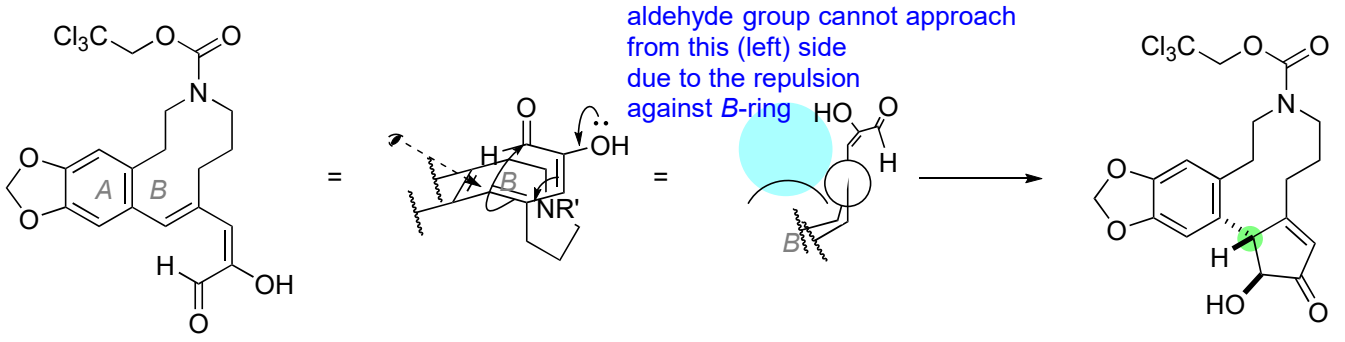


1-8' **1-8'a** **1-9' (minor)**

larger repulsion between
sp^3 carbon and *B*-ring

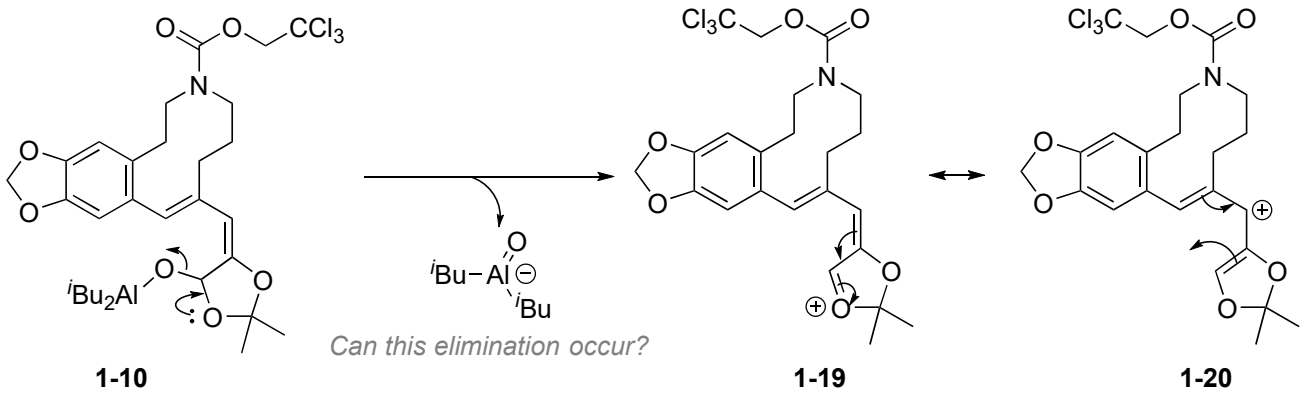
Discussion 3: synthesis of **1-13**

1. stereoselectivity



1-12 = **1-12a** (R' = $COOCH_2CCl_3$) = **1-12b** → **1-13**

2. another possible mechanism proposed by the author (via Nazarov cyclization)



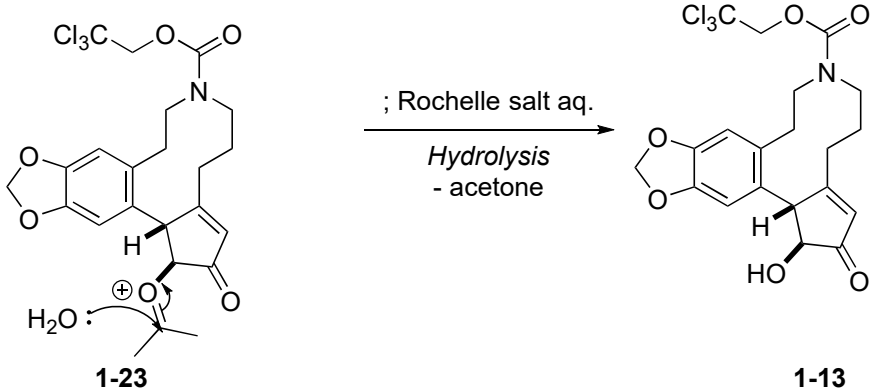
1-10 (before work-up)

4π *conrotatory*

Nazarov-type cyclization

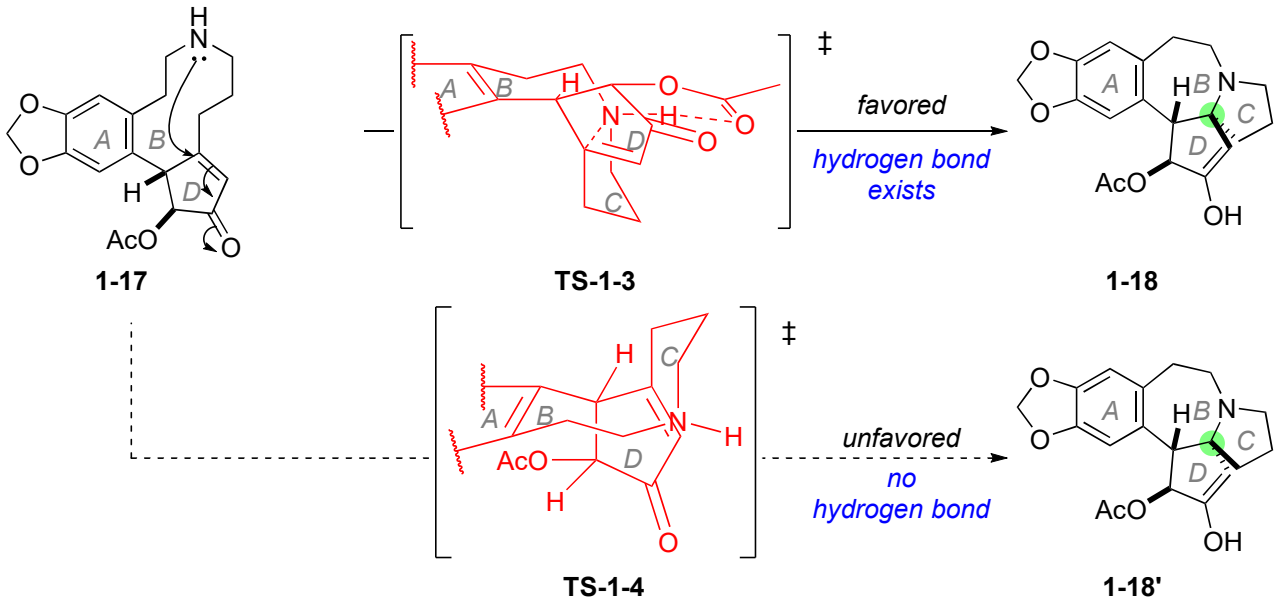
1-19 ↔ **1-20**

1-21 ↔ **1-22**



1-23 → **1-13**

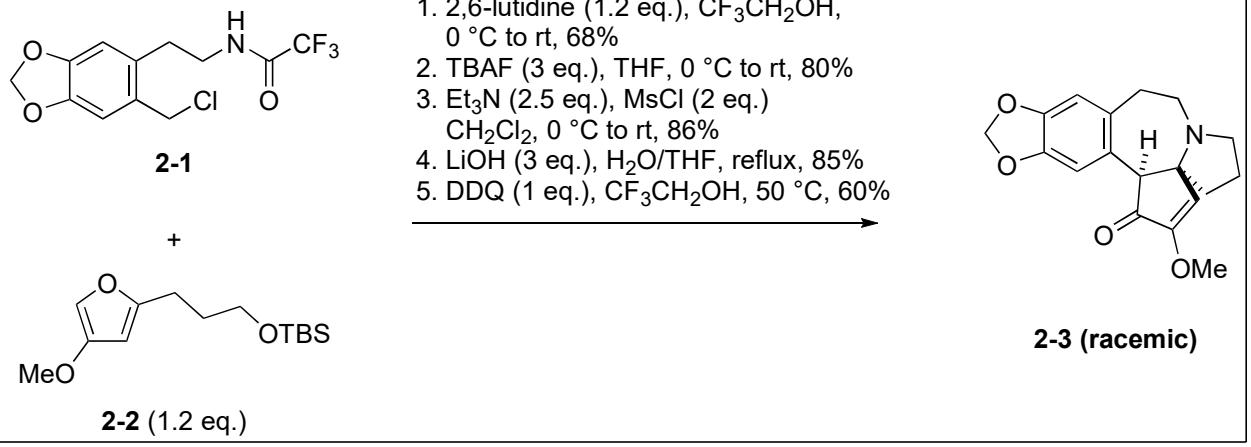
Discussion 4: stereoselectivity of transannulation



1-17 **TS-1-3** **1-18**

TS-1-4 **1-18'**

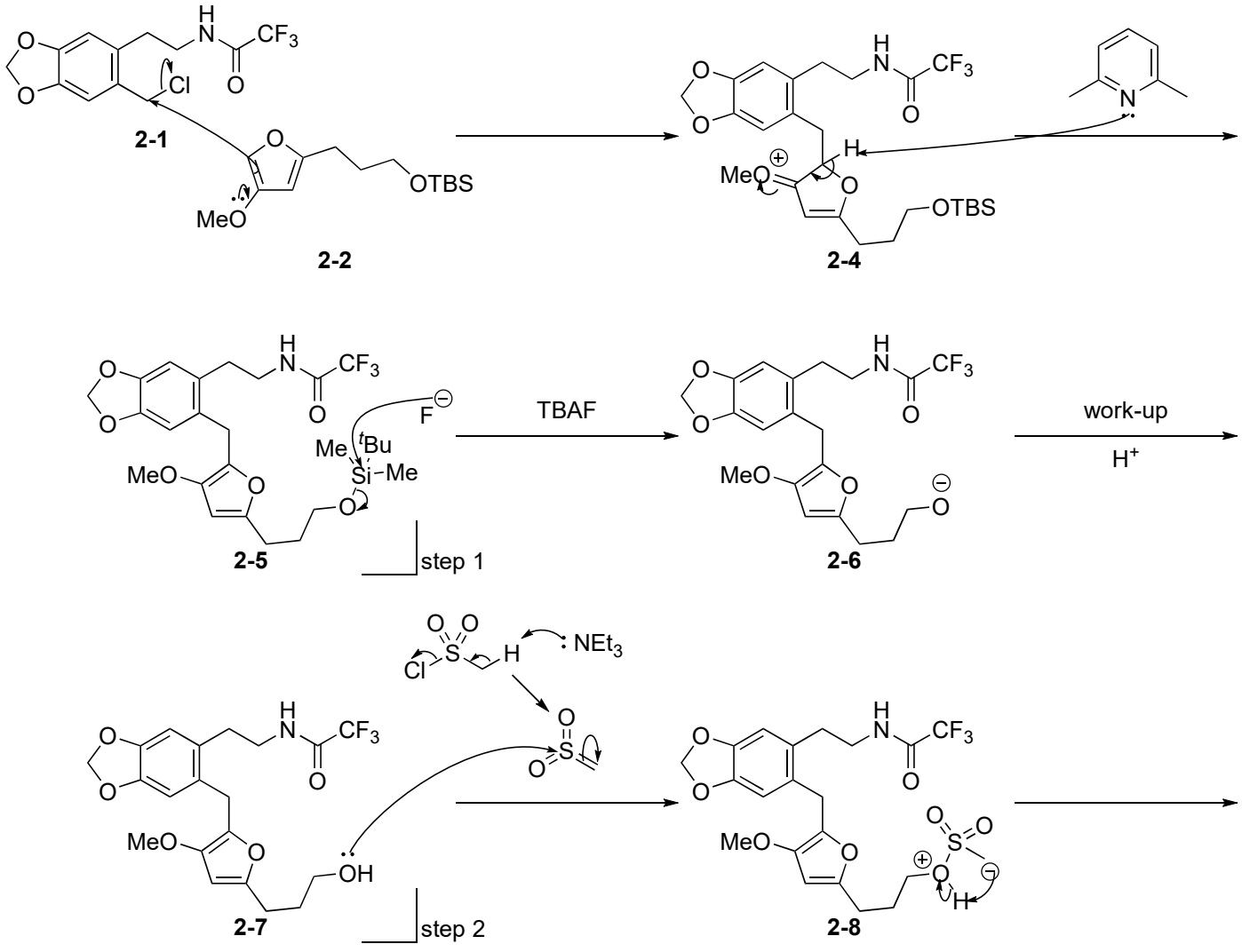
2.

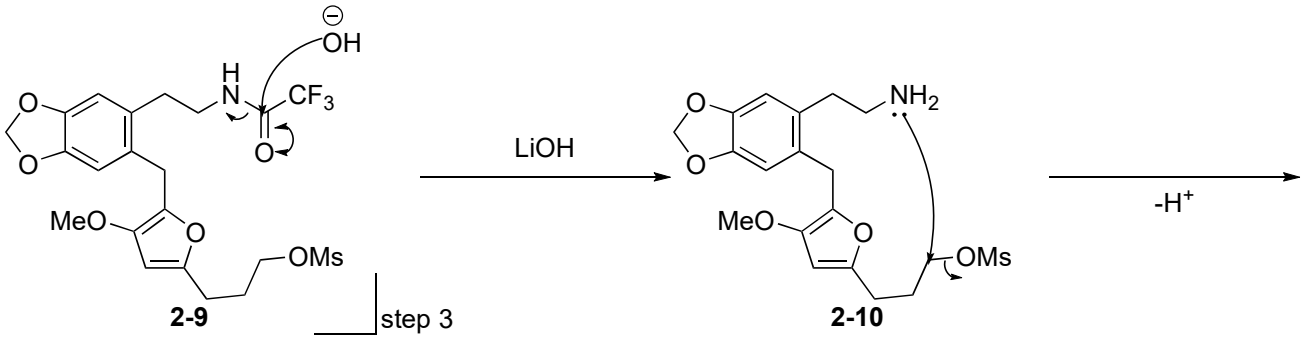


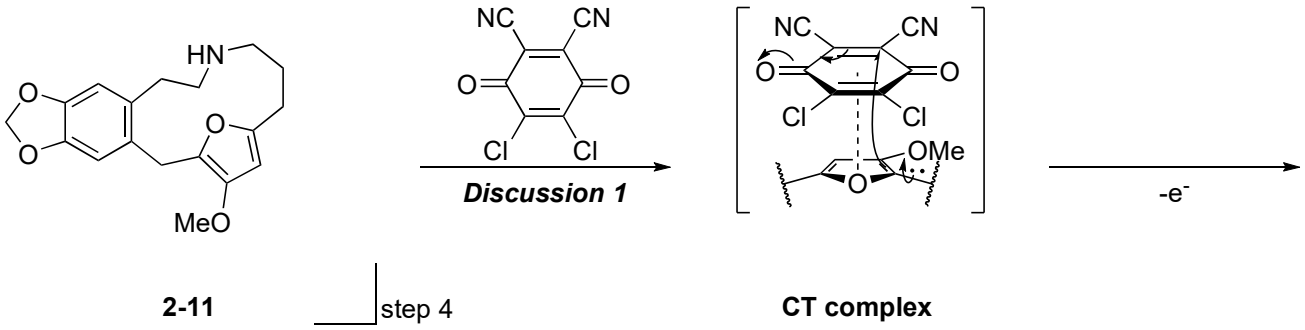
2-1 + **2-2** (1.2 eq.)

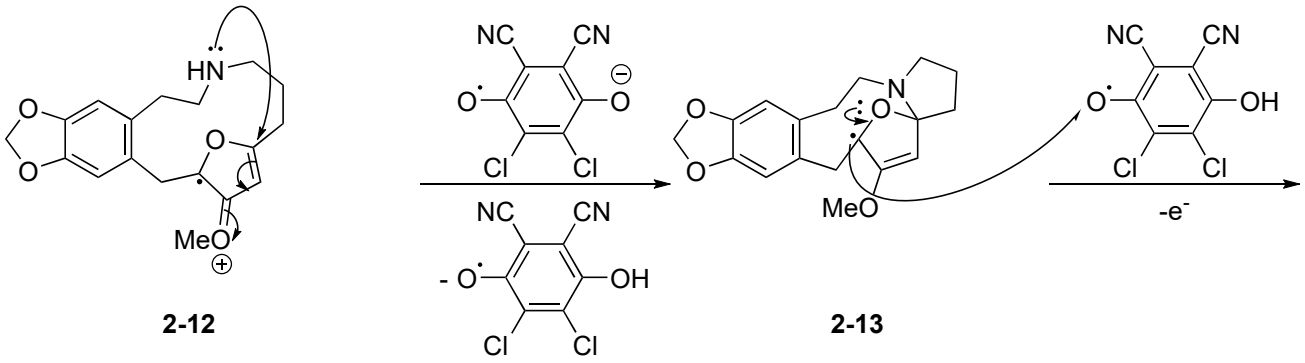
2-3 (racemic)

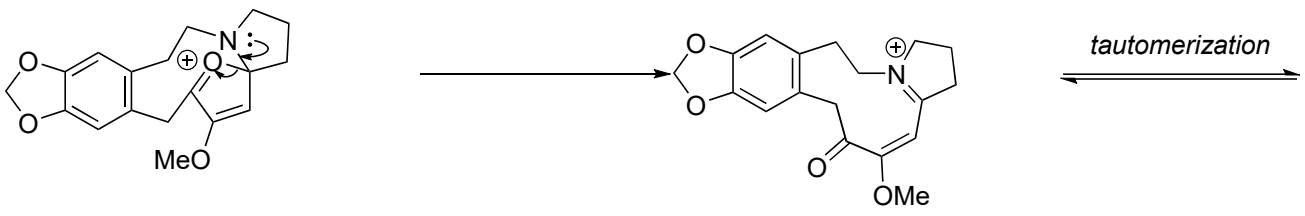
Ju, X.; Beaudry, C. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 6752.

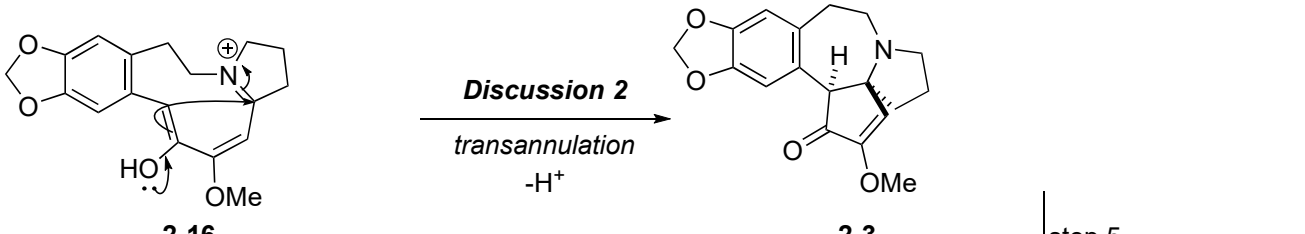



LiOH
-H+
2-9
step 3
2-10

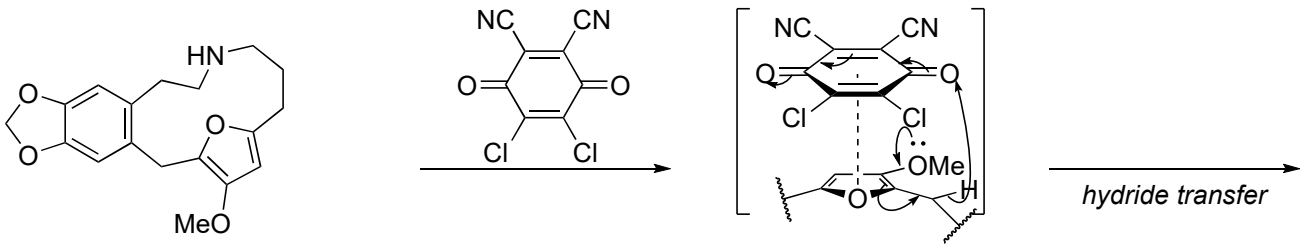

Discussion 1
-e-
2-11
step 4
CT complex


-e-
2-12
2-13

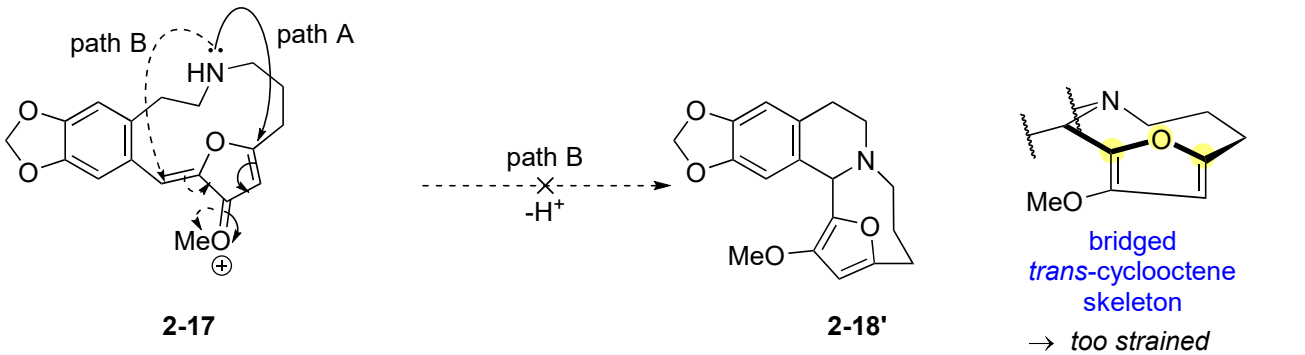

tautomerization
2-14
2-15


Discussion 2
transannulation
-H+
2-16
2-3
step 5

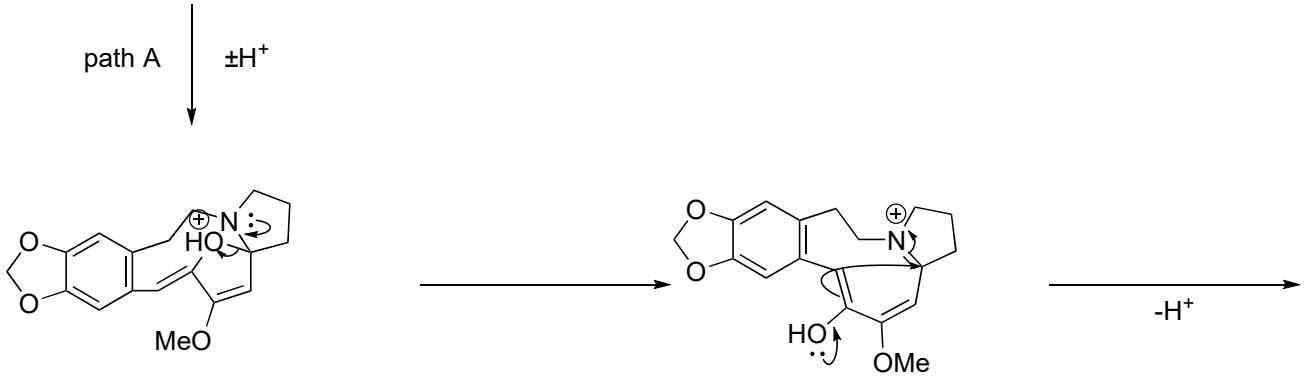
Discussion 1: another possible mechanism (via hydride transfer)



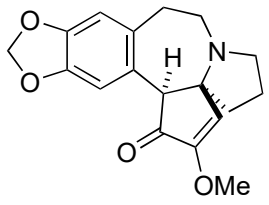
2-11 **CT complex**



2-17 **2-18'**



2-18 **2-16**



2-3

Discussion 2: streoselectivity of transannulation