Deconstructive Asymmetric Total Synthesis of Morphine-Family Alkaloid (−)-Thebainone A

Hou, S.-H.; Prichina, A. Y.; Dong, G.

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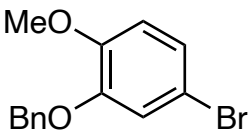
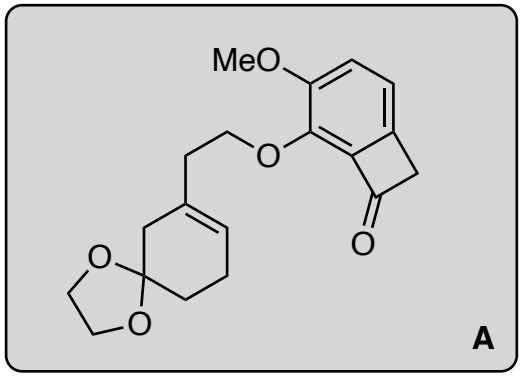


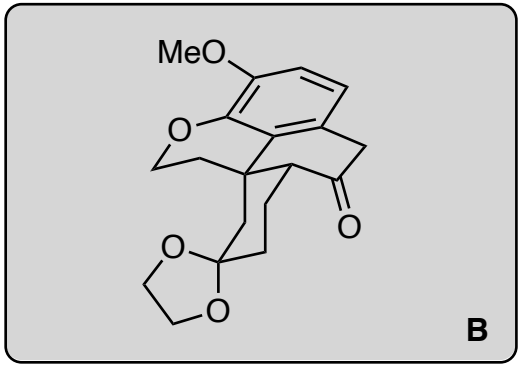
1

1–4



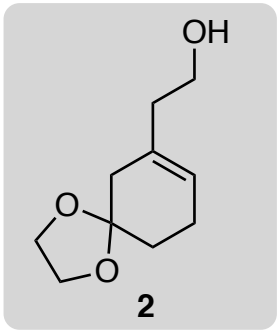
A

5



B

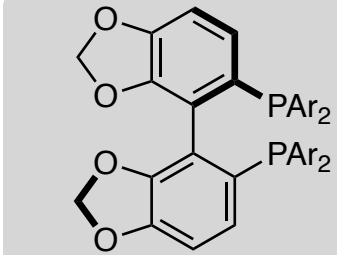
1) THF, *n*-BuLi, r.t., 16 h, *then* **1**, *then* LiTMP
2) PCC
3) $Pd(OH_2)/C$, H_2
4) **2**, DEAD, PPh_3



2

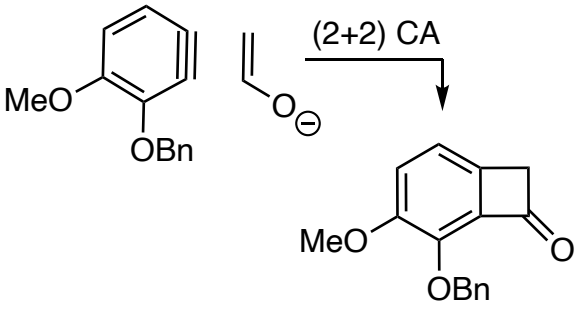
5) $[Rh(COD)_2]NTf_2$ (4 mol%), **L3** (4.8 mol%)
o-difluorobenzene, 130 °C, 48 h

"cut-and-sew"-reaction

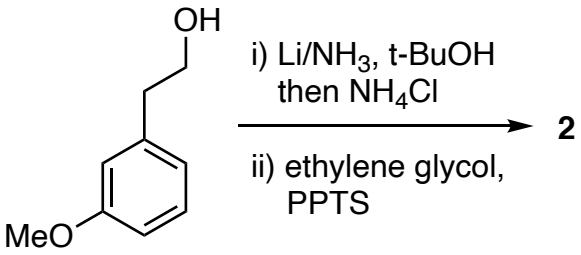


(*R*)-DTBM-segphos (**L3**)

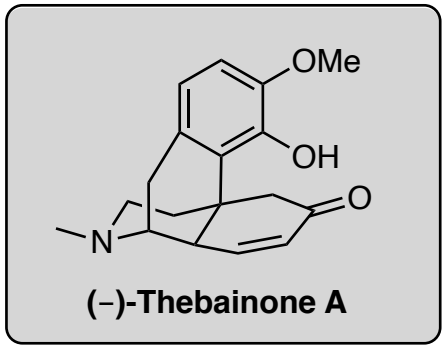
Please provide a mechanism for step 1.



Suggest a preparation for compound **2**.



Provide a mechanism for step 5.
HINT: The product of this key step contains four 6-membered rings.

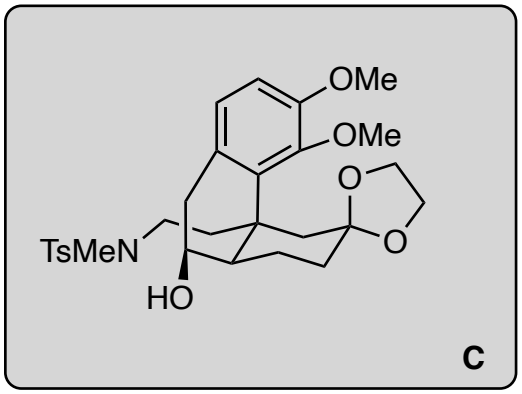


(−)-Thebainone A

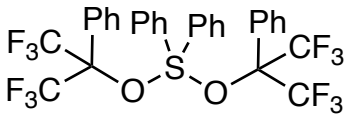
6–10

6) $LiAlH_4$
7) Ac_2O, *then* 2 M HCl
8) BBr_3
9) CH_2N_2, MeOH
10) $TMSOCH_2CH_2OTMS$, TMSOTf
then py, TsNHMe, Cs_2CO_3, *then* MeOH

What is the pKa of TsNHMe?
10



C



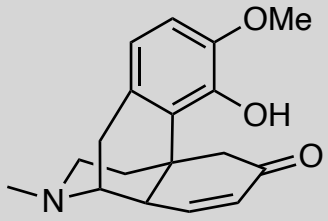
Martin's sulfurane - anti-elimination alternatives
- Burgess - via E_i - syn elimination
- MsCl, NEt_3 - E_2

11–14

11) Martin's sulfurane
12) sodium naphthalenide, *then* HCl
13) NaSEt
14) TFA, MeCN,
then $Pd(TFA)_2$, DMSO, 80 °C

Draw the structure of Martin's sulfurane? Name 2 alternatives.

14) developed by Tianning Diao and Shannon Stahl

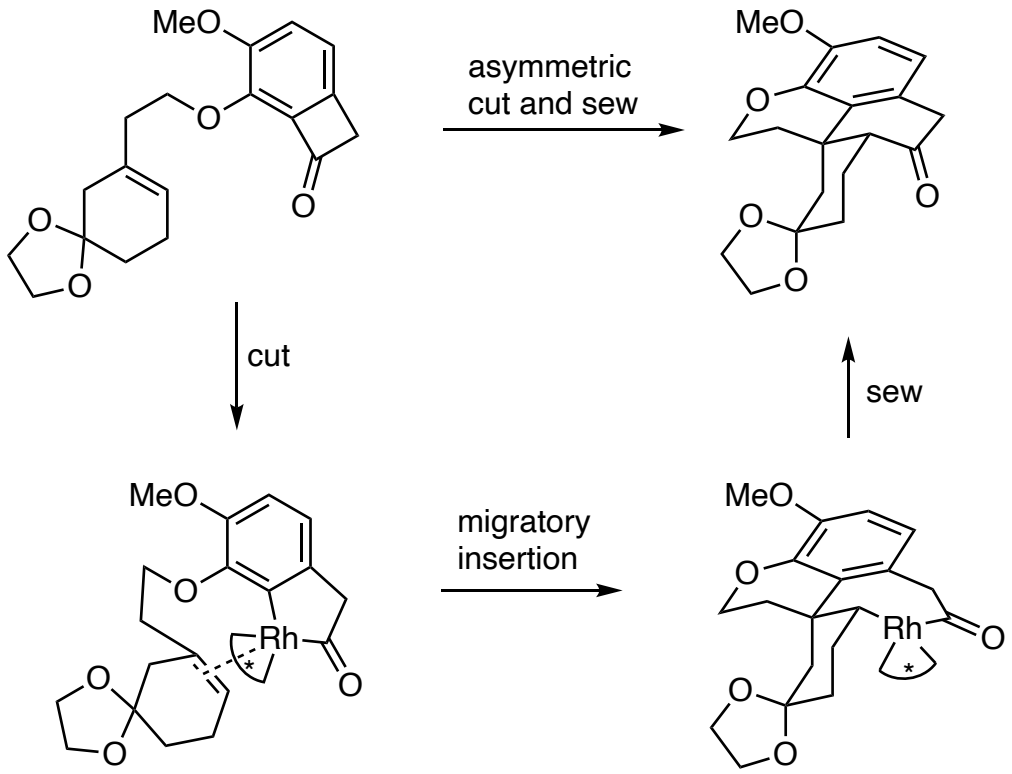


(–)-Thebainone A

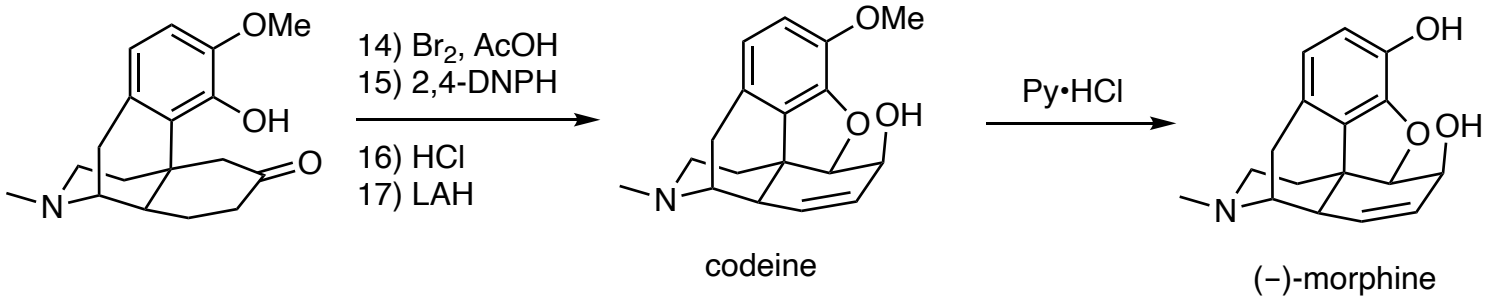
"selectivity (step 13) is likely due to more available s* orbital of the middle ether moiety, as its "flat" conformation is more disfavored due to sterics"

Suggest a synthetic transformation toward codeine or morphine from an appropriate intermediate.

Mechanism of step 5



Transformation to morphine



M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1952**, *74*, 1109–1110;
M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393.