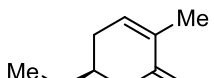
Total Synthesis of (–)-Ambiguine P Using Sequential Indole Fuctionalizations

Johnson, R. E.; Ree, H.; Hartmann, M.; Lang, L.; Sawano, S; Sarpong, R *J. Am. Chem. Soc.* **2019,** *141*, 2233–2237.

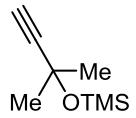


A

1-3

1) LiHMDS, indole, Cu(II) 2-ethyl hexanoate
2) LiHMDS + **1**, THF, -78 °C
3) PDC, DCM, rt; *then* 1N HCl, THF, 0 °C

1 =

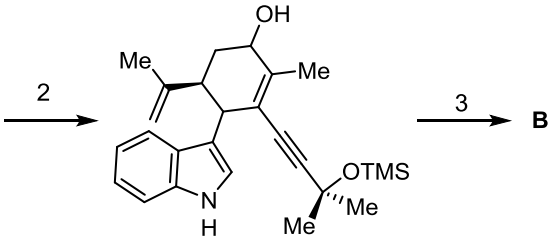


Name of **A***?* (*S*)-Carvone

Step 1: Cu(II) oxidative coupling, see Baran, P.; Richter, J. M. *J. Am. Chem. Soc.*, **2004**, *126*, 7450–7451

Name the reaction in step 2

Step 2: 1,2-addition of alkyne, then Babler-Dauben oxidative transposition



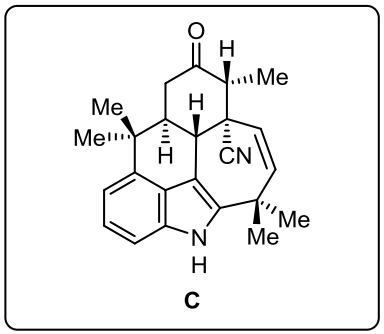
B

4-7

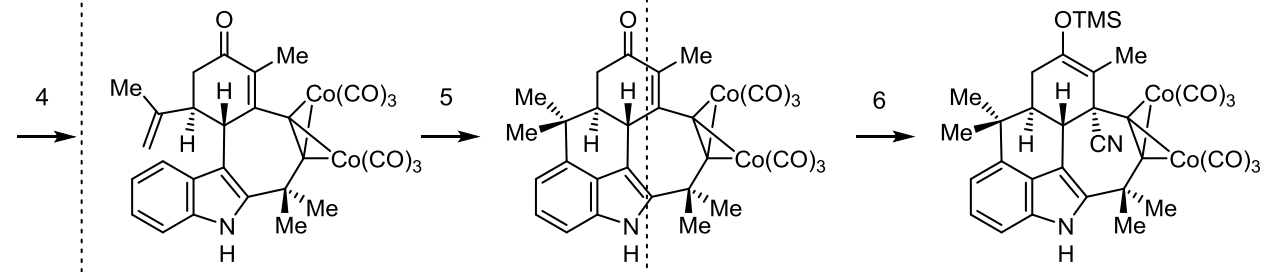
4) $Co_2(CO)_8$; *then* $BF_3{\cdot}OEt_2$, DCM
5) $AlCl_3$, MeOH, DCM, 0 °C to rt
6) Nagata's reagent, TMSCl, pyridine, MeCN
7) Bu_3SnH, PhH, 45 °C; *then* 2N HCl, MeOH

Name the reaction in step 4 and in step 5

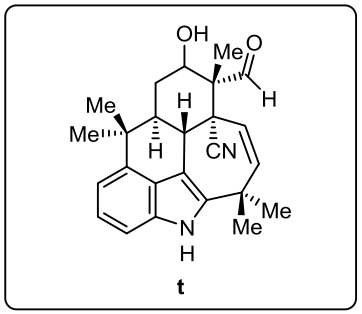
Step 4: Nicolas Reaction
Step 5: Friedel-Crafts reaction
Step 7: a) reduction of dicobalt group, then TMS enol ether hydrolysis



C

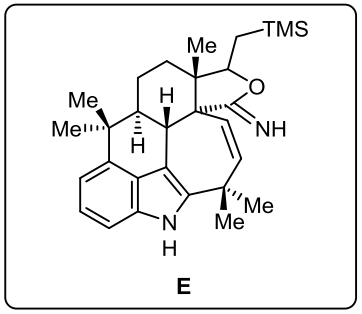


8-11



t

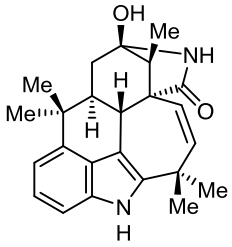
12-15



E

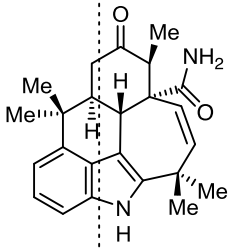
8) Wilkinson's catalyst, acetaldoxime, 30 °C, PhMe
9) NaHMDS, methyl formate, THF
10) $NaBH_4$, MeOH
11) Tf_2O, 2,6-di-tert-butylpyridine, DCM, -78 °C

8 →



2.3

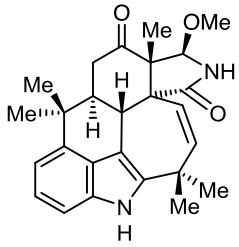
+



1

:

9 → use mixture from step 8

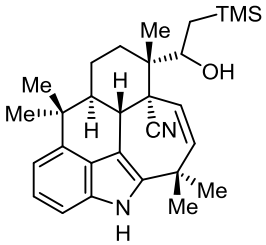


See S.I. for mechanistic proposal (S10)

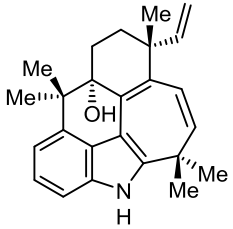
Step 8: Hydrolysis of nitrile

12) TCDI, DMAP, DCM, 45 °C
13) Bu_3SnH, AIBN, PhMe, 80 °C
14) $TMSCH_2Li$, THF
15) PPTS, DCE, 120 °C, μwave

14 →

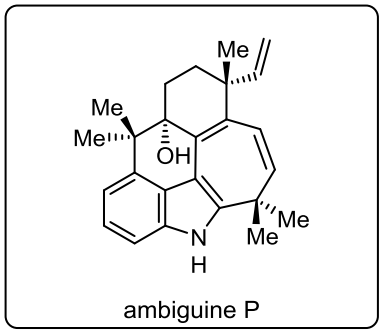


steps 14-16: Peterson-Type olefination + nitrile hydration



ambiguine P

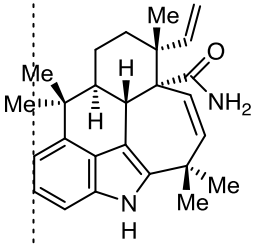
16-21



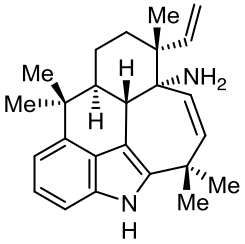
ambiguine P

16) TBAF, THF, 100 °C, μwave
17) PIDA, KOH, H_2O, dioxane
18) Ac_2O, HCO_2H, DCM
19) $COCl_2$, NEt_3, DCM, 0 °C\
20) KO*t*Bu, DMSO, μwave, 150 °C
21) SeO_2, dioxane

16



17



Step 17: Hofmann rearrangementt
Step 18: formylation and dehydration (step 19) yields isonitrile
Step 20: elimiation of isoitrile
Step 21: d.r. 1.5:1 in favor of ambiguine