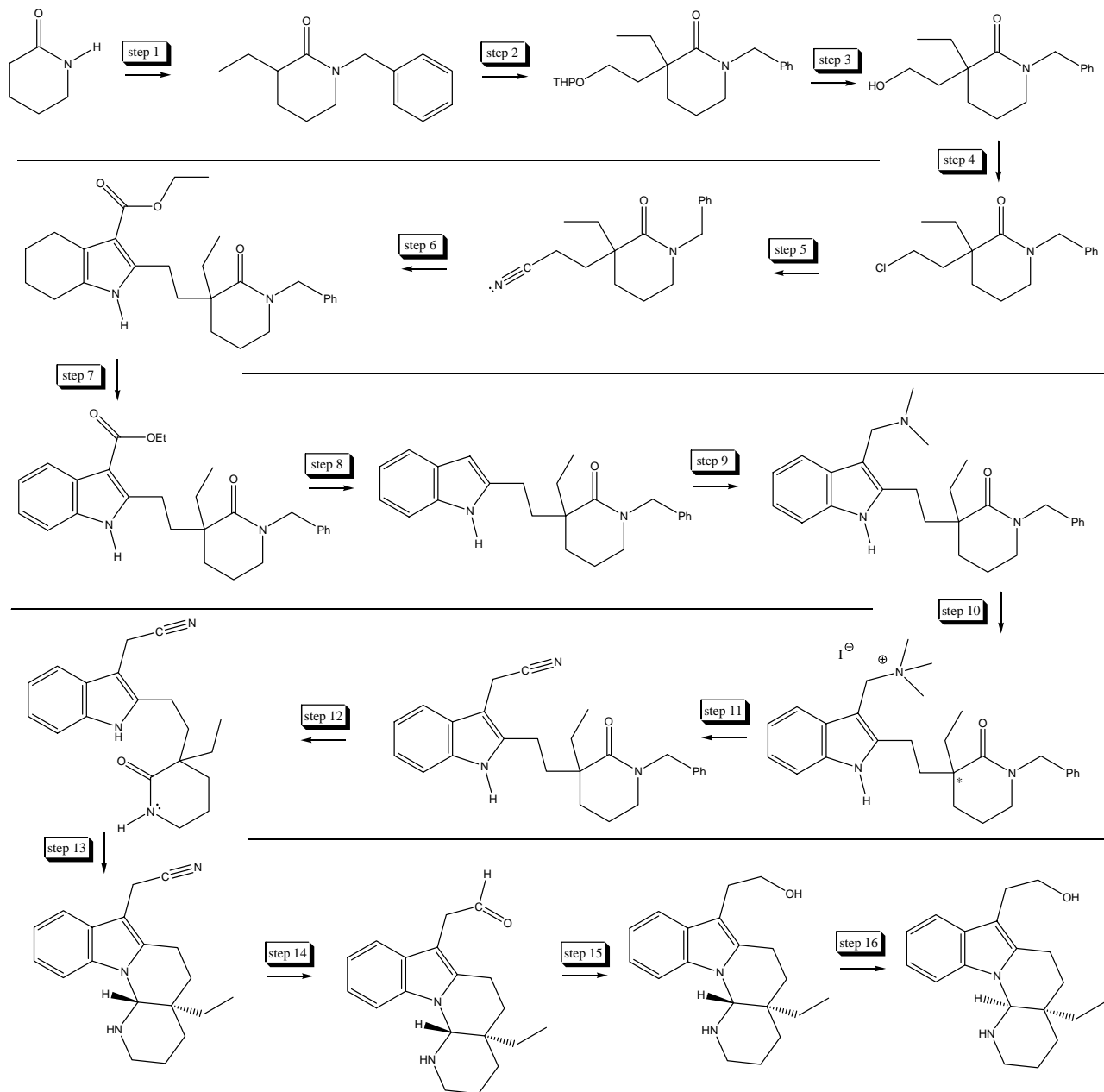


Match the step number in the synthesis with the letter of the reagents listed just below.



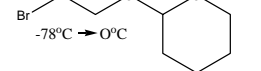
Reagents used in synthesis

A

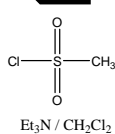
NaCN
DMF (solvent)

B

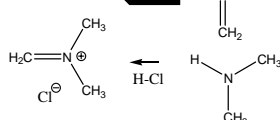
1. (i-Pr)₂NLi (LDA)/THF
2.



C



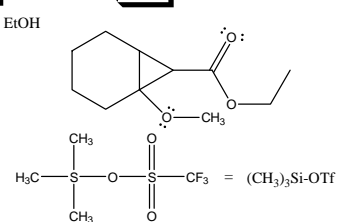
D



E

1. NaBH₄, EtOH
2. workup

F



(±)-goniomitine

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G

1. POCl₃ / toluene
2. NaBH₄

H

Pd / C

I

NaOH / H₂O /

J

catalytic TsO-H
CH₃OH / Et₃N

K

NaCN / CH₃CN
microwave

L

1. DIBALH, CH₂Cl₂
2. H₂SO₄ / H₂O

M

Na / NH₃ / THF

N

1. 2 eqs. n-BuLi/THF
2. CH₃CH₂-Br
3. C₆H₅CH₂Br

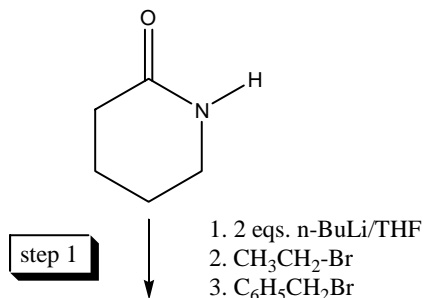
O

catalytic TsO-H
CH₃OH

P

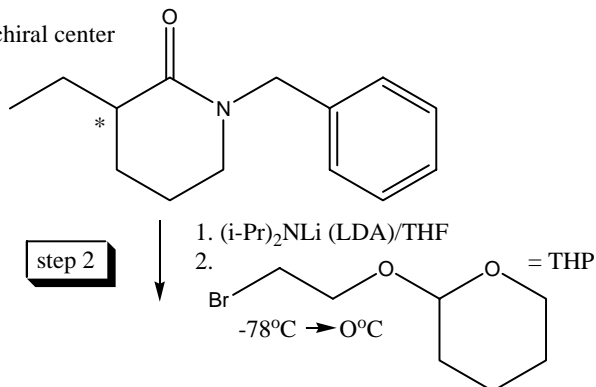
CH₃I / CH₃OH

Synthesis of (±)-goniomitine (with comments)

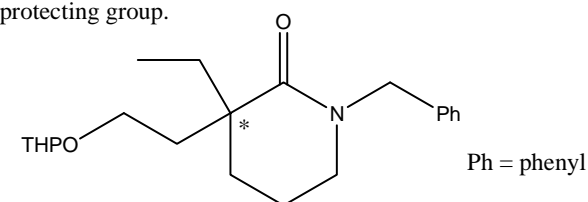


A dianion alkylates at the more reactive site, followed by alkylation at the less reactive site.

* = chiral center

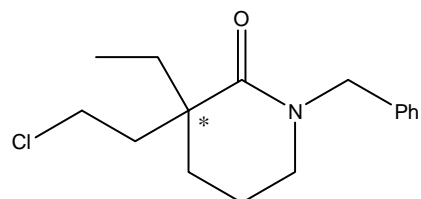
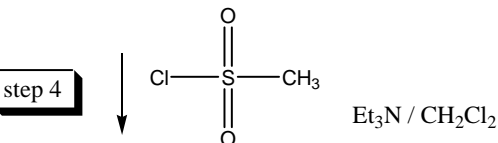
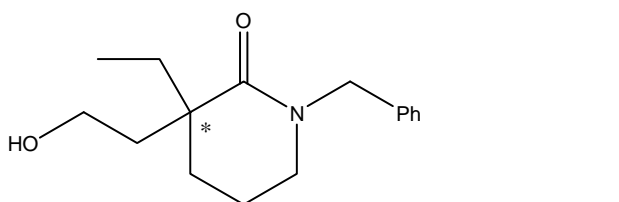


LDA removes an H to make an enolate, which is alkylated (the 3rd time in a row). THP is tetrahydropyran, an alcohol protecting group.

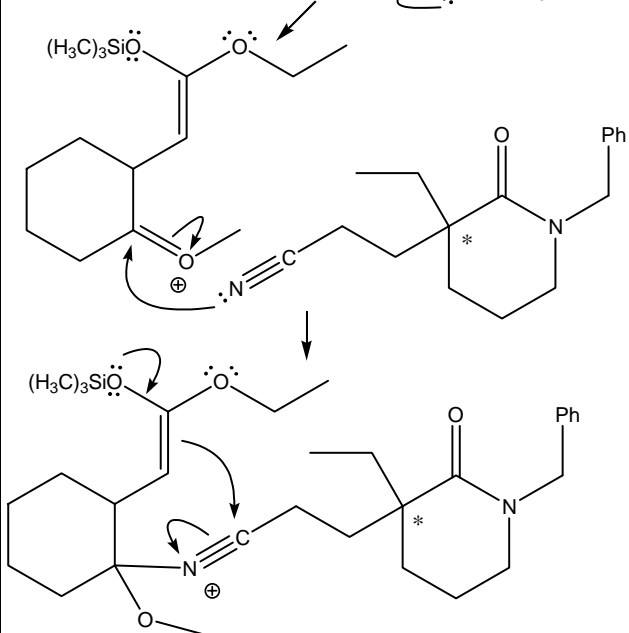
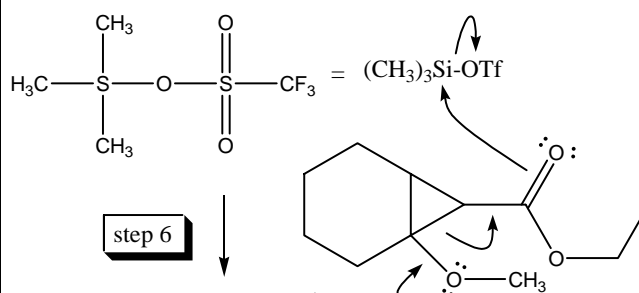


step 4

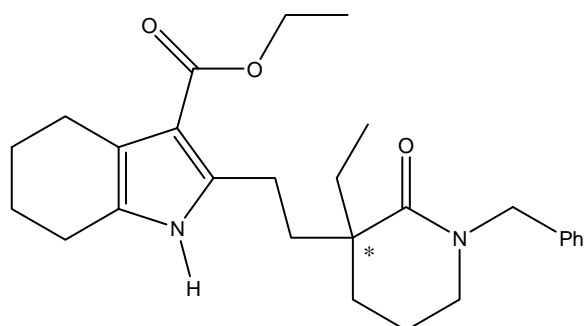
Cl-SO₂-CH₃
Et₃N / CH₂Cl₂



Cyanide is a good nucleophile and acetonitrile is a good S_N2 solvent (polar, aprotic). S_N2 reaction displaces the good chloride leaving group. The microwaves make the reaction work more efficiently by providing localized heating.



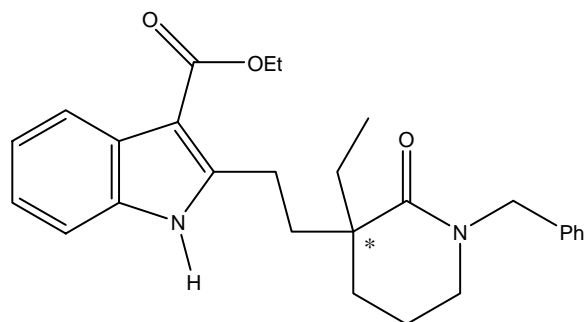
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step 7

Pd / C

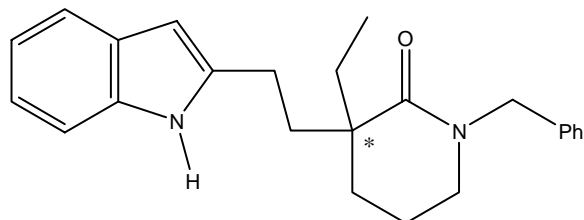
Reverse of hydrogenation (there's no $H_2(g)$). Pd is oxidizing instead of reducing. The driving force is aromatization.



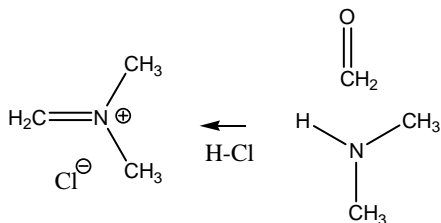
step 8

NaOH / H_2O / CH_3CH_2OH

Hydrolysis of ester to carboxylate, followed by decarboxylation ($-CO_2$). The leaving group is the sp^2 carbon of the indole ring, which immediately protonates.

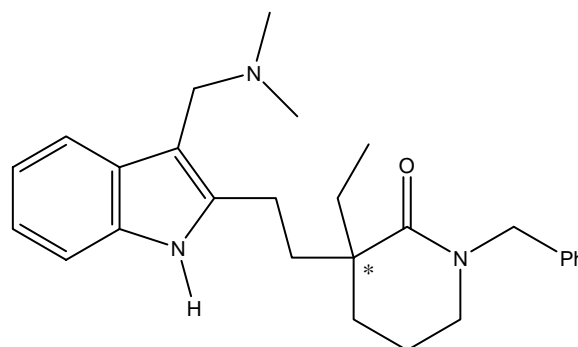


step 9



Enamine-like reaction with carbonyl-like protonated iminium made from an aldehyde, secondary amine and some HCl. The reaction makes a 3° amine (called the "Mannich" reaction).

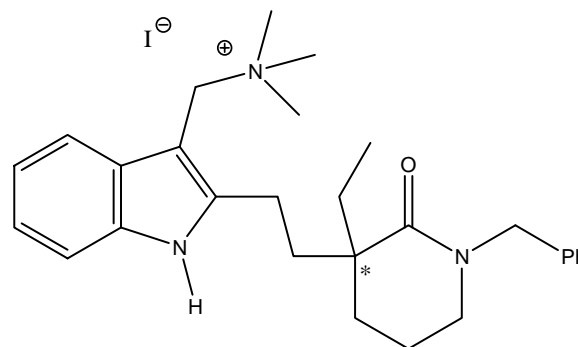
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step 10

 CH_3I / CH_3OH

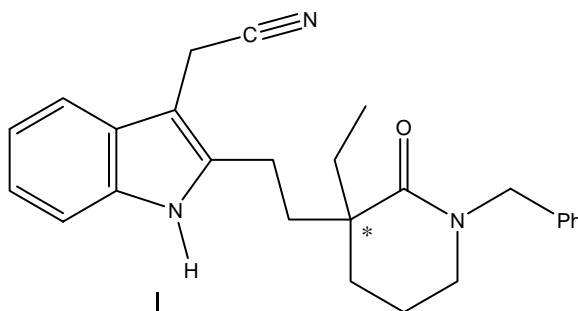
S_N2 methylation reaction by 3° amine on iodomethane, makes ammonium ion which becomes a good leaving group.



step 11

NaCN / DMF (solvent)

Cyanide does an S_N2 reaction with trimethylamine leaving group. DMF (dimethylformamide) is a good S_N2 solvent (polar, aprotic).

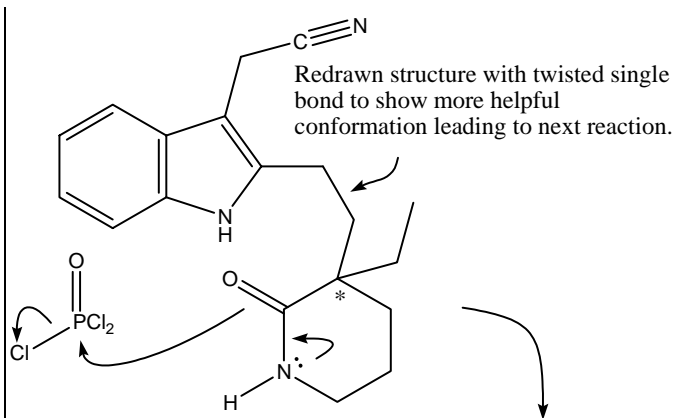


step 12

Na / NH_3 / THF

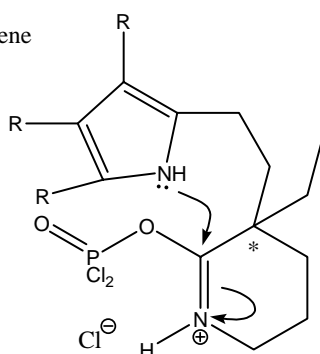
Radical anion forms in phenyl part of benzyl 3° amide protecting group is reduced to the 2° amide group. Think "LAH-like S_N2 reaction" at benzyl carbon, except LAH would react with the amide and nitrile.

Continue at top of next page.

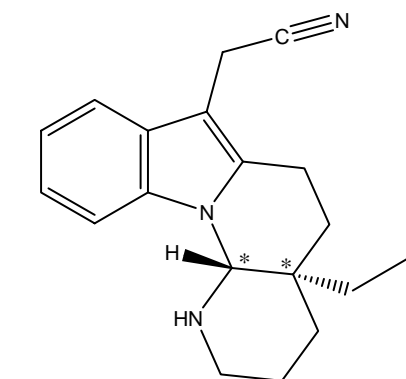


step 13

1. POCl₃ / toluene
2. NaBH₄



POCl₃ (think "acid-Cl") reacts with the amide C=O making an "imine-like" group that is attacked by the indole nitrogen atom in a carbonyl-like addition reaction. PO₂Cl₂ becomes a leaving group, leading to a C=N bond. NaBH₄ reduces a C=N group to an acetal-like group, having two nitrogen atoms.

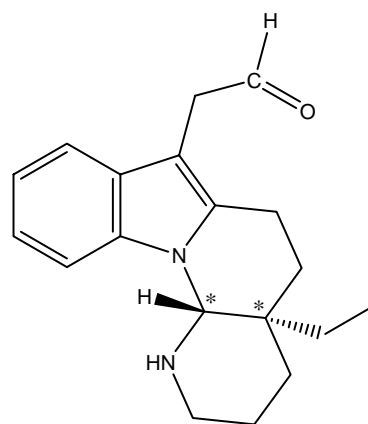


step 14

1. DIBALH, CH₂Cl₂
2. H₂SO₄ / H₂O

Diisobutylaluminum hydride reduces nitrile to aldehyde, after aqueous workup. If they used LiAlH₄ here, a 1° amine would have been the product.

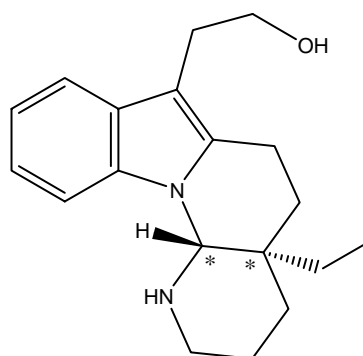
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step 15

1. NaBH₄, EtOH
2. workup

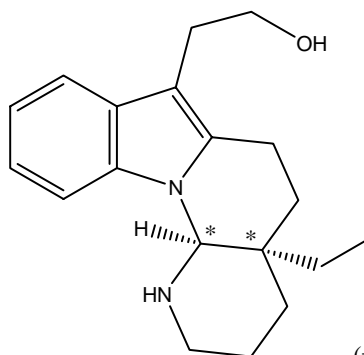
Sodium borohydride reduction of an aldehyde to a primary alcohol.



step 16

catalytic TsO-H / CH₃OH / Et₃N

Epimerization of "nitrogen" acetal. Protonation of nitrogen, ring makes a good leaving group. That ring opens and nitrogen comes back on the other side of the ring. Hydrogen atom is epimerized (switched to opposite configuration).



(±)-goniomitine

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