Divergent Total Syntheses of Rearranged Steroids Swinhoeisterols A-C

Huang, G.; Zhang, X.; Gu, Y.; Gui, J.

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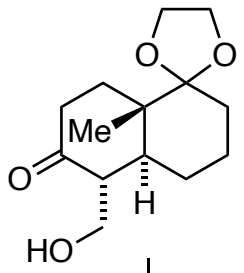

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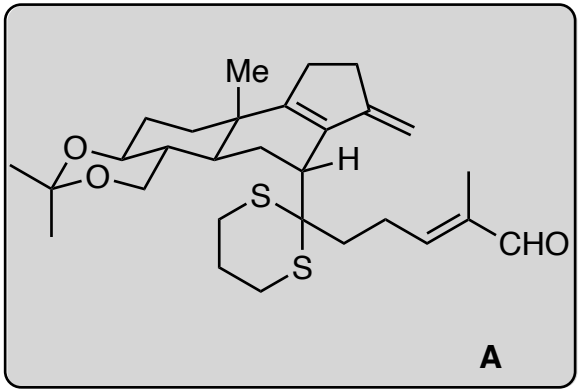
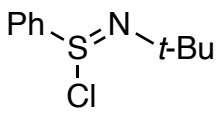


A

1) Li, *t*-BuOH, NH_3 (l)
2) *p*-TsOH, acetone
3) LiHMDS *then* **1**
4) Et_4NCl_3, NEt_3
5) **2**, *n*-BuLi, HMPA *then* substrate
6) KH, Comins' reagent
7) **3**, cat. $Pd(OAc)_2$, cat. PhCPhos, NMI, THF/DMA, 80 ˚C
8) TBAF•$3H_2O$, HMPA, 80 ˚C
9) TPAP, NMO, 4 Å MS



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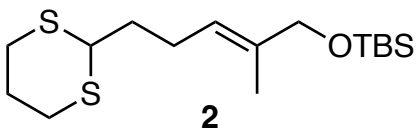

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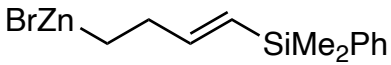
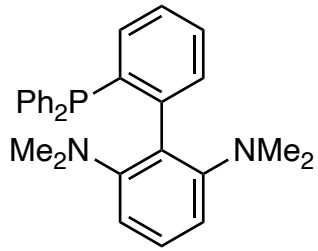
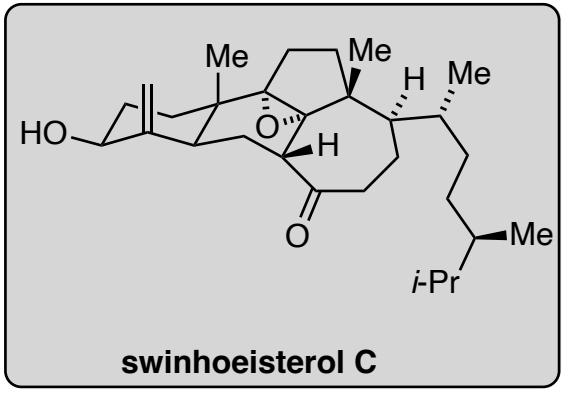


3

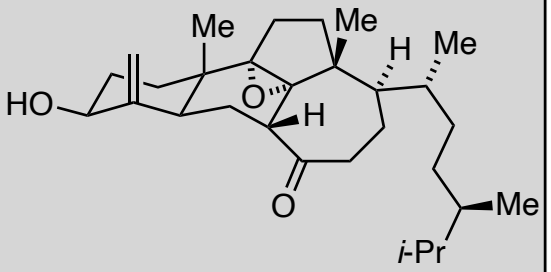
1) From what famous ketone is the starting material made? Propose a reasonable route from this molecule to the starting material. Propose a stereochemical rationale for the major product of step 1. See solution below.
7) Propose a reasonable mechanism.
Structure of PhCPhos:





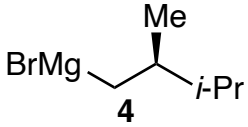
swinhoeisterol C

10-20



swinhoeisterol C

10) H_2N-DABCO, *t*-BuOK
11) $Fe(dpm)_3$, $Ph(i\text{-}PrO)SiH_2$
12) *t*-BuOK
13) DIBAL-H, -40 ˚C *then* NH_4Cl (aq.)
14) DIBAL-H
15) TsCl, DMAP
16) **4**, $CuBr{\bullet}SMe_2$
17) $HgCl_2$, THF/MeCN/H_2O
18) O_3, pyr./DCM
19) **5**, *n*-Bu_3P
20) $NaHCO_3$, H_2O_2



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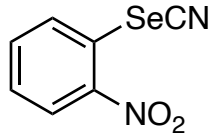

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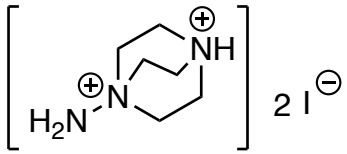
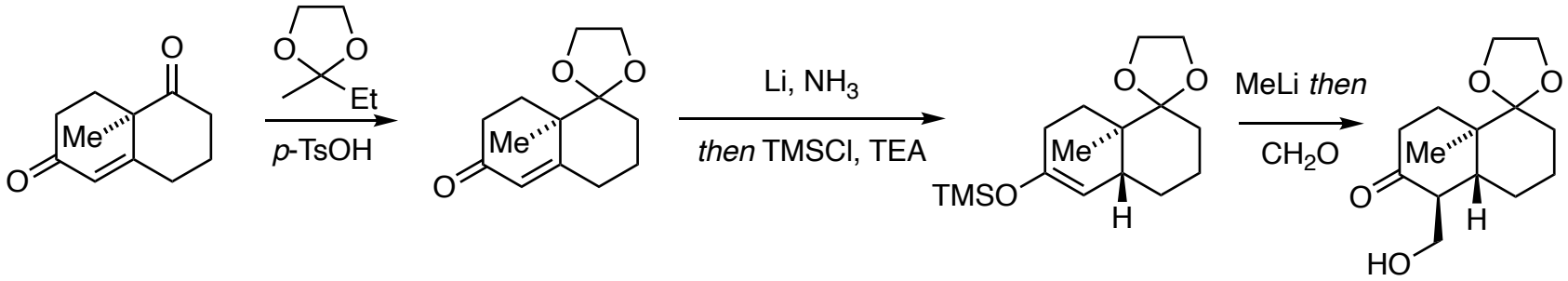
10) Structure of H_2N-DABCO:

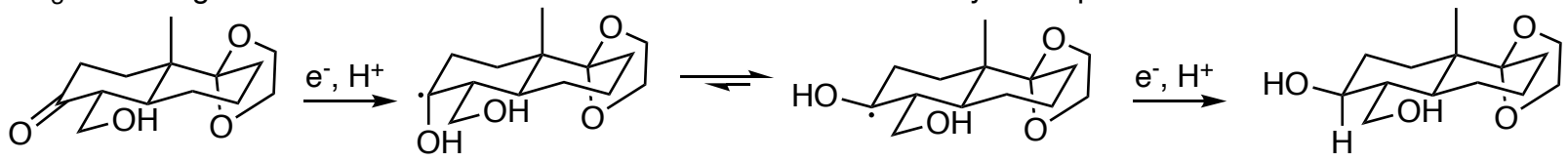


11) Who developed this type of reductive olefin coupling? Phil Baran.
12) Epimerization
17) Swinhoeisterol A was also made in 1 step from this intermediate.
19) Swinhoeisterol B was also made in 1 step from swinhoeisterol C.

Solution to step 1: The starting material is made from (+)-Wieland-Mischer ketone (the (+)-enantiomer is known from *ACIE* **2021**, *61*, e202112838) and the synthesis is shown below for the (–)-enantiomer (*JACS* **1988**, *110*, 8483-8487)



Li/NH_3 dissolving metal conditions allow for the formation of the thermodynamic product:



equatorial alcohol more stable

Solution to step 7: This is a Negishi/Heck cascade. Strategically, the use of the vinyl silane (rather than the terminal alkene) served to limit formation of isomeric cyclopentadienes via Pd-H insertion/deinsertion and subsequent 1,5-H shifts. The stereochemistry of the vinyl silane was confirmed by an NOE observed with the adjacent pseudo-equatorial hydrogen.