Total Synthesis of (+)-Granatumine A and Related Bislactone Limonoid Alkaloids via a Pyran to Pyridine Interconversion

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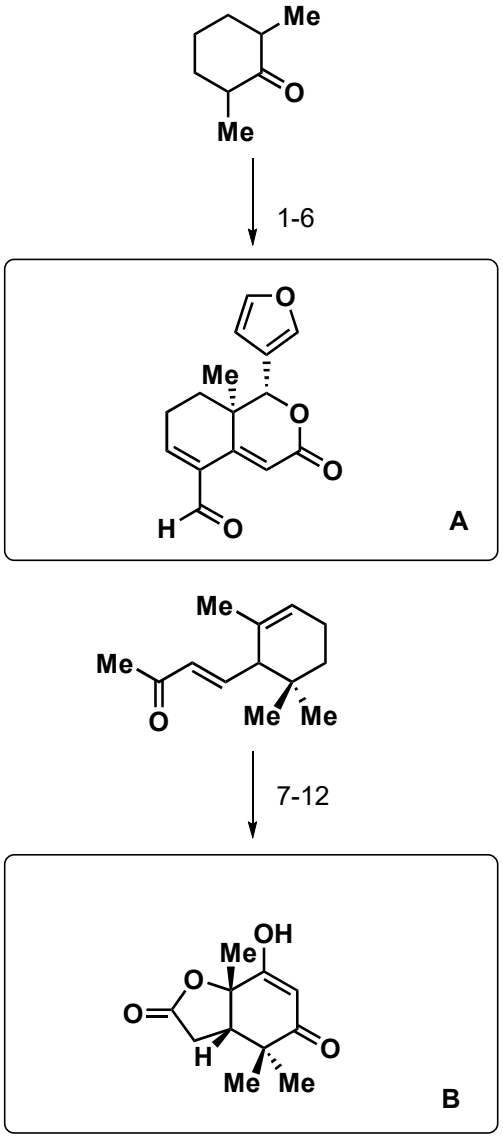
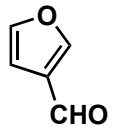
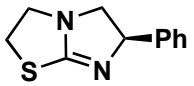


1) LDA(1.5 eq), ZnCl, THF, -40°C,
then allyl acetate, $[Pd(Allyl)Cl]_2$, 60°C
2) LDA, **1,** THF, -78 °C
3) Ac_2O, **2** (cat.), PhMe
4) LiHMDS, then Burgess reagent
5) SeO_2, Na2HPO4, 1,4-dioxane, 100°C
6) DMP

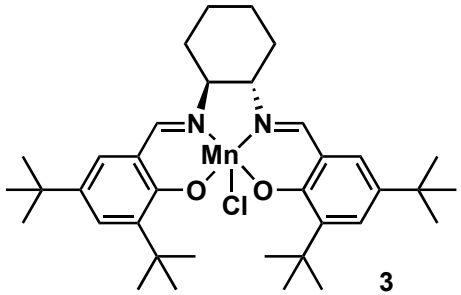


1



2

7) **3** (cat.), 4-PPNO, NaOCl
8) $[Rh(cod)(OH)]_2$, $PhMe_2SiH$
9) O_3, *then* Jones reagent
10) $Pd(TFA)_2$, DMSO, O_2, 80°C
11) urea•H_2O_2, DBN, H_2O
12) $Pd(OAc)_2$, XPhos, toluene

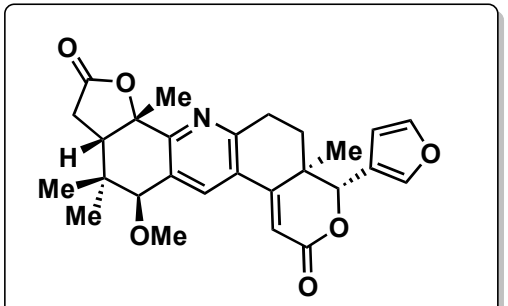


3

Step 1: Please provide a mechanism and two alternative approaches.
[See last page for mechanism]
Alternative approaches: Ketone to enone conversion followed by Saegusa oxidation or α-halogenation followed by elimination

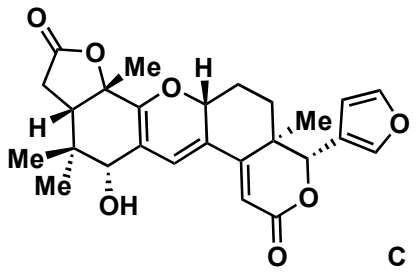
Step 9: A heterocycle is formed, please provide a mechanism.
[See last page for mechanism]

Step 12: Please provide a plausible mechanims
[See last page for mechanism]



(+)-Granatumine A

13-14



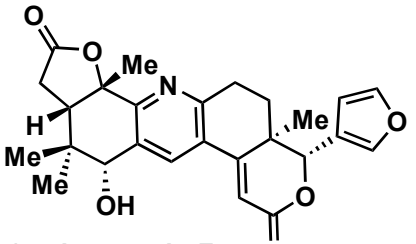
C

13) ethyldiammonium diacetate, **A**, 65°C
14) $LiBH_4$, $CeCl_3$, TFE/THF

15) $HO\text{-}NH_2 \bullet HCl$, $LiOAc \bullet 2H_2O$, 80°C

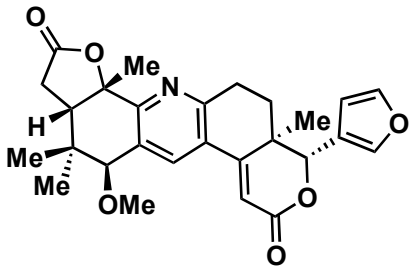
15

34%



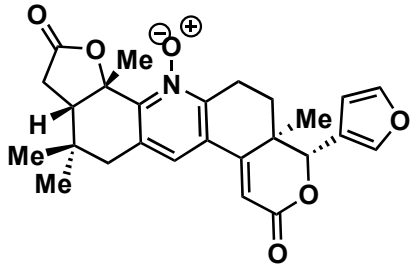
(+)-xylogranatin F
[misassigned structure]

16



(+)-Granatumine A

35%



D

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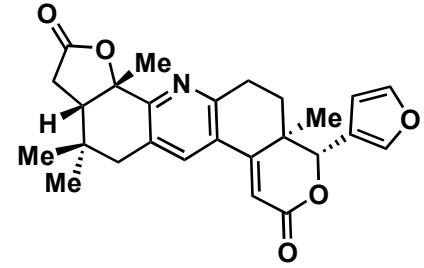


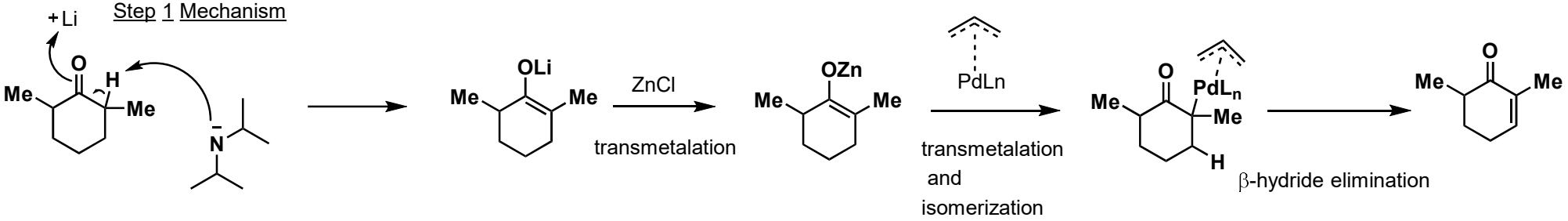
(+)-3-deoxy-xylogranatin F

Step 13: A cyclization occurs. Provide a mechanism for it and classify it.
[See last page for mechanism]
Oxa-6π electrocyclization

Step 15: Yields two products. Propose mechanisms for the formation of each
[See last page for mechanism]

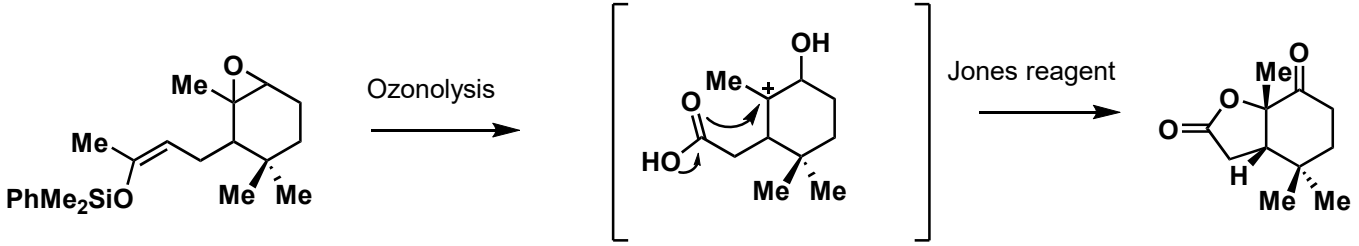
Step 16 and 17: Propose conditions for the convertions.
16: $SOCl_2$, *then* NaOMe
17: Zn, $CeCl_3$

Step 1 Mechanism

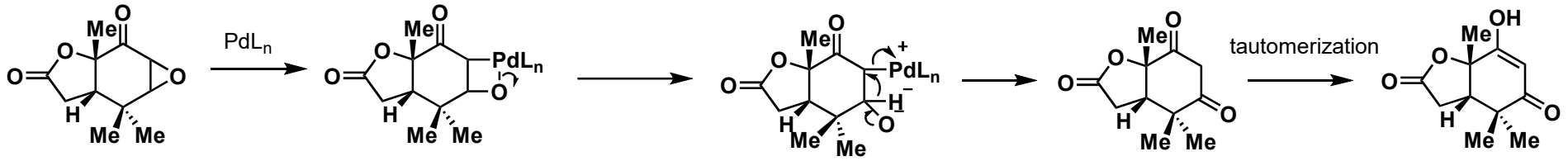


Note: transmetalation to Zn metal avoids Tsuji-Trost allylation products.

Step 9 Mechanism

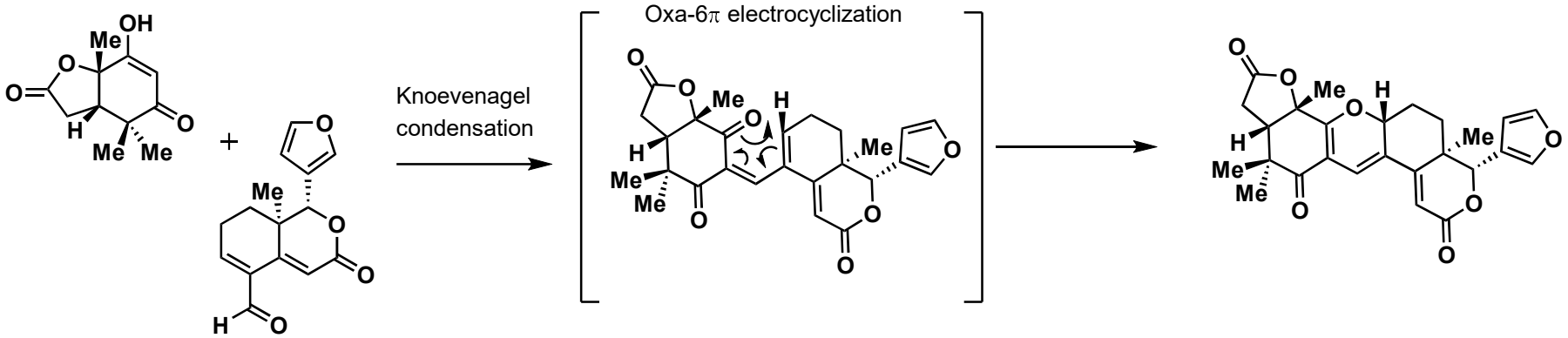


Step 12 Mechanism



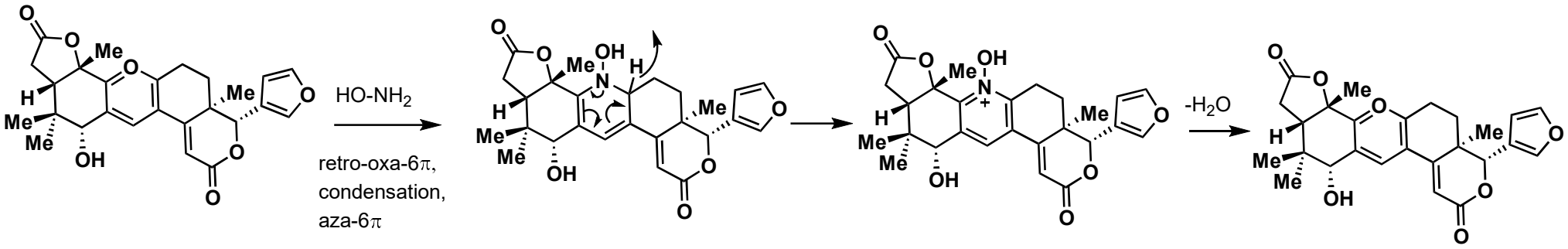
Note: one of two mechanisms proposed by Noyori et al. (Recl. Trav. Chim. Pays-Bas 107, 230-236, 1988)

Step 13 Mechanism



Note: The authors did initial computational investigations to determine the ketone regioselectivity of the electrocyclization. They found that the desired regioselectivity was kinectically and thermodinamically favored.

Step 15 Mechanism



Step 15 Mechanism (continued)