Synthetic Study of Palmerolide A

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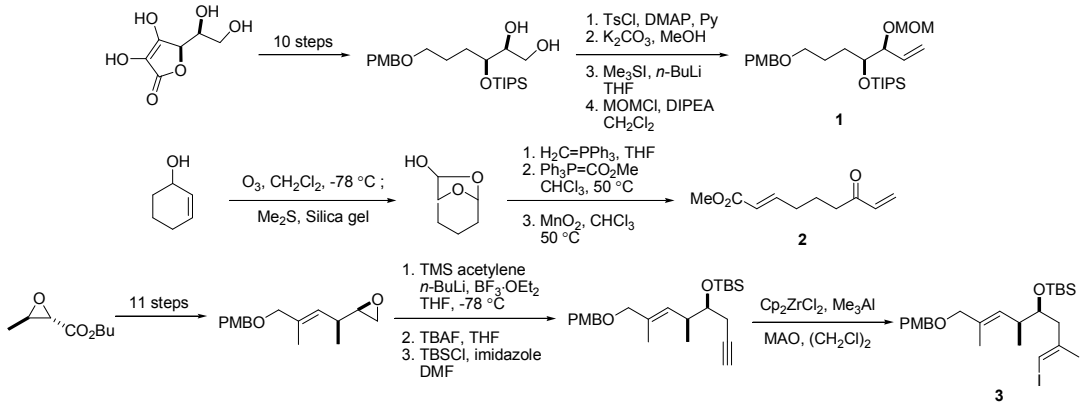
Palmerolide A is a polyketide which is isolated from circumpolar tunicate *Synoicam adareanum* found around Anvers island on the Antarctica by Baker in 2006. Palmerolide A has a 20-membered-macrolactone ring and polar enamide and carbamoyl unit. And shows V-ATPase inhibitory activity. V-ATPase is a proton pump which is distributed in organelle and it play a crucial role in serving protone into intracellular domain. This v-ATPase is involved in various diseases such as renal tubular acidosis, osteoporosis, cancer and so on. Although V-ATPase inhivitor is hoped as a novel therapeutic agent against these diseases, the inhibition mechanism of V-ATPase is still unclear. To solve this problem, We try to synthesize palmerolide A and co-crystallize with V-ATPase.

20-membered-macrolactone ring can be construted from three fragments (**1**-**3**) by cross-metathesis, macrolactonization and Pd-mediated cross coupling. I accomplished synthesis of these fragments from ascorbic acid, cyclohexenol, and epoxyester as shown in **scheme 1**. Synthesized **1** and **2** were coupled by cross-metathesis using Grubbs 2nd

Scheme 1.



generation catalyst (**scheme 2**). Now I try to construct macrolactone ring by means of Pd-mediated cross coupling followed by macrolactonization.

Scheme 2.