Synthesis of the C3-C12 Fragment of Laulimalide

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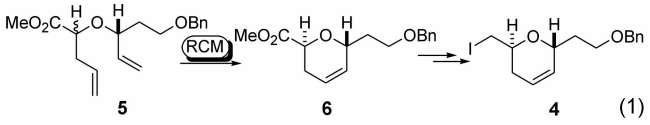
The antimiototic 20-membered macrolide laulimalide (**1**) also known as fijanolide B, isolated from sea sponges such as *Cacospongia mycofijiensis*,[1] *Hyatella* sp. *Spongia mycofijiensis*,[2] and *Fasciospongia rimosa*,[3] shows a potent biological activity against cell lines resistant to paclitaxel or epothilones since laulimalide binds to a site of microtubules in a mode distinct from taxoids.[4] The stabilization of polymerization by laulimalide leads to the inhibition of miotic spindle and apoptosis of cells.

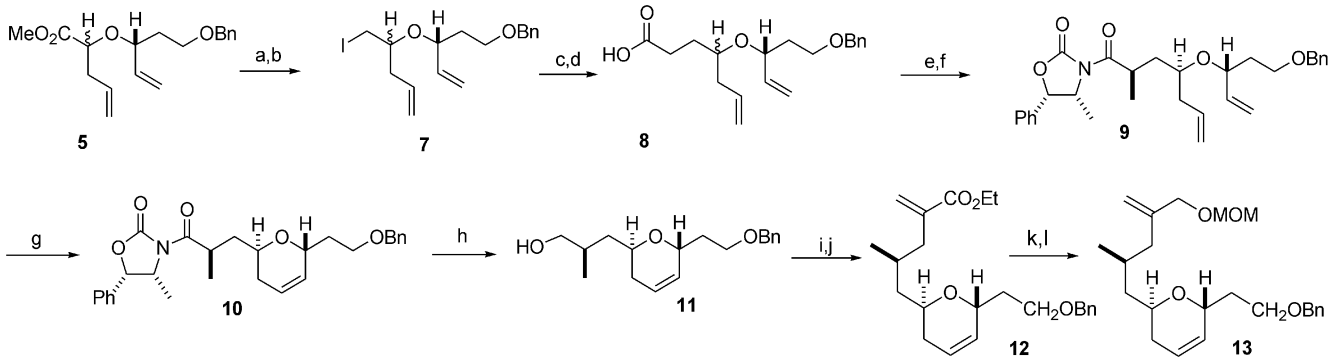
The structure of laulimalide determined by X-ray crystallographic study was reported in the literature.[3a] The remarkable biological activity as well as its structural features of laulimalide has inspired interests of organic chemists in its synthesis.[5-10] Previously we reported the synthesis of dihydropyran rings of laulimalide as a part of our synthetic effort toward laulimalide.[11] Herein we would like to report our synthetic efforts on the fragment C3-C12 of laulimalide.

Our retrosynthetic analysis of laulimalide (**1**) leads to two fragments of **2** and **3**. The subunit **3** can be prepared from compound **4** by exploiting the Wittig reaction on aldehyde. The dihydropyran ring of compound **4** can be provided by employing olefinic ring-closing metathesis (RCM). The subsequent transformation utilizing manipulations such as alkylation on chiral oxazolidinone and Horner-Wadsworth-Emmons reaction on side chains of **4** will provide subunit **3**.

At first, we thought the side chain at C-9 of the dihydropyran ring of **3** could be introduced by simple elongation of the side chain of compound **4**. (Eq. 1) However the nucleophilic substitution reaction of an enolate from (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-oxazolidin-2-one with iodide **7** did not yield any desired product. Likewise the reaction with a carbanion of malonate ester showed a lack of reactivity of **7** toward nucleophiles. Even when we change the iodide to a mesylate, the result was same. This behavior may be attributed to the presence of dihydropyran ring, which might render the approach of nucleophiles unfeasible. Thus we decided not to convert a dihydropyran ring prior to the elongation of backbone. This became our synthetic strategy toward subunit **3**.

Using this reaction route, compound **5**[11a] was converted to iodide **7** by the reduction with $LiAlH_4$ followed by treatment with iodine and triphenylphosphine (Scheme 1). The conversion of **7** to carboxylic acid **8** of extended backbone was preformed by decarboxylation of the intermediate of





Scheme 1. Reagents: a. $LiAlH_4$, THF, 98%; b. PPh_3, I_2, imidazole, 98%; c. Diethyl malonate, NaH, DMF, 98%; d. LiI, collidine, 97%; e. PvCl, Et_3N, THF; *n*-BuLi, (4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidinone, 64%; f. NaHMDS, MeI, THF, 61%; g. $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, 90%; h. $LiAlH_4$, THF, -78 °C, 85%; i. Ms_2O, Et_3N, CH_2Cl_2, 99%; LiBr, DMF, 40 °C, 94%; j. NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMSO, 50 °C, 6 h; CH_2O, K_2CO_3, 60%; k. DIBAL, -78 °C, 98%; l. MOMCl, iPr_2NEt, 71%.

malonate ester using LiI. The resulting **8** was transformed to the derivative of oxazolidinone by the reaction of mixed anhydride with an enolate of chiral oxazolidinone. The methylation upon this intermediate gave compound **9**. Now with this compound **9** in hand, it is a time to introduce a dihydropyran ring by carrying out the RCM reaction using Grubbs catalyst. The resulting oxazolidinone **10** from RCM reaction of **9** was reduced to alcohol **11**. The next step along the sequence was the introduction of an α,β-unsaturated ester group using the Horner-Wadsworth-Emmons reaction.[12] Thus, compound **11** was converted to a bromide intermediate *via* reaction of a mesylate with LiBr. Then, this bromide was transformed to a phosphate and subsequent *in-situ* reaction of this intermediate with formaldehyde provided the desired unsaturated ester **12**. The reduction of an ester group followed by protection with MOM group in due course finally provided the desired compound **13**.

In summary, we have reported the successful synthesis of the C3-C12 fragment of laulimalide using the introduction of a dihydropyran ring after the elongation of a side chain. Our on-going synthetic effort toward the synthesis of laulimalide will be reported in the near future.

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