Synthesis of 3,6-Dihydro-2*H*-pyran Subunits of Laulimalide Using Olefinic Ring Closing Metathesis. Part I

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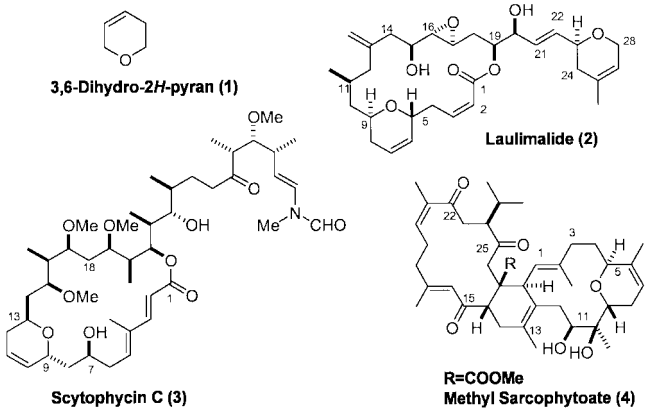
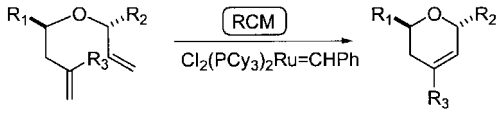
3,6-Dihydro-2*H*-pyrans (**1**) compose subunits of numerous biologically active natural products such as laulimalide (**2**),[1] scytophycin C (**3**),[2] and methyl sarcophytoate (**4**).[3] Especially among these, laulimalide possesses two dihydropyran rings, *i.e.* 2,6-disubstituted and 2,4-disubstituted 3,6-dihydro-2*H*-pyrans. Laulimalide has been recently known for its potent activity as an antimiotic agent like taxol® and epothilones. Unlike taxol®, laulimalide is biologically active against multi-drug cell lines.[4] This fact prompted us to be interested in the synthesis toward laulimalide. The one of key steps in our synthetic plan lies in the successful preparation of dihydropyrans. Herewith, we would like to describe the synthesis of 3,6-dihydro-2*H*-pyran subunits of laulimalide.

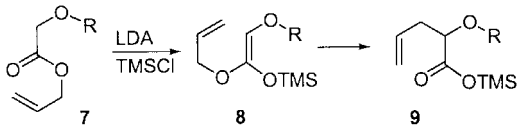


In general, two major methods have been used for the preparation of optically active 2,6-disubstituted 3,6-dihydro-2*H*-pyrans. The first method is the one using Ferrier-type reaction[5] on the glycal derivatives, which are prepared by the hetero-Diels-Alder reaction of Danishefsky's diene under the optically active catalysts.[6] So far this method has not been recommendable because of its relatively low e.e. values of the products. The second method is the one employing the conversion of *cis*-diol of D-mannose to a double bond.[7] This process is cumbersome in dealing with diverse derivatives of dihydropyrans. We have planned the synthesis of optically active 2,6-disubstituted 3,6-dihydro-2*H*-pyran using ring-closing metathesis (RCM) reaction employing Grubbs ruthenium benzylidene catalyst.[8] RCM reaction tolerates lots of functional groups and usually proceeds under the mild condition. Recently the application of RCM reactions in organic synthesis are overwhelmingly expanding.[9] Our approach was based on Eq. 1, which depicts that allyl-O-homoallyl compound undergoes RCM reaction to afford the dihydropyran ring.



5 **6** (1)

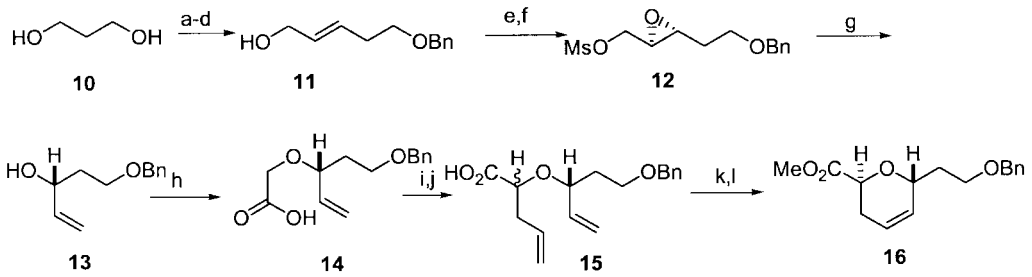
The only problem left for the synthesis is the formation of the ether linkage for 2,6-disubstituted dihydropyran. It is not easy to prepare ethers with both secondary alkyl groups. However, this problem can be resolved by Burkes tandem glycolate Claisen rearrangement (Eq. 2).[10]



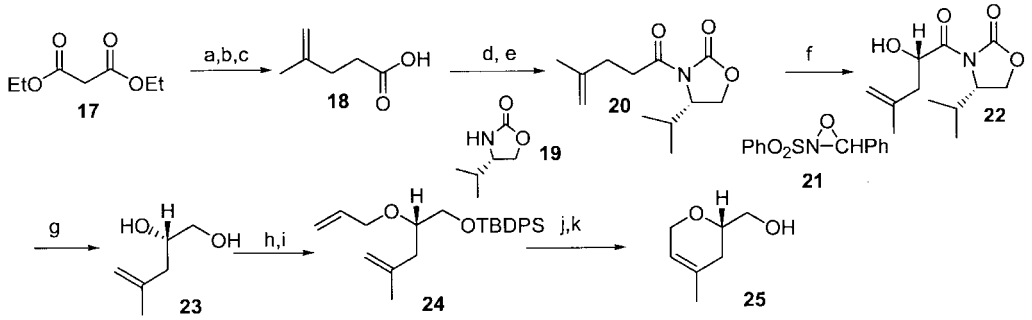
7 **8** **9** (2)

R= secondary alkyl

According to our approach, we decided to prepare 2,6-disubstituted dihydropyran from the substrate of glycolate Claisen rearrangement. First of all, 1,3-propanediol was monoprotected as benzyl ether by treatment with KO^{t}Bu and benzyl chloride in 1,4-dioxane. (Scheme 1) The resulting alcohol was subjected to Swern oxidation to furnish aldehyde and Horner-Wadsworth-Edmmons reaction of ethyl diisopropoxyoxyphosphorylacetate in THF at 0 °C upon this aldehyde provided the α,β-unsaturated ester, which was reduced to allylic alcohol by DIBAL. Then, Sharpless asymmetric epoxidation, mesylation reaction followed by the treatment of the mesylate with zinc dust and NaI provided the secondary allylic alcohol possessing the required stereochemistry. In order to prepare the homoallylic ether, sodium salt of allylic alcohol **13** was treated with sodium bromoacetate to provide acid **14** after acidic workup. Next step along the line was the esterification. Therefore, the treatment of **14** with DCC and allyl alcohol provided allylic ester, which was transformed to an intermediate of TMS enol ether by treatment with LDA and TMSCl. The intermediate was immediately rearranged to the corresponding homoallylic acid **15** as a mixture of isomers. At this stage we could not separate isomers. Instead, the separation was performed upon the treatment of acid with diazomethane. The separation of isomers of the esters was accomplished by the chromatographic method. R_f values of *R* and *S* isomers on silica gel TLC were 0.26 and 0.36, respectively for an eluent of hexane : ethyl acetate = 10 : 1. We obtained the desired *S*



Scheme 1. Reagents: [a]BnCl, KO^{t}Bu, 1,4-dioxane, reflux, 58%. [b](COCl)$_2$, DMSO, Et$_3$N. [c](^{i}PrO)$_2$POCH$_2$CO$_2$Et, KO^{t}Bu, THF, 62% (two steps). [d]DIBAL, THF, -78 °C, 92%. [e]Ti(O^{i}Pr)$_4$, D-DET, TBHP, CH_2Cl_2, 90%. [f]MsCl, Et$_3$N, dmap, CH_2Cl_2, 100%. [g]NaI, Zn dust, THF, reflux, 77%. [h]NaH, $BrCH_2CO_2H$, THF, reflux, 99%. [i]DCC. allyl alcohol, 94%. [j]LDA, HMPA, TMSCl, 74%. [k]CH_2N_2, ether, chromatographic separation, 73%. [l]$Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, 100%.



Scheme 2. Reagents: [a]NaOEt, CH_2=C(CH_3)CH_2Cl, 81%. [b]NaCl, DMSO, 140-180 °C, 77%. [c]NaOH, H_3O^+, 83%. [d]pivaloyl chloride, Et$_3$N; [e]*n*-BuLi, **19**, THF, 95% (two steps). [f]NaHMDS, **21**, THF, -78 °C, 72%. [g]$LiBH_4$, MeOH, THF, 99%. [h]TBDPSCl, NaH, THF, 88%. [i]NaH, allyl bromide, *n*-Bu$_4$Nl, THF, 70%. [j]$Cl_2(Cy_3P)_2Ru$=CHPh, 85%. [k]*n*-Bu$_4$NF, THF, 78%.

product in the ratio of 4 : 1 in 73% yield. Finally the RCM reaction of this *S* methyl ester using Grubbs' catalyst yielded the desired *trans* product **16** in 100% yield. In contrast, the other *R* isomer gave *cis* product in 64% yield. The stereochemistry of the product was identified by comparing 2D NOESY spectral data of each isomer.

As for the preparation of 2-hydroxymethyl-4-methyl-3,6-dihydro-2*H*-pyran (**25**), we utilized the protocol of Evans' oxazolidinone. Thus alkenyl carboxylic acid was prepared from diethyl malonate by standard method[11] and combined with (4*S*)-4-isopropyloxazolidin-2-one *via* mixed anhydride of pivalic acid.[12] The asymmetric hydroxylation reaction of oxazolidinone derivative using 2-benzenesulfonyl-3-phenyl-oxaziridine (**21**) provided α-hydroxy amide derivative **22**.[13]

Then, oxazolidinone ring of **22** was removed under the reducing condition utilizing $LiBH_4$ to obtain diol **23**. The selective protection of primary hydroxy group with TBDPSCl and Williamson ether synthesis under the phase transfer catalyst provided the substrate **24** for RCM.[14] The RCM reaction of **24** proceeded smoothly to dihydropyran ring compound, of which TBDPS group was removed to yield the desired dihydropyran **25**.

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