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

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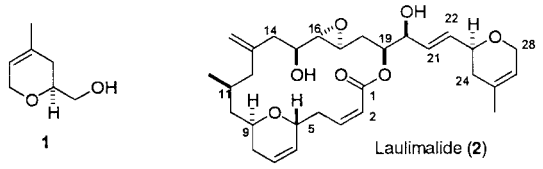
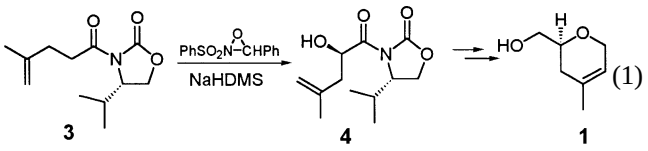
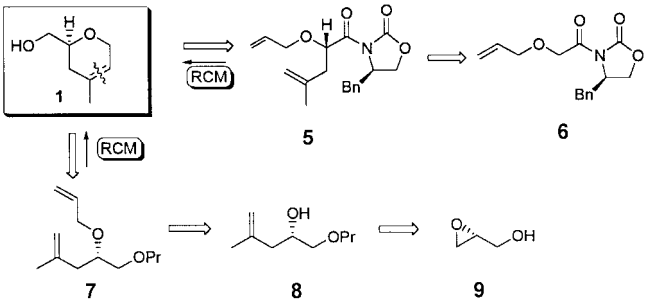
We are concerned about the synthesis of (2*R*)-2-hydroxymethyl-4-methyl-3,6-dihydro-2*H*-pyran (**1**) which is a building block for laulimalide (**2**),[1] which has microtubule stabilizing activity. We have already described the synthesis of **1** in the previous communication.[2] Herein we would like to report the improved synthesis of **1** utilizing olefinic ring closing metathesis (RCM).[3]



Preparation of 3,6-dihydro-2*H*-pyran in the previous communication required 2-benzenesulfonyl-3-phenyloxaziridine to introduce a hydroxy group at the α-position of carbonyl group (Eq. 1). In order to circumvent the cumbersome use of this oxaziridine reagent, we planned two other routes according to retrosynthetic analysis using RCM as shown in Scheme 1. First pathway is employing oxazolidinone as a chiral auxiliary. This methodology was implemented by Crimmins



and Choy.[4] The second pathway is utilizing optically active (*R*)-glycidol (**9**), which eliminate the usage of chiral auxiliary. Ring opening of the epoxide ring of protected (*R*)-glycidol with a Grignard reagent provides secondary homoallylic

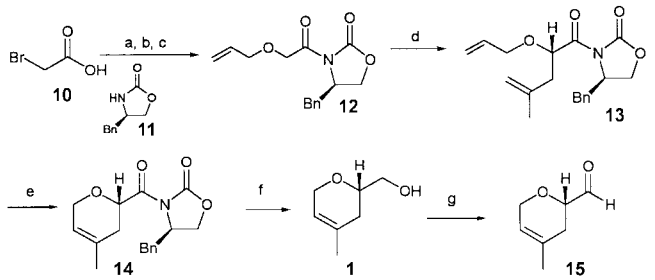


Scheme 1. Retrosynthetic Analysis

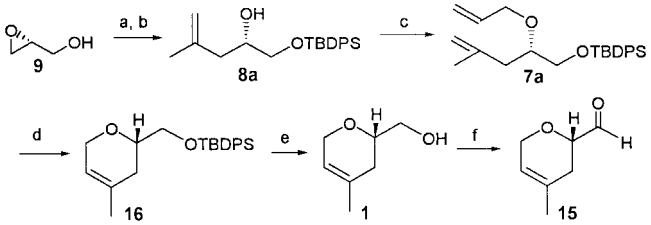
alcohol **8** that can be further used for Williamson ether synthesis. The preparation of secondary homoallylic alcohols from (*R*)-glycidol has been reported in the literature.[5] Relating to this methodology recently, several research groups independently reported synthesis of compound **1** from (*R*)-glycidol.[6,7,8] Ghosh *et al.* used trityl group as a protecting group.[6] In Ghoshs experiment, the reaction time for the preparation of trityl derivative of glycidol took 24 hours. In contrast, dihydropyran derivative adopted by Mulzer *et al.* to protect the hydroxy group of glycidol was facile to prepare.[7] But the resulting THP derivatives became a diastereomeric mixture.

In new synthetic routes according to the methodology using chiral oxazolidinone (Scheme 2), sodium salt of bromoacetic acid (**10**) was reacted with allyl alcohol in refluxing THF to give allyloxyacetic acid intermediate, which was subsequently converted to mixed anhydride by treatment with pivaloyl chloride. The reaction of anion of oxazolidinone **11** with this mixed anhydride provided compound **12**. The alkylation of **12** with methallyl iodide gave compound **13**. The olefinic RCM reaction in the presence of Grubbs' catalyst in CH_2Cl_2 transformed **13** to the desired dihydropyran compound **14**. The reductive removal of oxazolidinone auxiliary of **14** furnished the desired product **1**. Swern oxidation of hydroxy compound **1** yielded aldehyde **15**, which can provide further skeleton for laulimalide.

In the second reaction pathway (Scheme 3), (*R*)-glycidol (**9**) was used as a starting material. Hydroxy group of glycidol (**9**) was easily protected as *t*-butyldiphyenylsilyl (TBDPS) ether and opening of epoxide ring of this intermediate with



Scheme 2. *Reagents*: [a]NaH, allyl alcohol, 100%; [b]pivaloyl chloride, Et_3N, Et_2O; [c]*n*-BuLi, **11**, 74% (two steps); [d]CH_2=C(CH_3)CH_2I, NaHMDS, THF, -40 °C, 61%; [e]$Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, 65%; [f]$LiBH_4$, MeOH, THF, 85%; [g]$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.



Scheme 3. *Reagents*: [a]TBDPSCI, imidazole, CH_2Cl_2, 100%; [b]CH_2=$C(CH_3)$MgBr, THF, 93%; [c]NaH, allyl bromide, *n*-Bu_4NI, THF, 70%; [d]$Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, 85%; [e]*n*-Bu_4NF, THF, 78%; [f]$(COCl)_2$, DMSO, Et_3N, 87%.

2-propenyl magnesium bromide provided compound **8a**. The use of *t*-butyldiphyenylsilyl as a protecting group is not only offering facile derivatization but also is eliminating possibility of diastereoisomerism of THP derivatives. Reaction time was less than one hour (usually 30-50 min) in contrast to 24 hours for trityl derivatization for the case of Ghoshs experiment. We found that the Grignard reaction of isopropenyl magnesium bromide with this intermediate does not require the presence of copper salt as reported in the literature. The addition of only 1.1 equivalents of Grignard reagent to epoxide provided **8a** in the yield of 93%. The yield was quantitative even when we changed the protection group as benzyl ether. In both cases, we could not observe any regio isomers. The etherification of **8a** with allyl bromide yielded the substrate **7a** for RCM reaction. The RCM reaction was carried out smoothly in the presence of Grubbs' catalyst to obtain the desired dihydropyran **16**. The subsequent deprotection of silyl ether group furnished alcohol **1** and the Swern oxidation of **1** provided aldehyde **15** in our hands. Further elaboration of aldehyde **15** toward the total synthesis of laulimalide is in progress and will be reported in the near future.

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References

1. (a) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653-660. (b) Quiñoà, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642-3644. (c) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644-3646. (d) Tanaka, J. I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535-5538. (e) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem*. **2001**, 775-778. (f) Paterson, I.; de Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 213-216. (g) Dorling, E. K.; Ohler, E.; Mantoulidis, A.; Mulzer, J. *Synlett* **2001**, 1105-1108. (i) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 797-800. (k) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 801-803. (l) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2001**, *42*, 3399-3401. (m) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027-11028.
2. Lee, H. W.; Jeong, C.-S.; Yoon, S. H.; Lee, I.-Y. C. *Bull. Korean Chem. Soc*. **2001**, *22*, 791-792.
3. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446-452. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450. (c) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1992**, *114*, 3974-3975.
4. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653-5660.
5. Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960-7973.
6. Ghosh, A. K.; Wang, Y. *Tetrahedron Lett*. **2000**, *41*, 4705-4708.
7. Mulzer, J.; Hanbauer, M. *Tetrahedron Lett*. **2000**, *41*, 33-36.
8. Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett*. **2001**, *42*, 801-803.