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Evaluating Transition-Metal-Catalyzed Transformations for the Synthesis of Laulimalide

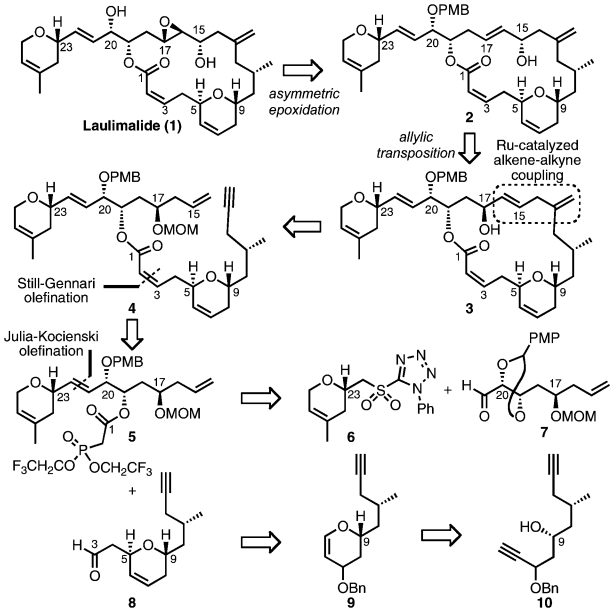
Barry M. Trost,* Dominique Amans, W. Michael Seganish, and Cheol K. Chung

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received September 17, 2009; E-mail: bmtrost@stanford.edu

Laulimalide (**1**), also called fijianolide B, is a structurally unique 20-membered marine macrolide isolated from several sources of marine sponges, such as *Cacospongia mycofijiensis*, *Hyattella* sp., and *Fasciospongia rimosa*.[1] Initially, it was shown that laulimalide displays potent cytotoxicity toward numerous NCI cell lines,[1b] but it did not attract the attention of synthetic chemists until Mooberry and coworkers[2] discovered that laulimalide displays microtubule stabilizing activity similar to that of paclitaxel and the epothilones. Both its unique pharmaceutical profile and challenging chemical architecture have attracted considerable interest, leading to numerous attempts and several successful syntheses of both the naturally occurring compound and some analogues.[3] These approaches have underscored several unique structural features that must be addressed via the development of new efficient and atom-economical transformations.[4]

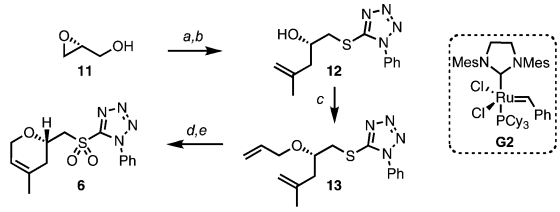
Scheme 1. Retrosynthetic Analysis of Laulimalide



To further illustrate the inherent versatility of the alkyne functional group in the context of complex natural product synthesis, we specifically intended to test the applicability of our Ru-catalyzed alkene−alkyne coupling to construct the laulimalide macrocycle. Thus, our retrosynthetic analysis for laulimalide was based on the notion that the natural product could be formed from 1,4-diene **3**, which we believed could be converted into allylic alcohol **2** via a stereospecific 1,3-allylic transposition (Scheme 1). Alternatively, a diastereoselective epoxidation of allylic alcohol **3** followed by a Payne rearrangement[5] could also provide access to laulimalide. 1,4-Diene **3** would arise from an intramolecular Ru-catalyzed alkene−alkyne coupling of enyne **4**,[6] in turn accessed from a Still−Gennari olefination[7] between two synthons of similar complexity: phosphonate **5** and aldehyde **8**. The northern fragment **5** could be generated via a Julia−Kocieński olefination[8] between phenyltetrazole sulfone **6** and aldehyde **7**. In addition, a Rh-catalyzed cycloisomerization applied to **10** would produce dihydropyran **9**, the precursor of the southern fragment **8**.

A protecting-group-free strategy allowed us to efficiently synthesize the required sulfone **6**, whose assembly began from (*R*)-glycidol **11** (Scheme 2). Conversion of the latter into the corresponding epoxysulfide followed by epoxide opening with isopropenylmagnesium bromide in the presence of copper iodide led to the corresponding secondary alcohol **12**, which needed to be transformed into diene **13**. While attempts at allylation under basic or acidic conditions were ineffective, addition of the zinc alkoxide of alcohol **12** to allylacetate in the presence of a catalytic amount of Pd(0) successfully resulted in the smooth formation of the desired allylated compound **13**.[9] Mo-catalyzed oxidation of the sulfide into the corresponding sulfone followed by a ring-closing metathesis using the second-generation Grubbs catalyst **G2** ultimately provided the desired dihydropyran **6**, which constitutes the side chain of laulimalide.

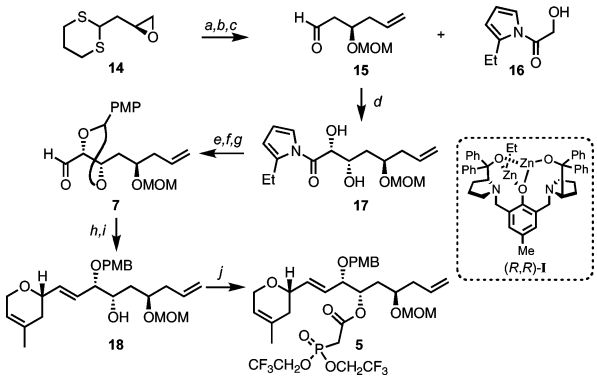
Scheme 2. Synthesis of the Dihydropyran Side Chain[a]



[a] Conditions: (a) DEAD, PPh_3, 1-phenyl-1*H*-tetrazole-5-thiol, THF, 82%; (b) CuI, propenylmagnesium bromide, THF, 99%; (c) Et_2Zn, 10 mol % $Pd(OAc)_2$, 25 mol % PPh_3, allyl acetate, THF, 62% (76% brsm); (d) 15 mol % $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$, H_2O_2, EtOH, 83%; (e) 3 mol % **G2**, CH_2Cl_2 (*c* 0.015 M), 95%.

Next, our attention turned to the preparation of syn 1,2-diol **7**, whose synthesis would hinge on the development of a novel direct asymmetric aldol-type reaction promoted by dinuclear Zn catalyst (*R*,*R*)-**I** using a donor partner at the carboxylic acid oxidation state (Scheme 3).[10] Thus, β-hydroxyaldehyde **15**, prepared from the known epoxide **14**, would be transformed into syn diol **7** using the above-mentioned methodology. As we needed to have access to the aldehyde functionality present in **7**, we decided to examine the utilization of hydroxy acylpyrroles as donors.[11,12] Extensive exploration of this transformation led us to consider the use of hydroxy 2-ethylacylpyrrole **16** in the presence of 15 mol % (*R*,*R*)-**I**, which gratifyingly furnished the desired syn 1,2-diol **17** with a 10:1 dr. Subsequent protection of the resulting diol as a PMP-acetal followed by a reduction/oxidation sequence provided the desired aldehyde **7**. With access to both sulfone **6** and aldehyde **7**, the envisaged Julia−Kocieński olefination was implemented and successfully furnished, after selective opening of the PMP-acetal with DIBAL-H,[13] the desired alcohol **18** as a single *E*-configured geometric isomer. Esterification between the latter compound and bis-(2,2,2-trifluoroethyl)phosphonoacetic acid under Yamaguchi conditions proceeded to give the targeted β-ketophosphonate **5** in near quantitative yield.

Scheme 3. Synthesis of the Northern Fragment **5**[a]

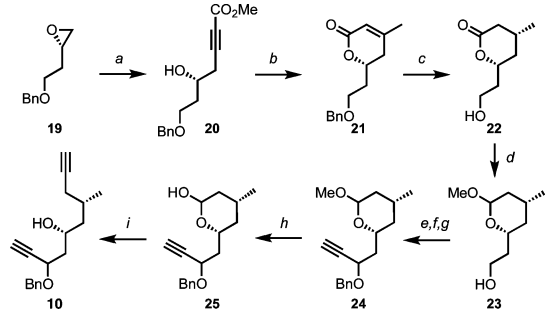


[a] Conditions: (a) $H_2C{=}CHMgBr$, CuI, THF, 95%; (b) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 97%; (c) MeI, $CaCO_3$, 9:1 MeCN/H_2O, 85%; (d) 15 mol % (*R*,*R*)-**I**, THF, 53%, 10:1 dr; (e) *p*-$MeOPhCH(OMe)_2$, 10-CSA, CH_2Cl_2, 81%; (f) $NaBH_4$, THF, 86%; (g) Dess−Martin periodinane, CH_2Cl_2; (h) **6**, LiHMDS, 3:1 DMF/HMPA, 64% over two steps; (i) DIBAL-H, CH_2Cl_2, 61%; (j) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, 2,4,6-trichlorobenzoylchloride, *i*-Pr_2EtN, THF, then DMAP, PhH, 99%.

The preparation of the targeted diyne **10** commenced from the known oxirane **19** derived from D-aspartic acid (Scheme 4).[14] Regioselective opening of **19** with the lithium salt of methyl propiolate furnished homopropargylic alcohol **20**, which in turn underwent a stereo- and regioselective cis addition of lithium dimethylcuprate followed by acid-catalyzed lactonization to afford α,β-unsaturated lactone **21**. Diastereoselective hydrogenation[15] and concomitant benzyl deprotection eventually gave rise to saturated lactone **22** as a single stereoisomer. Exposure of the latter to DIBAL-H and subsequent acetalization provided the mixed acetal **23**. Oxidation of the primary alcohol followed by Grignard addition and subsequent benzylation yielded propargylic alcohol **24**. Hydrolysis of acetal **24** under acidic conditions produced hemiketal **25**, allowing for the installation of another alkyne functionality. To this end, hemiketal **25** was exposed to the Ohira−Bestmann reagent to furnish the required diyne **10**.

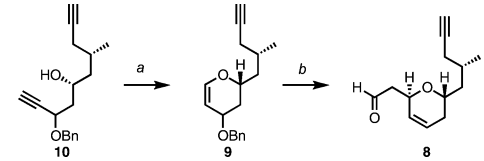
Having established a robust route to diyne **10**, we then turned our attention to the subsequent Rh-catalyzed cycloisomerization step.[16] The presence of two alkyne functional groups in the substrate raised an interesting question as to the chemoselectivity under these conditions. On the basis of previous studies in our group, we were confident that the six-membered-ring formation would be favored over the seven-membered-ring formation but remained uncertain whether the additional alkyne functionality would play any role in the reaction. Gratifyingly, exposure of bishomopropargylic alcohol **10** to 5 mol % $Rh(COD)Cl_2$ in the presence of an electron-poor bidentate phosphine ligand successfully afforded the desired dihydropyran in satisfying yield. Notably, none of the seven-membered-ring product could be detected via ^1H NMR analysis of the crude reaction mixture. The vinylogous acetal **9** thus obtained was ultimately activated under acidic conditions in the presence of *tert*-butyldimethylsilyl vinyl ether to produce the desired trans-disubstituted dihydropyran **8** almost exclusively (Scheme 5).

Scheme 4. Synthesis of the Diyne Precursor **10**[a]



[a] Conditions: (a) methyl propiolate, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, 93%; (b) CuI, MeLi, THF, then AcOH, PhH, 94%; (c) $Pd(OH)_2$, H_2, EtOAc, 97%; (d) DIBAL-H, CH_2Cl_2, then Dowex 50W × 8, MeOH, 99%; (e) TEMPO, NaOCl, KBr, $NaHCO_3$, CH_2Cl_2/H_2O, 97%; (f) ethynylmagnesium bromide, THF, 77%; (g) NaH, BnBr, DMF, 96%; (h) AcOH, H_2SO_4, H_2O, 82%; (i) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 57% (69% brsm).

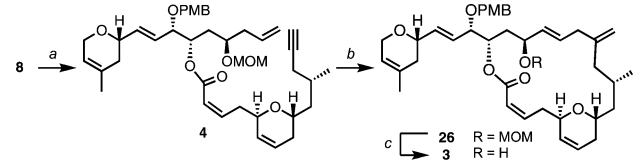
Scheme 5. Synthesis of the Southern Fragment **8**[a]



[a] Conditions: (a) 5 mol % $[Rh(COD)Cl]_2$, 10 mol % $[m\text{-}F(C_6H_4)]_2PCH_2CH_2P[m\text{-}F(C_6H_4)]_2$, DMF, 55%; (b) $CH_2{=}CHOTBS$, Montmorillonite K-10, CH_2Cl_2, 82%.

With both fragments **5** and **8** in hand, the coupling reaction could be implemented. Thus, condensation of the potassium salt of phosphonate **5** onto aldehyde **8** in the presence of 18-crown-6 provided the desired alkenoate **4** as a 1:5 mixture of *E* and *Z* isomers, which were easily separable by flash chromatography on silica gel (Scheme 6). Completion of enyne **4** set the stage to probe the challenging intramolecular alkene−alkyne coupling.[17] To this end, exposure of enyne **4** to 5 mol % $[CpRu(CH_3CN)_3]PF_6$ in acetone at 50 °C proceeded with exceptional efficiency to furnish the desired 1,4-diene **26** as a single regioisomer in 99% yield! Strikingly, only 15 min was required to perform this macrocycloisomerization with complete stereo-, chemo-, and regioselectivity. Notably, no isomerization of the (*Z*)-alkenoate could be detected. Deprotection of the MOM group under mild acidic conditions ultimately afforded the desired allylic alcohol **3**.

Scheme 6. Intramolecular Ru-Catalyzed Alkene−Alkyne Coupling[a]

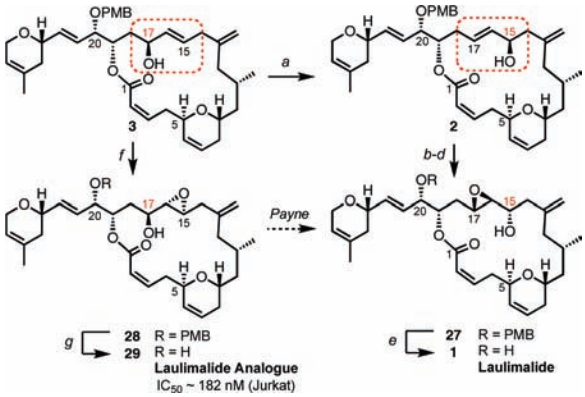


[a] Conditions: (a) **5**, KHMDS, 18-crown-6, THF, *E*/*Z* = 1:5, 62% (50% isolated *Z* isomer); (b) 5 mol % $[CpRu(CH_3CN)_3]PF_6$, acetone (*c* 0.001 M), 50 °C, 15 min, 99%; (c) PPTS, *t*-BuOH, 66%.

Upon completion of the targeted 1,4-diene **3**, we were in a favorable position to investigate the equally ambitious selective 1,3-allylic transposition in order to obtain the rearranged allylic alcohol **2**, the precursor of laulimalide. There are several known chemical transformations that in principle can provide allylic alcohol **2** from its regioisomer **3**, formally through a 1,3-allylic rearrangement. We first envisioned that conversion of allylic alcohol **3** into an allylic selenoxide would set the stage for a [2,3]-sigmatropic shift leading to the desired rearranged allylic alcohol epimeric to **2** at C15.[18] However, using standard Mitsunobu-type conditions[19] did not convert allylic alcohol **3** into the corresponding selenide. Alternatively, a diastereoselective epoxidation of allylic alcohol **3** followed by a Payne rearrangement[5] could potentially allow the formation of the rearranged epoxy alcohol **27**, a precursor of laulimalide. This approach was regrettably hampered by an intramolecular attack by the C17 hydroxyl group at the proximal ester under basic conditions, resulting in the formation of the corresponding ring-contracted

lactone. Being unable to perform the epoxide translocation, we sought another strategy that would allow us to obtain the natural product laulimalide from our intermediate **3**. It has previously been shown that the isomerization of allylic alcohols via 1,3-transposition of a hydroxy group can be catalyzed by a number of high-oxidation-state oxo complexes of transition metals such as V, W, Mo, and Re.[20] To our delight, the utilization of the Re oxo catalysis conditions developed by Osborn et al.,[21] which involve the highly active triphenylsilyl perrhenate catalyst $O_3ReOSiPh_3$, resulted in the clean formation of the rearranged product **2** with complete retention of configuration (Scheme 7). We found that using 1 equiv of the Re catalyst for 5 min at −50 °C in Et_2O was optimal in obtaining the rearranged allylic product **2** (78% isolated yield), which was easily separable from the remaining starting material **3** by flash column chromatography on silica gel (97% yield brsm). Subsequent inversion of the C15 stereogenic center following an oxidation/CBS-reduction sequence afforded the allylic alcohol epimeric to **2** at C15. Epoxidation of the latter compound using Sharpless conditions[22] followed by DDQ deprotection ultimately furnished laulimalide, whose spectral and physical data were in total agreement with those reported for the natural product.[1,23]

Scheme 7. Completion of the Synthesis of Laulimalide and a Potent Analogue[a]



[a] Conditions: (a) $O_3ReOSiPh_3$, Et_2O, 5 min, 78% (97% brsm); (b) Dess−Martin periodinane, CH_2Cl_2; (c) (*R*)-Me-CBS, BH_3·THF, THF, 93% over two steps; (d) (+)-DET, Ti(*i*-PrO)$_4$, TBHP, 4 Å MS, CH_2Cl_2, 88%; (e) DDQ, CH_2Cl_2/pH 7 buffer/*t*-BuOH, 89%; (f) (+)-DET, Ti(*i*-PrO)$_4$, TBHP, 4 Å MS, CH_2Cl_2, 86%; (e) DDQ, CH_2Cl_2/pH 7 buffer/*t*-BuOH, 71%.

It has been well-established that under mildly acidic conditions, laulimalide undergoes furan formation through an S_N2-type attack at the epoxide at C17 by the hydroxy group situated on the lateral chain at C20, leading to the so-called significantly less active isolaulimalide (IC_{50} = 20 000 nM).[1b] Therefore, there is undoubtedly a need to prepare laulimalide analogues designed in a fashion that would prevent furan formation but afford similar or improved activity in comparison to the natural product. With compound **3** in hand, a diastereoselective epoxidation under Sharpless conditions followed by DDQ deprotection led to the formation of laulimalide analogue **29**. We were pleased to observe that our analogue displayed significant activity against Granta 519 and Jurkat cell lines with IC_{50} values of 200 and 182 nM, respectively.

In conclusion, the use of atom-economical transformations such as a Rh-catalyzed cycloisomerization to form the endocyclic dihydropyran, a dinuclear Zn-catalyzed asymmetric glycolate aldol to prepare the syn 1,2-diol, and an intramolecular Ru-catalyzed alkene−alkyne coupling via isomerization to build the macrocycle enabled us to synthesize laulimalide by an efficient and convergent pathway. Interestingly, the designed synthetic route also allowed us to prepare an analogue of the natural product that possesses significant cytotoxic activity. More importantly, this work further highlights the power of the Ru-catalyzed alkene−alkyne coupling in the context of macrocyclizations via C−C bond formation.

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Supporting Information Available: Detailed experimental procedures, full characterization of all products, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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