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Synthesis of (−)-laulimalide: an agent for microtubule stabilization

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Abstract—An enantioselective synthesis of (−)-laulimalide is described. Key reactions include a convergent allylation coupling reaction, asymmetric conjugate addition, the allenylstannane Ferrier reaction and a chelation-controlled alkenylzinc addition as the basis for stereocontrol in critical elements of chirality.

Laulimalide, (**1**) a novel 20-membered macrolactone, was isolated from the marine sponges *Cacaspongia mycofijiensis*,[1] *Hyatella* sp.,[2] and *Fasciospongia rimosa*.[3] Efforts by Jefford and coworkers established the absolute configuration of **1** via X-ray diffraction studies.[3] It has been reported that laulimalide displays antitumor potency comparable to paclitaxel against breast and ovarian cancer cell lines, as well as potent activity against P388 murine lymphoma, A549 human lung, HT-29 human colon, and MEL28 tumor cell lines.[4] The mechanism for this cytotoxicity is attributed to the ability of laulimalide to stabilize and promote tubulin polymerization, leading to the formation of abnormal mitotic spindles, mitotic arrest and the initiation of apoptosis.[4] Significantly, laulimalide retains its activity in the multi-drug resistant SKVLB-1 cell line, suggesting some difference in the mode of action compared to Taxol®. While paclitaxel is a substrate for P-glycoprotein export, laulimalide does not exhibit this behavior, suggesting new opportunities for chemotherapy.[5] As a result, laulimalide has received recent attention as an important target, resulting in four reports of total synthesis.[6] Additionally, a number of groups have reported the preparation of components related to this objective, and the formation of relevant analogs.[7]

Our aims for the synthesis of laulimalide were inspired by a series of ongoing investigations in our laboratories. Strategies to be explored through synthesis included asymmetric allylation,[8] chelation-controlled alkenylzincate addition,[9] asymmetric conjugate addition with Yamamoto organocopper reagents[10] and the allenylstannane Ferrier reaction.[11] Herein, we report our efforts for the synthesis of (−)-laulimalide.

Our approach towards the synthesis of laulimalide relies on coupling of allylsilane **2** and aldehyde **3** (Fig. 1). The synthesis began with the asymmetric conjugate addition reaction of the *N*-enoyloxazolidinone **4** with the allylcopper species formed under Yamamoto conditions[12] (Scheme 1). The high diastereofacial selectivity of this reaction established the chirality at C_{11} in **2**, and subsequent methanolysis with oxazolidinone cleavage and ozonolysis provided the pure aldehyde **5**.[10] Construction of the pyran ring was carried out by utilization of an asymmetric hetero-Diels–Alder cycloaddition of **5** and the Danishefsky diene[13] **6** in the presence of 5 mol% of Jacobsen catalyst **7**.[14] After some

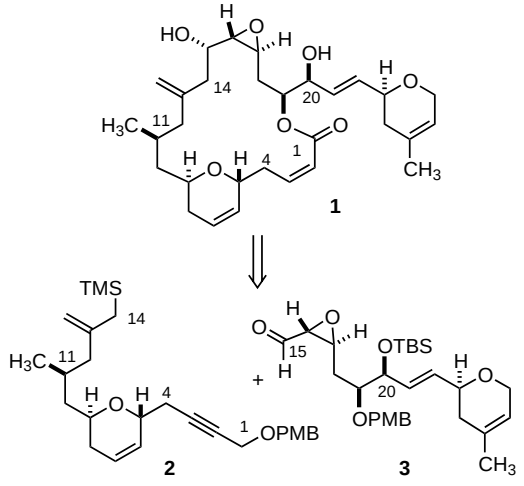

Figure 1. Retrosynthetic analysis.

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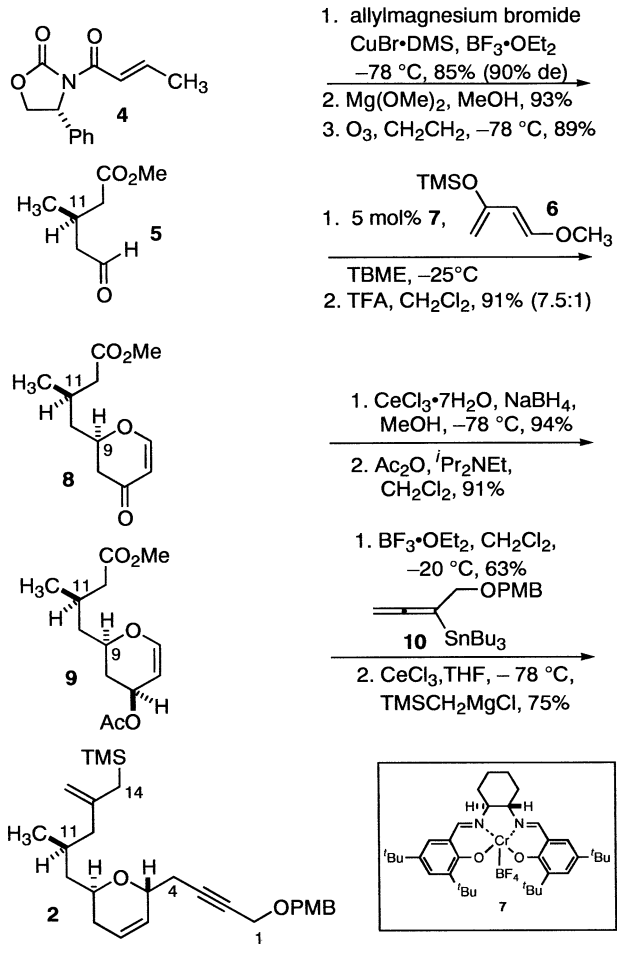
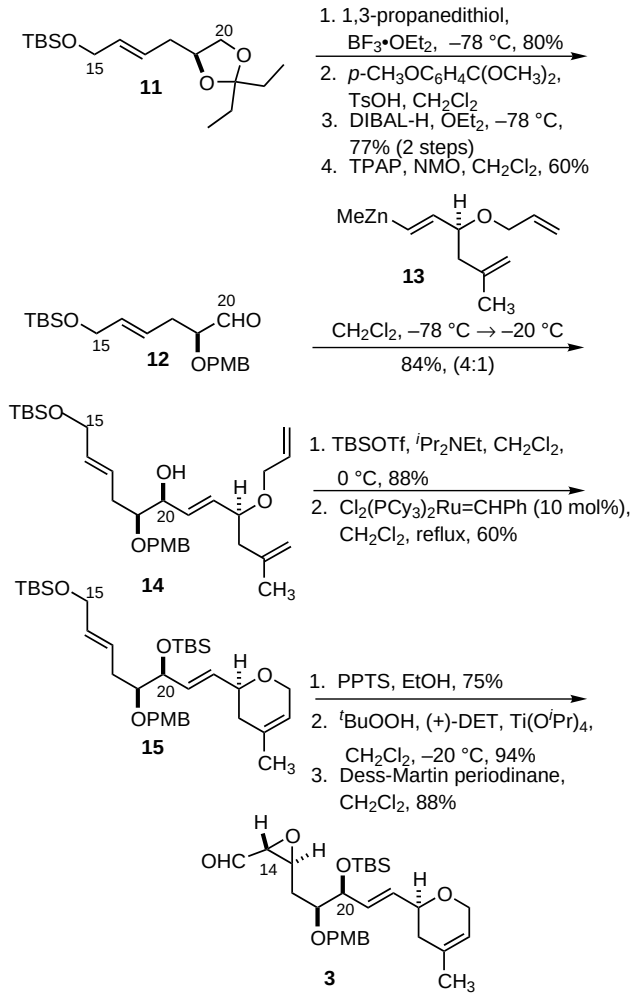


Scheme 1. Synthesis of the C_1–C_{14} component.

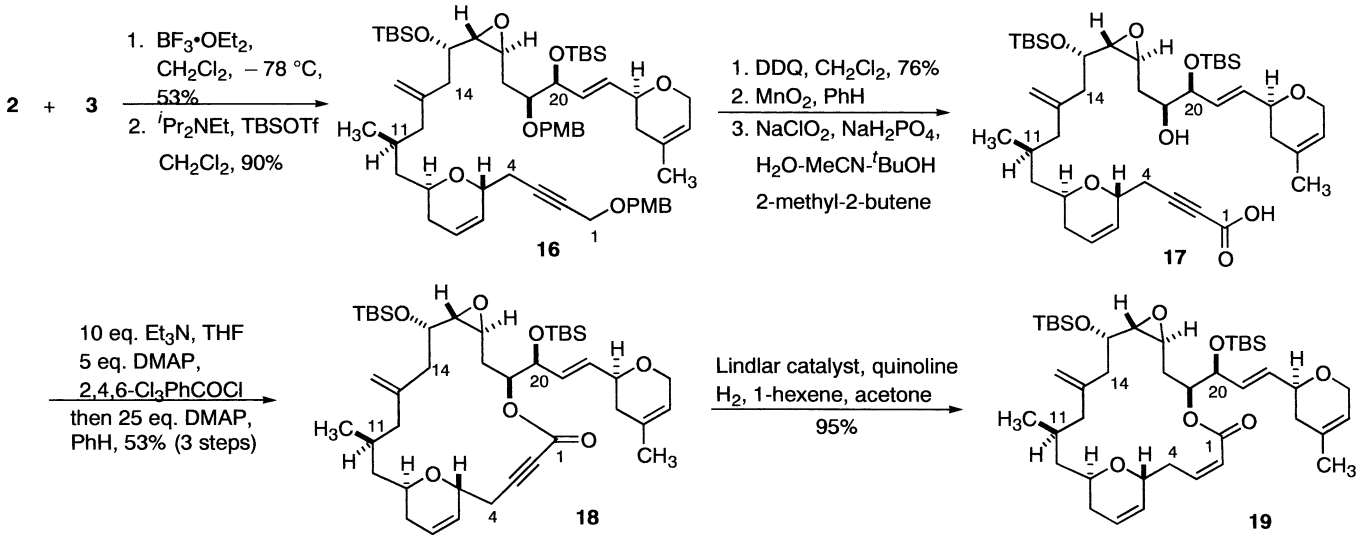
experimentation with the preparation of catalyst **7** and the Diels–Alder conditions, we reproducibly obtained the pyranone **8** in 91% yield as the major component of an inseparable mixture of two C_9 diastereomers (7.5:1 ratio).[15] While chromatographic separation of these isomers was not feasible on a preparative scale until later in the scheme, the mixture was used without difficulty in the ensuing steps.

A stereoselective Luche reduction and acetylation provided the equatorial acetate **9**. Efficient installation of the C_1–C_4 carbon component was achieved via the Lewis acid-catalyzed acetate solvolysis of **9** to form an intermediate oxocarbenium species for axial addition of the allenylstannane **10**.[16] The use of reactive allenylstannane **10** directly introduced the propargylic ether for subsequent oxidation to the desired acetylenic carboxylic acid. The stereochemical features of the *trans*-2,6-disubstituted dihydropyran ring were confirmed by the nOe observed in ^{1}H NMR studies of the C_4 propargylic methylene protons and the C_9 methine hydrogen. Preparation of the C_1–C_{14} component **2** was finalized through the cerium chloride mediated double addition of $TMSCH_2MgBr$,[17] which resulted in spontaneous Peterson elimination to provide the allylsilane moiety.[18]

The synthesis of the C_{15}–C_{28} component **3** as illustrated in Scheme 2 commenced with silyl ether **11**.[19] The hydrolysis of the ketal **11** posed problems due to the reactivity of the allylic silyl ether. By adapting a procedure which we had devised for studies of the total synthesis of (+)-phyllanthocin,[20] the Lewis acid-promoted ketal exchange at –78°C with 1,3-propanedithiol in methylene chloride led to the desired diol for conversion to optically active aldehyde **12**. Selective protection of the secondary alcohol was accomplished by ketalization with *p*-anisaldehyde dimethyl acetal and DIBAL reduction at –78°C with subsequent oxidation yielding **12**. Thus, our strategy for the formation of the vicinal (C_{19}–C_{20}) *syn*-diol of **1** was designed to effect a chelation-controlled nucleophilic addition of an *E*-alkenylzincate with the α-alkoxyaldehyde **12** as previously explored in these laboratories.[7b,9] However, the multitasking operations of formation of the *E*-alkenylhalide, lithium–halogen exchange, introduction of dimethylzinc and **12**, offset the advantages of higher diastereoselectivity. Utilization of a one-pot procedure, as devised by Wipf and coworkers,[21] employed hydrozirconation of a terminal alkyne[22] for in situ transmetallation with dimethylzinc to yield alkenylzinc species **13**, which underwent smooth addition to **12**. Preparative scale



Scheme 2. Synthesis of the C_{15}–C_{27} component.



Scheme 3. Completion of the synthesis.

reactions gave 84% yield of a mixture of C_{20} diastereomers **14** (4:1 ratio).[23,24] Following the silyl ether protection of **14**, a ring-closing metathesis was accomplished using Grubbs' catalyst.[25] At this point, the C_{20} diastereomers were conveniently separated by flash silica gel chromatography to yield pure **15**. Selective cleavage of the primary silyl ether, followed by Sharpless asymmetric epoxidation[26] and Dess–Martin oxidation provided the aldehyde **3** for coupling studies.

The completion of our synthesis of laulimalide, shown in Scheme 3, was proposed with the key element of a Felkin–Ahn addition of the allylic silane **2** to the enantiopure α,β-epoxyaldehyde **3**. The successful application of the allylation strategy, as well as the diastereofacial selectivity, was anticipated owing to our related studies leading to the syntheses of amphidinolides K and P.[8b,8c] In the event, the use of $BF_3{\cdot}OEt_2$ promoted the nucleophilic coupling of **2** and **3** at −78°C to yield a single homoallylic alcohol, which resulted in **16** upon protection as the *tert*-butyldimethylsilyl (TBS) ether.[27] Oxidative DDQ cleavage of the C_1 and C_{19} *para*-methoxybenzyl ethers gave a diol (76%), which was chemoselectively transformed to the desired *seco*-acid **17**. The crude carboxylic acid was used directly for Yamaguchi macrolactonization[28] to provide the macrocyclic acetylenic ester **18** in 53% overall yield (three steps) from the precursor diol. Lindlar reduction of **18** gave the desired 20-membered *Z*-enoate in 95% yield as characterized by the ^1H NMR data for the *cis*-vinylic hydrogens of the α,β-unsaturated carbonyl system. Attempts at removal of the TBS ethers (C_{15} and C_{20}) utilizing standard conditions proceeded with isomerization of the unsaturated lactone in addition to other side reactions. These problems have recently been resolved by Professor Michael Crimmins through the treatment of **19** with HF and Et_3N in CH_3CN, affording a total synthesis of **1**.[29] Thus, with the highly efficient preparation of the macrolactone **19**, we have delineated a convergent, efficient, and stereoselective route for the synthesis of the antitumor macrolide, (−)-laulimalide.[30]

In summary, we have described an efficient and highly convergent strategy for the synthesis of (−)-laulimalide. The key coupling of two fully functionalized components was accomplished via a stereocontrolled allylation strategy, which incorporated the C_{16}–C_{17} *trans*-epoxide at an early stage in the synthesis pathway. The carbon-Ferrier process has demonstrated the use of an allenic stannane, leading to the direct attachment of a propargyl substituent at C_1 of the dihydropyran nucleus. Our scheme provides flexibility and efficiency for the design of numerous derivatives of biological interest for continuing studies.[31]

Acknowledgements

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15. The diastereomeric ratio was determined by the integration of NMR signals for the diastereotopic pair of C_{10} methylene hydrogens in **8**. Chemical shifts for the major isomer **8** were observed at δ 1.91 and δ 1.41 whereas the minor (C_9) isomer exhibited a pair of multiplets at δ 1.79 and δ 1.61.
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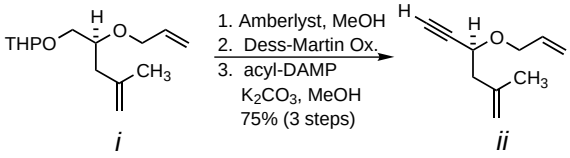
22. Our preparation of the requisite alkyne began with the copper-catalyzed oxirane opening of the known THP ether of (*R*)-(+)-glycidol (Aldrich) with subsequent *O*-alkylation with allyl bromide to provide ether (i) Methanolysis of the THP ether, Dess–Martin oxidation and reaction with the Bestmann acyl-DAMP reagent (Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521) directly provided alkyne (ii) In the course of our studies, a similar pathway was reported by Ghosh (see Ref. 7e).



i *ii*

23. Previous studies in our laboratories have correlated the relative stereochemical (*syn*- or *anti*-) assignments of these diol derivatives with observations of the ^{1}H-NMR chemical shift differences between the pair of diastereotopic benzylic protons on the C_{19} PMB ether. Typically, the *syn*-diastereomer was characterized as having a larger Δ_{AB} than the corresponding *anti*-diastereomer.
24. The ratio of diastereomeric alcohols was calculated by integration of the ^{1}H NMR signals for each of the diastereotopic methylene protons of the C_{19} PMB ether. Major: δ 4.62 (A of AB, $J_{AB}=10.9$ Hz) δ 4.43 (B of AB, $J_{AB}=10.9$ Hz). Minor: δ 4.57 (A of AB, $J_{AB}=11.2$ Hz), δ 4.50 (B of AB, $J_{AB}=11.2$ Hz).
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31. Note added in proof: After submission of this work, a related study has appeared: Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc*. **2002**, *124*, 4956.