Macrocyclization via Allyl Transfer: Total Synthesis of Laulimalide

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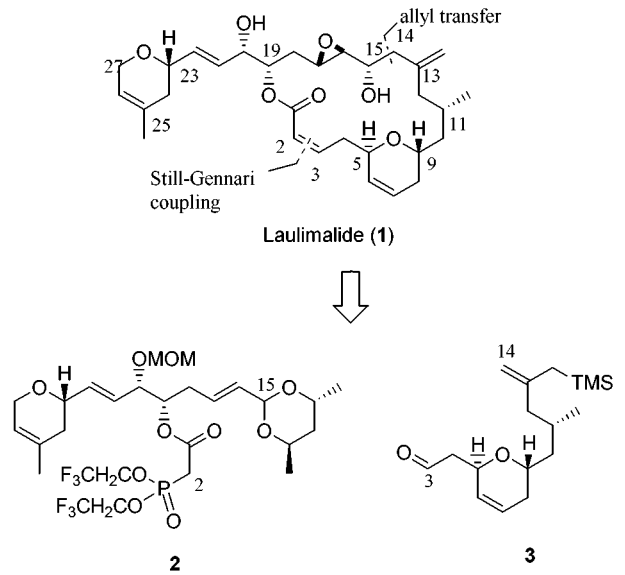
Laulimalide (**1**), a metabolite from various marine sponges,[1a−c] stabilizes microtubuli in eukaryotic cells and (along with other compounds, such as discodermolide,[2] eleutherobin,[3] and the epothilones[4]) has received much attention as a potential successor of paclitaxel[5] in the treatment of hitherto incurable tumors. A major advantage of **1** may be seen in its unusually high activity against multidrug resistant cell lines.[6] To date, despite a number of different approaches to individual fragments,[7a−j] only two total syntheses have been completed: one by Ghosh and Wang[8] and the second by Mulzer and Öhler.[9] Both approaches were not entirely stereocontrolled and made use of well-established macrocylization protocols (i.e. Yamaguchi lactonization and Horner-type olefination).

In this communication we describe a novel approach to **1** that features a silicon-mediated allyl transfer macrocyclization as the key step. Retrosynthetically the carbon skeleton of **1** was to be assembled from fragments **2** and **3** by generating the *Z*-2,3-olefin first and closing the ring by C14,15-bond formation. The introduction of the 16,17-epoxide was to be performed at the end via the regio- and stereoselective Sharpless epoxidation described earlier.[9]

The synthesis started from commercially available (*R*) ethyl hydrogen 3-methylglutarate **4**. which was elaborated (Scheme 1) into methyl ketone **13** in 10 steps with an overall yield of 57%. The RCM strategy for closing the dihydropyran ring ,which has been used previously by us[7e,f] and subsequently by others,[7d,h,i] again proved to be the method of choice.

For the introduction of the allyl silane moiety, **13** was converted into the enolate under kinetic control (KHMDS 1.5 equiv) and treated with $PhNTf_2$ (1.6 equiv)[10] to afford enol triflate **14** as a single isomer. Next, following Kuwajioma's protocol,[11] compound



14 was subjected to the reaction with $TMSCH_2MgBr$ (6 equiv) in the presence of $Pd(PPh_3)_4$ (30 mol %) to give, after 1 h, an unseparable 1:1 mixture of compound **15** and its $\Delta^{12,13}$-isomers. Quite obviously, the large amount of the catalyst and the long reaction time have led to isomerization. The similarity of the described protocol and the Stille coupling[12] prompted us to perform the reaction in the presence of LiCl. We were pleased to observe that in the presence of 5 equiv of LiCl and 5 mol % of $Pd(PPh_3)_4$, triflate **14** reacted with $TMSCH_2MgBr$ (2 equiv) to give, after 10 min, pure allyl silane **15** in 96% yield. Removal of the TES group (K_2CO_3-MeOH) followed by Dess−Martin oxidation afforded aldehyde **3**, which was thus available from **4** in 13 steps and 33% overall yield.

The synthesis of fragment **2** (Scheme 2) began from our previous intermediate **16**,[7f] which was oxidized to the aldehyde **17**. Ketalization with (*R*,*R*)-(+)-2,4-pentanediol[13] afforded acetal **18** in 98% yield. Removal of the TBDPS group and esterification of the corresponding alcohol **19** with $(CF_3CH_2O)_2P(O)CH_2COCl$ (1.6 equiv) provided phosphonate **2**.

Compound **2** was deprotonated (KHMDS, THF) and treated with aldehyde **3** to give pure *Z*-enoate **20a** in 82% yield.

The cyclization of **20a** was performed in 4×10^{-4} M CH_2Cl_2 solution with 2 equiv of $EtAlCl_2$[14] and provided macrolide **21** as a single isomer[15] in 82% yield. On monitoring the cyclization by TLC a transient intermediate was observed that was isolated and identified as olefin **20b**. We thus reasoned that the conversion of **20a** into **21** might, in reality, proceed *via* two parallel pathways. One is the direct cyclization of allyl silane **20a**. The second pathway involves first a moisture-induced protodesilylation of **20a** to **20b** which then undergoes the cyclization via an ene reaction. Indeed, when we subjected **20b** directly to the macrocyclization conditions, **21** was obtained in 56% yield, along with 30% of starting material. In light of these findings the cyclization was repeated under absolutely anhydrous conditions, now to proceed without any protodesilylation in 85% yield. To the best of our

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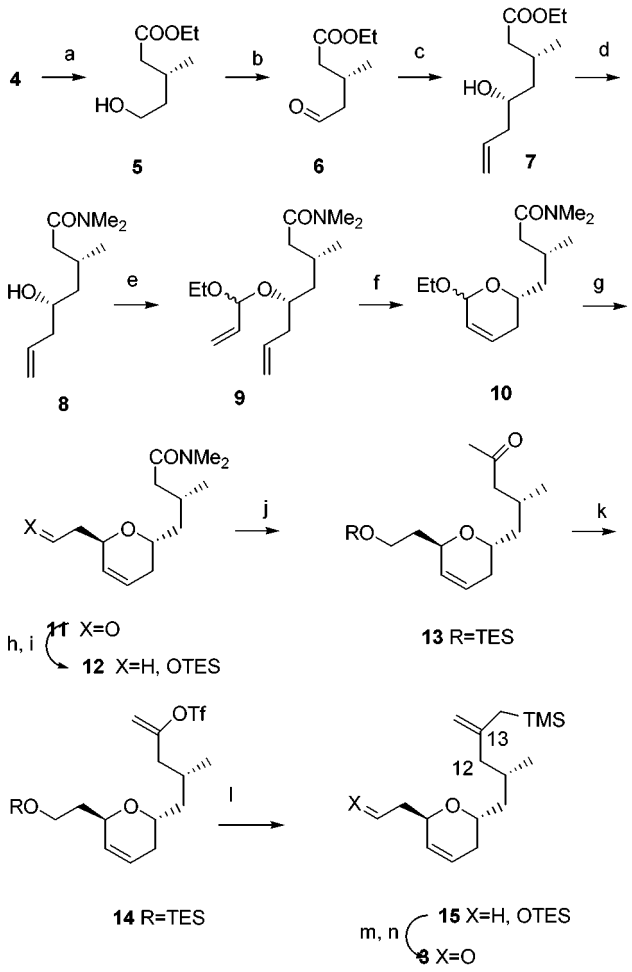
Scheme 1[a]

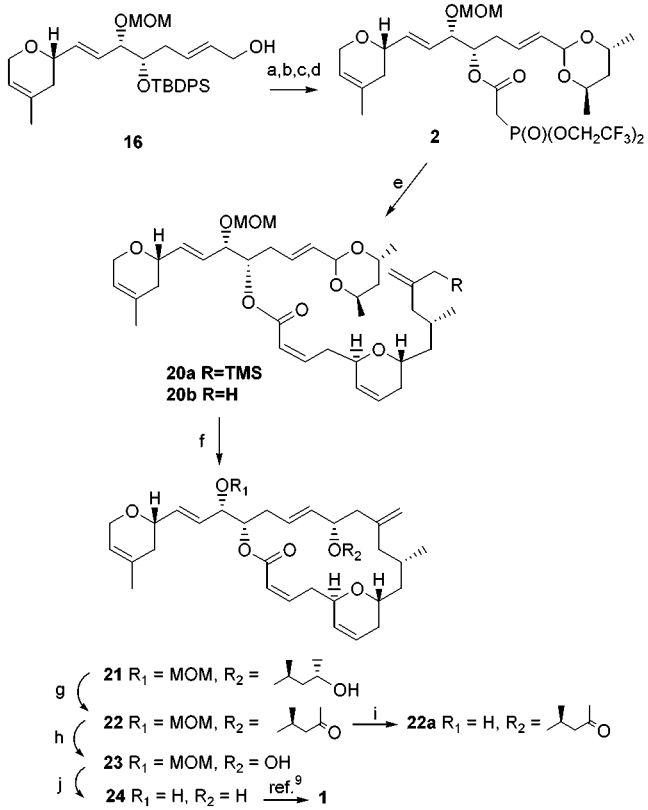


[a] Conditions: (a) $BH_3{\cdot}Me_2S$, 99%; (b) Dess−Martin oxidation, 96%; (c) (−)-Ipc_2B-allyl, 87%; (d) Et_2NH, EtOH, 98%; (e) acrolein-diethylacetal, TsOH, toluene, 92%; (f) 4 mol % Grubbs catalyst, CH_2Cl_2, 87%; (g) TBSO−CH═CH_2, $LiClO_4$, 92%; (h) $NaBH_4$, MeOH, 0 °C, 99%; (i) TESCl, pyridine, 92%; (j) MeLi, Et_2O, −75 °C, 90%; (k) KHMDS, $C_6H_5NTf_2$, THF, 80%; (l) 5 mol % $Pd(PPh_3)_4$, LiCl (5 equiv), $TMSCH_2MgBr$ (2 equiv), Et_2O, 96%; (m) K_2CO_3, MeOH, 0 °C, 98%, (n) Dess−Martin oxidation 90%.

knowledge, this is the first macrolide formation via allyl transfer, under conditions so mild that they do not induce the 2,3-*Z*−*E*-isomerization which has been so painfully experienced in other syntheses.[7j,8,9]

The removal of the protective groups R^1 and R^2 required some care. After oxidation of **21** to ketone **22** it turned out that R^1 and R^2 are orthogonal even under acidic conditions, i.e., **22** can be converted into **22a** and **23**, respectively. However, on attempting to transform **22a** into **24** with pTsOH complete *Z*−*E*-isomerization of the 2,3-double bond was observed. On the other hand, **23** could be smoothly deprotected to generate 16,17-deoxy-laulimalide **24**, which was identical (TLC and spectral data) with the compound obtained previously.[9] The conversion of **24** into **1** was performed via SAE ((+)DIPT, *t*BuOOH, $Ti(OiPr)_4$ in CH_2Cl_2) as described earlier.[9]

Scheme 2[a]



[a] Conditions: (a) Dess−Martin oxidation, 96%; (b) (*R*,*R*)-(+)-2,4-pentanediol (1.8 equiv), montmorillonite K-10, toluene, 98%, (c) TBAF, THF, 82%; (d) $(CF_3CH_2O)_2P(O)CH_2COCl$ (1.6 equiv), DMAP, −78 → 0 °C, 98%; (e) KHMDS, −78 °C, 40 min, then **3**, 1.2 equiv, 20 min, 82%; (f) $EtAlCl_2$ (2 equiv), −50 → 0 °C, 82%; (g) Dess−Martin oxidation, 90%; (h) TsOH, $CHCl_3$, 80%; (i) TFA, −78 °C, CH_2Cl_2, 90%; (j) Me_2BBr, −78 °C, 20 min, 96%.

In conclusion, the first fully stereocontrolled synthesis of laulimalide has been described. The synthesis is highly convergent by assembling the molecular skeleton from two comparably sized fragments **2** and **3** both of which are available from simple chiral starting materials. The longest linear sequence lists 19 steps with an overall yield of 21%. Novel features are the macrocyclization *via* competing allyl transfer type reactions and the orthogonality of two hydroxyl protecting groups, namely MOM and 4-oxo-pent-2-yl, respectively, which hopefully will allow an easy differentiation of the two allylic alcohol moieties. At any rate, the modular structure of our synthesis will make it applicable to a suitably wide variety of derivatives which will be used to clarify the pharmacophoric sections of the molecule.

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Supporting Information Available: Spectroscopic data and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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