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Total synthesis of the antitumor agent (–)-laulimalide

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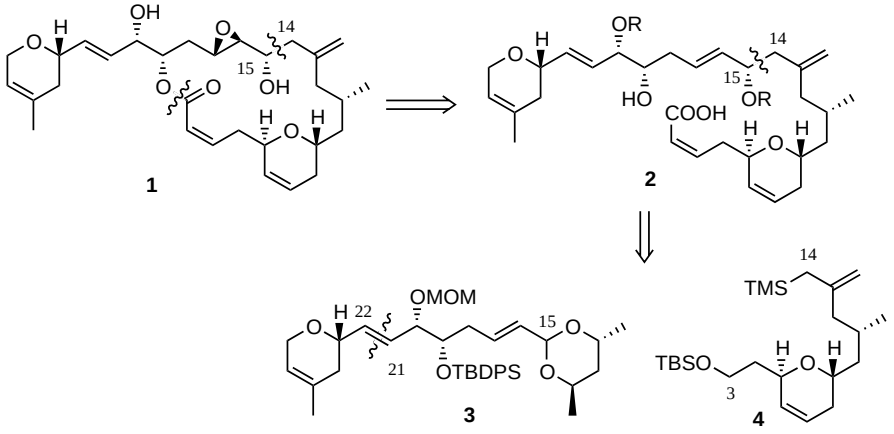
Abstract—A stereocontrolled synthesis of the title compound is described. Key steps are an allylsilane addition to a chiral acetal as the major coupling step and a Yamaguchi macrolactonization for ring closure.

The antimitotic macrolide laulimalide (**1**), also known as fijianolide B, was isolated from several sponges (*Cacospongia mycofijiensis*,[1a] *Hyattella* sp.,[1b] *Fasciospongia rimosa*[1c]) and shows high cytotoxicity against several NCI cell lines. The IC_{50} value of **1** against the KB cell line is 15 ng/mL and, additionally, the compound maintains a high level of potency against the multidrug resistant cell line SKVLB-1 ($IC_{50}=1.2$ μM).[2] Recently **1** was identified as sharing the same mechanism of action as the anticancer drug Taxol™ (paclitaxel). Apart from its potent microtubule-stabilizing properties **1** also inhibits the *P*-glycoprotein, which is responsible for multiple-drug resistance in tumor cells. The unique structural features and the restricted natural supply of **1** have triggered synthetic activities world-wide,[3] resulting in the first total synthesis by the Ghosh group[4a,b] followed by two syntheses from our laboratory[4c,e] and one by Paterson and coworkers.[4d]

Herein we report an approach to **1** via a Yamaguchi macrolactonization of *seco* acid **2**, the carbon skeleton of which was assembled by an addition of allylsilane **4** to the chiral acetal **3** (Scheme 1). Building blocks **3** and **4** have been prepared from (*S*)-α-hydroxybutyrolactone and ethyl (*S*)-2-methyl-3-hydroxypropionate, respectively.

The synthesis of **3** starts with TBDPS protected (*S*)-α-hydroxybutyrolactone **8** (Scheme 2) which was reacted with the lithium salt of diethyl methanephosphonate. Treatment with a second equivalent of base, quenching with TESCl and aqueous work-up delivered the phosphonate **6**.[5]



Scheme 1.

Keywords: marine metabolites; antitumor compounds; macrolactonization; allylsilane addition; chiral acetal.
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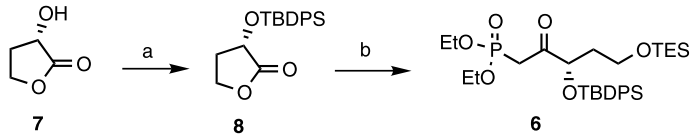
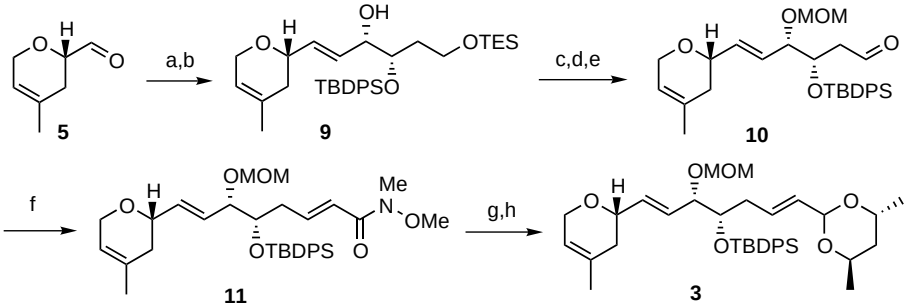


Scheme 2. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMF, rt (93%). (b) (i) $(EtO)_2P(O)CH_3$, BuLi, THF, −78°C then **8**, (ii) LDA, TESCl, THF, −78°C to rt, (iii) NH_4Cl, H_2O (79%).

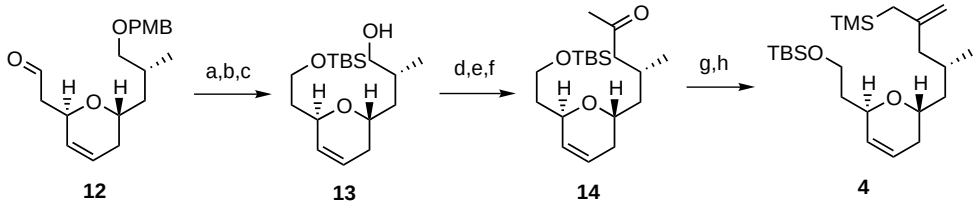
Phosphonate **6** was used in a Horner–Wadsworth–Emmons (HWE)-olefination with the known aldehyde **5** (Scheme 3).[3d] 1,2-Reduction of the resulting ketone under Luche conditions[6] delivered the desired *syn* isomer **9** almost exclusively (>20:1). Protection of the secondary alcohol as MOM ether, deprotection of the TES ether and Parikh–Doering oxidation[7] yielded aldehyde **10**, which was used in another HWE-olefination to produce the Weinreb amide **11**. Reduction to the unsaturated aldehyde and acetal formation with (*R*,*R*)-(−)-2,4-pentandiol[8] completed the synthesis of the C15–C27 fragment **3**.

For the synthesis of allylsilane **4** (Scheme 4), the known aldehyde **12**, readily available from (*S*)-2-methyl-3-hydroxypropionate in eight steps,[3c] was reduced to the alcohol and protected as the TBS ether. Removal of the PMB group yielded the alcohol **13**, which was elaborated into methyl ketone **14**. Deprotonation under kinetic control, treatment of the resulting enolate with $PhNTf_2$[9] to generate the enol triflate and palladium catalyzed coupling with $TMSCH_2MgCl$[10] in the presence of LiCl[4e] delivered allyl silane **4**.

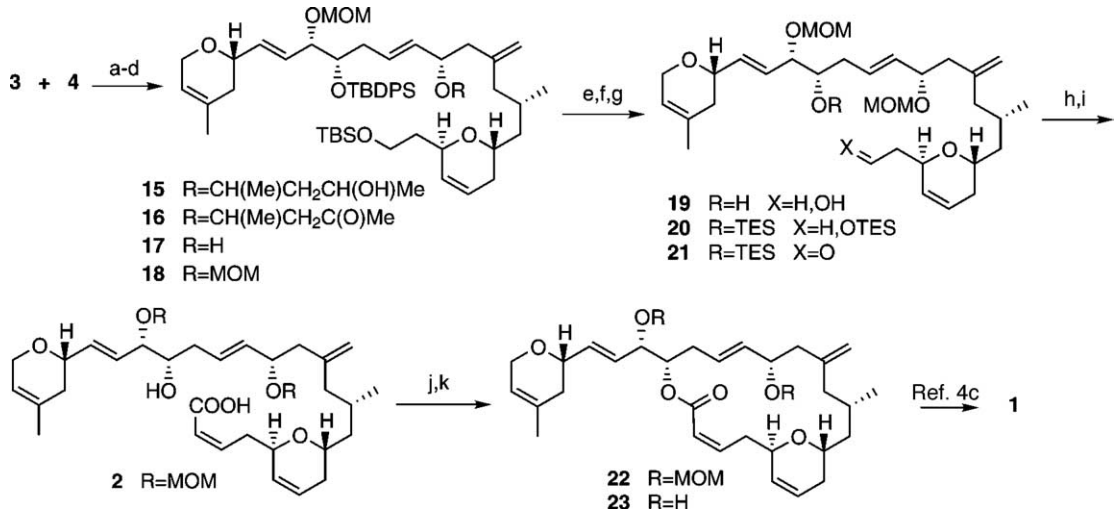
Addition of allyl silane **4** to the chiral acetal **3** was performed with several Lewis acids ($SnCl_4$/DMF, $EtAlCl_2$, $TiCl_4$/TEA) (Scheme 5); the best results were obtained with TEA-treated $TiCl_4$ to generate diastereomerically pure adduct **15** in 57% yield. After Dess–Martin oxidation of alcohol **15** to methyl ketone **16** the chiral auxiliary was removed in a retro-hetero-Michael reaction to form alcohol **17** which was protected as the MOM ether. Both the TBS and the TBDPS-protective groups were exchanged for TES, and selective Swern oxidation of the primary TES ether[11] yielded aldehyde **21** which was submitted to an Ando–Horner–Emmons olefination[12] with (diphenoxy-phosphoryl)-acetic acid 2-trimethylsilanyl-ethyl ester. Treatment of the resulting (*Z*)-enoate with TBAF yielded the *seco* acid **22** which was cyclized under Yamaguchi conditions to macrolactone **23** as a mixture of *Z* and *E* isomer (*Z*/*E*=1/2.7, separation of *Z*-isomer). Deprotection of the MOM ethers and selective Sharpless epoxidation as described earlier[4c] completed the synthesis of **1**, which was identical (^1H and ^{13}C NMR spectra, HPLC R_f) spectra with the compound described previously.[1,4a,c,d,f]



Scheme 3. *Reagents and conditions*: (a) **6**, LiCl, TEA, THF, 0°C to rt (81%). (b) $NaBH_4$, $CeCl_3$, MeOH, −78°C (94%). (c) MOMCl, DIEA, TBAI, DMF, rt. (d) *p*TsOH, MeOH, rt (85% over two steps). (e) Py·SO_3, DMSO, TEA, DCM, rt (95%). (f) $(EtO)_2P(O)CH_2C(O)N(OMe)Me$, NaH, THF, rt (92%). (g) DIBAH, THF, −78°C (89%). (h) (*R*,*R*)-(−)-2,4-Pentandiol, montmorillonite K-10, toluene, 40°C (99%).



Scheme 4. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0°C (95%). (b) TBSCl, imidazole, DMF, rt (90%). (c) DDQ, DCM/H_2O (10/1), rt (86%). (d) *p*TsCl, TEA, DMAP, DCM, rt. (e) NaCN, DMSO, 80°C (87% over two steps). (f) MeLi, Et_2O, 0°C (96%). (g) (i) KHMDS, THF, −100°C then **14**, (ii) $PhNTf_2$, THF, −100 to rt (81%). (h) $TMSCH_2MgCl$, LiCl, $Pd(PPh_3)_4$, Et_2O, rt (93%).



Scheme 5. *Reagents and conditions*: (a) $TiCl_4$, TEA, DCM, −60 to −20°C (57%). (b) DMP, $NaHCO_3$, DCM, rt (79%). (c) K_2CO_3, MeOH, rt (89%). (d) MOMCl, DIEA, TBAI, DMF, rt (97%). (e) TBAF, THF, rt (96%). (f) TESCl, pyridine, rt (89%). (g) $(COCl)_2$, DMSO, DCM, TEA, −50°C to rt (90%). (h) $(PhO)_2P(O)CH_2C(O)OCH_2CH_2TMS$, KHMDS, 18-crown-6, THF, −78°C (80%). (i) TBAF, THF, rt (89%). (j) (i) 2,4,6-Trichlorbenzoyl chloride, DIEA, THF, benzene, (ii) DMAP, benzene (60%).

In conclusion, we have described a total synthesis of laulimalide which is highly convergent and stereocontrolled except for the macrocyclization. The longest linear sequence is 27 steps with an overall yield of 2.1%.

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