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Synthesis of 8-(*S*)-methoxy-11-desmethyl laulimalide: a novel laulimalide analogue

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Abstract—A strategy is outlined which enables preparation of novel laulimalide analogues at C.8 and C.11. A representative analogue, 8-(*S*)-methoxy-11-desmethyl laulimalide, was synthesized via this route.

The marine natural product (−)-laulimalide (**1**, Fig. 1) was first isolated in 1988 from several sources of marine sponge and shown to be highly cytotoxic in a number of human cancer cell lines.[1] Later it was reported that **1** induces microtubule polymerization and stabilization similar to paclitaxel, but retains activity in a P-glycoprotein (PgP) over-expressing multidrug resistant cell line.[2] It was recently reported that laulimalide binds to a different site of the tubulin polymer than most other microtubule stabilizers and retains activity against cell lines containing mutations in the β-tubulin gene.[3] These reports have generated an enormous amount of excitement about the therapeutic potential of this natural product and as a result, there has been a surge of synthetic efforts toward **1** resulting in a number of total syntheses.[4,5] Despite these synthetic efforts, there have been few reports of biological evaluation of laulimalide analogues to date.[3,5,6]

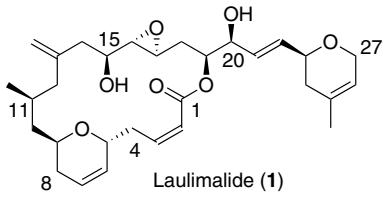

Figure 1. The marine natural product (−)-laulimalide with carbon numbering.

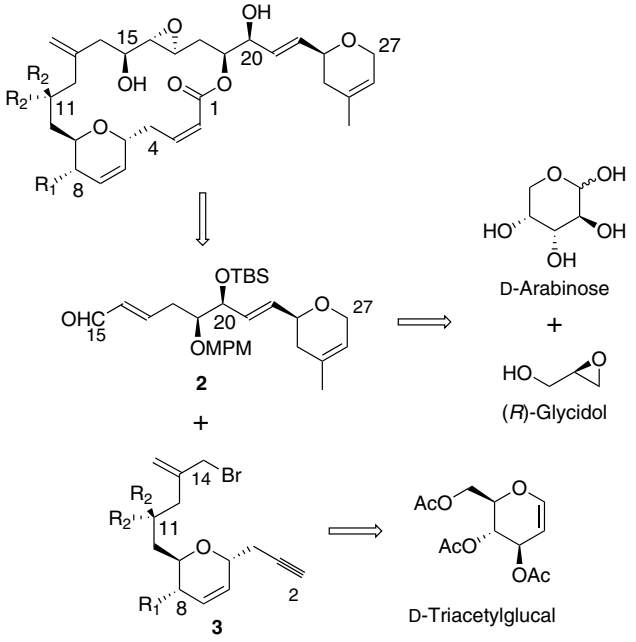

Figure 2. Strategy to access analogues at C.8 and C.11.

We recently reported a total synthesis of laulimalide and a series of analogues modified at C.2–C.3, C.15–C.17, and C.20.[5] In order to further probe the SAR of **1**, we wanted to explore changes in the C.8–C.11 region (Fig. 2). Paterson et al. recently reported the molecular modeling studies and syntheses of C.11 desmethyl laulimalide analogues.[6c] Modeling predicted little perturbation to the conformations of the C.1–C.4 and

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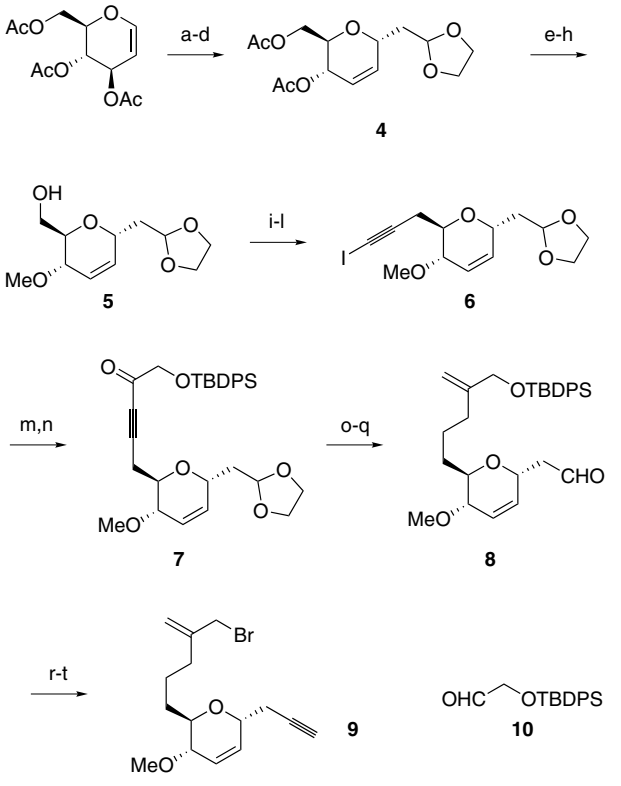
C.15–C.20 regions by removal of the C.11 stereocenter. We wished to extend this concept by rigidifying the conformation of the C.5–C.9 dihydropyran. Examination of the crystal structure of **1**,[1d] indicates the 2,6-*trans* substituents of the lower dihydropyran ring adopt a pseudo-axial and pseudo-equatorial relationship for C.4 and C.10, respectively. It was hypothesized that a α-substituent at C.8 would reinforce the conformation of the lower pyran and consequently the macrocycle. Thus a C.8 (*S*)-methoxy C.11 desmethyl analogue was targeted.

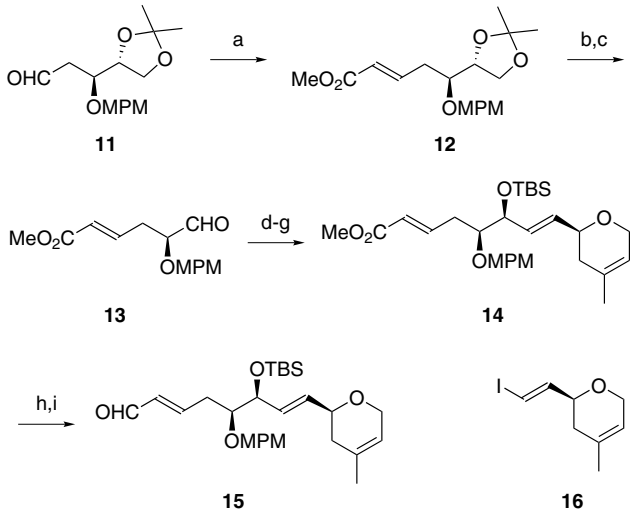
The requisite C.2–C.14 fragment was synthesized as outlined in Scheme 1. Triacetyl glucal underwent a carbon Ferrier reaction with allyltrimethylsilane to produce the allyl addition product with the 2,6 substituents exclusively *trans*.[7] The allyl addition product was converted to the crystalline dioxolane intermediate (**4**) in 50% overall yield through a standard sequence of dihydroxylation, diol cleavage,[8] and protection of the resultant aldehyde. Hydrolysis of the acetates, monoprotection of the primary alcohol as a TBS ether, and methylation of the secondary alcohol provided **5** following fluoride removal of the TBS.[9] The primary alcohol of **5** was homologated to the alkynyl iodide **6** via displacement of the corresponding triflate under carefully controlled conditions.[10] Alkynyl iodide **6** underwent efficient coupling with aldehyde **10**[11] to produce the ynone (**7**) after oxidation. The ynone **7** cleanly underwent a double Stryker-type reduction[12] to produce the corresponding ketone, which was methylenated under typical conditions. Selective removal of the dioxolane in the presence of the TBDPS ether was accomplished using 80% aqueous HOAc to produce aldehyde **8**. Corey–Fuchs protocol of aldehyde **8** produced the terminal alkyne. Removal of the silyl ether and conversion to the allylic bromide produced the C.2–C.14 fragment **9**.



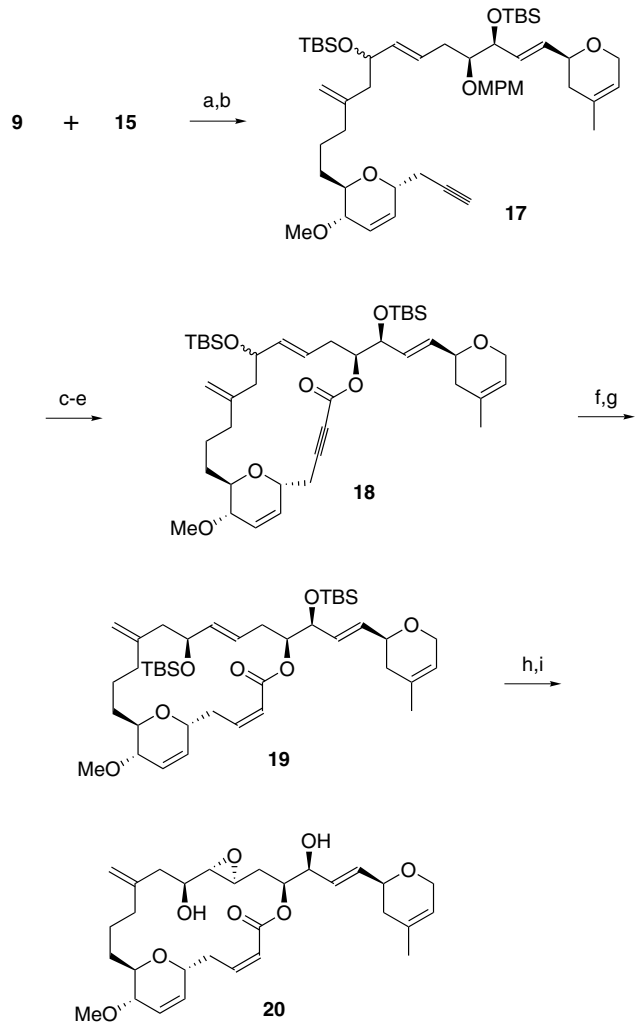
Scheme 1. Reagents and conditions: (a) TFA, TMS allyl silane, CH_3CN, 0 °C; (b) K_2OsO_4, NMO, THF/H_2O (2/1); (c) $NaIO_4$, CH_2Cl_2, aq $NaHCO_3$; (d) *p*-TsOH, $(CH_2OH)_2$, PhH, reflux, $-H_2O$ (50%); (e) K_2CO_3, MeOH; (f) TBSCl, imidazole, DMF, 10 °C; (g) NaH, MeI, DMF; (h) TBAF, THF (75%); (i) Tf_2O, 2,6-di-*t*-butylpyridine, CH_2Cl_2, −50 °C; (j) TMSCCLi, HMPA, THF, −78 °C (80%); (k) Cs_2CO_3, MeOH; (l) $AgNO_3$, NIS, acetone (70%); (m) 0.1% $NiCl_2/CrCl_2$, **10**, THF; (n) TPAP, NMO, CH_2Cl_2 (80%); (o) $[(Ph_3P)CuH]_6$ (0.6 M equiv), $PhCH_3$, trace H_2O (65%); (p) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C (90%); (q) 80% aq HOAc, 60 °C (50%); (r) CBr_4, Ph_3P, CH_2Cl_2, −78 °C; *n*-BuLi, THF, −78 °C; (s) TBAF, THF; (t) Ph_3P, NBS, CH_2Cl_2, 0 °C (70%).

The C.15–C.27 fragment was prepared as outlined in Scheme 2. The known aldehyde **11**,[13] available in six steps from D-arabinose, underwent Horner–Wadsworth–Emmons reaction to produce the α,β-unsaturated ester in a ~4:1 mixture of *E*:*Z* stereoisomers. During the course of this work, we found a convenient procedure for improving the ratio to almost exclusively *E* by treating crude **12** with catalytic Bu_3P in CH_3CN at 60 °C overnight.[14] Removal of the acetonide and periodate cleavage of the resultant diol produced the aldehyde **13**. The aldehyde was efficiently coupled with the known[15] vinyl iodide **16** under $NiCl_2/CrCl_2$ mediated conditions to give a ~1:2 α:β-mixture of diastereomers. Oxidation followed by reduction with L-Selectride®[16] produced the desired stereoisomer,[17] which was protected as the TBS ether **14**. DIBAL-H reduction of the methyl ester followed by Swern oxidation produced the enal coupling partner **15**.

Indium mediated coupling of **9** and **15** produced a ~1:1 mixture of diastereomeric alcohols at C.15 which were



Scheme 2. Reagents and conditions: (a) (i) $(MeO)_2POCH_2CO_2Me$, NaH, THF, 0 °C, (ii) Bu_3P (cat.), CH_3CN, 60 °C (85%); (b) 1 M HCl/THF (1/1); (c) $NaIO_4$, THF/H_2O (1/1), 0 °C (70%); (d) 0.1% $NiCl_2/CrCl_2$, **16**, DMSO (60%); (e) Dess–Martin periodane, CH_2Cl_2; (f) L-Selectride®, THF, −78 °C (50%); (g) TBSOTf, imidazole, DMF (90%); (h) DIBAL, CH_2Cl_2, −78 °C (80%); (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (85%).



Scheme 3. Reagents and conditions: (a) indium, THF/H_2O (3/1), HCl (cat.) (65%); (b) TBSOTf, DMAP, pyridine (80%); (c) (i) *n*-BuLi, THF, −78 °C, (ii) CO_2 (gas); (d) DDQ, CH_2Cl_2/H_2O (2/1) (70%); (e) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene (45%); (f) H_2, Lindlar cat., quinoline, hexane/CH_2Cl_2 (3/1) (80%); (g) HPLC; (h) H_2SiF_6, CH_3CN; (i) (+)-DIPT, Ti(O*i*Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −15 °C (50%).

protected as the TBS ethers (Scheme 3). Carboxylation of the alkyne of **17** and removal of the MPM group allowed for macrolactonization under Yamaguchi-type conditions[4b] to produce **18**. Lindlar reduction and chiral HPLC (Chiralpak® AD) separation of the C.15 diastereomers produced the *Z* enoate **19**. Deprotection and Sharpless epoxidation produced the 8-(*S*)-methoxy-11-desmethyl laulimalide (**20**).[18]

The route outlined above contains sufficient flexibility to provide additional analogues at C.8 and C.11 to further probe the structure–activity relationships of laulimalide analogues. For example, cuprate additions to the ynone **7** (Scheme 1) should provide access to various substituents at C.11 such as *gem* di-methyl analogues.[19]

In summary, the total synthesis of a novel analogue, 8-(*S*)-methoxy-11desmethyl laulimalide, has been accomplished. The key C.2–C.14 fragment is readily prepared from triacetyl glucal. The strategy provides the flexibility to access additional analogues modified in the C.8 and C.11 regions of laulimalide to further probe the SAR. Efforts in this area will be reported in due course.

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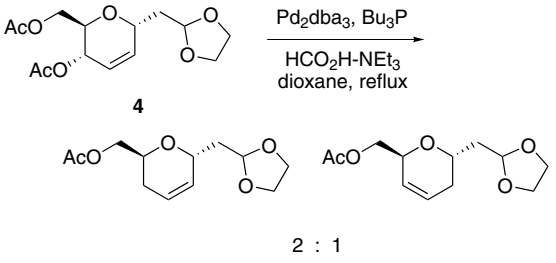
9. Intermediate **4** could be deacetoxylated to the laulimalide dihydropyran under standard conditions (Pd_2dba_3, Bu_3P, Hco_2H–NEt_3), albeit as a ~2:1 mixture favoring the desired isomer.



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