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Synthesis and biological evaluation of a *des*-dihydropyran laulimalide analog

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ABSTRACT

The preparation of a novel simplified Laulimalide analog via a highly convergent and efficient route and its biological evaluation are presented. The outlined route enables the synthesis of C_5–C_9 modified analog **2** and uses Julia–Kocienski olefination for fragment assembly and a regioselective Yamaguchi macrolactonization for ring closure. This strategy should be suitable for the generation of various new C_5–C_9 *des*-dihydropyran laulimalide derivatives for further SAR studies.

The marine macrolide laulimalide (**1**, Fig. 1) was contemporaneously isolated back in 1988 by two different groups from various marine sources.[1a,b] It proved to be highly cytotoxic in the low nanomolar range and induces microtubule polymerization similar to the frontline antitumor drug paclitaxel.[2]

The outstanding biological properties were an incentive for total synthesis since natural sources are extremely limited. In fact, different groups[3] have achieved total syntheses of **1** and recently also the total synthesis of its congeners isolaulimalide[1] and neolaulimalide[1c] was reported.[3m,4] In recent years the search for simplified biologically active and more stable analogs of **1** has been pursued with high intensity to identify an optimal clinical candidate.[5] Unfortunately this endeavor has not proven successful so far.

Evaluation of previous results shows that the modification of the C_{23}–C_{27} side chain led to dramatically less active analogs.[5e,g,i] Similarly, recently discovered natural members of the laulimalide family with side chain variations exhibit significantly reduced activity.[1d] Several other modifications led to inactive compounds and so far, only *des*-epoxy laulimalide,[3h,k,5a] C_{20}-OMe laulimalide,[3k,5a] C_{20}-OAc laulimalide,[3k] C_{15}-OAc laulimalide,[3k] and 11-*des*-methyl laulimalide[5b,f] retain activity even though they are 10 to 40 times less active than **1**.[3,5]

In Figure 2 it is shown which sections of **1** have been addressed by various research groups in order to find active, simplified derivatives. Since the C_5–C_9 region was not modified to generate simplified analogs so far, we (as well as other groups)[6] targeted our efforts at this area. We now present a strategy for replacing the C_5–C_9 *trans*-dihydropyran moiety by less complex motifs and illustrate this by the synthesis and biological evaluation of analog **2** (Fig. 1).

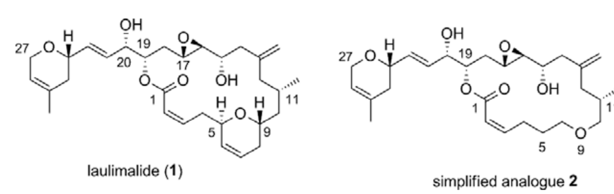

Figure 1. Structure of laulimalide (**1**) and the new analog **2**.

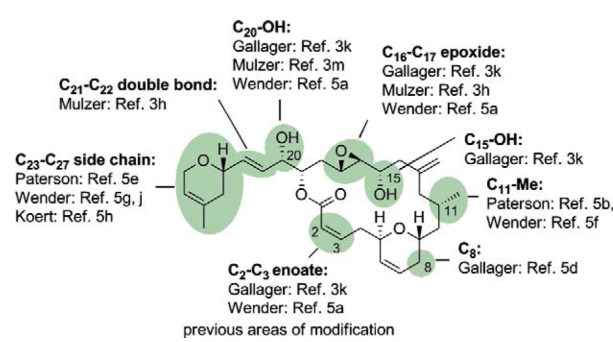

Figure 2. Overview of previously modified areas of **1**.

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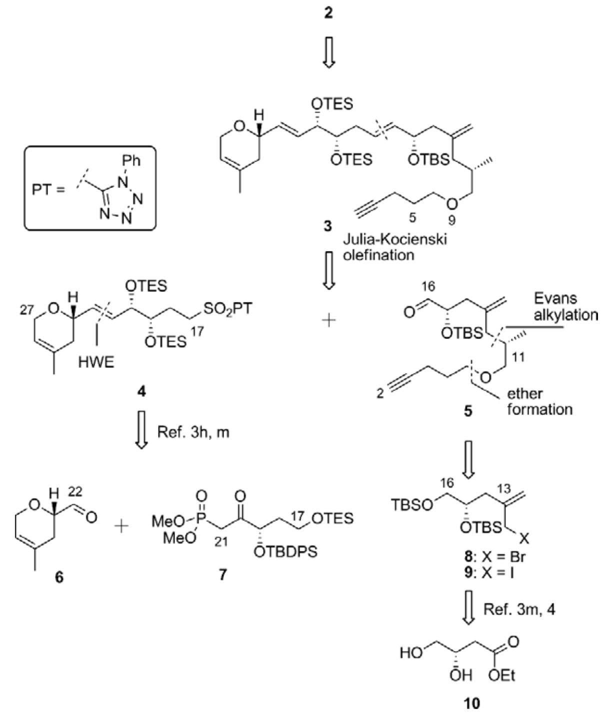
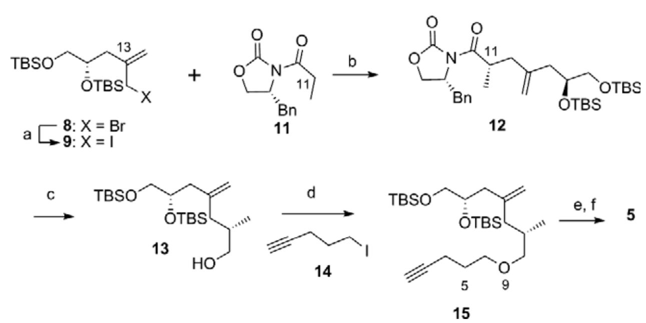


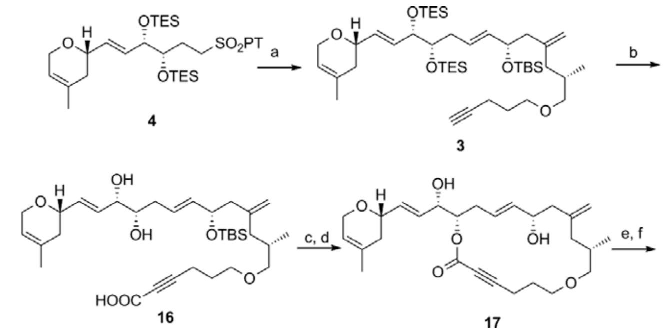
Scheme 1. Retrosynthesis. *Abbreviations*: HWE, Horner–Wadsworth–Emmons olefination; PT, 1-phenyl-1*H*-terazol; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl.



Scheme 2. Synthesis of aldehyde fragment **5**. Reagents and conditions: (a) NaI, acetone, reflux, 2 h (98%); (b) NaHMDS, THF, −78 to −30 °C (85%); (c) $LiBH_4$, H_2O, Et_2O, 0 °C (97%); (d) NaH (2 equiv), DMF, 0 °C, then 14 (2 equiv), rt, 14 h (55%); (e) NH_4F, MeOH, rt, 30 h (90%, 68% conversion); (f) IBX, MeCN, reflux, 15 min (98%). *Abbreviations*: Bn, benzyl; DMF, dimethylformamide; IBX, 2-iodoxybenzoic acid; NaHMDS, sodium bis(trimethylsilyl)amide; THF, tetrahydrofuran.

Compound **2** was selected, because it fits nicely into our established approach.[3m] In fact, compared to our recent synthesis of **1**,[3m] the number of steps can be reduced by five including the costly RCM and Brown allylation steps.[7] In Scheme 1 we present our retrosynthesis which utilizes our sulfone **4**.[3m,4] Aldehyde **5** is new and should be available from allylic bromide **8**[3m,4] or iodine **9**.

The synthesis of **5** (Scheme 2) started from allylic bromide **8** which was obtained from the commercially available diol **10** in four steps via a Kulinkovich reaction and subsequent cyclopropyl-allyl rearrangement.[3m,4] Evans alkylation of oxazolidinone **11** with bromide **8** gave a yield of 77% at 79% (>20:1 dr) conversion. The yield was increased to 85% by using iodide **9**, obtained from **8** by a Finkelstein reaction in almost quantitative yield. Reductive cleavage of the auxiliary delivered alcohol **13**. The ether formation to form fragment **15** was accomplished in acceptable yields of 55% by treatment of alcohol **13** with an excess of NaH and reaction with iodide **14**. Selective cleavage of the primary TBS-ether with NH_4F and final oxidation with IBX delivered fragment **5** in only six steps from **8**.



Scheme 3. Synthesis of analog **2**. Reagents and conditions. (a) KHMDS, THF, −78 °C, then **5** (78%); (b) *n*BuLi, CO_2, then 7% HF·pyridine, THF, −78 °C to rt (82%); (c) 2,4,6-$Cl_3C_6H_3C(O)Cl$, NEt_3, DMAP, benzene, rt (68%); (d) 35% HF·pyridine, THF, 0 °C to rt (93%); (e) H_2, Lindlar cat., quinoline, EtOAc/cyclohexene, rt (87%); (f) Ti(O*i*Pr)$_4$, (+) DIPT, *t*BuOOH, 4 Å MS, CH_2Cl_2, −20 °C (67%). *Abbreviations:* DIPT, diisopropyl tartrate; KHMDS, potassium bis(trimethylsilyl)amide; MS = molecular sieves.

Table 1
Inhibition of proliferation[a]

Cell line compound	MCF-7	PC-3 M IC_{50} (nM)	HCT-116
Laulimalide (**1**)	11.6 ± 0.5	5.9 ± 0.3	7.8 ± 0.8
Analog **2**	>10,000	>10,000	>10,000

[a] Cells were treated with varying concentrations of the compounds for 72 h. The values represent the means of three experiments ± SD.

Fragment **5** was coupled with sulfone fragment **4** by a completely *E*-selective Julia–Kocienski[8] olefination (no *Z*-product was observed) to deliver the key fragment **3** in 78% yield (Scheme 3). *Seco* acid **16** was prepared in a one pot-reaction: first the terminal alkyne was converted to the acid by treatment of **3** with *n*BuLi and quenching the anion with CO_2; then HF·pyridine was added to cleave both TES-ethers selectively. Macrolactonization under Yamaguchi conditions[9] gave the 20-membered macrolide exclusively and in good yields.[3f] Cleavage of the remaining TBS-protecting group furnished compound **17**. Finally Lindlar reduction to the labile *Z*-enoate was followed by selective Sharpless epoxidation (>20:1 dr) employing the established protocol to deliver the desired analog **2**.[10,3c,h]

Compound **2** was tested for its effect on the proliferation of selected tumor cell lines using laulimalide (**1**) as a standard. Unfortunately, **2** showed no cytotoxic activity (Table 1) and had no effect in a tubulin polymerization assay as well.

In summary we described an effective, convergent, and completely stereoselective route to the simplified laulimalide analog **2**. This route in principle can be extended to a variety of related C_5–C_9 modified compounds for further SAR studies. A first biological evaluation of **2** showed that the activity is lost when the C_5–C_9 dihydropyran moiety is removed, which suggests that it is part of the pharmacophore region. Nevertheless more analogs have to be synthesized to clarify the role of this specific region of laulimalide (**1**).

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10. *Compound* **2**: ^{1}H NMR: (600 MHz, $CDCl_3$) δ = 6.33 (ddd, *J* = 11.3, 9.4, 5.2 Hz, 1H), 5.89 (ddd, *J* = 15.7, 5.4, 1.3 Hz, 1H), 5.85–5.82 (m, 1H), 5.75 (ddd, *J* = 15.6, 5.9, 1.4 Hz, 1H), 5.42 (br s, 1H), 5.16 (ddd, *J* = 11.0, 5.4, 2.1 Hz, 1H), 4.89 (br s, 1H), 4.88 (br s, 1H), 4.23–4.20 (m, 1H), 4.19–4.16 (m, 2H), 4.06–4.02 (m, 1H), 3.76–3.72 (m, 1H), 3.45–3.40 (m, 2H), 3.34 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.15–3.06 (m, 2H), 2.97 (ddd, *J* = 7.3, 5.1, 2.3 Hz, 1H), 2.84 (dd, *J* = 4.3, 2.2 Hz, 1H), 2.43–2.37 (m, 2H), 2.26 (dd, *J* = 14.4, 2.6 Hz, 1H), 2.20–2.17 (m, 1H), 2.15–2.10 (m, 2H), 2.07–2.00 (m, 2H); 1.95–1.86 (m, 3H), 1.85–1.78 (m, 1H), 1.69 (br s, 3H), 1.67–1.58 (m, 2H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ = 167.5, 151.8, 144.4, 134.2, 131.3, 128.7, 119.8, 119.1, 114.9, 76.2, 73.6, 73.1, 72.6, 69.8, 68.1, 65.6, 60.7, 54.1, 41.1, 38.4, 35.7, 33.9, 31.2, 26.6, 23.0, 16.3, 16.0; IR (cm^{-1}): 2925, 2852, 1717, 1261, 1020, 875; $[\alpha]_D$ −51.2 (*c* 0.08, $CHCl_3$); HR-MS (ESI) calcd for $C_{27}H_{40}O_7Na$ $[M+Na]^+$: 499.2672, found: 499.2684.