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Synthesis of the C1–C12-dihydropyran segment of the antitumor agent laulimalide by ring closing metathesis

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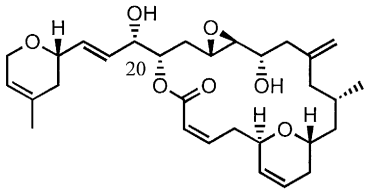
Abstract

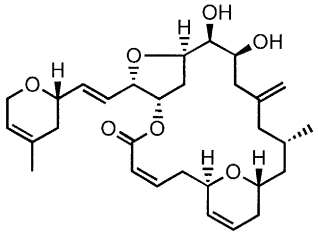
A stereocontrolled synthesis of the C1–C12 fragment **3** of laulimalide utilizing a ring closing metathesis with Grubbs' catalyst as the key step is described.

Keywords: marine metabolites; antitumor compounds; metathesis; dihydropyran.

In the development of novel antitumor drugs recent attention has been focused on microtubule stabilizing agents, the most popular ones being paclitaxel (Taxol™)[1] and the epothilones.[2] More recently several other antitumor agents showing a similar mode of action have been identified, among which laulimalide (**1**) is distinguished by a particularly high multidrug resistance (MDR).[3] Compound **1**, also known as fijianolide B, has been isolated, together with isolaulimalide (**2**), from the marine sponges *Cacospongia mycofijiensis*,[4] *Hyattella* sp.,[5] and *Fasciospongia rimosa*[6] and shows a strong cytotoxicity (IC_{50}=15 ng/mL) against the KB cell line, whereas **2**, which is easily obtained from **1** under acidic conditions[5] by nucleophilic attack of the C-20 hydroxyl group on the epoxide, shows much weaker cytotoxicity (IC_{50}>200 ng/mL).



1



2

So far no total synthesis of **1** has been reported, although major fragments have been prepared by the groups of Ghosh[7] and Nishiyama.[8,9] Our retrosynthetic concept is shown in Scheme 1 and features CC connections between C21 and C20 (Nozaki Kishi addition[10]) and between C13 and C12 (sulfone

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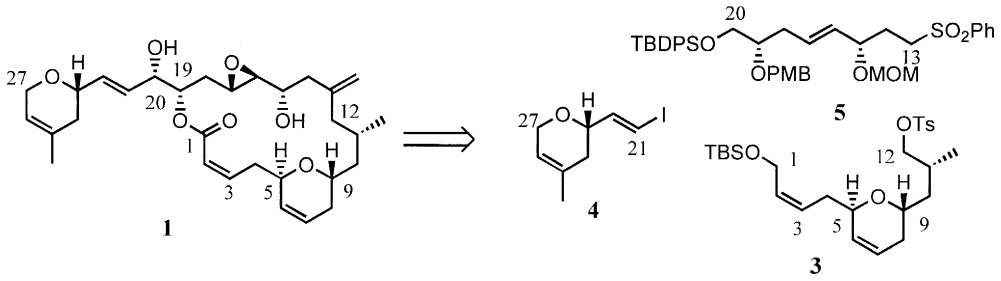
anion–tosylate alkylation). In this letter we describe a novel approach to the C1–C12 fragment **3**, which is centered around a ring closing metathesis (RCM) reaction[11] to form the crucial dihydropyran ring.

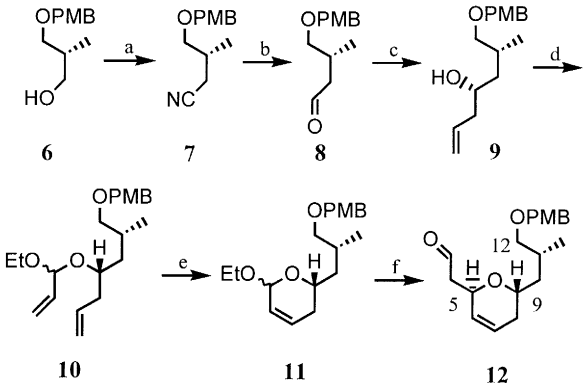


Scheme 1.

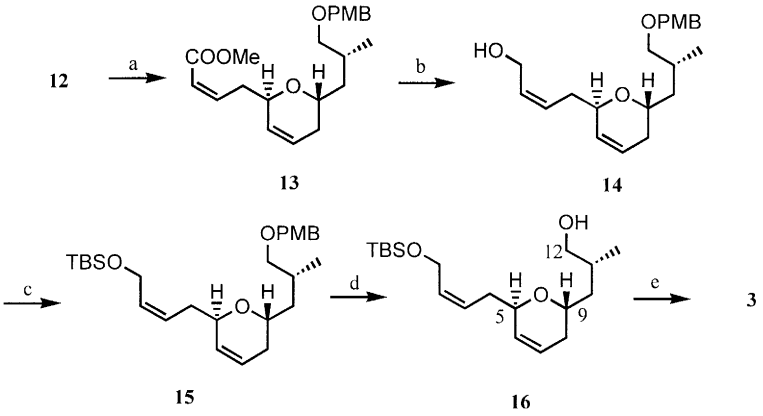
The known[12] alcohol **6**, readily prepared from commercially available ethyl (*S*)-2-methyl-3-hydroxybutyrate, was tosylated and converted into cyanide **7**, which, after reduction with DIBAH, yielded aldehyde **8** (Scheme 2). Diastereocontrolled allylation was first attempted according to the standard procedure by Brown[13] via in situ formation of the allylborane. The homoallylic alcohol **9** was produced in reasonable yield but with unsatisfactory diastereoselectivity (5:1). Application of the Duthaler Hafner reagent[14] increased the diastereoselectivity to >98:2, but even with a large excess of allyl titanium reagent (2 equiv.) the conversion was not complete. Finally, a modified Brown allylation[15] under 'salt-free conditions' was applied and gave good diastereoselectivity (20:1) and excellent chemical yield (90%). Transketalization of alcohol **9** with acrolein diethyl acetal, when carried out as described by Crimmins,[16] resulted in the formation of a 1:1 mixture of the diene **10** and starting material, which had to be recycled twice to give **10** in a combined yield of 82%. In an improved modification, the reaction was carried out in toluene under reduced pressure. Ethanol was removed azeotropically to achieve full conversion and 84% yield of **10** after workup. The key step in our synthesis, a ring closing metathesis (RCM) reaction,[17] proceeded smoothly with a minimum amount (1–2%) of Grubbs' catalyst to produce the desired dihydropyran **11** from **10** in 94% yield. Introduction of the C-3–C-4 appendage was first attempted with montmorillonite K-10[18] and the commercially available vinyloxytrimethylsilane to give aldehyde **12** in 65% yield. If the readily available[19] vinyloxy-*tert*-butyldimethylsilane was used the yield was increased to 81%. Application of other Lewis acids such as lithium perchlorate (3 M in ethyl acetate)[20] or $TiCl_2(OiPr)_2$[21] led to similar yields. Because of the simple handling and the low cost montmorillonite K-10 was the reagent of choice. In all experiments only the desired 1,3-*trans*-disubstituted dihydropyran was observed, whose relative configuration was determined by NOESY-NMR methods.[22]

The aldehyde **12** was submitted to a Still–Gennari–Horner olefination[23] with bis(2,2,2-trifluoroethyl)-phosphonoacetic acid methyl ester[24] (Scheme 3). Enoate **13** was obtained with excellent chemical yield (97%) but moderate *Z*:*E* selectivity (3:1). However, the two isomers could easily be separated by flash chromatography to yield 73% of *Z*-**13**, whose reduction to the alcohol **14** proceeded smoothly with DIBAH in 86% yield. After TBS protection of the 1-OH group the 12-PMB group was removed with DDQ to give the alcohol **16**, which was converted into the tosylate **3**, which now is ready for coupling with the C-13–C-20 fragment **5**. No isomerization of the double bond was observed in this sequence.

In conclusion, we have described a novel and efficient approach to the laulimalide fragment **3**[25] (12 steps, 8% overall yield). Further investigations towards the total synthesis of **1** are under way in our laboratory.



Scheme 2. Reagents and conditions: (a) (i) TsCl, pyridine, rt; (ii) NaCN, DMSO, 80°C (80%); (b) DIBAH, THF, −78°C to rt (80%); (c) (−)-$Ipc_2BCH_2CH{=}CH_2$, Et_2O, −100°C (90%); (d) $CH_2{=}CHCH(OEt)_2$, PPTS, toluene, 80 mbar, 35°C (84%); (e) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, reflux (94%); (f) $CH_2{=}CHOTBS$, montmorillonite K-10, CH_2Cl_2, rt (81%)



Scheme 3. Reagents and conditions: (a) $(CF_3CH_2O)_2P(O)CH_2COOMe$, KHMDS, 18-crown-6, THF, −78°C, then **12** (73%); (b) DIBAH, THF, −78°C to rt (86%); (c) TBSCl, imidazole, DMF, rt (78%); (d) DDQ, CH_2Cl_2:H_2O (10:1), rt (81%); (e) *p*TsCl, pyridine, rt (60%)

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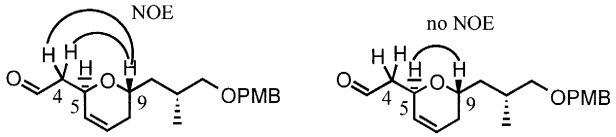
22. A strong NOE between H4a and H9 and between H4b and H9 was observed, whereas no NOE between H5 and H9 occurred, which was expected for 1,3-*trans*-disubstituted dihydropyrans. For NOE of a similar structure see also: Ref. 21



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25. Compound **3**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.06 (s, 6H); 0.89 (s, 9H); 0.92 (d, *J*=6.7 Hz, 3H); 1.16 (m, 1H); 1.51 (m, 1H); 1.89 (m, 2H); 2.04 (m, 1H); 2.28 (bt, *J*=7.0 Hz, 2H); 2.44 (s, 3H); 3.69 (m, 1H); 3.83 (dd, *J*=6.4 Hz, *J*=9.1 Hz, 1H); 3.96 (dd, *J*=5.1 Hz, *J*=9.1 Hz, 1H); 4.09 (m, 1H); 4.20 (d, *J*=5.7 Hz, 2H); 5.46 (m, 1H); 5.58 (m, 1H); 5.63 (m, 1H); 5.79 (m, 1H); 7.34 (d, *J*=8.1 Hz, 2H); 7.78 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ=−4.7; 16.6; 22.1; 23.3; 26.4; 29.8; 31.5; 32.9; 38.8; 59.9; 65.5; 72.6; 76.2; 124.7; 126.8; 128.4; 129.4; 129.6; 130.2; 131.9; 132.1.