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Synthesis of the C_1-C_{16} Fragment of the Marine Toxin, Laulimalide

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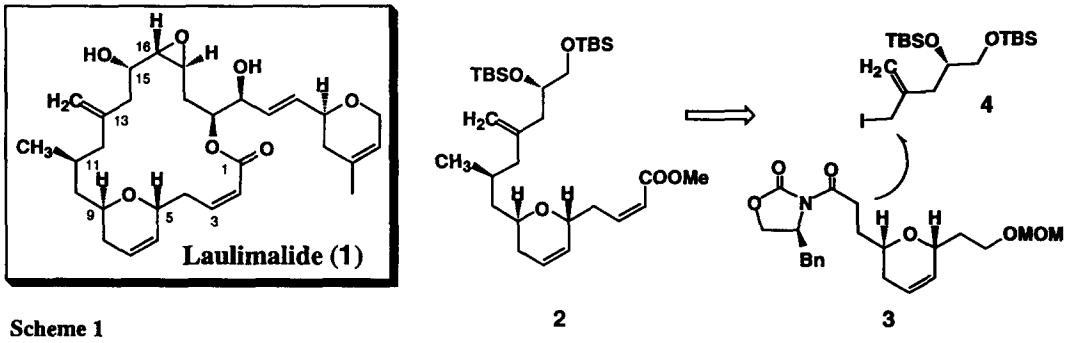
Abstract: The synthesis of the C_1-C_{16} fragment of laulimalide **1**, isolated from an Indonesian sponge, is described. The key step in the synthesis of this fragment involves an asymmetric induction by the Evans chiral oxazolidinone protocol. © 1997 Elsevier Science Ltd.

Laulimalide **1**, isolated from an Indonesian sponge, *Hyattella* sp., is the first 20-membered ring lactone to be observed from a marine sponge.[1] In addition to its potent cytotoxicity (IC_{50}=15 ng/mL) against the KB cell line,[1b] this unique macrolide **1** has been a quite attractive target for synthetic chemists. Efficient total synthesis might be expected to promote detailed evaluation of its biological activities which has hitherto been precluded by its limited availability from natural sources. A recent report pertinent to the X-ray crystallographic analysis which established the absolute configuration of **1**[2] prompted us to publish our synthetic investigation of laulimalide. We disclose herein the synthesis of the C_1 - C_{16} fragment **2** of this molecule.[3]



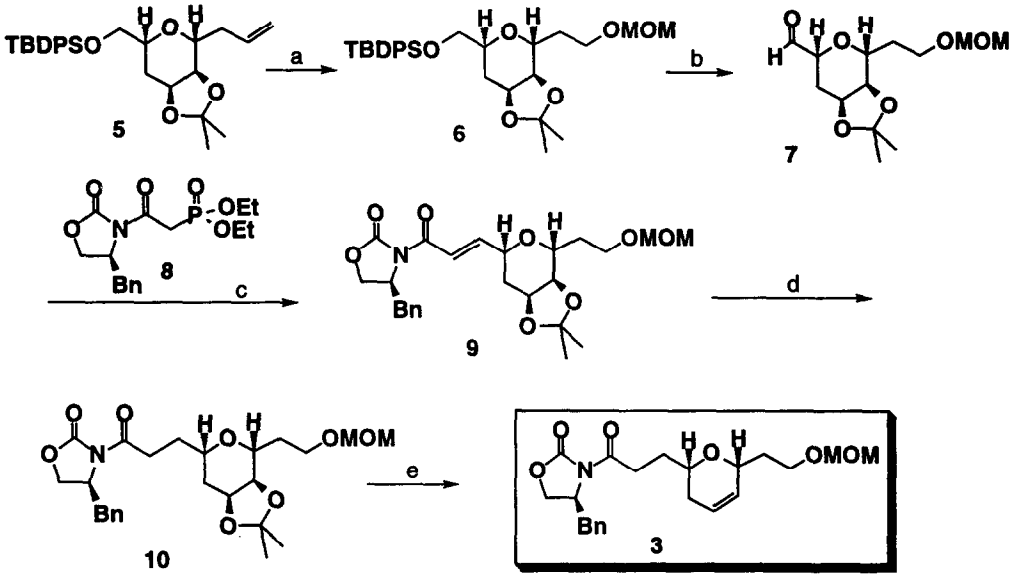
Scheme 1

As can be seen in Scheme 1, the retrosynthetic analysis indicated that the C_1 - C_{16} fragment **2** would be constructed by alkylation of the C_3 - C_{11} segment **3** with allyl iodide **4**. The stereochemistry newly introduced at the C_{11} position would be controlled by the Evans oxazolidinone protocol.

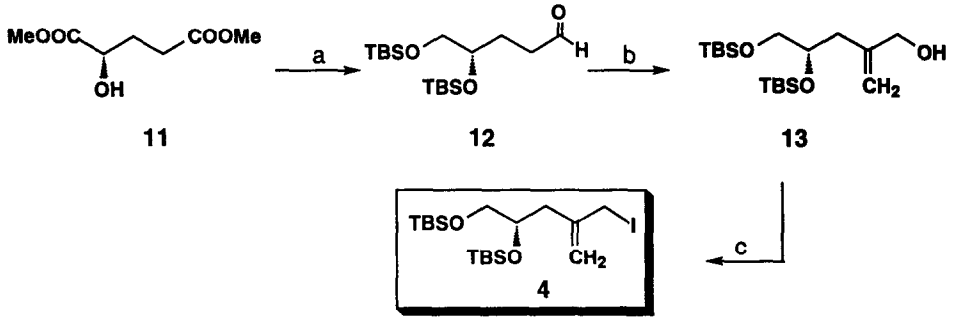
Synthesis of the C_3-C_{11} fragment 3.

Synthesis of the key intermediate **3** was started from ozonolysis of the known tetrahydropyran **5**, readily prepared from D-mannose.[4] Protection of the resulting primary alcohol as a methoxymethyl group afforded fully protected derivative **6**. Removal of a TBDPS group, followed by oxidation, gave the corresponding

aldehyde **7** in good yield. The Horner-Emmons reaction of this aldehyde with the chiral phosphonate **8**[5] afforded the *E* -olefin **9** in moderate yield. Olefin **9** was then hydrogenolized in the presence of a Wilkinson catalyst to give saturated ester **10**. After selective deprotection of an isopropylidene group, the resulting glycol underwent olefination to the key intermediate **3** in good yield.



Scheme 2. *Reagents*: a) i. O_3, MeOH, -78 °C, then $NaBH_4$ (72%); ii. MOMCl, $^iPr_2NEt$, CH_2Cl_2 (99%). b) i. TBAF, THF (95%); ii. Dess-Martin periodinane, CH_2Cl_2 (90%). c) i. **8**, NaH; **7**, THF, 0 °C (53%). d) H_2, $(PPh_3)_3RhCl$, EtOAc (75%). e) i. *p*TsOH, MeOH (99%); ii.$(Imid)_2C=S$, toluene, reflux; iii. $P(OEt)_3$, reflux (75% in 2 steps).



Scheme 3. *Reagents*: a) i. BH_3·Me_2S, $NaBH_4$/THF, 0 °C (97%); ii. TBSCl, imidazole/DMF (88%); iii. $LiAlH_4$/THF, 0 °C (91%); iv. SO_3·Pyr, DMSO, TEA/CH_2Cl_2 (84%). b) i. $CH_2=N^+(CH_3)_2I^-$, TEA/CH_2Cl_2 (84%); ii. $LiAlH_4$/THF (87%). c) i. MsCl, TEA/CH_2Cl_2; ii. NaI/Acetone (90%).

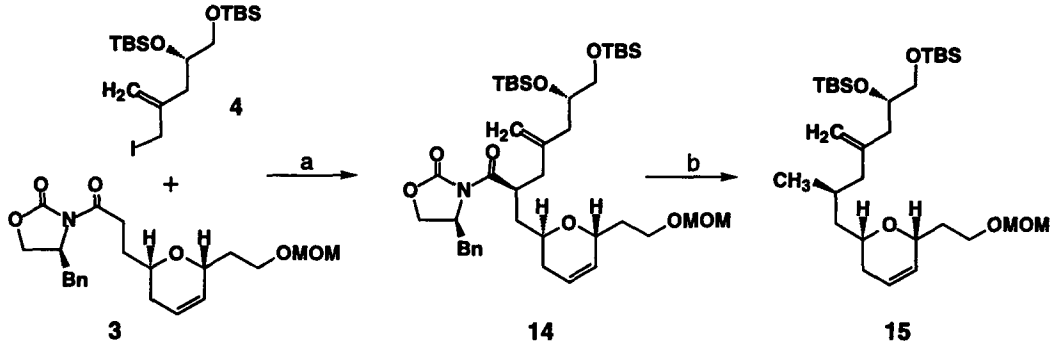
Synthesis of the C_{12}-C_{16} fragment

The synthesis of the coupling partner **4** was commenced with regioselective reduction of the C_{16} position of **11** derived from L-glutamic acid.[6] After protection of the resulting diol as TBS ethers, reduction of the C_{12} methyl

ester followed by oxidation afforded aldehyde **12**. Reaction of aldehyde **12** with Eschenmoser's reagent[7] in the presence of Et_3N provided an enal which, on reduction with $LiAlH_4$, afforded alcohol **13**. Halogenation of a primary alcohol via mesyl ester gave the desired allyl iodide **4**.

Coupling of the key intermediates 3 and 4.

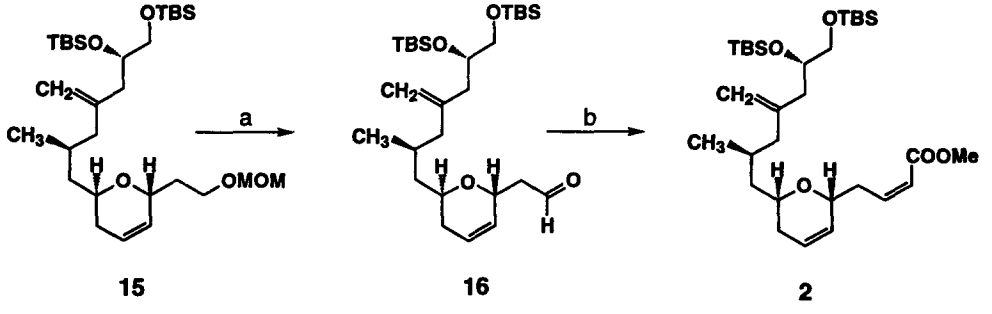
As mentioned in the retrosynthetic analysis, coupling of allyl iodide **4** with lithium enolate of **3** provided alkylated adduct **14**[8] in 60% yield. It was noteworthy that **14** was the sole alkylated adduct observed in the reaction mixture. Transformation of a carboximide to a methyl group, including removal of the chiral oxazolidinone auxiliary, was successfully conducted in three steps.



Scheme 4. *Reagents*: a) **3**, LDA, **4**/THF -78 °C to -20 °C (83%). b) i. $LiBH_4$/EtOH-H_2O (5:1) (93%); ii. MsCl, TEA/CH_2Cl_2; (97%); iii. $LiEt_3BH$/THF (85%).

Completion of the synthesis of the C_1-C_{16} fragment 2.

The final stage of this synthesis is a carbon-chain homologation of **15** to introduce the corresponding C_1 - C_2 segment. Thus, deprotection of the C_3 methoxymethyl group, followed by oxidation, afforded aldehyde **16**, which was treated with the Wittig reagent under the Mukaiyama - Suzuki conditions[9] to give the desired *Z* - olefin **2**.[10]



Scheme 5. *Reagents*: a) i. $TiCl_4$, CH_2Cl_2, -78 °C (79%); ii. SO_3·Pyr, DMSO, TEA, CH_2Cl_2 (80%). b) Ph_3P=CHCOOMe, MeOH (37%) (ref. 11).

We have successfully synthesized the C_1 - C_{16} fragment **2** of laulimalide, and further investigation toward the total synthesis of this natural product is now in progress.

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3. During preparation of this manuscript, a related investigation has been published: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427.
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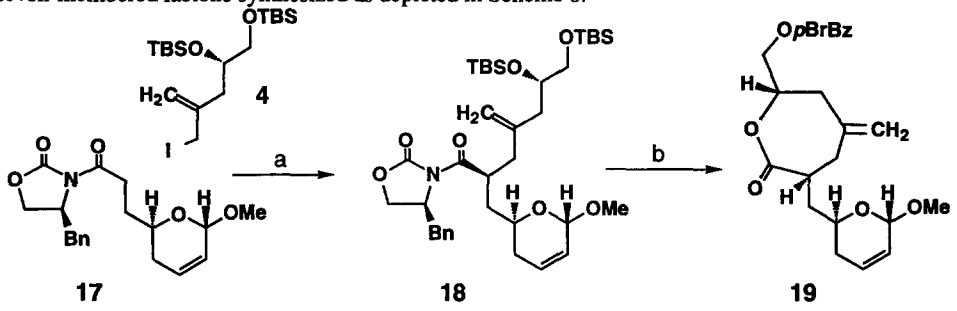
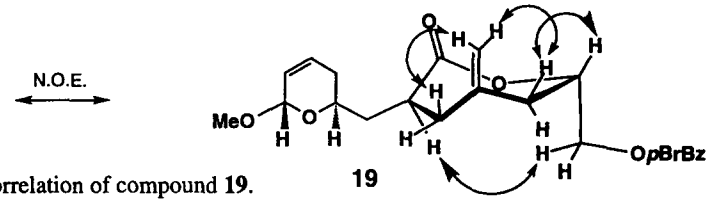
8. The stereochemistry of the C_{11} position was determined by N.O.E. experiments of the corresponding seven-membered lactone synthesized as depicted in Scheme 6.



Scheme 6. Reagents a) LDA, 4/THF -78 °C to -20 °C. b) i. TBAF/THF; ii. *p*BrBzCl/Pyridine.



The N. O. E. correlation of compound **19**.

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10. **2**: $[\alpha]_D^{21}$ -30.9° (*c* 0.25, $CHCl_3$); IR (film) 2950, 2240, 1735 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.40 (1H, ddd, *J*=11.4, 10.6, 3.67 Hz), 5.85 (2H, complex), 5.70 (1H, brd, *J*=10.6 Hz), 5.26 (1H, s), 5.11 (1H, s), 4.28 (1H, brs), 3.75 (2H, complex), 3.70 (3H, s), 3.53 (1H, dd, *J*=9.90, 5.28 Hz), 3.44 (1H, dd, *J*=9.90, 6.93 Hz), 3.06 (1H, m), 2.30 (1H, m), 2.17 (1H, dd, *J*=13.9, 3.67 Hz), 2.1-1.9 (5H, complex), 1.71 (2H, complex), 1.42 (1H, ddd, *J*=12.5, 7.30, 6.59 Hz), 0.89 (21H, complex), 0.11 (3H, s), 0.09 (3H, s), 0.06 (3H, s), 0.05 (3H, s); Calcd for $C_{29}H_{58}O_5Si_2$ (M^+): m/z 542.3819. Found: m/z 542.3814.
11. An instability of **16** under the reaction conditions caused an inseparable mixture of minor products, and the starting material could not be recovered. The corresponding *E*-isomer could not be obtained in this case.

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