Synthetic Approaches towards Laulimalide: Synthesis of the C_{12}-C_{29} Fragment

Atsushi Shimizu, Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223-8522, Japan

Fax +81-45-563-5967; E-mail: nisiyama@chem.keio.ac.jp

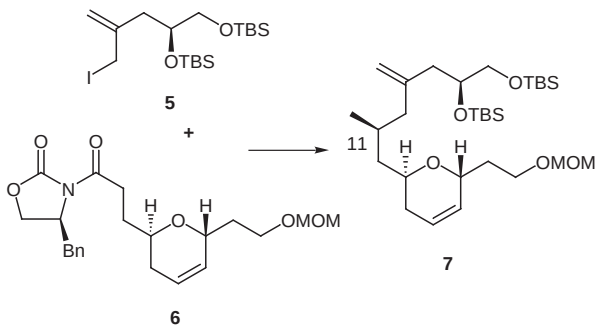
Received 17 August 1998

Abstract: A synthesis of the C_{12}-C_{29} fragment of laulimalide **1** is described. This synthesis involves the Julia trans-olefination as a key step.

Laulimalide **1** (also identified as fijianolide B) is a 20-membered macrolide, possessing potent cytotoxic activity (IC_{50}=15 ng/mL) against the KB cell line.[1] The first isolation from Indonesian marine sponge, Hyattella sp. was reported by Moore in 1988,[1] and independently by Crews in 1988 from a different marine sponge, Spongia mycofijiensis.[2] The absolute configuration of **1** was determined by Higa in 1996, based on the X-ray crystallographic analysis.[3] Contrary to an attractive macrolide structure including nine chiral centers and five double bonds, few synthetic investigations[4] related to this molecule have been reported, probably owing to no information of the absolute configuration until the above-mentioned crystallographic analysis. We report herein a synthesis of the C_{12}-C_{29} fragment which was effectively constructed by the Julia trans-olefination.[5]

Retrosynthetically as can be seen in Scheme 1, the sensitive epoxide bestriding between the C_{16} and C_{17} positions, would be introduced by the Sharpless protocol[6] at the final stage of the synthetic process. Accordingly the target molecule **1** could be transformed into olefin **2**, which was subsequently divided into two fragments **3** and **4**. In this context, a model coupling study employing **5** and **6** as substituents,[7] confirmed the production of the desired stereochemistry at the C_{11} position (Scheme 2). Fragment **3** could be divided into aldehyde **8** and phenylsulfone **9**.

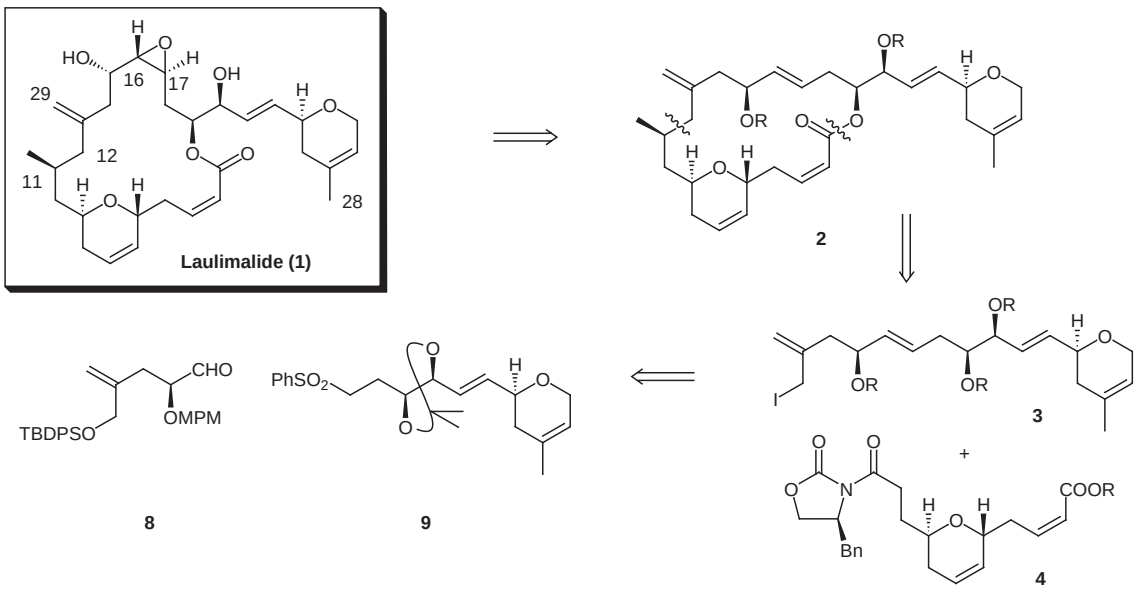
Synthesis of the key intermediate **8** was started from dimethyl ester **10**, derived from L-glutamic acid[8] (Scheme 3). Regioselective reduction, followed by protection of the resulting diol as a 4-methoxybenzylidene group afforded methyl ester **11**. Usual two-step reductive-oxidative manipulation of the ester portion in **11** gave aldehyde **12**. Reaction of aldehyde **12** with the Eschenmoser's reagent[9] provided an enal, which, on reduction with $LiAlH_4$, provided alcohol **13**. Protection of the primary alcohol as a TBDPS group; the acetal protective group was submitted to a reductive opening reaction with DIBAL to give a primary alcohol as a major isomer. Subsequent oxidation of the primary alcohol gave the desired key intermediate **8**.



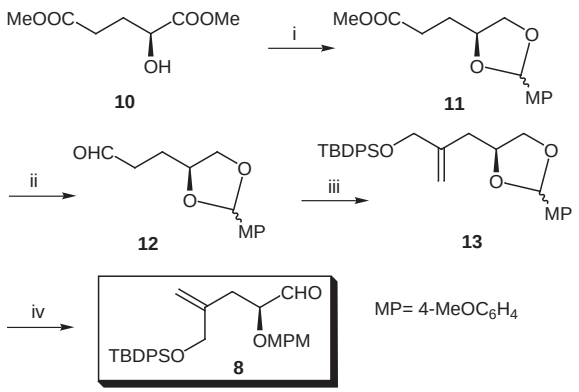
Scheme 2

Synthesis of the coupling partner **9** was initiated from methyl ester **14** derived from L-malic acid. Thus, treatment of **14** with $(MeO)_2P(O)CH_2Li$ resulted in the formation of intermediate **15**. Coupling of **15** and **16** according to the Jørgensen protocol[10] gave α,β-unsaturated ketone **17**. Diastereoselective reduction of the C_{20} ketone with L-Selectride furnished the desired 20*S*-alcohol **18**. Removal of the TBS group, followed by protection of the resulting diol as an isopropylidene group afforded **19**. Deprotection of the MPM group, then phenylsulfonylation of the primary alcohol via a mesyl ester gave the coupling partner **9**.

At the final stage, the aldehyde **8** and the sulfone **9** were coupled by means of Julia reaction employing nBuLi as a base, followed by the reductive elimination procedure. Because of the unstable character of

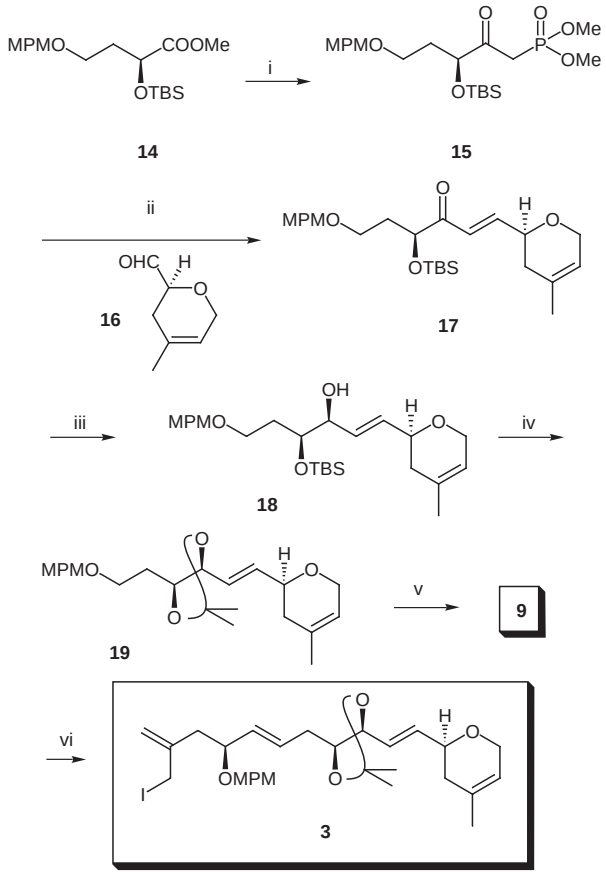


Scheme 1



Reagents and Conditions: i, a)BH_3•Me_2S, THF, 0 °C, 97%; b) 4-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, 78%. ii, a) $LiAlH_4$, THF, 0 °C, 91%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 99%. iii, a) $CH_2=N^+(CH_3)_2I^-$, Et_3N, CH_2Cl_2, 78%; b) $LiAlH_4$, THF, 0 °C, 98%; c) TBDPSCl, Et_3N, CH_2Cl_2, 96%. iv, a) DIBAL-H, CH_2Cl_2, -78 °C, 60% (with regioisomer 12%); b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 89%

Scheme 3



Reagents and Conditions: i, $(MeO)_2P(O)CH_2Li$, THF, -78 °C, 94%. ii, NaH, **16**, THF, 0 °C, 60%. iii, Li(s-Bu)$_3$BH, THF, -78 °C. iv, a) TBAF, THF; b) $Me_2C(OMe)_2$, PPTS, acetone, 35% in 3 steps. v, a) DDQ, H_2O-CH_2Cl_2 (1:10); b) MsCl, Et_3N, CH_2Cl_2 , 95% in 2 steps; c) $PhSO_2Na$, NaI, DMF, 80 °C, 48%. vi, a) nBuLi, **8**, Et_2O; b) Ac_2O, pyridine; c) 5% Na-Hg, EtOAc-MeOH (1:1), -20 °C, 32% in 3 steps; d) TBAF, THF; e) MsCl, Et_3N, CH_2Cl_2; f) NaI, acetone, 71% in 3 steps.

Scheme 4

aldehyde **8**, the total yield of this coupling reaction was unsatisfactory (32% in 3 steps). However this reaction gave rise to the required trans olefin between the C_{16}-C_{17} positions as a sole product. Deprotection of a TBDPS group, then halogenation of the primary alcohol via a mesyl ester gave the desired allyl iodide **3** (71% in 3 steps).

In conclusion, we have successfully synthesized the C_{12}-C_{29} fragment **3** of laulimalide, and further investigation toward the total synthesis of this natural product is now in progress.

References

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(11) Selected ^{1}H-NMR data ($CDCl_3$):
8: δ 1.06 (9H, s), 2.35 (1H, dd, *J*=7.92, 13.8 Hz), 2.46 (1H, dd, *J*=5.28, 13.8 Hz), 3.79 (3H, s), 3.83 (1H, ddd, *J*=1.98, 5.28, 7.92 Hz), 4.12 (2H, s), 4.40 (1H, d, *J*=11.5 Hz), 4.48 (1H, d, *J*=11.5 Hz), 4.99 (1H, s), 5.27 (1H, s), 6.82 (2H, d, *J*=8.58 Hz), 7.16 (2H, d, *J*=8.58 Hz), 7.34-7.46 (6H, complex), 7.64-7.68 (4H, complex), 9.55 (1H, d, *J*=1.98 Hz).
9: δ 1.35 (6H, s), 1.84-2.17 (4H, complex), 3.15 (1H, ddd, *J*=4.62, 11.2, 13.9 Hz), 3.67 (1H, ddd, 1H, *J*=4.95, 11.6, 13.9 Hz), 3.67 (1H, ddd, *J*=3.30, 8.58, 11.9 Hz), 3.97-4.07 (2H, complex), 4.19 (2H, brs), 5.42 (1H, brs), 5.65 (1H, dd, *J*=6.92, 15.5 Hz), 5.89 (1H, dd, *J*=5.28, 15.5 Hz), 7.55-7.70 (3H, complex), 7.90-7.93 (2H, complex).
3: δ 1.42 (3H, s), 1.43 (3H, s), 1.70 (3H, s), 1.91 (1H, brd), 2.05 (1H, m), 2.34-2.51 (4H, complex), 3.77 (1H, m), 3.80 (3H, s), 3.86-3.95 (3H, complex), 4.03-4.12 (2H, complex), 4.18 (2H, brs), 4.27 (1H, d, *J*=11.7 Hz), 4.51 (1H, d, *J*=11.7 Hz), 4.95 (1H, s), 5.28 (1H, s), 5.41 (1H, brs), 5.47 (1H, dd, *J*=7.81, 15.4 Hz), 5.68-5.75 (2H, complex), 5.90 (1H, ddd, *J*=3.91, 5.37, 16.2 Hz), 6.86 (2H, d, *J*=8.3 Hz), 7.22 (2H, d, *J*=8.3 Hz).