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Stereoselective total synthesis of (+)-mueggelone, a novel inhibitor of fish development

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Abstract

An efficient stereoselective total synthesis of (+)-mueggelone, a novel inhibitor of fish development, is described. Highlights of the strategy include the utilization of Sharpless asymmetric epoxidation, Yamaguchi lactonization and an olefin cross-metathesis as the key steps.
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(+)-Mueggelone (**1**) is a naturally occurring C18 lipid, containing a ten-membered lactone unit, isolated from a field-collected sample of *Aphanizomenon flos-aquae* in 1997.[1] This cyanobacterium is well known as a producer of several neurotoxins such as saxitoxin and neosaxitoxin.[2] (+)-Mueggelone has been shown to have an inhibitory effect on fish embryo larval development, and thought to play an ecologically important role in the inhibition of the development of herbivorous fish. In the presence of (+)-mueggelone at a concentration of 10 μg/mL, Zebra fish larva showed 45% mortality and the surving larvae showed edema in the heart region and thrombosis. Considering its selective biological profile, compound **1** has been identified by many scientists world-wide as an attractive synthetic target. Kithara et al. determined the absolute configuration of mueggelone by synthesizing all the four possible stereoisomers. To the best of our knowledge, only one synthesis of mueggelone has been reported in the literature to date.[3]

The novel structure and the scarcity of this natural material has prompted us to investigate the total synthesis of (+)-mueggelone. As part of our continuing interest in the total synthesis of bioactive natural products,[4] we herein report a total synthesis of (+)-meuggelone. Retrosynthetic analysis reveals that the target natural product mueggelone **1** can be obtained by cross olefin metathesis of the two key fragments **2** and **3**, which in turn are synthesized by the sequential transformations of propargyl alcohol **4** and 1,9-dihydroxynonane **5**, respectively (Scheme 1).

The synthesis of fragment **2** started with commercially available propargyl alcohol **4** (Scheme 2), which upon alkylation with ethylbromide gave 2-pentyne-1-ol **6**. Compound **6** was converted to its bromo derivative **7** and then coupled with propargyl alcohol to afford 1,4-diyne (skipped diyne) **8** in 70% yield.[5,6]

Selective reduction of the propargylic triple bond of 8 using $LiAlH_4$ gave the allylic alcohol **9** in 75% yield. Sharpless asymmetric epoxidation of allylic alcohol **9** yielded epoxide **10**, which was subjected to Lindlar hydrogenation to give the *cis*-olefin **11**.[7] Swern oxidation followed by a 1C-Wittig homologation of **11** yielded key intermediate **2** in good yield.[8]

The synthesis of lactone component **3** started from the commercially available 1,9-dihydroxynonane **5** (Scheme 3). Mono hydroxyl protection of **5** with *p*-methoxybenzylbromide in the presence of NaH gave **12** in 90% yield. Oxidation under Swern conditions and subsequent Wittig olefination afforded α,β-unsaturated ester **13**.[9] Ester **13** was then reduced with DIBAL-H to give allylic alcohol **14**,[10] which was converted to epoxyalcohol **15** under Sharpless conditions. The epoxy alcohol **15** was

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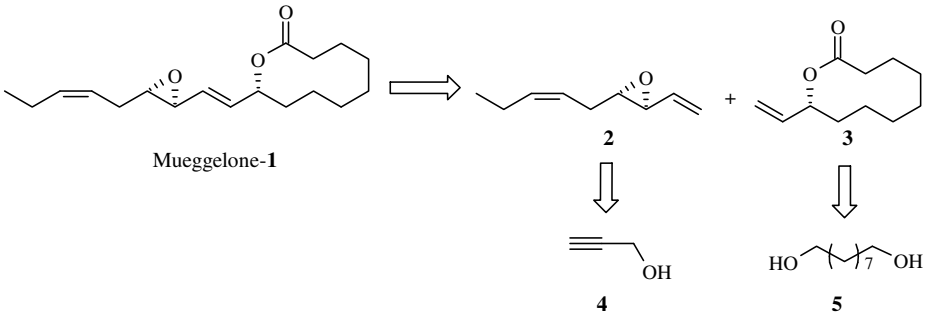
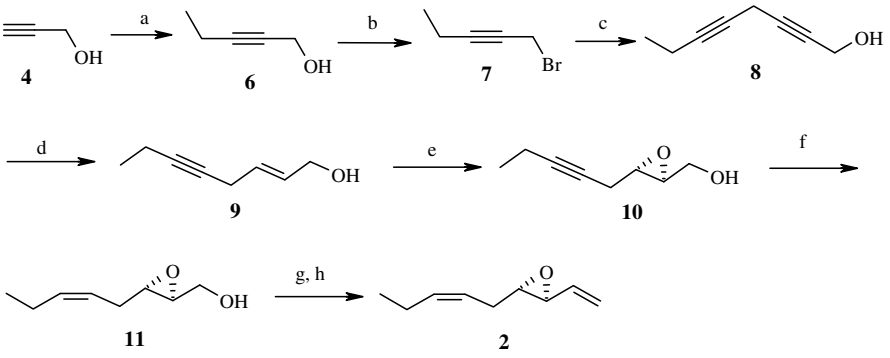
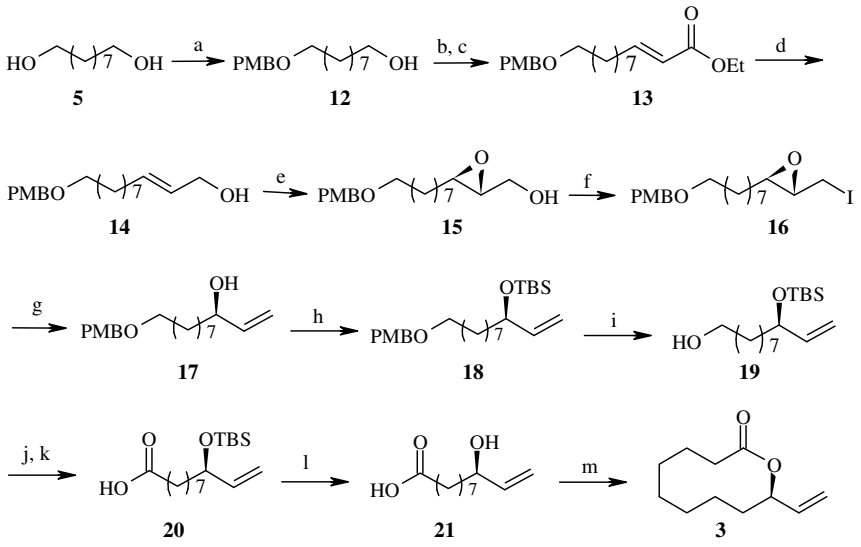


Scheme 1.

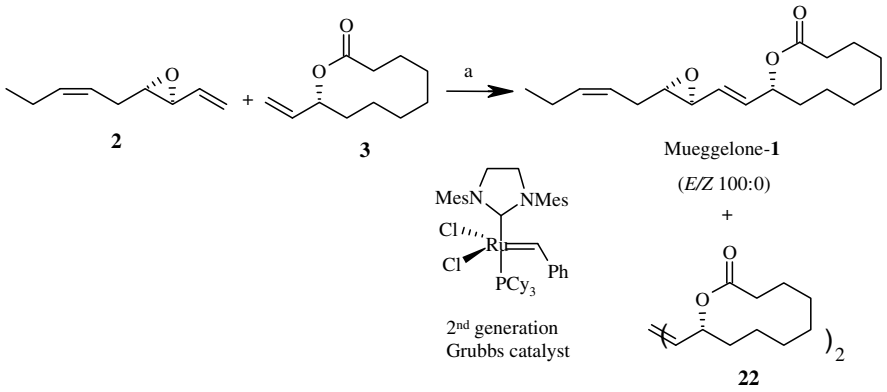


Scheme 2. Reagents and conditions: (a) *n*BuLi, HMPA, ethyl bromide, THF, −30 °C, 18 h, 70%; (b) PBr_3, Et_2O, 0–25 °C, 1 h, 80%; (c) Propargyl alcohol CuI, Na_2CO_3, TBAI, DMF, rt, 10 h, 70%; (d) $LiAlH_4$, Et_2O, reflux, 1 h, 75%; (e) (+)-DET, $Ti(^iPrO)_4$, TBHP, CH_2Cl_2, 4 Å MS, −20 °C, 90%; (f) Lindlars catalyst, benzene, 1 h, 90%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 80%; (h) PPh_3CH_3I, ^{t}BuOK, THF, 0–25 °C, 2 h, 70%.



Scheme 3. Reagents and conditions: (a) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, 0–25 °C, 1 h, 90%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 2 h, 90%; (c) $Ph_3P{=}CHCO_2Et$, benzene, 25 °C, 10 h, 80%; (d) DIBAL-H, CH_2Cl_2, 0–25 °C, 2 h, 95%; (e) (−)-DET, $Ti(^iPrO)_4$, TBHP, CH_2Cl_2, 4 Å MS, −20 °C, 90%; (f) Ph_3P, imidazole, I_2, 0–25 °C, 1 h, 90%; (g) Zn, CH_3OH, reflux, 1 h, 95%; (h) TBS-Cl, imidazole, CH_2Cl_2, rt, 80%; (i) DDQ, CH_2Cl_2–H_2O (9:1), 0–25 °C, 2 h, 85%; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 2 h, 90%; (k) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, ^{t}BuOH: 2-methyl,2-butene (3:1), 0–25 °C, 1 h, 85%; (l) HF, CH_3CN, 60%; (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, reflux, 12 h, 65%.

converted to the corresponding epoxy iodide **16** in 90% yield and subjected to a reductive ring opening reaction in the presence of zinc and methanol to yield secondary allylic alcohol **17**.[11] Protection of alcohol **17** as TBS ether **18** using TBSCl and imidazole followed by the deprotection of the PMB group with DDQ resulted in primary alcohol **19**. This hydroxyl functional group was oxidized to an aldehyde and then to acid **20**, sequentially.[12] The TBS-protected carboxylic acid **20** was converted to the hydroxy acid **21** by treatment with HF–CH_3CN and then converted to



Scheme 4. Reagents and conditions: (a) 2nd generation Grubbs catalyst, CH_2Cl_2, 25 °C, 2 h, 40%.

the key fragment **3** (10 membered lactone) using the Yamaguchi macrolactonization procedure.[13]

The final reaction was the olefin cross-metathesis between precursors **2** and **3**. Accordingly, the treatment of epoxy olefin **2** with **3** in the presence of Grubbs 2nd generation catalyst[14] in methylene chloride afforded the target compound (+)-mueggelone **1** in 40% yield with complete *E* selectivity, as determined by ^{1}H NMR spectroscopy. In this reaction, homodimer **22** was also obtained as a side product as confirmed by mass spectroscopy. The spectral data and optical rotation of compound **1** was found to be identical with that reported.[15]

In conclusion, an efficient total synthesis of (+)-mueggelone **1** has been achieved in a stereo-controlled manner using Sharpless asymmetric epoxidation, Yamaguchi lactonization, and olefin cross-metathesis as key steps (Scheme 4).

Acknowledgment

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15. *Spectral data of selected compounds. Compound* **10**: colorless oil; $[\alpha]_D^{20}$ −11.30 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97–3.85 (m, 1H), 3.69–3.55 (m, 1H), 3.13–3.02 (m, 2H), 2.65–2.52 (m, 1H), 2.47–2.36 (m, 1H), 2.22–2.09 (m, 2H), 1.13 (t, 3H, $J = 7.55$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.4, 73.4, 61.4, 58.2, 53.7, 21.8, 14.1, 12.5; HRMS. Calcd for $C_8H_{12}O_2Na$: 163.0734. found: 163.0734. *Compound* **15**: colorless oil; $[\alpha]_D^{20}$ +8.80 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, 2H, $J = 8.36$ Hz), 6.82 (d, 2H, $J = 9.06$ Hz), 4.39 (s, 2H), 3.89–3.80 (m, 1H), 3.79 (s, 3H), 3.64–3.53 (m, 1H), 3.38 (t, 2H, $J = 6.78$ Hz), 2.93–2.82 (m, 2H), 1.69–1.49 (m, 4H), 1.39–1.22 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.1, 113.8, 72.4, 70.3, 61.8, 58.3, 56.0, 55.2, 31.4, 29.7, 29.3, 29.2, 26.1, 25.8; HRMS: calcd for $C_{19}H_{30}O_4Na$: 345.2041, found: 345.2036. *Compound* **1**: colorless oil; $[\alpha]_D^{25}$ +29.0 (*c* 0.7, $CHCl_3$); {lit. $[\alpha]_D^{28}$ +28.7 (*c* 0.63, $CHCl_3$)}[3]; IR (film); ν_{max} 2931, 1730, 1465, 1236, 1068, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (dd, 1H, $J = 15.6$, 5.1 Hz), 5.54 (m, 1H), 5.46 (ddd, 1H, $J = 15.6$, 7.8, 1.4 Hz), 5.42–5.30 (m, 2H), 3.15 (dd, 1H, $J = 7.80$, 2.20 Hz), 2.87 (dt, 1H, $J = 5.3$, 2.20 Hz), 2.52 (ddd, 1H, $J = 15.5$, 6.2, 3.0 Hz), 2.36 (m, 2H), 2.20 (ddd, 1H, $J = 15.5$, 11.8, 2.6 Hz), 2.15–1.95 (m, 4H), 1.8–1.0 (m, 10H), 0.97 (t, 3H, $J = 7.5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 134.0, 132.7, 128.6, 121.5, 74.7, 59.0, 57.2, 35.0, 29.8, 29.5, 27.2, 24.3, 23.7, 23.5, 20.7, 20.7, 14.0; EIMS: 293 $[M+H]^+$.