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First total synthesis of mueggelone

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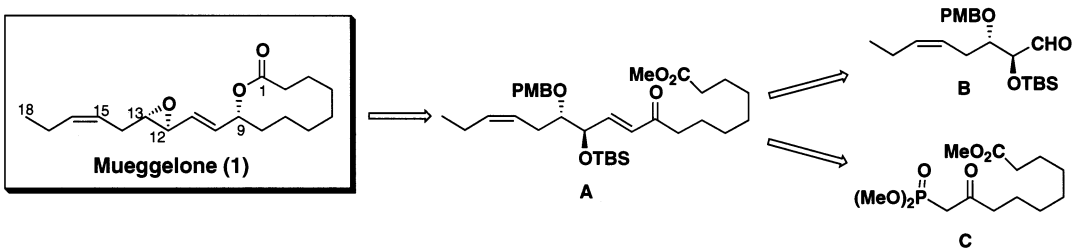
Abstract

All the four possible stereoisomers of mueggelone, an inhibitor of fish development, were efficiently synthesized in a stereoselective manner starting from D-arabinose, and the absolute configuration was determined to be 9*R*,12*S*,13*S*.

Keywords: asymmetric synthesis; reduction; lactonisation; epoxides.

Mueggelone (**1**), which has a 10-membered lactone and epoxide, was isolated[1] from a bloom-foaming strain of *Aphanizomenon flos-aquae* in 1997 (Scheme 1). With mueggelone at a concentration of 10 μg/mL, zebra fish larvae showed 45% mortality and the surviving larvae showed edema in the heart region and thrombosis. This compound is thought to play an ecologically important role in inhibition of the development of herbivorous fish. The stereochemistry of epoxide was proposed to be *trans* by spectroscopic analysis; however, the relative, as well as the absolute configuration of the three stereocenters remained unknown. Therefore, we undertook the synthesis of all the four possible stereoisomers of mueggelone (**1**, *ent*-**1**, **2**, *ent*-**2**) to determine the absolute configuration and to provide samples for further biological



Scheme 1.

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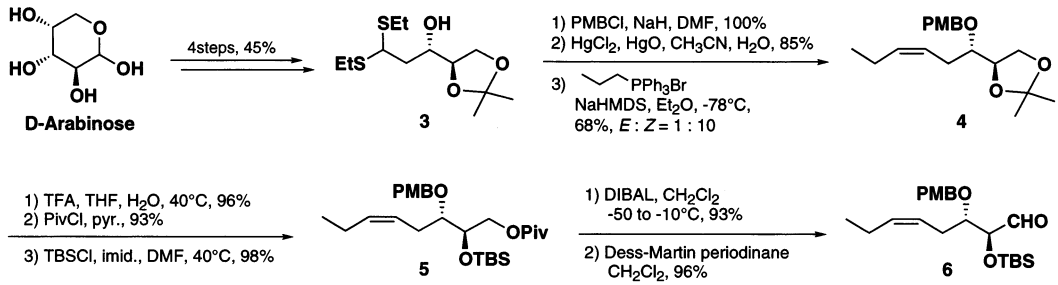
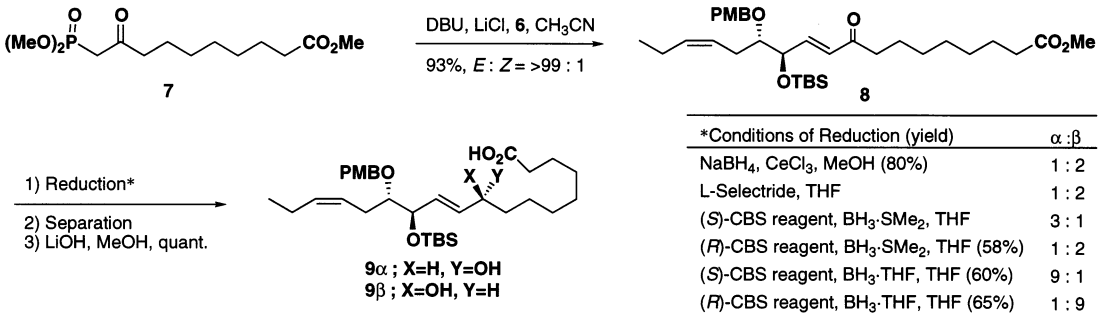
assay. Our synthetic strategy is illustrated in Scheme 1. We decided to utilize the key intermediate **A**, which could be transformed into any of the four stereoisomers via asymmetric reduction of ketone, macrolactonization and, finally, epoxide formation. Compound **A** was constructed by the Horner–Wadsworth–Emmons (HWE) reaction of the side chain part **B** with the lactone part **C**. Aldehyde **B** and phosphonate **C** was derived from commercially available compounds, D-arabinose and azelaic acid dimethyl ester, respectively.

The synthesis of the side chain part is outlined in Scheme 2. D-Arabinose was converted into alcohol **3** according to the known procedure.[2] Protection of the hydroxyl group, followed by dethioacetalization with mercury salt gave an aldehyde, which was submitted to the Wittig reaction to afford *Z*-olefin **4**. The best ratio ($E/Z=1{:}10$) was provided by using NaHMDS as a base, and the isomers were easily separated by silica gel column chromatography. The *Z*-olefin **4** was transformed into the corresponding primary alcohol in four steps, which was then mildly oxidized[3] to give the desired aldehyde **6**.



Scheme 2.

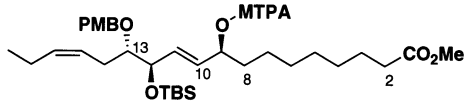
Phosphonate **7** (prepared from azelaic acid dimethyl ester, dimethyl methylphosphonate, *n*-BuLi, THF, −78°C, 22%) was subjected to the HWE reaction with the aldehyde **6** (Scheme 3). Under the condition using *n*-BuLi as a base, the E/Z ratio was 96:4; however, partial epimerization (25%) of the TBSO group was observed. On the other hand, the procedure employing DBU-LiCl[4] resulted in very little epimerization (1–2%) with excellent E/Z selectivity ($E/Z=>99{:}1$). In the next step, we tried several conditions for the asymmetric reduction of enone **8**, and the best selectivity was obtained with the CBS-reagent[5] and borane–THF complex. The resultant two isomers and other undesired isomers (10*Z* isomer, TBSO epimer) were cleanly separated by preparative HPLC and the stereochemistry of each isomer was confirmed by the modified Mosher's method (Table 1).[6] The difference in chemical shifts ensured the stereochem-



*Conditions of Reduction (yield)	α : β
$NaBH_4$, $CeCl_3$, MeOH (80%)	1 : 2
L-Selectride, THF	1 : 2
(*S*)-CBS reagent, $BH_3{\cdot}SMe_2$, THF	3 : 1
(*R*)-CBS reagent, $BH_3{\cdot}SMe_2$, THF (58%)	1 : 2
(*S*)-CBS reagent, $BH_3{\cdot}THF$, THF (60%)	9 : 1
(*R*)-CBS reagent, $BH_3{\cdot}THF$, THF (65%)	1 : 9

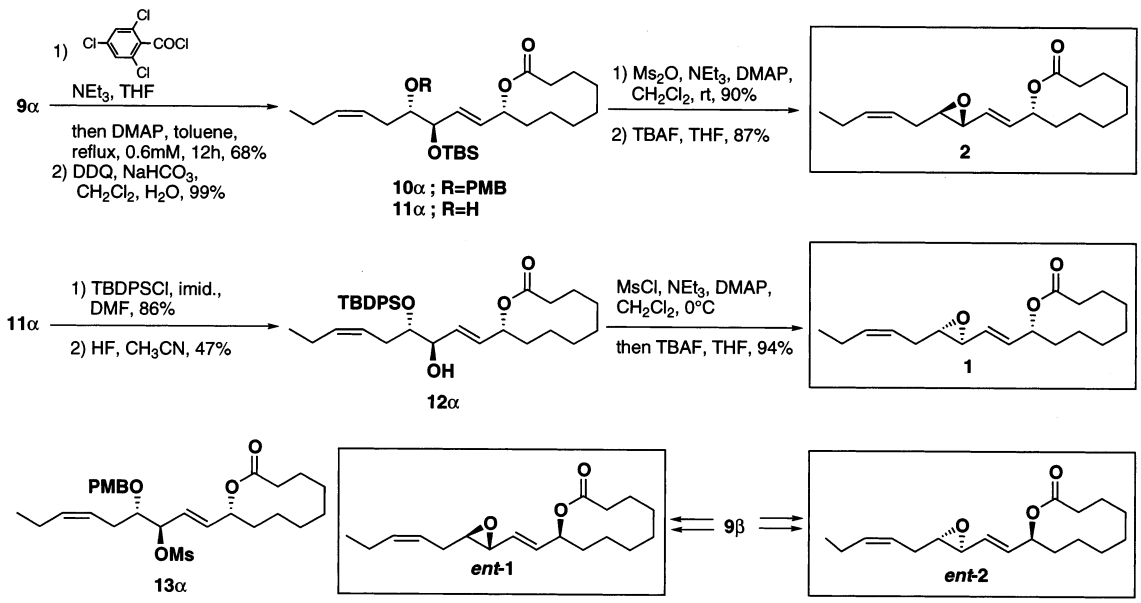
Scheme 3.

Table 1
^{14}C NMR (300 MHz, $CDCl_3$) data for (*S*)- and (*R*)-MTPA ester of the (9*S*) derivative



Position	^{1}H Chemical shift (δ)		$\delta_S-\delta_R$
	(*S*)-MTPA	(*R*)-MTPA	
2	2.28	2.29	−0.01
8	1.63	1.64	−0.01
10	5.68	5.60	0.08
11	5.94	5.83	0.11
12	4.14	4.12	0.02
13	3.32	3.30	0.02

istry. Hydrolysis with LiOH furnished pure hydroxycarboxylic acid **9α**/**β**, respectively. Lactonization of **9α** was successfully achieved by Yamaguchi's method[7] to provide **10α** in satisfactory yield (Scheme 4), together with a small amount of a dimeric lactone (5–10%). On the other hand, the Corey–Mukaiyama method[8] was found to give only several unassignable compounds. Removal of the PMB group with DDQ proceeded without complication. In the following epoxide formation stage, we thought that the stereochemistry of the epoxide could be controlled by the direction of elimination. Initially, we decided to synthesize the (12*R*,13*R*) isomer such as **2**. Mesylation of alcohol **11α**, followed by treatment with TBAF provided the



Scheme 4.

Table 2
^{13}C NMR (75.5 MHz, $CDCl_3$) data for natural mueggelone, **1**/*ent*-**1**, and **2**/*ent*-**2**

Carbon	Natural	**1**/*ent*-**1**	**2**/*ent*-**2**	Carbon	Natural	**1**/*ent*-**1**	**2**/*ent*-**2**
1	173.5	173.4	173.4	10	132.8	132.7	132.8
2	35.1	35.0	35.1	11	128.6	128.5	129.1
3	29.9	29.8	29.9	12	57.4	57.4	57.3
4	27.1	27.0	27.0	13	59.9	59.9	59.9
5	24.2	24.1	24.2	14	29.6	29.5	29.5
6	23.7	23.6	23.6	15	122.3	122.2	122.2
7	23.4	23.3	23.4	16	135.0	134.9	134.9
8	20.7	20.7	20.7	17	20.7	20.7	20.7
9	74.9	74.8	75.1	18	14.2	14.2	14.2

desired epoxylactone **2** in good yield. Next, we tried to obtain the (12*S*,13*S*) isomer in a similar manner. So, allylic mesylate **13α** was prepared from **10α**; however, it readily decomposed under the conditions of PMB deprotection. Therefore, we had to change the PMB group for another protecting group. Masking the hydroxyl group of **11α** with TBDPSCl was followed by selective removal of the TBS group with HF/acetonitrile to give the corresponding alcohol **12α**. It was mesylated and then treated with TBAF without purification to furnish **1**. Also, *ent*-**1** and *ent*-**2** were synthesized in the same way from **9β**.

With the four stereoisomers in hand, we carefully analyzed the NMR spectra and specific rotations. As for the ^1H NMR, there was little difference between **1**/*ent*-**1** and **2**/*ent*-**2** to distinguish them. However, in the ^{13}C NMR spectra (Table 2), an obvious difference was observed at the C-11 position (natural: 128.6 ppm, **1**/*ent*-**1**: 128.5 ppm, **2**/*ent*-**2**: 129.1 ppm), which suggested **1**/*ent*-**1** should be the reasonable natural isomer. In addition, the value of specific rotation (natural: +28.3, synthetic **1**: +28.7, synthetic *ent*-**1**: −28.2) showed that **1** must be the natural product, i.e. mueggelone has the absolute configuration[10] of 9*R*,12*S*,13*S*. At first we referred this to the absolute configuration of malyngic acid,[9] analogous to **1**; nevertheless, the stereochemistry at C-9 was found to be the opposite.

In conclusion, we have completed the first synthesis of mueggelone (and its stereoisomers), in 2.1% overall yield from D-arabinose, and determined the absolute configuration of mueggelone to be 9*R*,12*S*,13*S*. Work is under way to refine every step of the synthesis, and to submit these isomers to further biological assay. Results will be reported in a full account.

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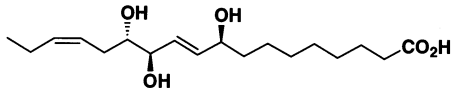
9. Malyngic acid is analogous to mueggelone, see: Cardellina II, J. H.; Moore, R. E. *Tetrahedron* **1980**, *36*, 993–996.



malyngic acid

10. Spectral data of synthetic **1**. IR (film): ν 2930, 1730, 1470, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.98 (3H, t, $J=7.5$ Hz, H-18), 1.05–1.80 (11H, m, Ha-3, H-4, H-5, H-6, H-7, H-8), 1.95–2.15 (3H, m, Hb-3, H-17), 2.20 (1H, m, Ha-2), 2.37 (2H, m, H-14), 2.53 (1H, ddd, $J=2.7$, 6.2, 15.2 Hz, Hb-2), 2.88 (1H, dt, $J=2.2$, 5.2 Hz, H-13), 3.16 (1H, dm, $J=7.5$ Hz, H-12), 5.25–5.60 (4H, m, H-9, H-11, H-15, H-16), 5.95 (1H, dd, $J=5.1$, 15.6 Hz, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.2, 20.7, 20.7, 23.3, 23.6, 24.1, 27.0, 29.5, 29.8, 35.0, 57.4, 59.9, 74.8, 122.2, 128.5, 132.7, 134.9, 173.4.