Synthetic Study towards (±)-Cyanolide A: Synthesis of the Intermediate of (±)-2-(6-ethyl-2-(4-methoxyphenyl)-1, 3-dioxan-4-yl) Acetaldehyde

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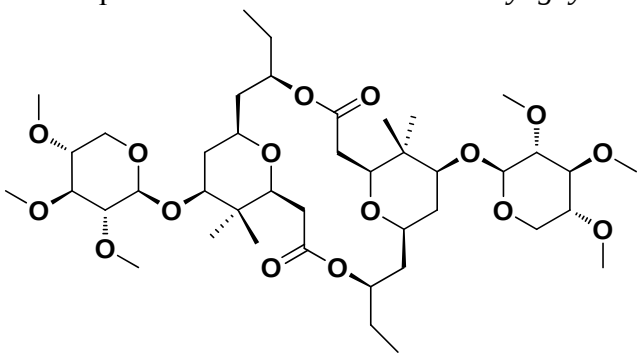
Abstract. Synthesis of (±)-2-(6-ethyl-2-(4-methoxyphenyl)-1, 3-dioxan-4-yl) acetaldehyde, an important intermediate of (±)-Cyanolide A **(1)**, was described, which was commenced from commercially available methyl acetoacetate.

Introduction

Marine organisms are important source of natural products which continue to provide synthetic organic chemists challenging, intriguing, and biological targets. Cyanolide A (as is shown in **Fig. 1**), discovered in 2010 by Gerwick and his co-workers, is a dimeric 16-membered macrolide which was isolated from the extracts of a Papua New Guinea collection of *Lyngbya bouillonii*[1].

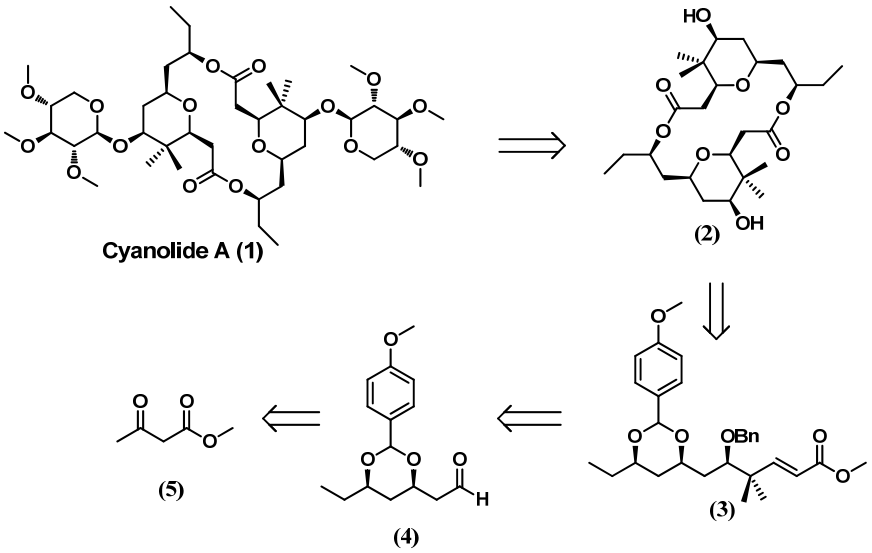


Cyanolide A

Fig. 1. Structure of Cyanolide A

Cyanolide A was demonstrated highly potent molluscicidal agent against the snail vector Biomphalaria glabrata (LC_{50} = 1.2 μM). Due to its novel biological activity, Cyanolide A is of particular interest for scientists: it could be an effective and selective molluscicide agent that has the potential to eradicate schistosomiasis. As a serious diseases threatened human's health, it was reported that more than 200 million people in developing countries have been infected, and more than 700 million people are at risk of this disease[2, 3]. Significantly, Cyanolide A was found to be noncytotoxic when tested against H-460 human lung adenocarcinoma and Neuro-2a mouse neuroblastoma cell lines (maximum test concentration of 35 μM). Herein, we described our synthetic strategy towards (±)-Cyanolide A and the present synthetic work of this molecule.

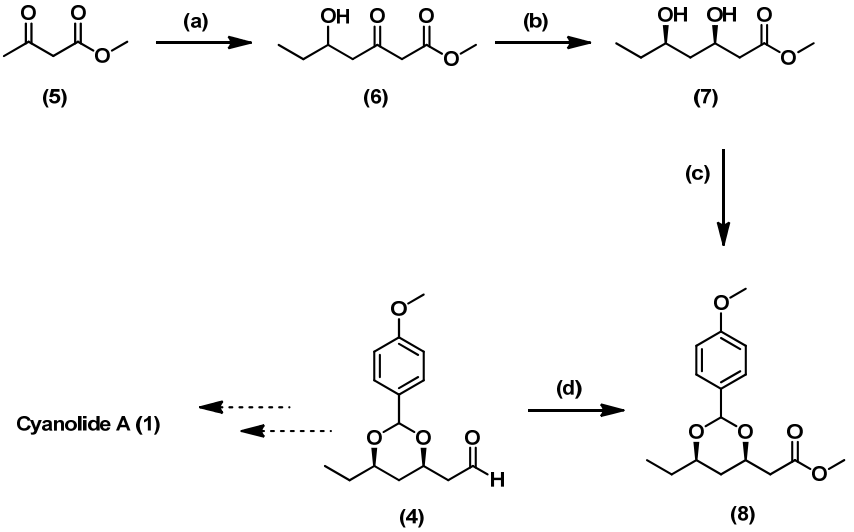
Our retrosynthetic analysis of (±)-Cyanolide A **(1)** is outlined in **Scheme 1**.



Scheme 1. Retrosynthetic analysis of (±)-Cyanolide A (1)

In our retroynthetic analysis, we envisioned that the target molecule could be achieved from dimerization of diol **(2)**. Compound **(2)** was then designed to be obtained from α, β-unsaturated ester **(3)** via a few steps. The α, β-unsaturated ester **(3)** could be got from the key intermediate aldehyde **(4)**. For compound 4, it could be readily prepared from the commercial available material methyl acetoacetate **(5)**. In this paper, we just reported our present synthetic work of the key intermediate aldehyde **(4)**.

The detailed synthetic route of aldehyde **(4)** is shown in **Scheme 2**. The synthesis was commenced with the commercially available compound methyl acetoacetate **(5)**, which was converted to the β-keto ester **(6)** via a nucleophilic addition with propionaldehyde[4, 5]. With the intermediate **(6)** in hand, we conducted a hydroxyl-directed reduction to prepare the syn-diol. Then the required 1, 3-diol **(7)** was performed from β-keto-ester **(6)** via a hydroxyl-directed reduction when treatment with BEt_3 and $NaBH_4$[6]. Subsequently, the 1, 3-diol was protected using *p*-anisaldehyde dimethyl acetal in the presence of *p*-TsOH to give the intermediate **(8)**. Finally, treatment with DIBAL-H in CH_2Cl_2 under -78 °C, the compound **(8)** was smoothly reduced to give the desired aldehyde **(4)**. Our synthetic work towards the total synthesis of (±)-Cyanolide A **(1)** is now going on based on the key intermediate aldehyde **(4)**.



(a) propionaldehyde, NaH, *n*-BuLi, THF, -78°C, 5 h, 64%; (b) BEt_3, $NaBH_4$, MeOH, THF, -78 °C, 2 h, 74%; (c) *p*-anisaldehyde dimethyl acetal, *p*-TsOH, CH_2Cl_2, rt, 30 min, 90%; (d) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 82%.

Scheme 2. Synthesis of key intermediate (±)-2-(6-ethyl-2-(4-methoxyphenyl)-1, 3-dioxan-4-yl) acetaldehyde (4)

Experimental

NMR spectra were recorded on Bruker AV-400MHz spectrometers. The solvents and reagents were purified and dried according to standard procedures: CH_2Cl_2, THF, were distilled from CaH_2 prior to use.

(±)-methyl 5-hydroxy-3-oxoheptanoate (6)

To a suspension of 60 percent sodium hydride (2.07 g) in 72 mL of dry THF under nitrogen at 0 °C was slowly added methyl acetoacetate **(5)** (5 g, 43.06 mmol), then the reaction mixture was stirred for 30 minutes. After that, the reaction mixture was cooled to -78 °C and was slowly added 2.4 M *n*-BuLi (21.53 mL). The mixture was stirred for another 30 minutes, then propionaldehyde (4.66 mL) was added and the mixture was stirred for another 5 hours. The reaction was allowed to warm to room temperature and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated, and the residue was purified by flash column chromatography (hexane/ethyl acetate = 4:1 to 1:1 as eluent) to afford the desired compound (±)-methyl 5-hydroxy-3-oxoheptanoate **(6)** as yellow oil (4.80 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.02-4.01 (m, 1H); 3.75 (s, 3H); 3.51 (s, 2 H); 2.73-2.61 (m, 2H); 1.65-1.37 (m, 2 H); 0.98-0.94 (t, 3 H).

(±)-methyl 3, 5-dihydroxyheptanoate (7)

To a stirred solution of (±)-methyl 5-hydroxy-3-oxoheptanoate **(6)** (4.5 g, 25.83 mmol) in 152 mL of anhydrous THF were slowly added a solution of 1 M BEt_3 (77.50 mL) and anhydrous MeOH (78 mL) at 0 °C. After stirring for 1 hour at room temperature, the reaction mixture was cooled at -78 °C and $NaBH_4$ (2.93 g) was added in one portion. After stirring for another 2 hours, TLC monitored compound **(6)** was completely consumed and the reaction was quenched at -78 °C by adding a methanolic buffer (pH = 7, AcONa/AcOH). After stirring for 16 hours at room temperature, the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated, and The residue was purified by flash column chromatography (hexane/ ethyl acetate = 5:1 to 2:1 as eluent) to afford the desired compound (±)-methyl 3, 5-dihydroxyheptanoate **(7)** as yellow oil (3.37 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.34-4.27 (m, 1 H); 3.91-3.80 (m, 1 H); 3.73 (s, 3 H); 2.53-2.52 (d, 2 H); 1.60-1.58 (m, 2 H); 1.56-1.47 (m, 2 H); 0.97-0.93 (t, 3 H).

(±)-methyl 2-(6-ethyl-2-(4-methoxyenyl)-1, 3-dioxan-4-yl) acetate (8)

To a solution of (±)-methyl 3, 5-dihydroxyheptanoate **(7)** (3 g, 17.03 mmol) in of dry CH_2Cl_2 (85 mL) under nitrogen at 0 °C was slowly added a commercial solution of *p*-anisaldehyde dimethyl acetal (5.80 mL) and *p*-TsOH (293.26 mg). The reaction mixture was stirred for 30 minutes at room temperature, and then it was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated, and The residue was purified by flash column chromatography (hexane/ ethyl acetate = 15:1 as eluent) to afford the desired compound (±)-methyl 2-(6-ethyl-2-(4-methoxyenyl)-1, 3-dioxan-4-yl) acetate **(8)** as yellow oil (4.51 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.33-6.77 (m, 4 H); 5.42 (s, 1 H); 4.23-4.17 (m, 1 H); 3.69 (s, 3 H); 3.67-3.64 (m, 1 H), 3.60 (s, 3 H); 2.67-2.61 (m, 1 H); 2.45-2.40 (m, 1 H); 1.64-1.56 (m, 2 H); 1.51-1.27 (m, 2 H); 0.91-0.88 (t, 3 H).

(±)-2-(6-ethyl-2-(4-methoxyphenyl)-1, 3-dioxan-4-yl) acetaldehyde (4)

To a solution of (±)-methyl 2-(6-ethyl-2-(4-methoxyenyl)-1, 3-dioxan-4-yl) acetate **(8)** (4 g, 13.60 mmol) in dry CH_2Cl_2 (68 mL) at -78 °C, was added a commercial solution of 1.5 M DIBAL-H (9.97 mL) slowly, and the mixture was stirred for 30 minutes at -78 °C. Then it was quenched by the addition of saturated potassium sodium tartrate solution. The mixture was warmed up to room temperature and filtered through a pad of Celite. The residue was washed with saturated NaCl solution and the resultant mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated, and The residue was purified by flash column chromatography (hexane/ ethyl acetate = 10:1 as eluent) to afford the desired compound (±)-2-(6-ethyl-2-(4-methoxyphenyl)-1, 3-dioxan-4-yl) acetaldehyde **(4)** as yellow oil (3.59 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.78 (s, 1 H); 7.34-6.79 (m, 4 H); 5.46 (s, 1 H); 4.34-4.28 (m, 1 H); 3.72 (s, 3 H); 3.70-3.67 (m, 1 H); 2.76-2.70 (m, 1 H); 2.57-2.51 (m, 1 H); 1.64-1.61 (m, 2 H); 1.42-1.36 (m, 2 H), 0.94-0.90 (t, 3 H).

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