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# SYNTHESIS OF 8-METHYL-2-*O*-METHYL-3,5-*O*-(1-METHYL ETHYLIDENE)-6,7,8,9-TETRADEOXY-D-GULO-6-NONENONIC ACID (6E)-γ-LACTONE

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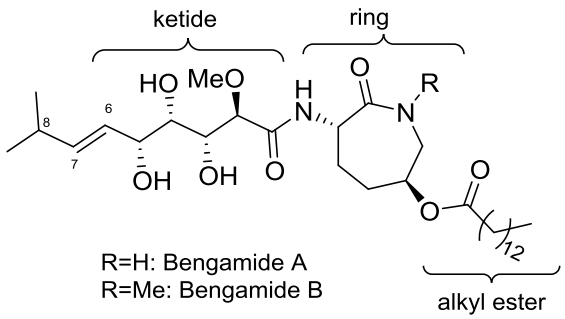
**Abstract**

Ketide side chain, 8-methyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene)-6,7,8,9-tetradeoxy-D-gulo-6-nonenonic acid (6E)-γ-lactone was synthesized starting from the commercial available α-D-glucoheptonic γ-lactone. The synthesis is useful for further synthesis of new and stable bengamide analogues containing an additional methyl group at C-8. The structures of synthetic compounds were determined by spectroscopic analysis, including MS and NMR.

**Keywords.** Bengamide, synthesis analogues antitumor.

## 1. INTRODUCTION

The bengamides, first isolated by Crews and co-workers from *Jaspis* sponges in 1986 [1], display a wide range of biological activities, including antitumor, antibiotic, and anthelmintic properties [2]. These interesting biological activities have made bengamides popular targets for synthesis [3] and biological studies [2, 4]. The cytotoxic mechanism of bengamides has been investigated, and it showed that they arrest cells at the G1 and G2/M phases of the cell cycle by binding to either methionine aminopeptidase type 1 (Met-Ap1) or type 2 (Met-Ap2). It was found that due to the isomerization of the double bond (C-6/C-7 to C-7/C-8), the structure of bengamides were unstable. This could affects the biological activities of bengamides. In order to avoid this isomerization, many analogues of bengamide with an additional methyl group at C-8 were synthesized and evaluated for their antitumor activity [5, 2].




In this paper, we described the synthesis of the ketide side chain of bengamides containing an additional methyl group at C-8 for further synthesis of bengamide analogues.

## 2. EXPERIMENTAL

### 2.1. General Experiment procedures

Melting points were recorded on a Buchi B-545 instrument and are uncorrected. Optical rotations were recorded on a Polax-2L polarimeter in MeOH, $CHCl_3$. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM500 FT-NMR spectrometer as indicated with either the $CDCl_3$ ($\delta_H$ 7.24 ppm, $\delta_C$ 77.0 ppm) or $CD_3OD$ ($\delta_H$ 3.30 ppm, $\delta_C$ 49.0 ppm) signal as internal standard. *J* values are expressed in Hz. The HMBC measurements were optimized to 7.0 Hz long-range couplings, and NOESY experiments were run with 150 ms mixing time. High resolution ESIMS were measured on a VARIAN 910 spectrometer. All chemicals were purchased from Merck and Sigma-Aldrich and used without any further purification.

### 2.2. Detailed synthetic protocols

**Synthesis of 3,5:6,7-bis-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (1)**

To a stirred slurry of α- D-glucoheptonic γ-lactone (1g, 4.8 mmol) in acetone (25 mL) was added 1.2 g $MgSO_4$. The slurry was cooled to

0°C, sulphuric acid (0.09 mL) was added, and the mixture was stirred for 6 h at room temperature. The solution was neutralized to pH 6 with $NH_4OH$. The solvent was disstiled under reduced pressure, water was then added, and the mixture was extracted with dichloromethane. The organic phase was removed under vacuum and the residue was crystallized from *n*-hexane/ethyl acetate (1/4, v/v) to afford (**1**) as a white crystalline solid (937 mg, 67.8 %).

$^1$H-NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm): 1.35 (3H, s, $CH_3$), 1.41 (3H, s, $CH_3$), 1.43 (3H,s, $CH_3$), 1.50 (3H, s, $CH_3$), 2.84 (1H, d, *J* = 10.5 Hz, OH), 3.83 (1H, dd, *J* = 1.5; 8.5 Hz, H-5), 3.91 (1H, dd, *J* = 4.0; 9.0 Hz, H-7a), 4.10 (1H, dd, *J* = 6.0; 9.0 Hz, H-7b), 4.32 (2H, m, H-4, H-6), 4.48 (1H, dd, *J* = 4.0; 10.5 Hz, H-2), 4.60 (1H, dd, *J* = 2.0; 4.0 Hz, H-3).

**Synthesis of 2-*O*-methyl-3,5:6,7-bis-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (2)**

Compound **1** (100 mg, 0.35 mmol) was dissolved in 50 ml of dichloromethane. The mixture was stirred under $N_2$. Iodomethane (0.312 ml, 5eq) was added immediately followed by addition of silver (I) oxide (160 mg, 26 mmol). Water (4 μL) was added to the reaction mixture. The reaction was stirred in the absence of light for 18 h at room temperature. The contents were filtered throuigh Celite, the undesired solid was discarded, and the filtrate was evaporated to dryness. The residue was crystallized from ethyl acetate/*n*-hexane (7:3) to obtain **2** (88 mg, 84.6 %) as white crystalline.

$^1$H-NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm): 1.34 (3H, s, $CH_3$), 1.42 (6H, s, 2 x $CH_3$), 1.48 (3H, s, $CH_3$), 3.64 (3H, s, $OCH_3$), 3.81 (1H, dd, *J* = 2.0; 8.5 Hz, H-5), 3.91 (1H, dd, *J* = 4.0; 9.0 Hz, H-7a), 4.09 (1H, dd, *J* = 6.5; 9.0 Hz, H-7b); 4.12 (1H, d, *J* = 3.5 Hz, H-2), 4.25 (1H, t, *J* = 2.0 Hz, H-4), 4.32 (1H, m, H-6), 4.70 (1H, dd, *J* = 2.0; 3.5 Hz, H-3).

**Synthesis of 2-*O*-methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (3)**

Compound **2** (100 mg, 0.33 mmol) was dissolved in 1.2 mL of a mixture of HOAc and $H_2O$ (1/1, v/v). The solution was stirred at room temperature for 1 h then evaporated to dryness under diminished pressure. The residue was crystallized from acetone/MeOH (1/5, v/v) to afford **3**) as a white crystalline (73 mg, 84.7 %).

$^1$H-NMR (500 MHz, $CD_3OD$): $\delta_H$ (ppm): 1.38 (3H, s, $CH_3$), 1.53 (3H, s, $CH_3$), 3.57 (3H, s, $OCH_3$), 3.60 (1H, dd, *J* = 5.0; 11.5 Hz, H-7a), 3.74 (1H, dd, *J* = 2.5; 11.5 Hz, H-7b), 3.80 (1H, m, H-6), 4.09 (1H, dd, *J* = 2.0; 9.0 Hz, H-5), 4.43 (1H, d, *J* = 4.0 Hz, H-2), 4.46 (1H, t, *J* = 2.0 Hz, H-4), 4.87 (1H, dd, *J* = 2.0; 4.0 Hz, H-3).

**Synthesis of 5-*O*-methyl-2,4-*O*-(1-methylethylidene-L-glucoronic acid γ-lactone (4)**

Sodium metaperiodate $NaIO_4$ (318 mg, 1.5 eq) was added to the solution of 2-*O*-methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-Lactone (**3**) (300 mg, 1.14 mmol) in 8 mL of the mixture of MeOH-$H_2O$ (1/1, v/v) with stirring at 0$^o$C. After being stirred at 0-5 $^o$C for 2 h, the mixture was filtered through the Celite. The filtrate was evaporated under reduced pressure. The residue was purified by chromatography, eluting with a *n*-hexane/EtOAc gradient to give **4** (209 mg, 80 %) as a white crystalline.

$^1$H-NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm): 1.53 (3H, s, $CH_3$), 1.56 (3H, s, $CH_3$), 3.66 (3H, s, $OCH_3$), 4.11 (1H, d, *J* = 3.5 Hz, H-5), 4.43 (2H, m, H-2, H-4), 4.75 (1H, dd, *J* = 2.0; 3.5 Hz, H-3), 9.60 (1H, s, CHO).

**Synthesis of 8-methyl-2-*O*-methyl-3,5-*O*-(1-methylethylidene) -6,7,8,9- tetradeoxy-D-gulo-6-nonenonic acid (6E)- γ-lactone (5)**

To a 25 mL round-bottom flask was added $CrCl_2$ (0.445 g), anhydrous THF (7 mL), and DMF (0.3 mL). The mixture was stirred under $N_2$ for 1 h. A solution of 5-*O*-methyl-2,4-*O*-(1-methylethylidene-L-glucoronic acid γ-lactone **(4)** (100 mg, 0.435 mmol), 1,1-diiodo-2,2 dimethylpropane (0.13 mL, 2 eq), 0.3 mL of DMF and 6.75 mL of anhydrous THF was added slowly to the reaction mixture. After the addition, the reaction mixture was stirred at ambient temperature for 12 h. The reaction was quenched with saturated aqueous $NH_4Cl$ to pH 7. The residue was partitioned with EtOAc/water and chomatographed ($CH_2Cl_2$/EtOAc, 96/4) to afford **5** (22 mg, 20%) as a white crystalline.

$[\alpha]^{22}_D$ -151.1 (c. 1.5 MeOH); mp 181-182 $^o$C; $^1$H-NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm): 1.04 (9H, s), 1.53 (3H, s, $CH_3$), 1.56 (3H, s, $CH_3$), 3.66 (3H, s, $OCH_3$), 3.98 (1H, m, H-5), 4.08 (1H, d, *J* = 4.0 Hz, H-2), 4.44 (1H, dd, *J* = 7.5; 1.5 Hz, H-4), 4.71 (1H, dd, *J* = 4.0; 2.0 Hz, H-3), 5.58 (1H, dd, *J* = 15.5; 7.5 Hz, H-6), 5.85 (1H, dd, *J* = 15.5; 1.0 Hz, H-7). $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta_C$ (ppm): 19.5 ($CH_3$), 29.2 (3 x $CH_3$), 30.9 ($CH_3$), 32.8 (C), 57.7 ($OCH_3$), 67.0 (CH), 68.9 (CH), 71.5 (CH), 78.4 (CH), 97.9 (C), 120.7 (CH), 144.9 (CH), 173.4 (C=O).

## 3. RESULTS AND DISCUSSION

Synthesis of the ketide side chain **5** was described in Scheme 1 by using the commercial

available D-glycero-D-gulo-heptonic acid γ-lactone as starting material as previously reported [6].

In the preparation of **5**, the bis-acetonide protection of D-glycero-D-gulo-heptonic acid γ-lactone was initially carried out in acetone with iodine as the catalyst [7]. However, this procedure suffered from a long reaction time, inconsistent regioselectivity, and poor quality of the isolated product. The reaction were then carried-out with acetone in the presence of $H_2SO_4$ and $MgSO_4$ to afford the bis-acetonide **1**.

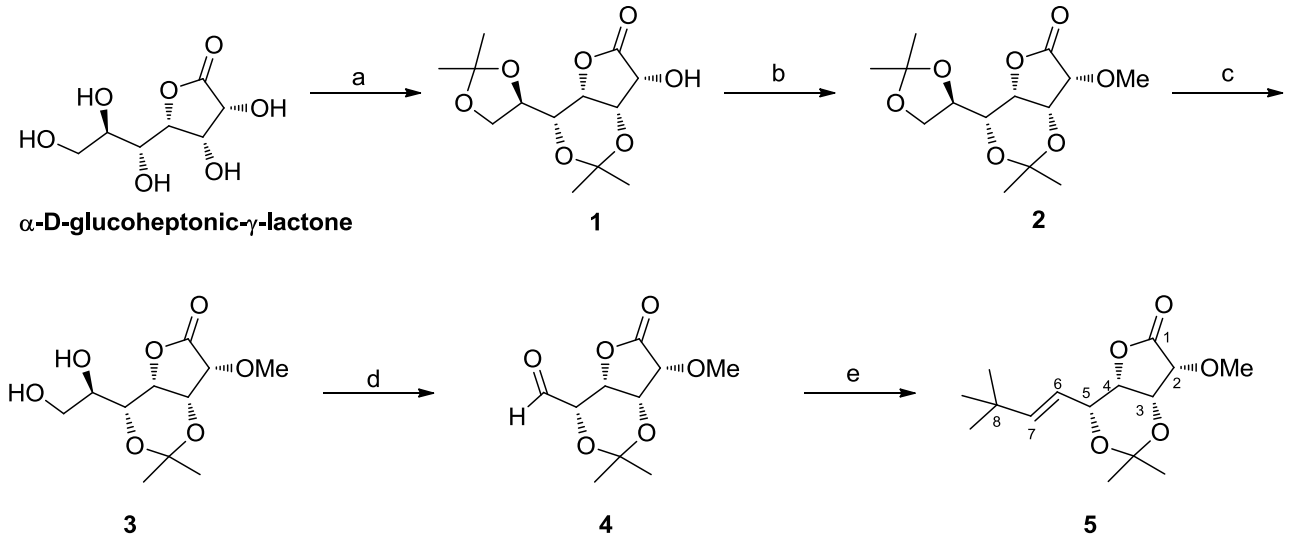
Due to the unstablity of the lactone ring toward the basic condition, the methylation of **1** must be achieved under mild condition. The unprotected hydroxyl group of **1** was then methylated by treatment with MeI in the presence of $Ag_2O$ at room temperature, providing **2** in high yield (84.6 %).

Our next objective was to achieve a selective removal of the terminal acetonide group of **2**. Selective deprotection of **2** was performed by using a mixture of $CH_3COOH/H_2O$ (1/1) at room temperature for 6h to give **3** in 66 % yield. In this weak acidic solution, the acetonide with 6-membered-ring was remained. It was found that using more stronger acids such as $H_2SO_4$ or HCl led to the full cleavage of bis-acetonide.

Conversion of the diol **3** to aldehyde **4** using sodium periodate (aqueous) in acetonitrile was found to be problematic for scale-up. The aldehyde intermediate is thermally labile, highly sensitive to both acidic and basic conditions and readily prone to hydration. The reaction should be carried-out by using a minimum amount of water to avoid extraction of the product from water. After completion of the reaction, the reaction mixture was filttred through Celite and water was absorbed onto magnesium sulfate. The crude product was purified by column chromatography on silica gel to furnish **4** in 80 % yield.

Finally, the olefination of aldehyde **4** to obtain the lactone fragment **5** was one of the most difficult and important in this synthesis. In this work, the ketide side chain **5** was prepared by using the Takai procedure [8]. Treatment of **4** with large excess of chromium dichloride and the 1,1-diiodo-2,2-dimethylpropane in a mixture of THF/DMF, affording the desired compound **5** in 20% yield.

Thus, the ketide side chain **5** was synthesized in 6 % overall yield, starting from the commercial available D-glycero-D-gulo-heptonic acid γ-lactone in five steps. This synthesis is useful for further development of preparation of bengamide analogues in order to discovery of new and stable bioactive bengamide-like structures.




*Scheme 1:* (a) $H_2SO_4$, $MgSO_4$, acetone, rt, 6 h, 67.8 %; b) MeI, $Ag_2O$, $CH_2Cl_2/H_2O$, rt, 18 h, 84.6 %; (c) $CH_3COOH/H_2O$ (1/1), rt, 6h, 66 %; d) $NaIO_4$, $MeOH/H_2O$ (1/1), 0 $^oC$, 2 h, 80 %; (e) $(CH_3)_3CCH_2I_2$, $CrCl_2$, THF/DMF (23/1), 20 %

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