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Synthesis of (3*S*,4*R*)-bengamide E

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Abstract

(3*S*,4*R*)-Bengamide E (**2**) was synthesized starting from D-glucono-*δ*-lactone (**3**) and the key deoxygenation step from **13** to **15** was achieved by the application of $NaBH_3CN$ and ZnI_2. Compared with natural bengamide E (**1**), the synthetic compound (3*S*,4*R*)-bengamide E (**2**) was inactive against the cell growth of HUVEC and cancer cells. These data represent the significance of the stereochemistry at C-3 and C-4 of bengamides for structural recognition and binding with the target(s).

Keywords: (3*S*,4*R*)-Bengamide E; Stereocenter; Deoxygenation

Bengamides were first isolated by Crews and co-workers from *Jaspis* sponges [1,2], which are classified as fused ketide-amino acid derivatives. It was demonstrated that bengamides are a family of potent cancer cell growth inhibitors [3,4] and anti-angiogenesis agents [5] as unique inhibitors of methionine aminopeptidase type I and type II (MetAP 1 and MetAP 2). Bengamide E (**1**) (Fig. 1), a representative member of bengamides, exhibits 3.3 μmol/L against MDA-MB-435 (human breast carcinoma cell) [4]. To investigate the importance of the stereochemistry at C-3 and C-4 of bengamide ketide side chain, we herein report the synthesis and biological evaluation of (3*S*,4*R*)-bengamide E (**2**) (Fig. 1).

The (3*S*,4*R*)-bengamide E was synthesized starting from D-glucono-*δ*-lactone (**3**) (Scheme 1). Bis-acetonide **4** was prepared from **3** according to the literature [6]; *O*-Methylation of **4** was done by MeI and NaH to afford **5** in 72% yield at −20 °C in THF without C-2 epimerization. After the reduction of carboxyl group of **5** into terminal alcohol **6** by $LiAlH_4$, compound **7** was prepared from **6** by using benzyl bromide and NaH with the catalysis of Bu_4NI and diol **8** was generated by removal of terminal acetonide protection of **7**. Then primary and secondary hydroxyl groups of **8** were protected by acetyl group and tetrahydropyranyl (THP) group, respectively. After a new chiral center was introduced by the THP protection, every succeeding product bearing THP has a diastereomer counterpart. Subsequently, treatment of the mixture of **9** with K_2CO_3 hydrolyzed acetyl group to give separable products of **10A** (more polar, 51% yield) and **10B** (less polar, 41% yield) and oxidation of **10A** and **10B** by Swern oxidation afforded aldehyde **11A** and **11B**, respectively. Julia olefination of aldehyde **11A** or **11B** gave low *E*-selectivity and yield (data not shown), whereas, Wittig–Horner reaction [7] of aldehyde **11A** or **11B** produced a single product of *E*-olefin **12A** or

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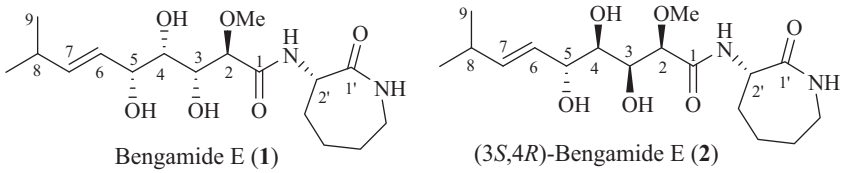
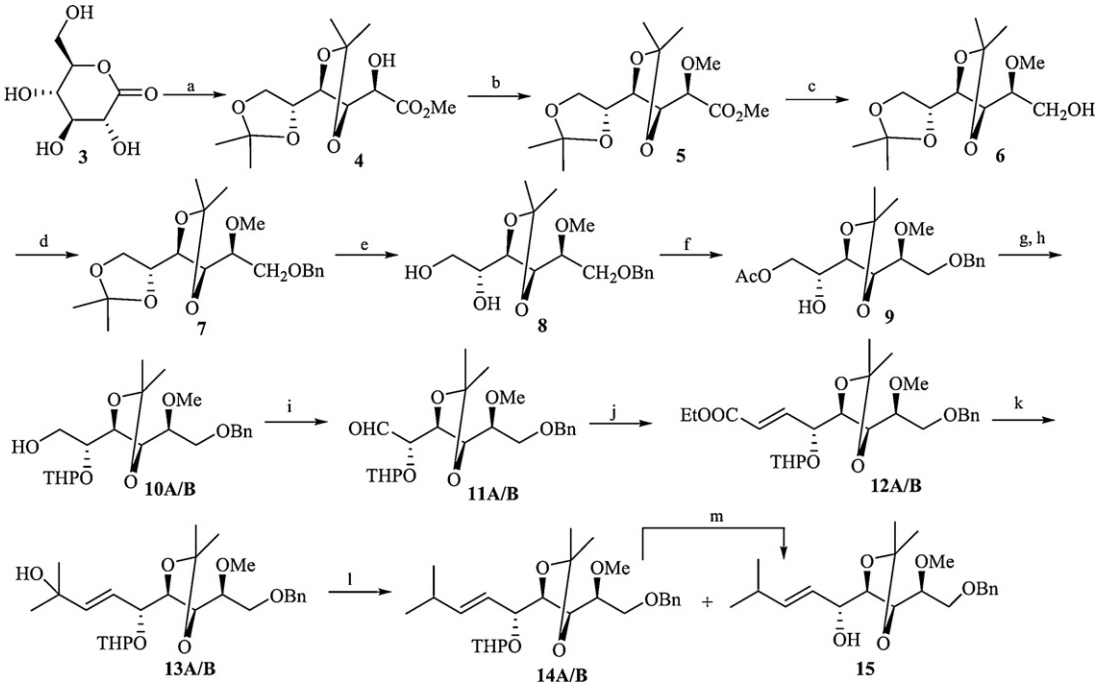


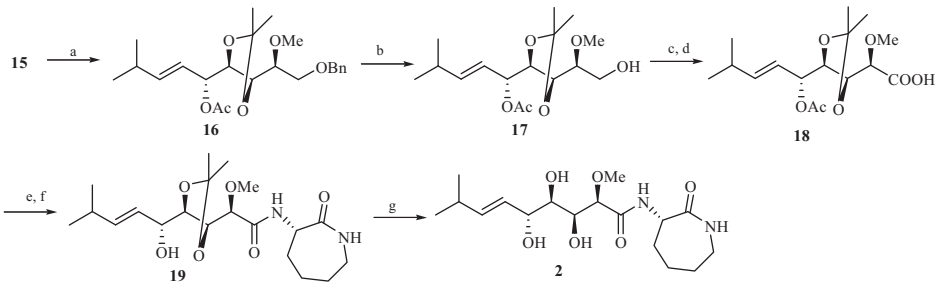
Fig. 1. Structures of bengamide E (**1**) and (3*S*,4*R*)-bengamide E (**2**).

12B in a good yield as expected, which was the required geometrical isomer. Reaction of **12A** with Grignard reagent MeMgI in Et_2O at 0 °C generated a tertiary alcohol **13A**. Strategically, removal of allylic tertiary hydroxyl group in **13A** could achieve the same olefin moiety as bengamide E side chain. Many approaches including Pd/C in EtOH, $Pd(OH)_2$ in EtOH, Raney Ni in EtOH or in H_2O and Et_3SiH in CH_2Cl_2 failed to deoxygenate **13A**. At the end, deoxygenation of **13A** was accomplished by the reduction with $NaBH_3CN$ and ZnI_2 in CH_2Cl_2, which was modified from the literature [8]. Reductive deoxygenation of **13A** by 3.0 equiv. $NaBH_3CN$ and 1.0 equiv. ZnI_2 afforded desired key intermediate **15** as well as THP-protected **14A** that was easily transformed into **15** by PPTS in 72% yield. As a result, the two-step process generated **15** in 62% yield in total without obvious dimerized and olefin isomerized byproducts. Through the same reactions as **12A** to **15**, the key intermediate **15** was furnished with the similar yields starting from less polar **12B**. The diastereomer mixtures were used for the subsequent production of **15** on a larger scale.

With the key intermediate **15** in hand, the free secondary hydroxyl group was protected with acetyl group, and subsequent debenzylation of terminal protection was carried out by DDQ at room temperature to afford C-1 primary alcohol **17**. Sequential oxidations of **17** with Dess-Martin periodinane (DMP) and $NaClO_2$ buffered with KH_2PO_4 generated carboxylic acid **18** [9]. Activation of carboxylic acid **18** was carried out by *N*-hydroxysuccinimide (NHS) with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and then coupling reaction was conducted by treatment of NHS-activated **18** with freshly prepared L-(−)-α-amino-δ-caprolactam [10] to furnish the coupled compound **19**. Finally, (3*S*,4*R*)-bengamide E (**2**) [11] was achieved by the treatment of **19** with dilute TFA at 0 °C (Scheme 2).



Scheme 1. Condition and regent: (a) Ref. [6]; (b) NaH, MeI, THF, −20 °C, 72%; (c) $LiAlH_4$, THF, 0 °C, 70%; (d) BnBr, NaH, $Bu_4N^+I^-$, THF, 86%; (e) 50% HOAc, 67%; (f) pyridine, AcCl, CH_2Cl_2, −80 °C, 63%; (g) DHP, PPTS, CH_2Cl_2; (h) K_2CO_3, MeOH/H_2O, 51% for **10A** (the more polar product) and 41% for **10B** (the less polar product); (i) Swern oxidation; (j) NaH, THF, $(EtO)_2P(O)CH_2CO_2Et$, 0 °C to rt, 82% for**12A** from **10A** and 72% for **12B** from **10B**; (k) MeMgI, Et_2O, 0 °C, 77% for **13A**, 86% for **13B;** (l) $NaBH_3CN$, ZnI_2, CH_2Cl_2, rt, 22% for **14A** and 47% for **15** from **13A** or 21% for **14B** and 38% for **15** from **13B**; (m) PPTS, EtOH, 50 °C, 72%.



Scheme 2. Condition and regent: (a) Ac_2O, TEA, CH_2Cl_2, 89%; (b) DDQ, CH_2Cl_2, 61%; (c) DMP, CH_2Cl_2; (d) $NaClO_2$, KH_2PO_4, acetone/H_2O, 86%; (e) NHS, DCC, DMAP, CH_2Cl_2, rt; (f) dioxane, saturated K_2CO_3, L-(−)-α-amino-δ-caprolactam, 42%; (g) 3:1:3 THF–H_2O–TFA, 0 °C, 61%.

Compound **2** was inactive up to 50.0 μmol/L against the cell growth of HUVEC (human umbilical vein endothelial cell), A549 (human non-small cell lung cancer cell), Bel-7402 (human hepatocarcinoma cell) and MCF-7 (human breast cancer cell) [12,13]. These structural modifications at C-3 and C-4 of bengamide side chain damaged biological activity severely, thus, suggesting that strict stereochemistry at C-3 and C-4 of bengamides is important for structural recognition and binding with the target(s).

Acknowledgments

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[11] Compound **2**: colorless semisolid; $[\alpha]_D^{20}$ + 33.8 (*c* 0.71, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (m, 1H), 6.40 (m, 1H), 5.76 (dd, 1H, *J* = 6.4, 15.6 Hz), 5.49 (m, 1H), 4.58 (m, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 3.84 (m, 1H), 3.72 (m, 1H), 3.48 (s, 3H), 3.28 (m, 2H), 2.29 (m, 1H), 2.03 (m, 1H), 1.83 (m, 2H), 1.62 (m, 1H), 1.43 (m, 1H), 0.99 (d, 6H, *J* = 6.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (m, 1H), 7.79 (d, 1H, *J* = 6.0 Hz), 5.58 (dd, 1H, *J* = 6.4, 15.6 Hz), 5.49 (dd, 1H, *J* = 6.0, 16.0 Hz), 4.68 (d, 1H, *J* = 5.7 Hz), 4.49 (d, 1H, *J* = 6.4 Hz), 4.34 (m, 1H), 4.29 (d, 1H, *J* = 6.4 Hz), 3.87 (m, 1H), 3.76 (m, 1H), 3.68 (d, 1H, *J* = 5.2 Hz), ∼3.35 (s, 3H, overlapped with HDO/H_2O), 3.19 (m, 1H), 3.08 (m, 1H), 2.26 (m, 1H), 1.92 (m, 2H), 1.75 (m, 1H), 1.67 (m, 1H), 1.35 (m, 1H), 1.16 (m, 1H), 0.96 (d, 6H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.6, 169.9, 137.8, 129.0, 83.8, 73.8, 71.7, 70.9, 58.7, 51.8, 41.2, 31.2, 30.7, 29.1, 28.0, 22.8, 22.7; HRESIMS calcd. for $C_{17}H_{30}N_2NaO_6$ 381.1996, found 381.1991 $[M+Na]^+$.
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