Synthetic Study towards (+)-Clavosolide A: Synthesis of the Intermediate of (*R*)-methyl 5-hydroxy-3-oxoheptanoate

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Keywords: (*R*)-methyl 5-hydroxy-3-oxoheptanoate, (+)-Clavosolide A, synthesis.

Abstract. The important intermediate, (*R*)-methyl 5-hydroxy-3-oxoheptanoate, of study towards to total synthesis of (+)- Clavosolide A (1) was described, which was commenced from commercially available D-phenylalanine.

Introduction

Marine sponges are greatly important source of bioactive metabolites providing many seemingly inexhaustible useful molecules [1]. Secondary metabolites of marine origins plays a significant role in drug development, which attacking the interesting of medicinal chemistry. In 2002, as disclosed the isolation and structural elucidation of Clavosolide A and related structures by Faulkner and coworkers [2], Clavosolide A has two novel marine diolide glycosides, comprising a C_2-symmetric 16-membered dimeric macrocycle ring (as shown in Fig. 1).

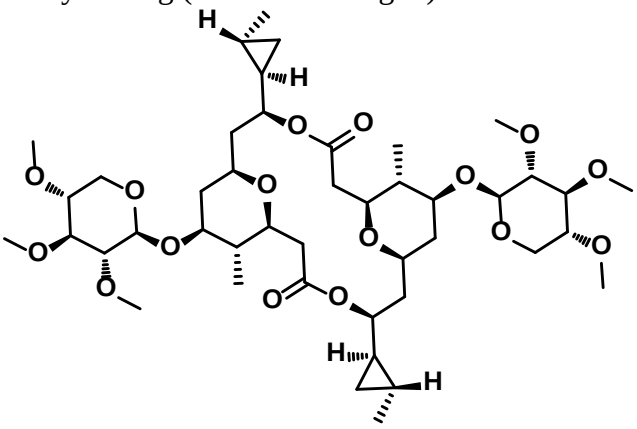
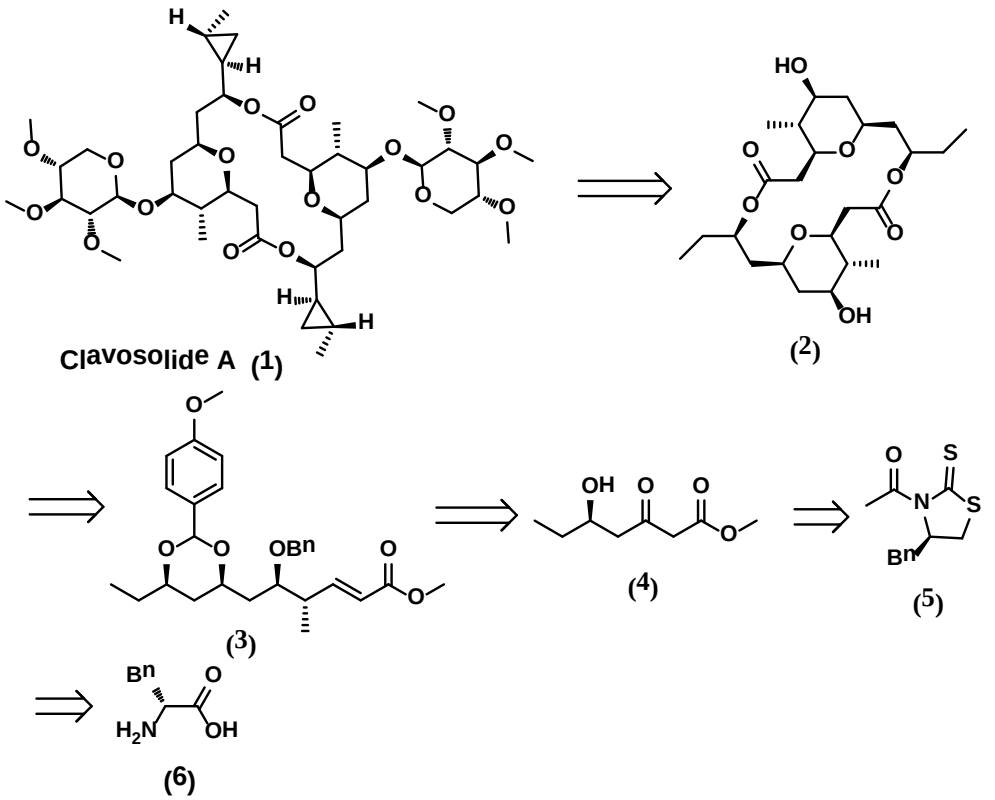


Fig. 1 Structure of Clavosolide A

The novel bioactivity and the complex chemical structure with highly functionalized 16-membered dimeric macrocyle attracted great interest from the synthetic communities. Since its isolation, Willis first finished the diastereomer of Clavosolide A, and Lee and co-workers obtained the product that was spectroscopically identical to the originally described structure and hence constituted the first total synthesis of Clavosolide A. Herein, we described our synthetic study towards to the key intermediate of (+)-Clavosolide A.

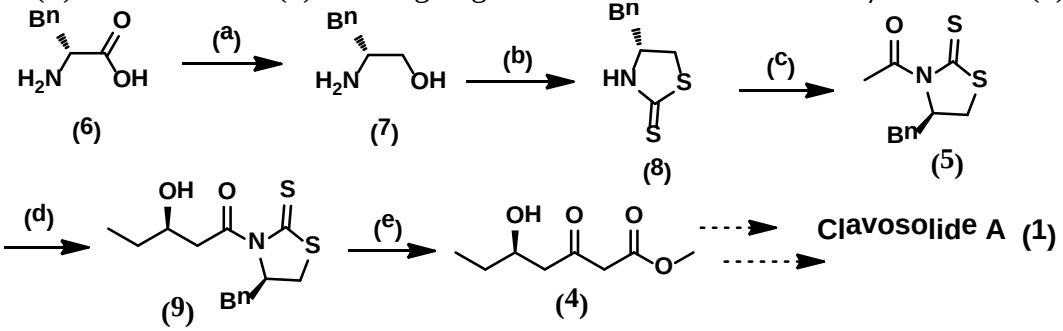
Our retrosynthetic analysis of (+)-Clavosolide A (1) is outlined in Scheme 1.



Scheme 1 Retrosynthetic analysis of (+)-Clavosolide 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. Compound (3) could be got from the intermediate *β*-keto ester (4). For compound (4), it could be readily prepared from the Evans chiral auxiliary reagent (5) which could be got from the commercial available material D-phenylalanine (6). In this paper, we just reported our present synthetic work of the intermediate *β*-keto ester (4).

The detailed synthetic route of *β*-keto ester (4) is shown in Scheme 2. The synthesis was commenced with the commercially available compound D-phenylalanine (6), which was converted to the *β*-amino alcohol (7) via a reduction reaction with $NaBH_4$ [3]. Then the required 1,3-thiazolidine-2-thiones (8) was performed from *β*-amino alcohol (7) via a general procedure when treatment with potassium hydroxide and CS_2 [4]. Subsequently, the 1,3-thiazolidine-2-thiones (8) reacted with acetyl chloride to produce the Evans chiral auxiliary reagent (5) in the presence of TEA and DMAP [3]. Compound (5) proceeded via an Evans Aldol reaction to afford compound (9) [5]. Finally, treatment with $MgCl_2$ and imidazole in THF at room temperature [6], the compound (9) was smoothly converted to the desired *β*-keto ester (4). Our future synthetic work towards the total synthesis of (+)-Clavosolide A (1) is now going on based on the intermediate *β*-keto ester (4).



(a) $NaBH_4$, I_2, THF, 85°C, 16 h; (b) CS_2, KOH, 100°C, 16 h, 74%; (c) TEA, DMAP, CH_3COCl, CH_2Cl_2, rt, 30 min, 90%; (d) propionaldehyde, $TiCl_4$, DIPEA, CH_2Cl_2, -78 °C, 30 min, 60%; (e) potassium salt of mono methyl malonate, $MgCl_2$, imidazole, THF, rt, 18h, 45.9%.

Scheme 2 Synthesis of key intermediate (R)-methyl 5-hydroxy-3-oxoheptanoate

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.

(*R*)-2-amino-3-phenylpropan-1-ol (7)

To a solution of D-phenylalanine (6) (3.0 g) in 40 mL of dry THF under nitrogen at 0 °C was slowly added $NaBH_4$ (1.72 g, 45.40 mmol), then I_2 (5.52 g, 21.79 mmol) dissolved in 20 mL of dry THF was added dropwise at 0 °C. The reaction mixture was refluxed at 85 °C for 16 hours. After that, the reaction mixture was cooled to rt and was slowly added MeOH (7 mL). The mixture was stirred at rt for 1 hours, followed by MeOH was removed and aqueous 20 percent KOH (38 mL) was added, then the mixture was stirred for another 3 hours. After the reaction 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 = 10:1 to 5:1 as eluent) to afford the desired compound (*R*)-2-amino-3-phenylpropan-1-ol (7) as white solid (2.20 g).

(*R*)-4-benzylthiazolidine-2-thione (8)

To a stirred solution of *β*-amino alcohol (7) (1.51 g, 10.00 mmol) in 50 mL of aqueous 1 N potassium hydroxide was added CS_2 (3.00 mL, 50.00 mmol). The reaction mixture was refluxed at 110 °C for 16 hours. 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 = 10:1 to 5:1 as eluent) to afford (*R*)-4-benzylthiazolidine-2-thione (8) as white crystal (1.55 g, 74%). ^{1}H NMR (400 MHz, CDCl3, ppm): δ 8.36 (m, 1 H); 7.32 (m, 2 H); 7.26 (m, 1 H); 7.18 (m, 2 H); 4.46 (dd, 1 H); 3.50 (m, 1 H); 3.25 (m, 1 H); 3.04 (m, 1 H); 2.93 (m, 1 H).

(*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethanone (5)

To a solution of (*R*)-4-benzylthiazolidine-2-thione (8) (2.41 g, 11.51 mmol) dissolved in dry CH_2Cl_2 (61 mL) under nitrogen at 0 °C was slowly added TEA (1.93 mL) and DMAP (281.31 mg, 2.30 mmol), then CH_3COCl (1.06 mL) was added dropwise at 0 °C. After stirring for 3 hours, the reaction 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 to 5:1 as eluent) to afford (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethanone (5) as yellow crystal (2.60 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.33 (m, 2 H); 7.27 (m, 3 H); 5.37 (m, 1 H); 3.41 (m, 2 H); 3.20 (dd, 1 H); 3.11 (m, 1 H); 2.87 (d, 1H); 1.18 (t, 3 H).

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxypentan-1-one (9)

To a solution of (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (5) (0.63 g, 2.49 mmol) dissolved in dry CH_2Cl_2 (14 mL) under nitrogen at 0 °C was slowly added $TiCl_4$ (0.55 mL), then the reaction was stirred at 0 °C for 5 minutes. DIPEA dissolved in dry CH_2Cl_2 (3 mL) was slowly added and the reaction was stirred at -78 °C for 30 minutes. Then the propionaldehyde dissolved in dry CH_2Cl_2 (6 mL) was slowly added at -78 °C for 30 minutes. Later, the reaction 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 = 20:1 as eluent) to afford (*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxypentan-1-one (9) as yellow oil (0.47 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.30 (m, 5 H); 5.40 (m, 1 H); 4.11 (m, 1 H); 3.65 (m, 1 H); 3.32 (m, 2 H); 3.11 (m, 2 H); 2.90 (m, 2 H); 1.54 (m, 4 H); 0.91 (m, 3 H).

(*R*)-methyl 5-hydroxy-3-oxoheptanoate (4)

To a solution of (*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxypentan-1-one (9) (0.33 g, 1.05 mmol) dissolved in dry THF (4.2 mL) under nitrogen at 0 °C, was slowly added potassium salt of mono methyl malonate (0.33 g, 2.10 mmol) and imidazole (0.14 g, 2.10 mmol), then $MgCl_2$ (0.20 g, 2.10 mmol) was added, after the mixture was stirred at room temperature for 18 hours. After the reaction 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 as eluent) to afford the desired compound (*R*)-methyl 5-hydroxy-3-oxoheptanoate (4) as yellow oil (0.19 g, 45.9%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.02 (s, 1 H); 3.78 (s, 3 H); 3.51 (s, 2 H); 2.73 (m, 3 H); 1.73 (s, 1 H); 1.50 (m, 2 H); 0.95 (m, 3 H).

Acknowledgement

We gratefully thank the National Natural Science Foundation of China (No. 21362012), Science and Technology Support Program of Jiangxi Province (No. 20151BBE50004), Natural Science Foundation of Jiangxi Province (No. 20151BAB203007), Science and Technology Plan Project of Jiangxi Province (No. 20151BBG70028) for the funding support.

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