Study on synthesis of (2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal

Shenkun Yang[1,a], Tianxiang Xu[1,b], Shuangping Huang[1,c]* and Xiaoji Wang[1, d]*

[1]School of Pharmacy, Jiangxi Science and Technology Normal University, Jiangxi, 330013, China

[a]470416898@qq.com, [b]3059859608@qq.com, [c]*185544590@qq.com, [d]*13767101659@163.com

Keywords: (2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal, actinoallolide A, Evans aldol, L-Phenylalanine, synthesis.

Abstract. The C19-C23 fragment (9) of the anti-trypanosomal natural product actinoallolide A was prepared via an elegant stereo-controlled route. We installed the chiral center at C20 through a standard Evans aldol reaction, and protected the secondary hydroxyl group via a silylanization.

Introduction

Human African Trypanosomiasis and American Trypanosomiasis are serious diseases affecting human health [1-2]. Several months ago, Masato Iwatsuki and coworkers isolated actinoallolide A-E from endogenous strains *Actinoallomurus fulvus* MK10-036 [3]. These novel natural products showed prominent activity against trypanosomiasis combined with a low toxicity compared with other clinic drug molecules [4-5]. Particularly, actinoallolide A was promising to become the lead cmpound of trypanosomiasis and its related diseases. Limited by low natural content, further biological testing and research of actinoallolide family was encumbered. Total synthesis is indispensable for preparing analogs to gain deeper insight into the mode of action and the pharmacologically active moieties of the molecule.

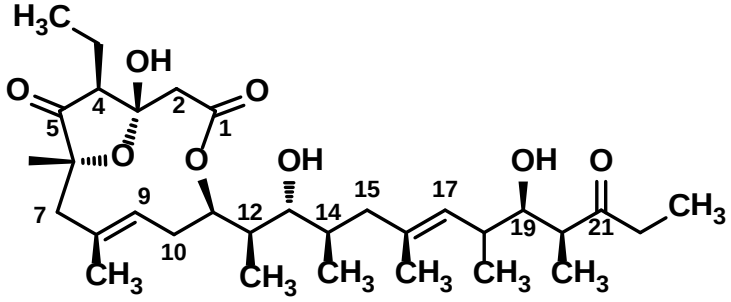

Fig. 1 Structure of actinoallolide A (1)

Structurally, actinoallolide A possesses a macrolacone, 11 stereocenters and 5 chiral hydroxyl groups. These structural characteristics also make the total synthesis of the molecule have great challenge and academic significance. Macrolactones contaning 12-membered ring has excellent biological activity like anti-bacterial [4] and anti-cancer [5]. Thus, total synthesis of actinoallolide A and its analogues has significant value on looking for new medicinal active compounds.

As shown in Fig. 2, our synthetic approach to (2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal (9) is via a seven-step route. Inexpensive commercial product L-phenylalanine (2) was initially reduced to alcohol (3), which was then converted to thiazolidinethione (4). Amide (5) could be obtained in high yield via a lysine propionylation of thiazolidinethione (4). An Evans aldol reaction between (5) and (6) proceeded in the presence of titanium tetrachloride and triethylamine to produce *trans* alcohol (7). After protected though a silylanization with chlorotriethylsilane, the secondary alcohol (7) was reduced to (2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal (9). The further study towards to actinoallolide A was going on in our lab from compound (9).

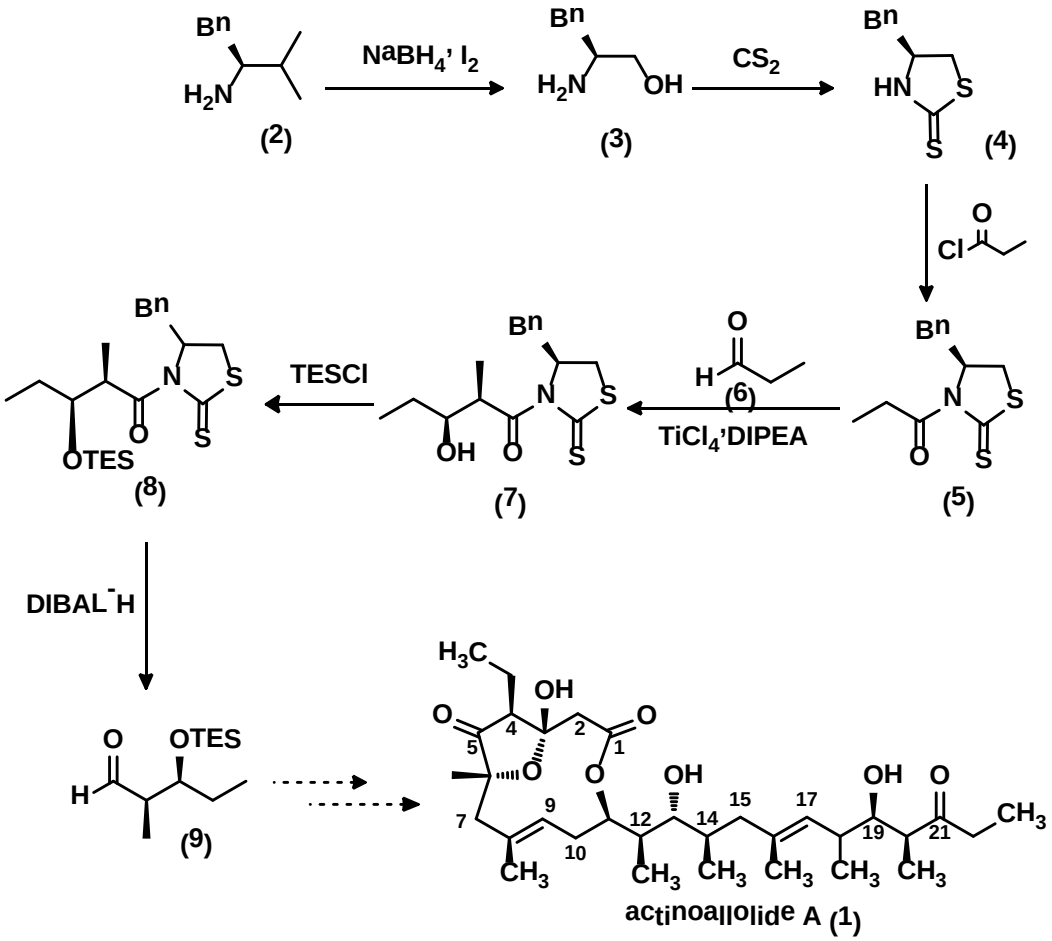

Fig. 2 Synthesis of key intermediate of actinoallolide A
(2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal (9)

Experimental

NMR spectra were recorded on a BRUKER AV-400MHz NMR (Nuclear Magnetic Resonance). The chemical shifts are recorded relative to an internal standard or relative to chloroform. All coupling constants, J, are reported in Hertz. All solvents are refined by standard method.

1.1 (S)-2-amino-3-phenylpropan-1-ol (3). To a solution of L-phenylalanine (10 g, 60.54 mol) in 140 mL THF was added $NaBH_4$ (5.73 g, 151.46 mmol) and the mixture was cooled to 0 ℃. A solution of iodine (18.4 g, 72.66mmol) in 60 mL THF was added dropwise. After adecreasing gas evolution the mixture was heated to reflux for 18 h. The flask was cooled to 0 ℃ and MeOH (24 mL) was added cautiously until the mixture became a clear solution. The resultingsolution slowly warmed to rt over 1 h and stirred at rt further 45 min. The solvent was removedunder reduced pressure and the white residue was dissolved in 126 mL of 20% aq. KOH andstirred at rt for 4 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL) and dried over Na_2SO_4, and concentrated on a rotary evaporator. Dry Column Vacuum Chromatography (DCVC) using SiO_2 and washing with EtOAc afforded (S)-2-amino-3-phenylpropan-1-ol (9.06 g, 59.9 mol, 99%); 1H NMR (400 MHz, $CDCl_3$) δ 2.49-2.56(m, 1 H), 2.78-2.83(m, 1 H), 3.08-3.16(m, 1 H), 3.36-3.42(m, 1 H) 3.61-3.66(m, 1 H), 7.18-7.37(m, 5H).

1.2 (S)-4-benzylthiazolidine-2-thione（4）. To a solution (S)-2-amino-3-phenylpropan-1-ol (3) (15 mmol) in 75 mL of aqueous 1 N potassium hydroxide was added CS_2 (75 mmol, 4.5 mL). The reaction mixture was stirred at 100 ℃ (bath at 110 ℃ and an efficient reflux condensation) for 16 h. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (2 x 75 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The crude product was further purified; 1H NMR (400 MHz, $CDCl_3$) δ 8.36 (bs,

1H), 7.32 (m, 2H), 7.26 (m, 1H), 7.18 (m, 2H), 4.46 (dd, *J* = 7.5, 15.0 Hz, 1H), 3.50 (dt, *J* = 7.9, 11.5 Hz, 1H), 3.25 (dt, *J* = 7.2, 11.5 Hz, 1H), 3.04 (m, 1H), 2.93 (m, 1H).

1.3 (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-propan-1-one (5). To a solution of thione（4） (1.30 g, 6.21 mmol) dissolved in CH_2Cl_2 (36 mL) was added triethylamine (1.04 mL,7.45 mmol) and 4-dimethylaminopyridine (0.15 g, 1.23 mmol) sequentially at 0 ℃. Freshly distilled propionyl chloride (0.70 mL, 8.07 mol) in CH_2Cl_2 (75 mL) added dropwise over 1 h. After stirring at rt for 3 h, satd. NH_4Cl (75 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were combined, washed with satd. $NaHCO_3$ (75 mL) and brine (75 mL), dried with Na_2SO_4, and concentrated on a rotary evaporator. Recrystallization from CH_3CN afforded pure (5) (1.55 g, 94%); 1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.40 (ddd, *J* = 3.8, 7.3, 10.9 Hz, 1H), 3.41 (m, 2H), 3.22 (dd, *J* = 3.7, 13.2 Hz, 1H), 3.10(qd, *J* = 7.1, 18.1 Hz, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H);

1.4 (2R,3S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylpentan-1-one (7). To a solution of acylated auxiliary S3 (7.1 g, 27 mmol) was dissolved in CH_2Cl_2 (215 mL). After cooling to 0 ℃, $TiCl_4$ (3.1 mL, 0.028 mmol) was added over 5 min. EtN^iPr_2 (5.15 mL, 30 mmol) was added. The mixture was stirred for 15 min at 0 ℃ and then cooled to -78 ℃. Propyl aldehyde (6) (2.3 mL, 30 mmol) was added and the mixture was warmed to 0 ℃ over 2 h. Satd. $NaHCO_3$ (50 mL) was added cautiously and then extracted with CH_2Cl_2 (3 × 300 mL). The organic layers were combined, washed with satd. brine (50 mL), dried with Na_2SO_4, and concentrated on a rotary evaporator. Flash chromatography with a gradient from hexanes to 1:1 hexanes/EtOAc afforded pure (7) (15.58 g, 90%); 1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.27 (m, 3H), 5.36 (ddd, *J* = 4.1, 7.2, 10.8 Hz, 1H), 4.63 (qd, *J* = 2.0, 7.1 Hz, 1H), 3.97 (m, 1H), 3.36 (dd, *J* = 7.2, 11.5 Hz, 1H), 3.24 (dd, *J* = 4.0, 13.2 Hz, 1H), 3.04 (dd, *J* = 10.4, 13.1 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 2.79 (d, J = 2.9 Hz, 1H), 1.61 (m, 1H), 1.45 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H).

1.5 (2R,3S)-2-methyl-1-(4-(3-phenylpropoxy)-2-thioxothiazolidin-3-yl)-3-((triethylsilyl)oxy) pentan-1-one (8). To a solution of ketone (7) (1.10 g, 3.4 mmol) in C2H2 (30 mL) was added imidazole (0.926g, 13.6 mmol). The mixture was then cooled to 0 ℃. Chlorotriethylsilane was added dropwise. Satd. $NaHCO_3$ (30 mL) was added cautiously and then extracted with CH_2Cl_2 (3 × 50 mL).Flash chromatography with a gradient from hexanes to 100:1 hexanes/EtOAc afforded pure (8) (1.23g, 83%); 1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.40 (ddd, *J* = 4.1, 7.2, 10.8 Hz, 1H), 4.63 (qd, *J* = 2.0, 7.1 Hz, 1H), 3.97 (m, 1H), 3.36 (dd, *J* = 7.2, 11.5 Hz, 1H), 3.24 (dd, *J* = 4.0, 13.2 Hz, 1H), 3.04 (dd, *J* = 10.4, 13.1 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 2.79 (d, *J* = 2.9 Hz, 1H), 1.61 (m, 1H), 1.45 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.8-1.0 (m, 12H), 0.7（t，6H).

1.6 (2S,3S)-2-methyl-3-((triethylsilyl)oxy)pentanal (9). The solution of (8) (0.2 g, 0.45 mmol) in C2H2 (5 ml) was cooled to -78 ℃.Then the diisobutylaluminium hydride（DIPEA-H, 1.5 mol/L） (0.45 mL， 0.675 mmol) was added dropwise. The mixture was stirred for 30 min, then quenched with MeOH (0.5 mL) and potassium sodium tartrate (5mL).Dry Column Vacuum Chromatography (DCVC) using SiO_2 and washing with a gradient from hexanes to 100:1 hexanes/EtOAc afforded pure (8) (0.09g, 87%); 1H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 4.06 (t,1H), 2.46 (m, 1H), 1.60 (m, 1H), 1.45 (m, 1H), 1.07 (d, 3H), 0.8-1.0 (m, 12H), 0.7 (t, 6H).

Acknowledgement

We gratefully thank the National Natural Science Foundation of China (No.21562020), Science a nd Technology Research Projects of the Education Department of Jiangxi Province (No. GJJ14579), Science and Technology Plan Project of Jiangxi Province (No. 20142BBE50006), Scientific Resear ch Fund of Jiangxi Provincial Education Department (No. KJLD12036), Training Fund for Excellen t young scientist of JiangXi Province (No. [2013]138) for the funding support.

References

[1] R. Viotti, C. Vigliano, B. Lococo, Ann. Intern. Med. 144 (2006) 724-734.

[2] P. J. Hotez, E. Dumonteil, L. Woc-Colburn, J. A. Serpa, S. Bezek, M. S. Edwards, C. J. Hall-mark, L. W. Musselwhite, B. J. Flink, M. E. Bottazzi, Plos. Neql. Trop. Dis. 6 (2012) e1498.

[3] I. Masato, Y. Inahashi, I. Aki, Organic letters. 17 (2015) 864-867.

[4] I. Yuki, I. Masato, I. Aki, M. Atsuko, H. Tomoyasu, O. Jun, S. Toshiaki, P. Watanalai, T. Yoko, T. Marcel, O. Kazuhiko, Ō. Satoshi, Org. Lett. 17 (2015) 864-867.

[5] E. Chatelain, J. Biomol. Screen.20 (2015) 22.

[6] J. Clayton, Nature. 465 (2015) S12.

[7] M. N. Donin, J. Pagano, J. D. Dutcher, C. M. Mckee, Antibiot. Ann. 1 (1953−1954) 179.

[8] Y. Takayasu, K. Tsuchiya, T. Aoyama, Y. J. Sukenaga, Antibiot. 54 (2001) 1111.