Study on synthesis of (R)-tert-butyl 4-formyl-2, 2- dimethylthiazolidine- 3 -carboxylate

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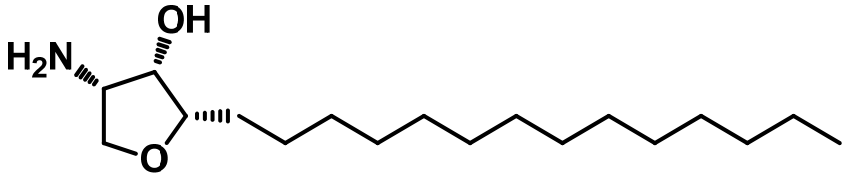
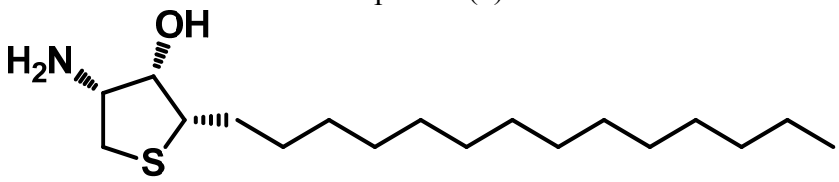
Abstract. (R)-tert-butyl 4-formyl-2,2-dimethylthiazolidine-3-carboxylate is an imntermediate of S-jaspine B known as a potential substitution of pachastrissamine (jaspine B) which shows effective biological activity. Herein we describe an elegant straightforward synthetic path for this attractive molecule intermediate.

Introduction

Jaspine B (1) (showed in Figure 1) is a natural occurring product with three chiral centers in a tetrahydrofuran ring. Since jaspine B has been firstly isolated form Okinawan marine sponge *Pachastrissa* sp. in 2002 by Higa and coworkers [1], many investigations has been attached to this attractive molecule and its analogs [2-4]. Jaspine B was observed to display remarkable cytotoxicity against several kinds of cancer cell lines. Andrieu-Abadie and co-workers reported that jaspine B induces apoptotic cell death in melanoma cells through a caspase-dependent pathway [5]. A lot of literatures have reported the syntheses of jaspine B [6-9].



Jaspine B (1)

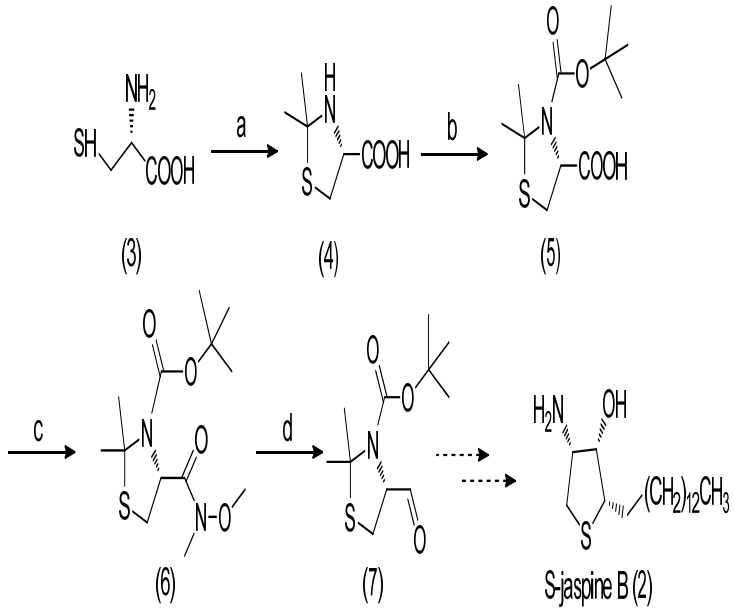


S-Jaspine B (2)

Fig. 1 Structure of jaspine B and S-jaspine B

Hongjun [10] et al made the bioisosteric substitution to replace of C with N in the aromatic ring to get S-jaspine B (2). They found that the ring oxygen atom of jaspine B is amenable to bioisosteric substitution with sulfur atoms. S-jaspine B showed more effective cytotoxicity against several kinds of tumor cell lines because the bioisosteric subsititution could systematically change both biological and physicochemical properties of jaspine B. To reach this outstanding compound, we employed a readily synthetic method developed by our group.

As depicted in Fig. 2, a four steps method to reach aldehyde (7) synthesized from the inexpensive subject L-cystine (3), which was primarily converted to thiazolidine (4) under the condition of reflux acetone in high yield. The thiazolidine (4) was sequentially protected with Boc to acquire intermediate (5) in the solution of a bit excess of di-tert-butyl dicarbonate (Boc2O) and iPr2Net in acetonitrile at room temperature. Next, intermediate (5) was transformed into N-methoxy-N-mythyl amide (6) in solution of N, O-dimethylhydroxylamine hydrochloride, iPr2Net and N, N’-dicyclohexylcarbodiimide in dichloromethane.



a) acetone, 60 ℃, 2 h, 97%

b) Boc2O, iPr2Net, MeCN, 25 ℃, 48 h, 72%

c) N, O-dimethyhydroxylamine hydrochloride, iPr2NEt, N, N'-Dicyclohexylcarbodiimide, DCM, 12 h, 70%

d) DIBAL-H, DCM, -78℃

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Fig. 2 Synthesis of key intermediate of S-jaspine B
(R)-tert-butyl 4-formyl-2,2-dimethylthiazolidine-3-carboxylate

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 (R)-2, 2-dimethylthiazolidine-4-carboxylic acid (4). L-Cysteine (10 g, 82.5 mmol) was refluxed at 60 °C in dry acetone (500 mL) under dry nitrogen for 2 h. Large white crystalline plates of the thiazolidine (13.2 g, 99%) were collected by filtration. This material was used without further purification: lH NMR (400 MHz, D_2O), δ 4.94 (1 H, t, J = 9 Hz, methine), 3.65 and 3.79 (2 H, dd, J = 9 Hz ,J = 18 Hz, methylene), 2.02 (3H, s) and 1.95 (3 H, s) (2,2-dimethyl).

1.2 (R)-3-(tert-butoxycarbonyl)-2,2-dimethylthiazolidine-4-carboxylic acid (5). (R)-2,2 -dimethylthiazolidine-4-carboxylic acid (13.2 g, 82.5 mmol) and di-tert-butyl dicarbonate (22.6 ml, 107 mmol) in dry acetonitrile was added $^{i}Pr_2NEt$ (15.7 mL, 90 mmol). The suspension was allowed to stir for 2 days. The MeCN was removed in vacuo, and the remaining oil was taken up in ether and concentrated in vacuo to an oily solid. The oily did was again taken up in ether, and the amine salt was removed from the ether solution by fitration through Celite. The ethereal filtrate was washed with 0.1 N HC1, water , and brine, dried, and concentrated to a clear oil that was dissolved in hexanes and concentrated in vacuo to a white solid. Crystallization from hexanes yielded white needles (17.3 g, 72%); 1H NMR (400 MHz, CDCl3) δ 5.09 (m) and 4.90 (m) (1 H, Cα-H), 3.30 (m, 2 H, Cβ-H2), 1.95 (s) and 1.90 (s) (6 H, isopropylidine methyls), 1.50 (s) and 1.60 (s) (9 H, tert-butyl).

1.3 (R)-tert-butyl 4-(methoxy(methyl)carbamoyl)-2, 2-dimethylthiazolidine-3-carboxylate (6). To a suspension of N,O-dimethylhydroxylamine hydrochloride (6 g, 61 mmol) in dry CH_2Cl_2 (120 mL) at 5 °C under argon, was added successively, neat $^iPr_2NEt$ (8 g, 61 mmol), acid (5) (16 g, 61 mmol) and DCC (13 g, 63 mmol) as solids. The mixture was stirred overnight at room temperature, DCU was filtered off, the filtrate was concentrated and the residue was taken up in ether. The organic phase was washed successively by 1 N HCl, H_2O, saturated $NaHCO_3$ and brine before flash chromatography on silicagel; 1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H, tert-C_4H_9); 2.97–3.08 (m, 1H, 5-CH (thia)); 3.18 (s, 3H, NCH_3); 3.30–3.43 (m, 1H, 5-CH (thia)); 3.73 (bs, 1H, OCH_3); 4.47–4.50 (m, 1H, 2-CHH(thia)); 4.63–4.76 (m, 1H, 2-CHH (thia)), 5.07 (m, 1H, 4-CH(thia)); 13C-NMR ($CDCl_3$) δ 26.51, 32.13, 33.09, 49.11, 59.06, 61.06, 80.47, 152.90, 170.93.

1.4 (R)-tert-butyl 4-formyl-2,2-dimethylthiazolidine-3-carboxylate (7). To a stirred solution of (6) (11.3 g, 32.3 mmol) in CH_2Cl_2 (150 mL) cooled to -78℃ was added DIBAL-H (39 mL, 39 mmol) dropwise. The solution was stirred at -78 ℃ for 1 h, and the reaction was quenched by the addition of sat.aq potassium sodium tartrate solution (65 mL). Then, the mixture was warmed up to r.t. and filtered through a pad of Celite. The residue was washed with sat. aq NaCl. The resulting mixture was extracted with CH_2Cl_2 (3×50 mL). The organic extract was concentrated to obtain the crude product, which was purified with flash chromatography on silica gel eluting with petroleum ether-ethyl acetate (20:1) to give 8.29 g (80% yield) of the aldehyde (7) as a colorless oil: 1H NMR (400 MHz, $CDCl_3$) δ1.36-1.81(m, 15H), 3.12(m, 2H), 4.48-4.66(m, 1H), 9.51(s, 1H).

Acknowledgement

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