Stereoselective Synthesis of (*S,E*)-2-(trimethylsilyl)ethyl 3-hydroxy-7-(tritylthio)hept-4-enoate

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Abstract: (*S,E*)-2-(trimethylsilyl)ethyl 3-hydroxy-7-(tritylthio)hept-4-enoate was synthesized from commercially available L-malic acid by the Julia-Kocienski olefination coupling method. This method provides a concise synthetic strategy for (*S,E*) -3-hydroxy-7-mercaptohept-4-enoic acid.

Keywords: (*S,E*)-3-hydroxy-7-mercaptohept-4-enoic acid, Julia-Kocienski olefination coupling, L-malic acid.

INTRODUCTION

Inhibition of histone deacetylase (HDAC) activity has been clinically validated as a novel therapeutic strategy for the treatment of cancer [1]. To date, natural products, such as largazole, spiruchostatins A and B, and the depsipeptides FR901375 and K228, have been reported to have potent HDAC-inhibitory activity [2-6]. All these natural products have a common motif, *(S,E)*-3-hydroxy-7-mercaptohept-4-enoic acid (Fig. **1**), which is essential for their HDAC-inhibitory activity. *(S,E)*-3-hydroxy-7-mercaptohept-4-enoic acid contains a seven-carbon framework with four functional groups and a chiral center. Although the preparation of (*S*)-3-hydroxy-7-mercaptohept-4-enoic acid has been reported during the total synthesis of natural products by several groups [7-15], it is nonetheless worthwhile to develop a more concise route.

Recently, we have published an efficient method for the total synthesis of largazole, in which a new approach for the synthesis of 3-hydroxy-7-mercaptohept-4-enoic acid was also developed [15]. This approach involved the production of *(S,E)*-3-hydroxy-7-mercaptohept-4-enoic acid by Julia-Kocienski olefination. The olefination led to geometric isomers with chirality at C5 and the E/Z ratio being 8:1, moreover, the derivatives with *trans* geometry had better biological activity. Therefore, we proceeded to develop an improved strategy, which would produce a more favorable E/Z ratio during the synthesis of *(S,E)*-3-hydroxy-7-mercaptohept-4-enoic acid.

RESULTS AND DISCUSSION

As outlined in Scheme **1**, we initially pursued the synthesis of **1** through Julia-Kocienski olefination between **7** and **8**, which were synthesized from propane-1,3-diol and L-malic acid, respectively [15]. The crucial olefination coupling of **7** and **8** proceeded smoothly to yield the desired product **9** as a mixture of E/Z stereoisomers (E/Z approximately.8:1, as determined by ^{1}H-NMR) with a yield of 80%.

At this point, we assumed that the steric structure of aldehyde **7** was the key factor for olefination. To verify this idea, we reversed the coupling partners, preparing aldehyde **20** by the monoprotection of propane-1,3-diol and Swern oxidation.

Our new synthesis route is outlined in Scheme **2**. Treatment of L-malic acid with $SOCl_2$ in methanol gave its dimethyl ester **11**, which was then reduced by borane–dimethylsulfide (BH_3–Me_2S). The diol **12** was sequentially silylated by tert-butyl TBSCl to generate **13** in 90% yield. The ester group of **13** was saponified by KOH, and then coupled with 2-(trimethylsilyl) ethanol to provide the ***2***-(*trimethylsilyl*)ethyl (TSE)-protected acid **15**, which gave alcohol **16** after selective removal of the t-butyldimethylsilyl (TBS)-protecting group on the primary alcohol. The Mitsunobu method was used for the formation of tetrazole **18**, which was then treated by m-CPBA to yield the sulfone **19**. Using NaHMDS as the base, the olefination coupling process generated compound **21** (E/Z approximately 4:1, as determined by ^{1}H-NMR) at –78 °C in 35% yield. After the selective removal of the primary TBS-protecting group, the Mitsunobu reaction was carried out with TrtSH to give a mixture of the *cis* and *trans* isomers of **23**, which could then be separated on a silica gel to provide the desired *E*-olefinic **23**.

EXPERIMENTAL

Solvents were purified in a conventional manner. Thin-layer chromatography was carried out on precoated GF254 plates (Qingdao, China). Flash-column chromatography was conducted on silica gel (200–300 mesh, Qingdao, China).

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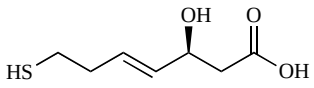
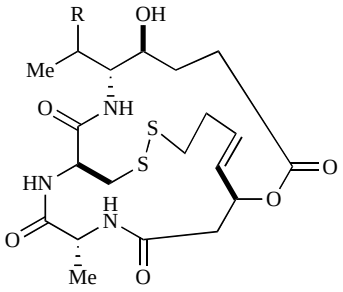
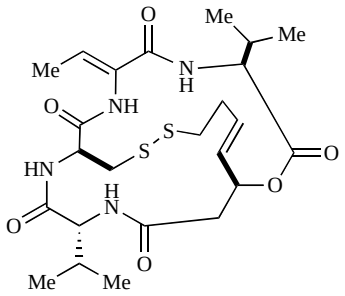


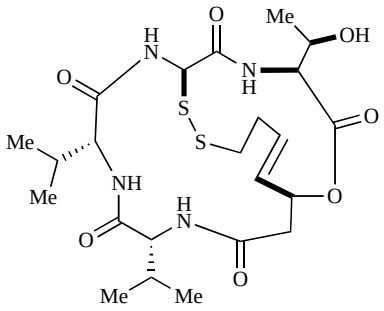
1: (*S*,*E*)-3-hydroxy-7-mercaptohept-4-enoic acid



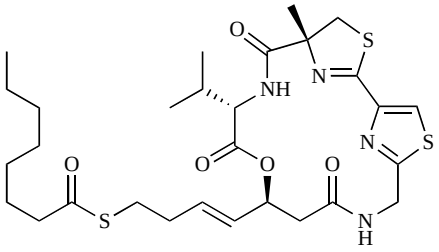
2: spiruchostatin A (R=Me)
3: spiruchostatin B (R=Et)



4: FK228

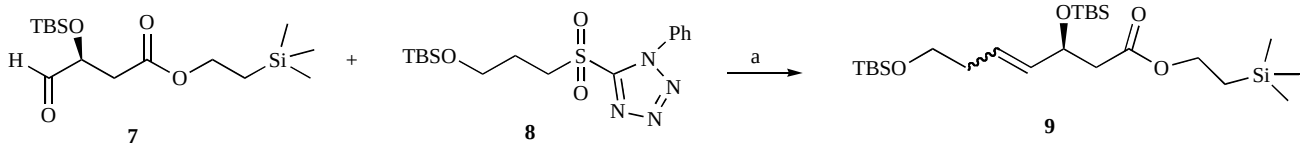


5: FR901375



6: largazole

Fig. (1). Structures of (**1**) (*S*,*E*)-3-hydroxy-7-mercaptohept-4-enoic acid (**2**) spiruchostatin A, (**3**) spiruchostatin B, (**4**) FK228, (**5**) FR901375 and (**6**) Largazole.



7 **8** **9**

Scheme 1. Preparation of (*S*)-2-(trimethylsilyl)ethyl 3,7-bis(tert-butyldimethylsilyloxy)hept-4-enoate, compound **9** (a) NaHMDS, THF, –78 °C, 80%.

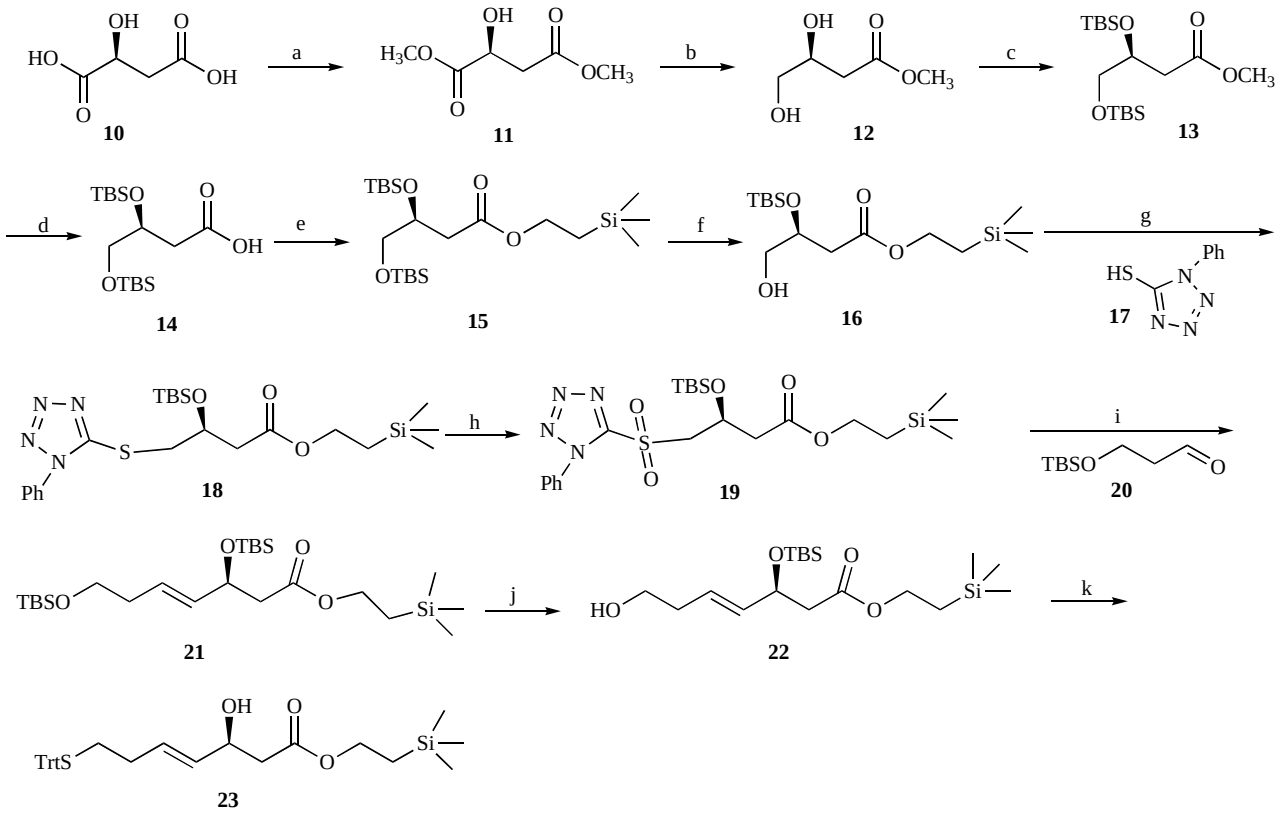
Optical rotations were determined with a Perkin-Elmermodel241MC polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were detected using a Bruker spectrometer, with tetramethylsilane (TMS) as an internal standard, and the chemical shifts were recorded in parts per million (ppm).

(*S*)-2-(trimethylsilyl)ethyl 3-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio) butanoate (18)

DEAD (4.36 g, 25.0 mmol) was added dropwise to a solution of **16** (8.355 g, 25.0 mmol) and Ph_3P (6.55 g, 25.0 mmol) in anhydrous THF (125 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, washed with water (50 mL), and extracted with EtOAc (3 × 60 mL), the combined organic phases were dried under anhydrous Na_2SO_4 and the solvent was removed by evaporation under vacuum. Flash chromatography on silica gel(eluent: heptane/EtOAc = 6/1, v/v) yielded **18** (12.36 g, 91%) as a white solid. $[\alpha]^{23}_{D}$ = –11.5(*c* = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 5H), 4.54 (m, 1H), 4.15 (m, 2H), 3.66 (dd, *J* = 13.6, 5.2, 1H), 3.58 (dd, *J* = 12.8, 5.6, 1H), 2.64 (dd, *J* = 15.2, 5.6, 1H), 2.57 (dd, *J* = 15.2, 5.6, 1H), 0.98 (t, *J* = 8.8, 2H), 0.85 (s, 9H) , 0.05(d, *J* = 8.8, 6H), 0.04 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) : 130.1, 129.7, 123.9, 67.8, 62.8, 41.7, 40.0, 25.7, 17.9, 17.4, –1.6, –4.7, –4.9 pm. MS (EI, *m/z*): 495 (M^+ + 1).

(*S*)-2-(trimethylsilyl)ethyl 3-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)butanoate (19)

Tetrazole **18** (4.94 g, 10.0 mmol) was dissovled in CH_2Cl_2 (50 mL) and cooled to 0 °C. M-CPBA (77%, 2.35 g,



Scheme 2. Preparation of (*S*,*E*)-2-(trimethylsilyl)ethyl 3-hydroxy-7-(tritylthio)hept-4-enoate **23** (a) $SOCl_2$/MeOH, reflux 92%; (b) borane (BH_3), Sodium borohydride ($NaBH_4$), THF, rt, 89%; (c) tert-butyl dimethyl chlorosilane (TBSCl), imidazole, dimethyl formamide (DMF), rt, 92%; (d) KOH, THF/H_2O;(e) dicyclohexylcarbodiimide (DCC), trimethylsily ethanol (TMSEOH), rt, 81% in two steps; (f) camphorsulfonic acid (CSA), $CHCl_3$/CH_3OH, –10 °C, 80%; (g) Diethyl azodicarboxylate (DEAD), Ph_3P, THF, rt, 91%; (h) m-chloroperbenzoic acid (m-CPBA),CH_2Cl_2, rt, 85%; (i) sodium hexamethyldisilazane (NaHMDS), THF, –78 °C, 35%; (j) CSA, $CHCl_3$/CH_3OH, 0 °C, 89%; (k) 1. triphenylmethyl thiol (TrtSH), DEAD, Ph_3P, rt, 70%; 2. CSA, $CHCl_3$/CH_3OH, rt, 61%.

10.5 mmol) was added in small portions, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a yellow oil **19** (4.47 g, 85%), which was directly used in the next step without further purification. $[\alpha]^{23}_D$ = –7.5 (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68–7.57 (m, 5H), 4.78 (m, 1H), 4.18–4.12 (m, 4H), 2.77 (dd, *J* = 13.6, 6.4, 1H), 2.57 (dd, *J* = 13.6, 5.2, 1H), 0.98 (t, *J* = 8.4, 2H), 0.82 (s, 9H) , 0.07 (d, *J* = 7.2, 6H), 0.03 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) : 131.4, 129.6, 125.2, 64.1, 63.1, 61.8, 42.0, 29.6, 25.6, 17.8, 17.4, –1.59, –4.9, –5.0 ppm. MS (EI, *m/z*): 527 (M^+ + 1).

(*S, E*) 2-(trimethylsilyl)ethyl 3,7-bis(*tert*-butyldimethyl-silyloxy)hept-4-enoate (21)

NaHMDS (1.0 M in THF, 5.0 mL) was added slowly with a syringe into the flask contained a solution of **19** (2.63 g, 5.0 mmol) and **20** (0.94 g, 5.0 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred for 2 h at –78 °C and then quenched by adding NH_4Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried under anhydrous Na_2SO_4, and the solvent was removed by evaporation under vacuum. Flash chromatography on silica gel (eluent: heptane/EtOAc = 10/1, v/v) yielded **21** (0.85 g, 35%) as a light yellow oil. $[\alpha]^{23}_D$ = –21.6 (*c* = 0.5, $CHCl_3$). ^{1}H-NMR (400 MHZ, $CDCl_3$): δ 5.63 (dt, *J* = 15.6, 6.8, 1H), 5.49 (dd, *J* = 15.6, 6.8, 1H), 4.54 (dd, *J* = 12.4, 7.2, 1H), 4.14 (m, 2H), 3.61 (t, *J* = 6.8, 2H), 2.49 (dd, *J* = 14.4, 8.4, 1H), 2.38 (dd, *J* = 14.4, 5.2, 1H), 2.22 (dd, *J* = 13.2, 6.4, 2H), 0.97 (dd, *J* = 8.4, 6.8, 2H) , 0.89 (s, 9H), 0.85 (s, 9H), 0.07–0.03 (m, 21H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 171.3, 134.0, 127.7, 126.4 (minor), 70.7, 66.1 (minor), 62.8, 62.5, 44.2, 35.7, 31.5 (minor), 26.0, 18.3, 17.3, –1.5, –4.2, –5.0, –5.3 pm. MS (EI, *m/z*): 489 (M^+ + 1).

(*S, E*)-2-(trimethylsilyl)ethyl 3-hydroxy-7-(tritylthio)hept-4-enoate (23)

The compound **21** (0.49 g, 1.0 mmol) was dissolved in CH_2Cl_2/MeOH (4/1 v/v, 45 mL), then, CSA (0.23 g, 1.0 mmol) in MeOH (1.5 ml) was added at –10 °C. The reaction mixture was vigorously stirred at –10 °C for 6 h under N_2 atmosphere, and then quenched with $NaHCO_3$ solution (5 mL). The resulting solution was successively washed with water(3 × 50mL) and brine (3 × 50mL). The organic phase was dried under anhydrous Na_2SO_4 and concentrated, to yield the oil **22**. DEAD (0.17 g, 1.0 mmol) was added dropwise to a solution of **22** (0.37 g, 1.0 mmol), TrtSH (0.276 g, 1.0 mmol), and Ph_3P (0.262 g, 1.0 mmol) in

anhydrous CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, washed with water, and extracted with EtOAc. The combined organic phases were dried under anhydrous Na_2SO_4, and the solvent was removed by evaporation under vacuum. Flash chromatography on silica gel (eluent: heptane/EtOAc = 10/1 v/v) yielded **23** (0.22 g, 43%) as a white foam. $[\alpha]^{23}_D = -15.7$ (c = 0.5, $CHCl_3$). ^{1}H-NMR(400 MHZ,$CDCl_3$): δ 7.25–7.38 (m, 15H), 5.53 (m, 1H), 5.37 (dd, J = 15.2, 6.0, 1H), 4.38 (m, 1H), 4.14 (m, 2H), 4.15 (t, J = 8.9, 2H), 2.42 (m, 2H), 2.04 (m, 2H) , 0.94 (m, 2H), 0.03 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 172.6, 145.1, 132.2, 130.3, 129.7, 128.0, 126.7, 68.7, 66.7, 63.2, 41.7, 31.6, 31.5, 17.5, –1.4 ppm. MS (EI, *m/z*): 542 (M^+ + Na).

CONCLUSION

In summary, (*S*,*E*)-2-(trimethylsilyl)ethyl 3-hydroxy-7-(tritylthio)hept-4-enoate was synthesized from commercial materials with an overall yield of 5%. This method may potentially be applicable for the synthesis of other analogs for structure–activity relationship studies. The application of this methodology to the preparation of novel largazole or other natural product analogs for biological evaluation is under way and will be reported in due course.

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