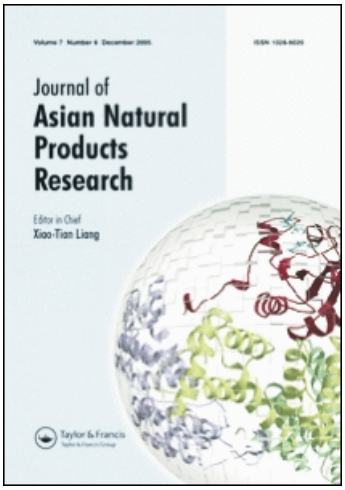

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Concise total synthesis of largazole

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The concise total synthesis of largazole was accomplished. The key step included the use of the Nagao thiazolidinethione auxiliary for the diastereoselective acetate aldol reaction and it acts as an acylating agent for the peptide formation.

Keywords: largazole; concise total synthesis; aldol reaction

1. Introduction

Largazole is a cyclic depsipeptide, isolated from a cyanobacterium of Floridian marine cyanobacterium *Symploca sp.* by Luesch and co-workers [1]. It possesses a combination of several interesting structural features, including a substituted 4-methyl thiazoline linearly fused to a thiazole, L-valine, and (3*S*,4*E*)-3-hydroxyl-7-thio-4-heptenoic acid. Largazole inhibits exceptionally potent and selective activity against the growth of highly invasive transformed human mammary epithelial cell [1]. Its biological mode of action has been proved to be a selective inhibitor of histone deacetylase (HDAC), which is believed to be the most relevant and tractable cancer target today [2].

The unique structure features and the therapeutic potential of largazole have stimulated the extensive study on the total synthesis of it and its derivatives. Luesch and co-workers [2] reported the first total synthesis of largazole based on macrocyclization and olefin cross-metathesis and led to the discovery that HDAC is the molecular target for largazole. Up to now, several total synthesis of largazole and its analogs have been published [3–8], with each reported synthesis employing protection and deprotection steps before the macrocyclization, and such operation was difficult due to the sensitivity of the reaction of the allylic alcohol moieties. Herein, we report a shorter procedure for total synthesis of largazole, and our route is better yielding.

2. Results and discussion

The synthetic strategy for largazole is illustrated in Scheme 1. We described the concise synthesis of largazole (**1**) in a convergent manner through the assembly and macrocyclization of liner precursor **2**. Further disconnection of **2** at the amide linkage provided two intermediates **3** and **4**. The thiazoline–thiazole derivative **3** was prepared with subunits **5** and **6** using a similar methodology developed by Charette. Furthermore, the intermediate **4** would be obtained from **7** through *O*-acylation with *N*-Fmoc-valine **8**.

Although (*R*)-2-methylcysteine methyl ester hydrochloride **5** [9] has been obtained by Donald A. Whiting using the

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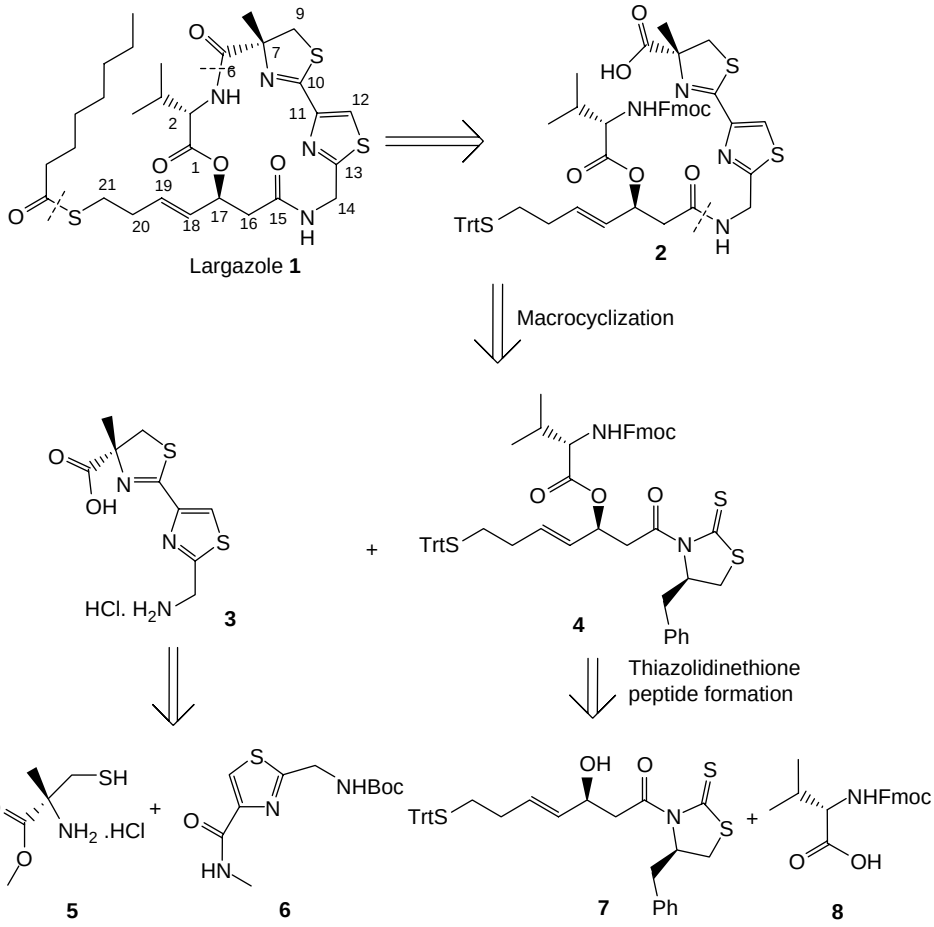
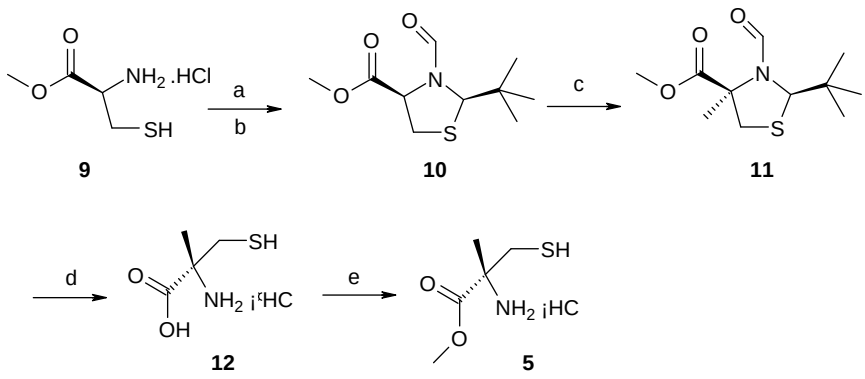


Scheme 1. Synthetic strategy for largazole.

Seebach's 'Self-regeneration of stereocenters' protocol, we prepared it by an improved method [10] of using NaHMDS instead of LDA in the alkylation step (Scheme 2). Substituting the LDA with the NaHMDS in our experiment led significant improvement in the yield from 56 to 90%.

The subunit **3** was efficiently constructed as follows (Scheme 3). The synthesis commenced with commercially available Boc-protected glycine amide, which was converted to thiazolyl amide **6** [11,12] in 65% yield over three steps. Using a similar methodology [13] developed by Charette, condensation of **6** with (*R*)-2-methyl-cysteine methyl ester hydrochloride **5** (Tf_2O, pyridine, CH_2Cl_2, -40°C to room temperature) provided **16** in 75% yield. Thiazoline–thiazole amine acid **3** was readily prepared from **16** by the removal of the methyl ester and then the *N*-Boc group.

Aldol reaction of the known aldehyde **18** [14] with the *N*-acetyl thiazolidinethione Nagao auxiliary **17** under Vilarrasa's $TiCl_4$ conditions [15] at low temperature (-90°C) was highly diastereoselective, yielding the major diastereomer β-hydroxycarbonyl unit **7** in 75% yield (Scheme 4). Subsequently, coupling of **7** with *N*-Fmoc-L-valine afforded ester **4**

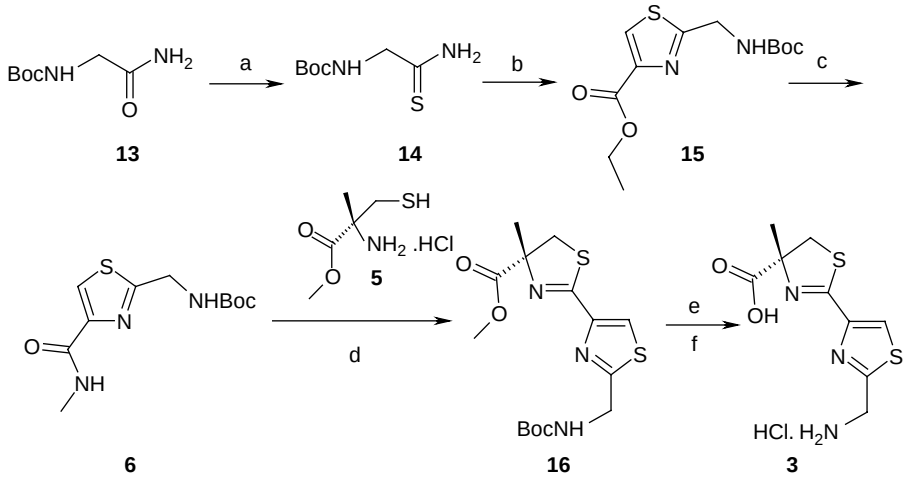


Scheme 2. Synthesis of compound **5**. Reagents and conditions: (a) *t*-Bu-CHO, Et_3N, reflux, 74%; (b) HCOOH, HCOONa, Ac_2O, rt, 85%; (c) NaHDMS, MeI, THF: DMPU: hexane = 6:1:1, −90°C, 90%; (d) 5M HCl, reflux, 90%; and (e) SO_2Cl_2, CH_3OH, reflux, 94%.

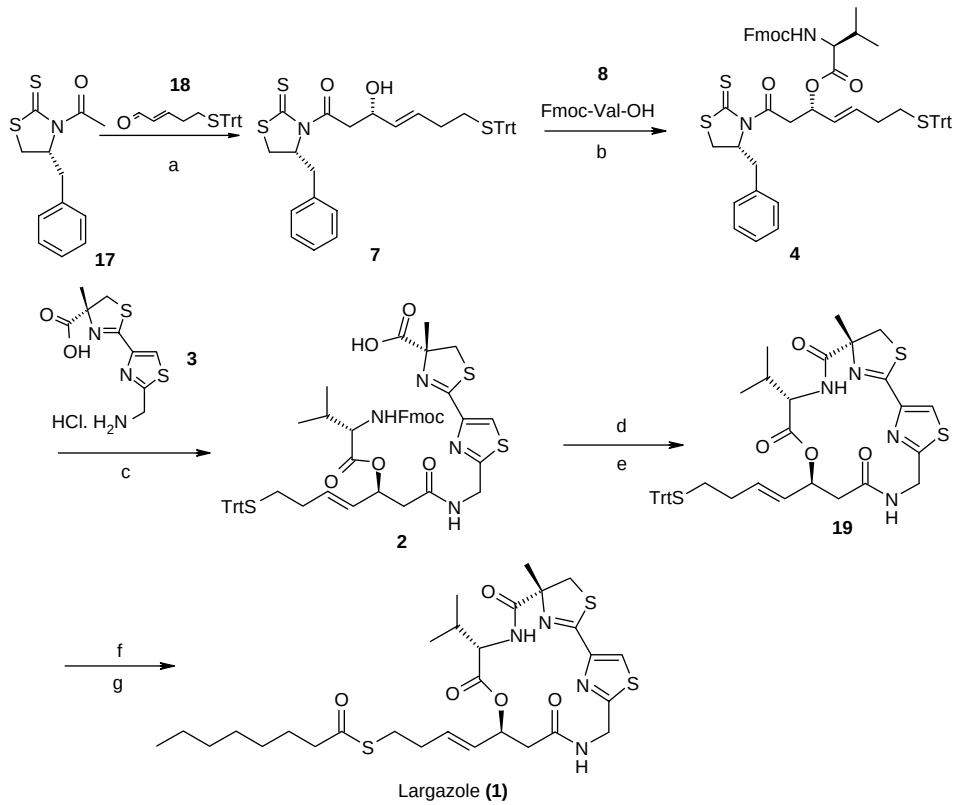
in 80% yield. As the thiazolidinethione in **4** can act as an acylating agent for the next amidation [16], the treatment of the fragment **4** with **3** afforded liner precursor **2** in 75% yield.

After the removal of *N*-Fmoc group in **2**, macrolactamization of **2** was effected under high dilution in the presence of HATU and HOBt, furnishing the desired macrocycle **19** [2] in 65% yield over two steps. Removal of the *S*-trityl group in **19** provided the crude thiol, which was directly acylated with octanoyl chloride to furnish largazole **(1)** [2] in 90% yield over two steps.

In conclusion, we have accomplished a concise total synthesis of largazole **(1)** from the *N*-acetylthiazolidinethione Nagao auxiliary **17** in 26.33% overall yield with seven steps. Our synthesis procedure was relatively shorter and did not need additional protection and deprotection steps. Such modification would be efficient and practical to provide an inexpensive



Scheme 3. Synthesis of compound **3**. Reagents and conditions: (a) Lawesson's reagent, DME, rt, 94.7%; (b) $BrCH_2COCOC_2H_5$, $CaCO_3$, C_2H_5OH, rt, 70%; (c) CH_3NH_2, C_2H_5OH, rt, 98.5%; (d) Tf_2O, pyridine, CH_2Cl_2, −40°C to rt, 75%; (e) NaOH, H_2O/dioxane, rt, 95%; and (f) HCl-AcOEt, rt, 94%.



Scheme 4. Synthesis of compound **1**. Reagents and conditions: (a) $TiCl_4$, DIPEA, CH_2Cl_2, −90°C, 75%; (b) Fmoc-Val-OH, EDCI, DMAP, DIPEA, CH_2Cl_2, 0°C to rt, 80%; (c) **3**, DMAP, DMF, rt, 75%; (d) Et_2NH, MeCN, rt; (e) HATU, HOBt, DIPEA, MeCN, rt, 65% (over two steps); (f) TFA, Et_3SiH, CH_2Cl_2, 0°C to rt; and (g) octanoyl chloride, Et_3N, CH_2Cl_2, 0°C to rt, 90% (over two steps).

supply of largazole **(1)** and its analogs for further study. The molecular structure of the product was determined by ^{1}H NMR, ^{13}C NMR, ESI-MS, and all the physical data matched the published data [2]. The optical rotation of the synthetic product $[\alpha]_D^{20} + 24$ (*c* 0.4, MeOH) was also consistent with the reported literature [1] for natural largazole $[\alpha]_D^{25} + 22$ (*c* 0.1, MeOH).

3. Experimental

3.1 General experimental procedures

All melting points were measured by a Yanaco model MP-500 V micro-melting point apparatus and are uncorrected. Optical rotations were collected at 589 nm on a Perkin-Elmer 241 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on the Varian 300 (75) or 600 (150) MHz NMR spectrometer with $CDCl_3$ as solvent. ESI-MS spectra were determined on a Micromass AutoSpec Ultima-TOF spectrometer. Reactions were monitored with TLC using GF254. Products were purified via column chromatography using the solvent system(s) indicated. Silica gel (160–200 mesh) was used for column chromatography. GF254 and silica gel (160–200) were made by Qingdao Haiyang chemical Co. Ltd, Qingdao, China. Tetrahydrofuran (THF) was freshly distilled over sodium or $LiAlH_4$. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were freshly

distilled over phosphorus pentoxide (P_2O_5). *N*,*N*-dimethylformamide (DMF) was dried with molecular sieve 4A. All the reagents were obtained from Beijing Chemical Works, Beijing, China.

3.2 4R-Methyl-2-tert-butyl-1,3-thiazolidine-4-carboxylate

To a suspension of **9** (1.74 g, 0.01 mol) and trimethylacetaldehyde in pentane (20 ml), triethylamine (1.6 ml, 0.011 mol) was added dropwise. The resulting suspension was heated under reflux with continuous removal of water for 24 h. The mixture was cooled and filtered, and the residue was then washed with ether. After removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (20:1 v/v) to afford 4*R*-methyl-2-tert-butyl-1,3-thiazolidine-4-carboxylate (1.5 g, 74%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of diastereomers (2.5:1); major isomer δ (ppm) 4.48 (s, 1H, C**H**C $(CH_3)_3$), 3.78 (s, 3H, CO_2CH_3), 3.26 (t, $J = 13.2$ Hz, 1H, C**H**H), 2.71 (t, $J = 9.9$ Hz, 1H, CH), 2.21 (t, $J = 13.2$ Hz, 1H, CH**H**), 1.07 (s, 9H, CHC(C**H**$_3)_3$); minor isomer δ (ppm) 4.52 (s, 1H, C**H**C$(CH_3)_3$), 4.14 (t, $J = 6.3$ Hz, 1H, C**H**CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 3.10 (dd, $J = 6.3$, 10.5 Hz, 1H, C**H**H), 3.02 (dd, $J = 6.3$, 10.5 Hz, 1H, CH**H**), 1.07 (s, 9H, CHC(C**H**$_3)_3$); HRESIMS: *m/z* 204.1077 $[M + H]^+$ (calcd for $C_9H_{18}NO_2$, 204.1058).

3.3 2R,4R-Methyl-2-tert-butyl-1,3-thiazolidine-3-formyl-4-carboxylate (10)

4*R*-Methyl-2-tert-butyl-1,3-thiazolidine-4-carboxylate (1.015 g, 5 mmol) and dihydration sodium formate (572 mg, 5.5 mmol) were dissolved in formic acid (20 ml) and cooled to 0°C. Acetic anhydride (1.42 ml, 15 mmol) was added dropwise. The solution was warmed to room temperature and then stirred for 4 h. The solvents were evaporated under reduced pressure, and the residue was then carefully neutralized with saturated $NaHCO_3$ solution and extracted with ethyl ether (20 ml ×3). The combined organic layers were dried over Na_2SO_4 and filtered. After removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (20:1 v/v), followed by crystallization from ethyl acetate–light petroleum ether to afford **10** (0.98 g, 85%) as a white crystal. Mp 78–79°C; $[\alpha]_D^{20}$ − 130 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of conformers (8:1); major conformer δ (ppm) 8.35 (s, 1H, CHO), 4.89 (t, $J = 9.0$ Hz, 1H, C**H**CO_2CH_3), 4.74 (s, 1H, C**H**C$(CH_3)_3$), 3.77 (s, 3H, CO_2CH_3), 3.27 (m, 2H, CH_2), 1.03 (s, 9H, CHC(C**H**$_3)_3$); HRESIMS: *m/z* 232.1004 $[M + H]^+$ (calcd for $C_{10}H_{18}NO_3S$, 232.1001).

3.4 2R,4R-Methyl-2-tert-butyl-3-formyl-4-methyl-1,3-thiazolidine-4-carboxylate (11)

To a 0.2 M solution of **10** (2.32 g, 10 mmol) in freshly distilled THF (50 ml) under an argon atmosphere, DMPU (8 ml, 1:6 of the THF volume), the iodomethane (2.49 ml, 40 mmol), and hexane (8 ml, 1:6 of the THF volume) were added, respectively. The resulting solution was then cooled to −90°C, and NaHMDS (6 ml, 12 mol, 2M solution in THF) was added dropwise (very slowly). The reaction mixture was stirred at −90°C for 1 h and quenched by the addition of a saturated aqueous solution of NH_4Cl. The reaction mixture was then allowed to warm to room temperature and extracted three times with AcOEt (50 ml ×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (20:1 v/v), followed

by crystallization from diethyl ether–light petroleum ether to afford **11** (2.1 g, 90%) as a white crystal. Mp 48–50°C; $[\alpha]_D^{20}$ − 108 (*c* 1.1, $CHCl_3$) (Lit.[9] $[\alpha]_D$ − 100.2 (*c* 1.39, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of conformers (2.3:1); major conformer δ (ppm) 8.29 (s, 1H, CHO), 4.66 (s, 1H, C**H**C$(CH_3)_3$), 3.81 (s, 3H, CO_2CH_3), 3.32 (d, $J = 11.4$ Hz, 1H, C**H**H), 2.72 (d, $J = 11.4$ Hz, 1H, CH**H**), 1.76 (s, 3H, CH_3), 1.07 (s, 9H, CHC(C**H**$_3)_3$); minor conformer δ (ppm) 8.41 (s, 1H, CHO), 5.31 (s, 1H, C**H**C$(CH_3)_3$), 3.82 (s, 3H, CO_2CH_3), 3.65 (d, $J = 12.3$ Hz, 1H, C**H**H), 2.86 (d, $J = 12.3$ Hz, 1H, CH**H**), 1.79 (s, 3H, CH_3), 0.92 (s, 9H, CHC(C**H**$_3)_3$); HRESIMS: *m/z* 246.1180 $[M + H]^+$ (calcd for $C_{11}H_{20}NO_3S$, 246.1158).

3.5 (R)-2-Methylcysteine hydrochloride (12)

5M hydrochloric acid (15 ml) was added to **11** (1.23 g, 5 mmol), and the solution was then heated under reflux in an atmosphere of argon for 3 days. The solution was washed with ethyl acetate (20 ml ×2), and then the aqueous layer was evaporated under reduced pressure to leave the hydrochloride salt **12** (0.77 g, 90%) as a pale yellow solid. Mp 155–157°C; $[\alpha]_D^{20}$ + 8.0 (*c* 1.0, H_2O) (Lit.[9] $[\alpha]_D$ + 8.13 (*c* 1.58 H_2O)); ^{1}H NMR (300 MHz, D_2O) δ (ppm) 3.25 (d, $J = 16.8$ Hz, 1H, CH**H**), 2.97 (d, $J = 16.8$ Hz, 1H, C**H**H), 1.65 (s, 3 H, CH_3).

3.6 Methyl (R)-2-methylcysteine hydrochloride (5)

To a solution of **12** (0.77 g, 45 mmol) in dry methanol (150 ml), $SOCl_2$ (5 ml, 67 mmol) was added dropwise at 0°C, and the solution was then heated under reflux in an atmosphere of argon for 6 h. The solvent was removed to give **5** (0.78 g, 94%) as an oil.

3.7 N-(tert-Butoxycarbonyl)thioglycinamide (14)

A solution of **13** (13.12 g, 0.075 mol) and Lawesson's reagent (22.62 g, 0.057 mol) in 1,2-dimethoxyethane (200 ml) was stirred for 4 h at room temperature. The reaction was concentrated and passed through a short plug of silica gel, washing with 100% EtOAc. After removal of the solvent by rotary evaporation, the residue was crystallized from ethyl acetate–light petroleum ether to afford **14** (13.5 g, 94.7%) as a white solid. Mp 122–124°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.20 (brs, 1H, NH), 4.16 (d, $J = 5.1$ Hz, 2H, CH_2), 1.46 (s, 9H, $(CH_3)_3C$); HRESIMS: *m/z* 213.0699 $[M + Na]^+$ (calcd for $C_7H_{14}N_2O_2NaS$, 213.0674).

3.8 Ethyl 2-(t-butoxycarbonylamino) methylthiazole-4-carboxylate (15)

To a solution of **14** (9 g, 47 mmol) in dry ethanol (150 ml), ethyl bromopyruvate (6.56 ml, 52 mmol) and calcium carbonate (4.7 g, 47 mmol) were added. The reaction mixture was stirred at room temperature for 5 h and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate, and this solution was washed with saturated $NaHCO_3$ solution and water successively, dried over Na_2SO_4, and filtered. After removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (5:1 v/v), followed by crystallization from ethyl acetate–light petroleum ether to afford **15** (9.4 g, 70%) as a white needle. Mp 98–99°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.12 (s, 1H, C=CHS), 5.28 (brs, 1H, NH), 4.67 (brs, 2H, NHC**H**$_2$), 4.43 (m, 2H, CH_3C**H**$_2$), 1.47 (s, 9H, $(CH_3)_3C$), 1.41 (t, $J = 7.2$ Hz, 3H, CH_2C**H**$_3$); HRESIMS: *m/z* 309.0909 $[M + Na]^+$ (calcd for $C_{12}H_{18}N_2O_4NaS$, 309.0885).

3.9 tert-Butyl (4-carbamoylthiazol-2-yl)methylcarbamate (6)

15 (5 g, 17 mmol) was dissolved in methylamine–alcoholic solution (20 ml) and stirred at room temperature for 1.5 h. After solvent removal by rotary evaporation, the residue was crystallized from ethyl acetate–light petroleum ether to afford **6** (4.5 g, 98.5%) as a white solid. Mp 127–128°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (s, 1H, C═CHS), 5.25 (brs, 1H, NH), 4.59 (d, $J = 5.7$ Hz, 2H, CH_2), 3.00 (d, $J = 5.4$ Hz, 3H, NHC**H**$_3$), 1.47 (s, 9H, $(CH_3)_3C$); HR-ESIMS: m/z 294.0883 $[M + Na]^+$ (calcd for $C_{11}H_{17}N_3O_3NaS$, 294.0882).

3.10 (R)-Methyl-2-(2-((tert-butoxycarbonylamino)methyl)thiazol-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylate (16)

To a solution of amide **6** (2.19 g, 8.09 mmol) in dry CH_2Cl_2 (40 ml), pyridine was added (1.85 ml, 26.68 mmol), and this resulting mixture was cooled down to −40°C. Tf_2O (1.42 ml, 8.89 mmol) was then added dropwise, and the reaction was stirred for 1 h at this temperature. Then, the solution was warmed to room temperature and stirred for 10 h. The reaction was cooled down to −40°C and **5** (1.26 g, 6.8 mmol) was added followed by the addition of pyridine (1.85 ml, 26.68 mmol). The resulting mixture was warmed up to room temperature and stirred for 10 h. After removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (3:1 v/v) to afford **16** (1.77 g, 75%) as a pale yellow oil. $[\alpha]_D^{20}$ − 13.8 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.95 (s, 1H, C═CHS), 5.29 (brs, 1H, NH), 4.62 (d, $J = 6.3$ Hz, 2H, $NHCH_2$), 3.87 (d, $J = 11.4$ Hz, 1H, CHHS), 3.76 (s, 3H, OCH_3) 3.27 (d, $J = 11.4$ Hz, 1H, CHHS), 1.64 (s, 3H, CH_3), 1.46 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm)173.6, 169.5, 162.9, 155.6, 148.5, 121.9, 84.5, 80.4, 52.9, 42.3, 41.5, 29.7, 28.3, 23.9, 19.2; HRESIMS: m/z 372.1052 $[M + H]^+$ (calcd for $C_{15}H_{22}N_3O_4S_2$, 372.1046).

3.11 Thiazoline-thiazole amine acid (3)

To a solution of **16** (108 mg, 0.4mmol) in dioxane, NaOH aqueous was added (32 mg, 0.8 mmol). The reaction mixture was stirred at room temperature for 1 h and then adjusted to pH 6 with 1N $KHSO_4$ solution. After evaporation, the residue was dissolved in water and adjusted to pH 3 successively and extracted three times with ethyl acetate (10 ml ×3). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The resulting crude was purified by crystallization from ethyl acetate–light petroleum ether to afford the acid (97 mg, 95%) as a white solid. Mp 75–80°C; $[\alpha]_D^{20}$ −52.4 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H, C═CHS), 5.34 (brs, 1H, NH), 4.63 (d, $J = 6.0$ Hz, 2H, $NHCH_2$), 3.89 (d, $J = 11.7$ Hz, 1H, CHHS), 3.67 (d, $J = 11.7$ Hz, 1H, CHHS), 1.69 (s, 3H, CH_3), 1.47 (s, 9H, $(CH_3)_3C$).

The acid (20 mg, 0.056 mmol) was dissolved in HCl–AcOEt at 0°C, and the reaction mixture was stirred for 2 h at this temperature. After removal of the solvent, dry ethyl ether was added. Then, a white solid appeared. The supernatant fluid was removed to afford **3** (15 mg, 94%) as a white solid.

3.12 3S-Hydroxyl-1-(4R-benzyl-2-thioxothiazolidin-3-yl)-7-tritylsulfanyl hept-4E-en-1-one (7)

17 (1 g, 4.78 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and cooled to −5°C. $TiCl_4$ (0.877 ml, 7.97 mmol) was added dropwise. After stirring for 30 min, the resulting yellow solution was cooled to −40°C. iPr$_2$NEt (1.315 ml, 7.97 mmol) was then

added dropwise, and the reaction mixture was stirred for 2 h at this temperature. The resulting solution was then cooled to −90°C. **18** was dissolved in dry CH_2Cl_2 (10 ml) and added dropwise to the reaction mixture. The reaction mixture was stirred at −90°C for 3 h and quenched by the addition of a saturated aqueous solution of NH_4Cl. The reaction mixture was then allowed to warm to room temperature and extracted three times with CH_2Cl_2 (50 ml ×3). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (15:1 v/v) to afford **7** (1.82 g, 75%) as a yellow oil. $[\alpha]_D^{20}$ − 105.1 (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.17–7.41 (m, 20H, ArH), 5.56–5.63 (m, 1H, CHOH), 5.47 (dd, $J = 5.7$, 15.6 Hz, 1H, CH═), 5.32–5.39 (m, 1H, CH═), 4.59 (m, 1H, CH), 3.56 (dd, $J = 5.1$, 14.4 Hz, 1H, CHH), 3.28–3.37 (m, 2H, CHH, CHHS), 3.20 (dd, $J = 5.1$, 14.4 Hz, 1H, CHHS), 2.91–3.07 (m, 1H, PhCHH), 2.86 (d, $J = 11.4$ Hz, PhCHH), 2.22 (t, $J = 6.6$ Hz, 2H, CH_2), 2.11 (t, $J = 6.6$ Hz, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 201.3, 172.6, 144.9, 136.4, 131.9, 130.1, 129.6, 129.4, 128.9, 127.8, 127.3, 126.6, 68.4, 68.3, 66.6, 45.6, 36.7, 32.1, 31.4, 31.3.

3.13 Ester (4)

7 (550 mg, 0.9 mmol), Fmoc-Val-OH (468 mg, 1.38 mmol), EDCI (265 mg, 1.38 mmol), and DMAP (11 mg, 0.09 mmol) were dissolved in dry CH_2Cl_2 (20 ml). The reaction was cooled to 0°C, and iPr$_2$NEt was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. This solution was washed with 1N HCl solution and water successively, dried over Na_2SO_4, and filtered. After the removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (10:1 v/v) to afford **4** (573 mg, 80%) as a yellow oil. $[\alpha]_D^{20}$ − 105.1 (*c* 0.28, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.77 (d, $J = 7.8$ Hz, 2H, ArH), 7.57 (d, $J = 7.2$ Hz, 2H, ArH), 7.18–7.40 (m, 24H, ArH), 5.86 (m, 1H, CH), 5.48–5.67 (m, 1H, CH═), 5.29–5.48 (m, 2H, CH═, CH), 4.17–4.40 (m, 4H, CH_2, 2CH), 3.49–3.69 (m, 2H, CH_2), 3.42 (m, 1H, CHHS), 3.18 (m, 1H, CHHS), 2.97 (t, $J = 10.8$ Hz, 1H, PhCHH), 2.84 (d, $J = 10.8$ Hz, 1H, PhCHH), 2.17 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 0.87 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2$CH), 0.80 (d, $J = 6.6$ Hz, 3H, $(CH_3)_2$CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 200.7, 172.8, 156.3, 143.9, 143.8, 141.3, 136.1, 129.5, 129.4, 128.9, 127.9, 127.8, 127.6, 127.3, 127.1, 125.1, 120.0, 67.9, 67.1, 57.0, 47.2, 40.2, 37.3, 32.3, 30.3, 22.6, 19.4, 19.2, 15.2.

3.14 Liner precursor (2)

3 (105 mg, 0.32 mmol) was dissolved in dry DMF (5 ml) and treated with DMAP (70 mg, 0.57 mmol). After stirring for 30 min, **4** in dry DMF (5 ml) was added to the mixture dropwise and stirred for an additional 2 h. The reaction was diluted with ethyl acetate (20 ml) and washed with 0.1 N HCl solution (50 ml ×2) and brine (30 ml). The organic layer was then dried over Na_2SO_4, filtered, and the solvent was removed by rotary evaporation. The resulting crude was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol mixture (50:1 v/v) to afford **2** (220 mg, 75%) as a white solid. Mp 108–110°C; $[\alpha]_D^{20}$ − 29 (*c* 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.80 (s, 1H, C═CHS), 7.76 (d, $J = 7.8$ Hz, 2H, ArH), 7.55 (d, $J = 7.2$ Hz, 2H, ArH), 7.19–7.40 (m, 19H, ArH), 6.86 (brs, 1H, NH), 5.67 (m, 1H, CH═), 5.62 (m, 1H, CH), 5.53 (m, 1H, CH═), 5.26

(d, $J = 8.4$ Hz, 1H, CH), 4.68 (m, 2H, CH_2), 4.30–4.39 (m, 2H, CH_2NH), 4.18 (t, 1H, CH), 3.78 (d, $J = 11.4$ Hz, 1H, CHHS), 3.32 (d, $J = 11.4$ Hz, 1H, CHHS), 2.59 (d, $J = 4.2$ Hz, CH_2), 2.18 (m, 2H, CH_2), 2.05 (m, 3H, $(CH_3)_2CH$, CH_2), 1.61 (s, 3H, CH_3), 0.86–0.90 (m, 6H, $(CH_3)_2CH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 175.1, 171.2, 169.3, 169.0, 164.5, 156.5, 147.5, 144.8, 143.6, 141.3, 134.0, 129.5, 127.8, 127.7, 127.5, 127.1, 126.6, 125.1, 125.0, 124.7, 123.1, 119.9, 120.0, 84.2, 72.3, 67.1, 66.6, 59.4, 47.1, 41.4, 41.0, 31.3, 31.1, 30.9, 29.7, 24.2, 18.9, 17.9, 17.8, 17.5; HRESIMS: *m/z* 979.3194 $[M + H]^+$ (calcd for $C_{55}H_{55}N_4O_7S_3$, 979.3227).

3.15 S-Trityl macrocycle (19)

2 (110 mg, 0.11 mmol) was dissolved in dry MeCN (10 ml), and Et_2NH (100 µl, 0.97 mmol) was added dropwise at room temperature. After stirring for 5 h and removal of the solvent, diethyl ether was added. Then, a white solid appeared. After the removal of the supernatant fluid, the crude product was then dissolved in dry MeCN (100 ml), and $i Pr_2NEt$ (74 µl, 0.44 mmol) was added dropwise. After stirring for 10 min, HATU (85 mg, 0.22 mmol) and HOBt (85 mg, 0.22 mmol) were added dropwise in dry MeCN (5 ml). The reaction mixture was stirred at room temperature for 10 h. The solvent was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate, and this solution was washed with saturated $NaHCO_3$ solution and water successively, dried over Na_2SO_4, and filtered. After removal of the solvent, the resulting crude was purified by flash chromatography on silica gel, eluting with dichloromethane–methanol mixture (100:1 v/v) to afford **19** (53 mg, 65%) as a white solid. Mp 191°C (Decomp.); $[\alpha]_D^{20} + 12$ (*c* 0.1, CH_3OH) (Lit.[3] $[\alpha]_D^{24} + 16.1$ (*c* 1, MeOH)); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (s, 1H, C═CHS), 7.17–7.39 (m, 15H, ArH), 6.57 (brs, 1H, NH), 5.70 (m, 1H, CH═), 5.62 (m, 1H, CH), 5.41 (dd, $J = 6.0$, 15.0 Hz, 1H, CH═), 5.23 (m, 1H, CH), 4.56 (dd, $J = 4.9$, 9.3 Hz, 1H, CHHNH), 4.12 (dd, $J = 4.9$, 9.3 Hz, 1H, CHHNH), 4.04 (d, $J = 11.4$ Hz, CHHS), 3.29 (d, $J = 11.4$ Hz, CHHS), 2.80 (m, 1H, CHHCO), 2.68 (dd, $J = 3.3$, 16.0 Hz, 1H, CHHCO), 2.20 (m, 2H, CH_2), 2.04 (m, 3H, CH_2, CH), 1.85 (s, 3H, CH_3), 0.68 (d, $J = 6.9$ Hz, 3H, $(CH_3)_2CH$), 0.52 (d, $J = 6.9$ Hz, 3H, $(CH_3)_2$ CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 173.2, 169.4, 168.6, 168.1, 146.9, 144.8, 133.1, 129.6, 127.9, 127.8, 127.2, 126.6, 124.6, 71.9, 66.6, 57.9, 43.3, 41.0, 40.6, 38.6, 33.9, 31.3, 31.2, 29.7, 24.0, 18.8, 16.8; HR-ESIMS: *m/z* 739.2443 $[M + H]^+$ (calcd for $C_{40}H_{43}N_4O_4$, 739.2440).

3.16 Largazole (1)

19 (30 mg, 0.04 mmol) was dissolved in dry CH_2Cl_2 (5 ml) and cooled to 0°C. The mixture was successively treated with Et_3SiH (13 ml, 0.08 mmol) and TFA (0.2 ml). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, before being concentrated and chromatographed (EtOAc) to provide a clear oil (15 mg, 0.03 mmol). The crude oil was dissolved in dry CH_2Cl_2 (5 ml) and cooled to 0°C. The mixture was successively treated with Et_3N (15 µl, 0.06 mmol) and octanoyl chloride (30 µl, 0.3 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h, then cooled to 0°C and quenched with CH_3OH. The solvent was evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated $NaHCO_3$ solution and water successively, dried over Na_2SO_4, and filtered. After removal of the solvent, light petroleum ether was added. Then, a white amorphous solid appeared. The supernatant fluid was removed to afford largazole **(1)** (22 mg,

90%) as a white amorphous solid. $[\alpha]_D^{20} + 24$ (*c* 0.4, CH_3OH) (Lit.[1] for natural largazole, $[\alpha]_D^{25} + 22$ (*c* 0.1, MeOH)); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (s, 1H, C═CHS), 7.16 (d, $J = 9.0$ Hz, 1H, NH), 6.42 (brs, 1H, NH), 5.82 (m, 1H, CH═), 5.67 (m, 1H, CH), 5.52 (dd, $J = 7.2$, 15.6 Hz, 1H, CH═), 5.29 (m, 1H, CH), 4.61 (dd, $J = 2.7$, 8.7 Hz, 1H, CHHNH), 4.28 (d, $J = 16.8$ Hz, 1H, CHHNH), 4.05 (d, 1H, $J = 11.4$ Hz, 1H, CHHS), 3.28 (d, $J = 11.4$ Hz, 1H, CHHS), 2.90 (t, $J = 7.2$ Hz, 2H, CH_2), 2.84 (d, $J = 14.7$ Hz, 1H, CHHCO), 2.69 (d, $J = 14.7$ Hz, 1H, CHHCO), 2.53 (t, $J = 8.4$ Hz, 2H, CH_2), 2.29–2.33 (m, 2H, CH_2), 2.10 (m, 1H, $CH(CH_3)_2$), 1.88 (s, 3H, CH_3), 1.62–1.68 (m, 2H, CH_2), 1.27–1.30 (m, 8H, 4× CH_2), 0.88 (t, $J = 6.0$ Hz, 3H, CH_3), 0.69 (d, $J = 7.2$ Hz, 3H, $(CH_3)_2CH$), 0.52 (d, $J = 7.2$ Hz, 3H, $(CH_3)_2CH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 169.4, 168.9, 167.9, 167.7, 164.5, 147.5, 132.7, 132.3, 130.9, 128.8, 128.4, 124.2, 84.4, 72.0, 65.6, 57.7, 44.1, 43.3, 41.1, 40.5, 34.2, 32.6, 31.6, 30.9, 30.6, 28.9, 27.9, 25.6, 24.2, 22.6, 19.2, 18.9, 16.6, 14.1, 13.7; HRESIMS: *m/z* 623.2382 $[M + H]^+$ (calcd for $C_{29}H_{43}N_4O_5S_3$, 623.2390).

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