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Total Synthesis of Thiangazole

Kenichi Akaji*

Institute for Protein Research, Osaka University, 3-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Yoshiaki Kiso

Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan

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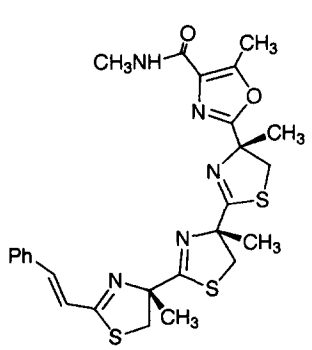
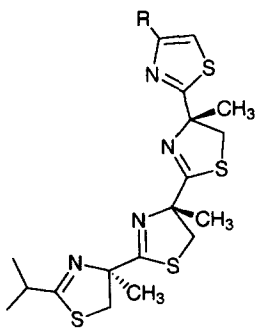
Abstract: A method for total synthesis of thiangazole (**1**), a tris-thiazoline-oxazole metabolite, is described. The key intermediate **9**, a linear tetrapeptide amide composed of three S-benzyl-2-methylcysteine residues and a O-benzyl-threonine amide, was synthesized in 4 steps using 2-chloro-1,3-dimethyl-imidazolidium hexafluorophosphate(CIP)-mediated activation. The successive thiazoline/oxazole rings were constructed by $TiCl_4$-mediated cyclodehydration followed by acid-catalyzed Robinson-Gabriel reaction without difficulty.

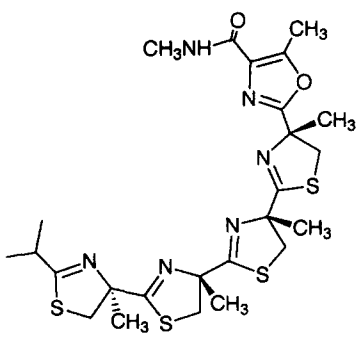
Thiangazole was isolated from a metabolite of *Polyangium spec.*, strain P13007 in 1992[1]. Thiangazole is a selective inhibitor of HIV-1 and shows no cell toxicity even at millimolar levels[2]. Structurally, thiangazole belongs to a family of polythiazoline natural products known as tantazoles[3] and mirabazoles[4], all which have been isolated from blue-green algae.



Thiangazole (1)



R=CH_3 ; Mirabazole B
R=H ; Mirabazole C



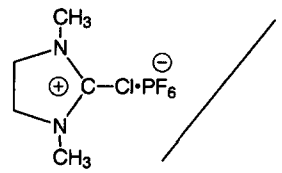
Tantazole B

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00604-3

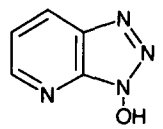
Due to its novel structural features as well as interesting biological activities, several methods for total syntheses of thiangazole have been reported[5-8]. Simultaneous formation of successive thiazolin rings by Lewis-acid mediated cyclocondensation[5] would be more efficient than stepwise ring formation[6]. However, efficient preparation of the necessary precursor is often difficult because of the extremely low reactivity of 2-methylcysteine. Thus, in the recent total synthesis of thiangazole and structurally related polyazoles, a new methodology for efficient oxazoline to thiazoline conversion was employed to facilitate synthesis[8].

We have developed a new coupling reagent, 2-chloro-1,3-dimethyl-2-imidazolinium hexafluorophosphate (CIP)[9], which in the presence of the additive 1-hydroxy-7-azabenzotriazole (HOAt) effectively couples sterically hindered α,α–dialkylamino acids[10] or N-methylamino acids[11]. Using this coupling reagent, we have achieved convergent syntheses of mirabazole C[12] and B[13]. In these syntheses, key intermediates prepared by CIP-mediated coupling reaction were employed for the simultaneous formation of multiple thiazoline rings. To extend our synthetic scheme to the synthesis of more complex natural products, we performed the total synthesis of thiangazole. Here, we describe the results and experimental details of the total synthesis of thiangazole using CIP/HOAt.

CIP



HOAt



Results and Discussion

Scheme 1 shows our retrosynthetic route of thiangazole. The successive thiazoline rings are formed by $TiCl_4$-mediated one-step cyclization according to Heathcock's procedure[14]. The terminal oxazole is constructed by acid-catalyzed Robinson-Gabriel cyclodehydration[15]. The linear tetrapeptide amide derivative, a key intermediate in this scheme, is constructed starting from threonine amide by successive coupling of three α–methylcysteine derivatives using CIP/HOAt. A Bn group cleavable by NH_3/Na is employed for the protection of side chain sulfhydryl and hydroxyl groups

Scheme 1

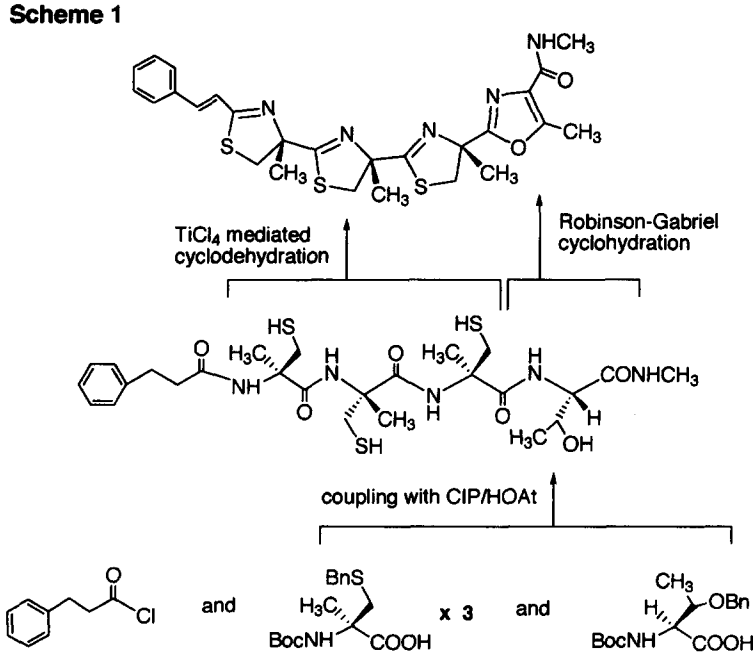
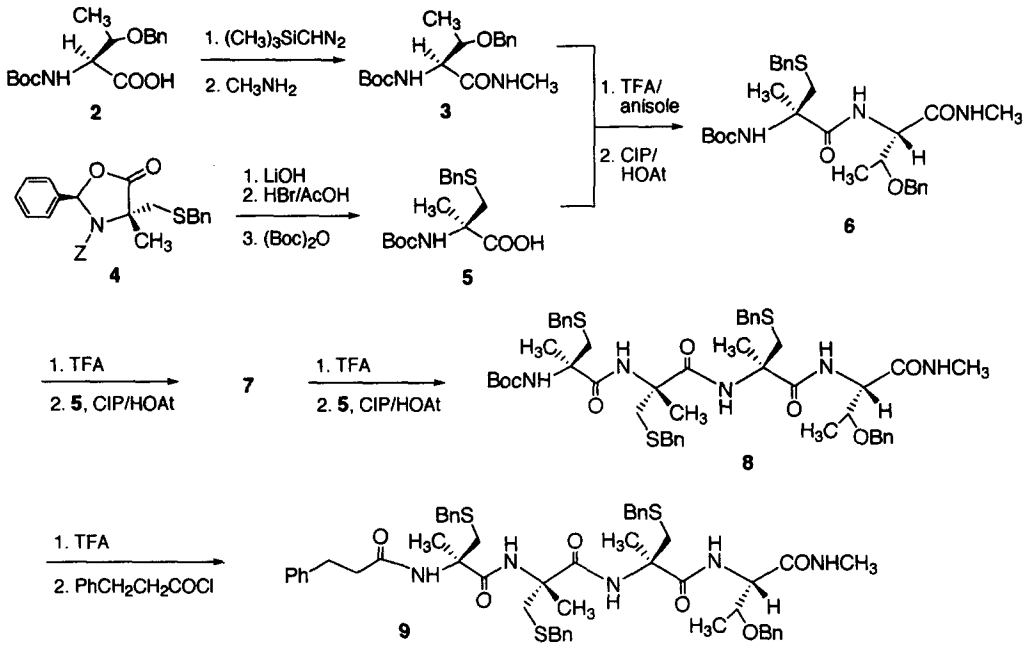


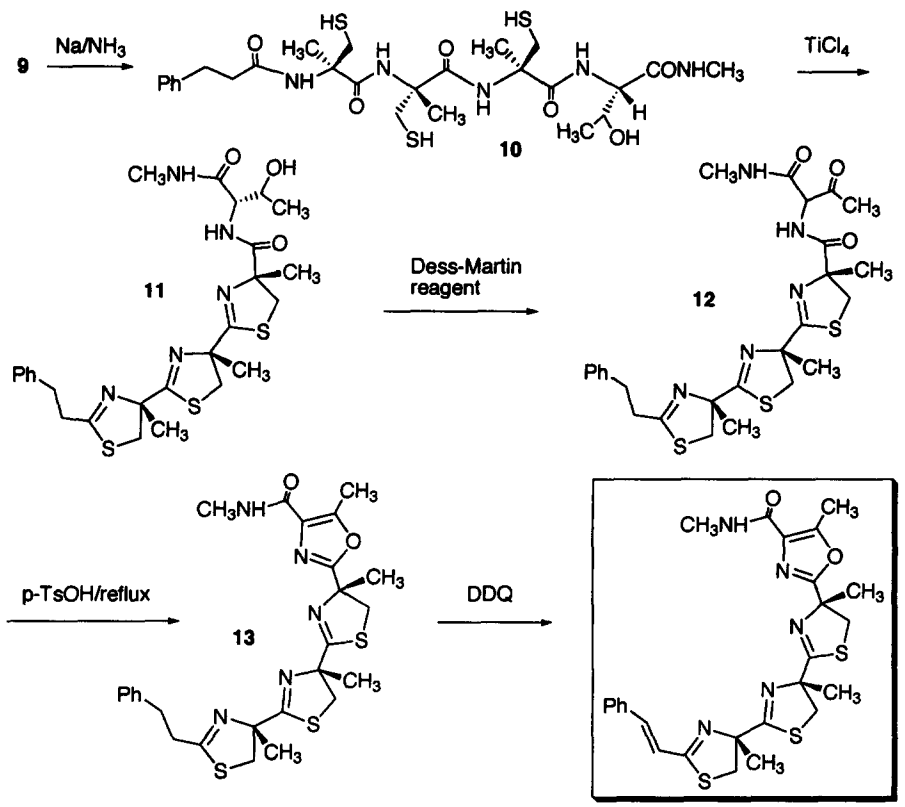
Figure 1. Synthetic route for linear precursor **9**



through the synthesis. As a temporary N^{α}-protecting group, TFA-labile Boc group is employed instead of a Z group employed in our previous syntheses to keep the HBr-labile Bn group of Thr intact during the chain elongation.

The key intermediate **9** was prepared according to the route shown in Fig. 1. The starting amino acid derivative, Boc-L-Thr(Bn)-NHMe **3**, was synthesized from commercially available Boc-L-Thr(Bn)-OH **2** by esterification with $(CH_3)_3SiCHN_2$ [16] followed by amidation with CH_3NH_2. Another amino acid derivative, Boc-(R)-MeCys(Bn)-OH **5**, was synthesized starting from the oxazolidinone **4** prepared by stereoselective alkylation[6]. The route for **5** involves the hydrolysis of **4**. The Z group of the product was then cleaved by HBr/AcOH and the resulting amino group was t-butoxycarbonylated with $(Boc)_2O$ to give **5** in 90 % yield. The Boc group of **3** was removed by treatment with TFA/anisole, and the product was coupled with **5** by a 12 hr reaction using CIP/HOAt. The desired dipeptide amide **6** was obtained with 77 % isolation yield, although the coupling of L-threonine methylester with (S)-α-methylserine derivative was reported to lead to considerably reduced yield[8]. For peptide chain elongation, the same deprotection by TFA/anisole and coupling of the product with **5** using CIP/HOAt were repeated twice. The desired tri- and tetrapeptide amide (**7** and **8**) were obtained in 72 % and 42 % isolated yields, respectively. The Boc group of **8** was then removed with TFA/anisole and the resulting amine was acylated with 3-phenylpropionyl chloride to obtain the linear precursor peptide **9** in 88% yield. Thus, the key intermediate **9** was efficiently synthesized starting from the C-terminal L-threonine amide by straightforward condensation using CIP/HOAt followed by acylation.

Figure 2. Synthetic route for thiangazole



Cyclization of the linear precursor **9** was conducted according to the route developed by Heathcock[14] (Fig. 2). Four benzyl groups were removed by brief treatment of **9** with sodium in ammonia. Without further purification, the product **10** was treated with titanium tetrachloride for the simultaneous cyclodehydration of the three S-deprotected cysteine residues to obtain trithiazoline **11**. The cyclization step proceeded smoothly to give **11** in 51 % isolated yield from **9**. However, the yield of **11** was significantly decreased to give a complex mixture when the period of reductive debenzylation was extended to more than 20 min. Side-chain alcohol of tetrathiazoline **11** was oxidized to **12** upon treatment with Dess-Martin reagent[17,18] to yield **12** in 58 %: the product was a 2:1 mixture of diastereoisomer at α–carbon of threonine. Since the threonine α–stereocenter is destroyed in the subsequent conversion, the mixture was used without separation. Thus, an oxazole ring was then formed by treatment of **12** with p-toluenesulfonic acid in refluxing benzene to yield **13** in 61 % without difficulty. Finally, the N-terminal phenylethyl side chain was dehydrogenated with dichlorodicyanoquinone[19] to complete the total synthesis of thiangazole. The synthetic material had the same spectroscopic properties as those reported for the natural product.

Conclusion

A novel coupling reagent, CIP/HOAt, was successfully used in the total synthesis of thiangazole. A straightforward route for the key intermediate **9** by the successive coupling of 2-(R)-methylcysteine was first achieved using CIP/HOAt as a condensation agent. The thiazoline and oxazole rings were formed according to Heathcock's procedure without difficulty, although careful control of the preceding reductive debenzylation was necessary. The present synthesis combined with our previous method show that the combination of CIP-mediated coupling and simultaneous thiazoline formation could be useful as a general scheme for the synthesis of polythiazoline natural products.

Experimental

General. Solvents were reagent grade and dried prior to use. All flash chromatography procedures were carried out on Wakogel FC-40 obtained from WAKO Pure Chemical Ind. Boc-L-Thr(Bn)-OH was purchased from Peptide Institute (Osaka). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone was purchased from WAKO Pure Chemical Ind. and used without further purification. Dess-Martin Periodinane (1,1,1-triacetoxy-1,1-dihydro-1.2-benziodoxol-3(1H)-one) was prepared according to the published procedure[18].

Melting points were uncorrected. ^{1}H and ^{13}C-NMR were recorded on a JEOL JNM-270 or Bruker DPX400 spectrometer. Optical rotation was determined with a Horiba SEPA-200 polarimeter using a 1 ml cell. FAB-MS was obtained on a JEOL JMS-SX102A spectrometer.

General method for removal of the Boc group. N^{α}-Boc derivative was dissolved in TFA-anisole (10:1, 5 equiv. of anisole) and the mixture was stirred for 2 h in an ice-bath. TFA was removed by evaporation at room temperature and the residue was washed with n-hexane. The N^{α}-deprotected product was obtained as an oil and used directly in subsequent reactions without further purification.

General method for isolation of the condensation product. The condensation product was dissolved in AcOEt and the extract was washed with 5% citric acid, 5% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed by evaporation. The residue was purified by appropriate column chromatography.

Boc-L-Thr(Bn)-$NHCH_3$ (3). To a stirred solution of Boc-L-Thr(Bn)-OH (5.0 g, 16 mmol) in MeOH (30 ml) at 4°C was added Me_3SiCHN_2 in hexane (25 ml of 2 M solution), and the mixture was stirred at 25°C for 3 h. A few drops of AcOH were added and the solvent was removed by evaporation. The residue was dissolved in AcOEt and the extract was washed with 5% $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed by evaporation. The residue was purified by silica-gel column chromatography to yield 5.2 g (quantitative) of Boc-L-Thr(Bn)-OMe as an oil.

To a stirred solution of Boc-L-Thr(Bn)-OMe (5.2 g, 16 mmol) in MeOH (30 ml) at 25°C was added 40% CH_3NH_2/MeOH (25 ml), and the mixture was stirred at 25°C overnight. The solvent of the mixture was removed by evaporation and the residue was extracted with AcOEt. The organic layer was washed with 5% citric acid and H_2O, dried over $MgSO_4$, and concentrated. The product was crystallized form n-hexane to

yield 3.4 g (65 %) of **3** as a solid: $[\alpha]_D^{23}$ +39.46 (c=1.3, $CHCl_3$), mp 124-125°C, IR ($CHCl_3$), 1714, 1674, 1489, 1394, 1369 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (d, J=6.3 Hz, 3H), 1.45 (s, 9H), 2.82 (d, J=4.6 Hz, 3H), 4.20 (qd, J=6.3 Hz, 2.8 Hz, 1H), 4.25 (br d, J=6.2 Hz, 1H), 4.54 (d, J=11.6 Hz, 1H), 4.61 (d, J=11.6 Hz, 1H), 5.49 (br d, J=6.2 Hz, 1H), 6.47 (br d, J=4.2 Hz, 1H), 7.26-7.38 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.63, 26.24, 28.30, 57.74, 71.66, 74.81, 80.09, 127.74, 127.83, 128.44, 138.04, 155.88, 170.49. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found. C, 63.52; H, 8.21; N, 8.69. FAB-MS, 323.1965 for $[M+H]^+$ (calcd 323,1971 for $C_{17}H_{27}N_2O_4$).

Boc-(R)-MeCys(Bn)-OH (5). To the stirred solution of **4** (10.6 g, 24 mmol) in THF/H_2O (3/1, 200 ml) was added LiOH•H_2O (2.0 g, 48 mmmol) according to the published procedure[12] to yield 8.6 g (quantitative) of Z-(R)-MeCys(Bn)-OH as an oil. To the stirred solution of Z-(R)-MeCys(Bn)-OH (8.6 g, 24 mmol) in $CHCl_3$ (8 ml) was added HBr/AcOH (80 ml) at 4°C, and the mixture was stirred for 60 min at 25°C. The resulting precipitate was extracted with H_2O and the aqueous phase was washed with $CHCl_3$. The pH of the aqueous layer was adjusted to 6 with 4N NaOH and the mixture was left to stand at 4°C overnight. The precipitate was filtered and dried to yield 5.0 g (93 %) of H-(R)-MeCys(Bn)-OH as a solid.

To a stirred solution of H-(R)-MeCys(Bn)-OH (2.0 g, 8.9 mmol) in 4N NaOH (22 ml) was added $(Boc)_2O$ (3.9 g, 17.8 mmol) in dioxane (20 ml) at 4°C. The mixture was stirred overnight at 25°C, and then ether (50 ml) was added to the reaction mixture. The aqueous layer was washed with ether and then acidified to pH 2 using cHCl. The mixture was extracted with AcOEt (100 ml), and the organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed by evaporation to yield 2.8 g (97 %) of **5** as an oil: $[\alpha]_D^{23}$ +5.69 (c=2.7, $CHCl_3$), IR ($CHCl_3$), 1709, 1497, 1454, 1369, 1165, 1057 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.56 (s, 3H), 3.13 (m, 2H), 3.72 (s, 2H), 5.50 (br s, 1H), 7.21-7.31 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.43, 28.32, 37.50, 59.93, 80.18, 127.13, 128.55, 128.62, 128.89, 138.11, 154,75, 178.11. FAB-MS, 326.1426 for $[M+H]^+$ (calcd 326.1444 for $C_{16}H_{24}NO_4S$).

Boc-(R)-MeCys(Bn)-Thr(Bn)-$NHCH_3$ (6). Boc-Thr(Bn)-$NHCH_3$ (**3**, 1.5 g, 4.7 mmol) was treated with TFA/anisole by the general method to give H-Thr(Bn)-$NHCH_3$ as an oil. To the solution of Boc-(R)MeCys(Bn)-OH (**5**, 2.1 g, 6.5 mmol) in THF (10 ml) were added DIEA (3.2 ml, 18.4 mmol), HOAt (0.6 g, 4,7 mmol), CIP (1.8 g, 6.5 mmol), and the deprotected Thr amide obtained above in THF (5 ml). The mixture was stirred for 12 h at 25°C. The crude product was isolated by the general method and purified by silicagel column chromatography ($CHCl_3$/MeOH, 40/1) followed by flash chromatography using hexane/AcOEt (2/1 to 1/2) to yield 1.9 g (77 %) of **6** as a solid: $[\alpha]_D^{24}$ -14.58 (c=1.1, $CHCl_3$), mp 112-113°C, IR ($CHCl_3$), 1684, 1668, 1497, 1456, 1369, 1080, 1016 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 (d, J=6.6 Hz, 3H), 1.33 (s, 9H), 1.52 (s, 3H), 2.78 (d, J=4.6 Hz, 3H), 2.82 (d, J=13.0 Hz, 1H), 2.87 (d, J=13.0 Hz, 1H), 3.71 (s, 2H), 4.32 (dd, J=8.3 Hz, 1.5 Hz, 1H), 4.44 (d, J=11.6 Hz, 1H), 4.48 (qd, J=6.6 Hz, 1.5 Hz, 1H), 4.56 (d, J=11.6 Hz, 1H), 5.10 (s, 1H), 6.85 (d, J=8.5 Hz, 1H), 7.21-7.33 (m, 11H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.23, 21.89, 26.25, 28.10, 37.72, 40.63, 57.90, 59.84, 71.79, 74,16, 80.97, 127.58, 127.64, 128.30, 128.84, 128.95, 137.64, 138.27, 155.51, 170.65, 172.81. Anal. Calcd for $C_{28}H_{39}N_3O_5S$: C, 63.49; H, 7.42; N, 7.93. Found. C, 63.57; H, 7.61; N, 7.93. FAB-MS, 530.2678 for $[M+H]^+$ (calcd 530.2689 for $C_{28}H_{40}N_3O_5S$).

Boc-(R)-MeCys(Bn)-(R)-MeCys(Bn)-Thr(Bn)-NHCH$_3$ (7). 2.1 g (4.0 mmol) of **6** was treated with TFA/anisole by the general method to give H-(R)-MeCys(Bn)-Thr(Bn)-NHCH$_3$ as an oil. To the solution of Boc-(R)-MeCys(Bn)-OH (**5**, 3.8 g, 11.7 mmol) in THF (15 ml) were added DIEA (5.5 ml, 32 mmol), HOAt (1.0 g, 7.3 mmol), CIP (3.3 g, 11 .7 mmol), and the deprotected dipeptide amide obtained above in THF (10 ml). The mixture was stirred for 72 h at 25°C. The crude product isolated by the general method was partially purified by silicagel column chromatography ($CHCl_3$/MeOH, 20/1). The product was purified by flash chromatography using hexane/AcOEt (2/1 to 1/2) followed by recrystallization from AcOEt with hexane to yield 2.1 g (72 %) of **7** as a solid: $[\alpha]_D^{24}$ +7.33 (c=1.1, $CHCl_3$), mp 119-120°C, IR ($CHCl_3$), 1716, 1668, 1506, 1497, 1456, 1371, 1159 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.18 (d, J=6.3 Hz, 3H), 1.40 (s, 9H), 1.55 (s, 3H), 2.76 (d, J=13.5 Hz, 1H), 2.79 (d, J=4.6 Hz, 3H), 2.81 (d, J=13.5 Hz, 1H), 2.88 (d, J=13.5 Hz, 1H), 2.99 (d, J=13.5 Hz, 1H), 3.64 (d, J=12.8 Hz, 1H), 3.69 (d, J=12.8 Hz, 1H), 3.69 (s, 2H), 4.37 (dd, J=8.3 Hz, 1.8 Hz, 1H), 4.42 (qd, J=6.3 Hz, 1.8 Hz, 1H), 4.42 (d, J=11.6 Hz, 1H), 4.52 (d, J=11.6 Hz, 1H), 4.91 (s, 1H), 7.05 (br d, J=8.3 Hz, 1H), 7.12 (s, 1H), 7.22-7.31 (m, 16H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.14, 21.85, 22.71, 26.31, 28.23, 37.45, 37.79, 38.71, 40.81, 58.47, 59.75, 59.78, 71.72, 74.14, 80.97, 127.42, 127.53, 127.69, 128.10, 128.73, 128.80, 128.84, 128.96, 137.54, 137.79, 138.56, 154.45, 170.71, 172.36, 174.27. Anal. Calcd for $C_{39}H_{52}N_4O_6S_2$: C, 63.56; H, 7.11; N, 7.60. Found. C, 63.77; H, 7.17; N, 7.61. FAB-MS, 737.3423 for $[M+H]^+$ (calcd 737.3407 for $C_{39}H_{53}N_4O_6S_2$).

Boc-(R)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-Thr(Bn)-NHCH$_3$ (8). 0.8 g (1.1 mmol) of **7** was treated with TFA/anisole by the general method to give H-(R)-MeCys(Bn)-(R)-MeCys(Bn)-Thr(Bn)-NHCH$_3$ as an oil. To the solution of Boc-(R)-MeCys(Bn)-OH (**5**, 0.53 g, 1.6 mmol) in THF (5 ml) were added DIEA (0.76 ml, 4.4 mmol), HOAt (0.15 g, 1.1 mmol), CIP (0.45 g, 1.6 mmol), and the deprotected tripeptide amide obtained above in THF (5 ml). The mixture was stirred for 48 h at 25°C. The crude product was isolated by the general method followed by silicagel colum chromatography ($CHCl_3$/MeOH, 40/1). The product was purified by flash chromatography using hexane/AcOEt (2/1 to 1/2) to yield the desired tetrapeptide amide **8** as a solid and an unreacted amine component as an oil. The isolated amine component was re-coupled with **5** by the same procedure described above and the desired product was purified by a procedure similar to that described above. The combined yield was 0.42 g (42 %): $[\alpha]_D^{24}$ +38.18 (c=1.0, $CHCl_3$), mp 136-138°C, IR ($CHCl_3$), 1701, 1670, 1522, 1506, 1497, 1456, 1373, 1157 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (d, J=6.3 Hz, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.46 (s, 9H), 1.52 (s, 3H), 2.70 (d, J=4.6 Hz, 3H), 2.75 (d, J=13.2 Hz, 1H), 2.79 (d, J=13.5 Hz, 1H), 2.86 (d, J=13.2 Hz, 1H), 3.02 (d, J=13.5 Hz, 1H), 3.27 (d, J=13.2 Hz, 1H), 3.29 (d, J=13.2 Hz, 1H), 3.54 (d, J=13.4 Hz, 1H), 3.61 (d, J=13.4 Hz, 1H), 3.63 (s, 2H), 3.64 (d, J=13.4 Hz, 1H), 3.70 (d, J=13.4 Hz, 1H), 4.32 (qd, J=6.3 Hz, 1.8 Hz, 1H), 4.46 (d, J=11.9 Hz, 1H), 4.50 (br d, J=8.2 Hz, 1H), 4.54 (d, J=11.9 Hz, 1H), 5.16 (s, 1H), 6.66 (s, 1H), 7.05 (br q, J=4.6 Hz, 1H), 7.21-7.28 (m, 20H), 7.43 (d, J=8.6 Hz, 1H), 7.57 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.66, 23.04, 23.29, 23.52, 26.25, 28.34, 37.64, 37.75, 37.79, 37.90, 38.24, 39.01, 58.22, 59.50, 59.68, 60.84, 71.39, 74.84, 81.62, 127.04, 127.20, 127.29, 127.47, 128.05, 128.46, 128.61, 128.71, 128.88, 128.95, 137.77, 137.90, 138.17, 138.90, 155.25, 170.98, 172,70, 172.95, 173,13. Anal. Calcd for $C_{50}H_{65}N_5O_7S_3$: C, 63.60; H, 6.94; N, 7.42. Found. C, 63.41; H, 6.94; N, 7.35. FAB-MS, 944.4142 for $[M+H]^+$ (calcd 944.4124 for $C_{50}H_{66}N_5O_7S_3$).

$C_6H_5CH_2CH_2CO$-(R)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-Thr(Bn)-$NHCH_3$ (9). Boc-tetrapeptide amide (**8**, 0.11 g, 0.12 mmol) was treated with TFA/anisole by the general method to give H-(R)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-Thr(Bn)-$NHCH_3$ as an oil and the product was dissolved in $CHCl_3$ (4 ml). To this solution was added Et_3N (0.16 ml, 1.2 mmol) and 3-phenylpropionyl chloride (87 µl, 0.6 mmol) at 4°C, and the mixture was stirred overnight at 25°C. $CHCl_3$ (10 ml) was added to the reaction mixture. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was purified by silicagel column chromatography (hexane/AcOEt, 1/2) followed by recrystallization with AcOEt/hexane to yield 0.1 g (88 %) of **9** as a solid: $[\alpha]_D^{24}$ +17.82 (c=0.6, $CHCl_3$), mp 92-93°C, IR ($CHCl_3$), 1670, 1506, 1497, 1456, 1375 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 (d, J=6.6 Hz, 3H), 1.25 (s, 3H), 1.29 (s, 3H), 1.59 (s, 3H), 2.39 (t, J=7.6 Hz, 2H), 2.70 (d, J=13.2 Hz, 1H), 2.75 (d, J=4.6 Hz, 3H), 2.77 (d, J=13.2 Hz, 1H), 2.87 (t, J=7.6 Hz, 2H), 2.91 (d, J=13.2 Hz, 1H), 2.92 (d, J=13.2 Hz, 1H), 3.16 (d, J=13.2 Hz, 1H), 3.17 (d, J=13.2 Hz, 1H), 3.58 (d, J=12.8 Hz, 1H), 3.63 (s, 2H), 3.65 (d, J=12.8 Hz, 1H), 3.68 (s, 2H), 4.39 (qd, J=6.6 Hz, 1.8 Hz, 1H), 4.46 (br d, J=6.8 Hz, 1H), 4.46 (d, J=11.2 Hz, 1H), 4.52 (d, J=11.2 Hz, 1H), 5.91 (s, 1H), 6.47 (s, 1H), 7.13-7.34 (m, 27H), 7.51 (s, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.02, 22.30, 22.62, 23.09, 26.33, 30.96, 37.57, 37.71, 37.79, 37.86, 38.44, 38.83, 39.91, 58.44, 59.51, 59.64, 61.08, 71.57, 74.59, 126.47, 127.08, 127.24, 127.38, 127.58, 128.03, 128.26, 128.50, 128.66, 128.70, 128.84, 128.91, 129.02, 137.72, 137.93, 138.02, 138.94, 140.29, 171.03, 171.86, 172.99, 173.04, 173.31. Anal. Calcd for $C_{54}H_{65}N_5O_6S_3$: C, 66.43; H, 6.71; N, 7.17. Found. C, 66.15; H, 6.87; N, 7.09. FAB-MS, 976.4174 for $[M+H]^+$ (calcd 976.4175 for $C_{54}H_{66}N_5O_6S_3$).

Trithiazoline-Thr-amide (11). Na was added portionwise to the NH_3 (30 ml) solution of **9** (0.17 g, 0.17 mmol) at -78°C until the reaction mixture became blue. After stirring for 10 seconds at -78°C, NH_4Cl was added in a portionwise manner until the blue color disappeared. The NH_3 was removed under a stream of N_2, and the residue was dried in vacuo. To the resulting solid was added CH_2Cl_2 (3 ml) and 1.0 M $TiCl_4$ solution in CH_2Cl_2 (10 ml), and the mixture was stirred overnight at 25°C. Saturated aqueous Na_2CO_3 (20 ml) was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was purified by silicagel column chromatography ($CHCl_3$/MeOH, 20/1) to yield 50 mg (51 %) of **11** as an oil: $[\alpha]_D^{23}$ -225.25 (c=0.4, $CHCl_3$), IR ($CHCl_3$), 1668, 1624, 1506, 1454, 1371 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (d, J=6.6 Hz, 3H), 1.51 (s, 3H), 1.59 (s, 3H), 1.62 (s, 3H), 2.80-2.86 (m, 2H), 2.83 (d, J=5.0 Hz, 3H), 2.97-3.04 (m, 2H), 3.19 (d, J=11.6 Hz, 1H), 3.25 (d, J=11.2 Hz, 1H), 3.29 (d, J=10.9 Hz, 1H), 3.62 (d, J=11.9 Hz, 1H), 3.69 (d, J=11.2 Hz, 1H), 3.75 (d, J=11.6 Hz, 1H), 4.22 (dd, J=7.9 Hz, 1.8 Hz, 1H), 4.40 (qd, J=6.6 Hz, 1.8 Hz, 1H), 6.63 (br q, J=5.0 Hz, 1H), 7.20-7.32 (m, 5H), 7.58 (d, J=7.9 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.19, 24.91, 25.66, 26.04, 26.11, 33.43, 35.87, 41.30, 43.09, 43,58, 56.41, 65.99, 83.51, 83.54, 84.39, 126.20, 128.37, 140.20, 171.50, 171.70, 176.10, 178.63, 179.39. FAB-MS, 562.1985 for $[M+H]^+$ (calcd 562.1980 for $C_{26}H_{36}N_5O_3S_3$).

Trithiazoline-Thr, keto- amide (12). To the CH_2Cl_2 (2 ml) solution of trithiazoline-Thr-amide (**11**, 50 mg, 89 µmol), was added 0.19 g (0.45 mmol) of Dess-Martin reagent and the mixture was stirred for 30 min at 25°C. CH_2Cl_2 (5 ml) was added and the mixture was washed with 1N NaOH, H_2O, and dried ($MgSO_4$). The solvent of the organic layer was removed by evaporation. The residue was purified by silicagel column

chromatography ($CHCl_3$/MeOH, 40/1) to yield 29 mg (58 %) of **12** as an oil: $[\alpha]_D^{22}$ -231.07 (c=0.56, $CHCl_3$), IR ($CHCl_3$), 1674, 1626, 1497, 1454, 1367 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 2.27 and 2.30 (s, 3H), 2.82-2.87 (m, 5H), 2.96-3.01 (m, 2H), 3.178 and 3.185 (d, J=11.6 Hz, 1H), 3.291 and 3.297 (d, J=11.6 Hz, 1H), 3.303 (d, J=11.2 Hz, 1H), 3.608 and 3.628 (d, J=11.6 Hz, 1H), 3.729 and 3.736 (d, J=11.5 Hz, 1H), 3.760 (d, J=11.2 Hz, 1H), 4.87 and 4.92 (d, J=5.6 Hz, 1H), 6.52 (br s, 1H), 7.22-7.30 (m, 5H), 8.10 and 8.15 (d, J=5.6 Hz, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.73, 24.98, 25.72, 25.93, 25.99, 26.67, 26.85, 27.01, 33.46, 35.91, 41.13, 43.09, 43.63, 63.56, 83.61, 84.26, 84.31, 126.22, 128.39, 140.27, 164,80, 165,34, 171.59, 175.29, 175.44, 178.63, 179.26, 179.64. FAB-MS, 560.1815 for $[M+H]^+$ (calcd 560.1824 for $C_{26}H_{34}N_5O_3S_3$).

Dihydrothiangazole (13). To the benzene (15 ml) solution of trithiazoline-Thr, keto-amide (**12**, 23 mg, 41 μmol), was added 40 mg (0.2 mmol) of TosOH and the mixture was refluxed under azeotropic distillation conditions with a Dean-Stark trap containing 4A molecular sieves for 15 h. The solvent was removed by evaporation and the residue was extracted with $CHCl_3$. The organic layer was washed with 1N NaOH, H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by silicagel column chromatography ($CHCl_3$/MeOH, 40/1) to yield 13.5 mg (61 %) of **13** as an oil: $[\alpha]_D^{22}$ -174.1 (c=0.6, $CHCl_3$), IR ($CHCl_3$), 1662, 1635, 1624, 1541, 1456, 1437 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.597 (s, 3H), 1.605 (s, 3H), 1.67 (s, 3H), 2.65 (s, 3H), 2.81-2.88 (m, 2H), 2.95 (d, J=5.3 Hz, 2H), 2.94-3.03 (m, 2H), 3.21 (d, J=11.2 Hz, 1H), 3.26 (d, J=11.5 Hz, 1H), 3.31 (d, J=11.2 Hz, 1H), 3.73 (d, J=11.5 Hz, 1H), 3.77 (d, J=11.2 Hz, 1H), 3.85 (d, J=11.2 Hz, 1H), 6.94 (br q, J=5.3 Hz, 1H), 7.20-7.32 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.70, 24.32, 25.50, 25.71, 26.08, 33.50, 35.94, 41.92, 43.06, 43.67, 79.39, 83.61, 126,24, 128.41, 129.13, 140.31, 153.37, 162.32, 162.48, 171.59, 178.13, 178.31. FAB-MS, 542.1710 for $[M+H]^+$ (calcd 542.1718 for $C_{26}H_{32}N_5O_2S_3$).

Thiangazole (1). To the benzene (3 ml) solution of dihydrothiangazole (**13**, 11 mg, 20 μmol), was added 9 mg (40 μmol) of DDQ and the mixture was refluxed for 1 h. A few drops of 1N NaOH were added to the reaction mixture and the solution was directly subjected to silicagel column chromatography ($CHCl_3$/MeOH, 40/1) to yield 5.5 mg (50 %) of **1** as an oil: $[\alpha]_D^{19}$ -213.2 (c=0.03, $CHCl_3$), IR ($CHCl_3$), 1662, 1635, 1581, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 2.65 (s, 3H), 2.95 (d, J=5.1 Hz, 2H), 3.22 (d, J=11.3 Hz, 1H), 3.29 (d, J=11.4 Hz, 1H), 3.38 (d, J=11.2 Hz, 1H), 3.76 (d, J=1.4 Hz, 1H), 3.83 (d, J=11.3 Hz, 1H), 3.87 (d, J=11.4 Hz, 1H), 6.91 (br q, J=5.1 Hz, 1H), 7.06 (d, J=16.2 Hz, 1H), 7.15 (d, J=16.2 Hz, 1H), 7.35-7.40 (m, 3H), 7.49-7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.75, 24.37, 25.53, 25.69, 26.14, 41.97, 42.48, 43.21, 79.44, 83.51, 83.68, 122.46, 127.62, 128.91, 129.16, 129.73, 135.11, 142.01, 153.40, 162.34, 162.50, 167.92, 178.08, 178.12. FAB-MS, 540.1569 for $[M+H]^+$ (calcd 540.1562 for $C_{26}H_{30}N_5O_2S_3$).

Abbreviations

Boc=tert-butoxycarbonyl, Bn=benzyl, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIEA=diisopropylethylamine, HOAt=1-hydroxy-7-azabenzotriazole, TFA=trifluoroacetic acid, Z=benzyloxycarbonyl.

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