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Convergent Synthesis of (-)-Mirabazole B using a Chloroimidazolidium Coupling Reagent, CIP

Naohiro Kuriyama [a,b], Kenichi Akaji [a], and Yoshiaki Kiso *[a]

[a] Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan

[b] YMC Co., Ltd., Kumiyama-cho, Kyoto 613, Japan

Abstract: (-)-Mirabazole B (**1**), an alkaloid consisting of four successive thiazoline/thiazole rings, has been synthesized in a convergent route. The key intermediate, a linear tripeptide amide **13** composing of three S-benzyl-2-methylcysteine residues, was prepared using 2-chloro-1,3-dimethyl-imidazolidium hexafluorophosphate (CIP) in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) as a coupling agent. The successive thiazoline/thiazole rings were constructed by $TiCl_4$-mediated cyclization followed by Hantzsch reaction without difficulty.

(-)-Mirabazole B (**1**) (Figure 1) was isolated from the terrestrial blue green alga *Scytonemea mirabile* by Moore and coworkers[1] in 1991. The structure including the stereochemistry of three asymmetric carbons was confirmed by the synthesis by Parsons and Heathcock[2] in 1994, although the details have not yet reported. Mirabazole B and structurally related mirabazoles,[1] tantazoles,[3] and thiangazole[4] belong to a novel class of natural products which have in common a unique array of successive thiazoline/thiazole, and oxazole rings. Because of the novel structural features as well as interesting biological activities,[5,6] a considerable attention has been focused on the synthesis of these novel alkaloids.[2,7-15]

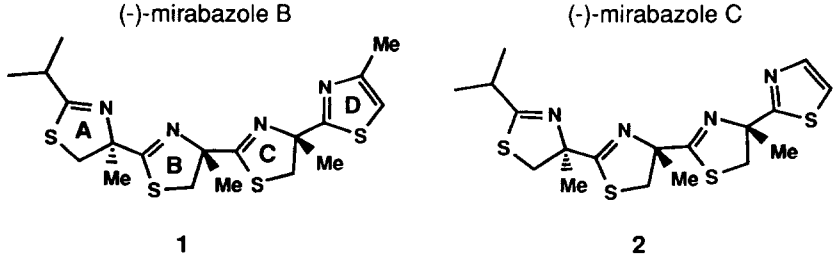

Figure 1. Structures of mirabazoles

We have previously reported a convergent synthesis of (-)-mirabazole C (**2**) featuring the use of CIP/HOAt (Figure 2) developed by us.[16] A key intermediate for the synthesis was obtained with the CIP/HOAt being the only coupling agent. In order to examine general applicability of the synthetic scheme, we undertook the convergent synthesis of (-)-mirabazole B following the (-)-mirabazole C synthesis. Herein, we describe the results and experimental details of our convergent synthesis of (-)-mirabazole B using the CIP/HOAt.

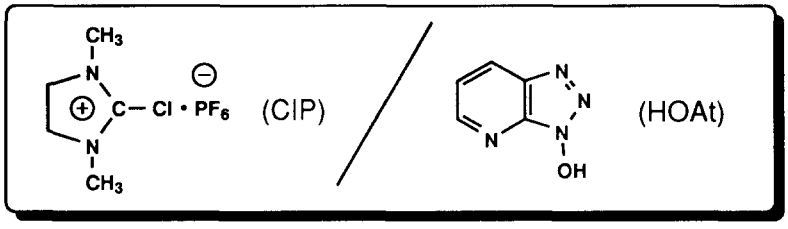

Figure 2. Structure of coupling reagent

RESULTS AND DISCUSSION

To construct the successive thiazoline rings, two different strategies have been adopted: one is the sequential formation of thiazoline rings[10,11] and the other is a simultaneous formation of thiazoline rings by Lewis acid-mediated cyclocondensation of an appropriate precursor peptide.[8,15] We selected the latter

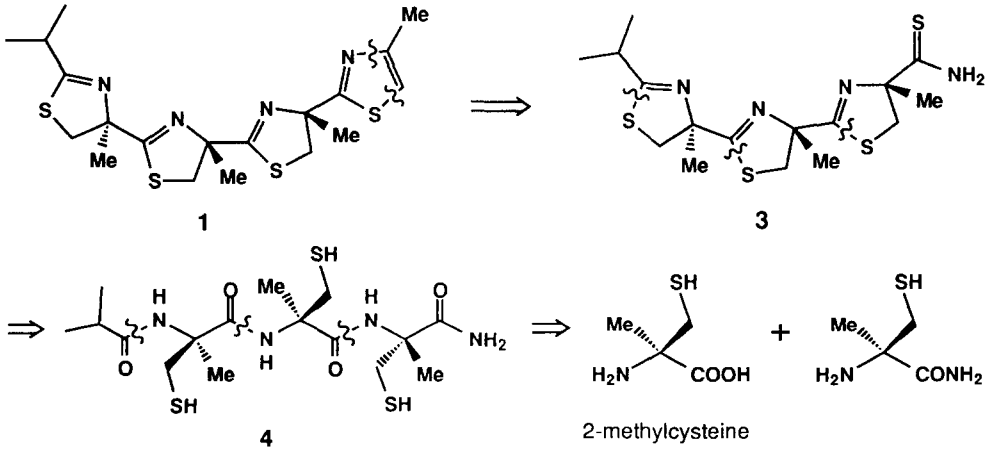

Figure 3. Retrosynthetic route of (-)-Mirabazole B

approach in our previous synthesis of (-)-mirabazole C since the convergent synthesis of precursor tripeptide consisting of 2-methylcysteine residues was successfully achieved by the use of CIP/HOAt. In the present synthesis, we adopted the same strategy but with slight modification described by Heathcock.[2] As shown in Figure 3, the A~C thiazoline rings are formed first by the $TiCl_4$-mediated one-step cyclization to avoid the side reaction caused by slow formation of unsubstituted terminal ring. The terminal thiazole ring is then constructed by the general procedure of Hantzsch[17] which consists in the cyclization between a thioamide and a halogenomethylketone group. The necessary tripeptide derivative **4** is prepared by the successive condensation of 2-methylcysteine derivatives using CIP/HOAt.

Figure 4 shows the synthetic route for Z-(R)-2-methylcysteine derivatives. The common precursor **6** was synthesized by stereoselective alkylation of oxazolidone **5** prepared from Z-D-Ala-OH and benzaldehyde according to the established procedure.[16] Three different (R)-2-methylcysteine derivatives were obtained from **6** using three different nucleophiles, i.e: using LiOH as nucleophile to yield carboxylic acid derivative **7**, using ammonia in aqueous EtOH to yield amide **8**, and using NaOMe to yield methylester **9**. Thus, a new α-methylcysteine derivative **8** was easily prepared starting from the known derivative **6**. Z-S-benzyl-(S)-2-methylcysteine **10** was similarly prepared starting from Z-L-Ala-OH.

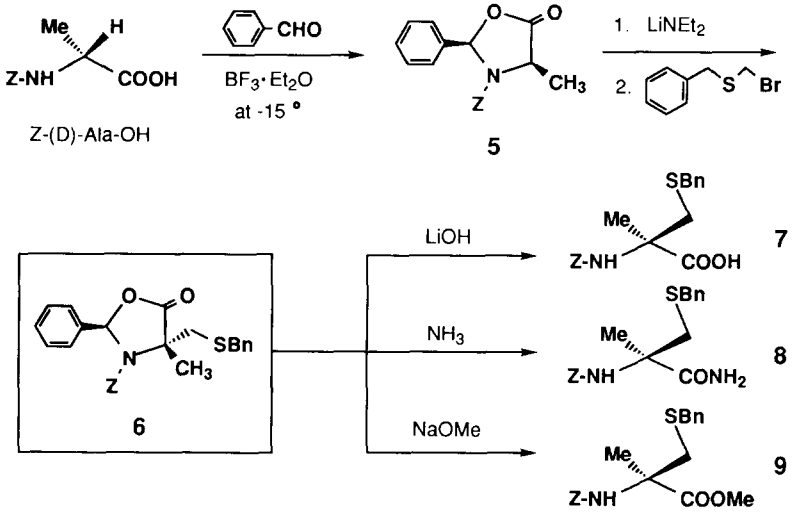

Figure 4. Synthetic route for (R)-2-methylcysteine derivatives

The tripeptide amide **13** was prepared according to the route shown in Figure 5. The N^{α}-Z group of Z-(R)-MeCys(Bn)-NH_2 **8** was removed by HBr/AcOH treatment and the product was coupled with **7**

by a reaction with CIP/HOAt for 24 h at 25°C to give a dipeptide amide **11** with a 57% isolation yield. The same deprotection by HBr/AcOH and the coupling by CIP/HOAt were repeated for the condensation of **11** and Z-(S)-MeCys(Bn)-OH **10** to give tripeptide amide **12** with a 50% isolation yield. Thus, desired di- and tripeptide amides (**11** and **12**) were obtained in reasonable yield using CIP/HOAt as a coupling agent. The Z group of **12** was then removed with HBr/AcOH, and the resulting amine was acylated with isobutyryl chloride to obtain **13**. The same key intermediate **13** could also be prepared via known tripeptide ester **16**,[7] although additional hydrolysis and coupling steps were necessary. The ester **16** was prepared in our present synthesis by the successive condensation of 2-methylcysteine derivatives using the CIP/HOAt instead of PyBroP[18] employed by Walker et. al.[7]

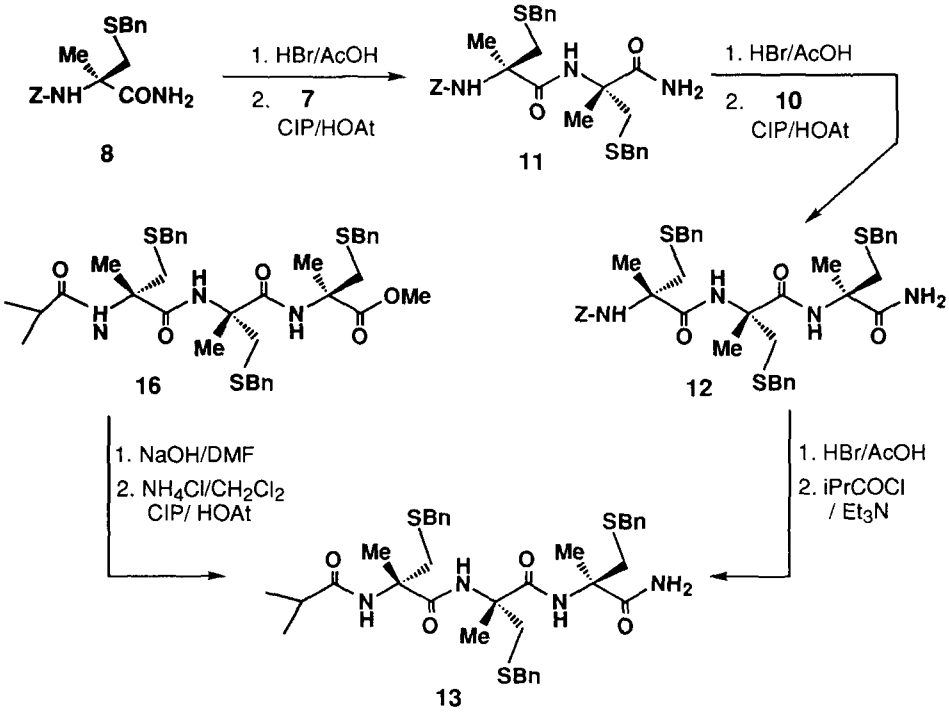

Figure 5. Synthetic route for the key intermediate tripeptide amide

Finally, the key intermediate **13** was converted to (-)-mirabazole B according to the route shown in Figure 6. Thiol protecting benzyl groups were removed by treatment of **13** with sodium in ammonia. The isolated crude trithiol product **17** was immediately treated with $TiCl_4$ in CH_2Cl_2 to obtain trithiazoline

amide **18** without difficulty. No detectable side product was obtained during the cyclization reaction, in contrast to 14% formation of side product derived from slow cyclization during the previous synthesis for (-)-mirabazole C.[16] The terminal amide of **18** was converted into the corresponding thioamide **3** by the use of Lawesson's reagent.[19] The fourth thiazole ring was then formed by condensation of the trithiazoline thioamide with chloroacetone according to the procedure of Hantzsch to give **1**. The synthetic material had the same ^{1}H-NMR spectra and specific rotation as those reported for the natural product.

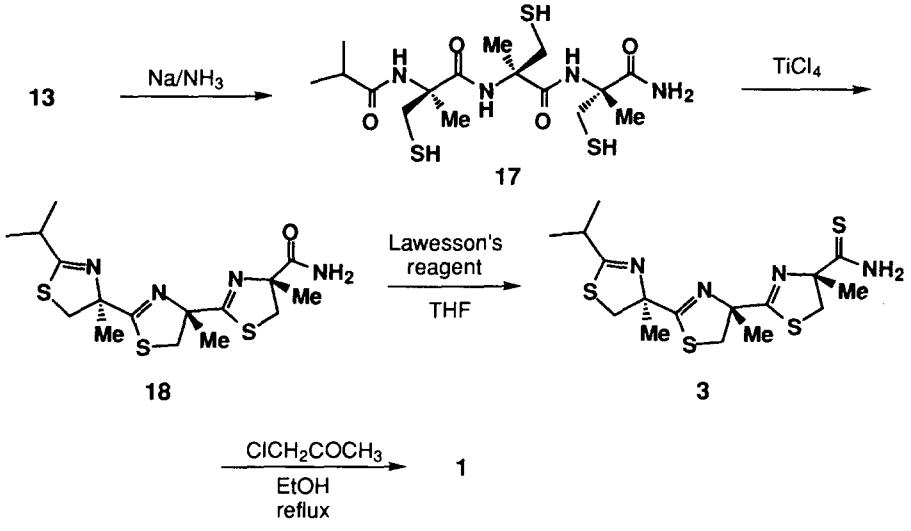

Figure 6. Synthetic route for (-)-Mirabazole B (**1**)

Conclusion

Convergent synthesis of (-)-mirabazole B was achieved using CIP/HOAt. Synthesis of key intermediate **13** was achieved starting from Z-(R)-MeCys(Bn)-NH_2, a newly prepared derivative, with CIP/HOAt being the coupling agent. Successive thiazoline/thiazole rings of (-)-mirabazole B were successfully constructed using the two-step cyclization where the A~C rings are formed first by the $TiCl_4$-mediated cyclization and then the D ring by Hantzsch reaction. The results of present synthesis combined with our previous synthesis show that the combination of $TiCl_4$-mediated cyclization and CIP/HOAt mediated coupling reaction could be a general synthetic scheme for the mirabazole family of alkaloids.

EXPERIMENTAL

General. All reactions involving air or moisture sensitive reagents were conducted under an atmosphere of N_2 in septum stoppered flasks. Solvents were reagent grade and dried prior to use. Silica-gel flash chromatography was carried out using YMC-Gel SIL-60 (10/20μm. YMC CO., Ltd.). n-Butyl lithium was purchased as a 1.6 M solution in hexane from Nakalai tescqe Co., Ltd. D and L-Alanine were purchased from WAKO Pure Chemical Ind. Ltd. Saturated HBr in acetic acid was obtained from WATANABE Chemical Ind. Ltd.

Melting points were uncorrected. ^{1}H- and ^{13}C-NMR were performed on a JEOL JNM-EX270 or Bruker AC300 spectrometer. Optical rotation was determined with a JASCO DIP-1000 polarimeter using a 1 mL cell. FAB-MS was obtained on a JEOL JMS-SX102A spectrometer equipped with the JMA-DA7000 data system.

General method for the removal of the Z group. To the 0.30 M solution of the N^{α}-Z derivative in CH_2Cl_2 was added an equal volume of HBr/AcOH at 4°C, and the mixture was stirred for 60 min at 25°C. The solvent was removed by azeotroping with heptane (2 times). To the oily residue was added 5% $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed by evaporation. The N^{α}-deprotected product was obtained as an oil and used directly in subsequent reactions without further purification.

General method for the isolation of the condensation product. The condensation product was dissolved in EtOAc 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 silica-gel column chromatography.

(2R,4S)-2-Phenyl-3-(carbobenzyloxy)-4-methyl-4-(((phenylmethyl)thio)methyl)-oxazolidin-5-one (6). To a stirred solution of diethylamine (10 mL, 97.2 mmol) in dry THF (120 mL) at -78°C was added 60 mL (97.2 mmol) of n-BuLi (1.6 M in hexane), and the mixture was stirred at 0°C for 10 min. The solution was cooled to -78°C, and a solution of 25.4 g (81.5 mmol) of **5**[16] in THF (120 mL) was added at -78°C. After the solution was stirred for 30 min, a solution of 23.7 g (105.9 mmol) of bromomethyl benzyl sulfide in 25 mL of THF was added at -78°C. The mixture was stirred for 4 h at -78°C, then allowed to slowly warm to 0°C. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL), and the product was extracted with ether (2 x 100 mL). The combined organic layer was washed with 5% $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography ($CHCl_3$) followed by flash chromatography (10/1, hexane/EtOAc) to yield 21.8 g (60%) of **6** as an oil. The product had the same NMR spectra, mass value, and specific rotation as those reported before.[16]

N^{α}-Z-S-benzyl-(R)-methylcysteine [Z-(R)-MeCys(Bn)-OH] (7). To the stirred solution of **6** (2.00 g, 4.47 mmol) in THF/H_2O (3/1, 80 mL) was added LiOH·H_2O (0.37 g, 8.94 mmol) at 4°C. The mixture was stirred overnight at 25°C, and then 5% $NaHCO_3$ (10 mL) was added to the reaction mixture. The aqueous layer was washed with n-hexane (20 mL) and then acidified to pH 2 using 2N-HCl. The mixture was extracted with EtOAc (100 mL), and the organic layer was washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to yield 1.59 g (quantitative) of **7** as an oil. The product had the same NMR spectra, mass value, and specific rotation as those reported before.[16]

Z-(S)-MeCys(Bn)-OH (**10**) was similarly prepared starting from Z-L-Ala-OH with 42% isolation yield.

N^{α}-Z-S-benzyl-(R)-methylcysteine amide [Z-(R)-MeCys(Bn)-NH_2] (8). To a stirred solution of **6** (1.70 g, 3.80 mmol) in EtOH (45 mL) was added 15 mL of 28% ammonia. After stirring overnight at 25°C, the ethanol was evaporated. Brine (40 mL) was added to the residue and the mixture was then extracted with EtOAc (3 x 50 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed by evaporation. The residue was purified by silica-gel column chromatography (2/3, hexane/EtOAc) to yield 1.17 g (86%) of **8** as an oil: $[\alpha]_D^{25}$ +7.48 (c= 1.0, MeOH); IR (KBr), 1714, 1693, 1681, 1600, 1494, 1454, 1392 cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6) δ 1.36 (s, 3H), 2.96 (d, *J*= 13.2 Hz, 1H), 3.17 (d, *J*= 13.5 Hz, 1H), 3.63 (s, 2H), 5.01 (s, 2H), 7.14-7.35 (m, 13H); ^{13}C-NMR (68 MHz, DMSO-d_6) δ 23.25, 36.33, 37.10, 58.88, 65.04, 126.66, 127.50, 127.63, 128.19, 128.67, 136.88, 138.65, 154.19, 174.82; FAB-MS, 359.144 for $[M+H]^+$ (calcd 359.143 for $C_{19}H_{22}N_2O_3S$).

Z-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 (11). Z-(R)-MeCys(Bn)-NH_2 (**8**, 0.64 g, 1.78 mmol) was treated with HBr/AcOH by the general method to give H-(R)-MeCys(Bn)-NH_2 as an oil. To the solution of Z-(R)-MeCys(Bn)-OH (**7**, 0.90 g, 2.50 mmol) in CH_2Cl_2 (6 mL) were added DIEA (1.23 mL, 7.12 mmol), HOAt (0.24 g, 1.78 mmol), CIP (0.74 g, 2.65 mmol), and the deprotected amide obtained above in CH_2Cl_2 (6 mL). The mixture was stirred for 24 h at 25°C. The product was isolated by the general method and purified by silica-gel column chromatography (30/1, $CHCl_3$/MeOH) followed by flash chromatography (1/1, hexane/EtOAc) to yield 0.57 g (57%) of **11** as a solid, mp 115-116°C: $[\alpha]_D^{25}$ +19.52 (c= 1.0, MeOH); IR (KBr), 1697, 1678, 1662, 1589, 1494, 1452, 1380 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.46 (s, 3H), 2.74 (d, *J*= 13.5 Hz, 1H), 2.92 (d, *J*= 13.8 Hz, 1H), 2.98 (d, *J*= 13.8 Hz, 1H), 3.35 (d, *J*= 13.5 Hz, 1H), 3.63 (s, 2H), 3.67 (s, 2H), 5.04 (d, *J*= 11.9 Hz, 1H), 5.08 (d, *J*= 12.2 Hz, 1H), 5.37 (br s, 1H), 5.49 (s, 1H), 6.67 (s, 1H), 7.25-7.33 (m, 16H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 22.80, 23.61, 37.34, 37.77, 38.88, 39.15, 59.21, 60.12, 67.45, 127.25, 127.43, 128.35, 128.53, 128.60, 128.64, 128.75, 128.84, 128.91, 128.98, 135.66, 137.66, 137.91, 155.75, 171.75, 175.34; FAB-MS, 566.216 for $[M+H]^+$ (calcd 566.215 for $C_{30}H_{36}N_3O_4S_2$).

Z-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 (12). Z-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 (**11**, 0.66 g, 1.16 mmol) was treated with HBr/AcOH by the general method to give H-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 as an oil. To the solution of Z-(S)-MeCys(Bn)-OH (**10**, 0.60

g, 1.66 mmol) in CH_2Cl_2 (5 mL) were added DIEA (0.81 mL, 4.64 mmol), HOAt (0.16 g, 1.16 mmol), CIP (0.48 g, 1.74 mmol), and the deprotected dipeptide amide obtained above in CH_2Cl_2 (5 mL). The mixture was stirred for 24 h at 25°C. The product was isolated by the general method and purified by silica-gel column chromatography (20/1, $CHCl_3$/MeOH) followed by flash chromatography (1/1, hexane/EtOAc) to yield 0.45 g (50%) of **12** as a solid, mp 48-50°C: $[\alpha]_D^{25}$ +18.44 (c= 1.0, MeOH); IR (KBr), 1666, 1600, 1525, 1494, 1454, 1373 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.37 (s, 3H), 1.48 (s, 3H), 2.76 (d, *J*= 13.5 Hz, 1H), 2.87 (d, *J*= 13.5 Hz, 1H), 2.89 (d, *J*= 13.5 Hz, 1H), 2.94 (d, *J*= 13.5 Hz, 1H), 3.43 (d, *J*= 13.2 Hz, 1H), 3.63 (d, *J*= 13.2 Hz, 1H), 3.64 (s, 2H), 3.66 (d, *J*= 13.2 Hz, 1H), 3.71 (d, *J*= 13.3 Hz, 1H), 3.72 (d, *J*= 13.3 Hz, 1H), 3.73 (d, *J*= 13.5 Hz, 1H), 4.89 (d, *J*= 11.9 Hz, 1H), 5.21 (br s, 1H), 5.22 (d, *J*= 11.9 Hz, 1H), 5.43 (s, 1H), 6.29 (s, 1H), 7.04 (s, 1H), 7.22-7.35 (m, 21H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 21.08, 23.84, 24.01, 37.21, 37.64, 37.77, 39.89, 59.35, 59.69, 59.74, 67.42, 126.97, 127.25, 127.63, 128.44, 128.58, 128.62, 128.78, 128.89, 128.96, 129.01, 135.72, 137.64, 139.09, 138.45, 155.68, 171.85, 172.97, 176.65; FAB-MS, 773.287 for $[M+H]^+$ (calcd 773.286 for $C_{41}H_{49}N_4O_5S_3$).

iPrCO-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 (13). To the CH_2Cl_2 (3 mL) solution of Z-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH_2 (**12**, 70 mg, 0.09 mmol) was added HBr/AcOH (3 mL) at 4°C, and the mixture was stirred for 60 min at 25°C. The CH_2Cl_2 and AcOH were removed by azeotroping with heptane (3 times) and the residue was dissolved in DMF (5 mL). To this solution were added Et_3N (0.08 mL, 0.54 mmol) and isobutyrylchloride (0.03 mL, 0.27 mmol) at 4°C and the mixture was stirred for 120 min at 25°C. CH_2Cl_2 was added to the reaction mixture. The organic layer was washed with H_2O, dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (1/2, hexane/EtOAc) to yield 48 mg (75%) of **13** as a solid, mp 66-68°C: $[\alpha]_D^{25}$ +26.27 (c= 1.3, $CHCl_3$); IR (KBr), 1662, 1600, 1525, 1494, 1454, 1373 cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d_6) δ 1.00 (d, *J*= 6.5 Hz, 3H), 1.03 (d, *J*= 6.5 Hz, 3H), 1.31 (s, 3H), 1.23 (s, 3H), 1.38 (s, 3H), 2.75 (d, *J*= 13.2 Hz, 1H), 2.80 (d, *J*= 13.2 Hz, 1H), 2.72-2.83 (overlapping m, 1H), 3.14 (d, *J*= 13.5 Hz, 1H), 3.16 (d, *J*= 13.5 Hz, 1H), 3.37 (br d, 2H), 3.63 (d, *J*= 13.2 Hz, 1H), 3.67 (d, *J*= 13.2 Hz, 1H), 3.70 (d, *J*= 13.2 Hz, 1H), 3.71 (d, *J*= 13.2 Hz, 1H), 3.73 (d, *J*= 13.3 Hz, 1H), 3.78 (d, *J*= 13.3 Hz, 1H), 6.82 (s, 1H), 6.96 (s, 1H), 7.25-7.36 (m, 16H), 7.94 (s, 1H), 8.13 (s, 1H); ^{13}C-NMR (68 MHz, DMSO-d_6) δ 18.92, 19.24, 21.45, 22.87, 23.25, 33.56, 36.57, 36.73, 36.92, 37.23, 38.20, 58.97, 59.10, 126.64, 126.72, 126.80, 128.19, 128.22, 128.28, 128.67, 128.75, 138.30, 138.52, 138.74, 171.85, 173.38, 175.59, 177.05; FAB-MS, 709.290 for $[M+H]^+$ (calcd 709.291 for $C_{37}H_{48}N_4O_4S_3$).

Z-(R)-MeCys(Bn)-OMe (9). To the THF (20 mL) solution of **6** (3.00 g, 6.70 mmol) was added 3 mL of NaOMe (4.60 M in MeOH) at 4°C. The solution was stirred for 60 min at 4°C. The reaction mixture was poured into ice-water and extracted with ether (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (8/1, hexane/EtOAc) to yield 2.20 g (88%) of **9** as an oil: $[\alpha]_D^{25}$ -

4.84 (c= 1.0, $CHCl_3$); IR (KBr), 1720, 1498, 1453, 1374 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.58 (s, 3H), 2.98 (d, *J*= 13.8 Hz, 1H), 3.30 (d, *J*= 13.5 Hz, 1H), 3.59 (d, *J*= 13.2 Hz, 1H), 3.65 (d, *J*= 13.5 Hz, 1H), 3.71 (s, 3H), 5.09 (s, 2H), 5.83 (br s, 1H), 7.19-7.37 (m, 10H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 23.43, 37.30, 52.90, 60.72, 66.58, 127.08, 128.05, 128.12, 128.48, 128.84, 136.31, 138.04, 154.55, 173.46; FAB-MS, 374.143 for $[M+H]^+$ (calcd 374.143 for $C_{20}H_{23}NO_4S$).

Z-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (14). Z-(R)-MeCys(Bn)-OMe (**9**, 0.53 g, 1.42 mmol) was treated with HBr/AcOH by the general method to give H-(R)-MeCys(Bn)-OMe as an oil. To the CH_2Cl_2 (5 mL) solution of Z-(R)-MeCys(Bn)-OH (**7**, 0.61 g, 1.70 mmol) were added DIEA (0.99 mL, 5.68 mmol), HOAt (0.19 g, 1.42 mmol), CIP (0.59 g, 2.13 mmol), and the deprotected ester obtained above in CH_2Cl_2 (5 mL). The mixture was stirred for 24 h at 25°C. The product was isolated by the general method and was purified by silica-gel column chromatography ($CHCl_3$) followed by flash chromatography (3/1, hexane/EtOAc) to yield 0.56 g (68%) of **14** as a solid, mp 105-106°C: $[\alpha]_D^{25}$ +16.40 (c= 1.0, $CHCl_3$); IR (KBr), 1735, 1658, 1520, 1494, 1453 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.54 (s, 3H), 2.93 (d, *J*= 13.2 Hz, 1H), 3.01 (d, *J*= 13.8 Hz, 1H), 3.13 (d, *J*= 13.8 Hz, 1H), 3.37 (d, *J*= 13.5 Hz, 1H), 3.64 (br d, 2H), 3.67 (s, 2H), 3.69 (s, 3H), 5.08 (s, 2H), 5.65 (s, 1H), 7.20-7.35 (m, 16H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 22.55, 23.01, 37.30, 37.62, 37.79, 38.97, 52.88, 60.10, 60.71, 66.73, 127.13, 127.22, 128.08, 128.51, 128.62, 128.89, 136.31, 138.02, 138.16, 154.84, 172.05, 173.40; FAB-MS, 581.215 for $[M+H]^+$ (calcd 581.214 for $C_{31}H_{36}N_2O_5S_2$).

Z-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (15). Z-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (**14**, 1.05 g, 1.80 mmol) was treated with HBr/AcOH by the general method to give H-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe as an oil. To the solution of Z-(S)-MeCys(Bn)-OH (**10**, 0.88 g, 2.44 mmol) in CH_2Cl_2 (7.5 mL) were added DIEA (1.25 mL, 7.20 mmol), HOAt (0.24 g, 1.80 mmol), CIP (0.75 g, 2.70 mmol), and the deprotected dipeptide ester obtained above in CH_2Cl_2 (7.5 mL). The mixture was stirred for 24 h at 25°C. The product was isolated by the general method and purified by silica-gel column chromatography (50/1, $CHCl_3$/MeOH) followed by flash chromatography (3/1, hexane/EtOAc) to yield 0.73 g (67%) of **15** as an oil: $[\alpha]_D^{25}$ +17.68 (c= 1.0, $CHCl_3$); IR (KBr), 1735, 1704, 1680, 1518, 1495, 1453 1372 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 2.79 (d, *J*= 13.2 Hz, 1H), 2.96 (d, *J*= 13.5 Hz, 1H), 3.07 (d, *J*= 13.5 Hz, 1H), 3.09 (d, *J*= 13.5 Hz, 1H), 3.14 (d, *J*= 13.5 Hz, 1H), 3.32 (d, *J*= 13.5 Hz, 1H), 3.57-3.73 (overlapping m, 6H), 3.68 (s, 3H), 5.01 (d, *J*= 12.2 Hz, 1H), 5.09 (d, *J*= 12.2 Hz, 1H), 5.38 (s, 1H), 6.67 (s, 1H), 7.21-7.40 (m, 21H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 22.48, 22.62, 23.12, 37.53, 37.59, 37.77, 37.84, 38.94, 39.22, 52.47, 59.37, 59.92, 59.99, 67.22, 126.93, 127.22, 127.34, 128.35, 128.42, 128.64, 128.73, 128.94, 135.86, 137.87, 138.21, 138.41, 155.36, 171.64, 172.00, 173.40; FAB-MS, 788.284 for $[M+H]^+$ (calcd 788.286 for $C_{42}H_{49}N_3O_6S_3$).

iPrCO-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (16). Z-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (**15**, 0.32 g, 0.41 mmol) was treated with HBr/AcOH by the general method to give H-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe as an oil and the

product was dissolved in CH_2Cl_2 (3 mL). To this solution were added Et_3N (0.34 mL, 2.44 mmol) and isobutyrylchloride (0.13 mL, 1.22 mmol) at 4°C and the mixture was stirred for 120 min at 25°C. CH_2Cl_2 was added to the reaction mixture. The organic layer was washed with H_2O, dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (2/1, hexane/EtOAc) to yield 0.24 g (81%) of **16** as an oil: $[\alpha]_D^{25}$ +32.92 (c= 1.0, $CHCl_3$); IR (KBr), 1735, 1660, 1520, 1495, 1453, 1373 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.10 (d, *J*= 6.9 Hz, 6H), 1.42 (s, 3H), 1.48 (s, 3H), 1.53 (s, 3H), 2.24 (heptet, *J*= 6.9 Hz, 1H), 2.81 (d, *J*= 13.5 Hz, 1H), 2.98 (d, *J*= 13.5 Hz, 1H), 3.08 (d, *J*= 13.5 Hz, 1H), 3.15 (d, *J*= 13.2 Hz, 1H), 3.16 (d, *J*= 13.3 Hz, 1H), 3.37 (d, *J*= 13.2 Hz, 1H), 3.62-3.75 (overlapping m, 6H), 3.69 (s, 3H), 6.03 (s, 1H), 6.63 (s, 1H), 7.26-7.32 (m, 15H), 7.47 (s, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 19.35, 19.53, 22.42, 23.41, 35.59, 37.46, 37.62, 37.75, 38.00, 38.76, 39.15, 52.43, 59.42, 59.58, 59.92, 126.91, 127.20, 127.42, 128.40, 128.60, 128.78, 128.87, 128.96, 138.21, 138.43, 171.57, 172.07, 173.44, 177.62; FAB-MS, 724.291 for $[M+H]^+$ (calcd 724.291 for $C_{38}H_{49}N_3O_5S_3$).

iPrCO-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH$_2$ (13). To the DMF (10 mL) solution of iPrCO-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-OMe (**16**, 0.62 g, 0.85 mmol) was added NaOH (0.50 g, 12.5 mmol) and the mixture was stirred overnight at 25°C. The pH of the solution was adjusted to 2 with 1N-HCl and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The solvent was removed by evaporation. The residue was dissolved in EtOAc (50 mL) and the solution was washed with H_2O, dried ($MgSO_4$), and rotary evaporated. The residue was dissolved in CH_2Cl_2 (5 mL). To this solution, NH_4Cl (0.04 g, 0.73 mmol), DIEA (0.51 mL, 2.92 mmol), HOAt (0.10 g, 0.73 mmol), CIP (0.30 g, 1.09 mmol) were added and the mixture was stirred for 24 h at 25°C. The product was isolated by the general method and was purified by silica-gel column chromatography (1/2, hexane/EtOAc) to yield 0.48 g (79%) of **13** as a solid. Its spectroscopic and physical data were identical to those of **13** prepared above.

Trithiazoline amide (18). To the NH_3 (30 mL) solution of iPrCO-(S)-MeCys(Bn)-(R)-MeCys(Bn)-(R)-MeCys(Bn)-NH$_2$ (**13**, 0.30 g, 0.42 mmol), 1.30 g of Na was added and the mixture was stirred for 60 min at -78°C. NH_4Cl was added in portion until the blue color disappeared. The NH_3 of the mixture was removed under a stream of N_2, and the residue was dried in vacuo. To the resulting solid was added CH_2Cl_2 (10 mL). To this slurry was added 0.27 mL of $TiCl_4$ and the mixture was stirred overnight at 25°C. The reaction mixture was quenched with saturated aqueous Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with H_2O, dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (1/4, hexane/EtOAc) to yield 92 mg (57%) of **18** as a solid, mp 103-105°C: $[\alpha]_D^{25}$ -42.76 (c= 1.0, $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.22 (d, *J*= 6.9 Hz, 3H), 1.23 (d, *J*= 6.9 Hz, 3H), 1.48 (s, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 2.83 (heptet, *J*= 6.9 Hz, 1H), 3.18 (d, *J*= 11.9 Hz, 1H), 3.20 (d, *J*= 11.5Hz, 1H), 3.27 (d, *J*= 11.4Hz, 1H), 3.62 (d, *J*= 11.8Hz, 1H), 3.66 (d, *J*= 11.5Hz, 1H), 3.78 (d, *J*= 11.5Hz, 1H), 5.79 (br s, 1H), 6.66 (br s, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 20.98, 21.16, 24.76,

26.06, 33.99, 40.97, 42.78, 42.85, 83.32, 83.52, 84.33, 177.43, 178.77, 179.42; FAB-MS, 385.117 for $[M+H]^+$ (calcd 385.119 for $C_{16}H_{25}N_4OS_3$).

Trithiazoline thioamide (3). To the THF (5 mL) solution of trithiazoline amide (**18**, 10 mg, 0.026 mmol), 74 mg (0.182 mmol) of Lawesson's reagent was added and the mixture was stirred overnight at 25°C. The solvent was removed by evaporation. The residue was dissolved in EtOAc (50 mL) and the solution was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (1/2, hexane/EtOAc) to yield 9 mg (86%) of **3** as a solid, mp 144-146°C: $[\alpha]_D^{26}$ -72.60 (c= 1.5, $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.23 (d, *J*= 6.9 Hz, 3H), 1.24 (d, *J*= 6.9 Hz, 3H), 1.57 (s, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 2.84 (heptet, *J*= 6.9 Hz, 1H), 3.19 (d, *J*= 11.5 Hz, 1H), 3.27 (d, *J*= 11.5Hz, 1H), 3.41 (d, *J*= 11.9Hz, 1H), 3.66 (d, *J*= 11.5Hz, 1H), 3.73 (d, *J*= 12.0Hz, 1H), 3.78 (d, *J*= 11.5Hz, 1H), 7.62 (br s, 1H), 8.48 (br s, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 21.00, 21.16, 26.11, 26.27, 27.38, 33.99, 42.80, 43.55, 83.30, 83.59, 89.27, 177.96, 179.04, 179.56, 212.37; FAB-MS, 401.096 for $[M+H]^+$ (calcd 401.096 for $C_{16}H_{25}N_4S_4$).

(-)-Mirabazole B (1). To the EtOH (3 mL) solution of trithiazoline thioamide (**3**, 5 mg, 0.012 mmol), 5 mg (0.065 mmol) of chloroacetone was added and the mixture was refluxed for 8 h. The solvent was removed by evaporation. The residue was dissolved in EtOAc (50 mL) and the solution was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and rotary evaporated. The residue was purified by silica-gel column chromatography (2/1, hexane/EtOAc) to yield 3 mg (57%) of **1** as an oil: $[\alpha]_D^{25}$ -159 (c= 0.1, $CHCl_3$) [lit.[1] $[\alpha]_D$ -166, c= 0.09, $CHCl_3$]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*= 6.9 Hz, 3H), 1.25 (d, *J*= 6.9 Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.74 (s, 3H), 2.46 (d, *J*= 1.0 Hz, 3H), 2.87 (heptet, *J*= 6.9 Hz, 1H), 3.28 (d, *J*= 11.4 Hz, 1H), 3.29 (d, *J*= 11.3Hz, 1H), 3.46 (d, *J*= 11.4Hz, 1H), 3.73 (d, *J*= 11.4Hz, 1H), 3.75 (d, *J*= 11.4Hz, 1H), 3.82 (d, *J*= 11.3Hz, 1H), 6.77 (q, *J*= 1.0 Hz, 1H) [lit.[1] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J*= 6.7 Hz, 3H), 1.24 (d, *J*= 6.8 Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.43 (s, 3H), 2.84 (qq, *J*= 6.7, 6.8 Hz, 1H), 3.27 (d, *J*= 11.3 Hz, 1H), 3.27 (d, *J*= 11.3Hz, 1H), 3.42 (d, *J*= 11.3Hz, 1H), 3.71 (d, *J*= 11.3Hz, 1H), 3.75 (d, *J*= 11.3Hz, 1H), 3.82 (d, *J*= 11.3Hz, 1H), 6.75 (s, 1H)]; FAB-MS, 439.113 for $[M+H]^+$ (calcd 439.112 for $C_{19}H_{27}N_4S_4$).

Abbreviations. DIEA=N,N-diisopropylethylamine, HOAt=1-hydroxy-7-azabenzotriazole, Bn=benzyl, Z=benzyloxycarbonyl, PyBroP = bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate, iPr=iso-propyl.

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