

A SYNTHESIS OF A HYDROXYVALINE-DERIVED THIAZOLE-4-CARBOXYLATE CONSTITUTING AN ANTIBIOTIC, THIOCILLINE I

Yasuchika Yonezawa, Hirofumi Saito, Syusuke Suzuki, and Chung-gi Shin*

Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686

Abstract A convenient synthesis of an important constituent segment, methyl (2*S*)-2-[1-(*N*-Boc)amino-2-hydroxy-2-methyl]propylthiazole-4-carboxylate (**2**), which is the Fragment C derivative of a macrocyclic antibiotic, thiocilline, is described. Reduction of methyl *N*-Boc-hydroxyvalinate (**4**) with NaBH₄, followed by oxidation with Dess-Martin reagent gave the corresponding formyl derivative, which was then thiazolated with H-L-Cys-OMe to give **2**.

Thiocilline I (**1**),¹ isolated from the culture of *Bucillus bodius*, is a macrocyclic antibiotic structurally very similar to micrococcins P,²⁻⁴ which are constructed of a (2*S*)-2-(1-amino-2-methyl)propylthiazole-4-carboxylate moiety as the Fragment C. On the other hand, in place of the above-mentioned thiazole derived from valine (Val), the natural **1** is also composed of an important (2*S*)-2-(1-amino-2-hydroxy-2-methyl)propylthiazole-4-carboxylate (**2**) moiety, which is thought to be also derived from a L-hydroxyvaline (HyVal) derivative, as shown in Figure 1. However, the synthesis of **2** has not yet been reported. Recently, since the first total syntheses of micrococcin P and P₁ have been already accomplished,⁵⁻⁷ for the total synthesis of **1**, the synthesis of **2** from Boc-L-HyVal-OH (**3**)⁸ was investigated. Herein, we wish to report a convenient synthetic method for **2** from two routes as follows.

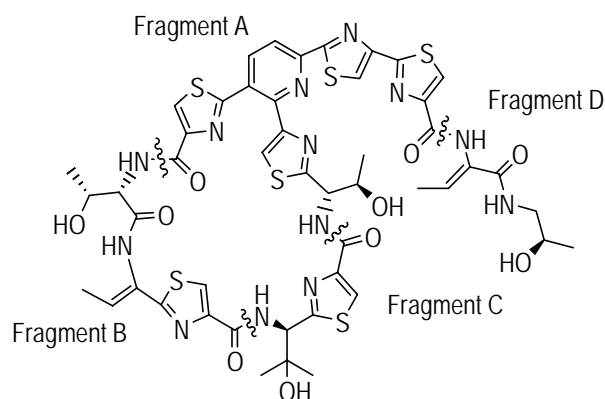
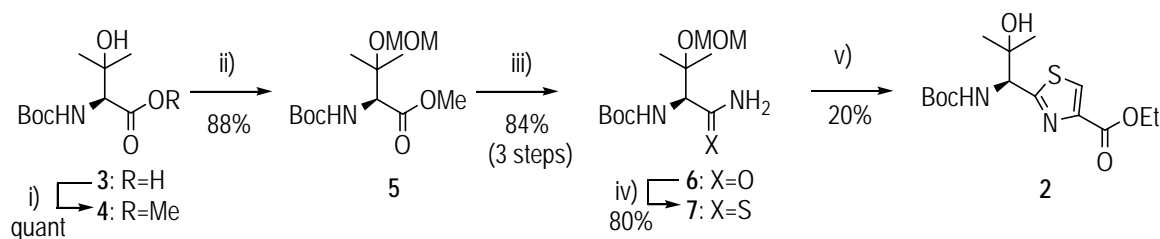


Figure 1. Thiocilline I (**1**)

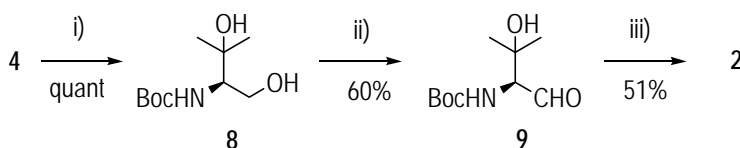
Esterification of (**3**) with MeI in the presence of KHCO₃, followed by protection of the hydroxy group of

the formed methyl ester (**4**) with methoxymethyl chloride (MOM-Cl) in the presence of (*i*-Pr)₂NEt gave Boc-L-3-(MOMO)HyVal-OMe (**5**). After ester hydrolysis of **5** with 1 M LiOH in a mixture of dioxane and H₂O (1 : 1 v/v), the generated carboxyl group was *in situ* treated with ethyl chloroformate in the presence of Et₃N and then with 28% aqueous NH₃ to give the corresponding carboxamide derivative (**6**). Subsequently, thioamidation of **6** with Lawesson's reagent gave the thioamide derivative (**7**), which is slightly unstable. Accordingly, without further purification, final thiazolation with ethyl 3-bromopyruvate in the presence of KHCO₃ and trifluoroacetic anhydride (TFAA) in the presence of pyridine formed 2-[1-(*N*-Boc-*N*-CF₃CO)aminothiazole derivative, the CF₃CO group of which was deprotected with 28% aqueous NH₃ gave the protected **2**; ethyl (1*S*)-2-[1-(*N*-Boc)amino-2-hydroxy-2-methyl]propylthiazole-4-carboxylate [(**P**)-**2**], by the Hantzsch method.⁹ Unfortunately, however, the overall yield of **2** from **3** in seven steps was found to be very low (12%). Therefore, an alternative and more effective synthetic method for the thiazole ring was studied (Scheme 1).



Scheme 1. Reagent and conditions: i) MeI, KHCO₃ / DMF, 0 °C, 30 min, rt, 6 h; ii) MOM-Cl, (*i*-Pr)₂NEt / DMF, 0 °C, 30 min, rt, 6 h; iii) (a) 1 M LiOH / dioxane-H₂O (1:1 v/v), 0 °C, 30 min, rt, 3 h; (b) ClCOOEt, Et₃N / THF, 0 °C, 15 min; (c) 28% aq. NH₃, 0 °C, 5 min; iv) Lawesson's reagent / DME, 40 °C, 12 h; v) (a) KHCO₃, ethyl bromopyruvate / DME, 0 °C, 30 min, rt, 12 h, (b) TFAA, pyridine, 0 °C, 30 min, rt, 6 h; (c) 28% aq. NH₃, 0 °C, 5 min.

Direct reduction of the ester group of **4** with NaBH₄ in EtOH gave the corresponding diol derivative (**8**), the primary hydroxyl group of which was oxidized with Dess-Martin reagent in CHCl₃ to give the expected formyl derivative (**9**). Because of its lability, however, without purification, thiazolination of **9** with H-Cys-OEt in the presence of Et₃N and then oxidation with MnO₂ in one-pot gave (**P**)-**2** in 51% yield.¹⁰ In this case, the overall yield increased to 31% from **4** in three steps (Scheme 2).



Scheme 2. Reagent and conditions : i) NaBH₄ / EtOH, 0 °C, 30 min, rt, 6 h; ii) Dess-Martin reagent, CHCl₃, 0 °C, 30 min, rt, 6 h; iii) (a) H-L-Cys-OEt, Et₃N, 0 °C, 30 min, rt, 3 h; (b) MnO₂, rt, 2 h.

The configurational structure of **2** could be clearly confirmed by the ¹H NMR spectral data

as well as satisfactory chemical analysis. In particular, from the ^1H NMR spectrum of synthetic **2**, the appearance of the chemical shifts of the thiazole ring proton at $\delta=8.13$ (s, 1H) and the hydroxy proton at $\delta=2.79$ (br s, 1H, OH) supports the formation of **2**.

In conclusion, since a synthesis of the important building block (**2**) was successfully achieved.

EXPERIMENTAL

The melting points were measured using a Yamato (Model Mp-21) micromelting point apparatus, and are uncorrected. The IR spectra were recorded using a Hitachi EPI-G2 spectrometer in KBr. The ^1H NMR spectra were measured with JEOL FX 200 and JNE 500 spectrometers in CDCl_3 solution with tetramethylsilane used as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH.

(2S)-2-(N-t-Butoxycarbonyl)amino-3-hydroxy-3-methylbutanoic Acid (3). According to the method reported previously,⁸ the compound (**3**) was prepared from Boc-D-Ser-OMe *via* (4S)-4-(1-hydroxy-1-methylethyl)-3-*t*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidine.

Methyl (2S)-2-(N-t-Butoxycarbonyl)amino-3-hydroxy-3-methylbutanoate (4). A suspension of **3** (1.66 g, 7.12 mmol), MeI (0.89 mL, 14.0 mmol), and KHCO_3 (1.78 g, 17.8 mmol) in DMF (70 mL) was stirred at 0 °C for 30 min and then at rt for 6 h. The reaction mixture was poured into water (70 mL) and then extracted with EtOAc (30 mL x 3). The combined extracts were washed with 5% $\text{Na}_3\text{S}_2\text{O}_3$ aqueous solution (50 mL x 3) and brine (50 mL x 3) and then dried over anhydrous Na_2SO_4 . Concentration *in vacuo* gave a residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **4** as a colorless syrup. Yield 1.72 g (98%). $[\alpha]_{\text{D}}^{27} -18.2^\circ$ (*c* 0.90, MeOH). IR 3435, 2979, 2360, 1718, 1506 cm^{-1} . ^1H NMR $\delta=1.33$ and 1.35 (each s, 6H, HyVal's CH_3 x 2), 1.46 (s, 9H, Boc's *t*-Bu), 2.79 (br s, 1H, OH), 3.77 (s, 3H, OCH_3), 4.25 (d, 1H, NHCH, $J=7.5$ Hz), 5.43 (br d, 1H, NH, $J=7.5$ Hz). *Anal.* Calcd for $\text{C}_{11}\text{H}_{21}\text{NO}_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.49; H, 8.78; N, 5.54.

Methyl (2S)-2-(N-t-Butoxycarbonyl)amino-3-methyl-3-(O-methoxy)methylbutanoate (5). To a solution of **4** (1.76 g, 7.12 mmol) in DMF (40 mL) was added, with stirring, (*i*-Pr) $_2\text{NEt}$ (0.024 mL, 0.14 mmol) and MOM-Cl (0.011 mL, 0.14 mmol) at 0 °C for 30 min and at rt for 6 h. The reaction mixture was poured into water (40 mL) and then extracted with EtOAc (50 mL x 3). The combined extracts were washed with brine (50 mL x 3) and dried over anhydrous Na_2SO_4 . Concentration *in vacuo* gave a residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **5** as a colorless syrup. Yield 1.66 g (88%). $[\alpha]_{\text{D}}^{28} +3.3^\circ$ (*c* 0.18, MeOH). IR 3465, 2979, 1716, 1507 cm^{-1} . ^1H NMR $\delta=1.32$ and 1.36 (each s, 6H, HyVal's CH_3 x 2), 1.44 (s, 9H, Boc's

t-Bu), 3.35 (s, 3H, MOM's OCH₃), 3.75 (s, 3H, OCH₃), 4.21 (d, 1H, NHCH, *J*=8.0 Hz), 4.70 (s, 2H, MOM's CH₂), 5.43-5.53 (br d, 1H, NH, *J*=8.0 Hz). *Anal.* Calcd for C₁₃H₂₅NO₆: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.45; H, 8.88; N, 5.04.

(2*S*)-2-(*N*-*t*-Butoxycarbonyl)amino-3-methyl-3-(*O*-methoxy)methylbutancarboxamide (6). A solution of **5** (2.95 g, 10.1 mmol) and 1 M LiOH (20.3 mL) in a mixture of dioxane-H₂O (1 : 1 v/v) (100 mL) was stirred at 0 °C for 30 min and then at rt for 3 h. The reaction mixture was washed with ether (50 mL x 3) and the aqueous solution was acidified to pH 3 with citric acid hydrate and then extracted with EtOAc (50 mL x 3). The combined extracts were washed with brine (50 mL x 3) and dried over anhydrous Na₂SO₄. Concentration *in vacuo* gave a residual syrup, to which were added, with stirring, THF (140 mL), and then Et₃N (1.54 mL, 11.1 mmol) and ClCOOEt (1.10 mL, 11.1 mmol) at 0 °C. After stirring for 15 min, the resulting solution was further stirred with 28% aqueous NH₃ (20 mL) at 0 °C for 5 min. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated *in vacuo* to give a crude syrup. The obtained syrup was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **6** as a colorless syrup. Yield 2.34 g (84%). [α]_D²⁴ +11.6° (*c* 0.16, MeOH). IR 3336, 2979, 2359, 1680 cm⁻¹. ¹H NMR δ=1.20, 1.36 (each s, 6H, HyVal's CH₃ x 2), 1.45 (s, 9H, Boc's *t*-Bu), 3.38 (s, 3H, MOM's OCH₃), 4.28 (d, 1H, NHCH, *J*=8.0 Hz), 4.76 (d, 1H, MOM's CHH, *J*=6.5 Hz), 4.82 (d, 1H, MOM's CHH, *J*=6.5 Hz), 5.50 (br s, 2H, NH, NHH), 6.61 (br s, 1H, NHH). *Anal.* Calcd for C₁₂H₂₄N₂O₅: C, 52.16; H, 8.75; N, 10.14. Found: C, 52.19; H, 8.44; N, 10.08.

(2*S*)-2-(*N*-*t*-Butoxycarbonyl)amino-3-methyl-3-(*O*-methoxy)methylbutanthiocarboxamide (7). A solution of **6** (2.34 g, 8.46 mmol) and Lawesson's reagent (1.88 g, 4.65 mmol) in DME (20 mL) was stirred at 40 °C for 12 h. After an insoluble material was filtered off, the filtrate was concentrated *in vacuo* to give a residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **7** as a yellow syrup. Yield 1.99 g (80%). IR 3349, 2978, 2936, 2839, 2358, 1676, 1597, 1571, 1504, 1255 cm⁻¹. ¹H NMR δ=0.97, 0.99, 1.14, 1.16 (each s, 6H, HyVal's CH₃ x 2), 1.27 (s, 9H, Boc's *t*-Bu), 3.59, 3.65, 3.70 (each s, 3H, MOM's OCH₃), 3.86 (d, 1/2H, NHCH, *J*=7.3 Hz), 3.93 (d, 1/2H, NHCH, *J*=7.3 Hz), 4.83-4.93 (m, 2H, MOM's CH₂), 6.77-6.85 (m, 1H, NH), 7.66-7.77 (m, 2H, NH₂). Without purification, the obtained syrup was utilized to the next reaction.

Ethyl (1*S*)-2-[1-(*N*-*t*-Butoxycarbonyl)amino-3-hydroxy-3-methyl]propylthiazole-4-carboxylate (2). To a solution of **7** (0.66 g, 22.5 mmol) in DMF (20 mL) were added, with stirring, KHCO₃ (0.34 g, 33.8 mmol) and ethyl bromopyruvate (0.71 mL, 56.2 mmol) at 0 °C for 30 min. After stirring for 12 h at rt, the resulting solution was again stirred with TFAA (0.95 mL, 6.75 mmol) and pyridine (1.10 mL, 13.5 mmol) and stirred at 0 °C for 30 min and then at rt for 6 h. Furthermore, the resulting solution was stirred with 28% NH₃ aqueous solution (15 mL) at 0 °C for 5 min. The reaction mixture was

concentrated *in vacuo* to give a residual syrup, which was dissolved in EtOAc (50 mL). The solution was washed with brine (50 mL x 3) and then dried over anhydrous Na₂SO₄. Concentration *in vacuo* gave a residual syrup, which was purified on a silica gel column using hexane and EtOAc (1 : 1 v/v) to give colorless crystals. Recrystallization from hexane-EtOAc gave **2** as a colorless powder. Yield 0.17 g (20%). mp 74-76 °C. $[\alpha]_D^{24} -41.3^\circ$ (c 0.16, MeOH). IR 3366, 2978, 2927, 2358, 1718, 1506, 1367 cm⁻¹. ¹H NMR δ =1.17 (t, 3H, Et's CH₃, *J*=7.0 Hz), 1.25 and 1.26 (each s, 6H, HyVal's CH₃ x 2), 1.43 (s, 9H, Boc's *t*-Bu), 2.79 (br s, 1H, OH), 4.37 (q, 2H, Et's CH₂, *J*=7.0 Hz), 4.87 (d, 1H, NHCH, *J*=9.7 Hz), 5.67 (br d, 1H, NH, *J*=9.7 Hz), 8.13 (s, 1H, Thiazole's H). *Anal.* Calcd for C₁₅H₂₄N₂O₅S: C, 52.31; H, 7.02; N, 8.13. Found: C, 52.02; H, 7.08; N, 8.39.

(2S)-2-(N-*t*-Butoxycarbonyl)amino-3-methyl-3-hydroxybutan-1-ol (8). A solution of **4** (0.95 g, 3.80 mmol) and NaBH₄ (0.29 g, 7.65 mmol) in EtOH (30 mL) was stirred at 0 °C for 30 min and then at rt for 6 h. To the resulting solution was added a small amount of saturated NH₄Cl aqueous solution. After evaporating EtOH *in vacuo*, the residual material was dissolved in EtOAc (50 ml) and the resulting solution was washed with brine (50 mL x 3) and then dried over anhydrous Na₂SO₄. Concentration *in vacuo* gave a residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **8** as colorless crystals. Recrystallization from EtOAc gave **8** as a colorless powder. Yield 0.82 g (98%). mp 37-38 °C. $[\alpha]_D^{25} +3.4^\circ$ (c 1.17, MeOH). IR 3398, 2978, 1691, 1509 cm⁻¹. ¹H NMR δ =1.24, 1.35 (each s, 6H, HyVal's CH₃ x 2), 1.45 (s, 9H, Boc's *t*-Bu), 2.85 (br s, 2H, OH x 2), 3.46 (m, 1H, NHCH), 3.80 (dd, 1H, CHHOH, *J*=3.4, 11.2 Hz), 4.02 (dd, 1H, CHHOH, *J*=3.2, 11.2 Hz), 5.42 (br d, 1H, NH, *J*=8.2 Hz). *Anal.* Calcd for C₁₀H₂₁NO₄: C, 54.77; H, 9.65; N, 6.39. Found: C, 54.52; H, 9.90; N, 6.35 .

(2S)-2-(N-*t*-Butoxycarbonyl)amino-3-methyl-3-hydroxypropan-1-al (9). A solution of **8** (0.84 g, 3.83 mmol) and Dess-Martin reagent (1.72 g, 4.21 mmol) in CHCl₃ (30 mL) was stirred at 0 °C for 30 min and then at rt for 6 h. The reaction mixture was concentrated *in vacuo* to give a residual syrup, which was dissolved in EtOAc (50 mL). The resulting solution was washed with brine (50 mL x 3) and then dried over anhydrous Na₂SO₄. Concentration *in vacuo* gave a residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **9** as a yellow syrup. Without purification, the crude syrup was utilized to the next reaction for the synthesis of **2**. IR 3423, 2979, 2362, 1697, 1513 cm⁻¹. ¹H NMR δ =1.32, 1.34 (each s, 6H, HyVal's CH₃ x 2), 1.45 (s, 9H, Boc's *t*-Bu), 2.79 (br s, 1H, OH), 4.23 (br d, 1H, NHCH, *J*=6.5 Hz), 5.44 (br d, 1H, NH, *J*=6.5 Hz), 9.80 (s, 1H, CHO).

Alternate Preparation of 2. A solution of **9** (0.23 g, 1.08 mmol) and H-L-Cys-OEtHCl (0.29 g, 1.72 mmol) in the presence of Et₃N (0.27 mL) in toluene (20 mL) was stirred at 0 °C for 30 min and then at rt

for 3 h. The reaction mixture was washed with saturated NaHCO₃ aqueous solution (50 mL x 3), 10% citric acid (50 mL x 3), and brine (50 mL x 3), and then dried over anhydrous Na₂SO₄. Concentration *in vacuo* gave a residual syrup, which was again dissolved in toluene (50 mL). The resulting solution was stirred with MnO₂ (1.41 g, 1.62 mmol) at rt for 2 h and then the MnO₂ was filtered off. The filtrate was concentrated *in vacuo* to give a residual syrup, which was purified on a silica gel column using a mixture of toluene and MeOH (12 : 1 v/v) to give colorless crystals. Recrystallization from hexane-EtOAc gave **2** as a colorless powder. Yield 0.19 g (51%). mp 74-76 °C.

ACKNOWLEDGEMENT

This work was supported in part by Grant-in Aid for Scientific Research No. 1264529 from the Ministry of Education, Science, Sports and Culture and by “High-Tech Research Project” from the Ministry of Education, Culture, Sports, Science and Technology.

REFERENCES

1. J. Shoji, T. Kato, Y. Yoshimura, and K. Tori, *J. Antibiot.*, 1981, **34**, 1126.
2. P. Brooks, A.T. Fuller, and J. Walker, *J. Chem. Soc.*, **1957**, 689.
3. J. Walker, A. Olesker, L. Valente, R. Rabanal, and G. Lukacs, *J. Chem. Soc., Chem. Commun.*, **1977**, 706.
4. B. W. Bycroft and M. S. Gowland, *J. Chem. Soc., Chem. Commun.*, **1978**, 256.
5. C. Shin, K. Okumura, M. Shigekuni, and Y. Nakamura, *Chem. Lett.*, **1998**, 139; K. Okumura, Y. Nakamura, and C. Shin, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 1561.
6. K. Okumura, A. Ito, D. Yoshioka, and C. Shin, *Heterocycles*, 1998, **48**, 1319; K. Okumura, T. Suzuki, Y. Nakamura, and C. Shin, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 2483.
7. M. A. Ciufolini and Y-C. Shen, *Org. Lett.*, 1999, **1**, 1843.
8. Y. Yonezawa, K. Shimizu, K-S. Yoon, and C. Shin, *Synthesis*, **2000**, 634.
9. W. M. Bredenkamp, C. M. Holzapfel, and W. J. van Zyl, *Syn. Commun.*, 1990, **20**, 2235.
10. Y. Hamada, M. Shibata, T. Sugiura, S. Kato, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252.