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

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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 $NaBH_4$, 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)propyl-thiazole-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 P_1 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.

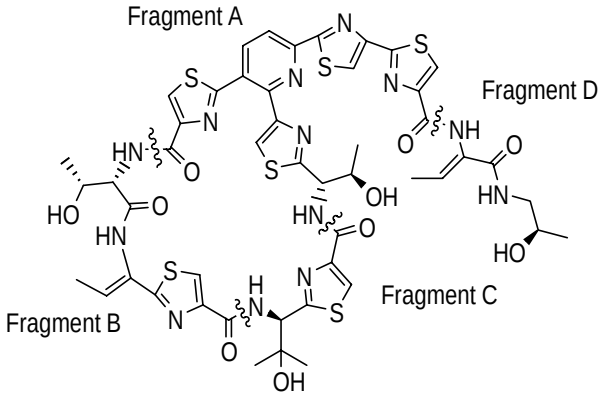
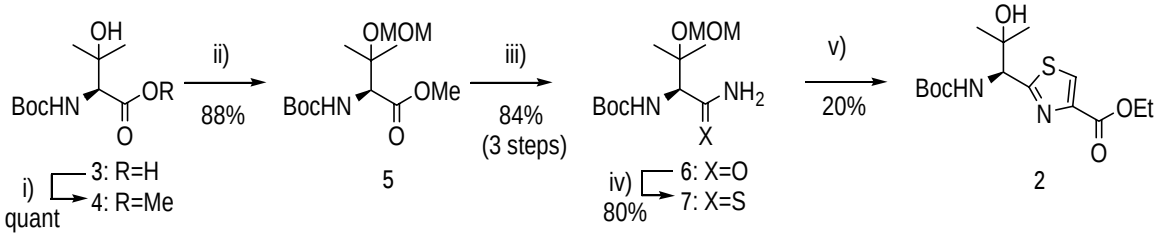


Figure 1. Thiocilline I (**1**)

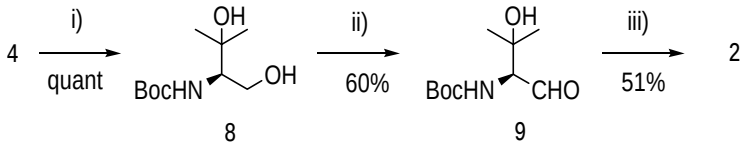
Esterification of (**3**) with MeI in the presence of $KHCO_3$, followed by protection of the hydroxy group of

the formed methyl ester (**4**) with methoxymethyl chloride (MOM-Cl) in the presence of (*i*-Pr)$_2$NEt gave Boc-L-3-(MOMO)HyVal-OMe (**5**). After ester hydrolysis of **5** with 1 M LiOH in a mixture of dioxane and H_2O (1 : 1 v/v), the generated carboxyl group was *in situ* treated with ethyl chloroformate in the presence of Et_3N and then with 28% aqueous NH_3 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 $KHCO_3$ and trifluoroacetic anhydride (TFAA) in the presence of pyridine formed 2-[1-(*N*-Boc-*N*-CF_3CO)aminothiazole derivative, the CF_3CO group of which was deprotected with 28% aqueous NH_3 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, $KHCO_3$ / DMF, 0 ^oC, 30 min, rt, 6 h; ii) MOM-Cl, (*i*-Pr)$_2$NEt / DMF, 0 ^oC, 30 min, rt, 6 h; iii) (a) 1 M LiOH / dioxane-H_2O (1:1 v/v), 0 ^oC, 30 min, rt, 3 h; (b) ClCOOEt, Et_3N / THF, 0 ^oC, 15 min; (c) 28% aq. NH_3 , 0 ^oC, 5 min; iv) Lawesson's reagent / DME, 40 ^oC, 12 h; v) (a) $KHCO_3$, ethyl bromopyruvate / DME, 0^oC, 30 min, rt, 12 h, (b) TFAA, pyridine, 0 ^oC, 30 min, rt, 6 h; (c) 28% aq. NH_3 , 0 ^oC, 5 min.

Direct reduction of the ester group of **4** with $NaBH_4$ in EtOH gave the corresponding diol derivative (**8**), the primary hydroxyl group of which was oxidized with Dess-Martin reagent in $CHCl_3$ 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 Et_3N and then oxidation with MnO_2 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) $NaBH_4$ / EtOH, 0 ^oC, 30 min, rt, 6 h; ii) Dess-Martin reagent, $CHCl_3$, 0 ^oC, 30 min, rt, 6 h; iii) (a) H-L-Cys-OEt, Et_3N, 0 ^oC, 30 min, rt, 3 h; (b) MnO_2, 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 ^{1}H NMR spectrum of synthetic **2**, the appearance of the chemical shifts of the thiazole ring proton at δ=8.13 (s, 1H) and the hydroxy proton at δ=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 ^{1}H 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.

(2*S*)-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* (4*S*)-4-(1-hydroxy-1-methylethyl)-3-*t*-butoxycarbonyl-2,2- dimethyl-1,3-oxazolidine.

Methyl (2*S*)-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 ^{o}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% $Na_3S_2O_3$ 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%). $[\alpha]_D^{27}$-18.2^o (*c* 0.90, MeOH). IR 3435, 2979, 2360, 1718, 1506 cm^{-1}. ^{1}H NMR δ=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, NHC*H*, *J*=7.5 Hz), 5.43 (br d, 1H, NH, *J*=7.5 Hz). *Anal*. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.49; H, 8.78; N, 5.54.

Methyl (2*S*)-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)$_2$NEt (0.024 mL, 0.14 mmol) and MOM-Cl (0.011 mL, 0.14 mmol) at 0 ^{o}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%). $[\alpha]_D^{28}$ +3.3^o (*c* 0.18, MeOH). IR 3465, 2979, 1716, 1507 cm^{-1}. ^{1}H NMR δ=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 OCH_3), 3.75 (s, 3H, OCH_3), 4.21 (d, 1H, NHC*H*, *J*=8.0 Hz), 4.70 (s, 2H, MOM's CH_2), 5.43-5.53 (br d, 1H, NH, *J*=8.0 Hz). *Anal*. Calcd for $C_{13}H_{25}NO_6$: 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-H_2O (1 : 1 v/v) (100 mL) was stirred at 0 ^oC 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 Na_2SO_4. Concentration *in vacuo* gave a residual syrup, to which were added, with stirring, THF (140 mL), and then Et_3N (1.54 mL, 11.1 mmol) and ClCOOEt (1.10 mL, 11.1 mmol) at 0 ^oC. After stirring for 15 min, the resulting solution was further stirred with 28% aqueous NH_3 (20 mL) at 0 ^oC for 5 min. The organic layer was dried over anhydrous Na_2SO_4 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%). $[\alpha]_D^{24}$ +11.6^o (*c* 0.16, MeOH). IR 3336, 2979, 2359, 1680 cm^{-1}. ^1H NMR δ=1.20, 1.36 (each s, 6H, HyVal's CH_3 x 2), 1.45 (s, 9H, Boc's *t*-Bu), 3.38 (s, 3H, MOM's OCH_3), 4.28 (d, 1H, NHC*H*, *J*=8.0 Hz), 4.76 (d, 1H, MOM's C*H*H, *J*=6.5 Hz), 4.82 (d, 1H, MOM's CH*H*, *J*=6.5 Hz), 5.50 (br s, 2H, NH, NH*H*), 6.61 (br s, 1H, N*H*H). *Anal*. Calcd for $C_{12}H_{24}N_2O_5$: 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 ^oC 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 CH_3 x 2), 1.27 (s, 9H, Boc's *t*-Bu), 3.59, 3.65, 3.70 (each s, 3H, MOM's OCH_3), 3.86 (d, 1/2H, NHC*H*, *J*=7.3 Hz), 3.93 (d, 1/2H, NHC*H*, *J*=7.3 Hz), 4.83-4.93 (m, 2H, MOM's CH_2), 6.77-6.85 (m, 1H, NH), 7.66-7.77 (m, 2H, NH_2). 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, $KHCO_3$ (0.34 g, 33.8 mmol) and ethyl bromopyruvate (0.71 mL, 56.2 mmol) at 0 ^oC 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 ^oC for 30 min and then at rt for 6 h. Furthermore, the resulting solution was stirred with 28% NH_3 aqueous solution (15 mL) at 0 ^oC 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 Na_2SO_4. 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 ^oC. $[\alpha]_D^{24}$ -41.3^o (*c* 0.16, MeOH). IR 3366, 2978, 2927, 2358, 1718, 1506, 1367 cm^{-1}. ^1H NMR δ=1.17 (t, 3H, Et's CH_3, *J*=7.0 Hz), 1.25 and 1.26 (each s, 6H, HyVal's CH_3 x 2), 1.43 (s, 9H, Boc's *t*-Bu), 2.79 (br s, 1H, OH), 4.37 (q, 2H, Et's CH_2, *J*=7.0 Hz), 4.87 (d, 1H, NHC*H*, *J*=9.7 Hz), 5.67 (br d, 1H, NH, *J*=9.7 Hz), 8.13 (s, 1H, Thiazole's H). *Anal*. Calcd for $C_{15}H_{24}N_2O_5S$: C, 52.31; H, 7.02; N, 8.13. Found: C, 52.02; H, 7.08; N, 8.39.

(2*S*)-2-(*N*-*t*-Butoxycarbonyl)amino-3-methyl-3-hydroxybutan-1-ol (8). A solution of **4** (0.95 g, 3.80 mmol) and $NaBH_4$ (0.29 g, 7.65 mmol) in EtOH (30 mL) was stirred at 0 ^oC for 30 min and then at rt for 6 h. To the resulting solution was added a small amount of saturated NH_4Cl 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 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 **8** as colorless crystals. Recrystallization from EtOAc gave **8** as a colorless powder. Yield 0.82 g (98%). mp 37-38 ^oC. $[\alpha]_D^{25}$ +3.4^o (*c* 1.17, MeOH). IR 3398, 2978, 1691, 1509 cm^{-1}. ^1H NMR δ=1.24, 1.35 (each s, 6H, HyVal's CH_3 x 2), 1.45 (s, 9H, Boc's *t*-Bu), 2.85 (br s, 2H, OH x 2), 3.46 (m, 1H, NHC*H*), 3.80 (dd, 1H, CH*H*OH, *J*=3.4, 11.2 Hz), 4.02 (dd, 1H, C*H*HOH, *J*=3.2, 11.2 Hz),5.42 (br d, 1H, NH, *J*=8.2 Hz). *Anal*. Calcd for $C_{10}H_{21}NO_4$: C, 54.77; H, 9.65; N, 6.39. Found: C, 54.52; H, 9.90; N, 6.35 .

(2*S*)-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 $CHCl_3$ (30 mL) was stirred at 0 ^oC 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 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 **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 CH_3 x 2), 1.45 (s, 9H, Boc's *t*-Bu), 2.79 (br s, 1H, OH), 4.23 (br d, 1H, NHC*H*, *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-OEt·HCl (0.29 g, 1.72 mmol) in the presence of Et_3N (0.27 mL) in toluene (20 mL) was stirred at 0 ^oC for 30 min and then at rt

for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ aqueous solution (50 mL x 3), 10% citric acid (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 again dissolved in toluene (50 mL). The resulting solution was stirred with MnO_2 (1.41 g, 1.62 mmol) at rt for 2 h and then the MnO_2 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 ^{o}C.

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