

Useful Synthesis of Fragment A–C–D of a Thiostrepton-type Macrocyclic Antibiotic, Thiocilline I

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Useful synthesis of the main Fragment A–C–D segment constructing a thiostrepton-type macrocyclic antibiotic, thiocilline I, was first achieved by coupling of the 2,3,6-polythiazole-substituted pyridine skeleton (Fragment A–C) with Fragment D.

Thiocilline I (**1**),¹ isolated from the culture of *Bucillus bodi-us*, is a unique macrocyclic antibiotic structurally very similar to micrococins P and P₁,² which comprise a (2*S*)-2-(1-amino-2-methyl)propylthiazole-4-carbonyl moiety as the Fragment C. On the other hand, in place of the above Val-derived thiazole moiety, the natural **1** is also composed of a (2*S*)-2-(1-amino-2-hydroxy-2-methyl)propylthiazole-4-carbonyl moiety (Fragment C), derived from a D-hydroxyvaline (HyVal),³ as shown in Figure 1. Recently, the total synthesis of micrococins has been reported.^{4–6} Similarly to the above cases, the interesting structure as well as the bioactivity of **1** attracted us to investigate its synthesis and structure-bioactivity relationship. Herein, we wish to report a useful synthesis of the Fragment A–C–D segment **22**, which is the most important skeleton for the total synthesis of **1**.

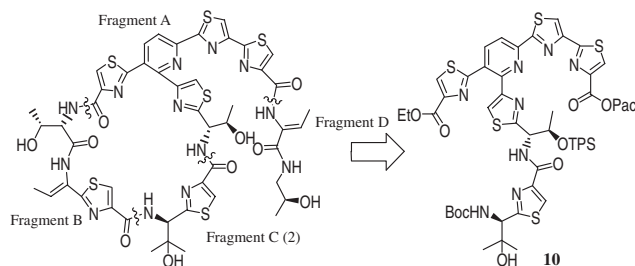
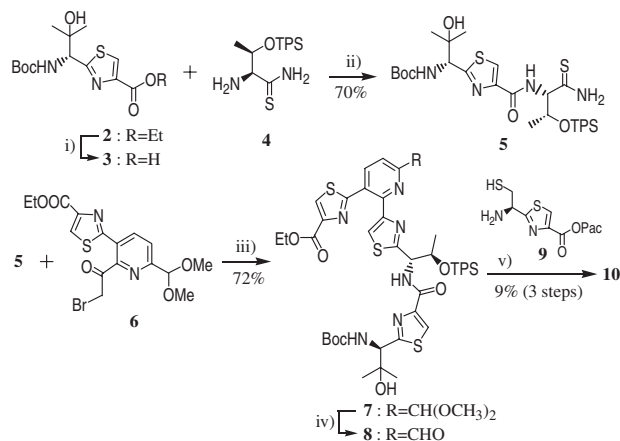


Figure 1. Thiocilline I (**1**).

First of all, to synthesize the Fragment A–C segment **10** as the main structure of **1**, ester hydrolysis of the HyVal-derived *N,O*-diprotected Fragment C **2**^{3b} with 1 M LiOH, followed by coupling of the formed hydrolyzate **3** with L-Thr(OTPS)-(S)NH₂ (**4**)⁷ (TPS = *t*-butyldiphenylsilyl) using BOP and (*i*-Pr)₂NEt (DIPEA) gave the dipeptide thiocarboxamide derivative **5**. Thiazolation of **5** with the authentic 2-bromoacetyl-3-[(4-ethoxycarbonyl)thiazol-2-yl]-6-dimethoxymethylpyridine (**6**)^{4,5} using KHCO₃ and (CF₃CO)₂O (TFAA) in the presence of pyridine, and then 28% aq. NH₃ by the Hantzsch method gave the precursor of the Fragment A–C structure **7**. After conversion of 6-acetal of **7** to the formyl group with 2 M HCl, the obtained 6-formyl derivative **8** was coupled intact with phenacyl (Pac) (*R*)-2-(1-amino-2-mercaptoethyl)thiazole-4-carboxylate (**9**) to give **10** by the Shioiri method,⁸ as shown in Scheme 1. However, the yield of **10** was very low (only 9% yield in 3 steps from **7**), because of a mass of material decomposed.

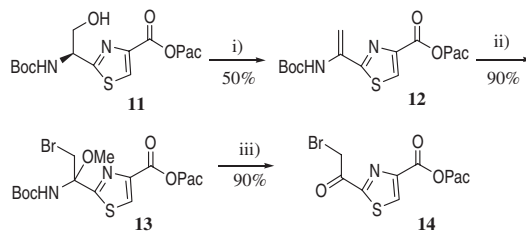
Accordingly, an alternative synthetic method for **10** needs to



Scheme 1. Reagents and conditions: i) 1 M LiOH/MeOH, ii) BOP, DIPEA/DMF, iii) a) KHCO₃/DME, b) TFAA, pyridine/DME, c) 28% aq. NH₃, iv) 2 M HCl/THF, v) a) **9**, Et₃N/toluene, b) MnO₂/toluene.

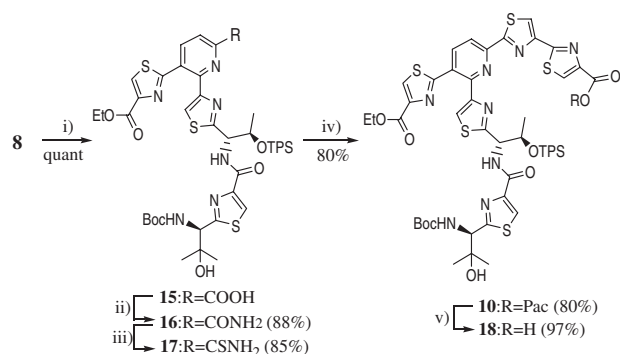
be investigated further. That is, to carry out the reaction by the Hantzsch method, in place of **8**, another substrate 6-thiocarboxamide derivative **17** and Pac 2-(bromoacetyl)thiazole-4-carboxylate (**14**) were synthesized as follows.

To synthesize **14**, β -elimination of Pac 2-[1-(*N*-Boc)amino-2-hydroxyethyl]thiazole-4-carboxylate (**11**), derived by thiazolation of Boc-L-Ser-(S)NH₂ with BrCH₂COCOOPac by the usual Hantzsch method, with methanesulfonyl chloride (Ms-Cl) in the presence of Et₃N and DBU gave the corresponding vinylthiazole derivative **12**. Then, bromination with NBS in MeOH gave 2-[1-(*N*-Boc)amino-1-methoxy-2-bromoethyl]thiazole derivative **13**, which was immediately treated with CF₃COOH (TFA) and H₂O to give the expected **14**, as shown in Scheme 2.



Scheme 2. Reagents and conditions: i) a) Ms-Cl, Et₃N/CHCl₃, b) DBU/CHCl₃, ii) a) NBS/THF, b) MeOH, iii) a) TFA, b) NaHCO₃, H₂O.

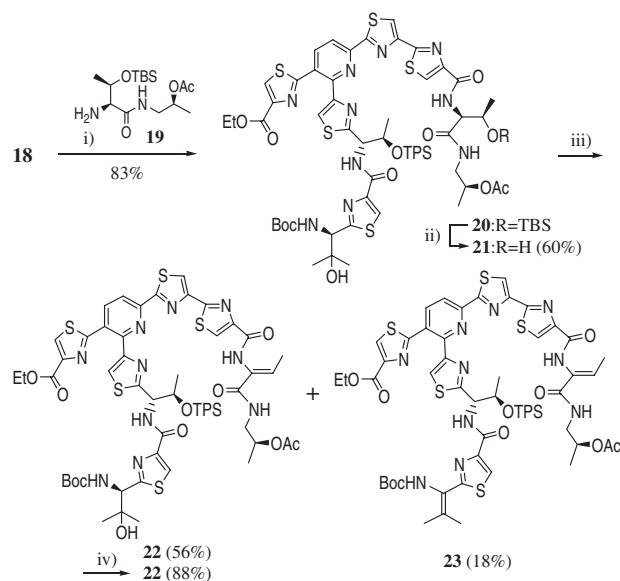
On the other hand, the 6-formyl group of **8** was oxidized with 2.67 M Jones reagent to give the corresponding 6-carboxypyridine derivative **15**, the carboxy group of which was amidated with ClCOOEt in the presence of Et₃N and with 28% NH₃ to give the carboxamide derivative **16**. Subsequent thioamidation



Scheme 3. Reagents and conditions: i) 2.67 M Jones reagent/acetone, ii) a) $ClCOOEt$, Et_3N /THF, b) 28% aq. NH_3 /THF, iii) Lawesson's reagent/DME, iv) a) **14**, $KHCO_3$ /DME, b) TFAA, pyridine/DME, c) 28% aq. NH_3 , v) 1 M $LiOH$ /THF.

with Lawesson's reagent gave the corresponding thiocarboxamide **17**. Consequently, the required thiazolization of **17** with **14** by the Hantzsch method gave **10** in 80% yield. The Pac ester was hydrolyzed with 1 M $LiOH$ to give 6-bisthiazole-4-carboxylic acid derivative **18**, as shown in Scheme 3.

Furthermore, fragment condensation of **18** with (2*S*,3*R*)-2-amino-3-(*O*-TBS)hydroxy-*N*-[(*S*)-2-acetoxypentyl]butanamide (**19**)⁹ by the BOP method was performed to give the precursor of Fragment A-C-D segment **20**. Selective deprotection of the TBS group of the Thr residue with 70% $AcOH$, followed by β -elimination of the deprotected intermediate **21** using $Ms-Cl$ and Et_3N and then DBU in $CHCl_3$ gave the protected Fragment A-C-D derivative **22**, similarly to the case of **12**. At that time, however, besides **22** (56%), undesirable compound **23** (18%), the tertiary alcohol of **21** also dehydrated, was formed. Accordingly, to examine what procedure produces the selective β -elimination of only the secondary alcohol of **21**, the substrate Boc-HyVal-Thr-OMe was independently prepared and then subjected to the β -elimination under various experimental conditions. As a



Scheme 4. Reagents and conditions: i) **19**, BOP, DIPEA/DMF, ii) 70% $AcOH$ /THF, iii) a) $Ms-Cl$ / Et_3N , b) DBU/ $CHCl_3$, iv) a) $Ms-Cl$, pyridine, b) DBU/ $CHCl_3$.

result, in the case using $Ms-Cl$ (1.30 equiv.) in pyridine (0.73 equiv.) as a solvent at 0 °C for 15 min, firstly, only the secondary alcohol was selectively protected with the Ms group to give the corresponding mesyloxy derivative, Boc-HyVal-Thr(Ms)-OMe, in 90% yield. Secondly, the O - Ms group was β -eliminated with DBU in $CHCl_3$ to give the expected Boc-HyVal- Δ Abu-OMe (Δ Abu = 2-amino-2-butenic acid residue) in 90% yield. Accordingly, similarly to the above case, the selective β -elimination of **21** with $Ms-Cl$ in pyridine and then with DBU was tried successfully to give only the desired **22**¹¹ in 88% yield.

It is believed that the success of the selective β -elimination of **21** can be best appreciated for the first total synthesis of **1**.

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References and Notes

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- 10 **10**: Colorless powder. mp 112–115 °C. $[\alpha]_D^{27} +18.4^\circ$ (c 0.98, $CHCl_3$).
- 11 **22**: Pale yellow powder. mp 119–122 °C. IR (KBr) 3400, 2930, 2856, 1717, 1670, 1531, 1473, 1241 cm^{-1} . $[\alpha]_D^{27} +17.1^\circ$ (c 0.28, $CHCl_3$). 1H NMR ($CDCl_3$) δ = 0.95 (d, 3H, $CH(OTPS)CH_3$, J = 6.6 Hz), 1.02 (s, 9H, TPS 's *t*-Bu), 1.24, 1.33 (each s, 6H, $C(OH)(CH_3)_2$), 1.27 (d, 3H, $CH(OAc)CH_3$, J = 6.6 Hz), 1.37 (t, 3H, Et 's CH_3 , J = 7.2 Hz), 1.45 (s, 9H, Boc 's *t*-Bu), 1.87 (d, 3H, Δ Abu's CH_3 , J = 6.6 Hz), 2.02 (s, 3H, Ac 's CH_3), 2.76 (br s, 1H, OH), 3.42–3.70 (m, 2H, $CH_2CH(OAc)$), 4.38 (q, 2H, Et 's CH_2 , J = 7.2 Hz), 4.51 (br d, 1H, $CH(OTPS)CH_3$, J = 6.6 Hz), 4.94 (br d, 1H, $BocNHCH$, J = 9.0 Hz), 5.03–5.06 (m, 1H, $CH(OAc)CH_3$), 5.35 (br d, 1H, $CHCH(OTPS)-CH_3$, J = 9.0 Hz), 5.63 (br d, 1H, $BocNH$, J = 9.0 Hz), 6.57 (q, 1H, $NHCH_2OAc$, J = 6.6 Hz), 6.65 (q, 1H, Δ Abu's CH , J = 6.6 Hz), 7.22–7.62 (m, 10H, TPS 's $Ph \times 2$), 7.91, 8.01, 8.14, 8.22, 8.25 (each s, 5H, thiazole's $H \times 5$), 8.21, 8.71 (each br s, 2H, $CONH \times 2$), 8.36, 8.38 (each d, 2H, pyridine's $HH \times 2$, J = 8.4 Hz). Anal. Calcd for $C_{62}H_{70}N_{10}S_5Si$: C, 56.44; H, 5.35; N, 10.61%. Found: C, 55.99; H, 5.50; N, 10.20%.