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

Shuusuke Suzuki, Yasuchika Yonezawa, and Chung-gi Shin*
Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686

(Received April 1, 2004; CL-040354)

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 bodius*, is a unique macrocyclic antibiotic structurally very similar to micrococcins P and P_1,[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 micrococcins 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**.

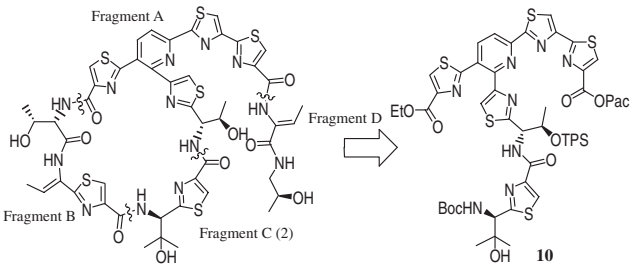
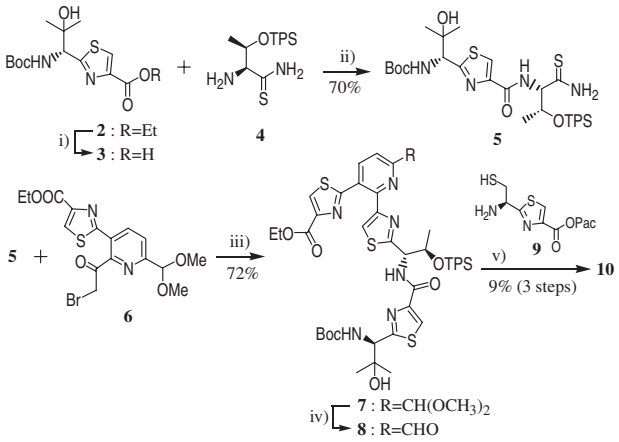


Figure 1. Thiocilline I (**1**).

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(TPS)-(S)NH_2 (**4**)[7] (TPS = *t*-butyldiphenylsilyl) using BOP and $(i\text{-Pr})_2$NEt (DIPEA) gave the dipeptide thiocarboxamide drivative **5**. Thiazolation of **5** with the authentic 2-bromoacetyl-3-[(4-ethoxycarbonyl)thiazol-2-yl]-6-dimethoxymethylpyridine (**6**)[4,5] using $KHCO_3$ and $(CF_3CO)_2O$ (TFAA) in the presence of pyridine, and then 28% aq. NH_3 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.

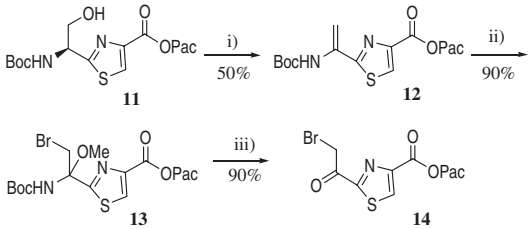
Accordingly, an alternative synthetic method for **10** needs to



Scheme 1. Reagents and conditions: i) 1 M LiOH/MeOH, ii) BOP, DIPEA/DMF, iii) a) $KHCO_3$/DME, b) TFAA, pyridine/DME, c) 28% aq. NH_3, iv) 2 M HCl/THF, v) a) **9**, Et_3N/toluene, b) MnO_2/toluene.

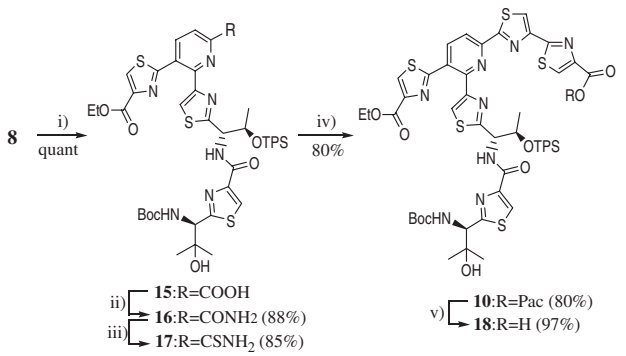
be investigated further. That is, to carry out the reaction by the Hantzsch method, in place of **8**, another substrate 6-thiocarboxamide derivative **17** and Pac 2-(bromoacetyl)thiazole-4-carboxylate (**14**) were synthesized as follows.

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)NH_2 with $BrCH_2COCOOPac$ by the usual Hantzsch method, with methanesulfonyl chloride (Ms-Cl) in the presence of Et_3N 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 CF_3COOH (TFA) and H_2O to give the expected **14**, as shown in Scheme 2.



Scheme 2. Reagents and conditions: i) a) Ms-Cl, $Et_3N/CHCl_3$, b) DBU/$CHCl_3$, ii) a) NBS/THF, b) MeOH, iii) a) TFA, b) $NaHCO_3$, H_2O.

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 Et_3N and with 28% NH_3 to give the carboxamide derivative **16**. Subsequent thioamidation

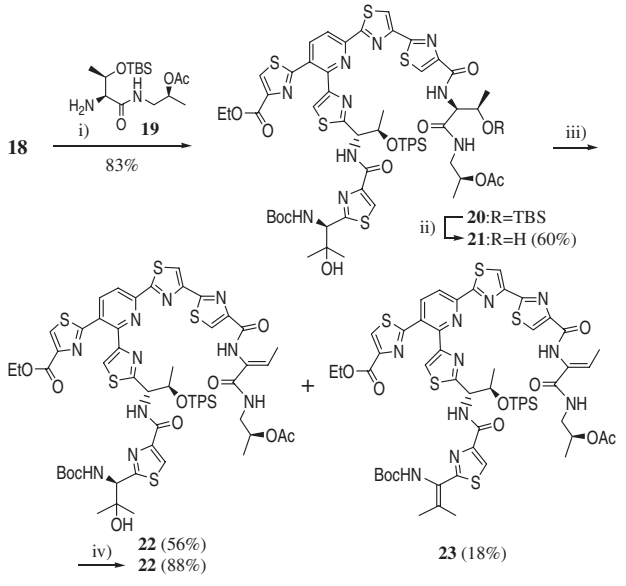


Scheme 3. Reagents and conditions: i) 2.67 M Jones reagent/acetone, ii) a) ClCOOEt, Et_3N/THF, b) 28% aq. NH_3/THF, iii) Lawesson's reagent/DME, iv) a) **14**, $KHCO_3$/DME, b) TFAA, pyridine/DME, c) 28% aq. NH_3, v) 1 M LiOH/THF.

with Lawesson's reagent gave the corresponding thiocarboxamide **17**. Consequently, the required thiazolation of **17** with **14** by the Hantzsch method gave **10**[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-acetoxypropyl]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 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-ΔAbu-OMe (ΔAbu = 2-amino-2-butenoic 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**.



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/$CHCl_3$.

This work was supported in part by Grant-in Aid for Scientific Reaserch No. 14550829 from the Ministry of Education, Culture, Sports, Science and Technology and by "High-Tech Research Project" from the Ministry of Education, Culture, Sports, Science and Technology.

References and Notes

1 J. Shoji, T. Kato, Y. Yoshimura, and K. Tori, *J. Antibiot.*, **34**, 1126 (1981).
2 a) P. Brooks, A. T. Fuller, and J. Walker, *J. Chem. Soc.*, **1959**, 689. b) J. Walker, A. Olesker, L. Valente, R. Rabanal, and G. Lukacs, *J. Chem. Soc., Chem. Commun.*, **1977**, 706. c) B. W. Bycroft and M. S. Gowland, *J. Chem. Soc., Chem. Commun.*, **1978**, 256.
3 a) Y. Yonezawa, K. Shimizu, K. Yoon, and C. Shin, *Synthesis*, **2000**, 634. b) Y. Yonezawa, H. Saito, S. Suzuki, and C. Shin, *Heterocycles*, **57**, 903 (2002).
4 C. Shin, K. Okumura, M. Shigekuni, and Y. Nakamura, *Chem. Lett.*, **1998**, 139.
5 K. Okumura, A. Ito, D. Yoshioka, and C. Shin, *Heterocycles*, **48**, 1319 (1998).
6 M. A. Ciufolini and Y.-C. Shen, *Org. Lett.*, **1**, 1843 (2000).
7 The compound **4** was derived from the corresponding carboxamide and Lawesson's reagent by the usual method.
8 Y. Hamada, M. Shibata, T. Sugiura, S. Kata, and T. Shioiri, *J. Org. Chem.*, **52**, 1252 (1987).
9 K. Okumura, T. Suzuki, Y. Nakamura, and C. Shin, *Bull. Chem. Soc. Jpn.*, **72**, 2483 (1999).
10 **10**: Colorless powder. mp 112–115 °C. $[\alpha]_D^{27}$ +18.4° (*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° (*c* 0.28, $CHCl_3$). ^1H NMR ($CDCl_3$) $\delta = 0.95$ (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, ΔAbu'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, C*H*(OTPS)CH_3, $J = 6.6$ Hz), 4.94 (br d, 1H, BocNHC*H*, $J = 9.0$ Hz), 5.03–5.06 (m, 1H, C*H*(OAc)CH_3), 5.35 (br d, 1H, C*H*CH(OTPS)-CH_3, $J = 9.0$ Hz), 5.63 (br d, 1H, BocNH, $J = 9.0$ Hz), 6.57 (q, 1H, N*H*CH_2OAc, $J = 6.6$ Hz), 6.65 (q, 1H, ΔAbu's CH, $J = 6.6$ Hz), 7.22–7.62 (m, 10H, TPS's Ph × 2), 7.91, 8.01, 8.14, 8.22, 8.25 (each s, 5H, thiazole's H × 5), 8.2l, 8.71 (each br s, 2H, CONH × 2), 8.36, 8.38 (each d, 2H, pyridine's HH × 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%.

Published on the web (Advance View) June 7, 2004; DOI 10.1246/cl.2004.814