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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), isolated from the culture of Bucillus bodi­us, is a unique macrocyclic antibiotic structurally very similar to micrococcins P and P₂, which comprise a (25)-2-[(l-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 I is also composed of a (25)-2-[(l-amino-2-hydroxy-2-methyl)propylthiazole-4-carbonyl moiety (Fragment C), derived from a 6-hydroxyvaline (HyVal), as shown in Figure 1. Recently, the total synthesis of micrococcins has been reported. Similarly to the above cases, the interesting structure as well as the bioactivity of I 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 I.

Figure 1. Thiocilline I (1).

First of all, to synthesize the Fragment A–C segment 10 as the main structure of I, ester hydrolysis of the HyVal-derived N,O-diprotected Fragment C 2₁₀ with 1 M LiOH, followed by coupling of the formed hydrolyzate 3 with L-Thr(TPS)-(S)NH₂ (4) (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-ethoxyacarbonyl)thiazol-2-yl]-6-dimethoxyethylpyridine (6) using KHCO₃ and (CF₃CO)₂O (TFAA) in the presence of pyridine, and then 28% aq. NH₃ gave the expected thiocarboxamide derivative 11. On the other hand, the 6-formyl group of 8 was oxidized with 2.67 M Jones reagent to give the corresponding 6-carboxylic acid 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 Et₂O 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) NBS/THF, b) MeOH, iii) TFA, b) NaHCO₃, H₂O.

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Scheme 3. Reagents and conditions: i) 2.67 M Jones reagent/acetone, ii) a) CICOEt, Et3N/THF, b) 28% aq. NH3/THF, iii) Lawesson’s reagent/DME, iv) a) 14, KHCO3/DME, b) TFAA, pyridine/DME, c) 28% aq. NH3, v) 1 M LiOH/THF.

With Lawesson’s reagent gave the corresponding thiacarbamoyl derivative 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 (2S,3R)-2-amino-3-(O-TBS)hydroxy-N-[(S)-2-acetoxypropyl]butanamide (19) 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 MsCl and Et3N and then DBU in CHCl3 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 CHCl3, 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 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
7. The compound 4 was derived from the corresponding carboxamide and Lawesson’s reagent by the usual method.
10. Colorless powder. mp 112–115°C. [α]D 27 +18.4° (c 0.98, CHCl3).
11. 22: Pale yellow powder. mp 119–122°C. IR (KBr) 3400, 2930, 2856, 1717, 1670, 1531, 1473, 1241 cm−1. [α]D 27 +17.1° (c 0.28, CHCl3). 1H NMR (CDCl3) δ = 0.95 (d, 3H, CH(OPTS)CH3, J = 6.6 Hz), 1.02 (s, 9H, TPS’s r-Bu), 1.24, 1.33 (each s, 6H, C(OH)(CH3)2), 1.27 (d, 3H, CH(OAc)CH3, J = 6.6 Hz), 1.37 (t, 3H, Et’s CH3, J = 7.2 Hz), 1.45 (s, 9H, Boc’s t-Bu), 1.87 (d, 3H, ΔAbu’s CH3, J = 6.6 Hz), 2.02 (s, 3H, Ac’s CH3), 2.76 (br s, 1H, OH), 3.42–3.70 (m, 2H, CH2CH(OAc)), 4.38 (q, 2H, Et’s CH2, J = 7.2 Hz), 4.51 (br d, 1H, CH(OPTS)CH3, J = 6.6 Hz), 4.94 (br d, 1H, BocNHCH, J = 9.0 Hz), 5.03–5.06 (m, 1H, CH(OAc)CH3), 5.35 (br d, 1H, CH(OPTS)CH3, J = 9.0 Hz), 5.63 (br d, 1H, BocNH, J = 9.0 Hz), 6.57 (q, 1H, NHCH2OAc, 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), 8.21, 8.71 (each br s, 2H, CONH × 2), 8.36, 8.38 (each d, 2H, pyridine’s NH × 2, J = 8.4 Hz).

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