Useful Synthesis of 2,3,6-Polythiazolesubstituted Pyridine Skeleton [Fragment A-C] of Peptide Antibiotic, Micrococcin P

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Practical synthesis of 2,3,6-trithiazolesubstituted pyridine skeleton [Fragment A-C] of peptide antibiotic micrococcin P was achieved from 3-cyano-6-dimethoxymethyl-2-pyridone in twelve steps.

A thiostrepton-type antibiotic, micrococcin P (**1**),[1] isolated from the culture of *Bacillus pumilus*, is a unique macrocyclic peptide, as shown in Figure 1. The peptide (**1**) includes a characteristic main structure, 2,3,6-polythiazolesubstituted pyridine skeleton [Fragment A-C: **2**] composed of polythiazole and dehydropeptide moieties. The interesting structure and bioactivity of **1** attracted us to investigate its total synthesis. The thiazole-dehydrotripeptide substructure called Fragment B-C was previously synthesized by us.[2] The synthesis of micrococcinic acid [2,3,6-(trithiazole)pyridine derivative] partially hydrolyzed Fragment A was already reported by Kelly et al.[3] Here, we have also achieved the efficient synthesis of the protected **2** by the different synthetic method.

At first, for the synthesis of the precursor of thiazole-

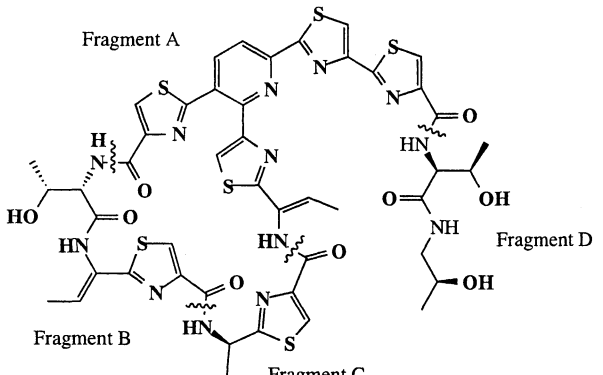
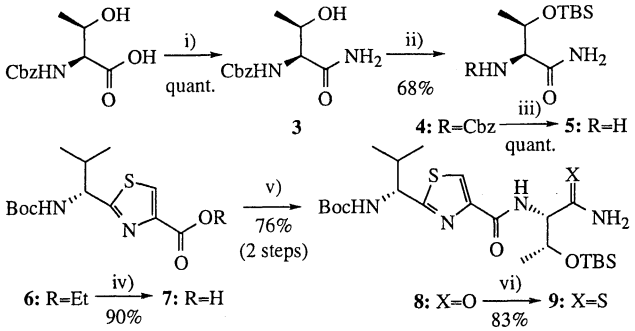


Figure 1. Micrococcin P (**1**).

dehydrodipeptide segment containing Fragment C part, *N*-benzyloxycarbonyl (Cbz) group of *N*-Cbz-L-Thr(TBS)-NH_2 (**4**) (TBS=*t*-butyldimethylsilyl), derived from *N*-Cbz-L-Thr-OH *via* the corresponding amide (**3**), was deprotected with 10% Pd-C to give H-Thr(TBS)-NH_2 (**5**). The obtained **5** was coupled with 2-[(*S*)-1-(Boc)amino-2-methylpropyl]thiazole-4-carboxylic acid (**7**),[4] derived from the corresponding ester (**6**) by hydrolysis with 1M LiOH, using diphenylphosphoryl azide (DPPA) as coupling reagent to give the expected dipeptide-NH_2 (**8**), which was then converted with Lawesson's reagent to the corresponding thioamide (**9**),[5] as shown in Scheme 1.

Further extension to Fragment A-C is illustrated in Scheme 2.

To obtain 3-bromoacetyl-2,6-disubstituted pyridine skeleton (**17**) as the coupling component with **9**, 3-cyano-6-dimethoxymethyl-2-pyridone (**12**),[6] which was derived from 1,1-dimethoxypropanone (**10**) *via* an intermediate **11**, was thioamidated with H_2S and then thiazolated by the cyclization with $BrCH_2COCOOEt$ by the modified Hantzsch method.[7] Subsequent triflation of the obtained 2-pyridone derivative (**14**) with



i) a) ClCOOEt, Et_3N, THF, 0 °C, 20 min, b) 28% NH_3, THF, 0 °C, 3 h, ii) TBSCl, imidazole, DMF, 0 °C, 30 min, r.t., 24 h, iii) 10% Pd-C, H_2, EtOH, r.t., 3 h, iv) 1M LiOH, H_2O/dioxane, 0 °C, 30 min, r.t., 4 h, v) DPPA, Et_3N, **5**, DMF, 0 °C, 3 h, r.t., overnight, vi) Lawesson's reagent, DME, r.t., 4 h.

Scheme 1.

triflic anhydride (Tf_2O) in the presence of dimethylaminopyridine (DMAP) gave 2-trifloxy derivative (**15**). Then, substitution of the trifloxy group with ethylvinyl ether[8] in the presence of $Pd(Ac)_2$ and 1,3-bis(diphenylphosphino)propane (dppp) as catalyst gave 2-(ethoxyvinyl)pyridine (**16**). Further, conversion[9] of **16** with *N*-bromosuccinimide (NBS) gave 2-bromoacetyl derivative (**17**) as an intermediate, which was subjected *in situ* to the coupling with **9**. The thiazolation of **17** with **9** using successive $KHCO_3$, trifluoroacetic anhydride (TFAA), and 28% NH_3, followed by the deprotection of TBS group of the obtained 2,3-dithiazolated pyridine (**18**) with tetrabutylfluoroammonium (TBAF) gave the corresponding alcohol (**19**)[10] containing the Fragment C moiety. After mesylation with methanesulfonyl chloride (MsCl) and subsequent β-elimination with DBU under sonication, the formed dehydropeptide **20** was hydrolyzed with 70% AcOH to give the corresponding 6-formylpyridine derivative (**21**). Subsequently, according to the Shioiri's method,[11] **21** was bithiazolated with phenacyl (Pac) 2-[(*S*)-1-amino-2-mercaptoethyl]thiazole-4-carboxylate, derived by the consecutive deprotections of Boc and isopropylidene groups of the corresponding thiazole-4-carboxylate (**22**)[12] with trifluoroacetic acid (TFA), to give the expected 6-bithiazolyl-2,3-dithiazolyl pyridine derivative (**23**).[13] Finally, the catalytic hydrogenolysis of Pac group of **23** with 10% Pd-C gave 2,3,6-polythiazolesubstituted pyridine derivative **2**.[14]

The structures of **23** and **2** were definitely determined by the ^1H NMR spectral data as well as by the satisfactory elemental analysis. All ring protons of the five thiazole moieties of **23** appeared at δ 8.21, 8.30, 8.57, 8.61, and 8.74 as singlets and 3,4-vicinal two protons on the pyridine ring appeared at δ 8.34 and 8.48 as two doublets (J=7.9Hz).

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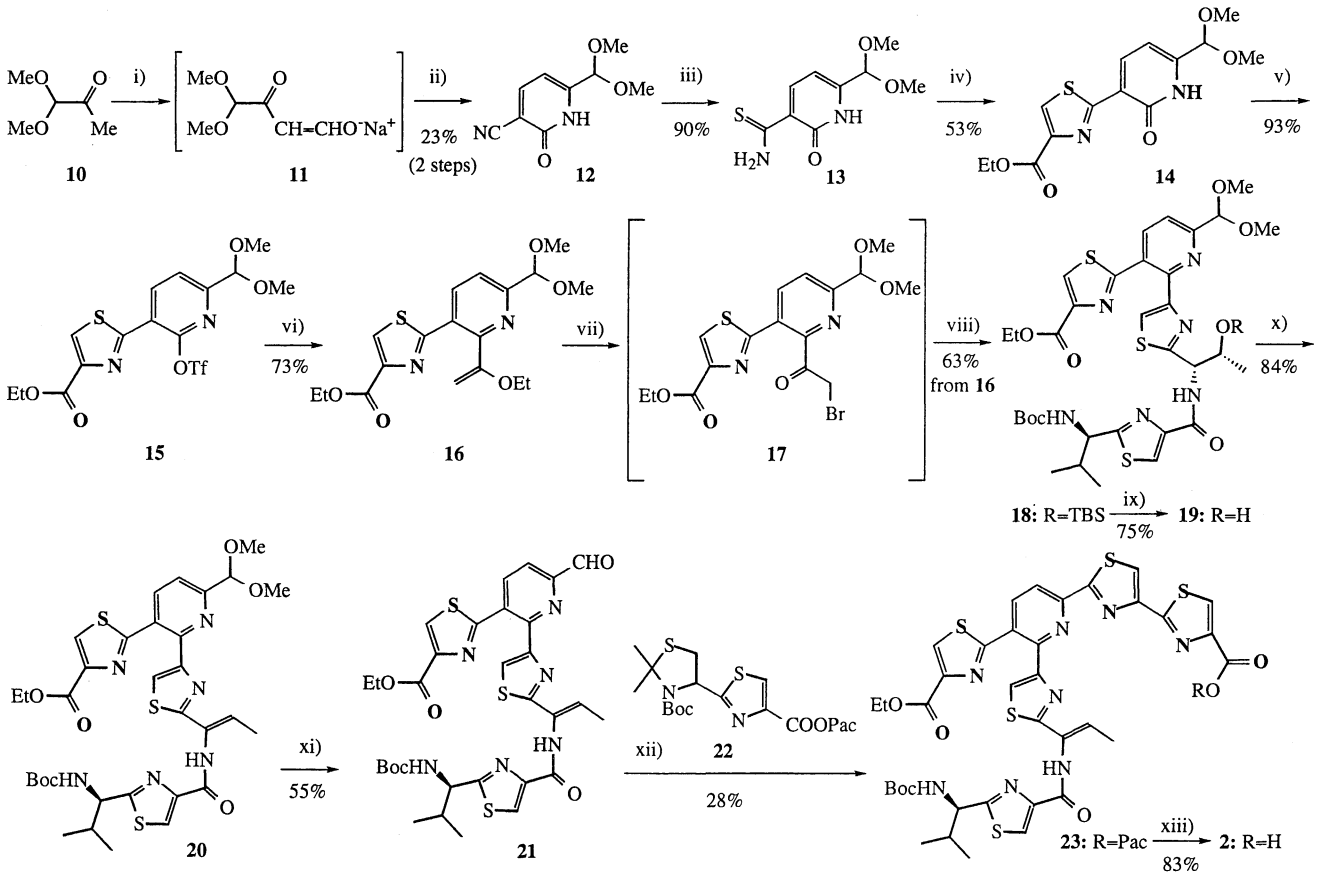

i) HCOOEt, NaOEt, THF, 45 °C, 5 h, r.t,, overnight, ii) $NCCH_2CONH_2$, H^+, H_2O, 60 °C, 16 h, iii) H_2S, DMAP, Et_3N, pyridine, r.t., 48 h, iv) a) $BrCH_2COCOOEt$, $KHCO_3$, 0 °C, 30 min, r.t., 24 h, b) TFAA, pyridine, 0 °C, 30 min, r.t., 24 h, v) Tf_2O, DMAP, pyridine, 0 °C, 30 min, r.t., overnight, vi) Ethyl vinylether, Et_3N, $Pd(OAc)_2$, dppp, toluene, reflux, 4 h, vii) NBS, THF / H_2O, r.t., 5 min, viii) a) **9**, $KHCO_3$, DME, r.t., overnight, b) TFAA, pyridine, 0 °C, 30 min, r.t., 3 h, c) 28% NH_3, ethyl acetate, r.t., 30 min, ix) TBAF, THF, 0 °C, 30 h, x) a) MsCl, Et_3N, DMSO, sonication, r.t., 30 min, b) DBU, DMSO, sonication, r.t., 3 h, xi) 70% AcOH, 45 °C 18 h, xii) a) **22**, TFA, CH_2Cl_2, r.t., 1 h, b) toluene, r.t., 15 min, c) MnO_2 , toluene, sonication, 2 h, xiii) 1M LiOH, THF, 0 °C, 2 h .

Scheme 2.

References and Notes

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5 **9 :** Mp 153-154 °C. $[\alpha]_D^{24}$ +59.3° (c 0.90, MeOH). IR (KBr) 3304, 3208, 2962, 2248, 1758, 1668 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.06 (s, 6H, TBS's CH_3x2), 0.78 (s, 9H, TBS's CH_3x3), 0.84 and 0.87 (each d, 6H, Ip's CH_3, *J*=6.3Hz), 1.08 (d, 3H, CH_3, *J*=6.3Hz), 1.37 (s, 9H, Boc), 2.18- 2.25 (m, 1H, Ip's CH), 4.30-4.37 (m, 1H, β-H), 4.52-4.63 (m, 2H, α-H and *CH*NHBoc), 7.71 (br d, 1H, NH, *J*=8.3 Hz), 8.01 (br d, 1H, NH, *J*=9.2 Hz), 8.14 (s, 1H, thiazole ring-H), 9.58 (br s, 1H, NH), 9.76 (br s, 1H, NH). Found:C, 51.66; H, 8.07; N, 10.26%. Calcd for $C_{23}H_{42}N_4O_4S_2Si$: C, 52.04; H, 7.98; N, 10.56%.

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10 **19 :** Colorless amorphous. IR (KBr) 3400, 3112, 2968, 2830, 2272, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 and 0.97 (each d, 6H, Ip's CH_3, *J*=6.6 Hz), 1.20 (d, 3H, MeCHOH's CH_3, *J*=6.6 Hz), 1.39 (t, 3H, Et's CH_3, *J*=7.3 Hz), 1.44 (s, 9H, Boc), 2.06 (br s, 1H, OH), 2.29-2.38 (m, 1H, Ip's CH), 3.44 (s, 6H, OCH_3x2), 4.28 (dq, 1H, Me*CH*OH, *J*=6.6 Hz and *J*=7.3 Hz), 4.42 (q, 2H, Et's CH_2, *J*=7.3 Hz), 4.65-4.84 (m, 1H, *CH*NHBoc), 5.19-5.27 (m, 2H, NH and *CH*NHCO), 5.43 (s,1H, *CH*$(OCH_3)_2$), 7.98 (br d, 1H, NH, *J*=9.2 Hz), 7.90 , 8.05 and 8.25 (each s, 3H, thiazole ring-H), 7.66 and 8.15 (each d, 2H, pyridine ring- H, *J*=7.9 Hz). Found: C, 52.40 ; H, 5.83 ; N, 10.66%. Calcd for $C_{33}H_{42}N_6O_8S_3 \cdot 0.5H_2O$: C, 52.43 ; H, 5.73 ; N, 11.12%.

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12 **22 :** Mp 153-154 °C. IR (KBr) 2936, 1698, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H, Boc), 1.83 and 1.98 (each s, 6H, CH_3x2), 3.45-3.56 (m, 2H, -SCH_2-), 5.61 (s, 2H, OCH_2CO), 5.67-5.75 (m, 1H, -BocNCH-), 7.48-7.99 (m, 5H, Ph), 8.25 (s, 1H, thiazole ring-H). Found: C, 57.03; H, 5.73; N, 5.86%. Calcd for $C_{22}H_{26}N_2O_5S_2$: C, 57.12 ; H, 5.67; N, 6.06%.

13 **23:** Mp 143-145 °C. $[\alpha]_D^{25}$ +15.8° (c 0.34 , $CHCl_3$). IR (KBr) 3448, 3118, 2974, 1701 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.88- 0.92 (m, 6H, Ip's CH_3), 1.32 (t, 3H, Et's CH_3, *J*=7.3 Hz), 1.41 (s, 9H, Boc), 1.69 (d, 3H, CH_3CH=, *J*=7.3 Hz), 2.24- 2.31 (m, 1H, Ip's CH), 4.33 (q, 2H, CH_3CH_2, *J*=7.3 Hz), 4.60-4.75 (m, 1H, *CH*NH Boc), 5.80 (s, 2H, OCH_2CO), 6.34 (q, 1H, CH_3CH=, *J*=7.3 Hz), 7.56-8.04 (m, 6H, Ph and NH), 8.21, 8.30, 8.57, 8.61, and 8.74 (each s, 5H, thiazole ring-H), 8.34 and 8.48 (each d, 2H, pyridine ring-H, *J*=7.9 Hz), 9.79 (br s, 1H, NH). Found: C, 54.68; H, 4.42; N, 11.16%. Calcd for $C_{45}H_{42}N_8O_8S_5$: C, 54.97; H, 4.31 ; N, 11.40%.

14 **2 :** Mp 198.5-204.5 °C. $[\alpha]_D^{24}$ +24.0° (c 0.30 in MeOH). ^1H HMR (DMSO-d_6) δ 0.87-0.91 (m, 6H, Ip's CH_3), 1.31 (t, 3H, Et's CH_3, *J*=7.3 Hz), 1.41 (s, 9H, Boc), 1.68 (d, 3H, CH_3CH=, *J*=7.3 Hz), 2.45 (m, 1H, Ip's CH), 4.32 (q, 2H, CH_3CH_2, *J*=6.9 Hz), 4.71 (m, 1H, *CH*NHBoc), 6.32 (q, 1H, CH_3CH=, *J*=6.9 Hz), 7.73 (d, 1H, NH, *J*=8.3 Hz), 8.13, 8.16, 8.29, 8.56 and 8.67 (each s, 5H, thiazole ring-H), 8.30 and 8.45 (each d, 2H, pyridine ring-H, *J*=8.3 Hz), 9.80 (br s, 1H, NH), 12.50 (br s, 1H, COOH). Found: C, 48.46; H, 4.12; N, 12.19%. Calcd for $C_{37}H_{36}N_8O_7S_5 \cdot 2.5H_2O$: C, 48.83; H, 4.54; N, 12.31%.