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Total Synthesis of the Antimycoplasma Antibiotic Micacocidin

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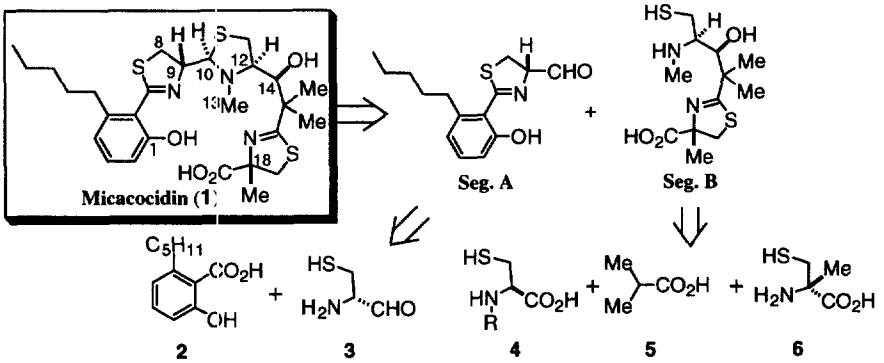
Abstract: A total synthesis of the antimycoplasma antibiotic micacocidin (**1**) is described. Construction of sterically hindered thiazoline **12** was achieved by a phosphorus pentachloride-mediated cyclization reaction of *S*-protected aryloylcysteine **11**, and compound **1** with desired chirality at C-10 was favorably obtained from diastereomeric mixture **30** through formation of the Zn complex **31**.

Keywords: Antibiotics; Thiazolines; Thiazolidines; Chelation.

Micacocidin (**1**), isolated from the culture broth of *Pseudomonas* sp. No. 57-250 in our laboratory as its stable metal complexes,[1,2] is a unique antibiotic which shows specific and potent antimycoplasma activity (MIC for *Mycoplasma pneumoniae* Mac. 6 ng/mL). The absolute stereostructure of the antibiotic was confirmed by X-ray crystallographic analysis of micacocidin A (**31**), a Zn complex of **1**. The structure, with five chiral centers, is comprised of a thiazolidine ring, two thiazoline rings and an *n*-pentylphenol moiety, which resembles the structures of siderophores, pyochelin[3] and yersiniabactin.[4] Due to its novel structural features as well as interesting biological activities, we attempted the total synthesis of **1**.



Scheme 1. Retrosynthetic analysis.

Retrosynthesis of micacocidin (1)

Among the five chiral carbons in micacocidin, we planned to utilize cysteine as chiral sources for C-9, C-12 and C-18, and to generate 14*S* secondary alcohol by stereoselective reduction of the ketone. We expected to obtain the desired chilarity at C-10 by formation of the Zn complex at the final stage. Furthermore, we constructed a thiazolidine ring containing C-10 carbon at as late a step in the total synthesis as possible, due to its labile structure. Based on these considerations, we retrosynthesized micacocidin to segment A from alkylsalicylic acid **2** and D-cysteine aldehyde, and segment B constructed from L-cysteine , isobutyric acid (**5**) and 2-methyl-*S*-cysteine (**6**), as shown in **Scheme 1**.

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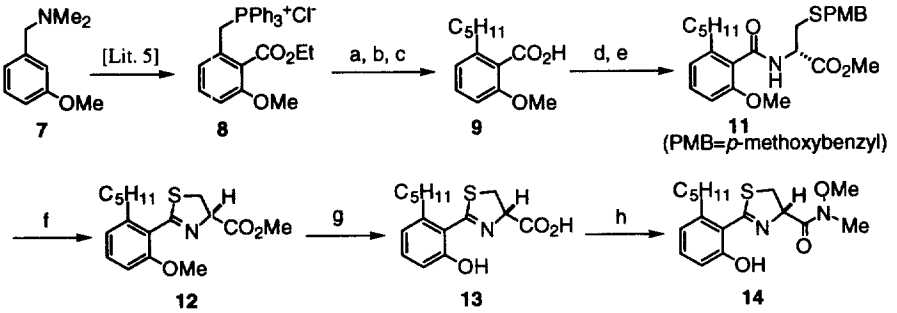
Synthesis of **14**, a precursor of segment A

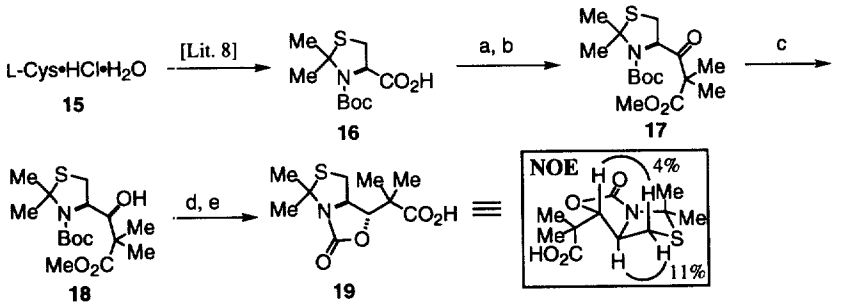
Condensation of *n*-pentylanisic acid **9**, prepared from 3-methoxy-*N*,*N*-dimethylbenzylamine (**7**) via phosphonium salt **8**,[5] with protected D-cysteine **10** provided amide **11**. Treatment of **11** with phosphorus pentachloride resulted in removal of the benzyl group with simultaneous cyclization reaction to yield thiazoline **12**, which noteworthily retained the stereochemistry of **10** (96%ee).[6] Demethylation of both ether and ester linkages of **12** was effected with boron tribromide to give carboxylic acid **13**, which was subsequently converted to Weinreb amide **14**, as the aldehyde precursor, although the thiazoline chirality was partly lost to 51%ee[6,7] at the stage of treatment with boron tribromide. (**Scheme 2**)



Scheme 2. Reagents and conditions: (a) $CH_3CH{=}CHCHO$, LDA / THF, -48°C-rt, 3.5 h; (b) H_2, Pd/C / EtOH, rt, 8 h, 80% in 2 steps; (c) NaOH / H_2O-DMSO, reflux 12 h, quant.; (d) $SOCl_2$, DMF / $Cl(CH_2)_2Cl$, reflux, 1 h; (e) D-Cys(PMB)OMe•HCl(**10**), Py / CH_2Cl_2, 0°C-rt, 1.5 h, 90% in 2 steps; (f) PCl_5 / CH_2Cl_2, 0°C-rt, 0.5 h, 86%; (g) BBr_3 / CH_2Cl_2, -78°C, 0.5 h then rt, 4 h; (h) MeONHMe•HCl, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), Et_3N / CH_2Cl_2, rt, 12 h, 40% in 2 steps.

Stereocontrolled introduction of C-14 secondary alcohol

Elongation to β-keto-carboxylate **17** from thiazolidine carboxylic acid **16**,[8] prepared from L-cysteine, was achieved by a carbonyldiimidazole method with methyl isobutyrate. Reduction of **17** with sodium borohydride proceeded stereoselectively in accordance with the Cram rule as expected to yield desired alcohol **18**, which was then converted to **19** through construction of an oxazolone ring with sodium hydride and subsequent hydrolysis. Configuration of **19** was substantiated by NOE examination as shown in **Scheme 3**.

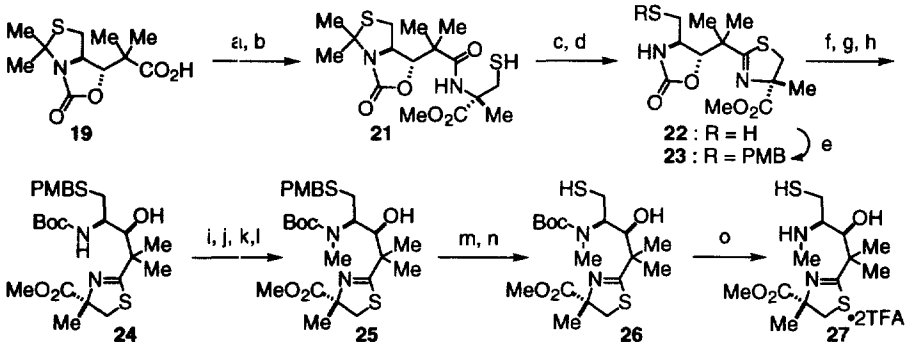


Scheme 3. Reagents and conditions: (a) $(Imid.)_2CO$ / THF, 0°C-rt, 1.5 h; (b) Me_2CHCO_2Me, LDA / Et_2O-THF, -78°C, 0.5 h, 72% from L-Cys (**15**); (c) $NaBH_4$ / EtOH, rt, 12 h, 62%; (d) NaH / THF, rt, 1.5 h; (e) NaOH / MeOH-H_2O, reflux, 5.5 h, 74% in 2 steps.

Synthesis of segment B **27**

Condensation of **19** with 2-methyl-*S*-cysteine methyl ester hydrochloride (**20**)[9] gave peptide **21**. Treatment of **21** with trifluoroacetic acid accomplished the cyclization reaction as well as removal of the acetonide moiety, which presumably was effected with H_2O generated *in situ*. Since the methyl ester group was mostly hydrolyzed during the reaction, the whole product was methylated with (trimethylsilyl)diazomethane[10] to give thiazoline **22**.

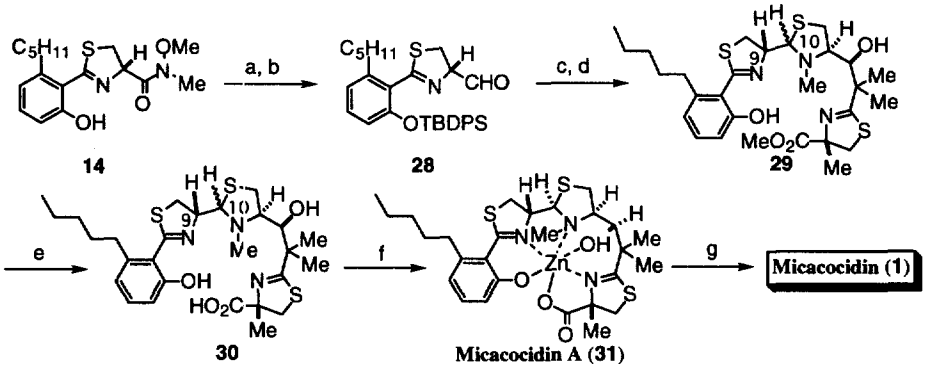
The thiol residue of **22** was then protected with a *p*-methoxybenzyl group, and cleavage of the oxazolone ring was achieved by introduction of a Boc group and subsequent treatment with cesium carbonate in methanol[11] to yield **24** with concomitant recovery of **23**. After protection of the generated secondary alcohol with *t*-butyldimethylsilyl (TBS) group, *N*-methylation using dimethyl sulfate and subsequent desilylation gave **25**. Regeneration of the thiol residue was achieved by substituting the PMB into the 3-nitro-2-pyridinesulfenyl (Npys) group then by treatment with tributylphosphine.[12] The Boc group in **26** was removed with trifluoroacetic acid to give **27** as segment B.(**Scheme 4**)



Scheme 4. Reagents and conditions: (a) $(Imid.)_2CO$ / THF, rt, 1 h; (b) 2-Me-*S*-CysOMe•HCl(**20**) / THF-DMF, rt, 4 h, 71% in 2 steps; (c) TFA-PhMe, reflux, 2 d; (d) $TMSCHN_2$ / CH_2Cl_2-MeOH, rt, 77% in 2 steps; (e) PMBCl, K_2CO_3 / DMF, rt, 1 h, 87%; (f) $(Boc)_2O$, DMAP / CH_2Cl_2, rt, 0.5 h; (g) Cs_2CO_3 / MeOH, rt, 15 h; (h) CH_2N_2 / Et_2O-MeOH, 0°C, 32% (+58% **23** recov.) in 3 steps; (i) TBSOTf, 2,6-lutidine / CH_2Cl_2, -78°C, 1.5 h, 95%; (j) Me_2SO_4, NaH / DMF, 90°C, 12 h; (k) TBAF, MS-4A / THF, rt, 4 h; (l) $TMSCHN_2$ / CH_2Cl_2-MeOH, rt, 74% in 3 steps; (m) Npys-Cl / CH_2Cl_2, 0°C, 0.5 h; (n) *n*-Bu_3P / Acetone-H_2O, rt, 0.5 h, 69% in 2 steps; (o) TFA-CH_2Cl_2, 0°C-rt, 1 h, quant.

Final assembly of segments to micacocidin (**1**)

After protection of the phenol residue in **14**, the Weinreb amide was reduced to labile aldehyde **28**[13] using lithium aluminum hydride. Without purification, segment A **28** was treated with segment B **27** in the presence of potassium acetate, and subsequently desilylated to yield micacocidin methyl ester (**29**) as a mixture of diastereomers which included the C-9 isomer.[14] After hydrolysis, the resulting acid **30** was treated with zinc chloride to isomerize the C-10 configuration to natural chirality. Finally, the zinc ion was released by treatment with dilute acid, and the resultant compound was purified by HPLC to furnish micacocidin (**1**).[15](**Scheme 5**)



Scheme 5. Reagents and conditions: (a) TBDPSCl, Imid. / DMF, 50°C, 2 h, 92%; (b) $LiAlH_4$ / THF, 0°C, 0.5 h; (c) **27**, AcOK / CH_2Cl_2, rt, 15 h; (d) TBAF / THF, 0°C, 0.5 h, 39% in 3 steps; (e) LiOH / THF-H_2O, rt, 0.5 h, quant ; (f) $ZnCl_2$ / MeOH-H_2O, rt, 12 h, 80%; (g) 5%$KHSO_4$aq., quant.

Acknowledgment

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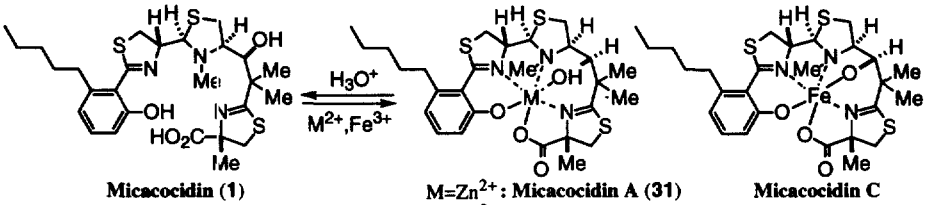
2. Micacocidin was isolated from the culture broth in chelated forms with Zn^{2+}, Cu^{2+} and Fe^{3+}, and initially named micacocidin A, B and C, respectively. Subsequently, it became clear that the metal ions were released from the chelates on treatment with dilute acid, while metal-free micacocidin was readily converted to the chelated forms. Details will be reported elsewhere by Kobayashi, S.; Ikenishi, Y.; Ino, A.; Sun, W.Y.; Takema, M.; Hayase, Y.



Micacocidin (1) — **M=Zn^{2+}: Micacocidin A (31)**, **M=Cu^{2+}: Micacocidin B** — **Micacocidin C**

3. (a) Cox, C.D.; Rinehart, K.L., Jr.; Moore, M.L.; Cook, J.C., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4256-4260. (b) Ankenbauer, R.G.; Toyokuni, T.; Staley, A; Rinehart, K.L., Jr.; Cox, C.D. *J. Bacteriol.* **1988**, 170, 5344-5351.
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6. The enantiomeric purity was determined by HPLC with chiralcel OD or OJ.
7. Enantiomerically purified **14** which was obtained by optical resolution with HPLC (chiralcel OJ), was used for condensation reaction of **28** with segment B **27** if necessary.
8. Kemp, D.S.; Carey, R.I. *J. Org. Chem.* **1989**, *54*, 3640-3646.
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10. Treatment with diazomethane resulted in dimethylation of both carboxyl and thiol moieties unselectively.
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13. Reduction of unprotected **14** gave, in low yield, extremely labile aldehyde which was not endurable for the following reaction.
14. Even if enantiomerically purified **14** was used for the segment condensation reaction, the C-9 isomer was formed although in reduced ratio [(9*R*,10*R*):(9*R*,10*S*):(9*S*,10*R*):(9*S*,10*S*)=60:15:19:6 in **29** by ^{1}H-NMR]. The C-9 isomer of **1** was separated finally by HPLC [ODS HG-5 (50 x 250 mm), 75% MeOH+1mM phosphate buffer (pH=7), 7.5 mL/min, det. UV 254 nm: Rt; **1** (9*R*,10*R*) 20.3 min, C-9 isomer (9*S*,10*R*) 18.5 min].
15. The synthetic micacocidin was identified with the natural compound by comparisons of HPLC behavior and spectroscopic properties {$[\alpha]^{24}_D$ -72.0±7.5 (c 0.15, MeOH) ; natural Micacocidin $[\alpha]^{22}_D$ -65.3±1.1 (c 0.93, MeOH)[2]}. The identification was further made by comparing the methyl ester **29**.