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# Synthetic studies of thiazoline and thiazolidine-containing natural products – 1. Phosphorus pentachloride-mediated thiazoline construction reaction

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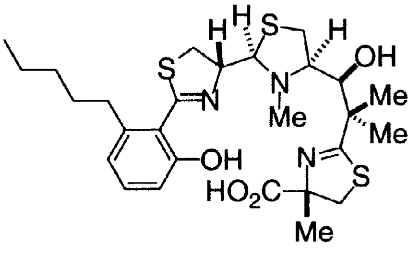
**Abstract**

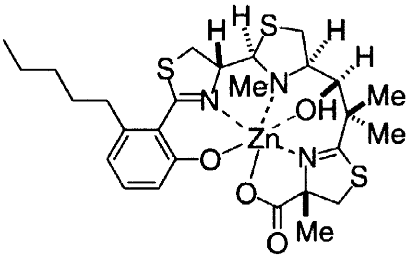
Phosphorus pentachloride effectively mediates the cyclization of *N*-acylcysteamine derivatives giving rise to thiazoline rings. Using this method, sterically hindered thiazoline analogs could be constructed and thus segment A (the left half) of micacocidin, a unique antimycoplasma antibiotic, was synthesized efficiently.

*Keywords: thiazolines; cyclization; phosphorus halogen compounds*

Mycoplasmas infect a wide range of domestic animals, fowl, insects and plants as well as humans, and the recent finding that mycoplasmas promote proliferation of HIV [1] has attracted a great deal of attention. In 1996, a new antibiotic micacocidin (**1**), which showed specific and potent activity for mycoplasmas, especially for *Mycoplasma pneumoniae*, was isolated in our laboratory in the form of stable metal complexes from the culture broth of *Pseudomonas* sp. Lot 57-250 [2]. The absolute stereostructure of micacocidin A (**2**), a Zn complex of **1** was determined by X-ray crystallographic analysis. Its biological activities and the novel structure, comprised of one alkylphenol unit and three characteristic thiazoline and thiazolidine skeletons with five chiral centers, prompted us to design a method for total synthesis of **1** [3].



**micacocidin (1)**



**micacocidin A (2)**

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Many kinds of biologically active compounds containing a thiazoline moiety have been discovered or chemically synthesized. Thiazoline skeletons were generally constructed either through condensation of nitrile or imino ester with cysteamine [4] or through acid-mediated cyclization of *S*-acyl or *N*-acylcysteamine derivatives [5]. However, these thiazoline analogs were usually labile, and if they contained a chiral carbon at C-4, they were readily epimerized [6]. The application of Burgess reagent to β-hydroxythioamide is a promising method for construction of the thiazoline skeleton [7]. We have applied this method in our synthetic study. However, in the case of sterically hindered 2-(2,6-disubstituted phenyl)thiazoline as contained in micacocidin (**1**), this method was unsuccessful mainly due to difficulty in the preparation of the corresponding thioamide. Therefore, we searched for an effective method by which sterically hindered thiazolines could be synthesized.

## Phosphorus pentachloride-mediated thiazoline construction

To find a new method for the construction of thiazolines, we found that phosphorus pentachloride ($PCl_5$) effected the thiazoline construction. That is, $PCl_5$ effectively mediated the cyclization of *N*-acylcysteamine derivatives **3** to give thiazolines **4** (**Table 1**).

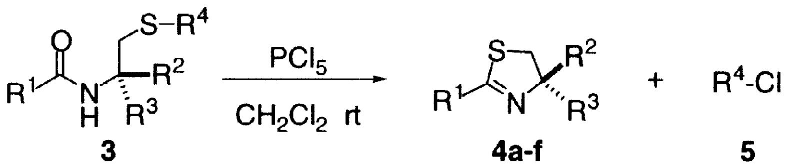


**Table 1.** $PCl_5$-mediated cyclization reactions

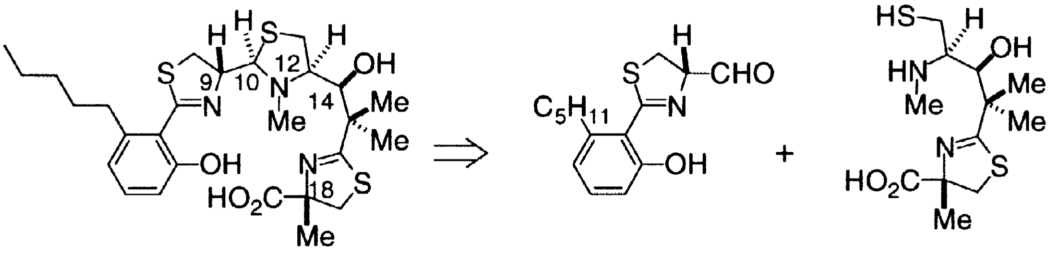
| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product | yield (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | H | H | PMB | **4a** | 72 |
| 2 | 2,6-$Me_2$-Ph | H | H | PMB | **4b** | 78 |
| 3 | 2,6-$Me_2$-Ph | H | H | Bn | **4b** | 19[a)] |
| 4 | 2,6-$Me_2$-Ph | H | H | H | **4b** | 44[b)] |
| 5 | Ph | $CO_2Et$ | H | PMB | **4c** | 80[c)] |
| 6 | Ph | CONHMe | H | PMB | **4d** | trace |
| 7 | Ph | H | H | Bz | **4a** | 73 |
| 8 | $Me_2CH$ | H | H | $COCHMe_2$ | **4e** | 89 |
| 9 | $Me_2CH$ | Me | $CO_2Me$ | $COCHMe_2$ | **4f** | 77 |

a) The major product in entry 3 was a thiol (**3**, $R^4$=H), but the reason is yet obscure.; b) The disulfide was obtained in 20%.; c) 99.7%*ee*.

By this method, not only 2-alkyl- as well as 2-aryl-thiazolines, but also sterically hindered thiazolines could be prepared in good yields. Alkyl and alkoxycarbonyl were shown to be successful substituents as $R^2$ and $R^3$ in **3** (entry 5,9). However, in the case of carbamoyl (entry 6), the starting compound was decomposed. On the other hand, a *p*-methoxybenzyl (PMB) group gave favorable results as the protecting group of thiol ($R^4$), which was recovered as chloride **5**[1] after the reaction. Unprotected substrate (entry 4) resulted in dimerization of the starting thiol. Interestingly, even in the case of acyl protected thiols (entry 8, 9), the reaction proceeded smoothly and stereoselectively, and the resulting thiazolines preserved high enantiomerical purity of the starting substrate (entry 5).

## Synthesis of segment A of micacocidin (1)

Our retrosynthesis of micacocidin (**1**) to segments A and B was as shown in **Scheme 1**, in which the labile thiazolidine ring was planned to be constructed at the latest stage possible. We considered that the C-10 chiral center, presumably generated as a mixture of the stereoisomers at the coupling reaction of segments A and B, may be converted into the desired configuration through formation of the Zn complex at the final stage. The $PCl_5$-mediated thiazoline construction reaction was applied to the synthesis of segment A. Synthesis of segment B (the right half of **1**) and subsequent coupling with segment A will be reported in the following paper [8].



**1** **Seg. A** **Seg. B**

**Scheme 1.** Retrosynthetic analysis

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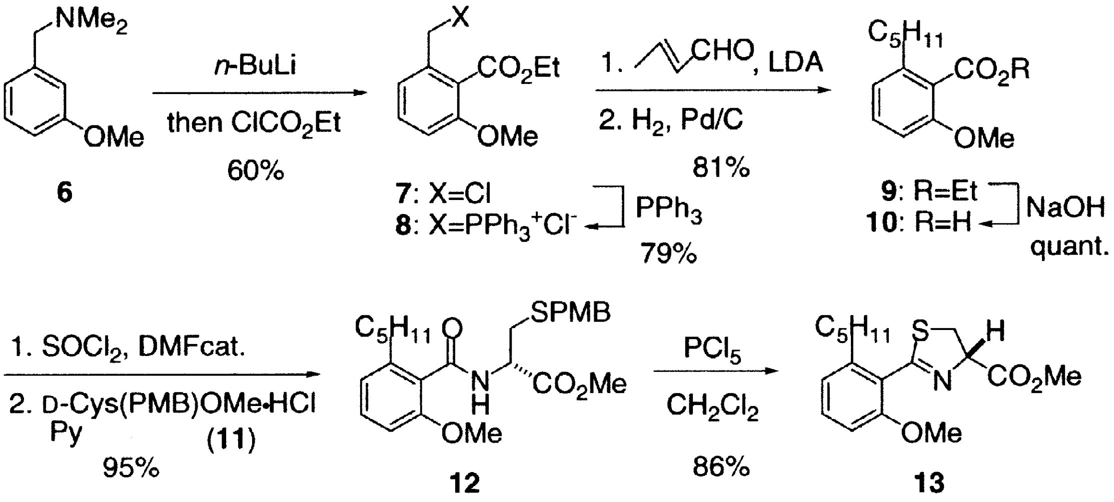
[1] The formation of **5** was suggested from the identification of PMBCl (by $^1$H-NMR and TLC) in conversion from **12** to **13**.

The alkylsalicylic unit required for the construction of segment A was synthesized according to the procedure reported by Kamikawa *et al.* [9]. Wittig reaction of crotonaldehyde with phosphonium salt **8**, prepared from 3-methoxy-*N,N*-dimethylbenzylamine (**6**) via benzyl chloride **7**, provided a diene *E/Z* mixture. After hydrogenation of the diene mixture, the resulting sterically hindered ester was hydrolyzed with aqueous NaOH-DMSO under reflux to give *n*-pentylanisic acid **10**. $PCl_5$-mediated cyclization of amide **12**, which was prepared by condensation of **10** with protected D-cysteine **11**, provided thiazoline **13** in good yield preserving high enantiomerical purity (96%*ee*). Another attempt to construct **13** either by condensation of a nitrile prepared from the acid **10** with cysteine or by cyclization of a thiol prepared by deprotection of **12** was unsuccessful.



**Scheme 2.**

Demethylation of both ether and ester moieties in **13** was achieved with boron tribromide to give carboxylic acid **15**, which was subsequently converted to Weinreb amide **16** using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), in which optical purity in the thiazoline moiety was partially lost (ca.50%*ee*). Phenolic ester **14** with 51%*ee*, initially formed after treatment of **13** with boron tribromide at low temperature, led us to presume that loss of the optical purity had already occurred at this stage. After protection of the phenol residue in **16** with *t*-butyldiphenylsilyl (TBDPS) group, the Weinreb amide was subjected to $LiAlH_4$ reduction to afford labile aldehyde **18** (protected segment A).[2]

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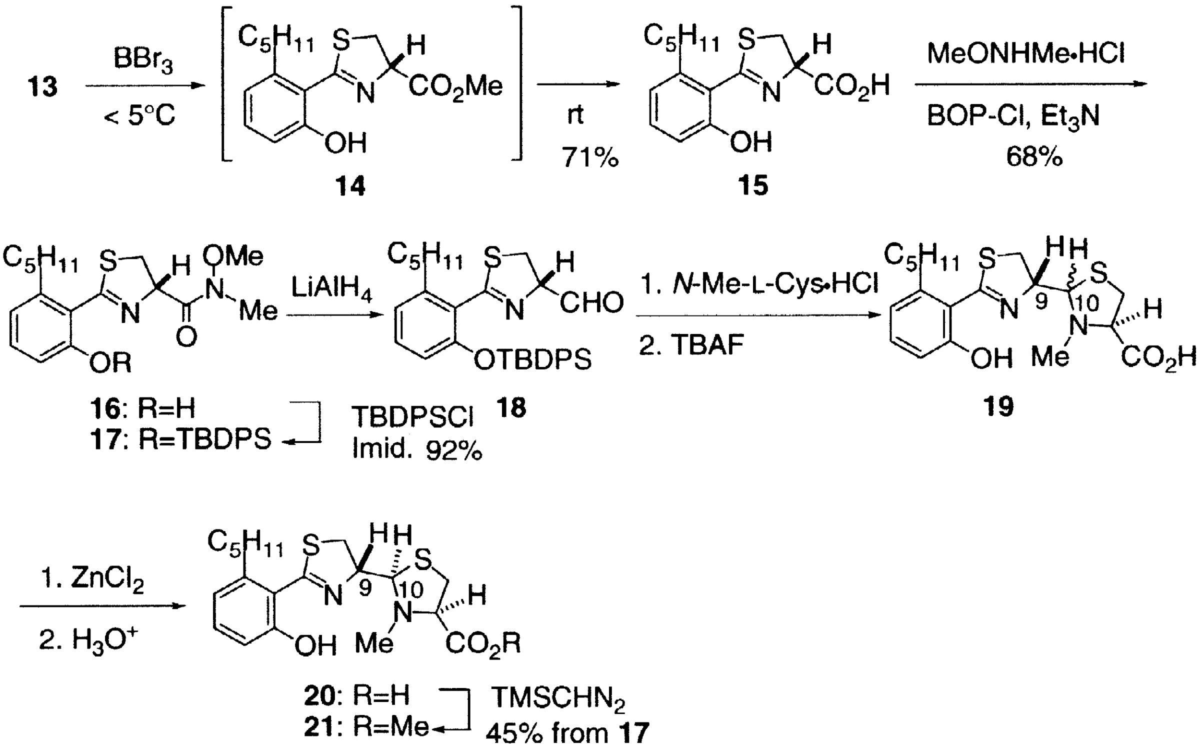
[2] Reduction of unprotected **16** resulted in low yield, and gave extremely labile aldehyde which was not endurable for the following condensation reaction.

Without further purification, **18** was treated with *N*-methyl-L-cysteine hydrochloride [10] followed by desilylation with tetrabutylammmonium fluoride (TBAF) to yield thiazolidine analogs **19** as a mixture of 4 diastereomers. Treatment of the mixture with $ZnCl_2$ resulted in isomerization at the C-10 carbon into the sterically favored *R* configuration to provide 5-pentylpyochelin **20** (9*R*:9*S* = ca.3:1; $^1$H-NMR). Comparison of $^1$H-NMR data for **20** and its methyl ester **21** with those of pyochelin [11] supported the structure of **20**.



Scheme 3.

In conclusion, segment A (the left half) of micacocidin (**1**) was efficiently synthesized using the phosphorus pentachloride-mediated thiazoline construction reaction. Successful synthesis of 5-pentylpyochelin **20** through condensation of TBDPS-Seg. A **18** with *N*-methyl-L-cysteine, suggested that condensation of **18** with segment B (the right half of **1**) and subsequent isomerization of the C-10 chiral carbon may allow production of micacocidin (**1**).

## Experimental section

**General.** Melting points were determined on a Yanagimoto micro melting point apparatus. IR spectra were recorded on a JASCO FT/IR-300E spectrometer with samples prepared as KBr pellets. $^1$H-NMR spectra were recorded on a JEOL GSX-270 spectrometer. Tetramethylsilane was used as an internal standard for spectra in $CDCl_3$ and DMSO-$d_6$. All solvents were dried over 3A or 4A molecular sieves before use. Chromatography was carried out on Merck silica gel 60. Preparative thin-layer chromatography (p-TLC) was carried out on 2.00 mm Merck silica gel $60F_{254}$ plates.

**$PCl_5$-mediated cyclization reaction. General procedure.** To an ice-cold solution of amide **3** in $CH_2Cl_2$ was added $PCl_5$ (2.10 eq.), and the mixture was stirred at room temperature for several hours. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in AcOEt and the organic extract was washed with sat.aq.$NaHCO_3$, brine, dried over $Na_2SO_4$ and then evaporated under reduced pressure. The residue was chromatographed (AcOEt/ hexane) to give thiazolines **4a-f**.

**2-Phenyl-thiazoline (4a).** IR $\nu_{max}$ 2942, 2849, 1609, 1491, 1316, 1240, 998 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) $\delta$ 3.42 (2H, t, $J$= 8.4 Hz), 4.47 (2H, t, $J$= 8.4 Hz), 7.43 (3H, m), 7.84 (2H, d, $J$= 7.8 Hz).

**2-(2,6-Dimetylphenyl)-thiazoline (4b).** IR $\nu_{max}$ 2920, 2851, 1623, 1465, 1221, 991, 920 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) $\delta$ 2.31 (6H, s), 3.48 (2H, t, $J$= 8.4 Hz), 4.46 (2H, t, $J$= 8.4 Hz), 7.03 (2H, d, $J$= 7.8 Hz), 7.16 (1H, t, $J$= 7.8 Hz).

**4-Ethoxycarbonyl-2-phenyl-thiazoline (4c).** IR $\nu_{max}$ 2981, 1739, 1596, 1447, 1229, 1189, 1030, 938 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) $\delta$ 1.34 (3H, t, $J$= 7.1 Hz), 3.64 (1H, dd, $J$= 11.2, 9.4 Hz), 3.72 (1H, dd, $J$= 11.2, 8.9 Hz), 4.30 (2H, q, $J$= 7.1 Hz), 5.27 (1H, t, $J$= 9.1 Hz), 7.43 (3H, m), 7.87 (2H, d, $J$= 8.2 Hz).

**2-Isopropyl-thiazoline (4e).** $^1$H-NMR ($CDCl_3$) $\delta$ 1.21 (3H, s), 1.24 (3H, s), 2.79 (1H, sept, $J$= 6.7 Hz), 3.24 (2H, t, $J$= 8.5 Hz), 4.21 (2H, t, $J$= 8.5 Hz).

**2-Isopropyl-4-methoxycarbonyl-4-methyl-thiazoline (4f).** $^1$H-NMR ($CDCl_3$) $\delta$ 1.21 (3H, s), 1.23 (3H, s), 1.54 (3H, s), 2.87 (1H, sept, $J$= 6.7 Hz), 3.11 (1H, d, $J$= 11.0 Hz), 3.72 (1H, d, $J$= 11.0 Hz), 3.79 (3H, s).

**Determination of optical purity.** Optical purity of the intermediate was determined by HPLC with a chiral column [Chiralcel OD or OJ (4.6 x 250 mm), *n*-hexane/*i*-PrOH = 95/5, 1.0 ml/min, det. UV 254 or 230 nm] as shown in **Table 2**.

**Table 2.**

| Compound | Chiralcel | Rt. (min.) |  | *ee* (%) |
|---|---|---|---|---|
|  |  | *S* isomer | *R* isomer |  |
| **4a** | OD | 7.5 | 17.0 | 99.8 |
| **13** | OD | 9.3 | 7.9 | 96.3 |
| **14** | OD | 7.3 | 8.6 | 51.3 |
| **16** | OJ | 15.8 | 16.9 | ca. 50 |

**Phosphonium salt 8.** To an ice-cold solution of 3-methoxy-*N*,*N*-dimethylbenzylamine (**6**) (25.0 g, 153 mmol) in THF (150 ml), was added *n*-BuLi (100 ml of 1.68 M in hexane, 1.10 eq.) dropwise over 10 min. The mixture was stirred at 0°C for 1 h and then cooled to -78°C, treated with $ClCO_2Et$ (30.6 ml, 2.60 eq.), and the whole mixture was stirred further at room temperature for 20 h. The reaction mixture was diluted with AcOEt, washed with water and brine, then dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed (silica 1 kg, AcOEt/hexane = 1/10) to give benzyl chloride **7** (21.08 g, 60%). $^1$H-NMR ($CDCl_3$) $\delta$ 1.40 (3H, t, $J$ = 7.3 Hz), 3.85 (3H, s), 4.43 (2H, q, $J$ = 7.3 Hz), 4.60 (2H, s), 6.92 (1H, d, $J$ = 8.6 Hz), 7.03 (1H, d, $J$ = 7.9 Hz), 7.36 (1H, dd, $J$ = 8.6, 7.9 Hz).

A mixture of **7** (21.08 g, 92.2 mmol) and $PPh_3$ (24.18 g, 1.00 eq.) in toluene (92 ml) was stirred at reflux for 3 d, and then cooled to room temperature. White crystalline powders of the phosphonium salt **8** (35.83 g, 48% in 2 steps from **6**) were collected by filtration. **8**; Mp 208-211°C (decomp.); IR $\nu_{max}$ 2994, 2745, 1710, 1586, 1445 cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$) $\delta$ 1.04 (3H, t, $J$ = 7.3 Hz), 3.75 (3H, s), 3.99 (2H, q, $J$ = 7.3 Hz), 4.95 (1H, s), 5.00 (1H, s), 6.56 (1H, dd, $J$ = 7.9, 1.8 Hz), 7.12 (1H, dd, $J$ = 8.5, 1.8 Hz), 7.30 (1H, dd, $J$ = 8.5, 7.9 Hz), 7.55 (6H, m), 7.73 (6H, m), 7.91 (3H, m); Anal. calcd. for $C_{29}H_{28}ClO_3P$ : C, 70.95; H, 5.75; Cl, 7.22. found: C, 70.84; H5.88; Cl, 7.34.

**Ester 9.** LDA (28.19 ml of 1.50 M in *c*-hexane, 1.05 eq.) was added to a suspension of phosphonium salt **8** (19.77 g, 40.3 mmol) in THF (80 ml) under a nitrogen atmosphere at -78°C over 10 min. The mixture was stirred at the same temperature for 15 min, and then at -48°C for 20 min. Crotonaldehyde (3.67 ml, 1.10 eq.) was added and the whole mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with $Et_2O$ and washed with brine, dried over $Na_2SO_4$ and then evaporated under reduced pressure. The residue was taken up in hexane, and insoluble $Ph_3P{=}O$ was removed by filtration through Celite. The filtrate was concentrated under reduced pressure to yield crude diene (11.26g, *E*/*Z* = ca.2/1).

Under a hydrogen atmosphere, a mixture of crude diene (11.26g) and 10% Pd/C (0.56g, 5wt%) in EtOH (80 ml) was stirred at room temperature for 2 d. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica 400 g, AcOEt/hexane = 1/10) to give **9** (8.22 g, 81%). IR $\nu_{max}$ 2932, 2859, 1730, 1471, 1267 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 6.7 Hz), 1.32 (4H, m), 1.38 (3H, t, *J* = 7.3 Hz), 1.60 (2H, m), 2.55 (2H, br-t, *J*=7.3 Hz), 3.82 (3H, s), 4.40 (2H, q, *J* = 7.3 Hz), 6.75 (1H, d, *J* = 8.5 Hz), 6.82 (1H, d, *J* = 7.3 Hz), 7.26 (1H, t, *J* = 8.5, 7.3 Hz); LSIMS *m/z* 501 [2M+H]$^+$, 251 [M+H]$^+$, 205; HR-LSIMS *m/z* 251.1650 [M+H]$^+$ (calcd 251.1647 for $C_{15}H_{23}O_3$).

**Carboxylic acid 10.** A solution of ester **9** (7.51 g, 30.0 mmol) in DMSO (45 ml) and 15% aq.NaOH (15 ml) was stirred at reflux for 15 h. After cooling to room temperature, water was added and the mixture was washed with $CH_2Cl_2$. The aqueous layer was acidified with 6N aq.HCl and extracted twice with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$ and evaporated to give pure **10** (6.81 g, quant.). IR $\nu_{max}$ 3019, 2931, 2869, 1701, 1472, 1267 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 6.7 Hz), 1.34 (4H, m), 1.63 (2H, m), 2.76 (2H, td, *J*=7.3 Hz), 3.90 (3H, s), 6.82 (1H, d, *J* = 8.5 Hz), 6.89 (1H, d, *J* = 7.9 Hz), 7.33 (1H, t, *J* = 7.9 Hz); LSIMS *m/z* 445 [2M+H]$^+$, 223 [M+H]$^+$, 205; HR-LSIMS *m/z* 223.1342 [M+H]$^+$ (calcd 223.1334 for $C_{13}H_{18}O_3$).

**Amide 12.** A solution of **10**, 1,2-dichloroethane (7.5 ml), $SOCl_2$ (0.40 ml, 1.10 eq.) and DMF (1 drop) was stirred at reflux for 0.5 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (2.3 ml), and added dropwise to a mixture of D-Cys(PMB)OMe•HCl **11** (1.60 g, 1.10 eq.), pyridine (1.01 ml, 2.50 eq.) and $CH_2Cl_2$ (6.0 ml) over 10 min at 0°C. The mixture was stirred at room temperature for 1 h, and concentrated to dryness. The residue was taken up in AcOEt and the organic extract was washed with sat.aq.$NH_4Cl$, sat.aq.$NaHCO_3$ and brine, dried over $Na_2SO_4$ and then evaporated under reduced pressure. The residue was chromatographed (silica 100 g, AcOEt/hexane = 1/2) to give **12** (2.18 g, 95%). Mp 71-73 °C; $[\alpha]^{24}_D$ +5.0 (c 1.01, $CHCl_3$); IR $\nu_{max}$ 3356, 2951, 2855, 1745, 1662, 1512, 1247 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.87 (3H, t, *J* = 6.7 Hz), 1.30 (4H, m), 1.60 (2H, m), 2.65 (2H, br-t, *J*=7.3 Hz), 2.93 (1H, dd, *J* = 14.0, 4.9 Hz), 3.06 (1H, dd, *J* = 14.0, 4.9 Hz), 3.72 (2H, s), 3.78 (9H, s), 5.07 (1H, dt, *J* = 7.9, 4.9 Hz), 6.58 (1H, br-d, *J* = 7.9 Hz), 6.75 (1H, d, *J* = 8.5 Hz), 6.83 (3H, m), 7.24 (3H, m); Anal. calcd for $C_{25}H_{33}NO_5S$: C, 65.33; H, 7.24; N, 3.05. found: C, 65.20; H, 7.21; N,3.09.

**Thiazoline ester 13.** Following treatment similar to the general procedure, amide **12** (2.07 g, 4.50 mmol) gave **13** (1.25 g, 86%). $[\alpha]^{27}_D$ -29.1 (c 1.00, $CHCl_3$); IR $\nu_{max}$ 2953, 2858, 1745, 1469, 1265 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 6.7 Hz), 1.30 (4H, m), 1.59 (2H, m), 2.61 (2H, br-t, *J*= 7.3 Hz), 3.69 (1H, dd, *J*= 11.0, 9.2 Hz), 3.77 (1H, dd, *J*= 11.0, 9.2 Hz), 3.80 (3H, s), 3.84 (3H, s), 5.30 (1H, t, *J*= 9.2 Hz), 6.74 (1H, d, *J*= 8.5 Hz), 6.83 (1H, d, *J*= 7.3 Hz), 7.26 (1H, t, *J*= 8.5, 7.3 Hz); LSIMS *m/z* 643 $[2M+H]^+$, 322 $[M+H]^+$, 262; HR-LSIMS *m/z* 322.1468 $[M+H]^+$ (calcd 322.1477 for $C_{17}H_{24}NO_3S$).

**Weinreb amide 16.** To a solution of thiazoline ester **13** (1.13 g, 3.52 mmol) in $CH_2Cl_2$ (7.0 ml) was added $BBr_3$ (7.38 ml of 1.00 M in $CH_2Cl_2$, 2.10 eq.) at -78°C. The mixture was stirred at the same temperature for 15 min, and then at room temperature for a further 3.5 h. Pieces of ice were added, and the whole mixture was diluted with AcOEt. The organic mixture was washed with water, brine, then dried over $Na_2SO_4$ and concentrated under reduced pressure to give acid **15** (0.73 g, 71%). IR $\nu_{max}$ 3031, 2929, 2857, 1730, 1598, 1452 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.90 (3H, t, *J*= 6.7 Hz), 1.35 (4H, m), 1.60 (2H, m), 2.92 (2H, m), 3.69 (2H, m), 4.29 (2H, br-s), 5.37 (1H, t, *J*= 9.2 Hz), 6.73 (1H, d, *J*= 8.5 Hz), 6.86 (1H, d, *J*= 7.9 Hz), 7.23 (1H, t, *J*= 8.5, 7.9 Hz).

A mixture of carboxylic acid **15** (686 mg, 2.34 mmol), MeONHMe•HCl (274 mmol, 1.20 eq.), BOP-Cl (655 mg, 1.10 eq.), $CH_2Cl_2$ (7.0 ml) and $Et_3N$ (0.82 ml, 2.50 eq.) was stirred at room temperature overnight, and then concentrated. The residue was taken up in AcOEt and the organic extract was washed with 5% aq.$KHSO_4$, sat.aq.$NaHCO_3$ and brine, dried over $Na_2SO_4$ and then evaporated under reduced pressure. The residue was chromatographed (silica 30 g, AcOEt/hexane= 1/2) to give Weinreb amide **16** (539 mg, 48% calculated from **13**). IR $\nu_{max}$ 3292, 2931, 2856, 1653, 1582, 1453, 1208 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.90 (3H, t, *J*= 6.7 Hz), 1.35 (4H, m), 1.63 (2H, m), 2.90 (1H, m), 3.30 (3H, br-s), 3.55 (1H, dd, *J*= 11.0, 9.8 Hz), 3.70 (2H, m), 3.84 (3H, s), 5.65 (1H, br-t, *J*= 7.3 Hz), 6.72 (1H, d, *J*= 7.9 Hz), 6.84 (1H, d, *J*= 7.9 Hz), 7.21 (1H, t, *J*= 7.9 Hz) ); LSIMS *m/z* 673 $[2M+H]^+$, 337 $[M+H]^+$, 248; HR-LSIMS *m/z* 337.1584 $[M+H]^+$ (calcd 337.1586 for $C_{17}H_{25}N_2O_3S$).

**TBDPS ether 17.** A mixture of Weinreb amide **16** (200 mg, 0.59 mmol), DMF (1.20 ml), TBDPSCl (343 mg, 2.10 eq.) and imidazole (170 mg, 4.20 eq.) was stirred at 50 °C for 2 h. After cooling to room temperature, the mixture was diluted with $Et_2O$ and washed with water, brine, then dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica 20 g, AcOEt/hexane = 1/6) to give **17** (315 mg, 92%). IR $\nu_{max}$ 2931, 2859, 1670, 1463, 1283 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.89 (3H, t, *J*= 6.7 Hz), 1.06 (9H, s), 1.33 (4H, m), 1.62 (2H, m), 2.63 (2H, br-t, *J*= 7.3 Hz), 3.30 (3H, br-s), 3.52 (1H, dd, *J*= 11.0, 9.2 Hz), 3.82 (3H, s), 4.01 (1H, br-t, *J*= 9.2 Hz), 5.67 (1H, br-t, *J*= 9.2 Hz), 6.21 (1H, d, *J*= 7.9 Hz), 6.72 (1H, d, *J*= 6.7 Hz), 6.82 (1H, t, *J*= 7.9, 6.7 Hz), 7.37 (6H, m), 7.74 (4H, m); LSIMS *m/z* 575 $[M+H]^+$, 517; HR-LSIMS *m/z* 575.2766 $[M+H]^+$ (calcd 575.2764 for $C_{33}H_{43}N_2O_3SSi$).

**5-Pentylpyochelin 20.** To an ice-cold solution of TBDPS ether **17** (75.0 mg, 0.13 mmol) in THF (2.00 ml) was added $LiAlH_4$ (5.40 mg, 1.10 eq.), and the mixture was stirred at the same temperature for 30 min. The reaction was quenched with AcOEt, then the mixture was poured into sat.aq.$NH_4Cl$ and extracted with AcOEt. The AcOEt layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated in vacuo to give crude aldehyde **18** as a bright yellow amorphous solid.

Without further purification, **18** was dissolved in $CH_2Cl_2$ (4.00 ml) and MeOH (1.0 ml), then AcOK (128 mg, 10.0 eq.) and *N*-Me-L-Cys•HCl (ca. 50% purity, 116 mg, 2.50 eq.) were added to the solution, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with AcOEt, washed with 5% aq.$KHSO_4$ and brine, dried over $Na_2SO_4$, and then concentrated in vacuo.

To an ice-cold solution of the residue in THF (3.00 ml) was added TBAF (1.00 M in THF, 0.13 ml, 1.00 eq.), and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with AcOEt and washed with 5% aq.$KHSO_4$, then extracted into sat.aq.$NaHCO_3$ The combined aqueous layer was acidified (pH=4) with conc.HCl and extracted again with AcOEt. The AcOEt layer was washed with brine, dried over $Na_2SO_4$, then concentrated in vacuo to give 5-pentylpyochelin **19** (37.0 mg) as a mixture of diastereomers.

To a solution of the residue (37.0 mg, 9.37 x $10^{-5}$ mol) in MeOH (2.50 ml), was added $ZnCl_2$ (32.0 mg, 2.5 eq.), and the whole mixture was stirred at room temperature overnight. The reaction mixture was diluted with AcOEt and washed with 5% aq.$KHSO_4$ to release the zinc ion. The organic layer was washed with brine, dried over $Na_2SO_4$, and then concentrated in vacuo to give 5-pentylpyochelin **20** (ca.3:1 mixture of diastereomers; $^1$H-NMR, 37.0 mg) as yellow caramel. IR $\nu_{max}$ 3014, 2930, 2859, 1725, 1581, 1464, 1209 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) [major isomer **20**] $\delta$ 0.90 (3H, t, *J* = 6.8 Hz), 1.35 (4H, m), 1.62 (2H, m), 2.72 (3H, s), 2.95 (2H, m), 3.21 (1H, dd, *J* = 11.4, 7.8 Hz), 3.29-3.54 (3H, m), 3.90 (1H, dd, *J* = 7.4, 5.8 Hz), 4.33 (1H, d, *J*= 8.6 Hz), 4.70 (1H, q, *J* = 8.6 Hz), 6.73 (1H, d, *J* = 6.9 Hz), 6.87 (1H, d, *J* = 7.2 Hz), 7.24 (1H, t, *J* = 7.2, 6.9 Hz).

**5-Pentylpyochelin methyl ester 21.** A solution of **20** (37.0 mg) in $CH_2Cl_2$ (3.00 ml) and MeOH (1.00 ml) was treated with $TMSCHN_2$ (1.00M in THF) until generation of $N_2$ gas ceased. The reaction was quenched with AcOH and the mixture was concentrated in vacuo. The residue was purified by p-TLC (AcOEt/hexane = 1/1) to give 5-pentylpyochelin methyl ester **21** (ca.3:1 mixture of diastereomers by $^1$H-NMR, 24.0 mg, 45% from **17**). IR $\nu_{max}$ 2955, 2870, 2716, 1739, 1581, 1447, 1208 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) [major isomer; presume 9*R*] $\delta$ 0.90 (3H, t, *J* = 6.9 Hz), 1.36 (4H, m), 1.62 (2H, m), 2.59 (3H, s), 2.97 (2H, t, *J* = 7.9 Hz), 3.13 (1H, dd, *J* = 10.7, 6.4 Hz), 3.23 (1H, dd, *J* = 10.7, 8.6 Hz), 3.41 (2H, m), 3.68 (1H, dd, *J* = 8.6, 6.4 Hz), 3.76 (3H, s), 4.50 (1H, d, *J*= 5.6 Hz), 4.94 (1H, td, *J* = 8.7, 5.6 Hz), 6.69 (1H, dd, $J = 7.6$, 1.2 Hz), 6.84 (1H, dd, $J = 8.2$, 1.2 Hz), 7.19 (1H, t, $J = 7.8$ Hz); [minor isomer; presume 9*S*] δ 0.90 (3H, t, $J = 6.9$ Hz), 1.36 (4H, m), 1.62 (2H, m), 2.60 (3H, s), 2.97 (2H, t, $J = 7.9$ Hz), 3.20-3.57 (4H, m), 3.77 (3H, s), 3.82 (1H, t, $J = 6.8$ Hz), 4.23 (1H, d, $J = 7.9$ Hz), 4.69 (1H, q, $J = 7.9$ Hz), 6.69 (1H, d, $J = 7.6$ Hz), 6.84 (1H, d, $J = 8.2$ Hz), 7.19 (1H, t, $J = 7.8$ Hz); LSIMS *m/z* 409 $[M+H]^+$, 248, 160; HR-LSIMS *m/z* 409.1612 $[M+H]^+$ (calcd 409.1620 for $C_{20}H_{29}N_2O_3S_2$).

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## References

[1] a) Lemaitre, M.; Guetard, D.; Henin, Y.; Montagnier, L.; Zerial, A. *Res. Viol.* **1990**, *141*, 5-16. b) Lo, S-C.; Dawson, M.S.; Wong, D.M.; Newtoon III, P.B.; Sonoda, M.A.; Engler, W.F.; Wang, R.Y.H.; Shin, J.W.K; Alter, H.J.; Wear, D.J. *Am. J. Trop. Med. Hyg.* **1989**, *41*, 601-616. c) Chowdhury, M.I.H.; Munakata, T.; Koyanagi, Y.; Kobayashi, S.; Arai, S.; Yamamoto, N. *Biochem. Biophys. Res. Commun.* **1990**, *170*, 1365-1370. d) Katseni, V.L.; Gilroy, C.B.; Ryait, B.K.; Ariyoshi, K.; Bieniasz, P.D.; Weber, J.N.; Robinson, D.T. *Lancet* **1993**, *341*, 271-273.

[2] a) Shionogi & Co., Ltd. Patent, WO 96/04262. b) Kobayashi, S.; Hidaka, S.; Kawamura, Y.; Ozaki, M.; Hayase, Y. *J. Antibiotics* **1998**, *51*, 323-327. c) Kobayashi, S.; Nakai, H.; Ikenishi, Y.; Sun, Y.; Ozaki, M.; Hayase, Y.; Takeda, R. *ibid.* **1998**, *51*, 328-332.

[3] Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron Lett.* **1998**, *39*, 3509-3512.

[4] a) Mulqueen, G.C.; Pattenden, G.; Whiting, D.A. *Tetrahedron* **1993**, *49*, 5359-5364. b) Boyce, R.J.; Pattenden, G. *ibid.* **1995**, *51*, 7313-7320. c) Boyce, R.J.; Mulqueen, G.C.; Pattenden, G. *ibid.* **1995**, *51*, 7321-7330. d) Rinehart, K.L.; Staley, A.L.; Wilson, S.R.; Ankenbauer, R.G.; Cox, C.D. *J. Org, Chem.* **1995**, *60*, 2786-2791. e) Kwiatkowski, S.; Crocker, P.J.; Chavan, A.J.; Imai, N.; Haley, B.E.; Watt, D.S.; Ho, R.-J. *Tetrahedron Lett.* **1990**, *31*, 2093-2096. f) Toya, Y.; Takagi, M.; Kondo, T.; Nakata, H.; Isobe, M.; Goto, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2604-2610. g) Caujolle, R.; Favrot, J.D.; Loiseau, P.R.; Payard, M.; Amarouch, H.; Lazrek, H.; Linas, M.D.; Segueda, J.P.; Loiseau, P.M.; Bories, C.; Gayral, P. *Pharm. Acta Helv.* **1991**, *66*, 237-240. h) Crawhall, J.C.; Elliott, D.F.; Hooper, K.C. *J. Chem. Soc.* **1956**, 4066.

[5] a) White, J.D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1997**, *119*, 103-111. b) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449-8450. c) Wipf, P.; Venkatraman, S. *J. Org, Chem.* **1995**, *60*, 7224-7229. d) Walker, M.A.; Heathcock, C.H. *ibid.* **1992**, *57*, 5566-5568. e) Akaji, K.; Kuriyama, N.; Kiso, Y. *ibid.* **1996**, *61*, 3350-3357. f) Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron* **1996**, *52*, 14543-14562.

[6] a) Wipf, P.; Fritch, P.C. *J. Am. Chem. Soc.* **1996**, *118*, 12358-12367. b) Wipf, P.; Fritch, P.C. *Tetrahedron Lett.* **1994**, *35*, 5397-5400.

[7] a) Wipf, P.; Miller, C.P. *Tetrahedron Lett.* **1992**, *33*, 907-910. b) Wipf, P.; Miller, C.P.; Venkatraman, S.; Fritch, P.C. *Tetrahedron Lett.* **1995**, *36*, 6395-6398. c) Wipf, P.; Xu, W. *J. Org, Chem.* **1996**, *61*, 6556-6562.

[8] Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron*, **following paper.**

[9] Kubo, I.; Kim, M.; Naya, K.; Komatsu, S.; Yamagiwa, Y.; Ohashi, K.; Sakamoto, Y.; Hirakawa, S.; Kamikawa, T. *Chem. Lett.* **1987**, 1101-1104.

[10] Blondeau, P.; Berse, C.; Gravel, D. *Can. J. Chem.* **1967**, *45*, 49.

[11] 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. c) Rinehart, K.L.; Staley, A.L.; Wilson, S.R.; Ankenbauer, R.G.; Cox, C.D. *J. Org, Chem.* **1995**, *60*, 2786-2791.