A Convenient Synthesis of Methyl 2-[2-(1-Amino)ethenyl-bithiazolyl] thiazoline-4-carboxylate, an Important Skeleton of Cyclothiazomycin

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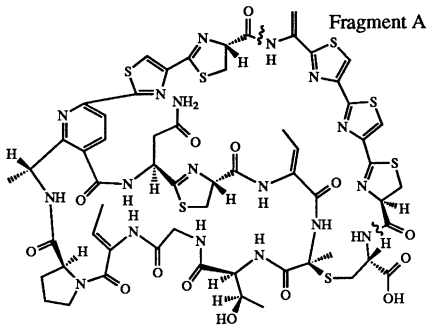
The convenient syntheses of a few methyl 2-(1-amino)alkenyl thiazoline-4-carboxylates and methyl 2-[2-(1-amino)ethenyl-bithiazolyl] thiazoline-4-carboxylate have been accomplished. The latter is an important partial skeleton of macrobicyclic peptide antibiotic cyclothiazomycin.

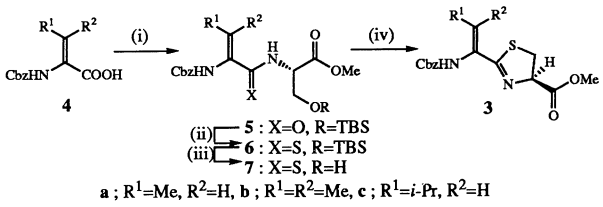
Antibiotic cyclothiazomycin (**1**),[1] obtained from the culture of *Streptomyces NR0516*, is a macrobicyclic peptide containing polythiazolyl-thiazoline dehydropeptide composed of a few (S)-2-substituted-thiazoline-4-carboxylic acid residues. The peptide (**1**) features a very unique structure, 2-[2-(1-amino)ethenyl-bithiazolyl]-thiazoline-4-carboxylic acid (**2**) segment (Fragment A), as shown in Fig. 1. More recently, we have reported the synthesis of 2-(1-amino)alkenyl-oxazoline-4-carboxylic acid[2] according to the Galeotti's oxazoline synthetic method.[3] However, there has been no report on the synthesis of the similar *N*-protected 2-(1-amino)alkenyl-thiazoline-4-carboxylate derivative (**3**), which is an important moiety in many thiostrepton antibiotics, such as siomycin A[4] and thiopeptin-Ba.[5] In connection with the total synthesis of **1**, herein we wish to report the novel synthesis of Fragment A(**2**), along with the general synthesis **3**.



Cyclothiazomycin (**1**)

Figure 1.

The coupling of *N*-benzyloxycarbonyl (Cbz) -α-dehydroamino acid (**4: a;** R^1=Me, R^2=H, **b;** R^1=R^2=Me, **c;** R^1=*i*-Pr, R^2=H) with L-H-Ser(TBS)-OMe (TBS=*t*-butyldimethylsilyl group) in the presence of *N*-hydroxysuccinimide (HOSu) by the usual dicyclohexylcarbodiimide (DCC) method gave the corresponding dehydrodipeptide derivative (**5**). Thioamidation of **5** with Lawesson's reagent and deprotection of the TBS group with 70% AcOH gave the *O*-free thiocarbonyl dipeptide (**7**). According to the method reported previously, subsequent thiazoline ring formation of **7** with Ph_3P and diethyl azodicarboxylate (DEAD) gave the expected methyl (*S*)-2-(1-Cbz-amino)ethenyl-thiazoline-4-carboxylates (**3a-c**) as shown in Scheme 1. Oxidation of the thiazoline ring with MnO_2 proceeded readily to give the corresponding thiazole derivatives, which were identical with the authentic samples reported earlier by us.[6] The yield of the each reaction step from **4** is about 75% and the yields of **3a-c** from **7** are listed in Table 1.



(i) DCC, HOSu, H-Ser(TBS)-OMe, CH_2Cl_2, 0 °C, 2 h, r.t., 8 h, (ii) Lawesson's reagent, DME, 50 °C, 8 h, (iii) 70%AcOH, r.t., 12h, (iv) Ph_3P, DEAD, THF, 0 °C, 15 min.

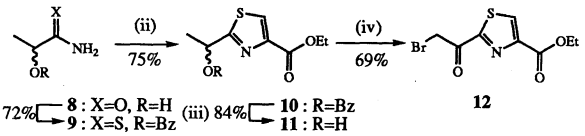
Scheme 1.

Table 1. The yields and ^{1}H NMR data of **3**

Compd No.	Yield / % [a]	Mp / °C [b]	^{1}H NMR, δ ($CDCl_3$) -CH= (Hz)	[α]$_D^{25}$ [c]
3a	71	syrup	6.15q (7.0)	+33.6°
3b	84	89-90	———	-20.4°
3c	67	92-93	5.90d (10.1)	+21.2°

[a] Calculated from corresponding thiodipeptide (**7**).
[b] Colorless needles from hexane-ethyl acetate.
[c] c 0.5, in MeOH.

For the synthesis of bithiazole segment of Fragment A, ethyl 2-bromoacetylthiazole-4-carboxylate (**12**) was thought to be an essential building block and was synthesized in five steps from Thr-NH_2 (**8**). Namely, protection of the hydroxyl group of **8** with benzoyl chloride (BzCl) and subsequent thioamidation with Lawesson's reagent gave the corresponding β-benzoyloxy thioamide (**9**). The direct thiazolation of **9** with $BrCH_2COCOOEt$ in trifluoroacetic acid anhydride (TFAA) in the presence of $KHCO_3$ according to the Hantzch's thiazole synthetic method[7] gave the corresponding thiazole-4-carboxylate (**10**). After deprotection of the Bz group by using NaOEt, the resultant 2-(1-hydroxy)ethyl

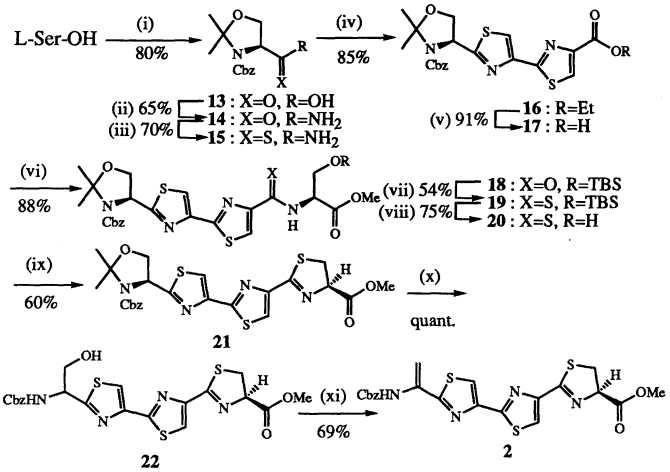


(i) (a) BzCl, pyridine, r.t., 3 h,(b) Lawesson's reagent, DME, r.t., 8 h, (ii) $KHCO_3$, $BrCH_2C(O)COOEt$,TFAA, pyridine, 0 °C, 30 min, r.t., 3 h, (iii) NaOEt, EtOH, 0 °C, 3 h, (iv) NBS, CCl_4, reflux, 6 h

Scheme 2.

derivative (**11**) was treated with *N*-bromosuccinimide (NBS) to give **12**,[8,9] as shown in Scheme 2.

Furthermore, protection of Cbz-Ser-OH with acetone dimethyl acetel (ADA) in the presence of *p*-toluenesulfonic acid (*p*-TosOH) gave the corresponding *N,O*-isopropylidene derivative (**13**). Amidation with NH_4OH and subsequent thioamidation with Lawesson's reagent furnished Cbz-*N,O*-isopropylidene-Ser(S)-NH_2 (**15**). The coupling of **15** with **12** by the Hantzch's method gave the corresponding bithiazole-4-carboxylate (**16**). After hydrolysis of the ester **16** with 1M LiOH, the coupling of the resultant free acid (**17**)[10] with H-Ser(TBS)-OMe by using BOP[11] gave bithiazole-4-carbonyldipeptide(**18**). Similarly, bithiazole-4-thiocarbonyldipeptide (**20**)[12] was obtained from **18** via *O*-TBS-protected-thiocarbonyldipeptide (**19**). Cyclization of **20** with Ph_3P and DEAD gave the corresponding thiazoline-4-carboxylate (**21**). Deprotection of isopropylidene group of **21** by using 70% AcOH gave 2-(1-hydroxymethyl) derivative (**22**). Finally, dehydration of **22** via the corresponding mesylate gave the desired Fragment A (**2**)[13] in 69% yield as shown in Scheme 3. The average yield of each reaction step from **13** is 76%.



(i) (a) CbzCl, $NaHCO_3$, ether-water, 0 °C, 2 h, r.t., 6 h, (b) ADA, *p*-TosOH, acetone, r.t., 8 h, (ii) (a) DCC, HOSu, 0 °C, 1 h, r. t., 8 h, (b) NH_4OH, 0 °C, 30 min, (iii) Lawesson's reagent, DME, r.t., 6 h, (iv) **12**, $KHCO_3$, TFAA, pyridine, DME, 0 °C, 1 h, r.t., 3 h, (v) 1M-LiOH, MeOH, 0 °C, 5 h, (vi) BOP, H-Ser(TBS)-OMe, 0 °C, 1 h, r.t., 6 h, (vii) Lawesson's reagent, THF, 50 °C, 8 h, (viii) n-Bu_4NF, THF, 0 °C, 1 h, (ix) Ph_3P, DEAD, THF, 0 °C, 20 min, (x) 70%AcOH, r.t., 5 h, (xi) MsCl, Et_3N, CH_2Cl_2, sonication, 35 °C, 1 h.

Scheme 3.

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9 **12**: Mp 68-69 °C (colorless powder). IR (KBr) 3448, 3118, 1731, 1704 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.43 (t, 3H, *J*=7.0 Hz), 4.46 (q, 2H), 4.81 (s, 2H, $BrCH_2$-), 8.50 (s, 1H, ring-H).

10 **17**: Mp 160-161 °C (colorless powder). $[\alpha]_D^{23}$ +61.3 ° (c 0.1, MeOH). IR (KBr) 3538, 2980, 1725, 1584,1569 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.63 and 1.83 (sx2, 3Hx2), 4.35 (d, 2H, *J*=3.0 Hz), 5.25-5.41 (m, 1H), 7.17 (s, 5H), 8.10 (s, 1H, ring-H), 8.30 (s, 1H, ring-H), 10.29 (br s, 1H, COOH).

11 BOP=Benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

12 **20**: Syrup. $[\alpha]_D^{24}$ +8.25 °(c 0.2, MeOH). IR (KBr) 3586, 3340, 2944, 1743, 1524 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.62 and 1.82 (sx2, 3Hx2), 3.86 (s, 3H), 4.04-4.35 (m, 1Hx3, Ser-αx2 and OH), 5.09 (s, 2H), 5.34-5.51 (m, 2Hx2), 7.19 (s, 5H), 7.92 (s, 1H, ring-H), 8.38 (s, 1H, ring-H), 9.93 (d, NH, *J* =7.7Hz).

13 **2**: Mp 185-186 °C (colorless powder). $[\alpha]_D^{23}$ -30.25 ° (c 0.1, MeOH). IR (KBr) 3394, 3118, 1740, 1602, 1530 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.69 (dABq, 2H, -CH_2S-, *J*=9.3 and 9.8 Hz), 3.84 (s, 3H, Me ester), 5.24 (s, 2H, -CH_2-), 5.32 (t, 1H, =NCH-, *J*=9.3 Hz), 5.42 (dd, 1H, vinyl-H, *J*=1.5 and 2.0 Hz), 6.18 (d, 1H, vinyl-H, *J*=1.5 Hz), 7.41 (s, 5H, Ph),7.83 (d, 1H, NH, *J*=2.0 Hz), 8.02 and 8.05 (sx2, 1Hx2, ring-Hx2).