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TOTAL SYNTHESIS OF ANTIBIOTIC ALTHIOMYCIN[1)]

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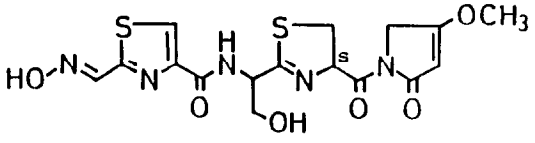
Summary: Antibiotic althiomycin was totally synthesized from D-cysteine *via* the procedures of the coupling with sodium salt of pyrrolinone, hydroxymethylation, and the coupling with the thiazole part, successively.

Althiomycin (1) is an antibiotic found by H. Umezawa and his collaborators in 1957 from *Streptomyces althioticus*.[2)] A unique structure of this antibiotic was proposed by three groups.[3,4,5)] Although the geometric configuration of the aldoxime was deduced to be *syn* form and the cysteine residue in the thiazoline moiety to be of *S*-configuration, *i.e.*, D-cysteine, the configuration of an asymmetric center on the serine residue is still ambiguous, because this antibiotic was always isolated as a mixture of diastereomers containing L- and D-serine residues. Therefore, it is assumed that the serine residue either



althiomycin (1)

exists in a racemic form in an original antibiotic or might be racemized during isolation procedure. Althiomycin manifests a very wide antibacterial spectrum not only for Gram-positive but also Gram-negative microorganisms. In spite of such remarkable biological activities, it has not been in practical use because of instability of the activity and insolubility in water. In order to modify properties of this antibiotic for purpose of the reuse, we first aimed a total synthesis of althiomycin.

The synthetic pathway is based on the "stepwise elongation method" from *C*-terminal to *N*-terminal. Methylation of pyrrolidine-2,4-dione (2)[6)] with

2 3

Fig. 1

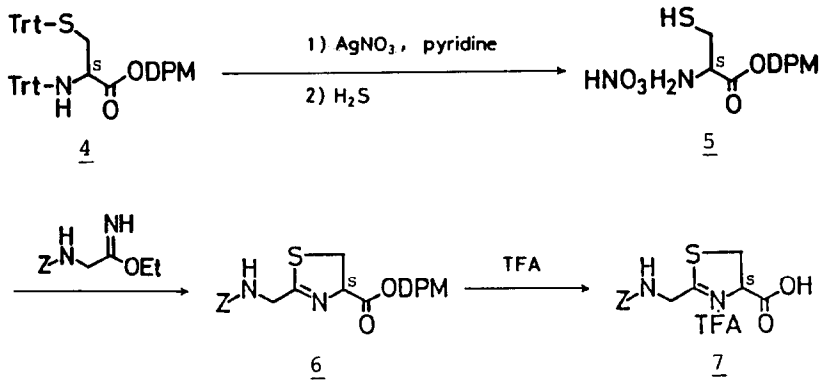


Fig. 2

diazomethane to give 4-methoxy-3-pyrrolin-2-one (3) was accompanied with formation of 2-methoxy-4-one isomer as a minor product (Fig. 1). Synthesis of the thiazoline part, *(S)*-2-(benzyloxycarbonylaminomethyl)-2-thiazoline-4-carboxylic acid (7), starting from glycine and D-cysteine, is illustrated in Fig. 2. Thus successive procedures of deprotection of trityl (Trt) group, coupling with ethyl benzyloxycarbonylaminoacetimidate,[7] and then removal of diphenylmethyl (DPM) group afforded the thiazoline carboxylic acid (7).

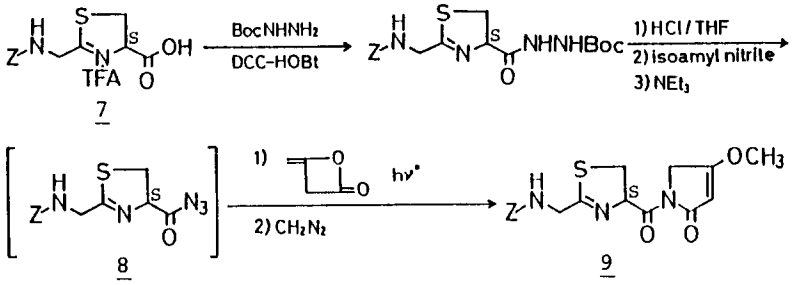
We attempted a coupling of the thiazoline derivative (7) with the pyrrolinone (3) using not only several carboxylic acid activation methods but also amino activation methods. However, the desired product could not be obtained by these methods so far because of the low reactivities of both the imino group in the pyrrolinone and the carboxylic function of the thiazoline part. Therefore, we next applied a photoreaction of the acid azide with diketene according to the method by T. Kato *et al.*[8] The conversion of the thiazoline carboxylic acid to the corresponding azide was carried out as shown in Fig. 3.i). The thiazoline carboxyazide (8) was coupled with diketene on irradiation with a 100 watt high-pressure mercury lamp (HALOS PIH-100) with a quartz filter at 0°C for 6 hrs, and then methylated with diazomethane to give the desired product (9).[9] This route was, however, found to be disadvantageous concerning the yield (∿8 %) and the reproducibility.

In order to improve this synthesis, we also tried the coupling method of sodium salt of pyrrolinone and the cysteine active ester (Fig. 3.ii). According to this pathway, the active ester (10) prepared from *N,S*-dityrityl-D-cysteine and *N*-hydroxy-5-norbornene-*endo*-2,3-dicarboxyimide (HONb) was coupled with 4-methoxy-3-pyrrolin-2-one sodium salt. The compound thus obtained was detritylated to give the cysteine derivative (12) with free amino and mercapto groups which was then coupled with ethyl benzyloxycarbonylaminoacetimidate to afford the thiazoline derivative (9). The total yield (45 %) from dityrityl-cysteine to this compound (9) through this route was much higher than that *via* the photoreaction. Formations of the imide bond as well as the thiazoline ring

in this compound (9) were confirmed by the downfield shift of methylene protons in pyrrolinone ring (0.3 ppm), and the long-range coupling between the *exo* methylene and the proton on *C*-4 of the thiazoline ring (2 Hz) respectively in NMR spectrum. Aldol condensation of the thiazoline-pyrrolinone compound (9) with formalin (35 %) in dimethyl sulfoxide at room temperature afforded a mixture of the desired hydroxymethylated product (13) and its anhydro compound.[10] However, by use of paraformaldehyde instead of formalin, this reaction gave solely the hydroxymethylated product (13) quantitatively.

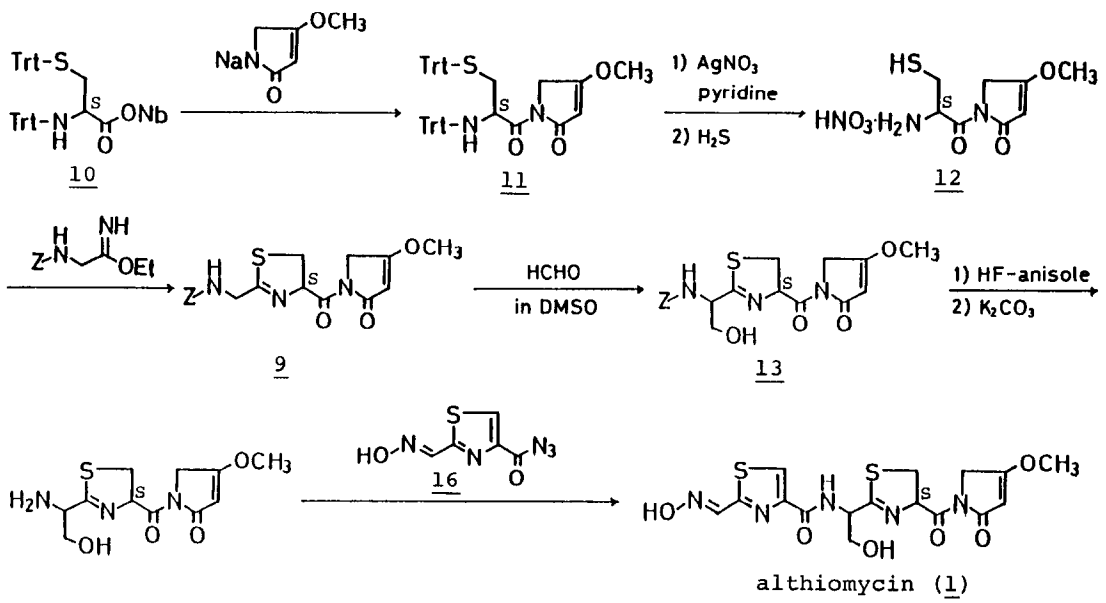
In the final step of the synthesis of althiomycin, the hydroxymethyl derivative (13) was deblocked with anhydrous hydrogen fluoride in the presence of anisole at 0°C for 20 min, and then coupled with the oxime of thiazole-

i) photoreaction



7 8 9

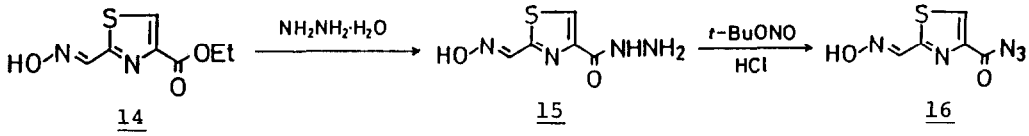
ii) sodium salt of pyrrolinone



10 11 12 9 13 16

althiomycin (1)

Fig. 3



14 15 16

Fig. 4

carboxyazide (16), which was synthesized from the aldoxime ester (14)[5] by treatment with hydrazine hydrate followed by azidation with *t*-butyl nitrite (Fig. 4), in the presence of potassium carbonate in *N*,*N*-dimethylformamide at room temperature for 3 hrs. Synthetic althiomycin purified by preparative thin-layer chromatography (chloroform-methanol 9:1) was completely identical with natural althiomycin in all respects including NMR, UV, TLC, RP-HPLC and antibacterial activity; yield 18 %, $[\alpha]_D^{20}$ +22.3° (methyl cellosolve) (natural $[\alpha]_D^{20}$ +20.8° (methyl cellosolve). The structure of althiomycin (1) was confirmed by this total synthesis for the first time.

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