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MACROLIDE RING CLOSURE. SILVER ION PROMOTED LACTONIZATION OF ω-HYDROXY THIOLESTERS OF 2-AMINO-4-MERCAPTO-6-METHYLPYRIMIDINE

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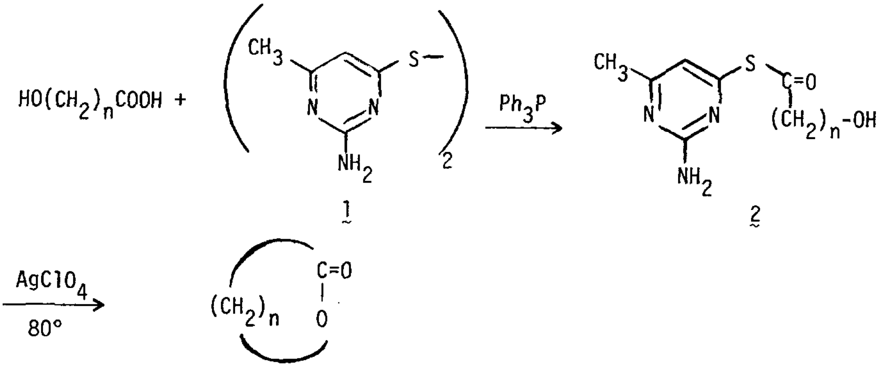
Macrolides are among the most chemically intriguing and therapeutically useful natural products known.[1,2] In recent years several hundred macrolides have been isolated from various Actinomycetes, and many of these possess strong activity against gram-positive bacteria. Their biological action involves the inhibition of protein synthesis by binding with ribosomes. The constitutional structure of these antibiotics reveals an unusual wealth of stereochemical features including a large ring lactone possessing an array of substituents with numerous asymmetric centers and conformational possibilities. As a result, these complex organic structures embody a considerable synthetic challenge which until recently seemed beyond the reach of synthetic chemists.[1] A seemingly direct route toward the synthesis of the macrocyclic lactone portion involves cyclization of an appropriate acyclic precursor, although both entropy and polymerization factors tend to disfavor it. As a result, only a handful of synthetically useful methods exist for closure to large ring lactones from the corresponding ω-hydroxy acids.

The reagent, 2,2'-dipyridyl disulfide, and triphenylphosphine form 2-pyridine thiolesters from ω-hydroxy acids, and under high dilution conditions these intermediates cyclize (at 140°C) to macrocyclic lactones in high yield.[3] Addition of silver salts is reported to accelerate this reaction; lactonization is reported to proceed in low yield at room temperature with added silver perchlorate.[4a] However, more detailed subsequent reports indicate that benzene at reflux is required for good yield in one case[4b] and in another case the reaction failed[4c] (for a diolide). 2-Methylpropane-2-thiol esters are also activated by thiophilic metal cations,[5] and this method has recently been used in a total synthesis of the macrolide, methymycin.[6]

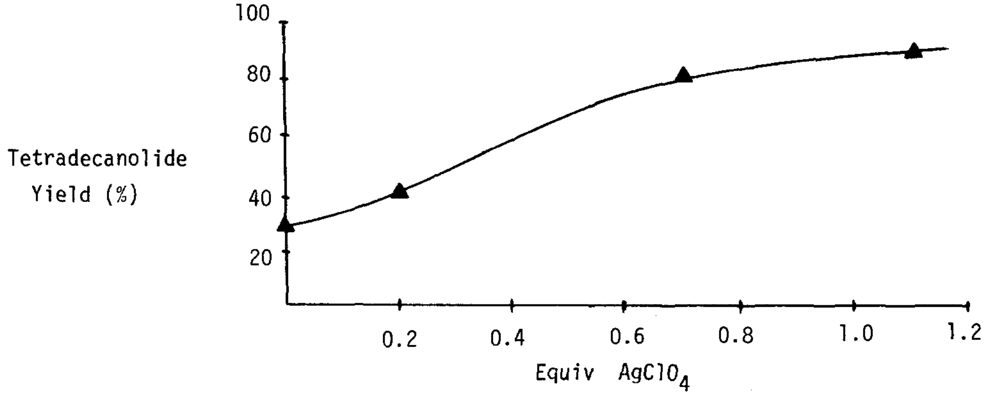
We wish to report that in the presence of silver perchlorate ω-hydroxy thiolesters of 2-amino-4-mercapto-6-methylpyrimidine give good yields of large ring lactones by refluxing in benzene (Scheme I). In a typical procedure, 14-hydroxytetradecanoic acid[7] (20.0 mg, 1.0 equiv), 4,4'-bis(2-amino-6-methylpyrimidyl) disulfide[11,12] (**1**, 34.4 mg, 1.5 equiv), triphenylphosphine (32.2 mg. 1.5 equiv) and dry benzene[13] (3 ml) were brought to reflux for 15 minutes to form the thiolester (2).[14] The heterogeneous mixture was diluted to 10 ml with benzene and added continuously over 5 h to a refluxing solution of anhydrous silver perchlorate (18.6 mg, 1.1 equiv) and hexadecane (gas chromatograph internal standard) in benzene (20 ml; foil-covered flask). The residue in the syringe was rinsed into the reaction mixture and refluxed for 5 h. At this time GC analysis,[15] making appropriate correction for detector response, revealed a 91% yield of tetradecanolide. A more difficult case, 11-hydroxyundecanoic acid,[7] in a similar experiment, gave a 41% yield of undecanolide.

Scheme I



It was found that 1.1 equiv of silver perchlorate gave the optimal yield. Thus, the yields were determined in experiments with different amounts of silver perchlorate for cyclization of 14-hydroxytetradecanoic acid under otherwise identical conditions (vide supra). The results are plotted in Figure I. We observed a 30% yield for lactonization in the absence of silver perchlorate,[16] and addition of more than 1.1 equiv of silver perchlorate did not affect the yield.

Figure I



The method for macrolide ring closure herein described is attractive because it gives good yields under mild conditions. In addition, all reagents are readily prepared, highly crystalline, and easily manipulated in small quantities. Preliminary kinetic experiments indicate that the thiolesters of type **2** undergo lactonization at approximately twice the rate of 2-pyridyl thiolesters on exposure to silver perchlorate.

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7. The ω-hydroxy acids were both synthesized in two steps starting from 11-bromodecanoic acid. 14-Hydroxytetradec-12-ynoic acid was prepared (ref 8) and could be hydrogenated cleanly using nickel boride "P1" (ref 9) as catalyst under 1 atm of hydrogen at room temperature. Pure 14-hydroxytetradecanoic acid (mp 89-90°C) was isolated by column chromatography (silica gel; $CHCl_3$-ether, 1:1) and twice recrystallized (hexane-$CHCl_3$, 19:1). Undecanolide was prepared (ref 10) and saponified to give 11-hydroxyundecanoic acid (mp 66-67°C; from 3:2 hexane-ethyl acetate).

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11. This substance is readily prepared from commercially available material. Thus, 2-amino-4-chloro-6-methylpyrimidine was treated with 5 equiv of NaSH·H_2O in degassed propylene glycol at 140°C for 3 h. The solution was diluted with water and neutralized with acetic acid. The collected precipitate was recrystallized from methanol giving pure 2-amino-4-mercapto-6-methylpyrimidine (mp 312-315°C, d; 72%). The mercaptan was dimerized with iodine (0.5 equiv) in boiling methanol containing potassium carbonate (3 equiv). The crude product can be purified by crystallization from ethanol or by chromatography on silica gel ($CHCl_3$-ethanol, 1:1) to give pure **1** in 56% yield (mp 207-209°C).
12. All new compounds showed nmr, ir, and microanalytical data consistent with the proposed structures.
13. Acetonitrile was equally satisfactory as solvent in the case of 14-hydroxytetradecanoic acid, but gave lower yields with 11-hydroxyundecanoic acid.
14. Formation of the thiolester is incomplete at 23°C after 10 h (*cf.* ref 3) and under the conditions described only 2% lactonization occurred.
15. Glass column (1.8 m x 2 mm) packed with 3% OV-1 on 80/100 Chromosorb W-HP programmed from 150-250°C. An authentic sample of tetradecanolide (ref 3) was prepared for calibration.
16. An 88% yield of tetradecanolide was obtained in the absence of silver salt in refluxing xylenes (140°C).

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