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SYNTHESIS OF LEPIOCHLORIN, AN ANTIBIOTIC METABOLITE OF A FUNGUS CULTIVATED BY ANTS

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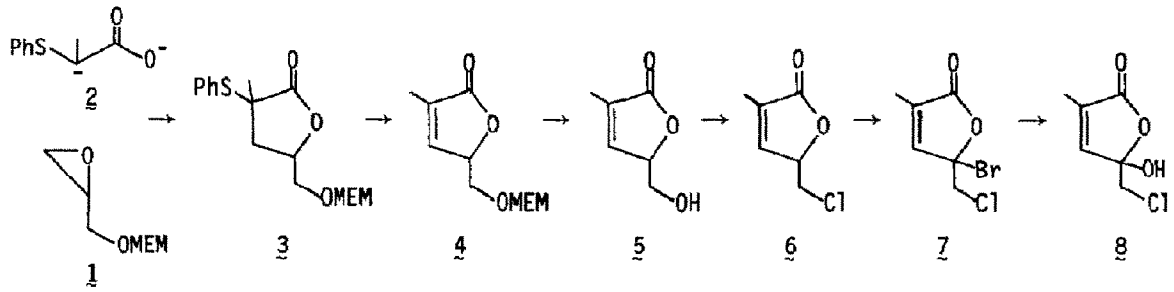
Abstract. The fungal metabolite lepiochlorin has been synthesized from allylmethoxyethoxymethyl ether and the dianion of 2-phenylthiopropionic acid. The resulting lactone was converted to the butenolide and halogen functions introduced by hydrolysis of the MEM group and treatment with thionyl chloride followed by N-bromosuccinimide. Reaction with silver acetate yielded lepiochlorin.

The cultivation of certain fungi as a major source of food by some species of ants has been known for a long time.[1] It was reported recently that one such fungus, a Lepiota species, when grown in the laboratory produces a chlorinated antibiotic, lepiochlorin, for which the structure 8 was proposed.[2]



MEM = $CH_3OCH_2CH_2OCH_2$-

We have confirmed this structure by synthesis as follows: reaction of allyl alcohol with β-methoxyethoxymethyl chloride (1.5 equiv) and diisopropylethylamine (1.5 equiv) in methylene chloride at room temperature for 12 hr gave the "MEM" ether in 80% yield (bp 46-48°C, 2.5 Torr). A solution of the ether in methylene chloride was refluxed overnight with meta-chloroperoxybenzoic acid (1 equiv) to form the epoxide 1 (bp 53-55°C, 0.25 Torr, 79%). 2-Phenylthiopropionic acid was prepared by addition of a solution of ethyl 2-bromopropionate in tetrahydrofuran (THF) to an excess of a suspension of sodium thiophenoxide in the same solvent. The mixture was stirred overnight and the product was isolated by partition between water and methylene

chloride. It was hydrolyzed by refluxing with an aqueous solution of potassium hydroxide to give the acid (bp 125-127°C, 0.1 Torr, 80%).

A solution of the acid in THF (N_2 atmosphere) was treated with lithium diisopropylamide (2 equiv) in THF-diethyl ether at 0°C. After 1 hr the solution of the dianion (2) was cooled to -65°C and a solution of 1 (1.1 equiv) in THF added gradually. The reaction mixture was ke overnight, and the product isolated as an oil which was dissolved in benzene and refluxed in presence of silica with a Dean-Stark trap to give a mixture of isomeric lactones 3 (90%). Th mixture was oxidized with meta-chloroperoxybenzoic acid (1 equiv) and the resulting sulfoxide was refluxed in benzene to give the unsaturated lactone 4 (90%).

Removal of the MEM group in 4 was accomplished by refluxing the ethereal solution with dilute hydrochloric acid (3 N) for 4.5 hr which gave an 85% yield of the alcohol 5: NMR δ 1. t, J 1.5 Hz, 3 H; 3.77 ABX m, 2 H; 5.0 m, 1 H; 7.11 m, 1 H.

The alcohol (5) was refluxed with thionyl chloride (1 equiv) and pyridine (1 equiv) in chloroform to give the corresponding chloride 6: NMR δ 2.01, t, J 1.6 Hz, 3 H; 3.72 ABX m, 2 H; 5.18 m, 1 H; 7.22 m, 1 H; MS m/e 146.0148 (10), $C_6H_7O_2Cl$; 97.0289 (100), $C_5H_5O_2$. The yield varied from 50-80%. Allylic bromination of 6 was effected by refluxing the solution in carbon tetrachloride for about 26 hr in the presence of N-bromosuccinimide (1.5 equiv) and a little benzoyl peroxide. Bromination occurred almost exclusively in the desired position. The bromo-chloro-lactone (7) was obtained as an oil: NMR δ 2.00, d, J 1.5 Hz, 3 H; 4.17 AB m, 2 H; 7.16 m, 1 H.

Treatment of a solution of 7 in THF with an aqueous solution of silver acetate containin a trace of acetic acid afforded a crystalline lactone, mp 74-74.5°C, 65% from 6, MS m/e 162.0 (0.13) $C_6H_7O_3Cl$, 113.0237 (100) $C_5H_5O_3$, whose NMR spectrum was identical to that reported for lepiochlorin (8). Comparison with an authentic sample (mp 74-74.5°C, mixed mp undepressed, infrared spectrum) confirmed the identity.

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References

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