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AN EFFICIENT AND STEREOSPECIFIC TOTAL SYNTHESIS OF *dl*-PROTOLICHESTERINIC ACID

R. E. Damon and R. H. Schlessinger
Department of Chemistry, University of Rochester
Rochester, New York 14627

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Herein, we describe the first stereospecific total synthesis of *dl*-protolichesterinic acid (1) a naturally occurring fungal metabolite which shows antibiotic activity.[1] Our synthesis of 1 is based on an antithetic sequence, *vide infra*, which leads to the butenolide 2, formaldehyde, and a carbonyl anion species derived from formic acid.[2] Salient features of this construction include: (a) utilization of tris(methylthio)methyl lithium as a carbonyl anion equivalent,[3] (b) substitution of both the beta and alpha positions of an electon deficient olefin using a conjugate addition-acylation sequence,[4] (c) realization of the synthetic objective 1 in 64% overall yield starting from the butenolide 2.[5]

To a solution (-78°) of tris(methylthio)methyl lithium[6] (1 equivalent, 1 molar in THF solution) was added (30 minutes) the butenolide 2 (1 equivalent, 1 molar in THF). After stirring four hours at -78°, the temperature of the reaction was increased to -40° and gaseous formaldehyde (generated by pyrolysis of paraformaldehyde, 10 equivalents, at 150 to 160°) was added in a nitrogen stream. The resulting reaction mixture was stirred an additional 1 hour at -40° and then worked-up in the usual manner to give adduct 3 (oil).[7] Treatment of 3 (1 equivalent) with mercuric oxide (5 equivalents) and boron trifluoride etherate (15 equivalents) in 80% aqueous THF solution (0.25 molar, four hours, at 22°) afforded the crystalline lactone acid 4 (mp 92 to 95°) in 80% overall yield from compound 2.

The conversion of 4 into *dl*-protolichesterinic acid was carried out in two steps. First, compound 4 (1 equivalent) was reacted with phosphorus pentachloride (2.2 equivalents) in ether (0.5 molar) for five hours at 22° to give the corresponding chloride 5 (crude mp 67 to 69°) in 95% yield. Second, crude 5 (1 equivalent, 0.25 molar in THF) was treated with potassium hydride (5 equivalents) for two hours at 22°.[8] Standard work-up of this reaction mixture followed by one crystallization from acetic acid gave pure *dl*-protolichesterinic acid (1) (mp 92 to 95°) in 85% yield (80% overall yield from compound 4).

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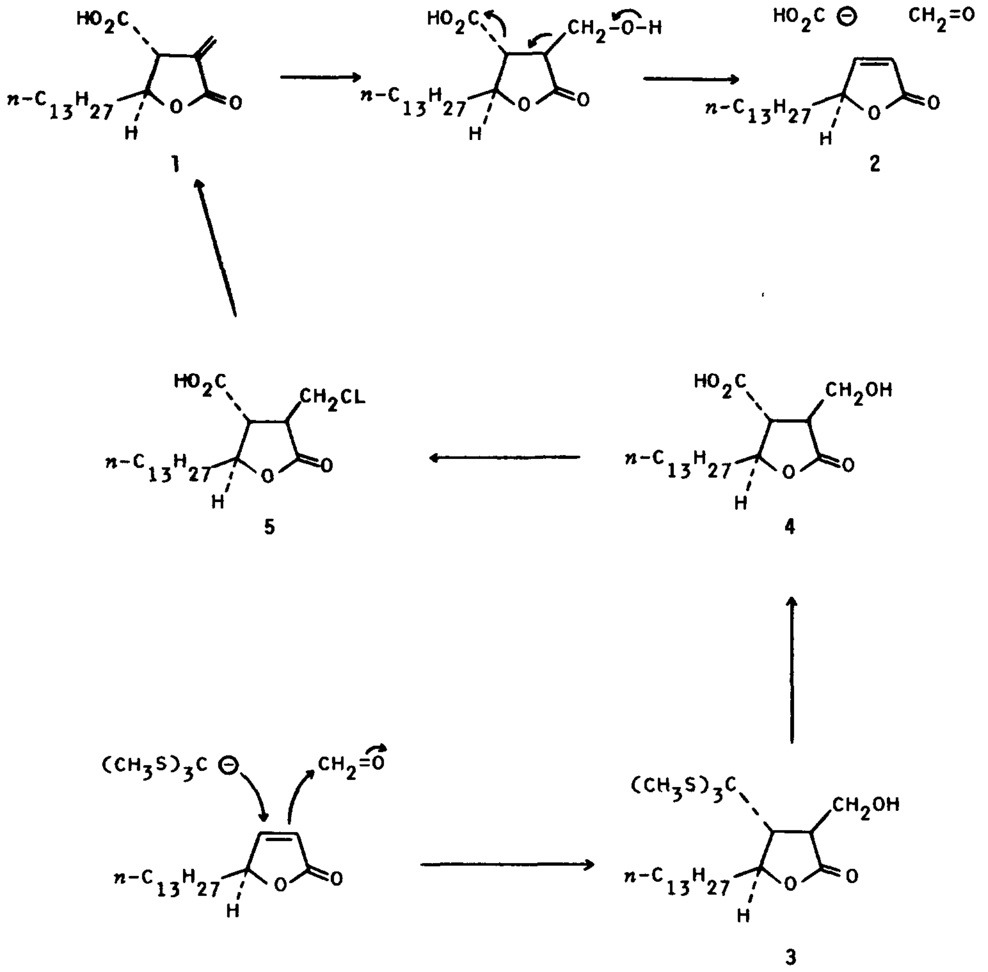
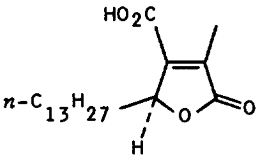
REFERENCES

1. W. B. Turner, "Fungal Metabolites," Academic Press, New York, 1971, pp. 288 to 289.
2. Non-stereospecific total syntheses of *dl*-protolichesterinic acid, conceptually quite different from that described here have been reported by (a) E. E. Van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, 80, 3079 (1958), (b) J. Martin, P. W. Watts, and F. Johnson, *J. Org. Chem.*, 39, 1676 (1974), and (c) R. M. Carlson and A. R. Oyler, *Tetrahedron Letts.*, 4099 (1975).
3. This anion was first reported by D. Seebach, *Angew. Chem. Int. Engl. Ed.*, 6, 442 (1967) who described some alkylation and acylation reactions of this and related anion systems.


HO2C
n-C13H27
H
O
1
CH2-O-H
HO2C ⊖
CH2=O
2
HO2C
CH2CL
5
HO2C
CH2OH
4
(CH3S)3C ⊖
CH2=O
(CH3S)3C
CH2OH
3

4. During the course of this work, A. Rahman, B. Manas, and R. A. J. Smith, *Chem. Comm.*, 216 (1975), reported the conjugate addition reaction of tris (phenylthio)methyl lithium to a variety of unsaturated ketone systems. We have found that tris(phenylthio)methyl lithium does not undergo conjugate addition to either unsaturated esters or lactones even at elevated temperatures. On the other hand, tris(methylthio)methyl lithium undergoes only 1,2-addition to unsaturated ketones. Thus, these two salts complement each other with respect to their synthetic utility.
5. Compound 2 (mp 45 to 47°) was prepared in 80% overall yield following the method outlined by J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 95, 7923 (1973).
6. This anion is best generated by treatment with *n*-butyllithium at -78° in THF solution. At temperatures above -40°, significant decomposition of this anion will occur (see reference 2).
7. All compounds exhibited satisfactory spectral and physical properties.
8. A variety of other base-solvent combinations were examined for this reaction. All other reaction conditions led to the formation of *dl*-lichesterinic acid (*i*) in good to excellent yields.



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