Tetrahedron Letters No. 42, pp 3993 - 3994.
0040-4039/78/1015-3993$02.00/0

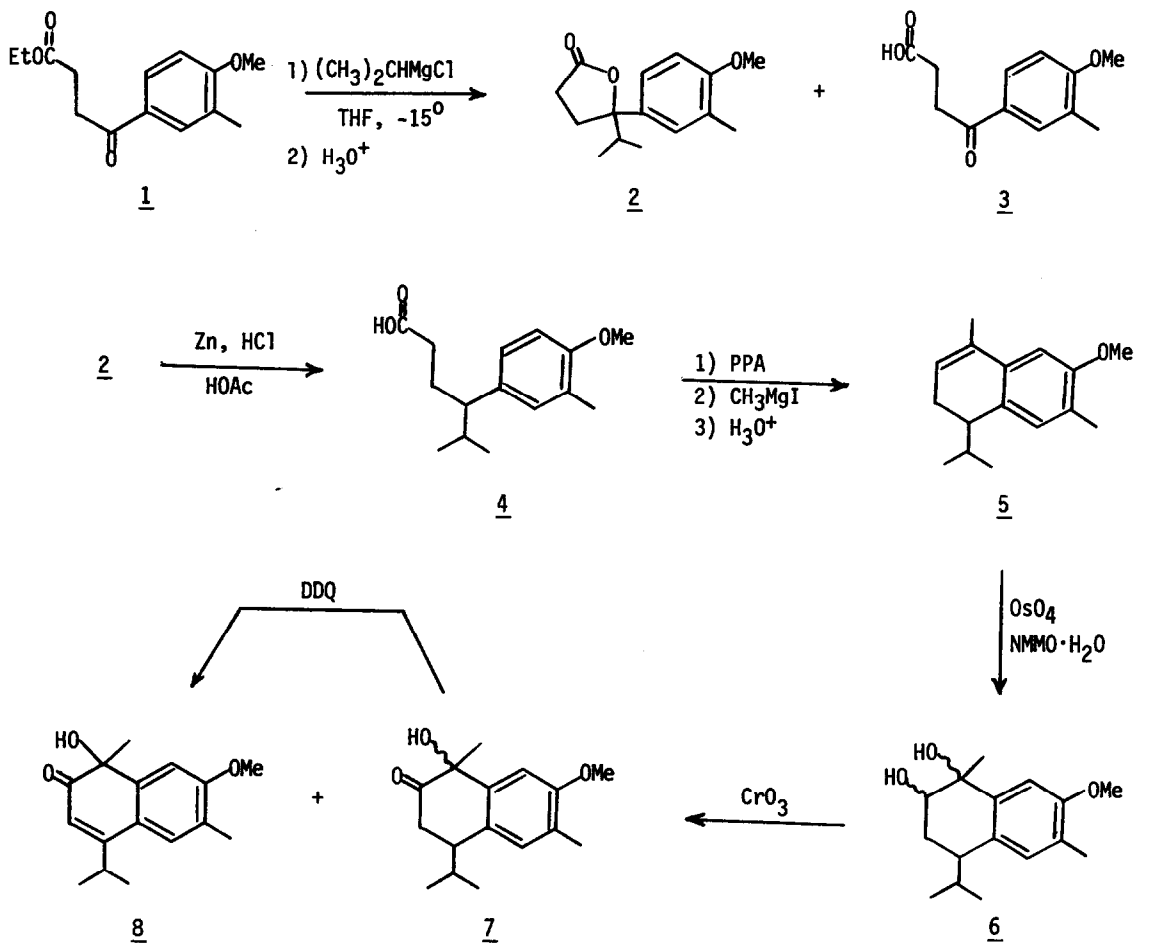
TOTAL SYNTHESIS OF LACINILENE C METHYL ETHER, A PROBABLE BYSSINOTIC AGENT

J. P. McCormick,* J. P. Pachlatko and T. R Schafer
Department of Chemistry, University of Missouri, Columbia, Missouri 65211

Lacinilene C methyl ether was isolated[1] from cotton trash and assigned structure 8. Other groups also have isolated this sesquiterpene and have reported evidence implicating this compound to be a causative agent of byssinosis, a debilitating disease prevalent in the textile industry.[2] Recently, structural assignment 8 was supported by total synthesis.[3] Both to confirm the structure and to provide samples for physiological studies we undertook the total synthesis of racemic 8, as outlined and described below, and have found our synthetic material to be identical with naturally occurring lacinilene C methyl ether.[4]

Alkylation, complicated by facile enolization, of ketoester 1[5] was best accomplished using isopropylmagnesium chloride in THF at -15° for 45 minutes to give a 42% yield, based on readily recycled ketoacid, of purified lactone 2 (m.p. 41-42°).[6] Reduction of the lactone using zinc and HCl in acetic acid provided carboxylic acid 4 nearly quantitatively. Cyclization of the unpurified acid was accomplished by treatment with polyphosphoric acid (PPA) at 80°. Subsequent treatment of the resulting tetralone with methylmagnesium iodide followed by aqueous acid work-up afforded dihydronaphthalene 5 in 87% overall yield, based on lactone 2, after chromatography. Oxidation of 5 to produce 8 was complicated by the ease of generation of aromatic species and by apparent facile oxidative carbon-carbon bond cleavage. Nevertheless, this transformation was accomplished by oxidation of 5, using OsO_4/NMMO·H_2O in acetone,[7] to give a mixture of diastereomeric diols 6, which was best further oxidized using Jones conditions to produce a mixture containing α-ketols 7 and the desired naphthalenone derivative 8 in a 2:1 ratio. Treatment of the reaction mixture with dichlorodicyanobenzoquinone (DDQ) effectively transformed 7 into 8. This three-step procedure afforded 8, after purification by chromatography on silica gel, in an isolated yield of 27%, based on dihydronaphthalene 5. Synthetic 8 (m.p. 102-104°) possesses physical and spectral properties which are in agreement with those of the naturally occurring lacinilene C methyl ether as characterized in this and other laboratories[1,2] and which establish the structure of this substance as 1-hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2(1H)-naphthalenone. Samples of the synthetic material have been made available for *in vitro* and *in vivo* assays, which currently are in progress.

Acknowledgment: We thank Cotton, Inc. for financial support of this work.



1 2 3 4 5 6 7 8

REFERENCES AND FOOTNOTES

1. R. D. Stipanovic, P. J. Wakelyn and A. A. Bell, Phytochemistry, 14, 1041 (1975).
2. a) P. W. Jeffs and D. G. Lynn, J. Org. Chem., 40, 2958 (1975); b) W. S. Lynn, S. Munoz, J.A. Campbell and P. W. Jeffs, Ann. N. Y. Acad. Sci., 221, 163 (1974); c) S. Northup. L. Presant, K. H. Kilburn, J. P. McCormick and J. P. Pachlatko, Fed. Proc., 35, 632 (1976).
3. P. W. Jeffs and D. G. Lynn, Tetrahedron Lett., 1617 (1978).
4. The optical activity and absolute configuration of the natural material are not known. Evidence suggests that in Gossypium hirsutum the substance occurs as a racemic mixture.[2a]
5. W. Cocker and D. M. Sainsbury, J. Chem. Soc., 3319 (1965).
6. Satisfactory C,H combustion analyses, ir, uv, nmr and mass spectral data were obtained for each purified intermediate, in addition to the final product.
7. V. VanRheenen, R. C. Kelly and D. Y. Cha, Tetrahedron Lett., 1973 (1976).

(Received in USA 15 August 1978; received in UK for publication 29 August 1978)