Tetrahedron Letters No. 13, pp 1097 - 1100, 1974. Pergamon Press. Printed in Great Britain.

A NEW METHOD FOR EXCLUSIVE α-METHYLENATION OF FUSED γ-BUTYROLACTONES via PYROLYSIS OF α-PHENYLSULFINYL LACTONES

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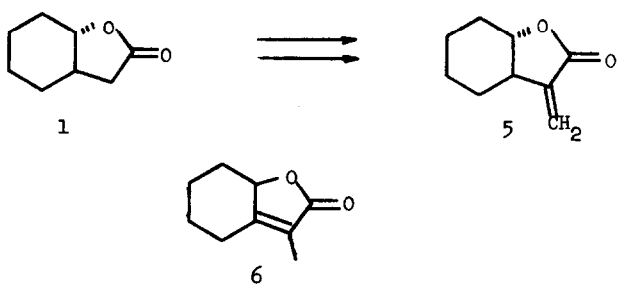
(Received in USA 12 November 1973; received in UK for publication 12 February 1974)

Work in our Laboratories has led to a number of new approaches for the construction of the α-methylene lactone structural unit employing α-hydroxymethyl,[1] α-carboxylic acid,[2] and α-phenylselenyl[3] lactones. Continued interest[4] in methods for the synthesis of α-methylene lactones prompts us to report a novel α-methylenation procedure for conversion of the trans-fused γ-butyrolactone 1 into the trans-fused α-methylene-γ-butyrolactone 5 with complete exclusion of the endocyclic isomer 6.

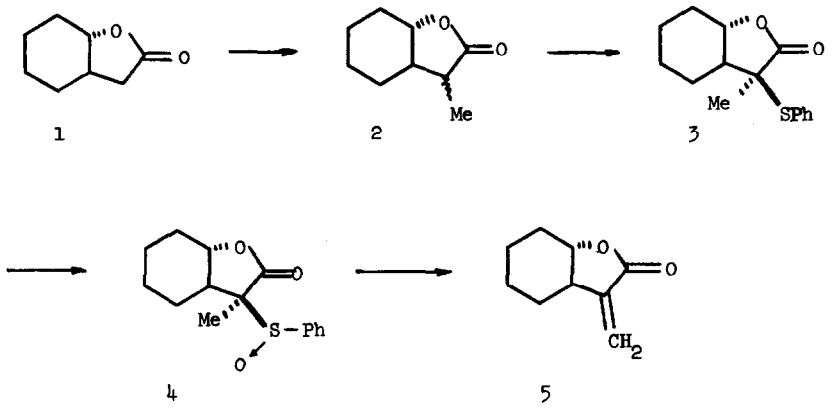


1 5 6

Our approach to α-methylene-γ-butyrolactone 5 utilizes the reported capabilities of sulfoxides to undergo thermal elimination.[5,6] Publication of our α-methylenation sequence is further prompted by the recent disclosure that thermolysis of α-methylsulfinyl lactone I affords butenolide II.[6] Our approach requires a stereospecific introduction of the α-phenylsulfenyl

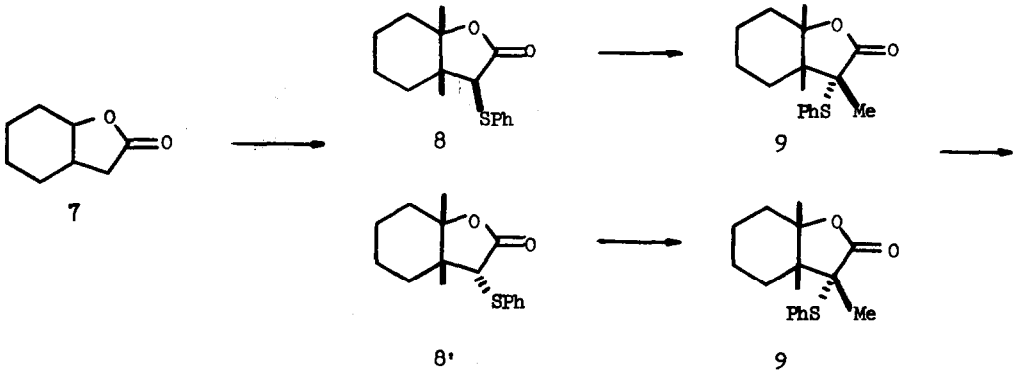
I II

substituent in order to establish the required anti relationship between the α-phenylsulfinyl group and the adjacent methine proton. The above requirement has been realized and we now outline the synthetic sequence.



To a tetrahydrofuran (THF) solution of lithium diisopropylamide (1.2 equivalents)(LDA) at -78° was added very slowly lactone 1 in THF. The lactone enolate at -78° was treated with a THF solution of methyl iodide (1.2 equivalents) containing hexamethylphosphoramide (HMPA) (1 equivalent). After addition was complete, the reaction temperature was raised to -40° and stirring was continued for 3 hours. Work-up afforded a 95% yield of pure monomethylated lactone 2. Stereospecific introduction of the α-phenylsulfenyl group was achieved as follows. The enolate of methylated lactone 2 prepared as described above was treated with diphenyldisulfide[7] (1.2 equivalents) in THF containing HMPA (1.2 equivalents) at -78°. The reaction was stirred for 30 minutes at -78°, warmed to -20° (30 minutes) followed by warming to room temperature. There was obtained an 81% isolated yield of pure crystalline α-phenylsulfenyl lactone 3 mp 120-121°. Oxidation with sodium meta-periodate[8] in aqueous methanol at room temperature afforded a 95% yield of crystalline sulfoxide 4. Thermolysis (ca. 1.5 hours) of the α-phenylsulfinyl lactone 4 proceeded smoothly at 115° (neat) resulting in a 93% yield of pure α-methylene-γ-butyrolactone 5 which was shown to be identical (ir, nmr, tlc, glc) with an authentic sample[1].

A similar sequence of reactions was applied to the cis-fused γ-butyrolactone 7. The success of the α-methylenation sequence is, however, dependent upon the proper stereochemical relationship between the α-phenylsulfinyl substituent and the adjacent methine proton. In order to achieve the required anti relationship in the cis-fused lactone 7, the order of introduction of the α-methyl and α-phenylsulfenyl groups must be reversed. α-Phenylsulfenylation of 7 employing the procedure described above afforded after purification by column chromatography (silica gel) a 2:1 mixture of α-phenylsulfenyl lactones 8 and 8' in 71% isolated yield. Methylation of 8 (as described above) resulted in exclusive formation of pure 9 in 91% isolated yield. As anticipated, methylation of 8' afforded a 70% isolated yield of pure 9. Oxidation of 9 with sodium meta-periodate generated the crystalline sulfoxide 10 in 82% yield. Pyrolysis of the α-phenylsulfinyl lactone 10 resulted in formation of the cis-fused α-methylene-γ-butyrolactone 11 in high yield. Lactone 11 was shown to be identical (ir, nmr, tlc, glc) with an authentic sample prepared by an alternate route.[3,9]



7 8 9 8' 9

10 11

This new α-methylenation procedure for the exclusive introduction of the α-methylene-γ-butyrolactone structural moiety present in a wide variety of sesquiterpenes[10] should prove useful in natural product synthesis. Furthermore, α-phenylsulfenyl lactone 3 represents a stable, protected form of an α-methylene lactone which allows for other structural modifications prior to pyrolysis. Such masked α-methylene lactones would be useful in the synthesis of highly functionalized sesquiterpenes (e.g. vernolepin[11]).

ACKNOWLEDGEMENT. We thank the National Cancer Institute (Public Health Service Research Grant #R01 CA 13689-02) and Eli Lilly and Company for generous support of this research.

References

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4. For an extensive compilation of existing syntheses of the α-methylene lactone structural unit, see P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, J. Amer. Chem. Soc., 95, 6848 (1973).
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9. All compounds exhibited nmr, ir, and mass spectral data in agreement with the assigned structures; in addition, satisfactory C,H analyses were obtained for all compounds.
10. For a complete listing of sesquiterpenes possessing the α-methylene-γ-butyrolactone structural unit see footnote 4.
11. S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, J. Amer. Chem. Soc., 90, 3596 (1968).