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A GENERAL SYNTHESIS OF 2-ALKYL TETRONIC ACIDS

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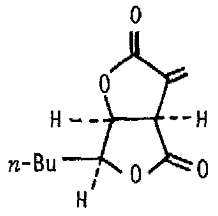
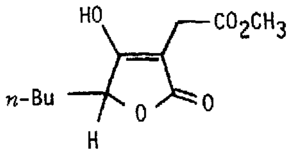
As part of a synthetic program directed towards the stereospecific total synthesis of the mold metabolite Canadensolide (1),[1] we required a simple preparation of the tetronic acid derivative 2. In spite of the fact that a variety of biologically active tetronic acids have been found in nature and have been extensively synthesized,[2] we were unable to find a simple and general method for the preparation of 2-alkyl tetronic acids such as that represented by the structure 3. Herein, we describe an efficient method (Scheme I) for the construction of these acids which has as its salient feature the preparation and utilization of alpha hydroxy thiomethyl esters.[3]



1



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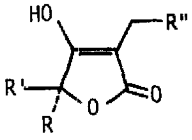
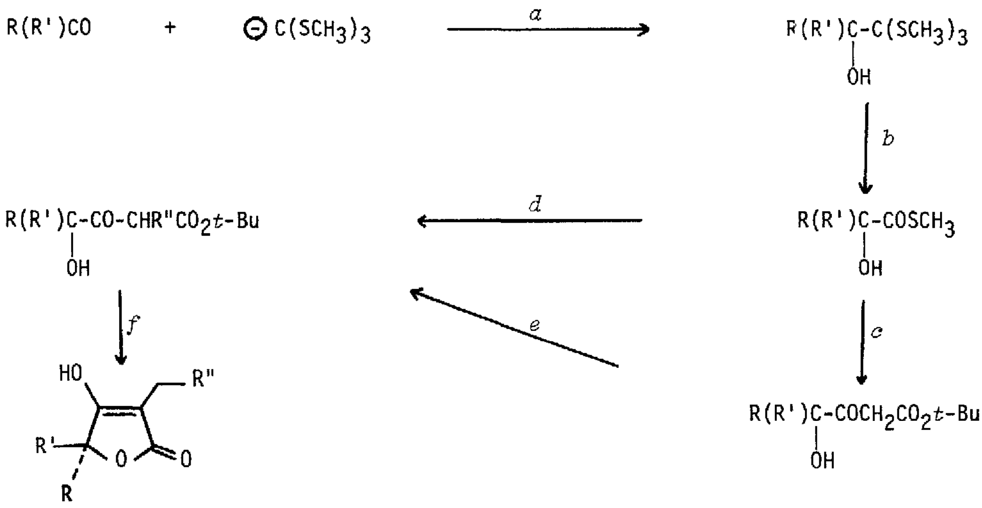


3

Alpha hydroxy thiomethyl esters are conveniently prepared using the following two step reaction sequence (reactions *a* and *b* of Scheme I). To a solution (-78°) of tris(methylthio)methyl

Scheme I

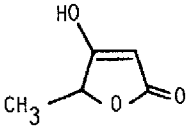


lithium[4] (1 equivalent, 1 molar in THF solution) was added the appropriate aldehyde or ketone in THF solution (2 molar). The resulting mixture was then stirred for 2 hours at -78°, hydrolyzed at -78° with saturated ammonium chloride, and then worked up in the usual manner to give the corresponding tris(methylthio) alcohol adducts in essentially quantitative yields.[5] Conversion of the tris(methylthio) residue into the corresponding thiomethyl ester was accomplished by adding, at 0°, boron trifluoride etherate (3 equivalents) to a mixture of the tris(methylthio) alcohol adduct (1 equivalent) and mercuric oxide (1 equivalent) suspended in a 1 molar solution of THF/H_2O (4:1). After stirring for 15 minutes, the reaction mixture was diluted with ether and filtered to remove a white solid. The filtrate was washed several times with sodium bicarbonate and the basic extracts then back washed with ether and chloroform. The combined organic extracts were dried and then evaporated to give the crude alpha hydroxy thiomethyl ester mixed with mercury salts. Filtration of this mixture through silica gel resulted in the isolation of pure alpha hydroxy thiomethyl ester in yields ranging from 80 to 95%.[6]

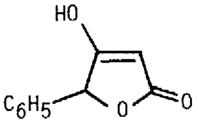
The thiomethyl esters, thus obtained, are excellent acylating agents and react with simple ester enolates in high yield to give the corresponding alpha hydroxy beta keto ester adducts (reactions *c* and *d* of Scheme I). In the case of reaction with the lithium enolate of *t*-butyl acetate (reaction *c* of Scheme I), 3 equivalents of the ester enolate are used (1 molar in THF solution, -78°)[7] and the thiomethyl ester (1 molar in THF) is added dropwise to the ester enolate solution. The temperature of the reaction is then raised to -55° and stirred for 3 hours. Standard work-up yields essentially pure alpha hydroxy beta keto ester adducts in 85 to 95% yields.[8] When more complicated ester enolates are employed (reaction *d* of Scheme I), only one equivalent of the ester enolate is used along with two extra equivalents of base (lithium diisopropylamide). The latter procedure gives comparable yields of the hydroxy keto ester adducts.

It is also possible to alkylate those alpha hydroxy beta keto ester adducts derived from *t*-butylacetate (reaction *e* of Scheme I) with reactive alkylating agents (allyl bromide, methyl iodo acetate, etc.). Typically these alkylation reactions are carried out by adding a 1 molar solution of potassium *t*-butoxide in *t*-butyl alcohol (1 equivalent) to a 1 molar solution of the alpha hydroxy beta keto ester (1 equivalent) dissolved in THF at 25°. After stirring for 10 minutes, the temperature of the reaction mixture is lowered to -40° and the alkylating agent (1 equivalent, neat) is then added and the resulting mixture stirred at -40° for 1 to 3 hours. Work-up in the usual manner gives the alkylated hydroxy keto ester in 80 to 95% yield.[9]

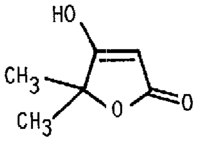
The conversion of these hydroxy keto esters into their corresponding tetronic acid analogues (reaction *f* of Scheme I) is best accomplished under the following conditions. The hydroxy keto ester (1 equivalent, 1 molar in acetonitrile) is treated with 1 equivalent of 70% perchloric acid at 0° for 2 hours. The reaction mixture is then added to saturated sodium bicarbonate (pH 8 to 9) and extracted with ether. The basic aqueous phase is then acidified with 6 N hydrochloric acid (pH 2) and extracted several times with ether. Evaporation of the ether solution, in all but one case, led directly to crystalline tetronic acid. A summary of some representative tetronic acids prepared in this manner together with their overall yields and melting points are given below.



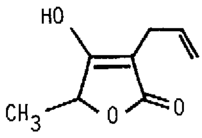
73%; 118-119°



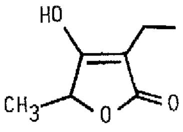
87%; 126-128°



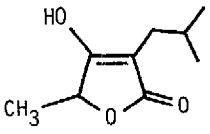
86%; 117-119°



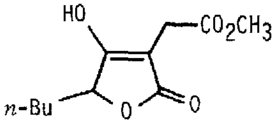
70%; 80-83°



77%; 73-74°



64%; 86-88°



66%; (oil)

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REFERENCES

1. The isolation of canadensolide has been reported by N. J. McCorkindale, J. L. C. Wright, P. W. Brian, S. M. Clarke, and S. A. Hutchison, *Tetrahedron Letts.*, 727 (1968). A synthesis of canadensolide has been reported by M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikshi, *J. Org. Chem.*, 40, 1932 (1975).

2. For leading references on tetronic acids see, a) A. Svendsen, and Per M. Boll, *ibid.*, 40, 1927 (1975); b) J. L. Bloomer and F. E. Kappler, *ibid.*, 39, 113 (1974); and c) L. J. Haynes and J. R. Plimmer, *Quart. Rev.*, 14, 292 (1960).

3. Alpha hydroxy thiomethyl esters are rare organic compounds and the method described herein is the only general procedure we have found for their preparation.

4. This anion was first reported by D. Seebach, *Angew. Chem. Int. Engl. Ed.*, 6, 442 (1976) who described some alkylation and acylation reactions of this and related anion systems. Tris-(methylthio)methyllithium is best generated by treatment of tris(methylthio)methane with *n*-butyllithium in THF at -78°.

5. These compounds were used without purification. Their purity was determined by nmr.

6. Alpha hydroxy thiomethyl esters exhibit broad OH absorption in the infrared at 3500 cm^{-1}, sharp C=O absorption at 1680 cm^{-1}, and SCH_3 resonance between 2.24 and 2.30 ppm in the nmr.

7. Since the products of these reactions before hydrolysis are dianion systems, the stoichiometry of the reaction requires the use of either three equivalents of ester enolate or one equivalent of ester enolate and two equivalents of base.

8. The structure of these materials was confirmed by their infrared and nmr spectra. No attempt was made to purify these compounds before their conversion into tetronic acids.

9. These alkylation reactions are less satisfactory with less reactive alkylating agents as some dialkylation (5 to 25%) is observed in these cases.

10. Satisfactory physical and spectral data were obtained for the tetronic acids described herein. For an extensive discussion of the infrared spectra of tetronic acids see, L. A. Duncanson, *J. Chem. Soc.*, 1207 (1953).