Tetrahedron Letters,Vol.27,No.29,pp 3345-3348,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF (±)-ISOAVENACIOLIDE AND (±)-AVENACIOLIDE

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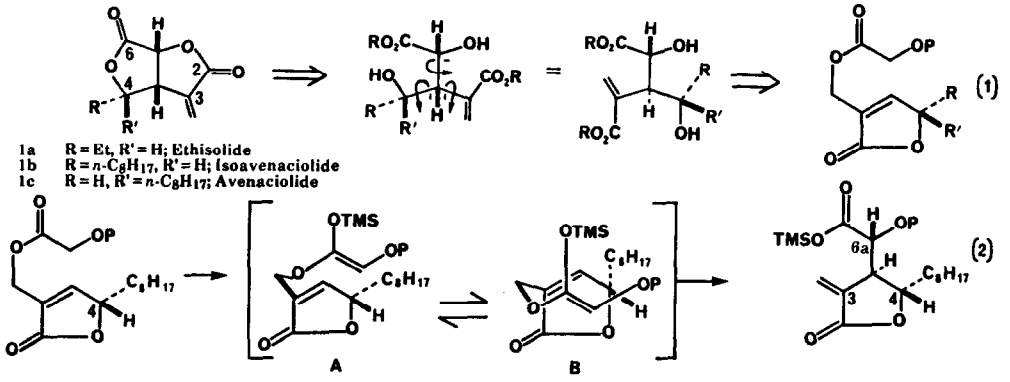
Abstract: The antifungal mold metabolites isoavenaciolide (**1b**) and avenaciolide (**1c**) have been synthesized in racemic form from a common precursor, α-methylene lactone **4**, obtained via a glycolate ester enolate Claisen rearrangement.

We recently reported[2] a total synthesis of the bislactone mold metabolite ethisolide (**1a**)[3a] based upon the antithetic plan presented in eq. 1. The premise that the butenolide glycolate ester shown would give the correct relative stereogenicity at the C(6a), C(3a), and C(4) sites for isoavenaciolide (**1b**)[3] derives support from the analysis in eq. 2, just as observed in the ethisolide (**1a**) synthesis.[2] It was anticipated that the C(4)-substituent would serve as a diastereocontrol element favoring [3,3]-sigmatropic rearrangement involving the less encumbered β-face of the butenolide olefin, as portrayed in conformation **B**. Of course, the resulting C(4)-stereochemistry would be exactly wrong for avenaciolide (**1c**). A surprisingly direct solution to this problem was found, and the production of both (±)-isoavenaciolide (**1b**)[3] and (±)-avenaciolide (**1c**)[4] from a common precursor is described below.[5]



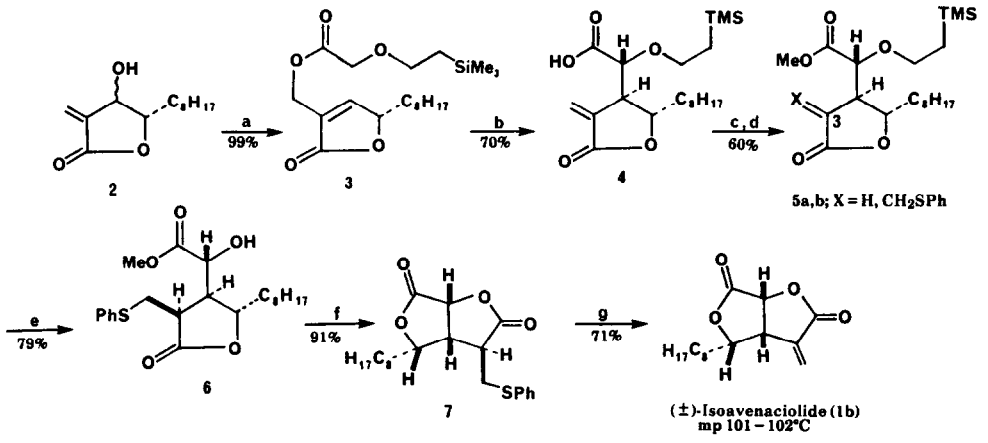
The α-methylene-β-hydroxy-γ-butyrolactone **2** (Scheme I) was prepared as a mixture of diastereomers by the procedure of Seebach.[6] Convergence to a single product in near quantitative yield was observed in the Mitsunobu coupling[7] of **2** and *O*-(2-trimethylsilyl)ethyl glycolic acid.[8] The coupling proceeded cleanly in the S_N2' sense to give the butenolide glycolate ester **3**. Ireland ester enolate Claisen rearrangement[9,10] of this substrate was effected by deprotonation in tetrahydrofuran (THF) at -100°C with lithium hexamethyldisilazide (LHMDS) in the presence of chlorotrimethylsilane (TMSCl).[11] The derived silyl ketene acetal was allowed to warm to ambient temperature to afford, after standard aqueous acid work-up, the rearrangement product **4** in 70% yield as a single diastereomer.[12]

Production of (±)-isoavenaciolide (**1b**) from **4** proceeded as in the ethisolide synthesis[2] in that the α-methylene lactone moiety had to be masked as the thiophenol adduct[13] (*vide infra*). To this end, addition of sodium thiophenoxide in ethanol followed by esterification with ethereal diazomethane converted **4** to an easily separable mixture of C(3) epimers **5a,b** (1.3:1). The major, less polar isomer was treated with $BF_3 \cdot Et_2O$ in CH_2Cl_2 to give the alcohol **6** (79%), which underwent the indicated *bis*-transesterification upon heating at reflux in toluene with camphorsulfonic acid (CSA). The product **7** (mp 120.5–121.5°C), formed in 91% yield, possesses the intact framework of isoavenaciolide.[14] Oxi-

dation to the sulfoxide (*m*-CPBA, $CHCl_3$, -20°C) and thermolysis ($PhCH_3$, 1.25 eq K_2CO_3, reflux, 5 h)[13] gave (±)-isoavenaciolide, mp 101 – 102°C (lit. 99 – 99.5°C,[3c] 99 – 101°C[3d]) in 71% yield.[15]

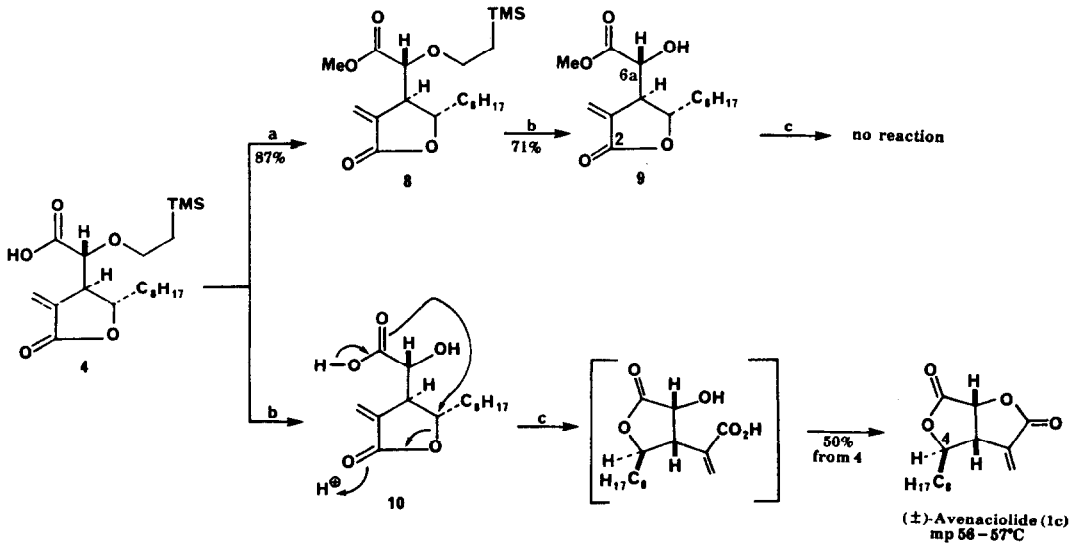
Initially, it was our intention to produce isoavenaciolide without resorting to the masking of the α-methylene unit in **4**. Accordingly (Scheme II), the ester **8** was prepared in 87% yield from **4** by the procedure of Kim,[16] and the β-(trimethylsilyl)ethyl ether was cleaved as before[2,17] to give the alcohol **9**. Although we expected the desired C(2)-transesterification by the C(6a)-hydroxyl (a 5-exo-trigonal process)[18] to be favored over the alternative nucleophilic attack on the β-carbon of the α-methylene lactone (5-endo-trigonal),[18] neither pathway was observed. The hydroxy ester **9** was recovered unchanged in numerous transesterification attempts.

SCHEME I



(a) $Me_3SiCH_2CH_2OCH_2CO_2H$, Ph_3P, DEAD, THF, 0 → 25°C. (b) 1.4 eq LHMDS, Me_3SiCl, THF, -100 → 25°C. (c) PhSNa, EtOH, 0 → 25°C. (d) CH_2N_2, Et_2O, 0 → 25°C. (e) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 → 25°C. (f) CSA, $PhCH_3$, reflux, 120 h. (g) *m*-CPBA, $CHCl_3$, -20°C; $PhCH_3$, 1.25 eq K_2CO_3, reflux, 5 h.

SCHEME II



(a) $ClCO_2CH_3$, Et_3N, DMAP, CH_2Cl_2, 0 → 25°C. (b) $BF_3 \cdot Et_2O$, 0 → 25°C. (c) CSA, $PhCH_3$, reflux.

Remarkably, the corresponding hydroxy acid **10** was reactive under the conditions (CSA, $PhCH_3$, reflux, 36 h) of attempted transesterification. However, the product of this reaction was not isoavenaciolide, but the C(4) epimer, (±)-avenaciolide (**1c**), mp 56–57°C (lit.[4k,n] 55–56°C), formed in 50% overall yield from **4** via the nucleophile/electrophile pairing indicated in **10**.[19]

Thus (±)-isoavenaciolide and (±)-avenaciolide are available from the common precursor **4** in five and two steps, respectively. These results combine with the earlier synthesis of ethisolide[2] to demonstrate a general route to this structurally related trio of mold metabolites.[20]

Acknowledgement. We gratefully acknowledge the National Institutes of Health, the Alfred P. Sloan Foundation, and the National Science Foundation for generous financial support. Industrial matching funds for the NSF Presidential Young Investigator Award from Stuart Pharmaceuticals, Rohm and Haas Company, DuPont, Union Camp, SOHIO, and Hardwicke Chemicals are greatly appreciated. High-field NMR spectra were obtained through the NSF Regional NMR Center at the University of South Carolina (CHE 82-07445). We are grateful to Professor Stuart Schreiber (Yale University) for providing spectra and a sample of (±)-avenaciolide for comparison.

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19. Our racemic avenaciolide was identical by high-field ^{1}H NMR and by ^{13}C NMR to a sample generously supplied by Professor Stuart Schreiber of Yale University.

20. Yields cited are for chromatographically and spectroscopically pure substances. All structural assignments are supported by IR, 400 MHz ^{1}H NMR, ^{13}C NMR, and mass spectrometric and elemental analyses. All chiral substances were produced as racemates; a single enantiomer is shown for simplicity.

(Received in USA 24 March 1986)