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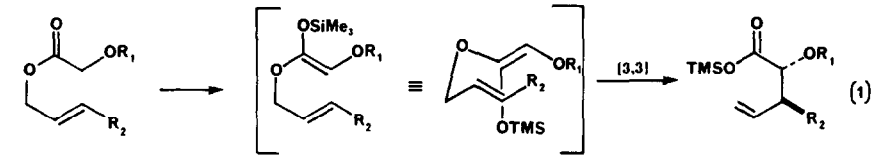
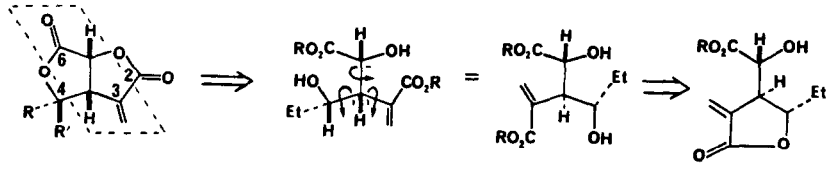
THE ESTER ENOLATE CLAISEN REARRANGEMENT. TOTAL SYNTHESIS OF (±)-ETHISOLIDE

Steven D. Burke*† and Gregory J. Pacofsky
Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208

Abstract: A total synthesis of the mold metabolite ethisolide (**1a**) is described, wherein a glycolate ester enolate Claisen rearrangement and an acid-induced intramolecular bis-transesterification are key steps.

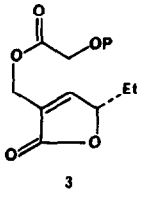
The ester enolate Claisen rearrangement[1] of glycolate esters, illustrated in eq. 1, has proven to be useful for the highly stereoselective production of α-alkoxy-β-alkyl-γ,δ-unsaturated esters.[2] Such an α-alkoxy-β-alkyl-γ,δ-unsaturated carbon chain can be found in the constitution of the three bislactone mold metabolites ethisolide (**1a**),[3a] isoavenaciolide (**1b**),[3] and avenaciolide (**1c**)[4] of which the last two show antifungal activity.[5]





1a R = Et, R' = H; Ethisolide
1b R = *n*-C_8H_{17}, R' = H; Isoavenaciolide
1c R = H, R' = *n*-C_8H_{17}; Avenaciolide

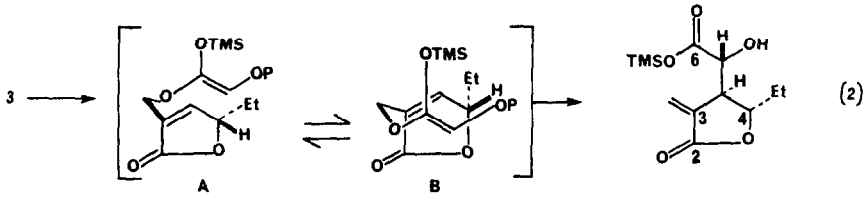
Scheme I



†Research Fellow of the Alfred P. Sloan Foundation; recipient of a National Science Foundation Presidential Young Investigator Award.

In Scheme I there is presented an analysis showing how the enclosed subunit for ethisolide (**1a**) correlates with that described in eq. 1. Retrosynthetic alcoholysis of the two lactones in **1a** leads to the corresponding bis (hydroxy ester). Rotation of 180° about the three indicated σ–bonds leads to an equivalent structure more obviously related to the product in eq. 1. Finally, lactonization of the indicated residues and application of a retrograde Claisen rearrangement affords the butenolide glycolate ester **3**.

The expectation that enolate Claisen rearrangement of **3** would lead to the desired relative stereochemistry at the C(6a), C(3a), and C(4) sites was based upon consideration of the chair-like rearrangement transition states **A** and **B** in eq. 2. On steric grounds, rearrangement via **A** involving the α-face of the butenolide olefin was expected to be disfavored. The rearrangement via the diastereomeric transition state **B**, however, would involve the less hindered β-face of the butenolide olefin and would afford the desired stereochemical outcome shown for the three contiguous asymmetric centers. The demonstration of the latter stereocontrol element and its application to the first total synthesis of (±)-ethisolide are recorded herein.

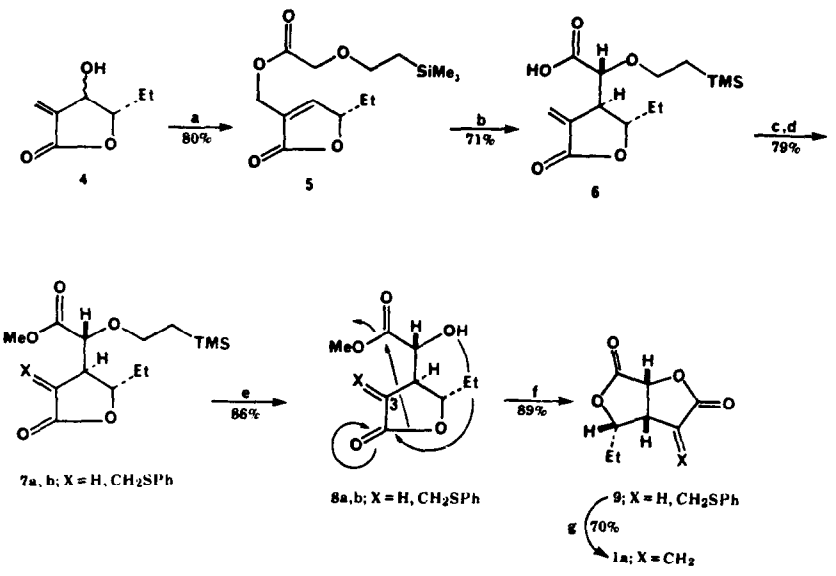


The β-hydroxy-α-methylene lactone **4** (Scheme II)[6] was prepared as a 3:1 mixture of diastereomers by the procedure of Seebach.[7] A Mitsunobu-type[8] coupling between **4** and *O*-(2-trimethylsilyl)ethyl glycolic acid[9] proceeded cleanly in the S_N2' sense to give in 80% yield the enolate Claisen substrate **5**. Deprotonation of the protected glycolate ester was effected with lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF) in the presence of chlorotrimethylsilane at -100°C.[10] The derived silyl ketene acetal underwent the [3,3]-sigmatropic shift as the reaction mixture was allowed to warm to 25°C. Standard work-up with 5% aq HCl afforded the carboxylic acid rearrangement product **6** in 71% yield in >20:1 diastereomeric excess.[11] The α-methylene lactone moiety was temporarily protected as the thiophenol adduct,[12] leading, after diazomethane esterification, to a 79% yield of the diastereomers **7a,b**. The β-(trimethylsilyl)ethyl ether[13] was cleaved with $BF_3 \cdot Et_2O$ in CH_2Cl_2 (0 → 25°C, 2 h, 86%) to give the easily separable diastereomers **8a** and **8b** (1:1).

The stereochemistry and functionality necessary for the production of (±)-ethisolide was thus available in the five steps described. The bis-transesterification indicated by the arrows in **8a,b** was effected with camphorsulfonic acid (CSA) in refluxing toluene (36 h) to give **9** in 89% yield, but on only one of the C(3) epimers. The other diastereomer failed to react under these conditions.[14]

With the ethisolide skeleton established, it remained to unmask the α-methylene lactone by the established procedure.[12] Oxidation of **9** (*m*-CPBA, $CHCl_3$, -20°C, 20 min) and thermolysis of the crude sulfoxide in refluxing toluene (6 h) gave in 70% yield (±)-ethisolide (**1a**), mp 108-110°C, with spectral data fully consistent with those published.[3a]

Scheme II



(a) $Me_3SiCH_2CH_2OCH_2CO_2H$, Ph_3P, DEAD, THF, 0 → 25°C, 1 h. (b) LHMDS, Me_3SiCl, THF, -100 → 25°C, 15.5 h; 5% aq HCl. (c) PhSNa, EtOH, 0 → 25°C, 1 h. (d) CH_2N_2, Et_2O, 0 → 25°C. (e) 4 eq $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 → 25°C, 2 h. (f) CSA, $PhCH_3$, reflux, 36 h. (g) *m*-CPBA, $CHCl_3$, -20°C, 20 min; $PhCH_3$, 4 eq K_2CO_3, reflux, 6 h.

This relatively short sequence thus allows easy synthetic access to a highly functionalized class of mold metabolites and demonstrates a high level of relative asymmetric induction by a stereocenter [C(4)] which dictates diastereofacial rather than conformational preference in a sigmatropic rearrangement. Application of this route to the syntheses of the biologically active congeners isoavenaciolide (**1b**)[3] and avenaciolide (**1c**)[4] is in progress.

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14. We are attempting to obtain crystallographic data to enable us to assign the structures of **8a** and **8b** so that this reactivity difference can be explained.

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