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A SYNTHETIC PRECURSOR OF (±)-TRICHODERMIN

Steven C. Welch and Rayman Y. Wong

Department of Chemistry

University of Houston

Houston, Texas 77004

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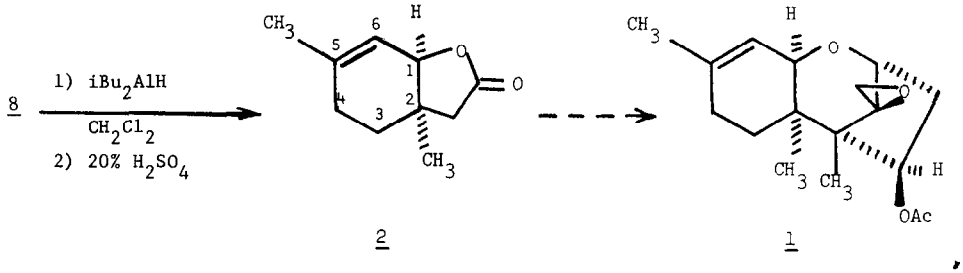
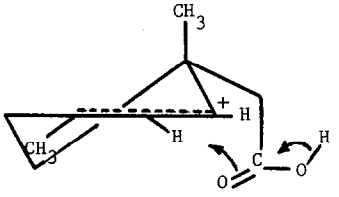
A number of sesquiterpenoid mold metabolites have been isolated and characterized recently. One important class of these naturally occurring substances, the trichothecane group, possesses an eminent degree of phytotoxic activity against certain pathogenic fungi.[1] The least structurally complicated member of this important class of mold metabolites is (-)-trichodermin (1). This tricyclic sesquiterpenoid was isolated out of the culture fluid of a strain of trichoderma virida. The structure and absolute stereochemistry of this unique phytotoxic metabolite was determined from chemical, spectroscopic, and X-ray diffraction data.[2,3,4] We wish to report, herein, the synthesis of a (±)-trichodermin intermediate, (±)-lactone 2.[5,6]

Synthetic Strategy



In our synthetic strategy we envisioned using the stereochemistry at position C-2 in enone-acid 8 to direct the stereochemistry of the allylic carbon-oxygen bond in trichodermin

by forming a cis-fused γ-lactone 2. The lactone ring can then be expanded and developed to produce (±)-trichodermin (1). This cis-fused γ-lactone might be constructed by a preferential, nonstereoselective hydride reduction of the enone function followed by an acid catalyzed intramolecular cyclization of the newly generated allylic alcohol moiety with the carboxylic acid group in close proximity. Examination of Dreiding models suggests that if this lactonization proceeds via an allylic carbonium ion intermediate 8a the cyclization will be highly regiostereoselective and should produce the desired cis-fused γ-lactone 2.



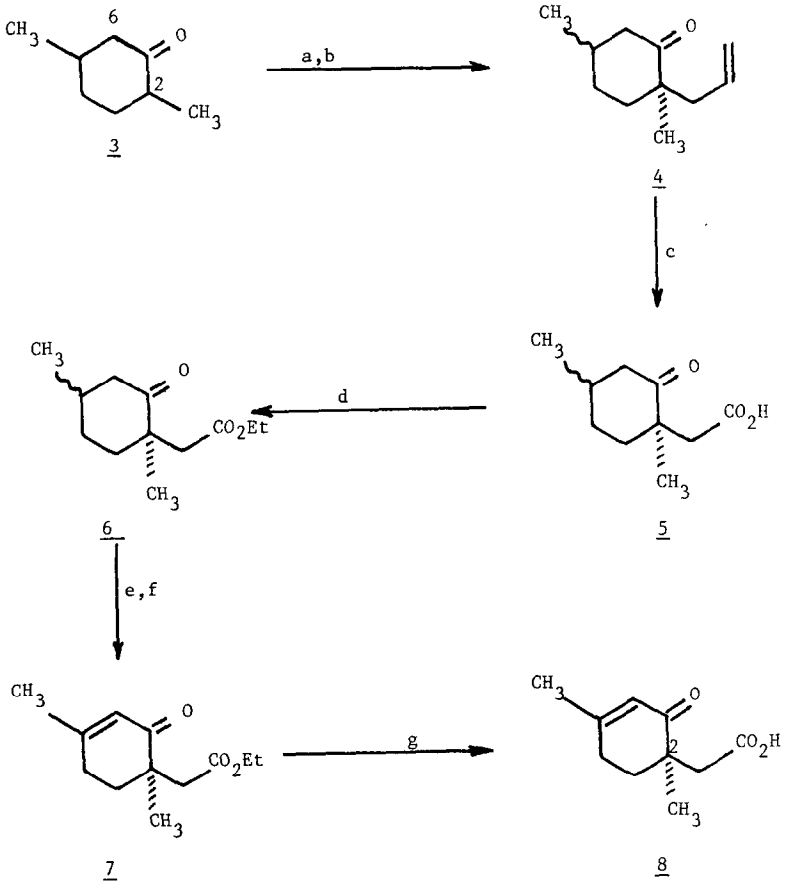
8a

The starting material chosen for the synthesis of lactone 2 is 2,5-dimethylcyclohexanone (3). Carefully controlled alkylation of ketone 3 using sodium hydride in 1,2-dimethoxyethane (DME) followed by allyl bromide produces keto-olefin 4 in 74% yield. This material does not appear to be contaminated to any significant extent by a monoalkylated product at position C-6.[8] This was confirmed by spectroscopic data, glc analysis, and further chemical transformations.[9] Oxidative cleavage of olefin 4 with a catalytic amount of ruthenium tetroxide and five equivalents of sodium metaperiodate in aqueous-t-butanol (4.5:1) gave keto acid 5 in 93% yield.[10] The carboxylic acid was then esterified quantitatively by treatment with ethyl iodide, anhydrous potassium carbonate in refluxing acetone.[11] Bromination of keto-ester 6 in glacial acetic acid followed by dehydrohalogenation of the crude bromoketone using anhydrous calcium carbonate in refluxing N,N-dimethylacetamide (DMA) produces enone-ester 7 in 88% yield.[12] Saponification of ester 7 with potassium hydroxide in aqueous-ethanol gives keto-acid 8 in 95% yield.

The reductive cyclization of keto-acid 8 to lactone 2 was accomplished as follows. Sequential treatment of enone-acid 8 with two equivalents of diisobutylaluminum hydride[13] in benzene-dichloromethane followed by quenching with 20% sulfuric acid produces the crystalline γ-lactone 2 in 89% yield, mp 48-49° [lit. mp 47-48°][6]. All spectral data ir (CCl_4) 1775 cm^{-1} (γ-lactone), 1670 cm^{-1} (C=C); nmr (CCl_4) δ 1.14 (σ, $-CH_3$), 1.75 (bs,vinyl-CH_3), 2.23 (s, $-CH_2COO$), 4.27 (m, CH-O), 5.47 (m,-C=CH-) are consistent with the cis-fused γ-lactone structure, no trans-fused γ-lactone was observed or isolated. The effectiveness and stereoselectivity of this

lactonization is confirmed by the reported alternative synthetic sequence.[6]

We are currently investigating alternative methods of converting lactone 2 to (±)-trichodermin (1) in a limited number of specific steps.



a) NaH, DME; b) $BrCH_2CH=CH_2$; c) RuO_4, $NaIO_4$, H_2O, t-BuOH; d) EtI, K_2CO_3, acetone; e) Br_2, HOAc; f) $CaCO_3$, DMA; g) KOH, EtOH, H_2O.

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References

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2) W. O. Gotfredsen and S. Vangedal, Proc. Chem. Soc., 188 (1964); Acta Chem. Scand., 19, 1088 (1965).

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5) During the course of these laboratory investigations an elegant total synthesis of (±)-trichodermin (1) via (±)-lactone 2 was reported; E. W. Colvin, R. A. Raphael, and J. S. Roberts, Chem. Commun., 853 (1971). Although the overall synthetic goal of our scheme is the same as that reported, our choice of starting material and synthetic route to both (±)-lactone and (±)-trichodermin are different.

6) All new compounds reported, herein, gave satisfactory elemental analyses. All structures, except (-)-trichodermin (1) that are represented as one enantiomer are, in fact, racemic.

7) Reduction of piperitone with lithium aluminum hydride produces a 64%:36% ratio of trans- to cis-piperitol respectively as reported by A. K. Macbeth and J. S. Shannon, J. Chem. Soc., 2852 (1952), and, therefore, the preferential reduction of enone-acid 8 was not expected to occur stereoselectively.

8) For two excellent reviews on alkylation of unsymmetrical ketones of this type, see: J. M. Conia, Rec. of Chem. Prog., 24, 42 (1963); H. O. House, Rec. of Chem. Prog., 28, 98 (1967).

9) glc analyses were conducted using 1/8 in.x 6 ft., stainless steel columns, with (a) 3% SE-30 on Vapaport 30, 100/120 mesh; (b) 5% FFAP on Varaport 30, 80/100 mesh; (c) 5% OV-17 on Varaport 30, 80/100 mesh.

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13) We would like to thank Dr. S. C. Watson of Texas Alkyls, Inc., Deer Park, Texas 77536 for the gracious gift of diisobutylaluminum hydride in benzene.