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Synthesis of farinomalein

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ABSTRACT

Farinomalein, a recently isolated maleimide from *Paecilomyces farinosus*, was synthesized in two steps from a readily available γ-hydroxybutenolide.

Entomopathogenic fungi such as *Paecilomyces farinosus* are a valuable source of bioactive natural products.[1–4] In the process of screening natural products for anti-oomycete activity, Nihira[1] isolated farinomalein (**1**), a relatively simple maleimide, from a strain of *P. farinosus* (Fig. 1). Farinomalein had activity comparable to the antibiotic amphotericin B in a bioassay for the inhibition of *Phytophthora sojae*, a plant pathogen that causes 1–2 billion dollars worth of damage to soybean crops.[5,6] We envisioned a straightforward strategy for the synthesis of **1** and related maleimides based on γ-hydroxybutenolides as starting materials.

The γ-hydroxybutenolide (5-hydroxy-2(5*H*)-furanone) moiety is found in many bioactive natural products, including manoalide and dysidolide.[7] γ-Hydroxybutenolides are readily prepared by several routes, primarily by the oxidation of furans and by Mannich-type reactions.[8–11] Although most work in this area has concentrated on the synthesis of γ-hydroxybutenolides, there is growing interest in the application of these compounds as synthetic intermediates for the synthesis of heterocycles and other compounds.[12–14] We foresaw γ-hydroxybutenolide **2**[8] (Scheme 1) as the starting material for two compounds that were potential intermediates for the synthesis of **1**: γ-hydroxybutenamide **3** and anhydride **4**.

γ-Hydroxybutenolide **2** is readily prepared from isovaleraldehyde and glyoxylic acid in one step (Scheme 2).[8] We typically prepare **2** in 10 g batches in 65–75% yield (the literature yield is slightly higher). The spectroscopic evidence points to the closed form as the major tautomer, but there is an indirect evidence for the rapid equilibration with the open chain tautomer.[15]

The reaction of γ-hydroxybutenolides with amines proceeds in a variety of modes.[8,12,16–20] In the case of the reaction of simple aliphatic primary amines with γ-hydroxybutenolides, two conflicting reports have emerged. In Faulkner's investigation of the reaction of phospholipase A_2 inhibitor luffariellolide with primary amines, γ-aminobutenolides were the proposed products,[16] whereas Ojika described the reaction of histamine and tryptamine with

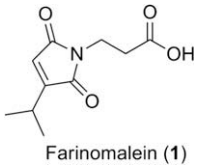
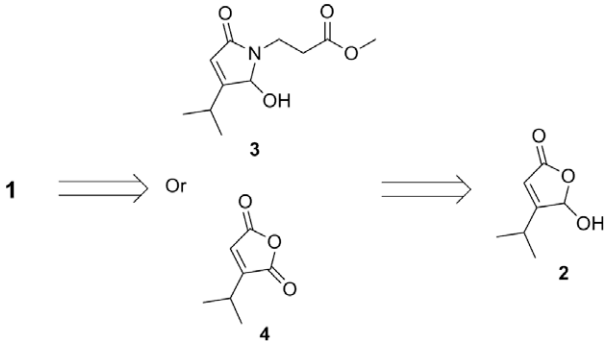
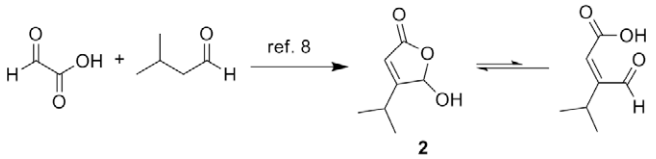


Figure 1. Structure of farinomalein (**1**)



Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis and tautomerism of **2**.

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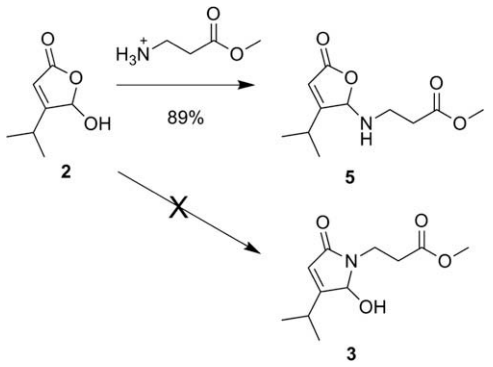
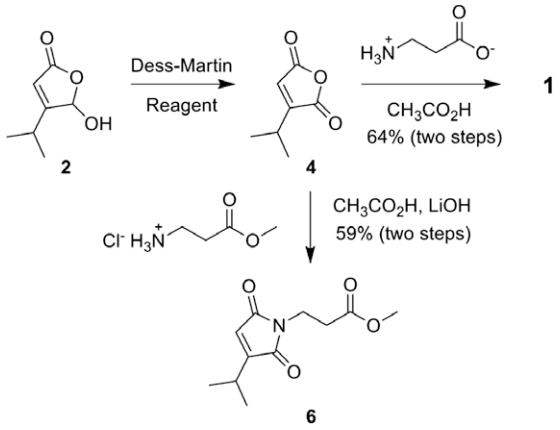


Scheme 3. Reaction of **2** with the methyl ester of β-alanine.



Scheme 4. Synthesis of farinomalein **1** and methyl ester **6**.

γ-hydroxybutenolides spongiabutenolide A and B as giving γ-hydroxybutenamides.[17] We have found the reaction of the methyl ester of β-alanine with **2** gave γ-aminobutenolide **5** (89% yield; Scheme 3).[21] The unsuccessful synthesis of **3** from **2** prompted us to consider the anhydride route to **1**.

There is literature precedent for the conversion of γ-hydroxybutenolides into anhydrides, but there are no systematic studies of this reaction.[22–26] Our study of the oxidation of **2** with some of the more common oxidants (PCC and $KMnO_4$) typically gave moderate yields of known anhydride **4**,[27] which was difficult to purify. The Dess–Martin periodinate oxidation of **2** to **4** proceeded cleanly, and just as importantly, the removal of the excess Dess–Martin periodinate and the periodinate side product was readily accomplished by a simple hexane extraction (Scheme 4). Although the conversion of an anhydride into a maleimide is typically performed in a two-step process as described by Rich,[28] the simplified one-step procedure recently optimized by Christmann[29] was appealing. Without further purification, anhydride **4** was used in the subsequent reaction with β-alanine in refluxing acetic acid to give farinomalein **1** (64% yield from **2**).[30] The spectroscopic properties of synthetic **1** were consistent with the reported data for **1** isolated from *P. farinosus*. The methyl ester of farinomalein (**6**), which was described in the original report of the isolation of **1**,[1] was also prepared in a similar fashion (59% yield from **2**).[31]

The two-step synthesis of maleimide **1** from γ-hydroxybutenolide **2** represents a new strategy for the synthesis of an important class of bioactive maleimides.[32] With the ready availability of γ-hydroxybutenolides from various sources, the synthesis of diverse maleimides is possible. The report by Lattmann[20] describing the one-step synthesis of maleimides from mucochloric acid and formamides appears to be a useful method for the synthesis of a narrow range of biologically active compounds but does not appear to be applicable for the synthesis of farinomalein and related maleimides. Scale-up of the oxidation (**2**→**4**) is limited by the expense and potential hazards of handling large quantities of the Dess–Martin periodinate, so we are continuing to investigate alternative oxidants for the oxidation of γ-hydroxybutenolides to anhydrides.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.083.

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21. *Spectral data for* **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77 (t, J = 1.5 Hz, 1H), 5.62 (dd, J = 1.1, 9.5 Hz, 1H), 3.65 (s, 3H), 3.01 (br q, J = 6.3 Hz, 2H), 2.61 (d of septets, J = 1.5, 6.9 Hz, 1H), 2.50 (m, 2H), 2.28 (m, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 172.8, 171.8, 116.9, 94.5, 51.7, 40.7, 35.2, 27.9, 21.3, 20.1. Not only were the coupling patterns more consistent with the proposed structure **5**, but also the γ-carbon resonated at δ 94.5, which is ~10 ppm higher than the expected carbon shift for the γ-carbon of a compound such as **3**. See: Mangaleswaran, S.; Argade, N. P. *Synthesis* **2004**, 1560–1562.
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30. *Experimental procedure for the synthesis of* **1**: γ-Hydroxybutenolide **2** (1.066 g, 7.50 mmol) was dissolved in CH_2Cl_2 (15 mL) and Dess–Martin periodinate (30 mL of a 15% solution in CH_2Cl_2, 6.14 g, 19.2 mmol) was added over 10 min.

After stirring at 22 °C for 18 h, the volatiles were removed on the rotary evaporator. The oily solid was extracted with hexanes (5 × 50 mL), and the solvent was removed on the rotary evaporator to give crude **3**. Without further purification, **3** was dissolved in CH_3CO_2H (7.5 mL) and β-alanine (0.80 g, 9.2 mmol) was added. The reaction mixture was refluxed for 1.5 h, allowed to cool to 60 °C, and the solvent was removed under vacuum. The crude product was taken up in EtOAc (100 mL), washed with 0.2 M HCl/brine (60 mL), dried over Na_2SO_4, and concentrated on the rotary evaporator to give crude **1**. Column chromatography (silica gel; 25 to 50% Et_2O in hexanes) gave pure farinomalein (1.010 g, 64% yield) as a white solid: mp 75–77 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.36 (d, J = 1.5 Hz, 1H), 3.73 (t, J = 7.3 Hz, 2H), 2.79 (d of septets, J = 1.5, 6.9 Hz, 1H), 2.57 (t, J = 7.2 Hz, 2H), 1.20 (d, J = 7.0 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.7, 172.4, 172.2, 157.2, 125.9, 34.8, 33.7, 27.1, 21.2. Chemical shifts were referenced to the solvent signals (δ_H 3.3 and δ_C 49.1) as done in Ref. 1.

31. *Spectral data for* **6**: ^{1}H NMR (CD_3OD, 400 MHz) δ 6.37 (d, J = 1.8 Hz, 1H), 3.74 (t, J = 7.0 Hz, 2H), 3.63 (s, 3H), 2.79 (d of septets, J = 1.8, 6.8 Hz, 1H), 2.59 (t, J = 7.3 Hz, 2H), 1.20 (d, J = 7.0 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.2, 172.4, 172.2, 157.2, 126.0, 51.4, 34.7, 33.8, 27.1, 21.2. Unlike the literature report,[1] we saw resolution of all of the carbonyl carbons of **6** in the ^{13}C NMR. In addition, the values for the downfield carbons did not match the literature report, which we attribute to concentration effects.
32. The oxidation of methyl lambertianate, a naturally occurring 3-substituted furan, to the corresponding anhydride followed by the reaction of primary amines is a closely related strategy for the synthesis of maleimides. Kharitonov, Y. V.; Shul'ts, E. E.; Shakirov, M. M.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2006**, *42*, 707–718.