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Total synthesis of farylhydrazones A and B

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ABSTRACT

Herein we report a concise total synthesis of farylhydrazones A and B, naturally occurring phenylhydrazones recently isolated from cultures of the *Cordyceps*-colonizing fungus *Isaria farinosa*, completed in six and five steps respectively starting from 2-nitrobenzoic acid. The synthesis is completely scalable, and highly convergent—making it adaptable for the preparation of analogues and investigation into the biological activity of these unique natural products.

Farylhydrazones A (**1**) and B (**2**) (Fig. 1) are naturally occurring phenylhydrazones recently isolated from cultures of the *Cordyceps*-colonizing fungus *Isaria farinosa*.[1] *Cordyceps sinensis*, recently reclassified as *Ophiocordyceps sinesis* and known in western culture as 'caterpillar fungus', contains a diverse array of interesting natural products with potent biological activity.[2] Caterpillar fungus has been extensively used in Chinese, Tibetan, and Nepalese traditional medicine for hundreds of years, with the oldest documented cases dating back to the 15th century.[3]

Hydrazones have been a useful scaffold in medicinal chemistry for many years. Hydrazone-containing organic compounds have been shown to possess potent biological activity including: antitumor, analgesic, antidepressant, antiviral, antimicrobial, and antimalarial.[4] Although initial testing of the antimicrobial and cytotoxic activities of **1** and **2** came back negative,[1] we were interested in developing a short, scalable, and convergent synthesis of **1** and **2** in order to make large amounts of the farylhydrazones and analogues for thorough biological testing. In light of the large number of medicinally useful compounds containing the hydrazone moiety, we are hopeful that farylhydrazones **1** and **2**, or derivatives thereof, might be found to possess interesting biological activity.

During the initial planning toward the synthesis of **1** and **2**, we were desirous to make the process as convergent as possible—thus making it highly amendable for analogue preparation. Retrosynthetic analysis for the synthesis of **1** and **2** is straightforward and shown in Figure 1. Upon inspection of natural products **1** and **2**, it is clear that **1** can be readily derived from **2** via a peptide coupling with a suitably protected glycine. Coupling of other amino acids, both natural and unnatural, would be a rapid and easy way to construct a library of farylhydrazone A analogues for biological testing. Disconnection of the hydrazone bond in **2** would give rise to pyruvic acid (**3**) and hydrazine **4**. Formation of hydrazine **4** was envisioned to be readily made from the commercially available and inexpensive[5] *o*-nitrobenzoic acid **5**. Analogues of **3** and **5** could theoretically be used in the same synthetic sequence for analogues to be used in structure–activity relationship (SAR) studies.

The synthesis of the farylhydrazones commenced with protection of the carboxylic acid in **5** as the methyl ester (Scheme 1). Esterification proceeded slowly (5 days) due to the deactivated nature of the arene, but provided the desired methyl ester in

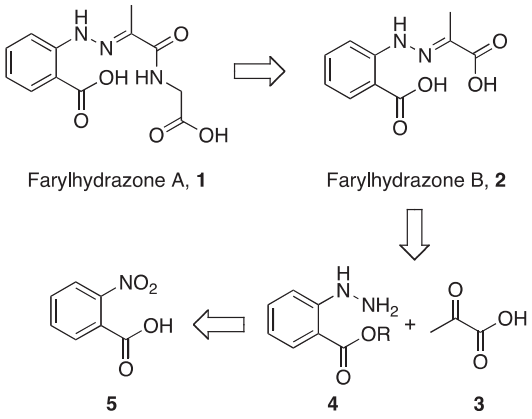

Figure 1. The farylhydrazones and retrosynthetic analysis.

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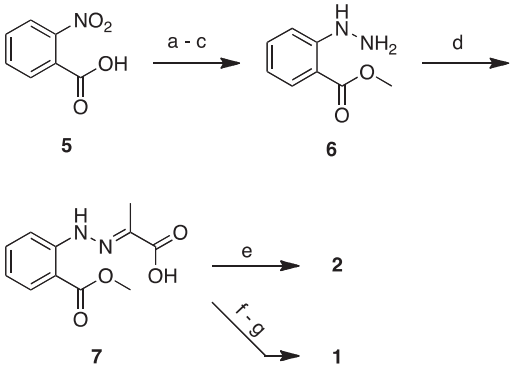

Scheme 1. Reagents and conditions: (a) H_2SO_4, MeOH, 65 °C, 5 d, 90%; (b) Zn dust (5.0 equiv), NH_4Cl (10.0 equiv), acetone/water (4:1), 40 °C, 12 h, 74%; (c) $NaNO_2$ (0.90 equiv), $SnCl_2{\cdot}2H_2O$ (1.8 equiv), HCl, H_2O, 0 °C, 1 h; (d) Pyruvic acid (1.7 equiv), HCl, H_2O, rt, 45 min, 46% (two steps); (e) NaOH (0.5 N), H_2O/MeOH (1:1), reflux, 1 h, 99%; (f) Gly-OMe·HCl (1.0 equiv), DMAP (2.0 equiv), EDC·HCl (1.0 equiv), CH_2Cl_2, 0 °C to rt, 16 h, 52%; (g) NaOH (0.5 N), H_2O/MeOH (1:1), reflux, 1 h, 70%.

excellent yield (90%). Esterification was followed by reduction of the nitro arene using zinc dust and ammonium chloride to give the corresponding aniline in good yield. Hydrazine formation using sodium nitrite and tin(II) chloride under acidic conditions furnished hydrazine **6**.[6] Coupling of **6** with pyruvic acid **3** under previously reported conditions used for hydrazine[7] provided farylhydrazone B methyl ester **7** in 46% yield (two steps). Saponification of **7** proceeded quantitatively and furnished farylhydrazone B (**2**) in five total steps from *o*-nitrobenzoic acid in 30% overall yield. Characterization data (^{1}H NMR, ^{13}C NMR, HRMS, IR and MP) of **2** were in excellent agreement with the same characterization data for the authentic sample.[8] Additionally, each step in the synthesis is scalable, thus allowing for the preparation of multigram quantities of **2**.

With large quantities of farylhydrazone B (**2**) in hand, we then turned our attention to the synthesis of farylhydrazone A (**1**) starting from farylhydrazone B methyl ester (**7**) (Scheme 1). Peptide coupling of **7** with glycine methyl ester hydrochloride salt using DMAP and EDC·HCl provided the coupled product which, upon saponification of the bis-methyl ester compound under identical conditions used in the synthesis of **2**, provided **1** in high yield (70%, six total steps, 11% overall yield). Characterization data (^{1}H NMR, ^{13}C NMR, HRMS, IR and MP) obtained for **1** matched with the data reported for the natural material.[8]

In conclusion, farylhydrazones A (**1**) and B (**2**), the first natural products found to contain the phenylhydrazone moiety, were synthesized in six and five steps respectively starting from *o*-nitrobenzoic acid in good overall yield (11% for **1** and 30% for **2**). Each step in the synthesis is amendable for the preparation of large amounts of **1** and **2**. Additionally, analogues of **1** and **2** can be easily envisioned due to the highly convergent nature of the synthesis. Studies on the biological activity of **1** and **2** and derivative synthesis are currently in progress in our laboratory.

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Supplementary data

Supplementary data (complete experimental details and spectroscopic data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.012.

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