Synthesis of analogs of fumonisin B1

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Abstract
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Disciplines
Chemistry | Environmental Chemistry | Inorganic Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

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Synthesis of Analogs of Fumonisin B₁

The fungus Fusarium moniliforme Sheldon is one of the most important ear rot pathogens of corn (Nywall, 1989). The toxicity of the mold was initially discovered when an isolate of *F. moniliforme* from corn grown in an area of Africa with a high incidence of esophageal cancer was tested (Marasas et al., 1981). This isolate induced quene leukoencephalmalacia in horses (Kriek et al., 1981), was hepatocarcinogenic to rats (Jaskiewicz et al., 1987), and was mutagenic to Salmonella typhimurium (Gelderblom et al., 1986). Fumonisins are considered tumor promoters because their culture material induces γ-glutamyltransaminase positive foci in rat liver, which is a well-established bioassay for tumor promoters (Norred et al., 1988; Plattner, 1992). Fumonisins are also known to be inhibitors of sphingosine biosynthesis (Wang et al., 1991). The isolation and structural elucidation of the fumonisins have been published (Bezvidenhout et al., 1983; Nyvall, 1992). Our hypothesis was that the tricarballylic side chains and the amine constituted the minimum functional requisites for activity. Our synthetic objectives therefore became analogs 1–3. No chloroformate and sodium carbonate (Bergmann and Zervas, 1932) to yield carbamate 5 in 75% yield. After a number of unsuccessful attempts to introduce the side chains, the Prevost reaction was examined (Wilson, 1987). The Prevost reaction (Scheme I) involves the oxidation of alkenes with iodine and silver carboxylates. Under anhydrous Prevost conditions, the reaction with cyclohexene yields the trans-diacyl derivative. However, the cis-diacyl derivative can be obtained when the reaction is conducted in the presence of water. The silver salt 6 (Brice and Simons, 1951) was quantitatively generated by reacting tricarballylic anhydride 7 (Emergy, 1981) with silver oxide in the absence of light. The reaction of trans-2-butene and 6 under the Prevost conditions yielded 80% of the anhydride 8. Carbamate 5 was then reacted with 2 equiv of 6 in the presence of 1 equiv of iodine in boiling benzene for 2 days to produce the bis(anhydride) 9 in 90% yield. Hydrolysis of anhydride 9 with 10:1 THF/water and a catalytic amount of CF₃CO₂H at 25 °C afforded the tetraacid 10 in quantitative yield. The removal of the N-benzyloxy carbonyl protecting group was not straightforward. Although hydrogenation with palladium on carbon (Pd/C) in ethanol/water and the use of a hydrogen-transfer reagent such as cyclohexene failed, the hydrogenation of 10 with PtO₂, Pd/C, trifluoroacetic acid, and acetic acid (Hays et al., 1991) afforded a 90% yield of analog 1. Purification of 1 was effected by high-performance liquid chromatography (HPLC) on a C₁₈ column.

The synthesis of analogs 2 and 3 began with ketone 11 (Tsuji and Hashiguchi, 1981). Reaction of the enolate of 11 (formed by the reaction of 11 with 1.2 equiv of LDA in THF) with aldehydes 12 and 13 (Scheme II) (Stammer and Khatri, 1979) at −78 °C afforded the β-hydroxy ketones 14a and 14b in 54 and 45% yields, respectively. Unfortunately, the aldol condensation with 12 showed low diastereoselectivity. The reaction of 14a,b with Me₂NBH(OAc)₃ (Evans and Chapman, 1986) in acetonitrile/acetic acid at 0 °C for 2 days produced diols 15a and 15b in 70 and 63% yields, respectively. The final steps of the synthesis of analogs 2 and 3 are the same as those for analog 1. The diols 15a,b were heated with the silver salt 6 in benzene providing 70% of 16a and 54% of 16b. Hydrolysis of 16a,b with THF/water/trifluoroacetic acid.
followed by hydrogenation with PtO₂, Pd/C, trifluoroacetic acid, and acetic acid yielded analogs 2 and 3. Purification of 2 and 3 was effected by HPLC. To determine more about the structural requirements for fumonisin activity, anhydride 8 was hydrolyzed to produce tetracacid 17.

Toxicity studies using in vitro assays was used to evaluate the comparative toxicity of analogs 1–3 and 17 to FB₁. In this assay all analogs and FB₁ were dissolved in dimethyl sulfoxide (DMSO) and incorporated into the cell culture media. The level of DMSO in any one culture did not exceed 1% of the total volume of media. Cells from a continuous cell line derived from rhesus monkey kidney cells (MA104) were grown to confluence in 96-well tissue culture plates. The growth medium [10% Serum Plus Dulbecco's modified Eagle's medium (DMEM) (Gibco Labs, Grand Island, NY)] was removed and replaced with maintenance medium [5% serum DMEM] and the cultures were evaluated for cell viability. The number of viable cells was determined by the addition of the tetrazolium dye MTT. Analogs 2 and 3 were more toxic than FB₁, and analog 1 was comparable in toxicity to FB₁. Analog 17, which contains only the tricarballylic side chain unit, was not toxic, even at levels of 250 ppm.

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LITERATURE CITED


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