Chemical Transformation of Hydrolyzed Fumonisin B_1 to Hydrolyzed Fumonisin B_2

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The fumonisins, a series of sphingosine-analog mycotoxins produced by the ubiquitous corn contaminant *Fusarium moniliforme*, are an important food safety concern because they are tumor promoters with sufficient chemical stability to persist through normal food processing. Removing propane-1,2,3-tricarboxylic acid side chains produces hydrolyzed fumonisins (HF), including HFB_1 and HFB_2, which retain biological activity. Detection of hydrolyzed fumonisins in food products has created a need for efficient methods to prepare them for use as analytical standards. In the present study conversion of the more abundant HFB_1 to HFB_2 was accomplished by selectively protecting the hydroxyl groups to be retained as the bis(acetonide), deoxygenating the remaining free hydroxyl, and removing the blocking groups. Deoxygenation was accomplished by two methods: (i) free radical-initiated homolytic cleavage of the *O*-phenoxythiocarbonyl ester in the presence of tributyltin hydride and (ii) $LiAlH_4$ reduction of the tosylate ester.

Keywords: *Fumonisins; Fusarium moniliforme; hydrolyzed fumonisin B_2; mycotoxins; partial synthesis; deoxygenation*

The fungus *Fusarium moniliforme* J. Sheldon is the major ear-rot fungus in temperate zones and a ubiquitous pathogen of stored corn worldwide (Marasas *et al.*, 1984). *F. moniliforme* produces a variety of mycotoxins including the fumonisins, a series of substituted long-chain alkylamines structurally analogous to sphingosine (Riley *et al.*, 1993; Shier, 1992), which are esterified with two propane-1,2,3-tricarboxylic acid (PTCA) moieties (Bezuidenhout *et al.*, 1988; Shier *et al.*, 1995). The most abundant member of the series is fumonisin B_1 (**1**) (FB_1), which typically represents 70% or more of the fumonisins produced by most isolates of *F. moniliforme* in field samples and in culture (Ross *et al.*, 1992). FB_1 has been shown to cause leukoencephalomalacia in horses (Marasas *et al.*, 1988), pulmonary edema in swine (Harrison *et al.*, 1990), hepatoma in rats (Gelderblom *et al.*, 1991), and cytotoxicity in certain differentiated mammalian cell types in culture (Shier *et al.*, 1991; Norred *et al.*, 1992). Fumonisin B_2 (**2**) (FB_2), which differs in structure from FB_1 in that it lacks a hydroxyl group on C-10 (Bezuidenhout *et al.*, 1988; Harmange *et al.*, 1994) (see Figure 1), is produced in substantially lower amounts by almost all isolates of *F. moniliforme* (Ross *et al.*, 1992). The PTCA side chains on FB_1 and FB_2 can be removed by alkaline hydrolysis to yield the corresponding backbones, which will be referred to herein as hydrolyzed fumonisins, HFB_1 (**3**) and HFB_2 (**4**), respectively. They have sometimes been referred to as aminopentols AP_1, AP_2 (Bezuidenhout *et al.*, 1988), and AP_3, but the term is a misnomer for AP_2 and AP_3, which are actually aminotetrols. Not only have HFB_1 and HFB_2 been shown to retain biological activity in mammalian cell culture and phytotoxicity bioassays despite loss of about half the molecular weight during conversion from the parent toxins, they also exhibited a broader spectrum of activity in mammalian cell culture bioassays. That is, they were toxic to undifferentiated cell lines

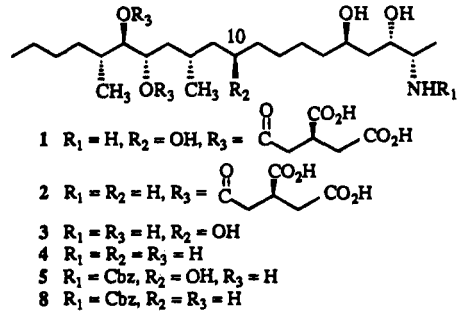

Figure 1. Chemical structures of fumonisin B_1 (**1**), fumonisin B_2 (**2**), hydrolyzed fumonisin B_1 (**3**), hydrolyzed fumonisin B_2 (**4**), the *N*-benzyloxycarbonyl derivative of hydrolyzed fumonisin B_1 (**5**), and the *N*-benzyloxycarbonyl derivative of hydrolyzed fumonisin B_2 (**8**).

(Abbas *et al.*, 1993) as well as to the differentiated cell lines which are sensitive to FB_1 and FB_2 (Shier *et al.*, 1991). This observation has prompted the suggestion that hydrolyzed fumonisins may be active metabolites in some systems (Shier, 1992; Abbas *et al.*, 1993). Hydrolyzed fumonisins are also of interest as potential intermediates in the biosynthesis of fumonisins in *F. moniliforme*.

Hopmans and Murphy (1993) observed that HFB_1 contaminated a variety of corn-derived processed food products including tortilla chips and canned yellow corn. They attributed the increased toxicity observed when *Fusarium proliferatum*-contaminated corn-based diet was exposed to high pH and heat (Hendrich *et al.*, 1993) to the production of hydrolyzed fumonisins, which appeared to be more toxic than intact fumonisins in rats. It is apparent from these observations that many of the processed food products which have been examined for only fumonisin content should be re-examined to determine if the processing that reduced fumonisin content (Sydenham *et al.*, 1991) served only to produce hydrolyzed fumonisins of equal or greater toxicity. This situation has created a demand for HFB_1 and HFB_2 for use as analytical standards, as well as for mechanism

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of action and biosynthesis studies. A convenient method for the production of HFB_1 has been described (Shier and Abbas, 1992). Therefore, we have developed the following method for the partial synthesis of HFB_2 (**4**) from the more abundant HFB_1 (**3**).

EXPERIMENTAL PROCEDURES

Materials. Pentafluorophenyl chlorothionoformate (PFT), tributyltin hydride (*n*-Bu_3SnH), benzyl chloroformate, dimethoxypropane (DMP), and camphosulfonic acid (CSA) were purchased from Aldrich Chemical Co., Milwaukee, WI. 2,2′-Azobis(2-methylpropionitrile) [azobis(isobutyronitrile), AIBN] was obtained from Janssen Chimica/Spectrum Chemical Manufacturing Corp., New Brunswick, NJ. Unless otherwise indicated, all other chemicals were purchased from Sigma Chemical Co., St. Louis, MO.

Instrumental Analysis. Nuclear magnetic resonance (NMR) spectra were determined in CD_3OD or $CDCl_3$ on a 300 MHz GE NMR Instruments Co. Model Omega HR spectrometer. Signals were assigned by chemical shift, by comparison with previously reported data, and by distortionless enhancement by polarization transfer (DEPT). Negative ion fast atom bombardment mass spectra (FAB-MS) were obtained by T. Krick, Department of Biochemistry, College of Biological Sciences, University of Minnesota, on a Kratos model MS-25 mass spectrometer equipped with a Kratos model FAB ion source using glycerol or thioglycerol as the matrix. HPLC analysis was carried out on a Shimadzu CR 501 ChromatoPac, with Shimadzu PF-535 fluorescence detector, excitation 333 nm, emission 444 nm.

Preparation of Compounds. *N-Benzyloxycarbonyl-HFB_1 (**5**).* HFB_1 (**3**) (25 mg, 62 μmol) was dissolved in 150 μL of water containing Na_2CO_3 (10 mg, 94 μmol). Benzyl chloroformate (13 μL, 90 μmol) was added slowly with continuous stirring for 15 min at room temperature. The reaction mixture was cooled in an ice bath and acidified with ~2 mL of concentrated HCl. The precipitation of product was allowed to proceed in an ice bath for 2 h. The solid was collected by filtration, washed with ice water, and chromatographed on a silica gel microcolumn (15 × 0.8 cm, eluted with 9:1 $CHCl_3$/EtOH) to produce 18.4 mg (34 μmol, 55% yield) of compound **5** as a yellow oily liquid: R_f = 0.5 ($CHCl_3$/MeOH 9:1, silica); FAB-MS 540 $[M + 1]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, 6.0 Hz, H-21), 0.89 (3H, t, 7.5 Hz, H-20), 0.96 (3H, d, 6.0 Hz, H-22), 1.17 (3H, d, 7.0 Hz, H-1), 3.37 (1H, dd, 3.0, 9 Hz, H-15), 3.6–3.59 (2H, m, H-5 and H-10), 3.68 (1H, m, H-2), 3.81 (1H, ddd, 3.0, 5.5, 11.0 Hz, H-14), 3.87 (H-3, t, 7.8 Hz, H-3), 5.03 (1H, d, 12 Hz, $NHCO_2CH_aH_b$Ph), 5.1 (1H, d, 11.6 Hz, $NHCO_2CH_aH_b$Ph), 5.5 (1H, d, 7.8 Hz, −NH), 7.24–7.42 (5H, m; $NHCO_2CH_aH_bPh$).

*N-Benzyloxycarbonyl-HFB_1 Bis(acetonide) (**6**).* Compound **5** (12 mg, 22 μmol) was dissolved in a mixture of 300 μL of acetone and 300 μL of DMP, mixed with a catalytic amount of CSA, and stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure to produce 15 mg of crude mixture, which was chromatographed on a silica gel microcolumn (15 × 0.8 cm, hexanes/EtOAc 2:1) to produce 11 mg (17.8 μmol, 81% yield) of compound **6** as a yellowish powder: R_f = 0.25 (hexanes/EtOAc 2:1, silica); FAB-MS 620 $[M + 1]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, 7.4 Hz, H-20), 0.97 (3H, t, 6.0 Hz, H-21), 0.98 (3H, d, 7.0 Hz, H-22), 1.13 (3H, d, 7.0 Hz, H-1), 3.62–3.68 (2H, m, H-5 and H-10), 3.71 (1H, dd, 5.0, 10.0 Hz, H-15), 3.87 (H-3, t, 7.8 Hz, H-3), 3.89 (1H, m, H-2), 4.1 (1H, ddd, 2.5, 3.5, 5.5 Hz, H-14), 5.03 (1H, d, 12 Hz, $NHCO_2CH_aH_b$Ph), 5.1 (1H, d, 11.6 Hz, $NHCO_2CH_aH_b$Ph), 5.3 (1H, d, 8.9 Hz, −NH), 7.3–7.8 (5H, m, $NHCO_2CH_aH_bPh$).

*N-Benzyloxycarbonyl-HFB_2 (**8**) by Free Radical-Initiated Homolytic Deoxygenation of **6**.* Compound **6** (11.5 mg, 18.6 μmol) was dissolved in 3 mL of CH_2Cl_2 and 1 mL of pyridine with addition of 30 μL of PFT and stirring for 16 h at room temperature. The solvent was evaporated to produce 20 mg of crude thionocarbonyl ester, which was dissolved in 5 mL of toluene containing 40 μL of *n*-Bu_3SnH and 2 mg of AIBN. The mixture was heated under reflux in nitrogen at 85 °C for 3 h and then evaporated under reduced pressure. The brown oily residue was applied to a silica gel column (18 × 1 cm) and eluted with 50 mL each of petroleum ether, $CHCl_3$, EtOAc, and finally MeOH. The methanolic fraction was concentrated under reduced pressure and treated with 1 N HCl at room temperature to remove the acetonide blocking groups to produce 9.6 mg (18.4 μmol, 98% yield) of compound **8** as a yellowish powder: R_f = 0.63 (hexanes/EtOAc 3:1, silica); FAB-MS, 524 $[M + 1]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, 6.2 Hz, H-21), 0.89 (3H, t, 7.5 Hz, H-20), 0.96 (3H, d, 6.1 Hz, H-22), 1.04 (3H, d, 7.0 Hz, H-1), 3.37 (1H, dd, 3.0, 9.0 Hz, H-15), 3.59 (1H, m, H-5), 3.87 (H-3, m, H-3), 3.81 (1H, ddd, 3.0, 5.5, 11.0 Hz, H-14), 4.01 (1H, m, H-2), 5.03 (1H, d, 12 Hz, $NHCO_2CH_aH_b$Ph), 5.1 (1H, d, 11.6 Hz, $NHCO_2CH_aH_b$Ph), 5.3 (1H, d, 7.8 Hz, −NH), 7.24–7.42 (5H, m, $NHCO_2CH_aH_bPh$).

*HFB_2 (**4**) by Hydrogenolysis of **8**.* The *N*-Cbz group of **8** (9.8 mg, 18.8 μmol) was removed by dissolving in 3 mL of MeOH and shaking with hydrogen at 45 psi over 50 mg of 10% Pd-C to produce 7.2 mg (18.5 μmol, 98% yield) of **4** with an overall yield of 43%. To facilitate analysis by NMR, compound **4** (5 mg) was peracetylated by dissolving in 500 μL of pyridine and 500 μL of Ac_2O and stirring at room temperature for 16 h. The excess Ac_2O and pyridine were removed under reduced pressure, and the residue was chromatographed on a silica gel microcolumn (15 × 0.8 cm, EtOAc/hexane, 2:1) to provide 4.6 mg of *N*-acetyl pentaester of **4** as a white powder: R_f = 0.46 (hexane/EtOAc 1:2, silica); FAB-MS 658 $[M + 1]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, 6.8 Hz, H-20), 0.95 (3H, d, 6.9 Hz, H-21), 0.99 (3H, d, 6.4 Hz, H-22), 1.12 (3H, d, 6.9 Hz, H-1), 1.23 (3H, m, H-19), 1.53–1.68 (2H, m, H-11), 1.73 (1H, m, H-12), 4.01 (1H, m, H-2), 4.85 (1H, dd, 3.6, 4.2 Hz, H-15), 4.86 (1H, m, H-5), 4.75–5.01 (1H, m, H-3), 5.17 (1H, ddd, 3.8, 3.8, 10.9 Hz, H-14). ^{13}C NMR, DEPT experiments (75 MHz, $CDCl_3$) δ 18.2 (q, C-1), 48.1 (d, C-2), 69.8 (d, C-3), 40.6 (t, C-4), 68.9 (d, C-5), 38.3 (t, C-6), 25.6 (t, C-7), 27.2 (t, C-8), 29.9 (t, C-9), 30.7 (t, C-10), 35.2 (t, C-11), 31.3 (t, C-12), 40.9 (t, C-13), 70.7 (d, C-14), 81.1 (d, C-15), 35.7 (t, C-16), 31.6 (t, C-17), 30.5 (t, C-18), 24.1 (q, C-19), 14.4 (q, C-20), 16.2.3 (q, C-21), 21.3 (q, C-22), 169.6 (−*C*ONH), 173.8, 170.9, 170.8, and 170.4 were assigned for four acetate carbonyl groups on carbons 3, 5, 14, and 15. ^{13}C NMR, DEPT experiments (75 MHz, $CDCl_3$), for *N*-acetyl pentaester of HFB_1 δ 18.3 (q, C-1), 48.2 (d, C-2), 69.6 (d, C-3), 40.4 (t, C-4), 71.9 (d, C-5), 36.1 (t, C-6), 25.6 (t, C-7), 25.4 (t, C-8), 35.3 (t, C-9), 70.1 (d, C-10), 34.1 (t, C-11), 25.2 (t, C-12), 35.4 (t, C-13), 70.8 (d, C-14), 77.4 (d, C-15), 33.6 (t, C-16), 31.84 (t, C-17), 28.5 (t, C-18), 22.7 (q, C-19), 13.9 (q, C-20), 15.4 (q, C-21), 20.4 (q, C-22), 169.8 (−*C*ONH), 173.7, 170.7, 170.5, 170.6, and 170.5 were assigned for five acetate carbonyl groups on carbons 3, 5, 10, 14, and 15.

*10-O-Tosyl-N-benzyloxycarbonyl-HFB_1 Bis(acetonide) (**7**).* Compound **6** (5 mg, 8.1 μmol) was dissolved in 2 mL of pyridine containing catalytic amounts of DMAP. The mixture was kept at −5 °C, and 3.2 mg of *p*-toluenesulfonyl chloride (16.8 μmol) was added in portions to the reaction mixture while stirring to produce a reddish precipitate. The mixture was allowed to stand overnight, and then 2 mL of water was added; the organic layer was separated, dried over anhydrous $MgSO_4$, and purified on a silica gel column (10 × 0.4 cm, hexanes/EtOAc, 1:1.5). The product was subjected to hydrogenolysis at 45 psi over 50 mg of 10% Pd-C to afford compound **7** obtained as 4 mg (6.3 μmol, 78% yield) of yellowish powder: R_f = 0.63 (hexanes/EtOAc 3:1, silica); FAB-MS 640 $[M + 1]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, 7.0 Hz, H-20), 0.97 (3H, d, 6.3 Hz, H-21), 0.98 (3H, d, 7.0 Hz, H-22), 1.15 (3H, d, 7.5 Hz, H-1), 2.3 (3H, s, CH_3PhSO_2−R), 3.68 (1H, dd, 5.0, 10.0 Hz, H-15), 3.69 (1H, m, H-5), 3.72 (H3, m, H-3), 3.99 (1H, m, H-2), 4.01 (1H, ddd, 3.0, 5.5, 12.1 Hz, H-14), 7.1 (2H, d, 8.2 Hz, CH_3PhSO_2−R), 7.9 (2H, d, 7.9 Hz, CH_3PhSO_2−R).

*HFB_2 (**4**) by $LiAlH_4$ Reduction of **7**.* Compound **7** (4.5 mg, 7.0 μmol) was dissolved in anhydrous ether and kept at 0 °C under nitrogen while an excess of $LiAlH_4$ was added cautiously in portions with stirring to produce a slurry mixture which was allowed to rise to room temperature overnight. The reaction mixture was quenched with a saturated solution of sodium potassium tartarate (Russel salt) until the slurry

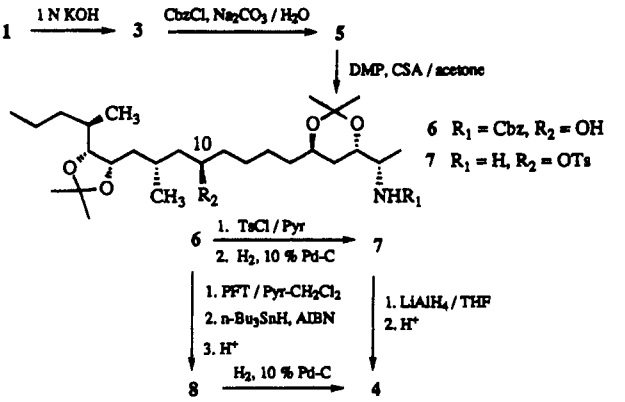

Figure 2. Synthesis of hydrolyzed fumonisin B_2 (4).

became clear. The mixture was stirred for an additional 1 h and extracted three times with 10 mL aliquots of EtOAc; the extracts were combined and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel column (10 × 0.4 cm, $CHCl_3$/MeOH/HAC 6:3:1) to produce 2.6 mg of **4** (6.7 μmol, 96% yield) as a pure white powder with an overall yield of 34%: R_f = 0.56 ($CHCl_3$/MeOH/NH_4OH 30:15:1); FAB-MS 390 $[M + 1]^+$; ^1H and ^{13}C NMR are the same as described above for HFB_2 prepared by free radical-initiated homolytic deoxygenation of **6**.

Comparison of Semisynthetic HFB_2 (4) to Authentic HFB_2. Authentic HFB_2 was prepared from FB_2 produced by *F. moniliforme* JW#1 grown on corn cultures and isolated and purified according to the method of Cawood *et al.* (1991). FB_2 was hydrolyzed and purified according to the method of Bezuidenhout *et al.* (1988). HPLC analysis was carried out by following a modification of the methods of Ueno *et al.* (1993) and Hopmans and Murphy (1993) using as mobile phase MeOH/0.1 M NaH_2PO_4 (80:20), pH 3.35, and a flow rate of 1.2 mL/min on an Econosil C_{18}, 5 μm, 250 × 4.6 mm column after precolumn derivatization with *o*-phthaldialdehyde (OPA). Authentic HFB_2 and HFB_1 were peracetylated as described above for semisynthetic HFB_2 and characterized by ^1H and ^{13}C NMR under the same conditions.

RESULTS AND DISCUSSION

Our strategy for the conversion of HFB_1 to HFB_2 was to selectively protect the hydroxyl groups at C-3, C-5, C-14, and C-15 of HFB_1 as the bis(acetonide) and then deoxygenate the remaining free OH at C-10. Figure 2 depicts the synthesis of HFB_2. The starting material, HFB_1 (**3**), was prepared according to the method of Shier and Abbas (1992) and converted to the *N*-Cbz-bis-(acetonide) derivative **6** according to the method of Hoye *et al.* (1994). Deoxygenation of **6** at the single free carbinol center at C-10 was accomplished by two methods: the free radical-initiated homolytic deoxygenation method of Robins *et al.* (1983) and $LiAlH_4$ reduction of the C-10 tosylate after removal of the *N*-Cbz blocking group.

Initial studies were carried out with the free radical-initiated homolytic deoxygenation method of Robins *et al.* (1983), which was of particular interest because it could in principle also be used for the partial synthesis of FB_2 from FB_1 by deoxygenation at C-10 of the *N*-Cbz-3,5-acetonide tetramethyl ester derivative of FB_1. The method converted **6** to HFB_2 (**4**), but the product was contaminated with tin-containing impurities that were difficult to remove. Attempts to prepare FB_2 from FB_1 by deoxygenating the *N*-Cbz-3,5-acetonide tetramethyl ester derivative of FB_1 yielded intractable mixtures.

In the second method, deoxygenation at C-10 of **6** was accomplished by $LiAlH_4$ reduction of the tosylate ester. Prior to $LiAlH_4$ reduction, the *N*-Cbz blocking group was removed by hydrogenolysis to give **7**, to prevent it from being reduced to the *N*-methyl derivative. $LiAlH_4$ reduction of **7**, followed by hydrolysis of the bis(acetonide) blocking groups during acid workup, proceeded smoothly to give HFB_2 (**4**) in higher purity than the free radical-initiated homolytic deoxygenation method.

HFB_2 produced semisynthetically from HFB_1 exhibited the same properties as authentic HFB_2 prepared by hydrolysis of FB_2 (Bezuidenhout *et al.*, 1988), including (i) migration on normal phase TLC (R_f = 0.56 on silica gel in $CHCl_3$/MeOH/concentrated NH_4OH 30:15:1), (ii) retention time (7.39 min) on reversed phase HPLC (Ueno *et al.*, 1993; Hopmans and Murphy, 1993), (iii) FAB-MS, and (iv) ^1H and ^{13}C NMR. The FAB-MS spectra of semisynthetic and authentic **4** both contained the major peak at *m/z* 390, which was assigned to $[M + H]^+$. Semisynthetic and authentic compound **4** were also characterized by ^1H and ^{13}C NMR of both unmodified and peracetylated (Ac_2O/pyridine) material, the latter of which gave better resolved, more easily interpreted spectra. Specifically, DEPT (Distortionless Enhancement by Polarization Transfer) experiments in ^{13}C NMR showed that one oxygenated methine carbon (CH−O) at 70.1 ppm in the spectrum of the starting material HFB_1 was replaced by a methylene carbon at 30.4 ppm in the spectrum of the HFB_2 produced from it.

Both HPLC retention time and peak splitting patterns in ^1H NMR spectra are sensitive to stereochemistry in molecules with more than one stereogenic center; the observation of identical retention time and ^1H NMR spectra implies the same stereochemistry in semisynthetic and authentic HFB_2 and, hence, the same absolute configurations at the stereogenic centers common to HFB_1 and HFB_2. This observation confirms by an independent method all relative and absolute configuration assignments made for HFB_2 by Harmange *et al.* (1994).

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