Syntheses and Mutagenicity of Fusarin C Ring Analogues

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Three practical synthetic pathways are established for the preparation of four types of substituted 3,4-epoxy-γ-butyrolactams which are fusarin C analogues: (A) 3,4-epoxy-5-hydroxy-5-phenyl-γ-butyrolactam was synthesized in three steps in 43% overall yield from phenyl glyoxal; (B) 3,4-epoxy-4,5-dimethyl-5-hydroxy-γ-butyrolactam was synthesized in 31% yield and four steps from 2,3-butanedione; (C) three 4,5-dialkyl-3,4-epoxy-5-hydroxy-γ-butyrolactams were synthesized from the corresponding alkyl ketones in six steps and modest overall yield. A total of 15 of the synthesized lactones, lactams, and acyclic intermediates were tested for mutagenicity in the Ames assay. No compound was more than weakly mutagenic in *Salmonella typhimurium* tester strains TA98 or TA100.

INTRODUCTION

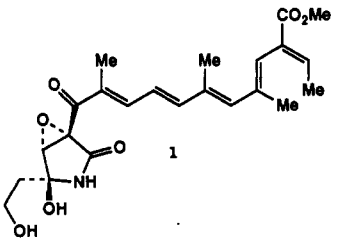
Fusarin C (1) (Chart I) (Weibe and Bjeldanes, 1981; Gaddamidi et al., 1985) is a mutagenic (Gelderblom et al., 1986) metabolite of the fungus *Fusarium moniliforme*. The fungus grows commonly on corn, wheat, rice, and other crops throughout the world (Gordon, 1960). Our studies of structure–mutagenic activity relationships of the fusarins required preparation of substituted ring analogues of these compounds. No total synthesis of fusarin C has been reported.

Our synthetic strategies were modeled after published syntheses of another mold product, cerulenin (2). The cerulenin syntheses converged on the epoxy-γ-butyrolactones **3a** and **3b**. Cerulenin is obtained from **3a** by aminolysis and mild oxidation and from **3b** by aminolysis alone (Corey et al., 1977; Boeckmann and Thomas, 1979; Jakubowski et al., 1982). Thus, for the present work epoxy-γ-butyrolactones of type **4** were required as intermediates for subsequent aminolysis procedures. A series of procedures involving malonate displacement or condensation reactions was used.

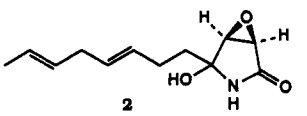
EXPERIMENTAL PROCEDURES

General. Unless otherwise noted, regents, absolute ethanol, and diethyl ether were purchased from commercial suppliers and used without further purification. Pyridine and tetrahydrofuran (THF) were distilled from calcium hydride immediately before use. Carbon tetrachloride was dried over molecular sieves (3 Å), and methanol was distilled from magnesium methoxide immediately prior to use. Boiling points were uncorrected. IR spectra were determined with a Perkin-Elmer Model 137 grating infrared spectrophotometer with ordinate scale for the region 4000–700 cm^{-1}. ^1H NMR spectra were determined with the UCB-200 and UCB-250 spectrometers (superconducting FT instruments operating at 200 and 250 MHz, respectively). Unless otherwise indicated, NMR spectra were measured using $CDCl_3$ solutions. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz. Electron-impact mass spectra (MS) were recorded on AEI-MS-12 (low resolution) CEC 21-110B (high resolution) instruments. Mass spectral data are tabulated as *m/z* (intensity expressed as a percent of total ion current) with structural formula of fragments. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA. Of the compounds prepared for this study, only compounds **5g**, **10c**, and **10d** have been described previously in the literature. Stereochemistry at C-5 of cerulenin and the lactones and lactams **3–6** was not established.

Chart I



1



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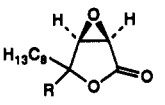
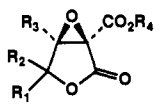
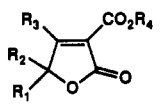


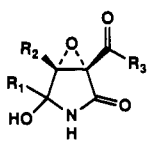
3a, R = H
b, R = OH



4a, R_1 = OH; R_2,R_3 = Me; R_4 = H
b, R_1 = OH; R_2,R_3,R_4 = Me
c, R_1 = H; R_2,R_4 = Me; R_3 = Et
d, R_1 = H; R_2 = *i*-Pr; R_3,R_4 = Me
e, R_1 = H; R_2,R_3,R_4 = Me



5a, R_1,R_3 = H; R_2 = *i*-Pr; R_4 = Et
b, R_1 = OH; R_2,R_3 = Me; R_4 = H
c, R_1 = OH; R_2,R_3,R_4 = Me
d, R_1 = H; R_2,R_4 = Me; R_3 = Et
e, R_1 = H; R_2 = *i*-Pr; R_3,R_4 = Me
f, R_1 = H; R_2,R_3,R_4 = Me
g, R_1 = H; R_2,R_4 = Me; R_3 = Ph



6a, R_1 = Ph; R_2 = H; R_3 = NH_2
b, R_1,R_2 = Me; R_3 = OMe
c, R_1 = Me; R_2 = Et; R_3 = OMe
d, R_1 = *i*-Pr; R_2 = Me; R_3 = OMe

Synthetic Procedures. *3-Carboxy-4,5-dimethyl-3,4-epoxy-5-hydroxy-γ-butyrolactone* (**4a**). A solution of lactone acid **5b** (Schultz and Godfrey, 1980) (0.172 g, 10 mmol) in distilled water (0.5 mL) was added at room temperature to a stirred solution of sodium hydroxide (0.06 g, 1.5 mmol) in water (0.1 mL). The catalyst, sodium tungstate dihydrate (0.007 g, 0.02 mmol), was added, and the reaction mixture was stirred further for 10 min at room temperature, 15 min at 0 °C, and 2 h at 65 °C. The volume was reduced by two-thirds, and the concentrate was poured into 5 mL of acetone. The precipitate was collected, washed with acetone, and dried in the air. The dried salt was added to a solution of barium chloride (0.033 g, 0.5 mmol) in water (1 mL). This mixture was stirred at 60 °C for 1 h, and the product was filtered, washed with cold water, and dried in air. A suspension of the barium salt and anhydrous $MgSO_4$ (0.5 g) in ether (5 mL) was stirred at 0 °C and treated dropwise with

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sulfuric acid (0.04 g) in ether (2 mL). This reaction mixture was stirred for 2 h at 0 °C and 15 h at room temperature. The mixture was filtered, and the solvent was removed from the filtrate to give white crystalline epoxy acid **4a**. This product was purified by column chromatography on silica gel with 10% CH_3CN in CH_2Cl_2 to give 7 mg (3.7%) of pure product: mp 155–158 °C; ^1H NMR (CD_3OD) δ 1.51 (s, 3), 1.66 (s, 3); MS 187 ($M^+ - 1$, 3, $C_7H_7O_6$), 171 (44, $C_7H_7O_5$), 143 (3, $C_6H_7O_4$), 126 (33, $C_6H_6O_3$), 115 (33, $C_5H_7O_3$), 83 (54, C_5H_7O), 69 (51, C_4H_5O), 45 (100, CO_2H).

4,5-Dimethyl-5-hydroxy-3-(methoxycarbonyl)-3,4-epoxy-γ-butyrolactone (**4b**). A solution of γ-butyrolactone **5c** (0.4 g, 2.15 mmol) in 1 mL of methanol at room temperature was treated with a solution (1.36 mL) of 3 N NaOH (0.35 mL, 4.73 mmol) in dry methanol and 1.0 mL of 30% hydrogen peroxide. The solution was stirred at 35–40 °C for 4.5 h. The product was extracted twice with ether (10 mL). The combined extracts were washed three times with brine and once with distilled water (2 mL) and dried over anhydrous Na_2SO_4. Following solvent removal, the crude product **4b** (0.25 g, 57.6%) was purified by chromatography on silica gel (60–200 mesh) with 2% CH_3CN in CH_2Cl_2 solvent to yield 0.22 g (49.8%) of white crystals: mp 110 °C; IR ($CHCl_3$) 3300 (OH), 1800 and 1750 (CO), 1435, 1370, 1300, 1220, 1115, 1060, 1030, 930, 900; ^1H NMR δ 1.58 (s, 3), 1.70 (s, 3), 3.92 (s, 3); MS 203 ($M^+ + 1$, 1, $C_8H_{11}O_6$), 185 (47, $C_8H_9O_5$), 129 (41, $C_6H_9O_3$), 99 (89, $C_5H_7O_2$), 93 (100, C_5H_7O).

4-Ethyl-3-(methoxycarbonyl)-5-methyl-3,4-γ-butyrolactone (**4c**). A solution of 5.5 mL (48 mmol) of 30% hydrogen peroxide and 2.8 mL (8.4 mmol) of 3 N NaOH in CH_3OH was added dropwise into a stirred solution of lactone **5d** (2.2 g, 11 mmol) in 15 mL of methanol at 0 °C. This reaction mixture was stirred for 8 h at 0 °C. The product, **4c**, was extracted twice with diethyl ether (10 mL). The combined organic extracts were washed three times with brine (5 mL) and once with distilled water (5 mL). The washed solution was dried, and the solvent was removed in vacuo to give an oily substance that slowly crystallized. The product, **4c**, was recrystallized from diethyl ether and petroleum ether (1.06 g, 41.7%): mp 43–44 °C; IR ($CHCl_3$) 2880, 1800, 1775, 1450, 1400, 1380, 1300, 1225, 1060, 1040, 940, 900; ^1H NMR δ 1.16 (t, 3, J = 7.5), 1.47 (d, 3, J = 7.0), 1.72 (m, 1, J = 7.5), 2.14 (m, 1, J = 7.5), 3.91 (s, 3), 4.70 (q, 1, J = 7.0); MS 200 (M^+, 1 $C_9H_{12}O_5$), 169 (31, $C_8H_9O_4$), 136 (100, $C_7H_4O_3$), 81 (55, C_6H_9), 59 (40, $COOCH_3$), 55 (39, C_4H_7), 53 (55, C_4H_5).

3,4-Epoxy-5-isopropyl-3-(methoxycarbonyl)-4-methyl-γ-butyrolactone (**4d**). A solution of 30% hydrogen peroxide (0.23 mL, 2 mmol) and 3 N NaOH in methanol (183 μL, 0.55 mmol) was added dropwise to a stirred solution of **5e** (0.1 g, 0.5 mmol) in 1 mL of methanol at room temperature. The reaction mixture was stirred further for 1.5 h, and 7 mL of diethyl ether was added. This mixture was washed five times with brine (2 mL) and once with distilled water (2 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a white crystalline product, **4d**, which was recrystallized from ethyl acetate and petroleum ether (0.07 g, 65.4%): mp 56–58 °C; IR ($CHCl_3$) 2880, 1800, 1775, 1450, 1380, 1320, 1225, 1075, 1025, 980; ^1H NMR δ 0.90 (d, 3, J = 7.0), 1.13 (d, 3, J = 7.0), 1.62 (s, 3), 2.06 (m, 1), 3.92 (s, 3), d 4.44 (d, 1); MS 214 (M^+, <1, $C_{10}H_{14}O_5$), 199 (9, $C_9H_{11}O_5$), 183 (5, $C_9H_{11}O_4$), 167 (36, $C_9H_{11}O_3$), 156 (77, $C_6H_7O_5$), 124 (98, $C_7H_8O_2$), 109 (10, C_7H_9O), 99 (24, $C_4H_3O_3$), 96 (62, $C_5H_4O_2$), 67 (100, C_4H_3O), 59 (54, $COOCH_3$), 55 (34, C_4H_7), 53 (46, C_4H_5).

4,5-Dimethyl-3,4-epoxy-3-(methoxycarbonyl)-γ-butyrolactone (**4e**). The epoxidation reaction procedures were as above. Compound **5f** (0.2 g, 1.2 mmol) gave the product **4e** (0.07 g, 31%), a colorless oil which was purified by silica gel column chromatography with 1.5% CH_3CN in CH_2Cl_2. This oily product slowly crystallized (mp 28–30 °C) at 5 °C: IR ($CHCl_3$) 2880, 1780, 1750, 1430, 1375, 1300, 1250, 1225, 1175, 1115, 1080, 1060, 1030, 960, 940, 900; ^1H NMR δ 1.44 (d, 3, J = 6.8), 1.63 (s, 3), 3.92 (s, 3), 4.64 (q, 1, J = 6.8); MS 187 ($M^+ + 1$, 5, $C_8H_{11}O_5$), 155 (28, $C_7H_7O_4$), 127 (29, $C_6H_7O_3$), 71 (63, C_3H_7CO), 59 (73, $COOCH_3$), 55 (100, C_4H_7).

4-Ethyl-3-(methoxycarbonyl)-5-methyl-3,4-didehydro-γ-butyrolactone (**5d**). A 100-mL round-bottom flask was charged with 15 g (50 mmol) of the bromodiester **10a** and 25 mL of 1,1,2,2,-tetrachloroethane. This solution was refluxed for 1.5 h, cooled, and distilled at low pressure to remove the solvent. The residual oil was distilled to give the viscous product **5d** (bp 144–145 °C, 3.4 min) in 32% yield (2.96 g): IR ($CHCl_3$) 2880, 1750, 1700, 1650, 1460, 1440, 1385, 1375, 1300, 1275, 1220, 1160, 1115, 1050, 930, 812, 800; ^1H NMR δ 1.22 (t, 3, J = 7.5), 1.51 (d, 3, J = 7.0), 2.55 (m, 1, J = 7.5), 3.08 (m, 1, J = 7.5), 3.89 (s, 3), 5.03 (q, 1, J = 7.0); MS 184 (M^+, 37, $C_9H_{12}O_4$), 153 (62, $C_8H_9O_3$), 152 (61, $C_8H_8O_3$), 141 (94, $C_7H_9O_3$), 125 (27, $C_7H_9O_2$), 109 (97, C_7H_9O), 96 (26, $C_5H_4O_2$), 81 (91, C_6H_9), 59 (40, $COOCH_3$), 55 (22, C_4H_7), 53 (100, C_4H_5).

5-Isopropyl-4-methyl-3-(methoxycarbonyl)-3,4-didehydro-γ-butyrolactone (**5e**). The solution of 13.3 g (62.0 mmol) of enediester **9b** (12.0 g, 67.2 mmol) of *N*-bromosuccinimide and 0.25 g of 2,2-azobis[2-methylpropionitrile] in 100 mL of dried carbon tetrachloride was refluxed for 3 h. This solution was cooled and filtered to remove the succinamides, and the solvent was removed from the filtrate in vacuo to give the crude product 2,4-dimethyl-3-bromo-1,1-bis(methoxycarbonyl)pent-1-ene (**10b**) (17.1 g, 94.2%). This bromo compound was distilled at 145 °C (1.45 mm) to give the lactone **5e**, a colorless oil: 5.4 g, 43.5%; IR ($CHCl_3$) 2880, 1750, 1700, 1650, 1460, 1440, 1385, 1375, 1300, 1250, 1240, 1200, 1160, 1115, 1100, 1060, 1040, 980, 812, 800; ^1H NMR δ 0.72 (d, 3, J = 6.9), 1.21 (d, 3, J = 6.9), 2.22 (m, 1, J = 6.9), 2.37 (s, 3), 3.89 (s, 3), 4.78 (d, 1); MS 198 (M^+, 10, $C_{10}H_{14}O_4$), 167 (15, $C_9H_{11}O_3$), 140 (36, $C_8H_{12}O_2$), 123 (22, $C_8H_{11}O$), 115 (71, $C_4H_3O_4$), 99 (74, $C_6H_{11}O$ or $C_4H_3O_3$), 83 (100, C_6H_{11}), 67 (56, C_5H_7), 59 (86, $COOCH_3$), 55 (92, C_4H_7).

4,5-Dimethyl-3-(methoxycarbonyl)-3,4-didehydro-γ-butyrolactone (**5f**). The solution of allylic bromoester **10c** (5.3 g, 20 mmol) in 1,1,2,2-tetrachloroethane (20 mL) was refluxed for 1 h. The product **5f** (1.5 g, 44%) was a colorless oil: bp 110–112 °C, 1.50 mmHg; IR ($CHCl_3$) 2880, 1775, 1700, 1650, 1460, 1440, 1385, 1375, 1300, 1225, 1200, 1160, 1115, 1100, 1040, 960, 940, 810, 800; ^1H NMR δ 1.50 (d, 3, J = 6.9), 2.38 (s, 3), 3.89 (s, 3), 4.93 (q, 1, J = 6.9); MS 170 (M^+, 12, $C_8H_{10}O_4$), 139 (39, $C_7H_7O_3$), 127 (100, $C_6H_7O_3$), 123 (35, $C_7H_7O_2$), 95 (50, $C_5H_3O_2$), 83 (31, $C_4H_3O_2$), 67 (88, C_5H_7), 59 (62, $COOCH_3$).

3-(Methoxycarbonyl)-5-methyl-4-phenyl-3,4-didehydro-γ-butyrolactone (**5g**). A solution of the allylic bromide **10d** (8 g, 24 mmol) in 1,1,2,2-tetrachloroethane (20 mL) was refluxed for 5.0 h. The product **5g** was obtained in 60% yield (3.4 g) and was a colorless crystalline solid [mp 92–100 °C; lit. (Berg and Kolsaker, 1978) mp 87–100 °C] after recrystallization from chloroform and hexane. Spectral data agree with the literature values.

3-Carbamoyl-3,4-epoxy-5-hydroxy-5-phenyl-γ-butyrolactam (**6a**). The diamide **7b** was dissolved in methanol, refluxed for 2 h, concentrated, and recrystallized to produce a near quantitative yield of white crystals: mp 138–139 °C; IR (KBr) 3320, 3120, 1740, 1670, 1595, 1560, 1250, 1150, 1090, 941, 900, 860, 810; ^1H NMR (DMOS-d_6) δ 4.10 (s, 1), 7.20 (s br, 2), 7.50 (m, 2), 7.60 (m, 1), 7.85 (m, 2), 9.35 (s br, 1); ^1H NMR (DMSO-d_6, D_2O) δ 4.30 (s, 1), 7.50 (m, 2), 7.70 (m, 1), 7.96 (m, 2); MS 234 (M^+, 2.4), 218 (2, $C_{11}H_8NO_4$), 147 (50, $C_9H_7O_2$), 115 (100, C_9H_7). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.45; H, 4.30; N, 11.96. Found: C, 56.74; H, 4.47; N, 11.93.

4,5-Dimethyl-3,4-epoxy-5-hydroxy-3-(methoxycarbonyl)-γ-butyrolactam (**6b**). Lactone **4b** (0.23 g, 1.1 mmol) in methanol (10 mL) was stirred for 25 min at room temperature with 15 M NH_4OH (0.46 mL, 6.9 mmol). Dichloromethane (25 mL) and 0.5 N HCl (8 mL) were added. This mixture was shaken thoroughly, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the crude product 0.19 g (82.6%) was recrystallized from ethyl acetate and petroleum ether to give a pure white crystalline product: mp 152–154 °C; ^1H NMR δ 1.53 (s, 3), 1.62 (s, 3), 1.66 (s, 3), 3.86 (s, 3), 4.22 (s br, 1), 6.73 (s br, 1); MS 201 (M^+, 1, $C_8H_{11}NO_5$), 185 (1, $C_8H_{11}NO_4$), 130 (16, $C_4H_4NO_4$), 86 (53, C_4H_8NO), 71 (71, C_4H_7O), 59 (69, $COOCH_3$), 55 (82, C_3H_3O and C_2HNO), 43 (100, C_2H_5N).

4,5-Dimethyl-3,4-epoxy-5-hydroxy-3-(methoxycarbonyl)-γ-butyrolactam (**6b**). Oxidation of hydroxy *cis*-epoxy amide **11c** (0.15 g, 0.74 mmol) produced **6b** in 12% yield (18 mg) as a white crystalline solid: mp 152–154 °C; ^1H NMR δ 1.53 (s, 3), 1.62 (s, 3), 1.66 (s, 3), 3.86 (s, 3), 4.22 (s br, 1), 6.73 (s br, 1); MS 201 (M^+, 1, $C_8H_{11}NO_5$), 185 (1, $C_8H_{11}NO_4$), 130 (16, $C_4H_4NO_4$), 86 (53, C_4H_8NO), 71 (71, C_4H_7O), 59 (69, $COOCH_3$), 55 (82, C_3H_3O), 43 (100, C_2H_5N).

3-Carbamoyl-3,4-epoxy-4-ethyl-5-hydroxy-5-methyl-γ-butyrolactone (**6c**). Dry pyridine (0.97 mL, 12 mmol) was added dropwise to a stirred mixture of chromium oxide (0.6 g, 6 mmol) in dry dichloromethane (20 mL) at room temperature. This mixture was stirred for 30 min, and a solution of hydroxy epoxy diamide **11a** (0.2 g, 1 mmol) in dry dichloromethane (20 mL) was added as one portion. This mixture was stirred for 1 h, and the reaction was quenched with 2-propanol (0.5 mL). Diethyl ether (70 mL) was added, and the mixture was stirred for 5 min and set aside for 30 min to precipitate reduced chromium oxide. This mixture was filtered, and the filtrate was washed twice with 5% aqueous sodium bicarbonate (2 mL), once with 0.5% aqueous HCl (2 mL), and once with distilled water (2 mL). The washed solution was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was recrystallized from acetone and hexane to yield **6c** (0.04 g, 20%): mp 140–142 °C; ^{1}H NMR δ 1.19 (t, 3, J = 7.5), 1.57 (s, 3), 2.01 (q, 1, J = 7.5), 2.15 (q, 1, J = 7.5), 5.87 (s br, 1), 6.80 (s br, 1), 7.53 (s br), 7.73 (s (br); MS 200 (M^+, <1, $C_8H_{11}N_2O_4$), 152 (58, $C_8H_8O_3$), 140 (45, $C_7H_8O_3$), 97 (42, C_6H_9O), 86 (71, $C_5H_{10}O$), 69 (100, C_5H_9), 57 (88, C_4H_9), 44 (90, $CONH_2$).

3,4-Epoxy-5-hydroxy-5-isopropyl-3-(methoxycarbonyl)-4-methyl-γ-butyrolactam (**6d**). The oxidation reaction procedures were used as described above with starting compound **11b** (0.12 g, 0.52 mmol). The product, **6d**, was recrystallized from ethyl acetate and hexane to give a white crystalline solid (28 mg, 23%: mp 123 °C; IR ($CHCl_3$) 3320, 3220, 2880, 1750, 1450, 1325, 1210, 1100, 1075, 1025, 930; ^{1}H NMR δ 1.04 (d, 3, J = 6.9), 1.11 (d, 3, J = 6.9), 1.69 (s, 3), 2.18 (q, 1, J = 6.9), 3.86 (s, 3), 4.30 (s br, 1), 7.06 (s br, 1); MS 230 (M^+ + 1, 11, $C_{10}H_{15}NO_5$ + H), 229 (M^+, 10, $C_{10}H_{15}NO_5$), 186 (43, $C_9H_{14}O_4$), 83 (30, C_5H_7O), 71 (40, C_4H_7O), 43 (100, C_3H_7).

1,1-Bis(ethoxycarbonyl)-1,2-epoxy-3-phenylpropan-3-one (**7a**). A solution of diethyl bromomalonate (4.78 g, 20 mmol) in absolute ethanol (40 mL) was slowly added to a stirred solution of potassium (0.46 g, 20 mmol) in absolute ethanol (10 mL) at −10 °C. Freshly distilled benzyloxaldehyde (2.68 g, 20 mmol) was added dropwise. The reaction mixture was stirred for 10 h at 0 °C and was poured into 40 mL of ice water. The product was extracted three times with 50 mL of diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed at reduced pressure. The viscous oily residue (light brown) was purified by silica gel column chromatography with 1.5% CH_3CN in CH_2Cl_2 to give 2.95 g (50%) of product **7a**: IR (neat) 2940, 1750, 1700, 1600, 1450, 1370, 1330, 1240, 1120, 1055, 912; ^{1}H NMR δ 1.08 (t, 3, J = 7.0), 1.19 (t, 3, J = 7.0), 4.04 (q, 2, J = 7.0), 4.19 (q, 2, J = 7.0), 4.70 (s, 1), 7.55 (m, 2), 7.70 (m, 1), 8.07 (m, 2); MS 292 (M^+, 4.4), 247 (19), 105 (100).

1,1-Dicarbamoyl-1,2-epoxy-3-phenylpropan-3-one (**7b**). A solution of epoxydiester **7a** (2.5 g, 8.6 mmol) in 20 mL of methanol was cooled to 0 °C in an ice–water bath. Ammonium hydroxide (15 M, 1.3 mL, 20 mmol) was added, and the reaction mixture was stirred at 0 °C for 3 h, diluted with 80 mL of ethyl acetate, and adjusted to pH 8.0 with 2 N HCl. The white precipitate was filtered and washed with chilled methanol (10 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic solutions were washed with distilled water. This solution was dried over anhydrous $MgSO_4$ and concentrated, and the product recrystallized from methanol to yield 1.73 g (85.5%) of product **7b**: mp 168–169 °C: IR (KBr) 3220, 1760, 1690, 1420, 1290, 1120, 940, 862; ^{1}H NMR (acetone-d_6) δ 4.71 (s, 1), 7.54 (m, 2), 7.68 (m, 1), 8.04 (m, 2); MS 234 (M^+, 1.1), 218 (15), 105 (93), 44 (100).

2,2-Bis(methoxycarbonyl)-1,1-diethylethene (**9a**). A 2-L, three-neck, round-bottom flask fitted with a mechanical stirrer, a rubber septum, a pressure-equalizing addition funnel, and a calcium chloride drying tube was charged with 450 mL of dry THF by syringe through the septum with 75 mL of dry carbon tetrachloride. The stirrer was started while the contents of the flask were cooled to 0 °C. Then 33 mL of titanium tetrachloride solution was added in the same manner into the cooled solvent. Into the cooled titanium tetrachloride solution was added THF dropwise 2 h to form a yellow complex, and this mixture was stirred for another hour at 0 °C. The rubber septum and the calcium chloride drying tube positions were exchanged, and the pressure-equalizing addition funnel was recharged by syringe through the septum with 12.9 g (0.15 mmol) of 3-pentanone **8a**, 19.8 g (0.15 mol) of dimethyl malonate, and 90 mL of THF. These reagents were added dropwise into the flask for 2 h, and the complex became a paler yellow. Then 50 mL of THF was used to wash the residue from the funnel into the reaction mixture, which was stirred for 2 h. Forty-three milliliters of dried pyridine and 75 mL of THF were placed in the pressure equalizing addition funnel by syringe and added dropwise for 3 h into the reaction mixture to give an orange color. This mixture was stirred for another 4 h at 0 °C and then for another 72 h at room temperature to give a beige mixture. The reaction was quenched by shaking with 75 mL of distilled water. The aqueous layer was saturated with sodium chloride, and the product was extracted with three 50-mL portions of THF. The combined organic layer was washed three times with 50 mL of saturated aqueous sodium chloride and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The crude product was distilled at reduced pressure to give 9.2 mL of unreacted dimethyl malonate at 47 °C (3.6 mmHg and 11.4 g (38%) of colorless oily product **9a**: bp 80–82 °C, <3.6 mmHg); IR (KBr) 2880, 1725, 1650, 1460, 1440, 1370, 1250, 1240, 1125, 1060; ^{1}H NMR δ 1.11 (t, 6, J = 7.5), 2.38 (q, 4, J = 7.5), 3.77 (s, 6); MS 200 (M^+, 2, $C_{10}H_{16}O_4$), 169 (69, $C_9H_{13}O_3$), 168 (66, $C_9H_{12}O_3$), 136 (100, $C_8H_8O_2$), 108 (63, C_7H_8O), 107 (51, C_7H_7O), 81 (96, C_6H_9), 80 (82, C_6H_8), 72, C_5H_9), 67 (50, C_5H_7), 59 (99, $C_2H_3O_2$), 55 (42, C_4H_7), 53 (88, C_4H_5).

1,1-Bis(methoxycarbonyl)-2,4-dimethylpent-1-ene (**9b**). The condensation reaction procedures were the same as those previously described. Dimethyl malonate was condensed with 4-methylpentan-2-one (15 g, 0.15 mol) to produce a colorless oil which was distilled at 88–89 °C (1.45 mmHg). The yield of product **11b** was 13.3 g (41.3%): IR (KBr) 2880, 1725, 1650, 1460, 1440, 1385, 1375, 1300, 1250, 1240, 1200, 1125, 1060; ^{1}H NMR δ 0.91 (d, 6, J = 7.0), 1.93 (m, 1, J = 7.0), 2.06 (s, 3), 2.28 (d, 2, J = 7.0), 3.76 (s, 3), 3.77 (s, 3); MS 214 (M^+, 3, $C_{11}H_{18}O_4$), 183 (56, $C_{10}H_{15}O_3$), 182 (49, $C_{10}H_{14}O_3$), 150 (100, $C_9H_{10}O_2$), 140 (69, $C_8H_{12}O_{12}$), 127 (65, $C_7H_{11}O_2$), 112 (87, $C_6H_8O_2$), 94 (67, C_7H_{10}), 82 (95, C_6H_{10}), 67 (71, C_5H_7), 59 (65, $C_2H_3O_2$), 55 (28, C_4H_7).

1,1-Bis(methoxycarbonyl)-2-methylbut-1-ene (**9c**). The condensation of 2-butanone (10.8 g, 0.15 mol) with dimethyl malonate (19.8 g, 0.15 mol) gave a colorless oily product, **9c**, 8.9 g (32%): bp 60–62 °C, 0.32 mmHg); IR (KBr) 2880, 1725, 1650, 1460, 1440, 1375, 1300, 1280, 1240, 1200, 1125, 1060; ^{1}H NMR δ 1.11 (t, 3, J = 7.5), 2.06 (s, 3), 2.35 (q, 2, J = 7.5), 3.76 (s, 3), 3.77 (s, 3); MS 186 (M^+, 1, $C_9H_{14}O_4$), 155 (32, $C_8H_{11}O_3$), 127 (24, $C_7H_{11}O_2$), 122 (100, $C_7H_6O_2$), 113 (47, $C_5H_9O_2$), 96 (21, C_6H_8O), 95 (33, C_6H_7O), 94 (62, C_7H_{10}), 67 (53, C_5H_7), 59 (86, $C_2H_3O_2$), 55 (42, C_4H_7), 43 (52, C_2H_3O).

1,1-Bis(methoxycarbonyl)-2-(2-bromoethyl)-2-ethylethene (**10a**). A 250-mL round-bottom flask was charged with 11 g (55 mmol) of 1,1-bis(methoxycarbonyl)-2,2-diethylethylene (**9a**), 11.3 g (63.3 mmol) of *N*-bromosuccinimide and 0.23 g of the catalyst 2,2-azabis[2-methylpropionitrile] (AIBN) with 100 mL of dried carbon tetrachloride. The reaction solution was refluxed for 3.5 h. The solution was cooled and filtered, and the residue was washed with chilled carbon tetrachloride. The solvent was removed in vacuo to give the crude product (16.13 g), which was

Table I. Mutagenic Activity of Fusarin C Synthetic Precursors and Analogues Assayed against *Salmonella* Strain TA100

	plate incorporation assay						
	1 μmol		100 nmol		10 nmol		
compd	+S9	−S9	+S9	−S9	+S9	−S9	mutagenic
4b	104	91	118	89	186	86	+
4d	189	91	95	92	88	132	+
4e	117	95	117	91	114	84	−
5c	105	118	100	92	114	107	−
5e	101	124	109	148	215	150	+
6a	93	97	107	103	117	98	−
6b	110	95	96	128	93	130	−
6d	105	88	98	127	93	129	−
7b	116	91	91	121	93	128	−
11b	84	128	96	144	88	130	−
quercetin, 15 μg	360	180					
DMSO	94	92					

Table II. Mutagenic Activity of Fusarin C Synthetic Precursors and Analogues Assayed against *Salmonella* Strain TA98

	plate incorporation assay						disk assay 2 mg		
	10 μmol		1.0 μmol		0.1 μmol				
compd	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	mutagenic
4b	33	14	37	28	55	20	-	-	+
4c	37	33	30	32	54	38	-	-	+
4d	251	128	100	75	43	38	+	+	+
4e	45	30	42	40	28	43	-	-	-
5c	0	0	36	0	44	25	-	-	-
5d	0	0	37	0	46	74	-	-	+
5e	0	0	26	0	39	27	-	-	-
5g	28	11	34	37	28	43	-	-	-
6a	21	21	29	20	39	23	-	-	-
6b	35	26	38	25	63	23	-	-	+
6c	54	36	50	33	53	28	-	-	+
6d	85	44	58	31	41	28	+	-	+
7b	40	31	48	28	51	27	-	-	+
11a	40	23	37	37	28	43	-	-	-
11b	38	44	54	28	62	29	-	-	+
quercetin, 15 μg	520	180							
DMSO	20	24							

distilled at 107–109 °C (0.3 mmHg) to give 13.3 g (86.3%) of the product **10a**, a colorless oil: IR ($CHCl_3$) 2880, 1725, 1650, 1460, 1440, 1385, 1300, 1250, 1240, 1200, 1115, 1100, 1060, 1000, 960, 935; ^1H NMR δ 1.21 (t, 3, J = 6.8), 1.81 (d, 3, J = 7.0), 2.58 (q, 2, J = 7.5), 3.80 (s, 3), 3.81 (s, 3), 5.58 (q, 1, J = 7.0); MS 278, 280 (M^+, 8, $C_{10}H_{15}BrO_4$), 246, 248 (7, $C_9H_{11}BrO_3$), 216, 214 (5, C_8H_7BrO), 199 (76, $C_{10}H_{15}O_4$), 167 (77, $C_9H_{11}O_3$), 135 (78, $C_8H_7O_2$), 109 (78, C_7H_9O), 95 (30, $C_5H_3O_2$), 81 (81, C_6H_9), 79 (92, Br), 67 (84, C_5H_7), 59 (100, $COOCH_3$), 53 (98, C_4H_5).

1,1-Bis(methoxycarbonyl)-3-bromo-2-methylbut-1-ene (**10c**) (*Paredes et al., 1985*). The reaction mixture of enediester **9c** (8 g, 43 mmol), *N*-bromosuccinimide (7.6 g, 49.5 mmol), and the catalyst AIBN (0.18 g) in carbon tetrachloride (100 mL) was refluxed for 2.5 h. The pale yellow, oily product **10c** was produced in 89.5% yield (10.2 g): bp 90–100 °C, 0.32 mmHg); IR ($CHCl_3$) 2880, 1725, 1650, 1460, 1440, 1385, 1300, 1250, 1240, 1060, 1040; ^1H NMR δ 1.76 (d, 3, J = 6.9), 2.14 (s, 3), 3.80 (s, 6), 5.67 (q, 1, J = 6.9); MS 265, 263 ($M^+ - 1$, 1, $C_9H_{13}BrO_4$), 235, 233 (35, $C_8H_9BrO_3$), 185 (72, $C_9H_{13}O_4$), 153 (78, $C_8H_9O_3$), 121 (67, $C_7H_5O_2$), 67 (100, C_5H_7), 59 (90, $COOCH_3$), 53 (82, C_4H_7).

1,1-Bis(methoxycarbonyl)-2-phenyl-3-bromobuten-1-ene (**10d**). The reaction of phenyl 2-bromopropyl ketone (29.6 g, 0.15 mol) and dimethyl malonate (19.8 g, 0.15 mol) produced a pale green crystalline product (9.8 g, 20%) [mp 65.5–66.5 °C; lit. (Berg and Kolsaker, 1978) mp 64–65 °C]. Spectral data agree with the literature values.

1,1-Dicarbamoyl-1,2-epoxy-2-ethyl-3-hydroxybutane (**11a**). Ammonium hydroxide (15 M, 0.15 mL) was added dropwise to the solution of epoxylactone **4c** (0.15 g, 0.75 mmol) in 2 mL of methanol at room temperature. This reaction mixture was further stirred at room temperature for 24 h. Dichloromethane (10 mL) and an aqueous 0.5 N HCl solution (5 mL) were added with 5 min of shaking. The aqueous layer was removed, and the organic layer was washed twice with brine (2 mL) and once with distilled water (2 mL). The washed organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a crude crystalline product which was recrystallized from ethyl acetate and petroleum ether as pale yellow crystals **11a** (0.034 g, 22.4%): mp 145 °C; ^1H NMR δ 1.19 (t, 3, J = 7.5), 1.47 (d, 3, J = 6.7), 1.61 (s br, 1), 2.08 (qq, 2, J = 7.5), 4.73 (q, 1, J = 6.7), 5.88 (s br, 2), 6.78 (s br, 2); ^1H NMR (DMSO-d_6) δ 1.04 (t, 3, J = 7.5), 1.38 (d, 3, J = 6.7), 1.57 (q, 1, J = 7.5), 2.12 (q, 1, J = 7.5), 3.88 (s, 3), 4.83 (q, 1, J = 6.7), 7.88 (s br, 2), 7.93 (d br, J = 1.0); MS 186 ($M^+ - 16$, 2, $C_8H_{12}NO_4$), 140 (5, $C_7H_{10}NO_2$), 97 (26, C_6H_9O), 86 (91, $C_5H_{10}O$), 71 (78, C_4H_7O), 69 (84, C_4H_5O), 57 (100, C_3H_5O).

1-Carbamoyl-2,4-dimethyl-1,2-epoxy-3-hydroxy-1-(methoxycarbonyl)pentane (**11b**). The solution of the starting lactone **4d** (0.1 g, 0.47 mmol) in 2 mL of methanol was cooled to 0 °C in an ice–water bath. Ammonium hydroxide (15 M, 0.2 mL) was added dropwise to the solution. This reaction mixture was stirred further for 30 min at room temperature. Dichloromethane (10 mL) and 0.5 N HCl (5 mL) were added to the reaction mixture. The organic layer was separated, washed twice with brine (1 mL), once with distilled water (1 mL), and dried over anhydrous Na_2SO_4. The solvent was removed, yielding a crude solid which was recrystallized from ethyl acetate and hexane to give a pure white crystalline product, **11b** (69 mg, 59%): mp 136–137 °C; ^1H NMR δ 0.94 (d, 3, J = 6.7), 1.03 (d, 3, J = 6.7), 1.42 (s, 3), 1.88 (m, 1), 2.79 (d, 1, J = 9.7), 3.88 (s, 3), 5.93 (s br, 1), 6.45 (s br, 1); MS 231 (M^+, 11, $C_{10}H_{17}NO_5$), 185 (22, $C_8H_{11}NO_4$), 167 (10, $C_8H_9NO_3$), 147 (28, $C_8H_7NO_2$), 127 (28, $C_5H_3O_4$), 11 (16, $C_5H_3O_3$), 105 (37, $C_4H_{11}NO_2$), 79 (26, C_6H_7), 59 (100, $COOCH_3$).

1-Carbamoyl-1,2-epoxy-3-hydroxy-1-(methoxycarbonyl)-2-methylbutane (**11c**). The aminolysis procedures were the same as those previously described. Epoxy lactone **4e** (0.1 g, 0.5 mmol) provided the product **11c** (50 mg, 49%) which was recrystallized from ethyl acetate and hexane: mp 88–90 °C; IR ($CHCl_3$) 3320, 3100, 2880, 1780, 1750, 1640, 1440, 1380, 1300, 1250, 1190, 1110, 1080, 1060, 1020, 960, 940, 900, 812, 800; ^1H NMR δ 1.44 (d, 3, J = 6.8), 1.63 (s, 3), 3.92 (s, 3), 4.65 (q, 1, J = 6.8); MS 202 ($M^+ - 1$, 13, $C_8H_{12}NO_5$), 186 (7, $C_8H_{12}NO_4$), 172 (10, $C_7H_{10}NO_4$), 155 (20, $C_7H_9NO_3$), 12 (40, $C_5H_6NO_2$), 83 (75, $C_4H_3O_2$), 58 (100, $COOCH_2$), 55 (91, C_4H_7).

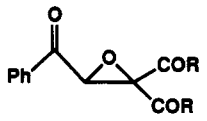
Mutagenicity Assays. Compounds in the amounts indicated in Tables I and II were dissolved in 0.1 mL of DMSO and tested for mutagenicity in *Salmonella typhimurium* tester strains TA98 and TA100 according to the method of Maron and Ames (1983). For the disk assay, 2.0 mg of each compound dissolved in 0.1 mL of DMSO was applied to a 6-mm sterile paper disk. The S9 mix was prepared from livers of Arochlor 1254-treated Sprague-Dawley rats. Quercetin was a positive control. Values in Tables I and II are means of triplicate determinations.

RESULTS AND DISCUSSION

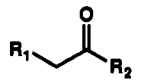
One approach to the synthesis of epoxy-γ-butyrolactams was based on the Darzens condensation (Newman and Magerlein, 1949; Oroshnik and Spoerri, 1945). The product 3-carbamoyl-3,4-epoxy-5-hydroxy-5-phenyl-γ-butyrolactam (**6a**) was prepared in 43% overall yield by a route involving three manipulations. In a single flask, phenyl glyoxal was treated with diethyl bromomalonate and sodium ethoxide to yield the α-ketoepoxydiester **7a** (Chart II). Aminolysis of the epoxydiester **7a** with ammonium hydroxide gave the α-ketoepoxydiamide **7b**. This compound was easily cyclized in refluxing methanol to give the epoxy-γ-butyrolactam **6a**.

A more generally applicable process for synthesis of target hydroxylactams was based on the Knoevenagel condensation. The product, 3,4-epoxy-4,5-dimethyl-5-hydroxy-3-(methoxycarbonyl)-γ-butyrolactam (**6b**) was synthesized from the known lactone acid **5b** (Schultz and Godfrey, 1980). This lactone acid was converted by

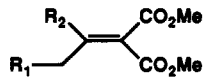
Chart II



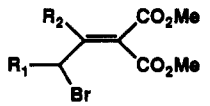
7a, R = OEt
b, R = NH_2



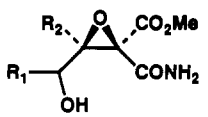
8a, R_1 = Me; R_2 = Et
b, R_1 = t-Pr; R_2 = Me
c, R_1,R_2 = Me



9a, R_1 = Me; R_2 = Et
b, R_1 = t-Pr; R_2 = Me
c, R_1,R_2 = Me



10a, R_1 = Me; R_2 = Et
b, R_1 = t-Pr; R_2 = Me
c, R_1,R_2 = Me
d, R_1 = Me; R_2 = Ph



11a, R_1 = Me; R_2 = Et
b, R_1 = t-Pr; R_2 = Me
c, R_1,R_2 = Me

treatment with diazomethane in ether to the lactone ester **5c** and then epoxidized with basic hydrogen peroxide to give epoxylactone ester **4b**. In a poorer yield process, lactone acid **5b** was converted to epoxylactone acid **4a** with hydrogen peroxide under basic conditions with $Na_2WO_4 \cdot 2H_2O$ catalyst and then esterified with diazomethane to produce **4b**. The aminolysis of epoxybutyrolactone ester **4b** gave the epoxybutyrolactam **6b**, presumably via the corresponding ketoepoxyamide.

The products **6b–d** were synthesized in six steps from dialkyl keto compounds and dimethyl malonate. In most cases the first step was the Knoevenagel condensation of the respective dialkyl ketone **8** and malonate with titanium tetrachloride catalyst as described (Schultz and Godfrey, 1980). The ester products **9** were brominated using *N*-bromosuccinimide with the free radical initiator 2,2-azobis-[2-methylpropionitrile] as catalyst to give bromoenediesters **10c** (Paredes et al., 1985) and **10a**. The bromodiester **10d** was prepared from phenyl 2-bromopropyl ketone as described (Berg and Kolsaker, 1978). The intramolecular cyclizations of the bromodiester products were accomplished by refluxing at 147 °C in 1,1,2,2-tetrachloroethane to eliminate methyl bromide and produce α,β-unsaturated γ-butyrolactones **5g** (Djerassi, 1948; Dauben et al., 1959; Rao, 1976) and **5d–f**. Epoxidations of unsaturated lactones **5d–f** were conducted using hydrogen peroxide under basic conditions to give α,β-epoxy-γ-butyrolactones **4c–e**. These intermediates were transformed by aminolysis to hydroxy *cis*-epoxy amides **11**. Collin's oxidation produced the target epoxy-γ-butyrolactams **6b–d** in modest yields.

The mutagenic activity of 15 representative synthetic compounds was investigated in *S. typhimurium* tester strains TA100 and TA98. Strain TA100 is reverted primarily by base substitution mutagens, and strain TA98 is reverted primarily by frame shift mutagens (Maron and Ames, 1983). Fusarin C is mutagenic in both tester strains when the liver homogenate (S9 mix) is included in the assay (Cheng et al., 1985).

The results of pour-plate assays against strain TA100 and TA98 are indicated in Tables I and II. Results of disk assays against strain TA98 are also presented in Table II. Compounds are considered mutagenic in these initial tests if the mean reversion rate of triplicate determinations was at least 2 times the background rate or if a ring of revertant colonies was obvious in the disk assay. By these criteria lactones **4b**, **4d**, and **5e** were weakly mutagenic in strain TA100 with addition of S9 mix. Compounds **4b–d**, **6b–d**, **7b**, and **11b** were weakly mutagenic in strain TA98 with addition of the S9 mix. Lactone **4d** was also mutagenic in strain TA98 without the S9 mix and was the most potent of the compounds tested. Compound **5d** was mutagenic without the S9 mix, and the highest doses of compounds **5c–e** were toxic to strain TA98. These results indicate that, compared to fusarin C, these ring analogues of fusarin C are at most only weakly mutagenic in *S. typhimurium* and imply that the side chain of fusarin C may be important in the potent mutagenic activity of this compound.

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Registry No. **4b**, 142438-57-1; **4c**, 142438-58-2; **4d**, 142438-59-3; **4e**, 142438-60-6; **5c**, 60971-98-4; **5d**, 142438-64-0; **5e**, 142438-65-1; **5f**, 142438-66-2; **6a**, 142438-61-7; **6b**, 142438-62-8; **6c**, 142438-63-9; **6d**, 142457-04-3; **7b**, 142438-70-8; **8a**, 96-22-0; **9a**, 142438-74-2; **9b**, 142438-69-5; **9c**, 18795-89-6; **10a**, 142438-67-3; **10b**, 142438-68-4; **10c**, 106352-20-9; **10d**, 69231-30-7; **11a**, 142438-72-0; **11b**, 142438-73-1; **11c**, 142438-71-9; diethyl bromomalonate, 685-87-0; benzyloxaldehyde, 1074-12-0; diethyl malonate, 105-53-3; 4-methylpenten-2-one, 108-10-1; 2-butanone, 78-93-3; phenyl 2-bromopropyl ketone, 87439-86-9.